The Frustrated Lewis Pair Concept Applied to the Functionalization of N-Heterocycles

von

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Erklärung


Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe bearbeitet.

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Part of this Ph. D. thesis have been published:


Мојим родићењима којима другујем за све ово и за још много више
» Ko чини добро,
од њега се још више добра очекује. «
-Ivo Andric-
Nobel laureate in literature 1961
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<td>--------------</td>
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A. Introduction
A. Introduction

1. Overview

The remarkable flowering of organometallic chemistry beginning from the second half of the 20th century up to now has enriched and transformed chemical science and technology to a degree and in ways that have few parallels in the history of the discipline. These include the discovery of radically new types of chemical compounds, novel structures and bonding modes, unprecedented reactivity patterns, powerful new synthetic methodologies, new materials and a whole new classes of catalyst and catalytic processes of remarkable versatility and selectivity. The huge impact of organometallic chemistry was once more demonstrated with the actual Nobel Prize award to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their impressive work on palladium-catalyzed cross-couplings in organic chemistry. Although much effort has been made in organic chemistry, the exponential increase in complexity of the building blocks and the constant demand for functionalized precursors claim new methods for their straightforward and efficient preparation. Conventional approaches including extensive protecting group strategies or radical reactions which seem to be more attractive are not satisfactory due to the bad atom economy and the difficult control. Organometallic compounds provide a general approach to complex molecules and numberless applications in total synthesis prove their suitability. A large number of metals was used in synthetic organic chemistry to overcome ongoing problems. Depending on the nature of the carbon-metal bond the reactivity towards numerous electrophiles can be excellent (organolithium compounds) but on the other hand a low selectivity is observed. Choosing organoboron reagents (almost covalent boron-carbon bond), which are well established organometallics due to their air- and moisture stability increases drastically the functional group tolerance but a lack of reactivity occurs. Often appropriate catalysts or harsh reaction conditions are required to promote the reactions of these nucleophiles.

---

2. Preparation of Functionalized Organomagnesium Reagents

2.1 Direct oxidative insertion of magnesium to organic halides

Almost 110 years have passed since Victor Grignard reported the preparation of ethereal solutions of organomagnesium compounds by direct oxidative insertion of magnesium metal to organic halides under inert atmosphere (Scheme 1, Eq. 1). Since then the so called Grignard reactions have constituted one of the most important classes of synthetic organic reactions. As a versatile mean of extending the carbon skeleton this class is without equal.

\[ \text{R-X} + \text{Mg} \rightarrow \text{R-MgX} \]  
\[ 2 \text{R-MgX} \rightarrow \text{R}_2\text{Mg} + \text{MgX}_2 \]

Scheme 1: Synthesis of Grignard reagents by oxidative insertion and Schlenk equilibrium.

Although the detailed mechanism is not yet fully clarified, a radical pathway is generally accepted. In solution, Grignard reagents (RMgX) are in equilibrium (Schlenk equilibrium) with R₂Mg and MgX₂ (Scheme 1, Eq. 2), depending on temperature, solvent, and the nature of the counterion X. Moreover, organomagnesium reagents are prone to form dimers or oligomers, which is influenced by the concentration.

For the formation of organometallic species, such a direct insertion combines several advantages, like atom economy and the low toxicity of magnesium. In addition, magnesium turnings are one of the cheapest reagents in organometal chemistry.

However, the presence of sensitive functional groups, such as cyano-, ester-, keto- or nitro-groups makes the insertion complicated. In pioneering studies, Rieke prepared highly activated magnesium powder (Mg*) using lithium in the presence of naphthalene with MgCl₂. This very reactive magnesium species was used for the preparation of different functionalized aryl magnesium reagents at -78 °C.

---

A. Introduction

Recently, Knochel et al. reported the convenient preparation of various aryl and heteroaryl magnesium reagents from aryl and heteroaryl halides by a direct magnesium insertion in the presence of LiCl.\textsuperscript{14} This salt has a fundamental role and serves several purposes. Firstly, it solubilizes the resulting organomagnesium compound and thus ensures a constantly clean metal surface. Secondly, it promotes the initial electron transfer by the electrophilic activation of the ring through complexation. Finally, the high ionic strength of LiCl solutions facilitates charge separation and accelerates the magnesium insertion.\textsuperscript{15} This new method allows the preparation of functionalized aryl and heteroaryl magnesium reagents which were previously inaccessible due to incompatibility of various functional groups with magnesium (Scheme 2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme2.png}
\caption{Scheme 2: Preparation of functionalized Grignard reagents using magnesium turnings in the presence of LiCl and subsequent quenching with electrophiles.}
\label{scheme2}
\end{figure}

2.2 The halogen/magnesium exchange reaction

An alternative preparation of organomagnesium reagents consists in the halogen/magnesium exchange reaction. In 1931, Prévost reported the first example of a bromine/magnesium exchange by reacting cinnamylmagnesium bromide (1a) with ethylmagnesium bromide (2) furnishing cinnamylmagnesium bromide (3a), however, only in low yields (Scheme 3).\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme3.png}
\caption{Scheme 3: First example of a halogen/magnesium exchange reaction.}
\label{scheme3}
\end{figure}

Over the years, this procedure has turned out to be the method of choice for preparing functionalized organometallic compounds of great synthetic utility. The requirement of such a reaction is that the generated magnesium reagent has to be more stable than the exchange reagent (sp > sp_2(vinyl) > sp_2(aryl) > sp_3(prim.) > sp_3(sec.)). Moreover, the formation rate of the new Grignard reagent also depends on the electronic properties of both the halogen atom and the organic molecule. The reactivity order (I > Br > Cl >> F) is also influenced by the halogen-carbon bond strength, by the electronegativity and polarizability of the halide. Knochel et al. reported the possibility to carry out the halogen/magnesium exchange reaction with substrates even bearing sensitive functional groups, by using either iPrMgBr or PhMgCl (Scheme 4). Thus, an oxygen-chelating functional group such as an ethoxymethoxy group in the aryl bromide (4a) enhances the Br/Mg exchange rate, allowing the preparation of the magnesium derivative (5a) at –30 °C within 2 h. Trapping with allyl bromide in the presence of catalytical amounts of CuCN-2LiCl furnished the aromatic nitrile (6a) in 80% yield. Ortho-nitro groups can also be tolerated. Thus, the nitro-substituted aromatic (4b) underwent a smooth I/Mg exchange with phenylmagnesium chloride within 5 min at –40 °C, leading to the expected Grignard reagent (5b). Quenching with benzaldehyde allowed the formation of the corresponding alcohol (6b) in 90% yield (Scheme 4).

Scheme 4: Examples of halogen/magnesium exchange reaction and trapping with electrophiles.

Further improvement of this work was accomplished by Knochel et al. using a stoichiometric amount of LiCl, which dramatically enhances the reactivity of the Grignard reagents by

---

breaking the aggregates of iPrMgCl.\textsuperscript{20} The new mixed organometallic iPrMgCl-LiCl allows the preparation of a broad range of functionalized aryl- and heteroarylmagnesium reagents starting from the bromides which are usually less expensive and more stable than the corresponding iodides. The desired Grignard reagents can thus be obtained in high yields and under mild conditions (Scheme 5).

\textbf{Scheme 5:} Rate acceleration of the bromine/magnesium exchange reaction by LiCl.

3. Preparation of Functionalized Organozinc Reagents

3.1 Direct oxidative insertion of zinc to organic halides

The oxidative insertion of zinc dust or foil into organic halides is the classical way to prepare organozinc compounds (7) (Scheme 6). \(^{21}\)

\[
\text{FG} - R - X + \text{Zn dust, THF conditions} \rightarrow \text{FG} - R - \text{ZnX} \\
7a: 80\% \\
7b: \geq 98\% \\
7c: 90\% \\
7d: 87\% \\
\]

\(\text{FG}=\text{CO}_2R, \text{CN}, \text{halide}, \text{NH}_2, \text{RNH}, (\text{TMSc})_2\text{N}, \text{RCO}_2\text{N}, (\text{RO})_2\text{N}, (\text{RO})_2\text{Si}, (\text{RO})_2\text{PO}, \text{RS, RSO}, \text{RSO}_2, \text{PhCO}\text{S}\)

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

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

**Scheme 6:** Preparation of functionalized organozinc reagents (7) by the direct insertion of zinc metal into the corresponding iodide.

Although this method tolerates a broad range of sensitive functional groups, such as esters, ketones and nitriles it suffers from two major drawbacks. Long reaction times are required and expensive iodides have to be used in most cases. Moreover, zinc slowly oxidizes in air and its surface is thus covered by an oxide layer. Remedy was found with the development of highly active zinc powder (Zn*) prepared by the reduction of zinc chloride with lithium naphthalenide pioneered by Rieke\(^{22}\) or the use 1,2-dibromethane in THF (5 mol%, reflux, 1-2 min), followed by the addition of TMSCl (1 mol%, reflux, 1 min).\(^{23}\) More recently, Knochel et al. reported that the addition of LiCl during the insertion of zinc dust into organic bromides or iodides leads to an enormous rate increase, as shown by the example of iodobenzene 8a.\(^{24}\)

---


Performing the zinc insertion without LiCl only 5% conversion could be achieved after 24 h at 50 °C. In contrary, performing the zinc insertion in the presence of stoichiometric amounts of LiCl at the same temperature furnishes the desired zinc compound (9a) within 7 h at 50 °C in more than 98% yield. Subsequent acylation with pivaloyl chloride in the presence of CuCN-2LiCl provided the ketone (10a) in 90% yield (Scheme 7).

Scheme 7: Preparation of phenylzinc iodide (9a) in the absence and in the presence of LiCl stoichiometric amounts of LiCl.

This method allows a convenient and high-yielding access to various alkyl, aryl and heteroarylzinc reagents under mild conditions. Additionally, all reactions proceed within a practical temperature range (25-50 °C) and can be extended to large scale preparation. The nature of the activation of zinc dust with LiCl is not yet clarified but it is assumed that LiCl rapidly removes the formed organozinc reagent from the metal surface by generating highly solubly RZnX·LiCl (9) complexes thus allowing a rapid reaction of further organohalide molecules with zinc avoiding the competitive deactivation of active metal surface.
4. Preparation of Functionalized Organoboron Reagents

4.1 Alkylation of organomagnesium or lithium reagents with trialkyl borate

The classical and at the same time efficient synthesis of aryl- and 1-alkenylboronic acids or their esters involves the treatment of a Grignard or organolithium reagent with trialkyl borate derivatives (Scheme 8).

\[
\text{ArMgX} + \text{B(OMe)}_3 \rightarrow \text{ArB(OH)}_2 \\
\text{H}_2\text{C} = \text{CHMgBr} + \text{B(OMe)}_3 \rightarrow \text{H}_2\text{C} = \text{CHB(OR)}_2
\]

Scheme 8: Preparation of organoboron reagents.

The first stereocontrolled synthesis of alkenylboronic acids and esters was achieved by the reaction of (Z)- or (E)-2-buten-2-ylmagnesium bromide with trimethyl borate (Scheme 9).

\[
\begin{align*}
\text{Me} & \quad \text{Br} \quad \text{H} \quad \text{Me} \\
\text{Mg} & \rightarrow \\
\text{B(OMe)}_3 & \rightarrow \\
\text{Me} & \quad \text{B(OH)}_2 \quad \text{H} \quad \text{Me}
\end{align*}
\]

Scheme 9: Stereocontrolled synthesis of alkenylboronic acid.

These classical methods may suffer from the contamination of the opposite stereoisomers or of bis-alkylation which leads to borinic acid derivatives and the formation of trialkylboranes. However, treating organolithium reagents with triisopropyl borate followed by acidification with HCl leads directly to alkyl-, 1-alkynyl- or 1-alkenylboronic esters in high yield avoiding such side reactions (Scheme 10).

\[
\begin{align*}
\text{RLi} + \text{B(OiPr)}_3 & \rightarrow \text{R-B(OiPr)}_2 \\
\text{HCl} & \rightarrow \\
\text{R-B(OiPr)}_2 &
\end{align*}
\]

Scheme 10: Preparation of organoboronic esters from organolithium reagents.

---


4.2 Pd-catalyzed cross-coupling reaction of aryl halides with bis(pinacolato)diboron
A very efficient route to arylboronic esters tolerating a wide range of functional groups, such as ester, nitrile or acyl groups has been described by Miyaura et al. Aryl halides are directly utilized in cross-coupling reactions with (alkoxy)diborons under Pd catalysis (Scheme 11).

\[
\text{Ar-X} + (\text{RO})_2\text{B-B(OR)}_2 \xrightarrow{\text{PdCl}_2(\text{dppf}), \text{KOAc, DMSO, 80°C}} \text{Ar-B(OR)}_2
\]

Scheme 11: Synthesis of arylboronic esters by cross-coupling reaction.

4.3 Hydroboration
Additionally, a more general way for the preparation of alkyl borane derivatives consists in the hydroboration of the corresponding olefin with dialkylboranes, such as 9-BBN or dicyclohexylborane (Scheme 12).\(^{28}\) The reaction is essentially quantitative and proceeds in a highly chemo-, regio- and diastereoselective manner through cis anti-Markovnikov addition from the less hindered side of double bond. The 9-alkyl-9-BBN derivatives thus obtained are particularly useful for the transfer of primary alkyl groups by the palladium-catalyzed cross-coupling reaction since the 9-alkyl group exclusively participates in a catalytic reaction cycle.

\[
\text{R-CHR}_2 \xrightarrow{9\text{-BBN}} \text{R-CHR}_3\text{B}
\]

Scheme 12: Hydroboration of 1-alkene to give alkylboron compound.

4.4 Borylation via C-H activation
The direct borylation of hydrocarbons catalyzed by a transition metal complex represents a further strategy for the preparation of organoboron reagents which has been studied by several groups. Rhenium-, rhodium-, iridium- and palladium-catalyzed C-H borylation of alkanes,

A. Introduction

arenes and benzylic positions of alkylarenes by pinacolborane for example, provide alkyl-, aryl-, heteroaryl- and benzylboron compounds, respectively (Scheme 13).\(^\text{29}\)

\[
\begin{align*}
\text{Ar-H} + \text{H-B} & \xrightarrow{\text{Cp}^\text{+R}h(1\text{A}_{1}C_{2}Me_{3})} \xrightarrow{2\text{mol\%}} \text{Ar-B} + \text{H}_{2} \\
& \xrightarrow{oC_{6}H_{6}/150 \degree C} \text{Ar-B} + \text{H}_{2}
\end{align*}
\]

**Scheme 13:** Direct aromatic borylation with pinacolborane.

4.5 Organotrifluoroborates

One of the most significant reasons for the extensive research on the preparation of organoboron reagents is their use in cross-coupling reactions. These compounds feature high compatibility with a broad range of functional groups, possess a relatively low toxicity and are stable to moisture. Additionally, they combine economy, efficiency and benignity *inter alia* in the synthesis of complex natural products or other challenging structures.\(^\text{30}\) More stable and therefore easier to isolate are organotrifluoroborates reported by Vedejs. Thus, any organoboron compound with two labile substituents can be rapidly and efficiently converted into the corresponding potassium organotrifluoroborate by using KHF\(_{2}\) (Scheme 14).\(^\text{31}\) In addition to the advantages of stability, favourable physical properties, scalability and operational simplicity that are inherent to the organotrifluoroborates, both atom economy and price speak clearly in favour of their use as well as the fact that all classes (aryl, heteroaryl, alkenyl, alkynyl and alkyl derivatives) have demonstrated the ability to undergo cross-coupling reactions.\(^\text{32}\) But applications in large scale turn out to be difficult due to the corrosive character of flourine.

\[
\begin{align*}
\text{RBX}_{2} + 2 \text{KHF}_{2} & \xrightarrow{\text{methanol or acetone}} \text{RBF}_{3}K + \text{KF} + 2 \text{XH} \\
& \quad \text{where } X = \text{halides, OR}, \text{NR}^\prime, \text{NR}^\prime\prime, \text{allyl}
\end{align*}
\]

**Scheme 14:** Preparation of potassium organotrifluoroborates.

---


5. Preparation and Application of TMP-Bases

5.1 Introduction
Directed metalation offers a straightforward access to functionalized aromatic and heterocyclic compounds. However, as mentioned directed lithiation using lithium bases like LDA or LiTMP suffer from many drawbacks including careful temperature control and especially incompatibility with many functional groups such as esters, nitriles or ketones. Alternative methods have been developed using magnesium amides and amidozincates such as Li[tBu₂(tmp)Zn] introduced by Kondo et al. However, the limited solubility of these bases in organic solvents as well as the requirement for an excess of the magnesium bases (2-12 equiv) to achieve high conversions has precluded their general use. Moreover, both the aminozincate and -magnesiate required in subsequent quenching reactions a large excess of the electrophile (up to 12 equiv in the case of magnesium, and for zinc up to 4 equiv) which restricted the scale-up of these reactions and consequently their utility in organic synthesis. Recently, the preparation of highly chemoselective 2,2,6,6-tetramethylpiperidyl (TMP) mixed metal/Li amides such TMPMgCl·LiCl (11), TMPZnCl·LiCl (12), TMP₂Mg·2LiCl (13), TMP₂Zn·2MgCl₂·2LiCl (14) and TMP₂Al·3LiCl (15) was reported, which allow the selective metalation of sensitive aromatic compounds and heterocycles (Scheme 15). This new generation of bases is easily prepared, highly soluble in THF and offers additionally long term stability under inert atmosphere at ambient temperatures.

5.2 Magnesium amide bases

Thus, the reaction of the polyfunctional arene (16a) with TMPMgCl-LiCl (11) provided the desired arylmagnesium species (17a) which led to the iodinated product (18a) in 88% yield (Scheme 16).

Scheme 16: Preparation of arylmagnesium reagent (17a) by using TMPMgCl-LiCl (11).

However, for poorly activated substrates such as benzonitriles (16b), only a sluggish metatalation is observed with TMPMgCl-LiCl (11). For this purpose TMP₂Mg·2LiCl (13) was developed featuring an improved kinetic basicity. By using the latter, benzonitrile (16b) was magnesiated within 3 h at -30 °C affording after transmetalation and Pd-catalyzed cross-coupling the corresponding biphenyl derivative (18b) in 70% yield (Scheme 17).

Scheme 17: Deprotonation of unactivated nitrile (16b) and subsequent functionalization.
5.3 Zinc amide bases

Metalations of sensitive heterocycles such as 2-phenyl-1,3,4-oxadiazole (16c) can only be carried out at temperatures below -78 °C because the metalated species start to decompose. Changing from lithium or magnesium to another metal, namely zinc, enables the metalation at 25 °C without any undesired side reactions. Thus, 16c is deprotonated at 25 °C with TMP$_2$Zn·2MgCl$_2$·2LiCl (14) within 20 min providing the heteroarylzinc compound (17c) which furnishes the expected product (18c) after quenching with PhSSO$_2$Ph in 75% yield (Scheme 18).

Scheme 18: Selective zinication of heterocycle 16c with TMP$_2$Zn·2MgCl$_2$·2LiCl (14) at 25 °C.

But only satisfactory results in terms of reaction selectivity and yield are obtained with some electron-poor heteroaromatics using the mild TMP$_2$Zn·2MgCl$_2$·2LiCl (14). To address this problem a chemoselective base was developed tolerating sensitive functionalities such as an aldehyde, a nitro group or sensitive heterocycles. Using this new base TMPZnCl·LiCl (12) several heteroarenes, like pyridazines and pyrimidines are cleanly zinicated at ambient temperature, as shown in Scheme 19, where 3,6-dichloropyridazine (16d) is metallated within 30 min affording after trapping with I$_2$ the desired product (18d) in 84% yield (Scheme 19).

Scheme 19: Direct metalation of 3,6-dichloropyrazine (16d) using TMPZnCl·LiCl (12) and subsequent trapping with I$_2$.

---


5.4 Aluminum amide bases

Another challenge are electron-rich compounds, which are also very difficult to metalse since aromatic ethers are poor ortho-directing groups even for lithiation reactions,\textsuperscript{43} not to mention magnesium and zinc amides. However, aluminum amides are powerful reagents for the metalse of such aromatic ethers, probably due to the coordination of the oxygen to the aluminum centre of the base. Thus, anisole (16e) was aluminated regioselectively at the ortho position with TMP\textsubscript{3}Al-3LiCl (15) within 11 h at ambient temperature and led after acylation with chlorobenzoyl chloride in presence of CuCN-2LiCl to the benzophenone (18e) in 74\% yield (Scheme 20).

Scheme 20: Selective ortho-alumination of anisole (16e) with TMP\textsubscript{3}Al-3LiCl (15) and subsequent copper-mediated acylation.

\textsuperscript{43} V. Snieckus, Chem. Rev. 1990, 90, 879.
6. Frustrated Lewis Pairs

First in 1923 Gilbert N. Lewis proposed a concept whereupon molecules that donate electron-pairs act as bases and conversely those which accept electron-pairs are classified as acids. Thus, combining a simple Lewis acid with a Lewis base results in neutralization similar to the corresponding combination of a Brønsted acid and base when water is formed. The notion of Lewis acid and base rationalized numerous reactions by assuming that Lewis acids offer low-lying lowest unoccupied molecular orbitals (LUMOs) to the lone electron-pair in the high-lying highest occupied molecular orbital (HOMO) of Lewis bases. This concept of Lewis acids and bases put forward some 90 years ago impacts across the discipline. It became a guiding principle in understanding both main group and transition metal chemistry and is a universal tool for understanding and predicting a broad spectrum of chemical reactivity in general. However, some reactions were discovered that appear to deviate from that Lewis’ axiom. While examining the interaction of pyridine with boranes, Brown and co-workers noted that in most of the combinations of Lewis acids and bases classical adduct formation was observed but not in the case of lutidine with BMe₃ (Scheme 21).  

\[
\text{Scheme 21: Treatment of lutidine with BF}_3 \text{ and BMe}_3.
\]

Based on molecular models, this anomalous result was attributed to the steric demand of the ortho-methyl groups of lutidine. But its impact on subsequent reactivity was not further pursued at that time. In 1950, Wittig et al. described that 1,2-didehydrobenzene, generated in situ from o-fluorobromobenzene, reacts with a mixture of the Lewis base triphenylphosphine and the Lewis acid triphenylboran to give the o-phenylenebridged phosphonium-borate 19a (Scheme 22). Some years later, Tochtermann, then a member of the Wittig school, observed the formation of the trapping product (19b), instead of the expected, usual formation of polybutadiene through anionic polymerization, upon addition of BPh₃ to the mixture of butadiene monomer and trityl anion initiator (Scheme 22).

Scheme 22: Early frustrated Lewis pairs.

Although these findings by Nobel laureates did not garner much attention at that time these works represent the first references to the curious and unique behaviour of sterically frustrated Lewis pairs. It led Tochtermann to coin the German term “antagonistisches Paar” to describe such non-quenched Lewis pairs. Over the intervening years, frustrated Lewis pairs have developed from chemical curiosities into a new strategy for the activation of a variety of small molecules. For instance, mixtures of frustrated phophines (PR₃, R = C₆H₃Me or tBu) and boranes (BR₃, R’ = C₆F₅) can easily cleave molecular hydrogen (H₂) in a heterolytic manner under very mild conditions (Scheme 23), and they can undergo addition reactions with olefins as well. Furthermore, compounds of the type R₂P-C₆H₄-BR’₂ have been shown to reversibly activate and liberate H₂ and act as effective hydrogenation catalyst for the reduction of C-N multiple bonds.

Scheme 23: Heterolytic cleavage of H₂ by phosphine and borane.

By analogy to transition metal chemistry, it is anticipated that a side-on interaction of H₂ with the Lewis acid BR₃ (R = C₆F₅, C₆H₅) results in polarization of H₂, thus facilitating protonation of an approaching phosphine resulting in the formation of 20-22 (Scheme 24). Attempts to observe such a Lewis acid-H₂ interaction were undertaken by treatment by B(C₆F₅)₃ with

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higher pressures of H₂ (4 atm). Monitoring these mixtures by ¹H- and ¹⁹F-NMR spectroscopy at temperatures as low as 190 K showed resonances attributable to free B(C₆F₅)₃. No other species were observed, and thus this experimental evidence suggests that a borane-H₂ adduct is not stable.[47a]

**Scheme 24:** Suggested mechanisms for heterolytic cleavage of H₂ by phosphine and borane.
7. Objectives

The development of highly chemoselective LiCl-complexed 2,2,6,6-tetramethylpiperidyl (TMP) metal amide bases allows the selective metalation of sensitive aromatics and heterocycles. However, attempts to magnesiate, zincate or aluminate unactivated pyridines with such bases proved to be unsatisfactory. The aim of this work was to investigate new metalating reagents, which have a good functional group compatibility but are still reactive enough to undergo typical interception reactions (Scheme 25).

![Scheme 25](image)

**Scheme 25:** General pathway for the metalation of poorly activated pyridines.

In addition, the total functionalization of the pyridine core using successive sequences (regio- and chemoselective metalations and trapping with different electrophiles) should be accomplished (Scheme 26).

![Scheme 26](image)

**Scheme 26:** Multiple regio- and chemoselective functionalizations of the pyridine core via directed metalation.

Moreover, the selective functionalization of amino-substituted pyridines, such as \(N,N\text{-}4\)-dimethylaminopyridine (DMAP) and (S)-nicotine was to be investigated (Scheme 27).

![Scheme 27](image)

**Scheme 27:** Regio- and chemoselective functionalization of DMAP and (S)-nicotine.
Furthermore, the new metalation procedure should be applied to the selective functionalization of the more complex alkaloid quinine (Scheme 28).

![Scheme 28: Regioselective functionalization of quinine.](image)

Finally, the *in situ* preparation of arylzinc compounds and their subsequent cross-coupling reactions with electrophiles under transition metal catalysis in an one-pot procedure was to be investigated (Scheme 29).

![Scheme 29: In situ generation of arylzinc reagents followed by Pd-catalyzed cross-coupling reaction.](image)
B. Results and Discussion
1. Functionalization of Pyridine and its Derivatives via Regio- and Chemoselective Metalation

1.1 Introduction

Invariably, azaheterocycles attract a lot of attention since their immense scientific and commercial value increases continuously. Their ubiquity, in particular that of pyridine derivatives, in transition metal chemistry, supramolecular chemistry, optoelectronic or luminescent materials drives chemists to design efficient and selective methods for their functionalization. Moreover, a large number of pharmaceuticals and natural products contain the pyridine scaffold.

![Chemical structures of etoricoxib (23), epibatidine (24), and ABT-594 (25)](image)

**Scheme 30:** Biologically active compounds containing a pyridine moiety.

The selective inhibitor of cyclooxygenase enzyme (COX-2) etoricoxib (23) reduces the generation of prostaglandins from arachidonic acid (Scheme 30).51 Among the different functions exerted by prostaglandins, their role in the inflammation cascade should be highlighted. The alkaloid epibatidine (24), a natural product isolated from South American frogs, was discovered in 1970s as a non-opiod analgesic agent with a potency 200-fold greater than that of morphine in mice.52 However, 24 is toxic or even lethal at doses only slightly higher than its effective analgesic dose. In part, this is due to the fact that in addition to being an agonist at central nicotinic receptors, 24 is also believed to block neuromuscular junctions.

---


B. Results and Discussion

resulting in respiratory paralysis and death. Nonetheless, this alkaloid served as an exciting lead in the search for novel analgesics. However, despite these structural similarities to epibatidine (24) ABT-594 (25) was discovered accidently during tests against Alzheimer's Disease. It combines namely potent analgesic activity with a highly satisfactory safety profile. Finally, lavendamycin (26), a naturally occurring pyridine derivative isolated from the fermentation broth of *Streptomyces lavendulae*, shows antimicrobial and cytotoxic properties. However, its biological interest is limited by its toxicity toward human cells that may be linked to the presence of the quinone moiety.

1.2 Functionalization of pyridine and its derivatives using lithium bases

As mentioned in above, the need for functionalized pyridine derivatives is still tremendous because they are extensively used in innumerable fields. The main approaches for substituted pyridines represent the construction of the pyridine ring and its metalation. Among metalations, the halogen-metal exchange has proven to be an efficient process. But often the parent halopyridines are not available and therefore a more straightforward route to functional derivatives is offered by direct metalations. Also the direct functionalization of pyridine by lithiation is difficult due to its π-deficiency character, and various alkyllithiums rather attack the azomethine bond in a nucleophilic manner than to abstract a proton. To overcome this side-reaction and to promote lithiation, alternatives such as the use of LDA or LiTMP have been proposed. However, equilibrated reactions were observed, implying trapping of

---

lithiated pyridines *in situ*.  In 1994, Schlosser *et al.* showed that LIC-KOR (a mixture of *n*-BuLi and *t*-BuOK known as superbase) allows a regioselective metalation of 3-fluoropyridine (27) but requires very low temperatures (Scheme 31).

![Scheme 31: Selective metalation of 3-fluoropyridine (27) using *n*BuLi/*t*BuOK (superbase).](image)

Nevertheless, this method is cumbersome for the ortho-metalation of pyridine (29a) because an excess of base is obligatory which has to be destroyed selectively before the subsequent reaction with an electrophile. Thus, only few compounds are efficiently accessible by this method (Scheme 32).

![Scheme 32: Metalation of pyridine (29a) using an excess of superbase.](image)

---

An elegant solution has been proposed by Kessar et al. who showed that a complexation of pyridine (29a) with BF₃ allows a low temperature α-lithiation of 29a (Scheme 33).

![Scheme 33: Metallation of BF₃-complexed pyridine using LiTMP and subsequent reaction with aldehyde.](image)

This procedure is also applicable to tertiary amines affording α-carbanions, which is remarkable since nitrogen does not provide sufficient stabilisation to an adjoining negative charge, unlike phosphorus and sulphur.

### 1.3 Regio- and chemoselective functionalization of pyridine and its derivatives using TMP-derived bases in the presence of BF₃·OEt₂

Recently, the preparation of various TMP-derived metal/Li-bases has been reported for the directed metatlation of sensitive aromatics and heteroaromatics, with a great compatibility with a broad range of functional groups. However, attempts to magnesiate, zincate, or aluminat unactivated pyridines with such bases proved to be unsatisfactory in terms of regioselectivity and yield. Thus, by using TMPMgCl-LiCl (11) only a partial magnesiation of pyridine (29a) is observed (less than 40%) at ambient temperature (Scheme 34).

![Scheme 34: Uncomplete metalation of pyridine (29a) using TMPMgCl-LiCl (11).](image)

This prompted us to explore the impact of BF₃·OEt₂ in directed metatalations using TMP-derived bases (11-15) (Scheme 35).

---

Scheme 35: Selective metalation of pyridine and its derivatives (29a-e) by complexation with BF₃ and subsequent addition of TMPMgCl-LiCl (11).

Thus, complexation of pyridine (29a) with BF₃·OEt₂ at 0 °C for 15 min and subsequent addition of TMPMgCl-LiCl (11) led to a metalation at position 2 within 20 min at -40 °C. After iodolysis, the 2-iodopyridine (30a) was obtained in 61% (entry 1; Table 1). Similarly, 4-phenylpyridine (29b) was firstly complexed with BF₃·OEt₂ and thereupon it reacted with TMPMgCl-LiCl (11) for 20 min at -40 °C providing after trapping with I₂ the product (30b) in 63% yield. Transmetalation of the intermediate with ZnCl₂ enabled a Negishi cross-coupling with ethyl 4-iodobenzoate in the presence of Pd(dba)₂ (5 mol%) and P(2-furyl)₃ (10 mol%) affording the functionalized derivative 30c in 84% yield (entry 2). Additionally, under the same conditions various aryl iodides reacted in a Negishi cross-coupling with the magnesiated intermediate to the corresponding 2,4-disubstituted pyridines 30d-f in 75-82% yield (entries 4-6). Also an acylation with benzoic chloride with previous transmetalation with CuCN·2LiCl could be performed leading to the pyridyl ketone 30g in 77% yield (entry 7). Even sensitive functionalities, such as nitriles or esters can be tolerated adopting this procedure. Thus, 4-cyanopyridine (29c) was selectively zinicated at position 3 by using TMP₂Zn·2MgCl₂·2LiCl (14) within 3 h at -20°C furnishing after transmetalation to copper with CuCN·2LiCl the allylated product 30h in 77% yield, whereas the iodolysis of the metalted species ended up in 71% yield (entries 8 and 9). While ethyl isonicotinate requires the use of TMP₂Mg·2LiCl and 12 h for complete deprotonation, ethyl nicotinate (29d) could be smoothly metalated at position 4 within 30 min at -40 °C by precomplexation with BF₃ using TMPMgCl-LiCl (11). Subsequent reaction with 3-bromocyclohexene, after addition of CuCN·2LiCl, led to 3,4-disubstituted pyridine 30j in 75% yield (entry 10). Furthermore, electron-rich substituted pyridines, such as 4-methoxypyridine (29e) can be metalted applying this procedure. Thus, after precomplexation with BF₃·OEt₂, 29e was selectively metalated using TMPMgCl-LiCl (11; -20 °C, 30 h) at position 2 furnishing after iodolysis the product 30k in 75% yield (entry 11).

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**Table 1: Products obtained by complexation with BF$_3$ and subsequent addition of the appropriate TMP-base.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temperature [°C] / Time [h]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%]$^a$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>29a</td>
<td>-40 / 0.25</td>
<td>I$_2$</td>
<td>30a</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>29b</td>
<td>-40 / 0.3</td>
<td>I$_2$</td>
<td>30b</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>29b</td>
<td>-40 / 0.3</td>
<td>I$_2$</td>
<td>30c</td>
<td>84$^b$</td>
</tr>
<tr>
<td>4</td>
<td>29b</td>
<td>-40 / 0.3</td>
<td>I$_2$</td>
<td>30d</td>
<td>82$^b$</td>
</tr>
<tr>
<td>5</td>
<td>29b</td>
<td>-40 / 0.3</td>
<td>I$_2$</td>
<td>30e</td>
<td>81$^b$</td>
</tr>
<tr>
<td>6</td>
<td>29b</td>
<td>-40 / 0.3</td>
<td>I$_2$</td>
<td>30f</td>
<td>75$^b$</td>
</tr>
<tr>
<td>7</td>
<td>29b</td>
<td>-40 / 0.3</td>
<td>I$_2$</td>
<td>30g</td>
<td>77$^c$</td>
</tr>
<tr>
<td>8</td>
<td>29c</td>
<td>-20 / 3</td>
<td>I$_2$</td>
<td>30h</td>
<td>77$^c$</td>
</tr>
<tr>
<td>9</td>
<td>29c</td>
<td>-20 / 3</td>
<td>I$_2$</td>
<td>30i</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>29d</td>
<td>-40 / 0.5</td>
<td>I$_2$</td>
<td>30j</td>
<td>75$^c$</td>
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#### Table 1 continued

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<td><img src="image" alt="29e" /></td>
<td><img src="image" alt="30k" /></td>
<td>75</td>
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</table>

[a] Yield of isolated analytically pure product. [b] Transmetalation with 1.1 equiv of ZnCl$_2$ and subsequent Negishi cross-coupling using Pd(dba)$_2$ and P(2-furyl)$_3$. [c] Transmetalation with 1.1 equiv of CuCN·2LiCl.
2. Functionalization of Quinoline (31a) and its Derivatives via Regio- and Chemoselective Metalation

2.1 Introduction

As mentioned in above, the functionalization of heteroaromatics is a matter of huge interest. Especially quinoline (31a) and its derivatives are found in many medicinal compounds including Talnetant (32),\(^ {70}\) a NK\(_3\) receptor antagonist, L746,530 (33) a therapeutic agent for asthma and inflammatory diseases,\(^ {71}\) or camptothecin (34) a natural product, which became lead for anticancer drug development due to its excellent cytotoxic activity (Scheme 36).\(^ {72}\) A prominent analog of the latter, Topotecan (35), is applied in cancer chemotherapy.\(^ {73}\) Besides, in the treatment of malaria infections quinoline-containing drugs, such as Mefloquine (36), have proven to be the most effective. Mefloquine (36) is considered a standard therapeutic agent for multi-drug resistant \textit{P. falciparum} malaria and is also well-tolerated for long-term malaria chemoprophylaxis.\(^ {74}\)


Scheme 36: Natural products and pharmaceuticals containing the quinoline skeleton.

2.2 Regio- and chemoselective functionalization of quinoline (31a) and its derivatives using TMP-derived bases in the presence of BF$_3$OEt$_2$

Scheme 37: Selective metalation of quinoline and its derivatives (31a-c) by complexation with BF$_3$ and subsequent addition of TMPMgCl-LiCl (11).

Thus, precomplexation with BF$_3$OEt$_2$ (1.1 equiv, 0 °C, 15 min) of quinoline (31a) followed by the addition of TMPMgCl-LiCl (11; 0 °C, 20 min) led to a selective metalation at position 2 affording after iodolysis the 2-idoquinoline (37a) in 75% yield (entry 1; Table 2). Transmetalation with ZnCl$_2$ and Negishi cross-coupling with different aryl iodides furnished the corresponding products 37b-d in 80-82% yield (entries 2-4). The presence of an electron-withdrawing group, such as a chlorine substituent in the case of 4-chloroquinoline (31b), accelerated the metalation, furnishing quantitatively the magnesiated intermediate within 10 min at -10 °C. Subsequent iodolysis led to 4-chloro-2-idoquinoline (37e) in 65% yield, alternatively a Negishi cross-coupling after transmetalation with ZnCl$_2$ gave the 2,4-disubstituted quinoline 37f in 70% yield (entries 5 and 6). Similarly, 4-bromoquinoline (31c) was metalated after complexation with BF$_3$OEt$_2$ (1.1 equiv, 0 °C, 15 min) using
B. Results and Discussion

TMPMgCl-LiCl (11; -10 °C, 20 min) affording after acylation with benzoyl chloride in the presence of CuCN·2LiCl the 2,4-disubstituted quinoline derivative 37g in 84% yield (entry 7).

Table 2: Products obtained by complexation with BF₃ and subsequent addition of TMPMgCl-LiCl (11).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temperature [°C] / Time [h]</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield [%]</th>
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</thead>
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<td>I₂</td>
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<td>75</td>
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<tr>
<td>2</td>
<td>31a</td>
<td>0 / 0.3</td>
<td>37b</td>
<td>80b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31a</td>
<td>0 / 0.3</td>
<td>37c</td>
<td>82b</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31a</td>
<td>0 / 0.3</td>
<td>37d</td>
<td>80b</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>31b</td>
<td>-10 / 0.2</td>
<td>I₂</td>
<td>37e</td>
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<td>6</td>
<td>31b</td>
<td>-10 / 0.2</td>
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<tr>
<td>7</td>
<td>31c</td>
<td>-10 / 0.3</td>
<td>I₂</td>
<td>37g</td>
<td>84c</td>
</tr>
</tbody>
</table>

[a] Yield of isolated analytically pure product. [b] Transmetalation with 1.1 equiv of ZnCl₂ and subsequent Negishi cross-coupling using Pd(dba)₂ and P(2-furyl). [c] Transmetalation with 1.1 equiv of CuCN·2LiCl.
3. Preparation of New Frustrated Lewis Pairs for the Regio- and Chemoselective Functionalization of Sensitive N-Heterocycles

The complexation of 4-phenylpyridine (29b) with BF₃·OEt₂ (1.1 equiv, 0 °C, 15 min) furnishes the intermediate (38). The subsequent addition of TMPMgCl·LiCl (11; 1.1 equiv, -40 °C, 20 min) generates a metalated pyridine derivative, which after transmetalation with ZnCl₂ and a subsequent Negishi cross-coupling with ethyl 4-iodobenzoate affords the product 30c in 84% yield (Scheme 38).

Scheme 38: Selective BF₃-triggered metalations.

In exploring the scope of this metolation method, we queried the nature of the generated organometallic intermediate in which the strong Lewis acid BF₃·OEt₂ and the strong Lewis base TMP were incorporated. To this, we performed an alternative experiment, in which 4-phenylpyridine was treated with a premixed solution of BF₃·OEt₂ (1.1 equiv) and TMPMgCl·LiCl (11; 1.1 equiv, -40 °C, 10 min), tentatively written as TMPMgCl·BF₃·LiCl (39), and compared the result with the above described two-step metolation with prior complexation with BF₃·OEt₂ and subsequent addition of TMPMgCl·LiCl (11) (Scheme 38). An efficient metolation with the reagent 39 occurs within 10 min at -40 °C. Transmetalation with ZnCl₂ and a Negishi cross-coupling reaction with the aryl iodide provides the 2-arylated pyridine (30c) in 70% yield (Scheme 38). This alternative metolation method involves a new frustrated Lewis pair TMPMgCl·BF₃·LiCl (39) that is quite reactive for the selective metilation of pyridines.
We have examined the mechanism and scope of this reaction in more detail. $^{11}$B-NMR, $^{19}$F-NMR, $^{13}$C-NMR measurements clearly indicate that the intermediate organometallic species 40 bears a carbon-boron bond as depicted in Scheme 38. This structure has also been supported by DFT-calculations. Thermodynamic analysis by DFT calculations shows that the structure 40A (with a C-B bond) is 13.5 kcal/mol thermodynamically more stable than the isomeric structure 40B (with a C-Mg bond; Scheme 39).

Scheme 39: Structure and reactivity of the new frustrated Lewis pair 39.

This finding indicates that otherwise difficult to prepare pyridyltrifluoroborates can be readily obtained in a one-pot procedure by highly regioselective C-H activations. The exact

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76 DFT calculations were carried out using the Gaussian03 Rev.B.04 program package with the nonlocal hybrid B3LYP exchange correlation functionals and the Møller-Plesset second-order correlation energy correction (MP2). The basis set denoted as 631SVP consists of the Ahlrich def2-SVP all electron basis set for Mg atoms and the 6-31G(d,p) basis set for other atoms. Unless otherwise stated energies refer to relative zero-point corrected electronic energies (MP2/631SVP//B3LYP/631SVP).
B. Results and Discussion

structure of the reagent 39 could not be clearly defined, despite numerous NMR-studies. However, DFT-calculations led to the tentative structures 39A and 39B showing that both are energetically favoured. NMR-studies confirm that 39 exists as several species in solution. The reaction pathways of 39A and 39B in the presence of pyridine (Py) have been modeled by DFT-calculations, which reveal that 39A and 39B may dissociate in the presence of pyridine to furnish a Py-BF$_3$ complex (38A) as well as TMPMgCl(THF)$_2$ (11A). The reaction of 38A with 11A proceeds thereafter via TS-1, which has a particularly low activation barrier (1.9 kcal/mol), to afford complex (40A). The alternative pathway involving the direct metalation of pyridine with 39A or 39B (no prior dissociation) proceeding via TS-2 has comparably a much higher activation energy (12.4 kcal/mol).

This calculation highlights the frustrated Lewis pair character of 39 and the facile reversibility of its formation in the presence of an appropriate substrate such as pyridine, and led us to examine the synthetic utility and reaction scope of this new class of reagents.

Pyridine (29a) similarly reacts with TMPMgCl-BF$_3$-LiCl (39; 1.1 equiv, –40 °C, 15 min) and furnishes after transmetalation with CuCN-2LiCl and a subsequent acylation with 4-chlorobenzoyl chloride (0.8 equiv, -40 °C to 25 °C, 12 h) the pyridyl ketone (41a) in 84% yield (Scheme 40). The lithiation of 2-methoxypyridine (29f) with lithium superbases produces a mixture of products unless a large excess of base is added. However, a regioselective metalation can be achieved by using the frustrated Lewis pair TMPMgCl-BF$_3$-LiCl (39) to produce, after acylation with 2-furoyl chloride the 2,6-disubstituted pyridine (41b) in 76% yield. The metalation of electron-poor pyridines such as 29d cannot be performed with any conventional lithium base because of extensive decomposition. The new reagent 39 allows this synthetic problem to be overcome. Thus, treatment of ethyl nicotinate (29d) with TMPMgCl-BF$_3$-LiCl (39; 1.5 equiv, –40 °C, 30 min) furnishes an organometallic intermediate which undergoes a smooth Negishi cross-coupling with 1-iodo-3-(trifluoromethyl)-benzene to give the functionalized pyridine (41c) in 71% yield. Other related sensitive heterocycles, such as 2-(methylthio)pyrazine (29g), are

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78 The pyridyl-2-trifluoroborate (40) was also prepared in an alternative way: an I/Mg exchange of 2-iodo-4-phenylpyridine followed by a transmetalation with BF$_3$-OEt$_2$ and ZnCl$_2$ also furnished the product 30c in 65% yield.


80 These calculations were done by B. A. Haag and are mentioned here for sake of clarity.


metalated with 39 (1.1 equiv, -40 °C, 10 min) affording 2-iodo-3-(methylthio)pyrazine (41d)\(^{83}\) in 81% yield after iodolysis (Scheme 40).

**Scheme 40:** Regioselective metalation of N-heterocycles with the frustrated Lewis pair 39.

In order to demonstrate the synthetic potential of the reagent 39, we have prepared two biologically active molecules: an antihistaminic drug, carboxinamine (42)\(^{84}\) and the haplophyllum alkaloid, dubamine (43),\(^{85}\) in two one-pot procedures (Scheme 41). Thus,

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83 This experiment was done by B. A. Haag and is mentioned here for sake of completeness.


treatment of pyridine (29a) with TMPMgCl-BF$_3$-LiCl (39; 1.1 equiv, -40 °C, 15 min) followed by the addition of 4-chlorobenzaldehyde leads to the alcoholate 44, which was in situ reacted with Cl(CH$_2$)$_2$NMe$_2$-HCl (1.2 equiv) and NaH (1.2 equiv, 50 °C, 2 h): this sequence provided carbinoxamine (42) in 72% yield. Similarly, the reaction of quinoline (31a) with TMPMgCl-BF$_3$-LiCl (39; 1.1 equiv, -40 °C, 15 min) furnishes the intermediate 45. Transmetalation with ZnCl$_2$ and a subsequent Negishi cross-coupling reaction with the aryl iodide affords dubamine (43) in 79% yield (Scheme 41).

\[ \text{Scheme 41: One-pot preparation of carbinoxamine (42) and dubamine (43).} \]

The reaction of magnesium pyridyltrifluoroborate with 4-chlorobenzaldehyde providing the alcoholate (44) is remarkable since usually aryl and heteroaryl trifluoroborates react with aldehydes only in the presence of a Rh-catalyst.\(^\text{86}\) We have briefly investigated the behavior of magnesium pyridyltrifluoroborate of type 46a obtained by an one-step metalation using TMPMgCl-BF$_3$-LiCl (39) prepared by mixing BF$_3$·OEt$_2$ with TMPMgCl-LiCl (11) at -40 °C (Scheme 42). Thus, the treatment of pyridine (29a) with TMPMgCl-BF$_3$-LiCl (39; 1.1 equiv, -40 °C, 10 min) leads to the organometallic intermediate (46a) which reacted with trifluoromethyl phenyl ketone (-40 to 25 °C, 1 h) leading to the carbinol (47a) in 72% yield. Similarly, the reaction of 41a with 4-chlorobenzaldehyde furnishes the desired alcohol (47b) in 68% yield without the need for any transition-metal catalyst within 1 h.

Scheme 42: Reaction of magnesium pyridyltrifluoroborate intermediate (46a) with carbonyl compounds.

During the study of the reaction scope of TMPMgCl-BF$_3$-LiCl (39), we realized that the two-step metatlation with prior precomplexation with BF$_3$-OEt$_2$ and subsequent addition of TMPMgCl-LiCl (11), TMP$_2$Zn-2MgCl$_2$-LiCl (14) or [(tBu)NCH(iPr)(tBu)]$_2$Al-3LiCl (15) in a second step proves to be more flexible and often results in higher yields. This two-step metatlation allows, in a number of cases, a complete switch of regioselectivity by using either TMP-derived bases (11 – 15) without BF$_3$-OEt$_2$ (metatlation procedure A) or metatlation of BF$_3$-precomplexed N-heterocycles (metatlation procedure B; Table 3).

Thus, 2-phenylpyridine (29h) is selectively magnesiated with TMPMgCl-LiCl (11; 2 equiv, 55 °C, 30 h) in the ortho-position of the phenyl substituent leading after iodolysis to the aryl iodide 48a in 85% yield. In contrast, precomplexation with BF$_3$-OEt$_2$ (1.1 equiv, 0 °C, 15 min) followed by the addition of TMPMgCl-LiCl (11; 1.5 equiv, 0 °C, 30 h) leads to a selective metatlation at position 6. Iodolysis of the intermediate affords 2-iodopyridine derivative (49a in 83% yield). A number of substituted pyridines (29f–m; entries 2-7) display this remarkable switch in selectivity. Thus, 3-fluoropyridine (29i) is magnesiated with TMPMgCl-LiCl (11; 1.1 equiv, -78 °C, 30 min) in position 2 furnishing after quenching with I$_2$ the 3,4-dihalopyridine 48b in 63% yield. After transmetatlation with ZnCl$_2$ and a Negishi cross-coupling with ethyl 4-iodobenzoate, the 2,3-disubstituted pyridine (48c) is obtained in 72% yield (entry 2). Precomplexation with BF$_3$-OEt$_2$ and metatlation with TMPMgCl-LiCl (11; 1.1 equiv, −78 °C, 30 min) provides the 4-metalted pyridine, which after iodolysis or cross-coupling with ethyl 4-iodobenzoate furnished the 3,4-disubstituted pyridines 49b and 49c (56 and 74% yield; entry 2). This complementary functionalization is also observed for 3-chloropyridine (29j) and 3-cyanopyridine (29k), and leads after similar reaction sequences to

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87 Although TMPMgCl-BF$_3$-LiCl (39) is conveniently prepared within 5 min at −40 °C, a study of its stability reveals that it decomposes slowly in the absence of a substrate within a few hours at −20 °C.
the 2,3-disubstituted pyridines 48d-g in 72-85% yield and to the 3,4-disubstituted pyridines 49d-h in 77-95% (Table 3, entries 3 and 4). The metalation of the electron-poor pyridine 29k is especially remarkable since such sensitive heterocycles are prone to polymerization during metalations. Thus, nicotinonitrile (29k) is selectively metalated at position 2 using TMP2Zn·2MgCl2·2LiCl (14) and furnishes, after a Negishi cross-coupling reaction, the 2,3-disubstituted pyridines 48e-f in 72-85% yield. Precomplexation with BF3·OEt2 and zinication with 14 (–30 °C, 30 min) provides the 3,4-disubstituted products 49f-g (70-79% yield; entry 4) after cross-coupling. Moreover, a trifluormethyl-substituted pyridine such as 29l can also be easily metalated with our procedure. Thus, metalation of 29l with TMPMgCl·LiCl (11; 1.1 equiv, -78 °C, 10 min) and subsequent Negishi cross-coupling furnishes the 2,3-disubstituted pyridine 48h in 69% yield (entry 5). Precomplexation with BF3·OEt2 (1.1 equiv, 0 °C, 15 min) and addition of TMPMgCl·LiCl (11) deprotonate 29l at position 4 leading after similar reaction sequence to the 3,4-disubstituted pyridine 49i in 65% yield (entry 5). Electron-deficient disubstituted pyridines, such as 3-bromo-4-cyanopyridine (29m), are metalated with TMPMgCl·LiCl (11; 1.1 equiv, –78 °C, 1 h) and a copper-mediated allylation with 3-bromocyclohexene affords the 1,2,3-trisubstituted pyridine 48i (65% yield; entry 6). In contrast, selective zinication occurs in position 4 after precomplexation with BF3·OEt2 (1.1 equiv, 0 °C, 15 min) and subsequent reaction with TMP2Zn·2MgCl2·2LiCl (14). Allylation affords then the 3,4,5-trisubstituted pyridine 49j (63% yield; entry 6). Electron-rich pyridines such as 2-methoxypyridine (29f) can also be deprotonated regioselectively using in this case the aluminium base [(tBu)NCH(iPr)(tBu)]3Al·3LiCl (15) which, in the absence of BF3·OEt2, is leading after acylation to the 2,3-substituted pyridine 48j (80% yield; entry 7). Precomplexation with BF3·OEt2 followed by metalation with TMPMgCl·LiCl (11) and iodolysis provides 2-iodo-6-methoxypyridine (49k; 75% yield; entry 7). This regioselectivity has been extended to functionalized quinoline derivatives. Thus, 6-methoxyquinoline (29n) is aluminated with [(tBu)NCH(iPr)(tBu)]3Al·3LiCl (15) in position 5 affording after transmetalation with ZnCl2 and a subsequent Negishi cross-coupling the 5,6-disubstituted quinoline 48k in 68% yield whereas a precomplexation with BF3·OEt2 using TMPMgCl·LiCl (11) leads after a copper-mediated acylation to the 2,6-disubstituted quinoline 49l (94% yield; entry 8). The regioselectivity of the metalation in the presence of BF3 may be best explained by assuming in the case of 3-substituted pyridines that the BF3-complexation at the pyridine-

88 The use of an Al-base is essential. A mixture of metalated regioisomers is obtained by using TMPMgCl·LiCl (11).
89 This experiment was done by A. Unsinn and is mentioned here for sake of completeness.
nitrogen leads to a substantial steric hindrance at position 2 favouring therefore position 4 for metalation.

**Table 3:** Switchable, regioselective metalations of N-heterocycles with TMP-bases in the presence or absence of BF$_3$-OEt$_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>TMP-base metalation (procedure A)$^a$</th>
<th>BF$_3$-triggered metalation (procedure B)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 29h" /></td>
<td><img src="image2" alt="Structure 48a" /> 85%</td>
<td><img src="image3" alt="Structure 49a" /> 83%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Structure 29i" /></td>
<td><img src="image5" alt="Structure 48b" /> 63% E=I; <img src="image6" alt="Structure 48c" /> E=pC$_6$H$_4$CO$_2$Et 72%$^b$; <img src="image7" alt="Structure 49b" /> E=I 56%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image8" alt="Structure 29j" /></td>
<td><img src="image9" alt="Structure 48d" /> 75%$^b$</td>
<td><img src="image10" alt="Structure 49d" /> E=CO(α-furyl) 78%$^c$; <img src="image11" alt="Structure 49e" /> E=pC$_6$H$_4$CO$_2$Et 95%$^b$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image12" alt="Structure 29k" /></td>
<td><img src="image13" alt="Structure 48e" /> 72%$^b$ E=pC$_6$H$_4$OMe; <img src="image14" alt="Structure 48f" /> 85%$^b$ E=Ph(C=CH)$_2$; <img src="image15" alt="Structure 48g" /> 73%$^c$ E=cyclohexene</td>
<td><img src="image16" alt="Structure 49f" /> E=mC$_6$H$_4$CF$_3$ 79%$^b$; <img src="image17" alt="Structure 49g" /> E=Ph(C=CH)$_2$ 70%$^b$; <img src="image18" alt="Structure 49h" /> E=I 77%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image19" alt="Structure 29l" /></td>
<td><img src="image20" alt="Structure 48h" /> 69%$^b$</td>
<td><img src="image21" alt="Structure 49l" /> 65%$^b$</td>
</tr>
<tr>
<td>6</td>
<td><img src="image22" alt="Structure 29m" /></td>
<td><img src="image23" alt="Structure 48i" /> 65%$^c$</td>
<td><img src="image24" alt="Structure 49j" /> 63%$^c$</td>
</tr>
<tr>
<td>7</td>
<td><img src="image25" alt="Structure 29f" /></td>
<td><img src="image26" alt="Structure 48j" /> 80%$^c$</td>
<td><img src="image27" alt="Structure 49k" /> 75%</td>
</tr>
</tbody>
</table>

*Note:* $^a$ All entries were carried out in toluene at room temperature. $^b$ Reactions were carried out under argon atmosphere. $^c$ Reaction was carried out under nitrogen atmosphere.
B. Results and Discussion

Table 3 continued

<table>
<thead>
<tr>
<th></th>
<th><img src="29n" alt="Chemical Structure" /></th>
<th><img src="48k" alt="Chemical Structure" /></th>
<th><img src="49l" alt="Chemical Structure" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>29n</td>
<td>48k: 68%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>49l: 94%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

[a] Yield of analytically pure isolated product. [b] Transmetalation with 1.1 equiv of ZnCl₂ and subsequent Negishi cross-coupling using Pd(dba)₂ and P(2-furyl)₃. [c] Transmetalation with 1.1 equiv of CuCN·2LiCl.
4. Regio- and Chemoselective Functionalization of Alkylpyridines

4.1 Isopropylpyridine

Using the two-step metalation procedure the selective functionalization could be extended to compounds with reactive substituents, such as an isopropyl group. The retention of the acidic side chain avoids protection/deprotection sequences while allowing immediate transformation of the reactive moiety. In this context, 2-isopropyl- (50) and 4-isopropylpyridine (51) were subjected to the two-step metalation in the presence of BF$_3$·OEt$_2$. Thus, 2-isopropylpyridine (50) was precomplexed with BF$_3$·OEt$_2$ (1.1 equiv, 15 min, 0 °C) and in a second step it was selectively metalated with TMP$_2$Mg·2LiCl (13) at position 6 without touching the acidic methyl proton of the side chain. Iodolysis of the intermediate (52) afforded 2-iodo-6-isopropylpyridine (53) in 70% yield (Scheme 43).

![Scheme 43: Regioselective metatlation of 2-isopropylpyridine (50).](image)

In analogous manner, 4-isopropylpyridine (51) was first treated with BF$_3$·OEt$_2$ (1.1 equiv, 15 min, 0 °C) and thereafter metalated exclusively at position 2 of the pyridine ring using TMP$_2$Mg·2LiCl (13) (Scheme 44). After transmetalation with ZnCl$_2$ and a subsequent Negishi cross-coupling with 1-iodo-4-methoxybenzene in the presence of a palladium catalyst the 2,4-disubstituted pyridine 54a was obtained in 81% yield. Furthermore, iodolysis of the magnesiated intermediate 55 leads to 2-iodo-4-isopropylpyridine (54b) in 72% yield (Scheme 44).

![Scheme 44: Regioselective metatlation of 4-isopropylpyridine (51).](image)
4.2 Methylpyridine

As the methyl group can be converted into an aldehyde, a carboxylic acid or subjected to olefination for preparing conjugated molecules, the quest for selective functionalization of compounds with retention of reactive substituents led to the investigation of methylpyridines. A selective lithiation of the pyridine ring can only be performed via halogen-metal exchange on the corresponding brominated derivatives due to the high acidity of the methyl protons. Thus, using conventional bases, such as LDA or LiTMP affected only the methyl groups. However, the development of a mixture of n-BuLi and LiDMAE exclusively directed the metalation towards the pyridine ring, leaving the methyl group unchanged. In the case of 4-methylpyridine (56a), the lithiation occurred in position 2, while 3-methylpyridine (56b) underwent a para-lithiation with n-BuLi/LiDMAE (Scheme 45).

![Scheme 45: Ring lithiation of methylpyridines using n-BuLi/LiDMAE.](image)

In the case of 2-methylpyridine (56c), mainly metalation at the methyl group was observed even when applying the above described two-step metalation procedure including precomplexation with BF₃·OEt₂. To overcome this problem, two TMS-substituents at the methyl group were introduced affording 58, which then could be selectively metalated with TMP₂Mg:2LiCl (13) in the presence of BF₃·OEt₂. Subsequent transmetalation with ZnCl₂ and Negishi cross-coupling with ethyl 4-iodobenzoate using as catalyst Pd(dba)₂ (5 mol%) and

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P(2-furyl)$_3$ (10 mol%) furnished the intermediate which after treatment with TBAF led to the 2,6-disubstituted pyridine 59 in 74% yield (Scheme 46).

![Scheme 46: Conditions for the metalation of the pyridine ring of 2-methylpyridine (56c).](image)

4.3 Functionalization of 2-methylpyridine (56c) in benzylic position

As mentioned in above, 2-methylpyridine (56c) is mainly metalated at the methyl group even when BF$_3$-OEt$_2$ is used. Hence, further studies on 56c were conducted to examine the scope of the metalation in benzylic position. Thus, 2-methylpyridine (56c) was subjected to the two-step metalation procedure BF$_3$-OEt$_2$/TMPMgCl-LiCl and subsequently quenched with allyl bromide in the presence of CuCN·2LiCl in moderate yield. While exploring the reactivity of the generated organometallic intermediate, we realized that TMPZnCl-LiCl (12) without precomplexation with BF$_3$-OEt$_2$ leads to better results concerning the reaction conditions and the yields of the isolated products (Scheme 47).$^{98}$

![Scheme 47: Arylation of 2-methylpyridine (56c) and subsequent cross-coupling reaction.](image)

Thus, 56c was metalated with TMPZnCl-LiCl (12) within 1 h at ambient temperature furnishing after Pd-catalyzed cross-coupling with 1-bromo-4-methoxybenzene (61a) the product 60a in 95% yield (entry 1, Table 4). In the case of 1-bromo-3-chlorobenzene (61b)

$^{98}$ Experiments were done by Stéphanie Duez and are given here for the sake of completeness.
the cross-coupling was best performed using Pd(OAc)$_2$ (2 mol%) and SPhos (4 mol%) leading to the product 60b in 66% yield. Similarly, the reactions of 1-bromo-4-fluorobenzene (61c) and 5-bromo-1H-indole (61d) afforded the compounds 60c and 60d in 78-86% yield.

Table 4: Products obtained by the zincation of 2-methylpyridine (56c) with TMPZnCl·LiCl (12) and subsequent Pd-catalyzed cross-coupling reaction with aromatic bromides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield [%]$^a$</th>
</tr>
</thead>
</table>
| 1     | Br-\(\text{CMe}^\text{Me}\) | Pd$_2$dba$_2$ 2 mol%  
SPhos 4 mol%  
3 h, 50 °C | \(60\text{a}\) | 95 |
| 2     | Br-\(\text{Cl}\) | Pd(OAc)$_2$ 2 mol%  
SPhos 4 mol%  
6 h, 50 °C | \(60\text{b}\) | 66 |
| 3     | Br-\(\text{F}\) | Pd(OAc)$_2$ 2 mol%  
SPhos 4 mol%  
6 h, 50 °C | \(60\text{c}\) | 78 |
| 4     | Br-\(\text{NH}\) | Pd(OAc)$_2$ 2 mol%  
SPhos 4 mol%  
7 h, 50 °C | \(60\text{d}\) | 86 |

$^a$ Yield of isolated analytically pure product.
5. Full Functionalization of 4-Cyanopyridine via Chemo- and Regioselective Metalation in the Presence or Absence of BF$_3$·OEt$_2$

As mentioned in above, pyridine is an important heterocyclic scaffold and its derivatives occupy a privileged position among substances of tremendous importance. We focused our attention on the full functionalization of this scaffold, starting from commercially available 4-cyanopyridine (29c), by performing successive regio- and chemoselective metalations using TMP derived bases, such TMPMgCl·LiCl (11) or TMP$_2$Zn·2MgCl$_2$·2LiCl (14), in the presence or absence of BF$_3$·OEt$_2$. Thus, complexation of 4-cyanopyridine (29c) with BF$_3$·OEt$_2$ (1.1 equiv, 0 °C, 15 min) followed by treatment with TMP$_2$Zn·2MgCl$_2$·2LiCl$^{99}$ (14; 1.1 equiv, -20 °C, 3 h) leads to the 3-zincated pyridine which can be trapped with bromine, leading to the 3,4-disubstituted pyridine 29m in 64%. Magnesation of this pyridine derivative 29m with TMPMgCl·LiCl (11; 1.1 equiv, -78 °C, 1 h) occurs at position 2, furnishing after a copper-mediated allylation with 3-bromocyclohexene the 1,2,3-trisubstituted pyridine 48i in 65% yield. In contrast, selective metalation at position 5 is achieved by precomplexation with BF$_3$·OEt$_2$ (1.1 equiv, 0 °C, 15 min) and subsequent addition of TMP$_2$Zn·2MgCl$_2$·2LiCl$^{99}$ (14; 1.1 equiv, -78 °C, 1 h). Transmetalation with CuCN·2LiCl and trapping with 3-bromocyclohexene affords the 3,4,5-trisubstituted pyridine 49j in 63% yield, which could be selectively magnesiated with TMPMgCl·LiCl (11; 1.1 equiv) at -78 °C within 1 h. However, subsequent reaction with ethyl cyanoformate furnished only the homocoupling product of the metalated pyridine moiety (Scheme 48).

Scheme 48: Homocoupling of the 3,4,5-trisubstituted pyridine 49j.

In contrast, the treatment of the 2,3,4-trisubstituted pyridine 48i with TMPMgCl·LiCl (11) led to a complete metalation at position 5 within 4 h at -30 °C. Iodolysis furnished the 2,3,4,5-tertrasubstituted pyridine 63 in 67% yield. Finally, the last position of the pyridine core could

$^{99}$ MgCl$_2$ in TMP$_2$Zn·2MgCl$_2$·2LiCl has been omitted for sake of clarity.
be metalated with $\text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$\textsuperscript{99} (14) within 20 h at ambient temperature. Transmetalation with $\text{CuCN} \cdot 2\text{LiCl}$ and trapping with ethyl 2-(bromomethyl)acrylate led to the fully substituted pyridine 64 in 62% yield. Using $\text{TMPMgCl} \cdot \text{LiCl}$ (11), only polymerisation could be detected, even at low temperatures.

**Scheme 49:** Full functionalization of pyridine starting from 4-cyanopyridine (29c).
6. Regio- and Chemoselective Functionalization of N,N-4-Dimethylaminopyridine (DMAP; 65)

6.1 Introduction
N,N-4-Dimethylaminopyridine (DMAP; 65) is a good example of a modern low-molecular organic catalyst with a powerful effect in synthetic organic chemistry including acylations reactions on nitrogen, oxygen or carbon or the development of new ligands for transition metals.  

Although somewhat more active catalysts of this type are nowadays available, the use of DMAP (65) is preferred in most cases, due to its reasonable price and good availability. Nevertheless, from pioneering works to the present, efforts have been made to elaborate more sophisticated analogues of DMAP (65). The modification of the 4-amino moiety has attracted much attention in terms of electronic properties and chirality and is therefore well studied.

6.2 Functionalization of DMAP (65) using lithium bases
In contrast to this, the functionalization of the pyridine core rather than the side chain appears to be a more challenging task. The literature reveals that for the functionalization of C-2 two lithiation methodologies are known. Analogously to Kessar’s strategy with pyridine, 65 was activated by conversion into the BF₃-adduct. Subsequent metalation at C-2 with LiTMP followed by reaction with pivaloyl chloride then gave the monosubstituted DMAP-derivative 65a and the 2,6-disubstituted derivative 65b in a ratio of 4 to 1 together with recovered DMAP (65). Only after careful flash chromatography the desired pure ketone could be obtained (Scheme 50).

Scheme 50: Metalation of 65 using LiTMP in the presence of BF₃·OEt₂.

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The second methodology for lithiation of 65 describes the use of BuLi-LiDMAE in the ratio of 2 to 1, known as superbase. It takes advantage of the lithium chelation by the pyridinic nitrogen ensuring stabilization of the subsequently formed 2-monolithiated intermediate by aggregate formation (Scheme 51).\textsuperscript{103}

![Scheme 51: Metalation of 65 using superbase.](image)

Nevertheless, both strategies suffer from some drawbacks: The first one leads to mixtures of mono- and disubstituted products, and the latter needs two equivalents of base, limiting its applicability.

### 6.3 Regio- and chemoselective metalation of DMAP (65) and its derivatives using TMP-derived bases in the presence of BF\textsubscript{3}\cdotOEt\textsubscript{2}

Using the above described two-step metalation protocol with prior precomplexation with BF\textsubscript{3}\cdotOEt\textsubscript{2} and subsequent addition of TMPMgCl-LiCl (11) in a second step, DMAP (65) is smoothly metalated (Scheme 52).

![Scheme 52: Metalation of 65 using TMPMgCl-LiCl (11) in the presence of BF\textsubscript{3}\cdotOEt\textsubscript{2}.](image)

Thus, precomplexation of DMAP with BF\textsubscript{3}\cdotOEt\textsubscript{2} (1.1 equiv, 0 °C, 15 min) followed by the addition of TMPMgCl-LiCl (11; 1.1 equiv, 0 °C, 1 h) leads to a selective metalation in position 2. Iodolysis of the intermediate affords the 2-iodo DMAP derivative 66a in 72% yield (entry 1, Table 5). Chlorination using 1,1,2-trichloro-1,2,2-trifluoroethane gives the 2-chloro DMAP derivative 66b in 70% yield (entry 2). Formation of a new C-C bond is readily

achieved by transmetalation with ZnCl$_2$ and a Negishi cross-coupling with 1-iodo-4-methoxybenzene in the presence of Pd(dba)$_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%) furnishing the 2-substituted DMAP derivative $66c$ in 81% yield (entry 3). Comparably, Pd-catalyzed cross-coupling of the zincated species with 1-iodo-3-( trifluoromethyl)benzene (under the same conditions as for the synthesis of $66c$) affords $66d$ in 79% yield (entry 4). Moreover, transmetalation with CuCN·2LiCl (1.1 equiv) and subsequent acylation with 4-chlorobenzoyl chloride leads to the pyridyl ketone $66e$ in 68% yield (entry 5). A sterically hindered 4-aminopyridine derivative such as $65d$ bearing a tetramethylpiperidyl moiety in position 4 was metalated under the same conditions and allylation with ethyl 2-(bromomethyl)acrylate gives the 2-allylated pyridine $66f$ in 71% yield (entry 6).

**Table 5:** Products obtained by complexation of DMAP and its derivatives with BF$_3$ and subsequent magnesiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product (yield)[$^a$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{NMe}_2$</td>
<td>I$_2$</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>C$_2$Cl$_3$F$_3$</td>
<td>$66b$: 70%</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>OMe</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>CF$_3$</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Cl</td>
<td>65</td>
</tr>
</tbody>
</table>
Table 5 continued

<table>
<thead>
<tr>
<th></th>
<th>65d</th>
<th>65f</th>
<th>66b</th>
<th>66c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
</tr>
</tbody>
</table>

[a] Yield of isolated analytically pure product. [b] Transmetalation with 1.1 equiv of ZnCl₂ and subsequent Negishi cross-coupling using Pd(dba)₂ and P(2-furyl)₃. [c] Transmetalation with 1.1 equiv of CuCN·2LiCl.

After selective functionalization at position 2 of DMAP (65) the next substrate to investigate was the 2-substituted chloro derivative (66b). In analogous manner, first precomplexation with BF₃·OEt₂ (1.1 equiv, 0 °C, 15 min) was carried out and then TMPMgCl·LiCl (11; 1.5 equiv) was added at 0 °C to deprotonate selectively at position 6. Iodolysis of the intermediated species furnished the 2,6-disubstituted DMAP derivative 66g in 80% yield. Transmetalation with CuCN·2LiCl and subsequent allylation with 3-bromocyclohex-1-ene afforded the expected 2,4,6-trisubstituted pyridine 66h in 78% yield.

Scheme 53: Metalation of 2-chloro DMAP derivative 66b using TMPMgCl·LiCl (11) in the presence of BF₃·OEt₂.
7. Regio- and Chemoselective Functionalization of (S)-nicotine (67)

7.1 Introduction
(S)-Nicotine, the most abundant alkaloid isolated from the tobacco plant, *Nicotina tabacum*,\(^\text{104}\) has drawn a lot of interest due to its potential role in therapeutics for central nervous system (CNS) diseases.\(^\text{105}\) This is attributed to its activity as an agonist on the nicotinic acetylcholine receptors. Nicotine has been observed to show favourable effects in the treatment of Parkinson’s disease, Alzheimer’s disease or Tourette’s syndrome along with other CNS related disorders.\(^\text{70,106}\) However, nicotine is non selective in its binding to acetylcholine sites, which is liable for the adverse side effects including addiction, action on the cardiovascular and gastrointestinal systems.\(^\text{107}\) Hence there is a need to develop nicotine analogues that are more selective in their binding to acetylcholine sites and thus are capable of exhibiting the beneficial properties of nicotine while minimizing undesirable side effects. The development of new pharmaceuticals based on the core nicotine structure has been limited by the lack of synthetic methods for preparing derivatives directly from commercially available natural nicotine.

7.2 Functionalization of (S)-nicotine using lithium and zinc bases
In most previous studies, reagents other than nicotine were used as starting materials for the synthesis of (S)-nicotine derivatives.\(^\text{70d,108}\) Since nonchiral compounds have been used as starting material, a low yielding resolution was often required to provide the desired enantiomer. Consequently, straightforward one-step modifications via directed metalation of the pyridine moiety were investigated for the enantioselective preparation of nicotine derivatives reducing both the length and the cost of the synthesis. To accomplish the deprotonative metalation of nicotine, several metalating agents have been screened. The choice of base was found to play a crucial role to access the desired lithiopyridine


intermediate. Thus, using a mixture of nBuLi/LiDMAE enables the lithiation in position 6 of the pyridine ring. Depending on the electrophile, also the formation of the C-2 regioisomer was observed. Selectively functionalizing the C-2 position of the pyridine ring proved to be most challenging due to the sterical hindrance of the pyrrolidine ring at the C-3 position and the selectivity of various bases was investigated. Comparing Li-derived bases, LiTMP methodology limits the functional group diversity. Possible only by trapping the lithio intermediate with base-compatible electrophiles - nicotine achieved the best results concerning regioselectivity. But the functionalization was made (Scheme 54).

![Scheme 54: Metalations of (S)-nicotine (67) with different metalating agents.](image_url)

A clean metalation at position 4 of the pyridine ring could be achieved with TMSCH$_2$Li at ambient temperature. The reactivity of TMSCH$_2$Li contrasts with that of n-BuLi, since BuLi/LiDMAE has been reported to induce selectively the C-6 lithiation of nicotine (67) (Scheme 55). A tentative explanation of this selectivity could be a cooperative chelating effect of the pyrrolidine nitrogen, placing TMSCH$_2$Li at the appropriate place to abstract the H-4 proton.

---

7.3 Regio- and chemoselective functionalization of (S)-nicotine (67) and its derivatives using TMP-derived bases in the presence of BF₃·OEt₂

The metalation methodologies described above produce either regioisomers of the metalated nicotine in different ratios and combinations (C-2 with C-4, or C-2 with C-6, or C-4 with C-6), require an excess of base and electrophile or lead to products in low yields. Hence we investigated the two-step metalation with prior precomplexation with BF₃·OEt₂ and subsequent addition of TMPMgCl-LiCl (11) in a second step (Scheme 56).

Thus, 67 was first treated with BF₃·OEt₂ (1.1 equiv) at 0 °C for 15 min. Addition of TMPMgCl-LiCl (11; 1.5 equiv, 0 °C, 2.5 h) led to a selective metalation at position 6. Subsequent transmetalation with CuCN-2LiCl and allylation with 3-bromocyclohex-1-ene afforded selectively the 6-substituted nicotine derivative 67a in 92% yield (Scheme 56).
8. Regio- and Chemoselective Functionalization of quinine (68)

8.1 Introduction
The Cinchona alkaloid quinine was the first and the only available remedy to treat malaria, a potentially fatal disease, which has been prevalent worldwide for more than three centuries.\textsuperscript{111} More recently, the interest in quinine was driven by the utility as a catalyst or ligand for asymmetric synthesis.\textsuperscript{112} For optimizing and fine-tuning the performance of the catalytic reaction the modification of the structure of the catalyst is a key factor. Besides, the need for new antimalarials, with different structures and modes of action, in order to deal with the development of resistance to the drugs in current use is continuously increasing.

8.2 Functionalization of quinine (68) using lithium and magnesium reagents
As mentioned in above, efficient and selective methodologies are required to satisfy the tremendous demand for derivatization of the quinine core. However, the modification of chinchona alkaloids are mostly confined to a few reactive positions,\textsuperscript{112c} and changes to the carbon skeleton tend to be laborious.\textsuperscript{113} A view in the literature reveals that, \textit{inter alia}, C-C bond formation at the vinyl group\textsuperscript{114} and functionalization at the C-2 position of the quinoline moiety\textsuperscript{115} are possible (Scheme 57).

B. Results and Discussion

**Scheme 57**: Arylation of 68 in position C-2 with PhLi after oxidative work-up.

In contrast, Grignard reagents (like PhMgCl) add stereoselectively in a 1',4'-nucleophilic aromatic manner to quinine (68). Spectroscopic data affirm the formal addition of C₆H₆ to the alkaloid (Scheme 58).\(^\text{116}\)

**Scheme 58**: Reaction of 68 with a Grignard reagent.

8.3 Regio- and chemoselective functionalization of quinine (68) in position 3 using mixed Mg/Li bases in the presence of BF₃·OEt₂

Our metalation protocol has been applied to this more complex scaffold and has allowed for the first time to selectively metlate position 3 of the quinoline ring of quinine (68). Primarily, we converted the alcohol function into a lithium alkoxide by treatment with MeLi (1 equiv) before an excess of BF₃·OEt₂ (2.2 equiv) and TMPMgCl-LiCl (11; 1.1 equiv) were added. This specific metalation in position 3 is tentatively triggered by a chelating effect of BF₃ with the tertiary amine. However, metalation with TMPMgCl-LiCl (11) without previous BF₃-complexation leads to a low conversion and a mixture of isomers which could not be isolated in pure form. Quenching with various electrophiles (iodine, C₂Cl₂Br₂, allyl bromide, iodobenzene, ethyl 4-iodobenzoate) in the presence of the appropriate catalyst produces the 3-substituted quinine derivatives 68a-e in 38-66% yield (Scheme 59).

B. Results and Discussion

8.4 Regio- and chemoselective functionalization of quinine (68) in position 2 using mixed Mg/Li bases in the presence of BF$_3$·OEt$_2$

In order to shift the metalation from position 3 to position 2 we increased the steric bulk near the quinuclidine nitrogen via the protection of the alcohol moiety with TIPSCl according to the procedure of Ogilvie.$^{117}$ Thus, the two-step metalation of 68f with BF$_3$·OEt$_2$ (1.1 equiv) followed by addition of TMPMgCl·LiCl (11; 1.5 equiv, 15 h) and subsequent allylation with allyl bromide (transmetalation with CuCN·2LiCl) furnished the product 68g in 21% yield. The deprotection with TBAF (3 equiv) leads to the 2-substituted quinine derivative 68h in 59% yield (Scheme 60).

Scheme 60: Functionalization of the TIPS-protected quinine derivative 68f at position 2 and subsequent deprotection.

Due to the comparably low yields we changed the protecting group to TBDMS according to the procedure of Sherrington\(^{118}\) furnishing the product 68i in 97% yield. The two-step metatation of 68i with BF\(_3\)-OEt\(_2\) (1.1 equiv) followed by addition of TMPMgCl-LiCl (11; 1.5 equiv, 15 h) and subsequent allylation with allylbromide (transmetalation with CuCN-2LiCl) furnished the product 68j in 41% yield. Iodolysis of the metalated species afforded the quinine derivative 68k in 44% yield. Moreover, cross-coupling reactions could also be performed with previous transmetalation with ZnCl\(_2\) in presence of Pd(dba)\(_2\) (5 mol%) and tfp (10 mol%) with ethyl 4-iodobenzoate furnishing 68l in 36% yield. Deprotection of the allylated 68j and the iodinated quinine derivative 68k led to the products 68m and 68n in 79 respectively 82% yield (Scheme 61).

Scheme 61: Functionalization of the TBDMS-protected quinine derivative (68i) at position 2 and subsequent deprotection.

The $^{13}$C- as well as the $^1$H-NMR show splitted signals of the corresponding protons and carbons due to limited rotability of the vinyl quinuclidine moiety caused by the bulk of the TIPS and the TBDMS protecting group. Thus, TIPS-ether 68f was deprotected with TBAF furnishing quinine (68) without splitted proton signals at position 2 (Scheme 62).
Scheme 62: 300 MHz $^1$H-NMR of 68f and of 68 at 25 °C.

The $^1$H-NMR of the TBDMS-protected iodoquinine derivative 68k was deprotected with TBAF furnishing the iodoquinine 68n without splitted methoxy proton signals (Scheme 63).
Scheme 63: 300 MHz $^1$H-NMR of the methoxy group of 68k and of 68n at 25 °C.
9. Palladium-catalyzed one-pot reactions of \textit{in situ} generated zinc reagents with aromatic bromides, chlorides and triflates

9.1 Introduction

Transition metal-catalyzed cross-coupling reactions have matured into an indispensable class of reactions for organic synthesis.\textsuperscript{119} Within a few decades, this methodology evolved into a routine tool for the preparation of fine chemicals and pharmaceutically active compounds in research and as well as in industry.\textsuperscript{120} As catalysts, palladium sources largely dominate the field of cross-coupling reactions due to its wide scope and excellent compatibility with many functional groups.\textsuperscript{121} Especially, the \textit{Suzuki} cross-coupling reaction has been used extensively owing to the air and moisture stability of boronic acids and their derivatives.\textsuperscript{122} Although this cross-coupling has a broad synthetic scope, it suffers from some limitations. The boronic derivatives have often to be prepared from the corresponding magnesium or lithium species which limits the presence of functional groups.\textsuperscript{123} Alternatively, organozinc reagents display in Pd-catalyzed cross-couplings (\textit{Negishi} cross-coupling) much higher reactivity\textsuperscript{124} and can readily be prepared in the presence of various functional groups. These environmentally friendly organometallics have, however, the drawback of being air and moisture sensitive.\textsuperscript{125} Recently, a very efficient LiCl-mediated direct insertion of zinc into unsaturated halides was reported.\textsuperscript{126} Using this method, a one pot-protocol avoiding the handling of sensitive organozinc intermediates was developed. Thus, in initial experiments ethyl 4-iodobenzoate (69a; 1.0 equiv) was treated with zinc dust (1.5 equiv) and LiCl (1.5 equiv) in THF. The zinc reagent 70a was obtained within 10 h at 50 °C (> 98% conversion,

Scheme 64. Then, 3-bromobenzonitrile (71a; 0.8 equiv) and PEPPSI-IPr\(^{127}\) (0.5 mol%) were added. After 1.5 h of reaction time at 25 °C, ethyl 3'-cyanobiphenyl-4-carboxylate (72a) was obtained in 83% isolated yield which was also tested during the optimization process.

Scheme 64: Preliminary experiments of one-pot Negishi cross-coupling reaction using the palladium catalyst PEPPSI-IPr.

The palladium catalyst PEPPSI-IPr, introduced by Organ, displays a broader applicability compared to the catalysts Pd(PPh\(_3\))\(_4\),\(^{128}\) which was also tested during the optimization process. This catalyst is easily synthesized and air-stable and shorter reaction times and higher yields can be generally achieved.

Scheme 65: PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenyl-imidazolium derivative.

---

\(^{127}\) PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenyl-imidazolium derivative.

9.2 PEPPSI-IPr catalyzed cross-coupling reactions of arylzinc halides with aryl bromides in the presence of zinc dust

The preparation of a variety of arylzinc reagents of type 70 and subsequent cross-coupling reaction in a one-pot procedure avoids the handling of these water- and air-sensitive organozinc intermediates. In situ generated polyfunctional arylzinc reagents obtained by the addition of zinc and LiCl to the corresponding aryl iodides 69a-j smoothly underwent Pd(0)-catalyzed cross-coupling reactions with aryl bromides 71b-l in the presence of PEPPSI-IPr as catalyst (Scheme 66).

![Scheme 66: One-pot Negishi cross-coupling of in situ generated zinc reagents with aryl bromides in presence of PEPPSI-IPr.]

Thus, reaction of ethyl 4-iodobenzoate with zinc dust (1.5 equiv) and LiCl (1.5 equiv) provided the desired arylzinc reagent 70a within 10 h at 50 °C (entry 1, Table 7). Subsequent Pd-catalyzed cross-coupling with 3-bromopyridine 71b led to the expected product 72b in 86% yield. Similarly, treatment of the meta-substituted ethyl iodobenzoate 69b with commercially available zinc dust in the presence of LiCl at 50 °C furnished after 12 h the corresponding zinc reagent 70b which led after cross-coupling with 2-chloroquinoline (71c) to the product in 85% yield (entry 2). Moreover, 4-cyano as well as 3-cyano-substituted aryl iodides 69c-d were smoothly converted to the corresponding zinc iodides 70c-d providing after Pd-catalyzed cross-coupling with different aromatic bromides 71d-e the products in 80-91% yield (entries 3-5). An ortho-substituted aryl iodide such as 2-trifluoromethyl-1-iodobenzene (69e) was readily converted to the intermediate zinc reagent 70e and underwent the expected cross-coupling reaction with 4-cyano-1-bromobenzene (71g) at 25 °C within 15 h providing the biaryl 72g in 97% yield (entry 6). Aromatic iodides bearing electron-donating groups are also good substrates, although the zinc insertion is slower (48-180 h; entries 7 and 8). The subsequent cross-coupling with an unsaturated halide furnishes the desired products 72h (92%; entry 7) and 72i (67%; entry 8). In addition, we have applied this one-pot protocol to heteroaromatic compounds, such as 2-iodothiophene (69h), 3-iodopyridine (69i), and 2-bromo-5-(carbethoxy)furan (69j), affording the expected cross-
coupling products 72j-m in 75–91% yields (entries 9-12). The cross-coupling could be further extended to other organic electrophiles such as aryl- and vinyl triflates (71k and 71l) in 75–78% yield (entries 13–14). In the case of 3-iodopyridine (69i), the amount of zinc and LiCl should be increased to 3.0 equiv to achieve full conversion to the corresponding organozinc intermediate.

Table 6: PEPSI-IPr catalyzed cross-coupling reaction of in situ generated arylzinc iodides 70a-j with aromatic bromides and chlorides 71b-l.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl iodide, conditions</th>
<th>Electrophile, conditions</th>
<th>Product</th>
<th>Yield [%]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69a (50 °C, 10 h)</td>
<td>71b (50 °C, 3 h)</td>
<td>72b</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>69b (50 °C, 12 h)</td>
<td>71c (40 °C, 20 h)</td>
<td>72c</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>69c (50 °C, 8 h)*</td>
<td>71d (25 °C, 5 h)</td>
<td>72d</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>69c</td>
<td>71e (25 °C, 2 h)</td>
<td>72e</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>69d (50 °C, 10 h)</td>
<td>71f (25 °C, 4.5 h)</td>
<td>72f</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>69e (25 °C, 48 h)</td>
<td>71g (25 °C, 15 h)</td>
<td>72g</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>69f (25 °C, 180 h)</td>
<td>71h (25 °C, 2 h)</td>
<td>72h</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>69g (25 °C, 48 h)</td>
<td>71g (25 °C, 0.5 h)</td>
<td>72i</td>
<td>67</td>
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</tbody>
</table>
Table 6 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structures</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td><img src="image1" alt="Structure" /></td>
<td>69h (25 °C, 1.5 h)</td>
<td>71i (25 °C, 1 h)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image2" alt="Structure" /></td>
<td>69i (50 °C, 12 h)</td>
<td>71g (50 °C, 5 h)</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Structure" /></td>
<td>EtO2C-Br</td>
<td>72k</td>
</tr>
<tr>
<td>11</td>
<td><img src="image4" alt="Structure" /></td>
<td>69j (30 °C, 3 h)</td>
<td>71b (50 °C, 5 h)</td>
</tr>
<tr>
<td>12</td>
<td><img src="image5" alt="Structure" /></td>
<td>69j</td>
<td>71j (50 °C, 20 h)</td>
</tr>
<tr>
<td>13</td>
<td><img src="image6" alt="Structure" /></td>
<td>69a</td>
<td>71l (25 °C, 4 h)</td>
</tr>
<tr>
<td>14</td>
<td><img src="image7" alt="Structure" /></td>
<td>69a</td>
<td>71n (25 °C, 4 h)</td>
</tr>
</tbody>
</table>

[a] Yield of isolated analytically pure product.

This procedure could be further extended to alkylzinc halides. Thus, addition of 4-iodobutanenitrile 73a to zinc dust (1.5 equiv) and LiCl (1.5 equiv) at 25 °C provided within 2 h the alkyl zinc intermediate (74a) which underwent a Pd-catalyzed cross-coupling with either ethyl 4-bromobenzoate 71m or 1-(4-bromophenyl)ethanone 71i leading to the products 75a and 75b in 86 and 70% yield, respectively (entries 1-2, Table 7). In an analogous manner, ethyl 4-bromobutanoate 73b was smoothly converted to the corresponding zinc intermediate 74b by direct zinc insertion within 12 h at 50 °C. Subsequent cross-coupling in an one-pot fashion with either aryl bromides or chlorides afforded the corresponding products 75c-e in 73-87% yield (entries 3-5).
Table 7: PEPPSI-IPr catalyzed cross-coupling reaction of \textit{in situ} generated alkylzinc iodides 74a-b with aromatic bromides and chlorides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl iodide, conditions</th>
<th>Electrophile, conditions</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73a (25 °C, 2 h)</td>
<td>71m (25 °C, 2 h)</td>
<td>75a</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>73a</td>
<td>71i (25 °C, 2 h)</td>
<td>75b</td>
<td>70</td>
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<td>3</td>
<td>73b (50 °C, 12 h)</td>
<td>71j (25 °C, 1 h)</td>
<td>75c</td>
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<tr>
<td>4</td>
<td>73b</td>
<td>71i (25 °C, 2 h)</td>
<td>75d</td>
<td>83</td>
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<tr>
<td>5</td>
<td>73b</td>
<td>71c (50 °C, 15 h)</td>
<td>75e</td>
<td>73</td>
</tr>
</tbody>
</table>

[a] Yield of isolated analytically pure product.
In this work, we have reported a new class of frustrated Lewis pairs based on BF$_3$·OEt$_2$ and LiCl-complexed Mg or Zn TMP-amides for the regioselective metalation of N-heterocycles including amino-substituted pyridines and alkaloids. Furthermore, the addition of such intermediate trifluoroborates to carbonyl derivatives without the need of catalyst was investigated. Finally, the preparation and application of polyfunctional zinc reagents were studied.

**Preparation and use of the new class of frustrated Lewis pairs TMPMgCl·BF$_3$·LiCl**

The new reagent TMPMgCl·BF$_3$·LiCl allows an efficient and regioselective metalation of sensitive N-heterocycles. Remarkably, the functional group compatibility was not affected by the high reactivity of the new reagent. Functionalities like an ester, a methoxy and a thiomethoxy were well tolerated during the metalation (Scheme 67).

This new protocol was also used for the preparation of two biologically active molecules: the antihistaminic drug, carbinoxamine and the haplophyllum alkaloid, dubamine, in two one-pot procedures.
Scheme 68: One-pot preparation of carboxinamide and dubamine.

The two-step metalation allows a complete switch of regioselectivity by using either TMP-derived bases without BF<sub>3</sub>-OEt<sub>2</sub> (Scheme 69) or metalation of BF<sub>3</sub>-precomplexed N-heterocycles (Scheme 70).

- TMP-base metalation:

\[
\text{Scheme 69: Regio- and chemoselective functionalization of N-heterocycles with TMP-bases.}
\]
B. Results and Discussion

- BF₃-triggered metalation:

\[
\text{N-Ph} \xrightarrow{1) \text{BF}_3\cdot\text{OEt}_2 (1.1 \text{ equiv}) \text{ 0 } ^\circ\text{C, 15 min} \atop \text{2) TMP-base (1-1.5 equiv) \text{ -78 to 25 } ^\circ\text{C} \atop \text{3) E}} \text{N-FG Ph} \xrightarrow{E} \text{N-FG E}
\]

**Scheme 70:** Regio- and chemoselective functionalization of N-heterocycles using BF₃·OEt₂ and TMP-bases.

In order to demonstrate the broad applicability of this methodology, a full functionalization sequence of the pyridine scaffold was accomplished starting from commercially available isonicotinonitrile (Scheme 71).
Scheme 71: Full functionalization of the pyridine core.

Additionally, we extended this method to the functionalization of the alkaloid quinine either in position 2 or in position 3 of the quinoline moiety (Scheme 72).

Scheme 72: Functionalization of quinine either at C3 or at C2 position of the quinoline ring.

Finally, it could be demonstrated that the intermediate magnesium pyridyltrifluoroborates add to carbonyl compounds, such as aldehydes and activated ketones without the need of any catalyst (Scheme 73).
The previously described methods can be extended to the functionalization of other unsaturated substrates, such as pyrimidines, pyrazines or pyridazines.

Preparation and application of arylzinc reagents

The LiCl-mediated direct insertion of commercially available zinc dust into alkyl halides and aryl iodides under mild conditions was explored. The highly functionalized zinc reagents are easily accessible and are storable over months without significant loss of reactivity. Moreover, their preparation and their transition metal-catalyzed cross-couplings were modified to an one-pot procedure providing access to diaryl products avoiding the handling of air and moisture sensitive zinc compounds (Scheme 74).
Scheme 74: Pd-catalyzed cross-couplings of in situ generated zinc reagents with aryl halides in the presence of zinc dust.
C. Experimental Section
1. General Considerations

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

1.1 Solvents

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

- \( \text{CH}_2\text{Cl}_2 \) was predried over \( \text{CaCl}_2 \) and distilled from \( \text{CaH}_2 \).
- \( \text{DMF} \) was heated to reflux for 14 h over \( \text{CaH}_2 \) and distilled from \( \text{CaH}_2 \).
- \( \text{EtOH} \) was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.
- \( \text{Et}_2\text{O} \) was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.
- \( \text{NMP} \) was heated to reflux for 14 h over \( \text{CaH}_2 \) and distilled from \( \text{CaH}_2 \).
- \( \text{Pyridine} \) was dried over \( \text{KOH} \) and distilled.
- \( \text{THF} \) was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.
- \( \text{Toluene} \) was predried over \( \text{CaCl}_2 \) and distilled from \( \text{CaH}_2 \).
- \( \text{Triethylamine} \) was dried over \( \text{KOH} \) and distilled.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

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

- \( i-\text{PrMgCl} \cdot \text{LiCl} \) solution in \( \text{THF} \) was purchased from Chemetall.
- \( i-\text{PrMgCl} \) solution in \( \text{THF} \) was purchased from Chemetall.
- \( \text{PhMgCl} \) solution in \( \text{THF} \) was purchased from Chemetall.
- \( n-\text{BuLi} \) solution in \( \text{hexane} \) was purchased from Chemetall.
- \( \text{TMPMgCl} \cdot \text{LiCl} \) was prepared according to a literature procedure (ref.35).
- \( \text{TMP}_2\text{Mg} \cdot 2\text{LiCl} \) was prepared according to a literature procedure (ref.37).
- \( \text{TMPZnCl} \cdot \text{LiCl} \) was prepared according to a literature procedure (ref.36).
- \( \text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl} \) was prepared according to a literature procedure (ref.38).
- \( [(t\text{Bu})\text{NCH}(i\text{Pr})(t\text{Bu})]_3\text{Al} \cdot 3\text{LiCl} \) was prepared according to a literature procedure (ref.39).
CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a Schlenk-tube under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salt was dissolved.

ZnCl₂ solution (1.00 M) was prepared by drying ZnCl₂ (100 mmol, 136 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.

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

ZnCl₂/LiCl solution (1.1/1.5 M) was prepared by drying LiCl (15.9 g, 375 mmol) and ZnCl₂ (37.5 g, 275 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.

1.3 Content and determination of organometallic reagents

Organzinc and organomagnesium reagents were titrated against I₂ in a 0.5 M LiCl solution in THF.¹²⁹

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

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

[(tBu)NCH(iPr)(tBu)]₃Al·3LiCl was titrated against menthol or 2-propanol using 4-(phenylazo)diphenylamine as indicator in THF.

1.4 Chromatography

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

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

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

1.5 Analytical data

**NMR** spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as \( \delta \)-values in ppm relative to the residual solvent peak of CHCl\(_3\) (\( \delta_H : 7.25, \delta_C : 77.0 \)). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).

**Mass spectroscopy:** High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.

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

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

**Melting points** (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.
C. Experimental Section

2. Typical Procedures (TP)

2.1 Typical Procedure for the metalation of heteroaromatics with hindered metal amide bases (TP1)
A dry and argon flushed 50-mL Schlenk-Tube, equipped with a magnetic stirring bar, was charged with a solution of the corresponding N-heteroarene (1.0 mmol) in dry THF (5 mL) and then cooled to the indicated temperature. A THF-solution of the indicated hindered metal amide base, titrated prior use, was added dropwise and the reaction mixture was stirred at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

2.2 Typical Procedure for the BF$_3$-triggered metalation of heteroaromatics with hindered metal amide bases (TP2)
A dry and argon flushed 50-mL Schlenk-Tube, equipped with a magnetic stirring bar, was charged with a solution of the corresponding N-heteroarene (1.0 mmol) in dry THF (5 mL) and cooled to 0 °C. BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) was added dropwise and stirred for 15 min at the same temperature. The reaction mixture was cooled to the given temperature followed by dropwise addition of a THF-solution of the indicated hindered metal amide base titrated prior use, and stirring the reaction mixture at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

2.3 Typical Procedure for the metalation with “TMPBF$_3$·MgCl·LiCl” (TP3)
A dry and argon flushed 50 mL Schlenk-Tube, equipped with a magnetic stirring bar, was charged with TMPMgCl·LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) and cooled to -40 °C. BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) was added dropwise and the resulting mixture was stirred for 10 min before the corresponding N-heteroarene (1.0 mmol) dissolved in dry THF (5 mL) was added. The reaction mixture was stirred at -40 °C for the indicated time. Complete metalation was monitored by GC-analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.
2.4 Typical Procedure for the BF₃-triggered metalation of quinine (68) with TMPMgCl·LiCl (TP4)

A dry and argon flushed 50-mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with a solution of quinine (1.0 mmol) in dry THF (4 mL) and cooled to 0 °C. MeLi (0.61 mL 1.0 mmol, 1.63 M in Et₂O) were added dropwise and stirred for 1 h at 25 °C. After cooling to 0 °C BF₃·OEt₂ (312 mg, 2.2 mmol) was slowly added and stirred for 15 min at the same temperature. After dropwise addition of a THF-solution of the hindered metal amide base TMPMgCl·LiCl (1, 1.1 mmol), titrated prior use, the reaction mixture was stirred for further 40 min at 0 °C.

2.5 Typical Procedure for one pot Negishi cross-coupling for biaryl synthesis (TP5)

Anhydrous LiCl was placed in an argon-flushed flask and dried using a heat gun under high vacuum (1 mbar). Zinc dust (<10 micron, Aldrich, 98+%) was added under argon, and heterogeneous mixture of Zn and LiCl was dried again on high vacuum. The reaction flask was flushed with argon, and then THF was added. Zn was activated by BrCH₂CH₂Br (5 mol%, heating to ebullition for 15 s) and TMSCl (1 mol%, heating to ebullition for 15 s). The substrate was added at room temperature, and the resulting reaction mixture was stirred at temperature T₁. The completion of the insertion reaction was checked by GC analysis of reaction aliquots quenched with sat. aqueous NH₄Cl solution (more than 96% conversion). After completion of zinc insertion, an aryl halide was added at room temperature, followed by addition of Pd catalyst. The resulting reaction mixture was stirred at temperature T₂. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with sat. aqueous NH₄Cl solution), the reaction mixture was quenched with sat. aqueous NH₄Cl solution (5 mL), followed by filtration. The aqueous phase was extracted with ether or EtOAc, and the combined organic phase was washed with brine and dried over MgSO₄. After concentration of the solution in vacuo, the crude residue was purified by flash silica gel chromatography.

2.6 Typical Procedure for one pot Negishi cross-coupling reaction between an alkyl zinc intermediate and a haloaryl (TP6)

Anhydrous LiCl was placed in an argon-flushed flask and dried using a heat gun under high vacuum (1 mbar). Zinc dust (<10 micron, Aldrich, 98+%) was added under argon, and heterogeneous mixture of Zn and LiCl was dried again on high vacuum. The reaction flask
was flushed with argon, and then THF was added. Zn was activated by BrCH₂CH₂Br (5 mol%), TMSCl (1 mol%), and I₂ (a THF solution, 2 mol%). The substrate was added at room temperature, and the resulting reaction mixture was stirred at temperature $T_1$. The completion of the insertion reaction was checked by GC analysis of reaction aliquots quenched with a solution of NH₄Cl in water (more than 96% conversion). After completion of zinc insertion, an aryl halide was added at room temperature, followed by addition of PEPPSI and 1,3-dimethylimidazolidin-2-one (DMI). The resulting reaction mixture was stirred at temperature $T_2$. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with sat. aqueous NH₄Cl solution), the reaction mixture was quenched with sat. aqueous NH₄Cl solution (5 mL), followed by filtration with cotton plug. The aqueous phase was extracted with Et₂O or EtOAc, and the combined organic phase was washed with brine and dried over MgSO₄. After concentration of the solution in vacuo, the crude residue was purified by flash silicagel chromatography.
3. Preparation of functionalized pyridine derivatives by complexation with BF$_3$·OEt$_2$ and subsequent addition of TMP-base

Synthesis of 3-bromoisonicotonitrile (29m):

According to TP2, a mixture of isonicotinonitrile (29c; 208 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMP$_2$Zn·2MgCl$_2$·2LiCl (14; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-20 °C, 3 h). The reaction mixture was cooled to -78 °C and Br$_2$ (352 mg, 2.2 mmol) dissolved in CCl$_4$ (2 mL) was added dropwise. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 30 min. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) and extracted with CH$_2$Cl$_2$ (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the product 29m as white solid (234 mg, 64%). The analytical data were found to match literature data.$^{130}$

M. p. (°C): 96.6-98.2.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm= 8.91 (s, 1H), 8.69 (d, $J$ = 4.9 Hz, 1H), 8.54 (d, $J$ = 4.9 Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm= 152.7, 148.5, 126.8, 123.3, 122.2, 114.8, 99.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3752, 3108, 3078, 3014, 2964, 2362, 2340, 2238, 1972, 1918, 1772, 1740, 1704, 1572, 1534, 1498, 1470, 1402, 1280, 1218, 1204, 1104, 1088, 1026, 848, 784, 730, 694, 668.

MS (EI, 70 eV) m/z (%): 183 [M$^+$] (100), 181 (97), 103 (88), 76 (31), 75 (14).

HRMS (EI) for C$_6$H$_3$BrN$_2$ (181.9480): 181.9483.

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C. Experimental Section

Synthesis of 2-iodopyridine (30a)

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

According to TP2, a mixture of pyridine (29a; 158 mg, 2.0 mmol) and BF\textsubscript{3}-OEt\textsubscript{2} (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 2.2 mmol, 1.2 M in THF) (-40 °C, 15 min). A solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH\textsubscript{4}Cl solution (9 mL), NH\textsubscript{3} (conc.) (1 mL) and sat. aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (2 mL) followed by extraction with Et\textsubscript{2}O (3x30 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et\textsubscript{2}O, 10:1) furnished the compound 30a as colorless oil (250 mg, 61% yield).

The analytical data were found to match literature data.\textsuperscript{131}

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): $\delta$ / (ppm) = 8.55 (m, 1H), 7.70-7.73 (m, 1H), 7.22-7.35 (m, 2H).

Synthesis of 2-iodo-4-phenylpyridine (30b)

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

According to TP2, a mixture of 4-phenylpyridine (29b; 310 mg, 2.0 mmol) and BF\textsubscript{3}-OEt\textsubscript{2} (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 2.2 mmol, 1.2 M in THF) (-40 °C, 20 min). A solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH\textsubscript{4}Cl solution (9 mL), NH\textsubscript{3} (conc.) (1 mL) and sat. aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (2 mL) followed by extraction with Et\textsubscript{2}O (3x30 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et\textsubscript{2}O, 10:1) furnished the compound 30b as yellow oil (354 mg, 63% yield).

C. Experimental Section

**1H-NMR (300 MHz, CDCl$_3$):** $\delta$ / (ppm) = 8.37 (d, $J = 5.1$ Hz, 1H), 7.92 (s, 1H), 7.52-7.61 (m, 2H), 7.39-7.52 (m, 4H).

**13C-NMR (75 MHz, CDCl$_3$):** $\delta$ / (ppm) = 150.7, 150.1, 136.3, 132.5, 129.5, 129.1, 126.7, 121.0, 118.8.

**IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$):** 3054, 2924, 2656, 2430, 2284, 2192, 1954, 1804, 1684, 1576, 1522, 1500, 1452, 1362, 1296, 1158, 1118, 1072, 1048, 1000, 984, 878, 842, 774, 756, 726, 688, 610.

**MS (70 eV, EI) m/z (%):** 281 [M$^+$] (49), 154 (100), 127 (32), 77 (12), 57 (13).

**HRMS (EI) for C$_{11}$H$_8$IN (280.9701):** (280.9691).

### Synthesis of ethyl 4-(4-phenylpyridin-2-yl)benzoate (30c):

![Chemical Structure](image)

A) Preparation of 30c via metalation BF$_3$·OEt$_2$-precomplexed 4-phenylpyridine:

A mixture of 4-phenylpyridine (29b; 310 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 3.0 mmol, 1.2 M in THF) according to TP 2 (-40 °C, 20 min). ZnCl$_2$ (2.2 mL, 2.2 mmol, 1 M in THF) was added at -40 °C and was stirred for 30 min. Pd(dba)$_2$ (56 mg, 5 mol%) and P(2-furyl)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (441 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. After GC analysis of a hydrolyzed aliquot showed full conversion sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) were added and the layers were separated followed by extraction using Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the product 30c as pale yellowish solid (407 mg, 84% yield).

B) Preparation of 30c via metalation with “TMPBF$_3$·MgCl-LiCl”:

According to TP3, BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl-LiCl (11; 1.85 mL, 2.2 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this
temperature for 10 min before 4-phenylpyridine (29b; 310 mg, 2.0 mmol) diluted in dry THF (10 mL) was added dropwise. After stirring for 10 min, ZnCl$_2$ (2.2 mL, 2.2 mmol, 1 M in THF) was added at -40 °C and stirred for 30 min. Pd(dbpa)$_2$ (56 mg, 5 mol%) and P(2-furyl)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (441 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. After GC analysis of a hydrolyzed aliquot showed full conversion sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) were added and the layers were separated followed by extraction using Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the product 30c as pale yellowish solid (339 mg, 70% yield).

M.p. (°C): 72.5-78.7.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 8.76 (d, $J = 5.1$ Hz, 1H), 8.10-8.19 (m, 4H), 7.96-7.98 (m, 1H), 7.66-7.71 (m, 2H), 7.43-7.54 (m, 4H), 4.41 (q, $J = 7.3$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 166.3, 156.7, 150.0, 149.8, 143.1, 138.1, 130.9, 130.0, 129.3, 129.2, 127.1, 126.9, 121.0, 119.2, 61.1, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3058, 2988, 1708, 1608, 1594, 1570, 1546, 1500, 1466, 1446, 1410, 1386, 1368, 1310, 1270, 1194, 1176, 1158, 1124, 1104, 1076, 1044, 1024, 1016, 1002, 988, 978, 918, 886, 872, 862, 836, 808, 780, 758, 740, 732, 694, 672, 638, 626, 614.

MS (70 eV, EI) $m/z$ (%): 303 [M$^+$] (72), 275 (29), 258 (100), 227 (10), 202 (13), 129 (12), 115 (10).

HRMS (EI) for C$_{20}$H$_{17}$O$_2$N (303.1259): 303.1250.

Synthesis of 4-(4-phenylpyridin-2-yl)benzonitrile (30d)

According to TP2, a mixture of 4-phenylpyridine (29b; 155 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl-LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (-40 °C, 20 min). ZnCl$_2$ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at -40 °C and
stirred for 30 min at the same temperature. Pd(dba)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (183 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by extraction with Et$_2$O (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 30d as white solid (168 mg, 82% yield).

M. p. (°C): 140.9-142.5

$^1$H-NMR (300 MHz, CDC$_3$): $\delta$ (ppm) = 8.76 (dd, $J = 5.1, 0.7$ Hz, 1H), 8.14-8.19 (m, 2H), 7.93-7.75 (m, 1H), 7.74-7.79 (m, 2H), 7.64-7.71 (2H), 7.43-7.56 (4H).

$^{13}$C-NMR (75 MHz, CDC$_3$): $\delta$ (ppm) = 155.8, 150.4, 149.7, 143.5, 138.0, 132.5, 129.3, 129.2, 127.5, 127.0, 121.4, 119.1, 118.8, 112.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3046, 2922, 2852, 2224, 1926, 1738, 1606, 1588, 1564, 1540, 1498, 1466, 1412, 1380, 1316, 1298, 1272, 1108, 1076, 1042, 888, 834, 824, 764, 722, 708, 692, 648, 630, 614.

MS (70 eV, EI) m/z (%): 256 [M$^+$] (100), 227 (13), 154 (9), 85 (10), 71 (12), 57 (23).

HRMS (EI) for C$_{18}$H$_{12}$N$_2$ (256.1000): 256.0988.

Synthesis of 2-(3-methoxyphenyl)-4-phenylpyridine (30e)

![Chemical Structure](image)

According to TP2, a mixture of 4-phenylpyridine (29b; 310 mg, 2.0 mmol) and BF$_3$OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 2.2 mmol, 1.2 M in THF) (-40 °C, 20 min). ZnCl$_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise at -40 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-methoxybenzene (374 mg, 1.6 mmol) dissolved in THF.
C. Experimental Section

(2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) followed by extraction with Et₂O (3×30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 6:1) furnished the compound 30e as yellowish oil (340 mg, 81% yield).

H-NMR (300 MHz, CDCl₃): δ / (ppm) = 8.73 (dd, J = 5.1, 0.7 Hz, 1H), 7.90-7.91 (m, 1H), 7.58-7.72 (m, 4H), 7.36-7.54 (m, 5H), 6.96-7.02 (m, 1H), 3.91 (s, 3H).

C-NMR (75 MHz, CDCl₃): δ / (ppm) = 160.1, 157.9, 150.0, 149.3, 141.0, 138.5, 129.7, 129.1, 129.0, 127.1, 120.4, 119.4, 118.9, 115.1, 112.2, 55.4.

IR (Diamond-ATR, neat) ν (cm⁻¹): 3002, 2930, 2834, 2362, 1934, 1740, 1590, 1580, 1542, 1498, 1458, 1430, 1390, 1378, 1324, 1296, 1276, 1258, 1210, 1178, 1076, 1050, 1038, 1000, 872, 842, 774, 758, 716, 690, 656, 642, 614.

MS (70 eV, EI) m/z (%): 261 [M⁺] (67), 260 (100), 231 (37), 217 (7), 189 (5), 154 (7), 131 (8), 127 (7), 114 (5), 109 (7), 95 (6).

HRMS (EI) for C₁₈H₁₅NO (261.1154): 261.1146.

Synthesis of 4-phenyl-2-(3-(trifluoromethyl)phenyl)pyridine (30f)

According to TP2, a mixture of 4-phenylpyridine (29b; 155 mg, 1.0 mmol) and BF₃·OEt₂ (156 mg, 1.1 mmol) reacted with TMPMgCl-LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (−40 °C, 20 min). ZnCl₂ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at −40 °C and stirred for 30 min at the same temperature. Pd(dba)₂ (28 mg, 5 mol%) and P(o-fur)₃ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (217 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL) and NH₃ (conc.) (0.5 mL) followed by extraction with Et₂O (3×20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo.
Vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 7:1) furnished the compound 30f as yellow oil (180 mg, 75% yield).

¹H-NMR (300 MHz, CDCl₃): δ / (ppm) = 8.78 (dd, J = 5.0, 0.8 Hz, 1H), 8.36 (s, 1H), 8.26 (d, J = 7.7 Hz, 1H), 7.96 (dd, J = 1.7, 0.6 Hz, 1H), 7.68 – 7.74 (m, 3H), 7.63 (t, J = 7.7 Hz, 1H), 7.45 – 7.58 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃): δ / (ppm) = 156.5, 150.3, 149.7, 140.2 131.2 (q, J = 32.4 Hz), 130.2 (q, J = 1.2 Hz), 129.2, 129.2, 127.1, 125.6 (q, J = 3.7 Hz), 124.2 (q, J = 27.2 Hz), 123.9 (q, J = 3.7 Hz), 121.0, 118.8.

IR (Diamond-ATR, neat) ν (cm⁻¹): 3062, 3030, 1594, 1544, 1466, 1432, 1382, 1334, 1310, 1292, 1268, 1234, 1164, 1118, 1092, 1072, 1048, 1024, 1002, 990, 920, 886, 846, 804, 758, 726, 692, 662, 642, 614.

MS (70 eV, EI) m/z (%): 299 [M⁺] (100), 278 (6), 230 (7), 154 (7).

HRMS (EI) for C₁₈H₁₂F₃N (299.0922): (299.0909).

Synthesis of phenyl(4-phenylpyridin-2-yl)methanone (30g)

According to TP2, a mixture of 4-phenylpyridine (29b; 310 mg, 2.0 mmol) and BF₃·OEt₂ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (-40 °C, 20 min). CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M solution in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, benzoyl chloride (778 mg, 3 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) and extracted with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 5:1) furnished the compound 30g as yellowish solid (399 mg, 77% yield).

M. p. (°C): 66.9-68.4.

¹H-NMR (300 MHz, CDCl₃): δ / (ppm) = 8.76 (d, J = 4.4 Hz, 1H), 8.25-8.29 (m, 1H), 8.07-8.14 (m, 2H), 7.66-7.76 (m, 3H), 7.56-7.64 (m, 1H), 7.43-7.56 (m, 5H).
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$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 194.0, 155.6, 149.6, 149.0, 137.4, 136.3, 132.9, 131.0, 129.5, 129.2, 128.1, 127.0, 123.8, 122.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3052, 2362, 1736, 1652, 1590, 1542, 1446, 1320, 1310, 1280, 1258, 1236, 1184, 1076, 1028, 992, 968, 954, 926, 912, 856, 780, 764, 748, 722, 700, 688, 654, 614.

MS (70 eV, EI) $m/z$ (%): 259 [M$^+$] (51), 230 (100), 202 (6), 182 (11), 154 (9), 127 (11), 105 (41), 77 (70), 51 (13).

HRMS (EI) for C$_{18}$H$_{13}$NO (259.0997): 259.0982.

Synthesis of 3-(cyclohex-2-en-1-yl)isonicotinonitrile (30h)

According to TP2, a mixture of isonicotinonitrile (29c; 208 mg, 2.0 mmol) BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMP$_2$Zn-2MgCl$_2$·2LiCl (14; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-20 °C, 3 h). CuCN-2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (7i; 258 mg, 1.6 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) and extracted with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 30h as brown oil (227 mg, 77% yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 8.70 (s, 1H), 8.62 (d, $J$ = 4.9 Hz, 1H), 7.49 (d, $J$ = 4.9 Hz, 1H), 6.00-6.13 (m, 1H), 5.63-5.69 (m, 1H), 3.80-3.85 (m, 1H), 2.14-2.16 (m, 3H), 1.53-1.81 (m, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 150.4, 147.8, 143.3, 131.1, 126.3, 125.5, 120.0, 115.5, 38.4, 31.2, 24.6, 20.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3024, 2932, 2862, 2838, 2232, 1682, 1652, 1584, 1548, 1480, 1446, 1432, 1408, 1346, 1316, 1298, 1192, 1154, 1138, 1082, 1060, 1044, 984, 890, 880, 834, 796, 774, 760, 724, 704, 684, 618.

MS (70 eV, EI) $m/z$ (%): 184 (78), 183 [M$^+$] (100), 169 (41), 154 (70), 143 (15), 128 (7).
HRMS (EI) for $\text{C}_{12}\text{H}_{12}\text{N}_2$ (184.1000): 184.0994.

**Synthesis of 3-iodoisonicotinonitrile (30i)**

According to TP2, a mixture of isonicotinonitrile (29c; 208 mg, 2.0 mmol) and $\text{BF}_3\cdot\text{OEt}_2$ (312 mg, 2.2 mmol) reacted with $\text{TMP}_2\text{Zn}\cdot2\text{MgCl}_2\cdot2\text{LiCl}$ (14; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-20 °C, 3 h). A solution of iodine (1.0 g, 4.0 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous $\text{NH}_4\text{Cl}$ solution (9 mL), $\text{NH}_3$ (conc.) (1 mL) and sat. aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (3 mL) followed by extraction with $\text{Et}_2\text{O}$ (3x30 mL). The combined organic layers were dried over $\text{Na}_2\text{SO}_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/$\text{Et}_2\text{O}$, 4:1) furnished the compound 30i as white solid (327 mg, 71% yield). The analytical data were found to match literature data.$^{132}$

M. p. (°C): 115.8-117.3.

$^1\text{H}-\text{NMR}$ (300 MHz, $\text{CDCl}_3$): $\delta$ / (ppm) = 9.11 (s, 1H), 8.72 (d, $J = 4.9$ Hz, 1H), 7.52 (d, $J = 4.9$ Hz, 1H).

$^{13}\text{C}-\text{NMR}$ (75 MHz, $\text{CDCl}_3$): $\delta$ / (ppm) = 158.0, 148.9, 128.0, 127.1, 117.0, 96.3.

IR (Diamond-ATR, neat) $\vec{\nu}$ (cm$^{-1}$) = 3070, 3006, 2360, 2236, 1912, 1736, 1568, 1540, 1526, 1464, 1392, 1276, 1216, 1198, 1162, 1146, 1084, 1018, 974, 934, 836, 780, 746, 730, 684, 668.

MS (70 eV, EI) $m$/z (%): 230 [M$^+$] (50), 127 (100), 103 (64), 75 (98), 50 (47).

HRMS (EI) for $\text{C}_6\text{H}_3\text{IN}_2$ (229.9341): (229.9314).

**Synthesis of ethyl 4-(cyclohex-2-en-1-yl)nicotinate (30j)**

According to **TP2**, a mixture of ethyl nicotinate (**29d**: 302 mg, 2.0 mmol) BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (**11**: 1.8 mL, 1.2 M in THF) (-40 °C, 30 min). CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (**7i**: 258 mg, 1.6 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) and extracted with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound **30j** as colorless oil (266 mg, 75% yield).

**1H-NMR (300 MHz, CDCl$_3$):** $\delta$ / (ppm) = 9.00 (s, 1H), 8.59 (d, $J = 5.2$ Hz, 1H), 7.31 (d, $J = 5.2$ Hz, 1H), 5.94-6.03 (m, 1H), 5.57-5.63 (m, 1H), 4.28-4.45 (m, 3H), 2.06-2.21 (m, 3H), 1.59-1.76 (m, 2H), 1.35-1.51 (m, 4H).

**13C-NMR (75 MHz, CDCl$_3$):** $\delta$ / (ppm) = 166.2, 156.9, 151.8, 151.0, 129.8, 128.3, 125.9, 123.6, 61.3, 37.5, 31.4, 24.9, 20.9, 14.2.

**IR (Diamond-ATR, neat) $\tilde{v}$ (cm$^{-1}$):** 2930, 1716, 1588, 1552, 1482, 1446, 1404, 1366, 1320, 1270, 1232, 1202, 1164, 1148, 1102, 1056, 1040, 1018, 986, 902, 886, 844, 784, 724, 710, 692, 672, 612.

**MS (70 eV, EI) $m/z$ (%):** 231 [M$^+$] (18), 185 (100), 167 (55), 156 (35), 77 (13).

**HRMS (EI) for C$_{14}$H$_{17}$NO$_2$ (231.1259):** (231.1247).

**Synthesis of 2-iodo-4-methoxypyridine (30k)**

According to **TP2**, a mixture of 4-methoxypyridine (**29e**: 218 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (**11**: 2.5 mL, 3.0 mmol, 1.2 M in THF) (-20 °C, 30 h). A solution of iodine (1.0 g, 4.0 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration
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the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et₂O, 4:1) furnished the compound 30k as yellowish oil (353 mg, 75% yield).

\[^1\text{H-NMR} (300 \text{ MHz, CDCl}_3): \delta / (\text{ppm}) = 8.13 \text{ (d, } J = 5.8 \text{ Hz, } 1\text{H}), 7.24 \text{ (d, } J = 2.4 \text{ Hz, } 1\text{H}), 6.79 \text{ (dd, } J = 5.7, 2.8 \text{ Hz, } 1\text{H}), 3.81 \text{ (s, } 3\text{H}).\]

\[^{13}\text{C-NMR} (75 \text{ MHz, CDCl}_3): \delta / (\text{ppm}) = 165.7, 151.0, 120.2, 118.3, 110.5, 55.4.\]

\[\text{IR (Diamond-ATR, neat) } \tilde{\nu} (\text{cm}^{-1}): 3006, 2924, 2852, 2288, 1712, 1576, 1554, 1544, 1468, 1432, 1386, 1374, 1300, 1264, 1252, 1228, 1112, 1054, 1022, 980, 824, 718, 690, 682.\]

\[\text{MS (70 eV, EI) } m/z (\%): 235 \text{ [M}^+\text{]} (75), 108 (100), 93 (14).\]

\[\text{HRMS (EI) for } \text{C}_6\text{H}_6\text{INO (234.9494): 234.9491.}\]

4. Preparation of functionalized quinoline derivatives by complexation with BF₃·OEt₂ and subsequent addition of TMP-base

**Synthesis of 2-iodoquinoline (37a)**

According to TP2, a mixture of quinoline (31a; 258 mg, 2.0 mmol) and BF₃·OEt₂ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 20 min). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL), NH₃ (conc.) (1 mL) and sat. aqueous Na₂S₂O₃ solution (2 mL) followed by extraction with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et₂O, 4:1) furnished the compound 37a as brown solid (384 mg, 75% yield). The analytical data were found to match literature data.¹³³


\[^1\text{H-NMR} (300 \text{ MHz, CDCl}_3): \delta / (\text{ppm}) = 8.03-8.08 \text{ (m, } 1\text{H}), 7.77-7.81 \text{ (m, } 1\text{H}), 7.73-7.76 \text{ (m, } 2\text{H}), 7.69-7.73 \text{ (m, } 1\text{H}), 7.54-7.60 \text{ (m, } 1\text{H}).\]

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$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 149.6, 137.1, 132.0, 130.3, 128.8, 127.8, 127.1, 127.1, 119.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3052, 3040, 2920, 2474, 2358, 2216, 1962, 1956, 1934, 1850, 1824, 1736, 1700, 1660, 1612, 1576, 1558, 1548, 1488, 1458, 1446, 1416, 1348, 1328, 1294, 1284, 1266, 1246, 1140, 1118, 1094, 1074, 1054, 1012, 986, 950, 936, 866, 852, 820, 778, 750, 742, 616.

MS (70 eV, EI) $m/z$ (%): 255 [M$^+$] (53), 128 (100), 101 (15), 77 (7).

HRMS (EI) for C$_9$H$_6$IN (254.9545): 254.9535.

**Synthesis of ethyl 4-(quinolin-2-yl)benzoate (37b)**

According to TP2, a mixture of quinoline (31a; 129 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (0 °C, 20 min). ZnCl$_2$ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at 0 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by extraction with Et$_2$O (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 37b as white solid (222 mg, 80% yield).

**M. p. (°C):** 88.9-90.4.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.11-8.33 (m, 6H), 7.78-7.91 (m, 2H), 7.69-7.77 (m, 1H), 7.49-7.57 (m, 1H), 4.43 (q, $J$ = 7.21 Hz, 2H), 1.44 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 166.4, 156.0, 148.2, 143.6, 136.9, 131.0, 130.0, 129.8, 127.4, 126.7, 118.9, 61.0, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 2984, 2870, 2400, 2274, 1702, 1666, 1616, 1606, 1596, 1576, 1554, 1540, 1512, 1494, 1458, 1444, 1432, 1406, 1394, 1366, 1314, 1268, 1242, 1212,
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1182, 1170, 1146, 1128, 1104, 1048, 1016, 976, 940, 872, 862, 842, 824, 794, 772, 704, 674, 620.

**MS (70 eV, EI) m/z (%)**: 277 [M⁺] (80), 232 (100), 204 (62), 116 (8), 102 (13).

**HRMS (EI) for C₁₈H₁₄NO₂ (277.1103):** (277.1099).

**Synthesis of 2-(3-(trifluoromethyl)phenyl)quinoline (37c)**

According to **TP2**, a mixture of quinoline (31a; 129 mg, 1.0 mmol) and BF₃·OEt₂ (156 mg, 1.1 mmol) reacted with TMPMgCl-LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (0 °C, 20 min). ZnCl₂ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at 0 °C and stirred for 30 min at the same temperature. Pd(dba)₂ (28 mg, 5 mol%) and P(o-fur)₃ (23 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (218 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL) and NH₃ (conc.) (0.5 mL) followed by extraction with Et₂O (3×20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 10:1) furnished the compound 37c as yellow solid (224 mg, 82% yield).

**M. p. (°C):** 79.1-80.9.

**¹H-NMR (300 MHz, CDCl₃); δ (ppm) =** 8.48 (s, 1H), 8.37 (d, J = 7.7 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.82-7.94 (m, 2H), 7.53-7.82 (m, 4H).

**¹³C-NMR (75 MHz, CDCl₃); δ (ppm) =** 155.5, 148.2, 140.4, 137.1, 131.3 (q, J = 32.3 Hz), 130.7 (q, J = 1.1 Hz), 129.9, 129.8, 129.3, 127.5, 127.4, 126.8, 125.8 (q, J = 3.7 Hz), 124.4 (q, J = 3.9 Hz), 124.2 (q, J = 272.4 Hz), 118.5.

**IR (Diamond-ATR, neat) ν (cm⁻¹):** 2362, 2340, 1740, 1598, 1508, 1432, 1350, 1326, 1284, 1268, 1236, 1170, 1096, 1074, 892, 832, 806, 786, 758, 694, 652.

**MS (70 eV, EI) m/z (%):** 273 [M⁺] (100), 252 (9), 204 (34), 101 (4).

**HRMS (EI) for C₁₆H₁₀F₃N (273.0765):** (273.0772).
Synthesis of 4-(quinolin-2-yl)benzonitrile (37d)

According to TP2, a mixture of quinoline (31a; 129 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl-LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (0 °C, 20 min). ZnCl$_2$ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at 0 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (183 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by extraction with Et$_2$O (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 3:1) furnished the compound 37d as yellow solid (184 mg, 80% yield).

M. p. (°C): 128.2-129.9.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 8.25-8.34 (m, 3H), 8.18 (d, $J = 8.5$ Hz, 1H), 7.74-7.93 (m, 5H), 7.59 (t, $J = 7.29$ Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) = 154.9, 148.2, 143.7, 137.2, 132.6, 130.1, 129.9, 128.0, 127.5, 127.1, 118.8, 118.6, 112.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3061, 3030, 2828, 2728, 1758, 1693, 1599, 1584, 1497, 1470, 1455, 1449, 1426, 1368, 1304, 1256, 1210, 1186, 1174, 1164, 1109, 1083, 1048, 1031, 1009, 948, 912, 895, 866, 865, 844, 834, 819, 800, 755, 739, 713, 711, 695, 663, 649, 631, 629, 623, 618, 609.

MS (70 eV, EI) m/z (%): 230 [M$^+$] (100), 202 (5), 115 (7), 101 (7), 75 (5).

HRMS (EI) for C$_{16}$H$_{10}$N$_2$ (230.0844): (230.0819).

Synthesis of 4-chloro-2-iodoquinoline (37e)
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According to TP2, a mixture of 4-chloroquinoline (31b; 327 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 2.5 mL, 3.0 mmol, 1.2 M in THF) (-10 °C, 10 min). A solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 5:1) furnished the compound 37e as yellowish solid (376 mg, 65% yield).

M. p. (°C): 116.9-118.5.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / (ppm) = 8.14-8.20 (m, 1H), 8.02-8.08 (m, 1H), 7.84 (s, 1H), 7.72-7.79 (m, 1H), 7.61-7.68 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / (ppm) = 149.8, 142.4, 131.2, 131.2, 129.2, 128.0, 125.6, 124.4, 116.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3054, 1922, 1804, 1714, 1610, 1562, 1540, 1492, 1480, 1444, 1424, 1390, 1366, 1318, 1258, 1246, 1200, 1146, 1136, 1088, 1074, 974, 946, 866, 852, 826, 752, 690.

MS (70 eV, EI) m/z (%): 289 [M$^+$] (6), 179 (100), 151 (39), 116 (16), 89 (20), 76 (12).

HRMS (EI) for C$_9$H$_5$ClIN (288.9155): 288.9152.

Synthesis of 4-chloro-2-(3-(trifluoromethyl)phenyl)quinoline (37f)

According to TP2, a mixture of 4-chloroquinoline (31b; 327 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 2.5 mL, 3.0 mmol, 1.2 M in THF) (-10 °C, 10 min). ZnCl$_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise at -10 °C and stirred for 30 min at the same temperature. Pd(db$a$)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (435 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same
temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 10:1) furnished the compound 37f as yellow oil (345 mg, 70% yield).

**M. p. (°C):** 78.6-80.2.

**$^1$H-NMR (300 MHz, CDCl$_3$):** $\delta$ / (ppm) = 8.42-8.46 (m, 1H), 8.28-8.35 (m, 1H), 8.16-8.26 (m, 2H), 7.97 (s, 1H), 7.76-7.83 (m, 1H), 7.70-7.76 (m, 1H), 7.60-7.68 (m, 2H).

**$^{13}$C-NMR (75 MHz, CDCl$_3$):** $\delta$ / (ppm) = 155.4, 150.0, 143.6, 139.3, 131.4 (q, $J = 32.5$ Hz), 130.8, 130.6 (q, $J = 1.2$ Hz), 130.2, 129.4, 127.7, 126.3 (q, $J = 3.7$ Hz), 125.5, 124.4 (q, $J = 3.8$ Hz), 124.1 (q, $J = 272.6$ Hz), 124.0, 118.7.

**IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$):** 2924, 2852, 1614, 1582, 1550, 1502, 1486, 1468, 1432, 1400, 1342, 1312, 1294, 1270, 1234, 1184, 1166, 1130, 1110, 1096, 1068, 1022, 976, 954, 890, 864, 846, 804, 792, 760, 724, 694, 670, 650.

**MS (70 eV, EI) $m/z$ (%):** 307 [M$^+$] (100), 272 (65), 252 (16), 203 (8), 101 (8).

**HRMS (EI) for C$_{16}$H$_9$ClF$_3$N (307.0376):** 307.0379.

**Synthesis of (4-bromoquinolin-2-yl)(phenyl)methanone (37g)**

According to TP2, a mixture of 4-bromoquinoline (31b; 208 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl-LiCl (11; 1.3 mL, 1.5 mmol, 1.2 M in THF) (-10 °C, 20 min). CuCN-2LiCl (1.1 mL, 1.1 mmol, 1 M solution in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, benzyol chloride (155 mg, 1.1 mmol) was added at -10 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) and extracted with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 50:1) furnished the compound 37g as white solid (262 mg, 84% yield).
M. p. (°C): 138.7-140.1.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta /$ (ppm) = 8.42 (s, 1H), 8.17-8.29 (m, 4H), 7.71-7.86 (m, 2H), 7.60-7.66 (m, 1H), 7.47-7.55 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta /$ (ppm) = 192.3, 154.1, 147.2, 135.7, 135.2, 133.3, 131.4, 131.0, 130.9, 129.7, 128.5, 128.2, 126.8, 124.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3308, 3056, 2922, 2416, 1950, 1772, 1666, 1600, 1568, 1548, 1492, 1458, 1444, 1406, 1362, 1316, 1304, 1274, 1262, 1206, 1178, 1158, 1118, 1074, 1024, 1002, 984, 966, 948, 914, 886, 866, 830, 814, 796, 778, 766, 734, 700, 686, 656, 628, 604.

MS (70 eV, EI) $m/z$ (%): 311 [M$^+$] (9), 285 (29), 283 (30), 232 (100), 204 (36), 127 (26), 105 (70), 77 (63), 51 (15).

HRMS (EI) for C$_{16}$H$_9$BrClNO (310.9946): 310.9898.

5. Preparation of the title compounds by premixing BF$_3$·OEt$_2$ and TMPMgCl·LiCl

Synthesis of (4-chlorophenyl)(pyridin-2-yl)methanone (41a)

According to TP3, BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) was added dropwise to TMPMgCl·LiCl (11; 0.92 mL, 1.1 mmol, 1.2 m in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before pyridine (29a; 79 mg, 1.0 mmol) diluted in dry THF (5 mL) was added dropwise. After stirring for 15 min CuCN·2LiCl (1.1 mL, 1.1 mmol, 1 m in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 4-chlorobenzoyl chloride (7b; 149 mg, 0.8 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) and extracted with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 41a as white solid (146 mg, 84% yield).
M. p. (°C): 81.5-82.7.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 8.69-8.74 (m, 1H), 8.01-8.09 (m, 3H), 7.88-7.96 (m, 1H), 7.48-7.55 (m, 1H), 7.42-7.48 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 192.0, 154.3, 148.2, 139.5, 137.5, 134.4, 132.4, 128.5, 126.5, 124.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3086, 3060, 1658, 1582, 1568, 1488, 1468, 1434, 1402, 1312, 1304, 1290, 1282, 1240, 1182, 1158, 1088, 1048, 1016, 996, 974, 964, 934, 896, 852, 800, 752, 742, 724, 692, 670, 632, 618.

MS (70 eV, EI) $m/z$ (%): 218 [M+H$^+$] (100), 203 (39), 189 (73), 154 (18), 139 (66), 111 (39), 73 (72), 45 (62).

HRMS (EI) for C$_{12}$H$_9$ON (217.0294): 218.0365.

**Synthesis of 2-furyl(6-methoxypyridin-2-yl)methanone (41b)**

According to TP3, BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) was added dropwise to TMPMgCl-LiCl (1; 0.92 mL, 1.1 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before 2-methoxypyridine (29f; 109 mg, 1.0 mmol) diluted in dry THF (5 mL) was added dropwise. After stirring for 15 min CuCN-2LiCl (1.1 mL, 1.1 mmol, 1.2 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 2-furoyl chloride (104 mg, 0.8 mmol) was added at -40 °C. The reaction mixture was warmed slowly to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) and extracted with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 5:1) furnished the compound 41b as yellow solid (124 mg, 76% yield).


$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 8.06-8.09 (m, 1H), 7.69-7.82 (m, 3H), 6.93-6.97 (m, 1H), 6.58-6.61 (m, 1H), 4.02 (s, 3H).
C. Experimental Section

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 178.5, 163.1, 151.2, 151.1, 147.5, 139.2, 123.1, 117.5, 115.1, 112.2, 53.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3126, 3106, 3006, 2950, 2850, 1632, 1612, 1586, 1554, 1470, 1458, 1436, 1388, 1364, 1336, 1284, 1272, 1222, 1202, 1184, 1146, 1084, 1076, 1038, 1020, 992, 968, 920, 906, 880, 872, 838, 814, 792, 758, 722, 714, 664, 636, 618.

MS (70 eV, EI) $m/z$ (%): 203 [M$^+$] (86), 174 (100), 146 (24), 117 (17), 95 (59).

HRMS (EI) for C$_{11}$H$_9$O$_3$N (203.0582): 203.0583.

**Synthesis of ethyl 4-[3-(trifluoromethyl)phenyl]nicotinate (41c)**

![Chemical Structure](image)

According to TP3, BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (11; 1.85 mL, 2.2 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before ethyl nicotinate (29d; 302 mg, 2.0 mmol) diluted in dry THF (10 mL) was added dropwise. After stirring for 15 min ZnCl$_2$ (2.2 mL, 2.2 mmol, 1 M in THF) was added at -40 °C and stirred for 30 min. Pd(dba)$_2$ (56 mg, 5 mol%) and P(2-furyl)$_3$ (46 mg, 10 mol%) dissolved in THF (4 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (435 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. After GC analysis of a hydrolyzed aliquot showed full conversion sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) were added and the layers were separated followed by extraction using Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 1:1) furnished the product 41c as yellow oil (335 mg, 71% yield).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ / (ppm): 9.12 (s, 1H), 8.78 (d, $J = 4.9$ Hz, 1H), 7.35 (d, $J = 5.1$ Hz, 1H), 7.66-7.73 (m, 1H), 7.48-7.61 (m, 3H), 4.17 (q, $J = 7.1$ Hz, 2H), 1.07 (t, $J = 7.1$ Hz, 3H).
C-NMR (75 MHz, CDCl$_3$) $\delta$ / (ppm): 165.7, 151.2, 150.5, 149.6, 139.2, 131.4 (q, $J = 1.4$ Hz), 130.9 (q, $J = 32.6$ Hz), 128.9, 125.3 (q, $J = 3.7$ Hz), 125.0 (q, $J = 3.8$ Hz), 123.8 (q, $J = 272.5$ Hz), 61.7, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3058, 2984, 2940, 2916, 2876, 1720, 1588, 1548, 1478, 1436, 1406, 1368, 1336, 1306, 1272, 1256, 1216, 1166, 1124, 1098, 1076, 1052, 1042, 1016, 906, 846, 826, 808, 788, 704, 660, 624.

MS (70 eV, EI) m/z (%): 295 [M$^+$] (38), 267 (41), 250 (100), 228 (35), 149 (31), 85 (24), 71 (33), 69 (19), 59 (42), 43 (23).

HRMS (EI) for C$_{15}$H$_{12}$O$_2$NF$_3$ (295.0820): 295.0824.

Synthesis of of 2-iodo-3-(methylthio)pyrazine (41d)

According to TP3, BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (11; 1.85 mL, 2.2 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before thiomethylpyrazine (29g; 252 mg, 2.0 mmol) diluted in dry THF (10 mL) was added dropwise. After stirring for 10 min at the same temperature a solution of iodine (762 mg, 3 mmol) in THF (3 mL) was added and the reaction mixture was slowly warmed to 25 °C. The reaction solution was quenched with sat. aqueous NH$_4$Cl solution (5 mL), NH$_3$ (5 mL, 2 M) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) and extracted with CH$_2$Cl$_2$ (3x10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/EtOAc, 95:5) furnished the product 41d as off-white solid (408 mg, 81% yield).

M. p. (°C): 90.8-92.5.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 8.30 (d, $J = 2.4$ Hz, 1H), 7.95 (d, $J = 1.0$ Hz, 1H), 2.50 (s, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 162.7, 142.1, 138.9, 118.6, 15.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 2918, 2018, 1534, 1486, 1418, 1402, 1318, 1188, 1132, 1056, 1022, 970, 838, 772, 672.

MS (70 eV, EI) m/z (%): 253 (10), 252 [M$^+$] (100), 125 (72), 109 (10), 81 (19).
HRMS (EI) for C₅H₅IN₂S (251.9218): 251.9212.

Synthesis of carbinoxamine (42; 2-[(4-chlorophenyl)(pyridin-2-yl)methoxy]-N,N-dimethylethanamine):

According to TP3, BF₃·OEt₂ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (11; 1.85 mL, 2.2 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min pyridine (29a; 158 mg, 2.0 mmol) diluted in dry THF (1 mL) was added dropwise. After 10 min at -40 °C a solution of 4-chlorobenzaldehyde (281 mg, 2.2 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was slowly warmed to 25 °C and further stirred for 1 h. Thereafter, 1-chloro-N,N-dimethylaminoethane hydrochloride (346 mg 2.4 mmol) was added neat at 25 °C followed by addition of sodium hydride (96 mg, 2.4 mmol, 60 wt% in mineral oil) and catalytic amounts of sodium iodide at the same temperature. The reaction mixture was refluxed for 2 h. After cooling down the reaction mixture to 25 °C, it was diluted with Et₂O (5 mL) and quenched with aqueous sodium hydroxide (10 mL, 2 M). The aqueous phase was extracted with EtOAc (4x15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatographical purification on neutral aluminium oxide (silica gel, pentane/EtOAc/methanol, 8:2:1) furnished 42 as yellow oil (419 mg, 72% yield).

¹H-NMR (300 MHz, CDCl₃): δ / (ppm): 8.47 (dd, J = 4.9, 0.8 Hz, 1H), 7.62 (dt, J = 7.7, 1.8 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.10 (dt, J = 4.8, 1.1 Hz, 1H), 5.43 (s, 1H), 3.57 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 5.9 Hz, 2H), 2.23 (s, 6H).

¹³C-NMR (75 MHz, CDCl₃): δ / (ppm): 161.2, 148.9, 139.6, 136.8, 133.3, 128.4, 128.2, 122.4, 120.5, 84.3, 67.6, 58.8, 45.9.

IR (Diamond-ATR, neat) ν (cm⁻¹): 3396, 2942, 2864, 2820, 2770, 2362, 2334, 1588, 1572, 1490, 1468, 1434, 1406, 1370, 1328, 1294, 1274, 1190, 1116, 1088, 1040, 1014, 994, 958, 852, 806, 766, 748, 718, 700.
**C. Experimental Section**

**MS (70 eV, EI) m/z (%):** 291 [M$^+$] (5), 218 (9), 201 (12), 167 (27), 139 (13), 71 (68), 58 (100).

**HRMS (EI) for C$_{16}$H$_{20}$ClN$_2$O (291.1264):** 291.1249.

**Synthesis of dubamine (43; 2-(1,3-benzodioxol-5-yl)quinoline)**

![Diagram of dubamine](Image)

According to **TP3**, BF$_3$-OEt$_2$ (156 mg, 1.1 mmol) was added dropwise to TMPMgCl-LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before quinoline (31a; 129 mg, 1.0 mmol) diluted in dry THF (5 mL) was added dropwise. After stirring for 20 min ZnCl$_2$ (1.1 mL, 1.1 mmol, 1 M in THF) was added at -40 °C and stirred for 30 min. Pd(dbca)$_2$ (28 mg, 5 mol%) and P(2-furyl)$_3$ (23 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 5-iodo-1,3-benzodioxole (198 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. After GC analysis of a hydrolyzed aliquot showed full conversion sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) were added and the layers were separated followed by extraction using Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 20:1) furnished the product 43 as yellowish solid (158 mg, 79% yield).

**M. p. (°C):** 94-95.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / (ppm): 8.11-8.18 (m, 2H), 7.63-7.81 (m, 5H), 7.46-7.52 (m, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.03 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / (ppm): 156.6, 148.8, 148.4, 148.0, 136.7, 134.0, 129.7, 129.4, 127.4, 127.0, 126.1, 121.8, 118.6, 108.4, 107.9, 101.3.

**IR (Diamond-ATR, neat) v (cm$^{-1}$):** 3050, 3008, 2896, 2780, 1596, 1558, 1496, 1486, 1454, 1444, 1426, 1354, 1292, 1254, 1234, 1222, 1206, 1162, 1138, 1110, 1098, 1048, 1036, 932, 908, 892, 860, 838, 828, 814, 800, 784, 742, 720, 682, 624, 604.

**MS (70 eV, EI) m/z (%):** 249 [M$^+$] (100), 220 (3), 191 (17), 163 (3), 128 (3), 96 (6).

**HRMS (EI) for C$_{16}$H$_{11}$O$_2$N (249.0790):** 249.0787.
Synthesis of 2,2,2-trifluoro-1-phenyl-1-(pyridin-2-yl)ethanol (47a)

According to TP3, BF₃·OEt₂ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before pyridine (29a; 158 mg, 2.0 mmol) diluted in dry THF (1 mL) was added dropwise. After stirring for 10 min 2,2,2-trifluoro-1-phenylethanone (383 mg, 2.2 mmol) diluted in dry THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with NaOH (10 mL, 2 M) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/EtOAc, 3:1) furnished 47a as yellow oil (365 mg, 72%).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.57-8.62 (m, 1H), 7.71-7.77 (m, 1H), 7.62-7.67 (m, 2H), 7.45-7.50 (m, 1H), 7.30-7.40 (m, 4H), 6.95-7.05 (s, br, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 155.0, 147.2, 138.3, 137.4, 128.6, 128.4, 127.0, 125.0 (q, J = 286.0 Hz), 124.0, 122.9,

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3286, 2928, 2856, 2362, 1734, 1718, 1594, 1576, 1498, 1468, 1450, 1436, 1406, 1262, 1196, 1150, 1120, 1096, 1072, 1050, 1036, 1002, 966, 948, 932, 912, 780, 760, 750, 736, 698, 684, 656, 628.

MS (EI, 70 eV): m/z (%) = 253 [M⁺] (2), 141 (5), 127 (9), 111 (14), 97 (32), 85 (52), 83 (31), 71 (68), 69 (35), 57 (100), 41 (25).

HRMS (EI) for C₁₃H₁₀F₃NO (253.0714): 253.0722.

Synthesis of (4-chlorophenyl)(pyridin-2-yl)methanol (47b):

According to TP3, BF₃·OEt₂ (312 mg, 2.2 mmol) was added dropwise to TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) at -40 °C and the resulting mixture was stirred at this temperature for 10 min before pyridine (29a; 158 mg, 2.0 mmol) diluted in dry THF (2 mL)
was added dropwise. After stirring for 10 min 4-chlorobenzaldehyde (2.2 mmol, 309 mg) was added and slowly warmed to 25 °C. The reaction mixture was quenched with NaOH (10 mL, 2 M) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane / EtOAc = 2:1) furnished 47b as pale yellow solid (298 mg, 68%).

M. p. (°C): 96.3-97.5.

¹H-NMR (300 MHz, D₆-acetone): δ / (ppm): 8.52 (d, J = 4.1 Hz, 1H), 7.78 (dt, J = 7.6, 1.8 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.25 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 5.90 (s, 1H), 5.64 (br s, 1H).

¹³C-NMR (75 MHz, D₆-acetone): δ / (ppm): 163.4, 149.0, 143.9, 137.6, 133.1, 129.0, 128.8, 123.0, 121.1, 75.6.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3142, 2848, 1592, 1572, 1492, 1468, 1438, 1410, 1334, 1192, 1114, 1090, 1056, 1018, 1002, 856, 812, 770, 748, 624.

MS (70 eV, EI) m/z (%): 221 (31), 220 (24), 219 [M⁺] (100), 217 (41), 216 (16), 215 (22), 203 (17), 202 (18), 201 (47), 200 (12), 190 (17), 188 (46), 16 (33), 141 (18), 139 (40), 111 (25), 108 (40), 80 (22), 79 (94), 78 (24), 77 (21).

HRMS (EI) for C₁₂H₁₀ClNO (219.0451): 219.0444.

6. Preparation of functionalized N-heterocycles using TMP-bases

Synthesis of 2-(2-iodophenyl)pyridine (48a)

![Structure of 2-(2-iodophenyl)pyridine](image)

According to TP1, 2-phenylpyridine (29h; 2.0 mmol, 310 mg) reacted with TMPMgCl·LiCl (11; 3.3 mL, 4.0 mmol, 1.2 M in THF) (55 °C, 30 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL), NH₃ (conc.) (1 mL) and sat. aqueous Na₂S₂O₃ solution (2 mL) followed by extraction with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the
solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et\textsubscript2O, 4:1) furnished the compound 48a as yellowish oil (478 mg, 85% yield).

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript3): \(\delta / (\text{ppm}) = 8.70\) (ddd, \(J = 4.9\) Hz, 1.8 Hz, 1.0 Hz, 1H), 7.93-7.97 (m, 1H), 7.72-7.81 (m, 1H), 7.38-7.52 (m, 3H), 7.27-7.33 (m, 1H), 7.03-7.11 (m, 1H).

\textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript3): \(\delta / (\text{ppm}) = 160.6, 149.0, 144.8, 139.7, 136.1, 130.3, 129.7, 128.2, 124.5, 122.5, 96.6\) ppm.

IR (Diamond-ATR, neat) \(\tilde{\nu} (\text{cm}^{-1}) = 3048, 3006, 1606, 1588, 1580, 1566, 1478, 1456, 1424, 1416, 1288, 1232, 1148, 1094, 1074, 1046, 1022, 1010, 988, 946, 890, 866, 790, 744, 720, 654, 630, 614\).

MS (70 eV, EI) \(m/z\) (%): 281 [M\textsuperscript{+}] (100), 155 (11), 154 (87), 153 (12), 128 (16), 127 (50), 126 (12).

HRMS (EI) for C\textsubscript{11}H\textsubscript{8}IN (280.9701): 280.9682.

\textbf{Synthesis of 3-fluoro-2-iodopyridine (48b)}

\begin{center}
\begin{tikzpicture}
\node [shape=circle,draw,inner sep=0pt,minimum size=1cm] (n) at (0,0) {N};
\node [shape=circle,draw,inner sep=0pt,minimum size=0.2cm] (f) at (0.5cm,0.5cm) {F};
\node [shape=circle,draw,inner sep=0pt,minimum size=0.2cm] (i) at (0.5cm,-0.5cm) {I};
\end{tikzpicture}
\end{center}

According to TP1, 3-fluoropyridine (29i; 97 mg, 1.0 mmol) reacted with TMPMgCl\cdot LiCl (11; 0.9 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 30 min). A solution of iodine (0.5 g, 2 mmol) in THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH\textsubscript{4}Cl solution (4.5 mL), NH\textsubscript{3} (conc.) (0.5 mL) and sat. aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (2 mL) followed by extraction with Et\textsubscript{2}O (3x20 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et\textsubscript{2}O, 10:1) furnished the compound 48b as colorless oil (140 mg, 63% yield).

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript3): \(\delta / (\text{ppm}) = 8.21\) (d, \(J = 4.3\) Hz, 1H), 7.20-7.33 (m, 3H).

\textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript3): \(\delta / (\text{ppm}) = 158.9\) (d, \(J = 258.4\) Hz), 146.6 (d, \(J = 5.0\) Hz), 124.1 (d, \(J = 3.5\) Hz), 122.2 (d, \(J = 20.7\) Hz), 106.8 (d, \(J = 28.4\) Hz).

IR (Diamond-ATR, neat) \(\tilde{\nu} (\text{cm}^{-1}) = 3060, 1580, 1445, 1415, 1265, 1205, 1060, 1045\).

MS (70 eV, EI) \(m/z\) (%): 223 [M\textsuperscript{+}] (100), 127 (12), 96 (67), 76 (33), 69 (10).

HRMS (EI) for C\textsubscript{5}H\textsubscript{3}FIN (222.9294): 222.9281.
Synthesis of ethyl 4-(3-fluoropyridin-2-yl)benzoate (48c)

According to TP1, 3-fluoropyridine (29i; 196 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (-78 °C, 30 min). ZnCl₂ (2.2 mL, 2.2 mmol, 1 M in THF) was added and the mixture was stirred for 30 min at the same temperature. Pd(dbac)₂ (56 mg, 5 mol%) and P(2-furyl)₃ (46 mg, 10 mol%) dissolved in THF (4 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (442 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and was stirred for 12 h at the same temperature. The reaction mixture was quenched with a mixture of sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) followed by extraction with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 4:1) furnished the compound 48c as yellow oil (282 mg, 72% yield).

¹H-NMR (300 MHz, CDCl₃): δ (ppm): 8.52-8.56 (m, 1H), 8.15-8.17 (m, 1H), 8.12-8.14 (m, 1H), 8.05-8.08 (m, 1H), 8.02-8.05 (m, 1H), 7.48-7.56 (m, 1H), 7.28-7.35 (m, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.40 ppm (t, J = 7.2 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ (ppm): 166.3, 157.7 (d, J = 261.6 Hz), 145.3 (d, J = 5.4 Hz), 144.9 (d, J = 10.8 Hz), 139.1 (d, J = 5.4 Hz), 131.0, 129.6, 128.7 (d, J = 6.2 Hz), 124.6 (d, J = 20.6 Hz), 124.3 (d, J = 4.1 Hz), 61.1, 14.3.

IR (Diamond-ATR, neat) ν (cm⁻¹): 3066, 2982, 2362, 2338, 1940, 1712, 1610, 1596, 1578, 1512, 1442, 1402, 1368, 1312, 1268, 1248, 1186, 1096, 1060, 1034, 1016, 864, 838, 800, 786, 742, 730, 698, 640, 630.

HRMS (ESI) for C₁₄H₁₃FNO₂ (M+H⁺) (246.0930): 246.0923.

Synthesis of ethyl 4-(3-fluoropyridin-2-yl)benzoate (48d)
According to TP1, 3-chloropyridine (29j; 113 mg, 1.0 mmol) reacted with TMPMgCl-LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 45 min). ZnCl$_2$ (1.1 mL, 1.1 mmol, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by extraction with Et$_2$O (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 3:1) furnished the compound 48d as yellow solid (157 mg, 75% yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 8.59-8.64 (m, 1H), 8.11-8.18 (m, 2H), 7.76-7.86 (m, 3H), 7.26-7.31 (m, 1H), 4.41 ($J$ = 7.1 Hz, 2H), 1.40 ($J$ = 7.2 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 166.2, 155.4, 147.5, 142.1, 138.4, 130.7, 130.3, 129.4, 129.2, 123.6, 61.1, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3050, 2982, 2938, 2904, 1712, 1612, 1572, 1554, 1426, 1398, 1366, 1310, 1268, 1178, 1100, 1088, 1038, 1028, 1014, 862, 794, 786, 748, 702, 636, 628.

HRMS (ESI) for C$_{14}$H$_{13}$ClNO$_2$ (M+H$^+$) (262.0635): 262.0627.

**Synthesis of 2-(4-methoxyphenyl)nicotinonitrile (48e)**

According to TP1, nicotinonitrile (29k; 208 mg, 2.0 mmol) reacted with TMP$_2$Zn·2MgCl$_2$·2LiCl (14; 2.75 mL, 2.2 mmol, 0.8 M in THF) (25 °C, 12 h). Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (4 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 1-iodo-4-methoxybenzene (221 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was
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quenched with sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) followed by extraction with Et₂O (3×30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/EtOAc, 3:1) furnished the compound 48e as yellow solid (286 mg, 85% yield).

M. p. (°C): 138.1-139.3.

¹H-NMR (300 MHz, CDCl₃): δ / (ppm): 8.82 (dd, J = 4.9 Hz, 1.8 Hz, 1H), 8.02 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.93 (ddd, J = 9.4 Hz, 3.0 Hz, 2.6 Hz, 2H), 7.29 (dd, J = 7.9 Hz, 4.9 Hz, 1H), 7.03 (ddd, J = 9.4 Hz, 3.0 Hz, 2.6 Hz, 2H), 3.87 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / (ppm): 161.3, 160.4, 152.5, 141.9, 130.4, 129.5, 120.9, 117.9, 114.1, 106.7, 55.4.

IR (Diamond-ATR, neat) ʋ (cm⁻¹): 3064, 2846, 2224, 1606, 1582, 1572, 1554, 1516, 1458, 1432, 1312, 1252, 1192, 1182, 1114, 1038, 1018, 836, 826, 812, 788, 776, 722, 632, 616.

MS (70 eV, EI) m/z (%): 210 [M⁺] (100), 195 (8), 167 (22), 139 (9).

HRMS (EI) for C₁₃H₁₀N₂O (210.0793): 210.0790.

Synthesis of 2-(1-phenylvinyl)nicotinonitrile (48f)

According to TP1, nicotinonitrile (29k; 208 mg, 2 mmol) reacted with TMP₂Zn·2MgCl₂·2LiCl (14; 3.1 mL, 2.2 mmol, 0.71  M in THF) (25 °C, 12 h). Pd(dba)₂ (56 mg, 5 mol%) and P(o-fur)₃ (46 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of (1-iodovinyl)benzene (368 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 55 °C and stirred for 20 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) followed by extraction with Et₂O (3×30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 1:1) furnished the product 48f as yellow oil (280 mg, 85% yield).
Synthesis of 2-(cyclohex-2-en-1-yl)nicotinonitrile (48g)

According to TP1, nicotinonitrile (29k; 208 mg, 2.0 mmol) reacted with TMP₂Zn-2MgCl₂·2LiCl (14; 3.1 mL, 2.2 mmol, 0.71 M in THF) (25 °C, 12 h). CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added at -30 °C and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (258 mg, 1.6 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) and extracted with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 4:1) furnished the compound 48g as colorless oil (216 mg, 73% yield).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.80 (dd, J = 5.0, 1.8 Hz, 1H), 7.96 (dd, J = 7.9, 1.7 Hz, 1H), 7.24-7.35 (m, 1H), 6.00-6.07 (m, 1H), 5.73-5.78 (m, 1H), 4.01-4.18 (m, 1H), 2.07-2.30 (m, 3H), 1.72-1.98 (m, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 168.2, 152.7, 140.7, 129.6, 126.8, 121.1, 116.6, 108.6, 42.7, 29.9, 24.5, 21.6.

IR (Diamond-ATR, neat) ν (cm⁻¹): 3026, 2932, 2860, 2836, 2226, 1580, 1562, 1446, 1430, 1232, 1166, 1136, 1096, 1060, 990, 900, 888, 806, 772, 722, 680, 658, 612.

MS (70 eV, EI) m/z (%): 184 [M⁺] (36), 155 (100), 142 (16), 118 (13).

HRMS (EI) for C₁₁H₁₀N₂ (184.0844): 184.0835.
Synthesis of ethyl 4-(3-(trifluoromethyl)pyridine-2-yl)benzoate (48h)

According to TP1, 3-(trifluoromethyl)pyridine (29l; 147 mg, 1.0 mmol) reacted with TMPMgCl-LiCl (11; 0.8 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 10 min). ZnCl₂ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)₂ (28 mg, 5 mol%) and P(o-fur)₃ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was slowly warmed to 55 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL) and NH₃ (conc.) (0.5 mL) followed by extraction with Et₂O (3×30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 9:1) furnished the compound 48h as colorless oil (162 mg, 69% yield).

\(^1\)H-NMR (300 MHz, CDCl₃): \(\delta / \text{ppm} = 8.85 (d, J = 4.1 \text{ Hz}, 1\text{H}), 8.07-8.17 (m, 3\text{H}), 7.58 (d, J = 8.3 \text{ Hz}, 2\text{H}), 7.45 (dd, J = 7.7, 5.0 \text{ Hz}, 1\text{H}), 4.40 (q, J = 7.1 \text{ Hz}, 2\text{H}), 1.41 (t, J = 7.1 \text{ Hz}, 3\text{H})\).

\(^13\)C-NMR (75 MHz, CDCl₃): \(\delta / \text{ppm} = 166.1, 157.3 \text{ (q, J = 1.7 Hz), 151.8, 143.1, 134.9 \text{ (q, J = 4.8 Hz), 130.8, 129.2, 128.7 \text{ (q, J = 1.7 Hz), 125.0 \text{ (q, J = 32.0 Hz), 123.4 \text{ (q, J = 273.5 Hz), 122.2, 61.1, 14.2.}}})\)

IR (Diamand-ATR, neat) \(\tilde{\nu} \text{ (cm}^{-1} \text{)} = 2984, 1714, 1590, 1576, 1440, 1406, 1368, 1320, 1272, 1226, 1164, 1132, 1112, 1102, 1088, 1028, 1016, 862, 816, 804, 790, 762, 740, 706, 678\).

MS (EI, 70 eV): \(m/z \ (%) = 295 [M^+ (32), 267 (61), 250 (100), 222 (42), 202 (7), 71 (5).]

HRMS (EI) for C₁₅H₁₂F₃NO₂ (295.0820): 295.0819.
Synthesis of 3-bromo-2-cyclohexylisonicotinonitrile (48i)

According to TP1, 3-bromisonicotinonitrile (29m; 366 mg, 2.0 mmol) reacted with TMPMgCl-LiCl (11; 1.85 mL, 2.2 mmol, 1.2 M in THF) (-78 °C, 1 h). CuCN-2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (258 mg, 1.6 mmol) was added at -78 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) and extracted with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 5:1) furnished the compound 48i as yellowish oil (274 mg, 65% yield).

¹H-NMR (300 MHz, CDCl₃) δ (ppm): 8.63 (d, J = 4.9 Hz, 1H), 7.84 (d, J = 4.9 Hz, 1H), 5.90-5.98 (m, 1H), 5.61-5.68 (m, 1H), 4.08-4.15 (m, 1H), 2.00-2.17 (m, 3H), 1.78-1.89 (m, 1H), 1.53-1.72 (m, 2H).

¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 165.2, 148.3, 129.0, 127.1, 124.6, 124.3, 122.2, 115.5, 42.6, 28.4, 24.5, 21.3.

IR (Diamond-ATR, neat) ʋ (cm⁻¹): 3026, 2932, 2860, 2836, 2238, 2192, 1680, 1650, 1568, 1536, 1446, 1432, 1394, 1382, 1344, 1326, 1298, 1266, 1238, 1192, 1156, 1136, 1114, 1082, 1060, 1048, 1022, 944, 916, 892, 838, 810, 784, 760, 744, 720, 702, 634, 618.

MS (70 eV, EI) m/z (%): 262 [M⁺] (33), 235 (100), 223 (16), 198 (21), 183 (20), 155 (11), 142 (10), 79 (5), 67 (19).

HRMS (EI) for C₁₂H₁₁BrN₂ (262.0106): 262.0115.

Synthesis of (2-methoxypyridin-3-yl)(phenyl)methanone (48j):
According to TP1, 2-methoxypyridine (29f; 218 mg, 2.0 mmol) reacted with [(tBu)NCH(iPr)(tBu)]₃Al·3LiCl (15; 6.67 mL, 2.0 mmol, 0.3 M in THF) (25 °C, 2 h). The reaction mixture was cooled to -40 °C and a solution of ZnCl₂ (2.2 mL, 2.2 mmol, 1 M in THF) was added followed by the addition of CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF). After stirring for 20 min at the same temperature benzyol chloride (308 mg, 1.6 mmol) was added, the reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) and extracted with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 5:1) furnished the compound 48j as white solid (341 mg, 80% yield).

M. p. (°C): 80.2-81.5.

¹H-NMR (300 MHz, CDCl₃): δ / (ppm): 8.31 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.71 (dd, J = 7.3, 2.1 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.47 – 7.40 (m, 2H), 7.00 (dd, J = 7.3 Hz, 5.1 Hz, 1H), 3.87 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / (ppm): 194.7, 161.1, 149.2, 138.9, 137.2, 133.3, 129.7, 128.4, 122.7, 116.5, 53.7.

IR (Diamond-ATR, neat) ʋ (cm⁻¹): 2984, 1654, 1596, 1576, 1468, 1448, 1406, 1322, 1312, 1302, 1284, 1256, 1232, 1180, 1152, 1104, 1014, 952, 944, 930, 858, 830, 816, 784, 770, 706, 686, 646.

MS (70 eV, EI) m/z (%): 213 [M⁺] (92), 184 (13), 136 (94), 122 (95), 105 (100), 77 (64), 60 (10), 57 (10), 51 (15), 45 (10), 43 (52).

HRMS (EI) for C₁₃H₁₁NO₂ (213.0790): 213.0784.

Synthesis of 4-(6-methoxyquinolin-5-yl)benzonitrile (48k)

According to TP1, 6-methoxyquinoline (29n; 318 mg, 2.0 mmol) reacted with [(tBu)NCH(iPr)(tBu)]₃Al·3LiCl (15; 2.0 mmol, 6.67 mL, 0.3 M in THF) (-78 °C, 1 h). ZnCl₂
(2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (4 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (503 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with Et$_2$O (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/EtOAc, 4:1) furnished the compound 48k as white solid (354 mg, 68% yield).

M. p. (°C): 183.4-185.0.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 8.77 (dd, $J$ = 4.3, 1.7 Hz, 1H), 8.11 (dd, $J$ = 8.3, 1.8 Hz, 1H), 7.82 – 7.73 (m, 4H), 7.41 – 7.37 (m, 2H), 7.14 (d, $J$ = 2.8 Hz, 1H), 3.97 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 157.2, 148.0, 143.8, 141.7, 140.2, 135.3, 131.8, 131.3, 130.1, 123.1, 121.7, 119.1, 111.2, 106.0, 55.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 2224, 1606, 1596, 1472, 1444, 1426, 1400, 1380, 1372, 1340, 1312, 1234, 1212, 1202, 1188, 1176, 1150, 1122, 1114, 1046, 1026, 988, 964, 918, 882, 850, 836, 798, 784, 770, 744, 660, 642, 604.

MS (70 eV, EI) $m/z$ (%): 260 [M$^+$] (65), 259 (100), 244 (9), 229 (10), 216 (24).

HRMS (EI) for C$_{17}$H$_{12}$N$_2$O (260.0950): 260.0943.

7. Preparation of functionalized N-heterocycles by complexation with BF$_3$·OEt$_2$ and subsequent addition of TMP-base

Synthesis of 2-iodo-6-phenylpyridine (49a)

![Chemical structure of 2-iodo-6-phenylpyridine (49a)]

According to TP2, a mixture of 2-phenylpyridine (29h; 310 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 3 mmol, 1.2 M in THF) (0 °C, 30 h). The reaction mixture was cooled to -30 °C and a solution of iodine (4 mmol, 1 g) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched
with sat. aqueous NH$_4$Cl solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 40:1) furnished the compound 49a as yellowish solid (467 mg, 83% yield).

**M. p. (°C):** 81.7-82.9.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm): 7.93-7.99 (m, 2H), 7.67 (dd, $J = 7.8$, 0.8 Hz, 1H), 7.63 (dd, $J = 7.8$, 0.8 Hz, 1H), 7.38-7.49 (m, 3H), 7.37 (t, $J = 7.8$ Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm): 159.0, 138.0, 137.7, 133.1, 129.5, 128.8, 126.9, 119.3, 118.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3050, 3032, 1568, 1542, 1422, 1384, 1166, 1114, 1048, 980, 972, 800, 774, 756, 728, 696, 662, 622, 612.

MS (70 eV, EI) $m/z$ (%): 281 [M$^+$] (55), 154 (100), 127 (26), 77 (8).

HRMS (EI) for C$_{11}$H$_8$NI (280.9701): (280.9693).

**Synthesis of 3-fluoro-4-iodopyridine (49b)**

According to TP2, a mixture of 3-fluoropyridine (29i; 97 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (11; 0.9 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 30 min). A solution of iodine (0.5 g, 2 mmol) in THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL), NH$_3$ (conc.) (0.5 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 10:1) furnished the compound 49b as white solid (125 mg, 56% yield).

**M. p. (°C):** 95.5-96.1.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.34 (s, 1H), 8.04 (d, $J = 4.7$ Hz, 1H), 7.72 (t, $J = 4.9$ Hz, 1H).
**C. Experimental Section**

**13C-NMR (100 MHz, CDCl<sub>3</sub>):** δ / (ppm) = 160.8, 158.2, 145.9, 145.9, 137.6, 137.3, 134.1, 92.6, 92.4.

**IR (Diamond-ATR, neat) ν (cm<sup>-1</sup>):** 3060, 1570, 1550, 1475, 1415, 1260, 1202, 1050, 1040.

**MS (70 eV, EI) m/z (%):** 223 [M<sup>+</sup>] (100), 127 (7), 96 (26), 69 (22).

**HRMS (EI) for C<sub>5</sub>H<sub>3</sub>FIN:** 222.9294.

**Synthesis of ethyl 4-(3-fluoropyridin-4-yl)benzoate (49c)**

\[
\begin{align*}
\text{CO}_2\text{Et} & \\
\text{F} & \\
\text{N} & \\
\end{align*}
\]

According to TP2, a mixture of 3-fluoropyridine (29i; 97 mg, 1.0 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 30 min). ZnCl<sub>2</sub> (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)<sub>2</sub> (28 mg, 5 mol%) and P(o-fur)<sub>3</sub> (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH<sub>4</sub>Cl solution (4.5 mL) and NH<sub>3</sub> (conc.) (0.5 mL) followed by extraction with Et<sub>2</sub>O (3×20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et<sub>2</sub>O, 3:1) furnished the compound 49c as yellow solid (145 mg, 74% yield).

**M. p. (°C):** 60.4-62.9.

**1H-NMR (300 MHz, CDCl<sub>3</sub>):** δ / (ppm): 8.56 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.10-8.18 (m, 2H), 7.63-7.70 (m, 2H), 7.37-7.45 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H).

**13C-NMR (75 MHz, CDCl<sub>3</sub>):** δ / (ppm): 166.0, 156.5 (d, J = 258.2 Hz), 145.0 (d, J = 5.4 Hz), 139.0 (d, J = 25.8 Hz), 137.1 (d, J = 1.3 Hz), 135.2 (d, J = 10.6 Hz), 131.2, 130.0, 128.8 (d, J = 3.4 Hz), 124.1, 61.3, 14.3.
**Experimental Section**

**IR (Diamond-ATR, neat) \( \tilde{\nu} \) (cm\(^{-1}\)):** 2986, 2908, 1710, 1668, 1604, 1576, 1546, 1482, 1464, 1450, 1418, 1400, 1362, 1312, 1280, 1268, 1234, 1210, 1186, 1156, 1130, 1110, 1062, 1034, 1020, 1012, 972, 912, 882, 868, 858, 842, 828, 776, 736, 712, 698, 672, 644, 618.

**HRMS (ESI) for \( \text{C}_{14}\text{H}_{13}\text{FNO}_{2} \) (M+H\(^{+}\)) (246.0930):** 246.0923.

**Synthesis of (3-chloropyridin-4-yl)(2-furyl)methanone (49d)**

![Chemical Structure of 49d](image)

According to **TP2**, a mixture of 3-chloropyridine (\( 29j; \) 228 mg, 2.0 mmol) and BF\(_3\)-OEt\(_2\) (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (\( 11; \) 1.8 mL, 2.2 mmol, 1.2 M in THF) (-78 °C, 45 min). CuCN-2LiCl (2.2 mL, 2.2 mmol, 1 M solution in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 2-furoyl chloride (209 mg, 1.6 mmol) was added at -78 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH\(_4\)Cl solution (9 mL) and NH\(_3\) (conc.) (1 mL) and extracted with Et\(_2\)O (3x30 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and after filtration the solvents were evaporated \textit{in vacuo}. Flash column chromatographical purification (silica gel, pentane/Et\(_2\)O, 1:1) furnished the compound 49d as brown oil (259 mg, 78% yield).

**M. p. (°C):** 64.3-65.6.

**\(^1\)H-NMR (300 MHz, CDCl\(_3\)):** \( \delta / \text{(ppm)}: \) 8.71 (s, 1H), 8.61 (d, \( J = 4.9 \text{ Hz}, 1H \)), 7.71 (dd, \( J = 1.8, 0.8 \text{ Hz}, 1H \)), 7.37 (dd, \( J = 4.9, 0.7 \text{ Hz}, 1H \)), 7.14 (dd, \( J = 3.7, 0.8 \text{ Hz}, 1H \)), 6.61 (dd, \( J = 3.7, 0.8 \text{ Hz}, 1H \)).

**\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)):** \( \delta / \text{(ppm)}: \) 179.3, 151.1, 150.0, 148.8, 147.4, 144.6, 128.8, 122.6, 122.1, 113.1.

**IR (Diamond-ATR, neat) \( \tilde{\nu} \) (cm\(^{-1}\)):** 3142, 3118, 3074, 2362, 1634, 1584, 1562, 1460, 1400, 1394, 1324, 1272, 1246, 1202, 1170, 1148, 1100, 1080, 1036, 970, 958, 918, 892, 876, 838, 794, 772, 754, 720, 666, 616.

**MS (70 eV, EI) m/z (%):** 207 [M\(^{+}\)] (43), 141 (15), 127 (14), 111 (10), 99 (32), 95 (95), 85 (65).

**HRMS (EI) for \( \text{C}_{10}\text{H}_{6}\text{ClNO}_{2} \) (207.0087):** 207.0075.
C. Experimental Section

Synthesis of ethyl 4-(3-chloropyridin-4-yl)benzoate (49e)

According to TP2, a mixture of 3-chloropyridine (29j; 97 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (11; 0.92 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 45 min). ZnCl$_2$ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by extraction with Et$_2$O (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 3:1) furnished the compound 49e as yellow solid (200 mg, 95% yield).

M. p. (°C): 64.9-66.7.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / (ppm) = 8.70 (s, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.16 (m, J = 8.5 Hz, 2H), 7.55 (m, J = 8.5 Hz, 2H), 7.29 (d, J = 4.9 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / (ppm) = 165.9, 150.0, 147.7, 146.7, 140.6, 130.8, 130.0, 129.6, 128.9, 125.0, 61.2, 14.3.

IR (Diamond-ATR, neat) ν (cm$^{-1}$): 2982, 2908, 1710, 1670, 1612, 1584, 1474, 1450, 1408, 1396, 1364, 1310, 1278, 1214, 1188, 1180, 1128, 1108, 1044, 1028, 1012, 974, 868, 856, 844, 838, 774, 740, 716, 700, 648, 636.

HRMS (ESI) for C$_{14}$H$_{13}$ClNO$_2$ (M+H$^+$) (262.0635): 262.0627.

Synthesis of 4-[3-(trifluoromethyl)phenyl]nicotinonitrile (49f)

$^1$H-NMR (300 MHz, CDCl$_3$): δ / (ppm) = 8.70 (s, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.16 (m, J = 8.5 Hz, 2H), 7.55 (m, J = 8.5 Hz, 2H), 7.29 (d, J = 4.9 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / (ppm) = 165.9, 150.0, 147.7, 146.7, 140.6, 130.8, 130.0, 129.6, 128.9, 125.0, 61.2, 14.3.

IR (Diamond-ATR, neat) ν (cm$^{-1}$): 2982, 2908, 1710, 1670, 1612, 1584, 1474, 1450, 1408, 1396, 1364, 1310, 1278, 1214, 1188, 1180, 1128, 1108, 1044, 1028, 1012, 974, 868, 856, 844, 838, 774, 740, 716, 700, 648, 636.

HRMS (ESI) for C$_{14}$H$_{13}$ClNO$_2$ (M+H$^+$) (262.0635): 262.0627.
According to TP2, a mixture of nicotinonitrile (29k; 208 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMP$_2$Zn-2MgCl$_2$·2LiCl (14; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-30 °C, 30 min). Pd(db)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (4 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (435 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with Et$_2$O (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 1:2) furnished the compound 49f as white solid (313 mg, 78% yield).

M. p. (°C): 125.6-128.2.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / (ppm): 8.98 (s, 1H), 8.86 (d, $J = 5.2$ Hz, 1H), 7.75-7.87 (m, 3H), 7.64-7.73 (m, 1H), 7.49 (d, $J = 5.2$ Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / (ppm): 154.0, 153.1, 150.7, 136.2, 131.7 (q, $J = 33.0$ Hz), 131.7 (q, $J = 1.3$ Hz), 129.8, 127.0 (q, $J = 3.7$ Hz), 125.3 (q, $J = 3.8$ Hz), 123.7, 123.6 (q, $J = 272.6$ Hz), 116.1, 108.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3070, 2226, 1614, 1584, 1544, 1482, 1430, 1406, 1334, 1308, 1266, 1230, 1188, 1166, 1110, 1100, 1078, 1042, 1000, 934, 924, 852, 838, 806, 776, 756, 724, 700, 658, 624.

MS (70 eV, EI) m/z (%): 248 [M$^+$] (100), 228 (11), 221 (7), 201 (12), 152 (3).

HRMS (EI) for C$_{13}$H$_7$F$_3$N$_2$ (248.0561): 248.0550.

Synthesis of 4-(1-phenylvinyl)nicotinonitrile (49g)

According to TP2, a mixture of nicotinonitrile (29k; 104 mg, 1 mmol) reacted with TMP$_2$Zn-2MgCl$_2$·2LiCl (14; 1.6 mL, 1.1 mmol, 0.71 M in THF) (-30 °C, 30 min). Pd(db)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of (1-iodovinyl)benzene (184 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was
warmed to 25 °C and stirred for 48 h at the same temperature. The reaction mixture was
quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by
extraction with Et$_2$O (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and
after filtration the solvents were evaporated in vacuo. Flash column chromatographical
purification (silica gel, pentane/Et$_2$O, 2:1) furnished the product 49g as yellowish oil (115 mg,
70% yield).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta / \text{ppm} = 8.92$ (s, 1H), 8.76 (d, $J = 5.1$ Hz, 1H), 7.34-7.41 (m,
3H), 7.32 (d, $J = 5.3$ Hz, 1H), 7.24 (dd, $J = 6.7, 2.9$ Hz, 2H), 5.97 (s, 1H), 5.64 (s, 1H).
$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta / \text{ppm} = 153.6, 152.9, 152.4, 144.7, 138.2, 128.8, 128.7,
127.3, 124.2, 119.9, 115.8, 109.6.

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

MS (EI, 70 eV): $m/z$ (%) = 206 [M+] (100), 151 (10), 77 (8), 57 (11).

HRMS (EI) for C$_{14}$H$_{10}$N$_2$ (206.0844): 206.0835.

**Synthesis of 4-iodonicotinonitrile (49h)**

According to TP2, a mixture of nicotinonitrile (29k; 208 mg, 2.0 mmol) and BF$_3$·OEt$_2$
(312 mg, 2.2 mmol) reacted with TMP$_2$Zn·2MgCl$_2$·2LiCl (14; 3.1 mL, 2.2 mmol, 0.71 M in
THF) (-30 °C, 30 min). A solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and
slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl
solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (3 mL) followed by
extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and
after filtration the solvents were evaporated in vacuo. Flash column chromatographical
purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 49h as white solid
(355 mg, 77% yield). The analytical data were found to match literature data.$^{134}$

M. p. (°C): 159.9-161.3.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta / \text{ppm} = 8.73$ (s, 1H), 8.39 (d, $J = 5.2$ Hz, 1H), 7.92 (d, $J =
5.4$ Hz, 1H).

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C-NMR (75 MHz, CDCl₃): \( \delta / \text{ppm} = 153.1, 152.1, 134.0, 118.8, 117.3, 109.6 \).

IR (Diamond-ATR, neat) \( \nu (\text{cm}^{-1}) \): 3254, 3084, 2960, 2242, 1612, 1584, 1568, 1502, 1486, 1450, 1436, 1426, 1368, 1314, 1292, 1278, 1266, 1232, 1192, 1156, 1138, 1046, 1000, 988, 950, 898, 804, 778, 754, 728, 702, 658.

MS (70 eV, EI) \( m/z \) (%): 230 [M⁺] (100), 127 (10), 103 (77), 75 (20).

HRMS (EI) for C₆H₃IN₂ (229.9341): 229.9339.

Synthesis of ethyl 4-(3-(trifluoromethyl)pyridin-4-yl)benzoate (49i)

According to TP2, a mixture of 3-(trifluoromethyl)pyridine (29i; 147 mg, 1.0 mmol) and BF₃·OEt₂ was reacted with TMPMgCl-LiCl (11; 0.8 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 10 min). ZnCl₂ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)₂ (28 mg, 5 mol%) and P(o-fur)₃ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was slowly warmed to 55 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL) and NH₃ (conc.) (0.5 mL) followed by extraction with Et₂O (3×30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 10:1) furnished the compound 49i as white solid (154 mg, 65% yield).

M. p. (°C): 68.8-80.5.

\(^1\)H-NMR (300 MHz, CDCl₃): \( \delta / \text{ppm} = 8.98 \text{ (s, 1H)}, 8.10-8.19 \text{ (m, 4H)}, 8.02 \text{ (dd, } J = 8.3, 1.7 \text{ Hz, 1H)}, 7.85-7.95 \text{ (m, 1H)}, 4.42 \text{ (q, } J = 7.1 \text{ Hz, 2H)}, 1.43 \text{ (t, } J = 7.2 \text{ Hz, 3H}).

\(^13\)C-NMR (75 MHz, CDCl₃): \( \delta / \text{ppm} = 166.1, 159.4 \text{ (q, } J = 1.7 \text{ Hz)}, 146.7 \text{ (q, } J = 3.9 \text{ Hz)}, 141.7, 134.1 \text{ (q, } J = 3.7 \text{ Hz)}, 131.8, 130.1, 127.2, 125.5 \text{ (q, } J = 33.1 \text{ Hz)}, 123.6 \text{ (q, } J = 272.4 \text{ Hz)}, 120.4, 61.2, 14.3 \).
C. Experimental Section

**IR (Diamand-ATR, neat) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2988, 2400, 1712, 1602, 1586, 1566, 1512, 1470, 1448, 1414, 1386, 1374, 1322, 1278, 1262, 1242, 1168, 1130, 1096, 1082, 1036, 1010, 966, 944, 874, 866, 836, 786, 748, 694, 676, 644, 628, 612.

**MS (EI, 70 eV):** m/z (%) = 295 [M\(^+\)] (42), 267 (53), 250 (100), 222 (35), 202 (6), 71 (3).

**HRMS (EI) for C\(_{15}\)H\(_{12}\)F\(_{3}\)NO\(_2\) (295.0820):** 295.0809.

**Synthesis of 3-bromo-5-cyclohex-2-en-1-ylisonicotinonitrile (49j)**

According to TP2, a mixture of 3-bromoisonicotinonitrile (29m; 366 mg, 2.0 mmol) and BF\(_3\)-OEt\(_2\) (312 mg, 2.2 mmol) reacted with TMP\(_2\)Zn·2MgCl\(_2\)-2LiCl (14; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-78 °C, 1 h). CuCN-2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (258 mg, 1.6 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH\(_4\)Cl solution (9 mL) and NH\(_3\) (conc.) (1 mL) and extracted with Et\(_2\)O (3x30 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et\(_2\)O, 5:1) furnished the compound 49j as yellowish oil (266 mg, 63% yield).

**\(^1\)H-NMR (300 MHz, CDCl\(_3\)):** \( \delta \) (ppm): 8.72 (s, 1H), 8.56 (s, 1H), 5.97-6.13 (m, 1H), 5.55-5.70 (m, 1H), 3.72-3.90 (m, 1H), 2.02-2.26 (m, 3H), 1.47-1.80 (m, 3H).

**\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)):** \( \delta \) (ppm): 150.4, 149.7, 148.3, 145.6, 131.3, 125.8, 122.7, 113.9, 38.8, 31.0, 24.6, 20.5.

**IR (Diamond-ATR, neat) \( \tilde{\nu} \) (cm\(^{-1}\)):** 3024, 2932, 2860, 2836, 2236, 1650, 1528, 1448, 1432, 1404, 1344, 1302, 1272, 1248, 1222, 1198, 1160, 1130, 1058, 1044, 996, 932, 906, 894, 882, 856, 842, 802, 780, 754, 744, 724, 714, 626.

**MS (70 eV, EI) m/z (%):** 263 [M+H\(^+\)] (100), 247 (49), 235 (40), 211 (8), 183 (10), 166 (28), 155 (12), 142 (14), 54 (18).

**HRMS (EI) for C\(_{12}\)H\(_{11}\)BrN\(_2\) (262.0106):** 262.0114.
Synthesis of 2-iodo-6-methoxypyridine (49k)

According to TP2, a mixture of 2-methoxypyridine (29f; 218 mg, 2.0 mmol) and BF₃·OEt₂ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 60 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL), NH₃ (conc.) (1 mL) and sat. aqueous Na₂S₂O₃ solution (2 mL) followed by extraction with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 150:1) furnished the compound 49k as yellowish solid (353 mg, 75% yield).

M. p. (°C): 49.1-50.3.

$^{1}$H-NMR (300 MHz, CDCl₃): δ / (ppm): 7.29 (dd, J = 7.5, 0.7 Hz, 1H), 7.13-7.19 (m, 1H), 6.67 (dd, J = 8.2, 0.9 Hz, 1H), 3.90 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl₃): δ / (ppm): 163.4, 139.6, 127.5, 113.7, 109.9, 54.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm⁻¹): 3010, 2980, 1590, 1576, 1548, 1458, 1436, 1406, 1390, 1306, 1286, 1252, 1220, 1190, 1154, 1114, 1072, 1022, 980, 878, 780, 720, 652, 606.

HRMS (ESI) for C₆H₇INO (M+H⁺) (235.9572): 235.9566.

Synthesis of (4-methoxyphenyl)(6-methoxyquinolin-2-yl)methanone (49l):

According to TP2, a mixture of 6-methoxyquinoline (29n; 318 mg, 2.0 mmol) and BF₃·OEt₂ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.83 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -40 °C and CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 4-methoxybenzoyl chloride (273 mg, 1.6 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for
12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) and extracted with Et₂O (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/EtOAc, 2:1) furnished the compound as white solid (441 mg, 94% yield).

M. p. (°C): 138.1-139.3.

H-NMR (300 MHz, CDCl₃): δ / (ppm): 8.27 (ddd, J = 9.4, 2.8, 2.4 Hz, 2H), 8.21 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 9.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 9.2, 2.8 Hz, 1H), 7.13 (d, J = 2.8 Hz, 1H), 6.98 (ddd, J = 9.4, 2.8, 2.4 Hz, 2H), 3.97 (s, 3H), 3.89 (s, 3H).

C-NMR (75 MHz, CDCl₃): δ / (ppm): 191.8, 163.6, 159.3, 152.8, 142.4, 135.7, 133.9, 131.7, 130.2, 129.2, 123.2, 121.4, 113.5, 104.9, 55.7, 55.5.

IR (Diamond-ATR, neat) ν (cm⁻¹): 3006, 2932, 2842, 1646, 1620, 1596, 1512, 1498, 1480, 1434, 1406, 1384, 1344, 1330, 1308, 1292, 1256, 1232, 1186, 1162, 1134, 1120, 1108, 1022, 972, 944, 904, 850, 830, 812, 792, 782, 754, 732, 710, 652, 634, 612.

MS (70 eV, EI) m/z (%): 293 [M⁺] (84), 278 (13), 265 (87), 250 (23), 234 (15), 135 (100), 107 (13), 92 (11), 77 (15).

HRMS (EI) for C₁₈H₁₅N(O₃) (293.1052): 293.1046.

8. Preparation of the isopropylpyridine derivatives

Synthesis of 2-iodo-6-isopropylpyridine (53)

According to TP2, a mixture of 2-isopropylpyridine (50; 121 mg, 1.0 mmol) and BF₃·OEt₂ (156 mg, 1.1 mmol) reacted with TMP₂Mg:2LiCl (13; 2.5 mL, 1.5 mmol, 0.6 m in THF) (-78 °C, 15 h). A solution of iodine (0.5 g, 2 mmol) in THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL), NH₃ (conc.) (0.5 mL) and sat. aqueous Na₂S₂O₃ solution (2 mL) followed by extraction with Et₂O (3x20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 100:1) furnished the compound 53 as colorless oil (173 mg, 70% yield).
C. Experimental Section

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 7.59 (d, $J = 7.67$ Hz, 1H), 7.30 (s, 1H), 7.16-7.22 (m, 1H), 3.03-3.18 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 169.8, 138.2, 132.4, 119.7, 117.1, 36.0, 22.5.

Synthesis of 2-(4-methoxyphenyl)-N,N-dimethylpyridin-4-amine (54a)

According to TP2, a mixture of 4-isopropylpyridine (51; 242 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMP$_2$Mg·2LiCl (13; 5 mL, 3.0 mmol, 0.6 M in THF) (-78 °C, 40 h). ZnCl$_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) was then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (374 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with Et$_2$O (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 54a as yellow oil (297 mg, 81% yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.55 (d, $J = 5.1$ Hz, 1H), 7.96 (m, 1H), 7.52 (s, 1H), 7.06 (dd, $J = 5.1, 1.3$ Hz, 1H), 7.00 (m, $J = 9.0$ Hz, 2H), 3.86 (s, 3H), 2.85-3.03 (m, 1H), 1.32 (s, 3H), 1.29 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 160.3, 158.4, 157.0, 149.2, 132.1, 128.2, 119.8, 118.3, 114.0, 55.3, 33.8, 23.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 2962, 1600, 1580, 1552, 1514, 1472, 1460, 1422, 1400, 1364, 1306, 1274, 1246, 1202, 1174, 1108, 1054, 1030, 992, 904, 828, 780, 756, 648, 632.

MS (70 eV, EI) m/z (%): 228 [M$^+$] (15), 212 (100), 185 (11), 169 (9).

HRMS (EI) for C$_{14}$H$_{16}$N$_2$O (228.1263): 228.1333.
Synthesis of 2-iodo-4-isopropylpyridine (54b)

According to TP2, a mixture of 4-isopropylpyridine (51; 121 mg, 1.0 mmol) and BF₃·OEt₂ (156 mg, 1.1 mmol) reacted with TMP₂Mg·2LiCl (13; 2.5 mL, 1.5 mmol, 0.6 M in THF) (-78 °C, 40 h). A solution of iodine (0.5 g, 2 mmol) in THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL), NH₃ (conc.) (0.5 mL) and sat. aqueous Na₂S₂O₃ solution (2 mL) followed by extraction with Et₂O (3x20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et₂O, 25:1) furnished the compound 54b as yellow oil (178 mg, 72% yield).

¹H-NMR (300 MHz, CDCl₃): δ / (ppm) = 8.26 (d, J = 5.1 Hz, 1H), 7.6 (s, 1H), 7.14 (dd, J = 5.2, 1.3 Hz, 1H), 2.74-2.91 (m, 1H), 1.26 (s, 3H), 1.23 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / (ppm) = 160.2, 150.1, 133.3, 121.7, 118.0, 33.3, 22.8.

IR (Diamond-ATR, neat) ν (cm⁻¹): 2962, 2926, 2870, 1580, 1534, 1454, 1388, 1378, 1364, 1324, 1282, 1234, 1208, 1148, 1124, 1074, 986, 898, 880, 838, 784, 776, 734, 686.

9. Preparation of the methylpyridine derivatives

Synthesis of 2-(bis(trimethylsilyl)methyl)pyridine (58)

This compound was prepared following the literature procedure. The analytical data were found to match literature data.

¹H-NMR (400 MHz, CDCl₃): δ / (ppm): 8.30 (dd, J = 5.2 Hz, 1H), 7.37 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.80-6.85 (m, 2H), 1.85 (s, 1H), -0.02 (s, 18H).
Synthesis of ethyl 4-(6-methylpyridin-2-yl)benzoate (59)

According to TP2, a mixture of 2-(bis(trimethylsilyl)methyl)pyridine (58; 238 mg, 1.0 mmol) and BF$_3$-OEt$_2$ (156 mg, 1.1 mmol) reacted with TMP$_2$MgCl·2LiCl (14; 2.5 mL, 1.5 mmol, 0.6 M in THF) (-78 °C, 15 h). ZnCl$_2$ (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise at -78 °C and stirred for 30 min at the same temperature. Pd(dba)$_2$ (28 mg, 5 mol%) and P(o-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. The crude mixture was diluted in THF (5 mL) and TBAF (1 g, 3.2 mmol) was added. After stirring for 12 h the reaction mixture was quenched with sat. aqueous NaCl solution (5 mL) followed by the extraction with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane / Et$_2$O = 10:1) afforded the product 59 (159 mg, 82%) as colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 7.99-8.20 (m, 4H), 7.61-7.71 (m, 1H), 7.51-7.61 (m, 1H), 7.14 (d, $J = 5.6$ Hz, 1H), 4.33-4.48 (m, 2H), 2.64 (d, $J = 1.3$ Hz, 3H), 1.41 (t, $J = 5.8$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 166.4, 158.6, 155.6, 143.6, 137.0, 130.5, 129.9, 126.8, 122.4, 118.0, 61.0, 24.6, 14.3.

MS (70 eV, EI) m/z (%): 241 [M$^+$] (36), 196 (80), 168 (31), 113 (18), 97 (36), 85 (58), 71 (83), 57 (100).

HRMS (EI) for C$_{15}$H$_{15}$NO$_2$ (241.1103): (241.1091).
10. Preparation of benzylpyridine derivatives

Synthesis of 2-(4-methoxybenzyl)pyridine (60a)

According to TP1, 2-methylpyridine (56c; 186 mg, 2.0 mmol) was reacted with TMPZn-LiCl (12; 2.3 mL, 3.0 mmol, 1.3 M in THF) (25 °C, 1 h). Pd(dba)$_2$ (22 mg, 2 mol%) and S-Phos (33 mg, 4 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-bromo-4-methoxybenzene (61a; 299 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 50 °C and stirred for 3 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (10 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, hexane/Et$_2$O, 7:3) furnished the compound 60a as yellow oil (303 mg, 95% yield). The analytical data were found to match literature data.\textsuperscript{136}

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.50-8.56 (m, 1H), 7.56 (td, $J$ = 7.7, 1.9 Hz, 1H), 7.14-7.20 (m, 2H), 7.05-7.12 (m, 2H), 6.80-6.87 (m, 2H), 4.09 (s, 2H), 3.77 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 161.4, 158.2, 149.3, 136.5, 131.6, 130.0, 122.9, 121.1, 114.0, 55.2, 43.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3006, 2954, 2932, 2908, 2834, 2360, 2340, 1736, 1610, 1588, 1568, 1540, 1510, 1472, 1434, 1374, 1300, 1244, 1176, 1148, 1108, 1090, 1034, 994, 916, 852, 842, 806, 782, 748, 726, 712, 628, 604.

MS (70 eV, EI) $m/z$ (%): 199 [M$^+$] (57), 198 (100), 184 (52), 167 (12), 156 (15), 121 (15).

HRMS (EI) for C$_{13}$H$_{13}$NO (199.0997): 199.0975.

Synthesis of 2-(3-chlorobenzyl)pyridine (60b)

According to TP1, 2-methylpyridine (56c; 186 mg, 2.0 mmol) was reacted with TMPZn-LiCl (12; 2.3 mL, 3.0 mmol, 1.3 M in THF) (25 °C, 1 h). Pd(OAc)$_2$ (9 mg, 2 mol%) and S-Phos (33 mg, 4 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-bromo-3-chlorobenzene (61b; 306 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 50 °C and stirred for 6 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (10 mL) followed by extraction with Et$_2$O (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, hexane/Et$_2$O, 7:3) furnished the compound 60b as yellow oil (216 mg, 66% yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.55 (d, $J = 4.4$ Hz, 1H), 7.59 (td, $J = 7.7, 1.8$ Hz, 1H), 7.08-7.24 (m, 6H), 4.12 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 160.1, 149.5, 141.5, 136.7, 134.3, 129.8, 129.2, 127.3, 126.6, 123.1, 121.5, 44.2.

IR (Diamond-ATR, neat) $\nu$ (cm$^{-1}$): 3062, 3010, 2970, 2930, 2362, 2340, 1956, 1870, 1736, 1718, 1590, 1570, 1472, 1430, 1376, 1364, 1304, 1264, 1244, 1218, 1200, 1164, 1146, 1078, 1050, 996, 926, 866, 834, 776, 746, 694, 682, 634, 618.

MS (70 eV, EI) $m/z$ (%): 203 [M$^+$] (22), 202 (100), 167 (71), 139 (4), 84 (11).

HRMS (EI) for C$_{12}$H$_{10}$ClN (203.0502): 203.0471.

Synthesis of 2-(4-fluorobenzyl)pyridine (60c)

According to TP1, 2-methylpyridine (56c; 186 mg, 2.0 mmol) was reacted with TMPZn-LiCl (12; 2.3 mL, 3.0 mmol, 1.3 M in THF) (25 °C, 1 h). Pd(OAc)$_2$ (9 mg, 2 mol%) and S-Phos (33 mg, 4 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-bromo-4-fluorobenzene (61c; 280 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 50 °C and stirred for 6 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (10 mL) followed by extraction with Et$_2$O (3×30 mL). The combined organic layers were
dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 4:1) furnished the compound 60c as brown oil (234 mg, 78% yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.52-8.56 (m, 1H), 7.58 (td, $J = 7.6$, 1.7 Hz, 1H), 7.18-7.23 (m, 2H), 7.07-7.13 (m, 2H), 6.94-7.00 (m, 2H), 4.11 (s, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 161.5 ($J = 244.6$ Hz), 160.7, 149.4, 136.6, 135.2 ($J = 3.1$ Hz), 130.5 ($J = 7.9$ Hz), 123.0, 121.3, 115.3 ($J = 21.3$ Hz), 43.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm$^{-1}$): 3068, 3046, 3008, 2924, 2362, 2340, 1892, 1738, 1600, 1588, 1570, 1506, 1472, 1434, 1416, 1298, 1216, 1158, 1098, 1050, 1016, 994, 916, 846, 812, 790, 748, 726, 708, 628.

MS (70 eV, EI) $m/z$ (%): 187 [M$^+$] (22), 186 (100), 109 (8), 93 (10), 83 (8).

HRMS (EI) for C$_{12}$H$_{10}$FN (187.0797): 187.0742.

**Synthesis of 5-(pyridin-2-ylmethyl)-1H-indole (60d)**

![Synthesis of 5-(pyridin-2-ylmethyl)-1H-indole (60d)](image.png)

According to TP1, 2-methylpyridine (56c; 186 mg, 2.0 mmol) was reacted with TMPZn-LiCl (12; 3.1 mL, 4.0 mmol, 1.3 M in THF) (25 °C, 1 h). Pd(OAc)$_2$ (9 mg, 2 mol%) and S-Phos (33 mg, 4 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 5-bromo-1H-indole (61d; 314 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 50 °C and stirred for 7 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (10 mL) followed by extraction with Et$_2$O (3×30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et$_2$O, 6:4) furnished the compound 60d as red solid (287 mg, 86% yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.51-8.57 (m, 1H), 8.19 (br, s, 1H), 7.49-7.58 (m, 2H), 7.29-7.34 (m, 1H), 7.15-7.20 (m, 1H), 7.05-7.14 (m, 3H), 6.47-6.51 (m, 1H), 4.26 (s, 2H).
**C. Experimental Section**

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 162.1, 149.1, 136.5, 134.7, 130.8, 128.2, 124.4, 123.5, 123.1, 121.0, 120.9, 111.1, 102.5, 44.8.

**IR (Diamond-ATR, neat)** $\tilde{\nu}$ (cm$^{-1}$): 3116, 3098, 3028, 3004, 2902, 2360, 2340, 1736, 1592, 1570, 1474, 1456, 1438, 1366, 1344, 1336, 1316, 1286, 1226, 1218, 1140, 1106, 1094, 1004, 916, 902, 890, 842, 816, 794, 774, 756, 736, 656, 630, 606.

**MS (70 eV, EI) m/z (%):** 208 [M$^+$] (70), 207 (100), 130 (48), 127 (18), 44 (62).

**HRMS (EI) for C$_{14}$H$_{12}$N$_2$ (208.1000):** 208.0933.

**11. Preparation of polyfunctionalized pyridine derivatives**

**Synthesis of 3-bromo-2-(cyclohex-2-en-1-yl)-5-iodoisocitononitrile (63):**

![Chemical structure](image)

According to TP1, 3-bromo-2-(cyclohex-2-en-1-yl)isonicotinonitrile (48i; 526 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (11; 2.5 mL, 3.0 mmol, 1.2 M in THF) (-30 °C, 4 h). A solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane / Et$_2$O = 10:1) furnished the compound 63 as yellow oil (521 mg, 67%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / (ppm) = 8.90 (s, 1H), 5.90-6.07 (m, 1H), 5.56-5.72 (m, 1H), 2.00-2.22 (m, 3H), 1.80-1.94 (m, 1H), 1.54-1.75 (m, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / (ppm) = 164.1, 155.5, 130.9, 129.5, 123.3, 116.7, 93.6, 42.5, 28.5, 24.6, 21.4.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1}$ = 3746, 3736, 3024, 3018, 3004, 2970, 2942, 2936, 2906, 2896, 2362, 2340, 2284, 1792, 1736, 1718, 1540, 1496, 1490, 1482, 1474, 1436, 1420, 1406, 1364, 1340, 1320, 1294, 1264, 1228, 1214, 1164, 1142, 1128, 1044, 1024, 934, 822, 722, 640, 624, 610.

**MS (EI, 70 eV) m/z (%):** 389 [M$^+$] (65), 360 (99), 359 (100), 321 (23), 308 (40), 154 (21).
Synthesis of ethyl 2-((5-bromo-4-cyano-6-(cyclohex-2-en-1-yl)-3-iodopyridin-2-yl)methyl)acrylate (64):  

According to **TP1**, 3-bromo-2-(cyclohex-2-en-1-yl)-5-iodoisonicotinonitrile (\(63;\) 389 mg, 1.0 mmol) reacted with TMP\(_2\)Zn·2MgCl\(_2\)·2LiCl (\(14;\) 1.5 mmol, 2.0 mL, 0.75 M in THF) (25 °C, 20 h). The reaction mixture was cooled to -30 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature ethyl 2-(bromomethyl)acrylate (232 mg, 1.2 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH\(_4\)Cl solution (4.5 mL) and NH\(_3\) (conc.) (0.5 mL) followed by extraction with Et\(_2\)O (3×20 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentane/Et\(_2\)O, 20:1) afforded the product \(64\) as yellow oil (311 mg, 62%).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta / (\text{ppm}) = 6.27-6.32 (\text{m}, 1\text{H}), 5.77-5.88 (\text{m}, 1\text{H}), 5.50-5.58 (\text{m}, 1\text{H}), 5.43-5.46 (\text{m}, 1\text{H}), 4.15 (\text{q}, J = 7.1 \text{Hz}, 2\text{H}), 3.92-4.03 (\text{m}, 3\text{H}), 2.00-2.12 (\text{m}, 2\text{H}), 1.90-1.98 (\text{m}, 1\text{H}), 1.80-1.89 (\text{m}, 1\text{H}), 1.59-1.75 (\text{m}, 2\text{H}), 1.14-1.31 (\text{m}, 4\text{H}).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta / (\text{ppm}) = 166.8, 163.3, 161.0, 137.8, 132.3, 129.1, 127.1, 127.1, 120.4, 117.9, 96.8, 61.2, 44.3, 42.5, 28.1, 25.0, 21.6, 14.6.

\(\text{IR (Diamond-ATR, neat): } \tilde{\nu} / \text{cm}^{-1} = 2980, 2934, 2838, 2360, 2340, 1718, 1654, 1646, 1630, 1540, 1522, 1506, 1430, 1414, 1388, 1368, 1338, 1324, 1296, 1258, 1216, 1184, 1148, 1114, 1096, 1044, 1026, 956, 916, 894, 858, 838, 824, 784, 768, 668, 658.

\(\text{MS (EI, 70 eV) m/z (%): } 501 \text{ [M}^+\text{]} (99), 500 (27), 470 (65), 426 (56), 374 (100), 346 (19), 219 (11), 192 (21).

\(\text{HRMS (EI) for } \text{C}_{18}\text{H}_{18}\text{BrIN}_2\text{O}_2 (499.9596): } 499.9589.\)
12. Preparation of functionalized DMAP derivatives

Synthesis of 4-(2,2,6,6-tetramethylpiperidin-1-yl)pyridine (65d)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with 4-iodopyrididine (205 mg, 1.0 mmol). After cooling to -40 °C, iPrMgCl·LiCl (0.90 mL, 1.1 mmol, 1.2 M in THF) was added dropwise and stirred for 30 min. ZnCl₂ (0.55 mL, 0.55 mmol, 1 M in THF) was added and the mixture was stirred for 30 min at the same temperature. CuCl₂LiCl (1.1 mL, 1.1 mmol, 1.0 M in THF) was added dropwise at -50 °C and the resulting mixture was stirred for an additional 30 min. N-lithium tetramethylpiperidine (2.0 mmol; prepared by adding nBuLi (2 mmol) to a 0.5 M solution of tetramethylpiperidine in THF (284 mg, 2 mmol) at 0 °C and stirring for 30 min) was added dropwise to the resulting cuprate, and the mixture was stirred for 1 h at -50 °C. The reaction mixture was cooled to –78 °C, then a solution of PhI(OAc)₂ (354 mg, 1.1 mmol) in dry THF (10 mL) was added slowly over a period of 60 min. The reaction mixture was then warmed to -50 °C and stirred for 3 h. Et₂O (100 mL) was poured into the crude reaction mixture. The organic phase was washed with 2 x 10 mL portions of aqueous NH₄OH (2.0 M) and extracted with Et₂O. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Flash column chromatographical purification (Al₂O₃ III, pentane/ether; 1:5) furnished the product 65d as yellow solid (65 mg, 30%).

M. p. (°C): 52.7-54.7.

¹H-NMR (400 MHz, D₆-DMSO): δ / ppm = 8.43-8.51 (m, 2H), 7.12-7.17 (m, 2H), 1.65-1.73 (m, 2H), 1.48-1.54 (m, 4H), 0.97 (s, 12H).

¹³C-NMR (100 MHz, D₆-DMSO): δ / ppm = 154.1, 149.8, 129.0, 53.6, 41.3, 29.3, 17.6.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3077, 2999, 2962, 2926, 2865, 2852, 2361, 2338, 1934, 1738, 1641, 1586, 1539, 1490, 1456, 1406, 1377, 1364, 1353, 1278, 1245, 1210, 1188, 1174, 1128, 1082, 1060, 1036, 996, 972, 924, 914, 863, 831, 775, 670, 658.

MS (EI, 70 eV): m/z (%) = 218 [M⁺] (4), 203 (100), 147 (45), 135 (59), 126 (36), 69 (43).

HRMS (EI) for C₁₄H₂₂N₂ (218.1783): (218.1775).
**Synthesis of 2-iodo-N,N-dimethylpyridin-4-amine (66a)**

![Chemical structure](image)

According to **TP2**, a mixture of DMAP (65; 244 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc) afforded the product **66a** (323 mg, 72%) as yellow oil.

**$^1$H-NMR (300 MHz, CDCl$_3$):** δ / ppm = 7.89 (d, $J = 6.1$ Hz, 1H), 6.88 (d, $J = 2.2$ Hz, 1H), 6.43 (dd, $J = 6.0$, 2.3 Hz, 1H), 2.96 (s, 6H).

**$^{13}$C-NMR (100 MHz, CDCl$_3$):** δ / ppm = 154.8, 149.5, 119.2, 116.4, 105.5, 39.1.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1}$ = 3008, 2882, 2816, 1580, 1506, 1436, 1394, 1372, 1294, 1260, 1220, 1124, 1064, 970, 956, 806, 780, 682.

**MS (EI, 70 eV):** m/z (%) = 248 [M$^+$] (98), 121 (78), 106 (17), 95 (14), 61 (14), 43 (100).

**HRMS (EI) for C$_7$H$_9$IN$_2$:** (247.9810); (247.9808).

**Synthesis of 2-chloro-N,N-dimethylpyridin-4-amine (66b)**

![Chemical structure](image)

According to **TP2**, a mixture of DMAP (65; 244 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). C$_2$Cl$_3$F$_3$ (412 mg, 2.2 mmol) dissolved in THF (3 mL) was added at 0 °C and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic
layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, hexane/EtOAc, 1:5) afforded the product 66b (219 mg, 70%) as yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$/ ppm = 7.94 (d, $J$ = 5.8 Hz, 1H), 6.44 (d, $J$ = 2.2 Hz, 1H), 6.38 (dd, $J$ = 6.1, 2.2 Hz, 1H), 2.97 (s, 6H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$/ ppm = 156.0, 152.1, 148.9, 105.8, 105.3, 39.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 2922, 2360, 1918, 1594, 1520, 1444, 1420, 1404, 1384, 1296, 1270, 1224, 1188, 1134, 1080, 1066, 980, 808, 716, 698, 612.

MS (EI, 70 eV): m/z (%) = 156 [M$^+$] (66), 155 (100), 119 (5), 92 (8), 57 (7).

HRMS (EI) for C$_7$H$_9$ClN$_2$ (156.0454): 156.0436.

**Synthesis of 2-(4-methoxyphenyl)-N,N-dimethylpyridin-4-amine (66c)**

According to TP2, a mixture of DMAP (65; 244 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -30 °C and ZnCl$_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (374 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with Et$_2$O (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, hexane/EtOAc, 1:5) afforded the product 66c (295 mg, 81%) as yellow solid.

M. p. (°C): 120.0-125.1.
1H-NMR (300 MHz, CDCl₃): δ / ppm = 8.27 (d,  J = 6.6 Hz, 1H), 7.91-7.83 (m, 2H), 6.99-6.91 (m, 2H), 6.81 (d,  J = 2.7 Hz, 1H), 6.45 (dd,  J = 6.2, 2.6 Hz, 1H), 3.82 (s, 3H), 3.04 (s, 6H).

13C-NMR (100 MHz, CDCl₃): δ / ppm = 160.3, 156.7, 155.2, 148.4, 132.2, 128.3, 113.9, 105.0, 102.8, 55.3, 39.3.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3434, 3196, 3032, 2932, 2640, 2442, 2030, 1946, 1638, 1594, 1576, 1540, 1512, 1448, 1438, 1418, 1404, 1390, 1376, 1302, 1268, 1236, 1182, 1172, 1128, 1110, 1060, 1020, 994, 984, 960, 868, 850, 832, 804, 786, 736, 698, 646, 632.

MS (EI, 70 eV): m/z (%) = 228 [M⁺] (99), 213 (100), 185 (43), 170 (11), 141 (9), 114 (9), 92 (4).

HRMS (EI) for C₁₄H₁₆N₂O (228.1263): 228.1258.

Synthesis of N,N-dimethyl-2-(3-(trifluoromethyl)phenyl)pyridin-4-amine (66d)

According to TP2, a mixture of DMAP (65; 244 mg, 2.0 mmol) and BF₃·OEt₂ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (11; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 1 h). The reaction mixture was cooled to -30 °C and ZnCl₂ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature Pd(dbai)₂ (56 mg, 5 mol%) and P(o-fur)₃ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (435 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL) and NH₃ (conc.) (1 mL) followed by extraction with Et₂O (3×20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, hexane/EtOAc, 1:7) afforded the product 66d (335 mg, 79%) as yellowish solid.

M.p. (°C): Decomp. at 230.
C. Experimental Section

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.24 (d, $J = 7.0$ Hz, 1H), 8.04 (d, $J = 7.8$ Hz, 1H) 7.98 (s, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.63 (t, $J = 7.8$ Hz, 1H), 6.84 (d, $J = 2.7$ Hz, 1H), 6.73 (dd, $J = 7.0$ Hz, 2.7 Hz, 1H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ / ppm = 157.0, 151.1, 142.8, 134.9, 131.5 (q, $J = 32.8$ Hz), 130.0, 127.2 (q, $J = 3.7$ Hz), 124.2 (q, $J = 4.0$ Hz), 123.6 (q, $J = 272.7$ Hz), 106.2, 104.7, 40.1.

IR (Diamond-ATR, neat): $\bar{\nu}$ / cm$^{-1}$ = 3338, 2922, 2854, 2275, 1638, 1564, 1458, 1377, 1334, 1305, 1024, 808, 700.

MS (EI, 70 eV): m/z (%) = 266 [M$^+$] (80), 251 (100), 223 (53), 195 (19), 175 (12), 154 (16), 121 (21), 71 (16), 57 (25), 43 (58).

HRMS (EI) for C$_{14}$H$_{13}$F$_3$N$_2$ (266.1031): 266.1025.

Synthesis of (4-chlorophenyl)(4-(dimethylamino)pyridin-2-yl)methanone (66e)

According to TP2, a mixture of DMAP (65; 244 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 1.8 mL, 2.2 mmol, 1.2 m in THF) (0 °C, 1 h). The reaction mixture was cooled to -40 °C and CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 m in THF) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 4-chlorobenzoyl chloride (280 mg, 1.6 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) and extracted with Et$_2$O (3x40 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, hexane/EtOAc, 1:4) afforded the product 66e (284 mg, 68%) as yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.17 (d, $J = 5.8$ Hz, 1H), 7.97-7.90 (m, 2H), 7.34-7.27 (m, 2H), 7.12 (d, $J = 2.7$ Hz, 1H), 6.49 (dd, $J = 5.8$, 2.7 Hz, 1H), 2.91 (s, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 193.1, 154.4, 154.4, 148.1, 138.5, 134.7, 132.0, 127.8, 108.1, 106.8, 38.7.
C. Experimental Section

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3088, 2918, 2818, 1662, 1584, 1540, 1486, 1430, 1398, 1376, 1338, 1282, 1264, 1174, 1148, 1088, 1066, 1016, 980, 932, 862, 842, 818, 792, 768, 736, 724, 686.

MS (EI, 70 eV): m/z (%) = 260 [M$^+$] (66), 245 (64), 232 (48), 225 (45), 219 (34), 217 (100), 189 (50), 154 (20), 141 (26), 139 (83), 111 (94), 75 (36).

HRMS (EI) for $\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{O}$ (260.0716): 260.0711.

Synthesis of ethyl 2-((4-(2,2,6,6-tetramethylpiperidin-1-yl)pyridin-2-yl)methyl)acrylate (66f):

According to TP2, a mixture of 4-(2,2,6,6-tetramethylpiperidin-1-yl)pyridine (65d; 371 mg, 1.7 mmol) and BF$_3$-OEt$_2$ (266 mg, 1.9 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 3 mmol, 1.2 M in THF) (0 °C, 1.5 h). The reaction mixture was cooled to -40 °C and CuCN·2LiCl (1.7 mL, 1.7 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at the same temperature before ethyl 2-(bromomethyl)acrylate (386 mg, 2.0 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) and extracted with Et$_2$O (3x40 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (Al$_2$O$_3$ III, pentane/ Et$_2$O, 4:1) afforded the product 66f (397 mg, 71%) as colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.42 (d, $J = 5.4$ Hz, 1H), 7.03 (s, 1H), 6.98 (d, $J = 5.4$ Hz, 1H), 6.28 (s, 1H), 5.53 (s, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 2H), 1.67-1.77 (m, 2H), 1.49-1.59 (m, 4H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.00 (s, 12H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 166.7, 159.0, 155.5, 149.2, 138.9, 129.0, 126.9, 126.6, 60.7, 54.1, 41.8, 40.6, 29.6, 18.1, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1} = 2970, 2930, 2870, 1716, 1632, 1588, 1542, 1474, 1456, 1446, 1428, 1378, 1364, 1326, 1294, 1244, 1186, 1174, 1130, 1096, 1034, 998, 982, 944, 926, 854, 842, 816, 778, 714.

MS (EI, 70 eV): $m/z$ (%) = 330 [M$^+$] (1), 315 (100), 247 (5), 173 (4), 69 (7).

HRMS (EI) for C$_{20}$H$_{30}$N$_2$O$_2$ (330.2307): 330.2310.

**Synthesis of 2-chloro-6-iodo-$N,N$-dimethylpyridin-4-amine (66g)**

According to TP2, a mixture of 2-chloro-$N,N$-dimethylpyridin-4-amine (66b; 313 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 3 mmol, 1.2 M in THF) (0 °C, 3 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL), NH$_3$ (conc.) (1 mL) and sat. aqueous Na$_2$S$_2$O$_3$ solution (2 mL) followed by extraction with Et$_2$O (3x30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/EtOAc, 1:1) afforded the product 66g (452 mg, 80%) as white solid.

**M. p. (°C):** 119.0-120.1.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 6.84 (d, $J = 2.2$ Hz, 1H), 6.45 (d, $J = 2.2$ Hz, 1H), 2.98 (s, 6H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ / ppm = 156.1, 150.2, 115.9, 115.7, 105.4, 39.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1} = 3114, 2928, 2806, 1584, 1500, 1428, 1416, 1396, 1366, 1346, 1284, 1226, 1160, 1100, 1082, 1068, 984, 964, 808, 754, 702.

MS (EI, 70 eV): $m/z$ (%) = 282 [M$^+$] (100), 155 (38), 119 (7).

HRMS (EI) for C$_7$H$_8$ClIN$_2$ (281.9421): 281.9419.
Synthesis of 2-chloro-6-cyclohex-2-en-1-yl-N,N-dimethylpyridin-4-amine (66h)

According to TP2, a mixture of 2-chloro-N,N-dimethylpyridin-4-amine (66b; 157 mg, 1.0 mmol) and BF$_3$·OEt$_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (II; 1.3 mL, 1.5 mmol, 1.2 M in THF) (0 °C, 3 h). The reaction mixture was cooled to -30 °C and CuCN·2LiCl (1.1 mL, 1.1 mmol, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature 3-bromocyclohex-1-ene (193 mg, 1.2 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aqueous NH$_4$Cl solution (4.5 mL) and NH$_3$ (conc.) (0.5 mL) and extracted with Et$_2$O (3x20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, hexane/EtOAc, 1:1) afforded the product 66h (185 mg, 78%) as colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 6.32 (d, $J = 2.4$ Hz, 1H), 6.28 (d, $J = 2.2$ Hz, 1H), 5.91-5.84 (m, 1H), 5.77-5.69 (m, 1H), 3.48-3.38 (m, 1H), 2.96 (s, 6H), 2.10-1.99 (m, 3H), 1.74-1.54 (m, 3H).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ / ppm = 165.6, 156.6, 151.4, 129.1, 128.5, 103.3, 103.2, 43.7, 39.3, 30.3, 25.0, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3020, 2928, 2860, 2836, 1662, 1590, 1528, 1504, 1422, 1366, 1326, 1294, 1214, 1184, 1126, 1064, 980, 934, 914, 896, 888, 822, 810, 748, 726, 710.

MS (EI, 70 eV): $m/z$ (%) = 236 [M$^+$] (88), 221 (48), 209 (40), 207 (100), 201 (39), 195 (23), 191 (15), 181 (12), 170 (38), 156 (12), 57 (19), 43 (17).

HRMS (EI) for C$_{13}$H$_{17}$ClN$_2$: 236.1080: 236.1076.
13. Preparation of functionalized (S)-nicotine derivative

Synthesis of 2-(cyclohex-2-en-1-yl)-5-((S)-1-methylpyrrolidin-2-yl)pyridine (67a)

According to TP2, a mixture of (S)-nicotine (67; 162 mg, 1.0 mmol) and BF₃·OEt₂ (156 mg, 1.1 mmol) reacted with TMPMgCl-LiCl (11; 1.3 mL, 1.5 mmol, 1.2 M in THF) (0 °C, 2.5 h). The reaction mixture was cooled to -30 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature 3-bromocyclohex-1-ene (160 mg, 1.1 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (4.5 mL) and NH₃ (conc.) (0.5 mL) followed by extraction with Et₂O (3×20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (Al₂O₃ III, pentane / Et₂O = 1:1) afforded the product 67a (223 mg, 92%) as red oil.

¹H-NMR (300 MHz, CDCl₃): δ / (ppm) = 8.43 (s, 1H), 7.63 (dd, J = 8.0, 1.3 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 5.87-5.96 (m, 1H), 5.74-5.84 (m, 1H), 3.55-3.58 (m, 1H), 3.17-3.29 (m, 1H), 3.03-3.07 (m, 1H), 1.48-2.41 (m, 14H).

¹³C-NMR (75 MHz, CDCl₃): δ / (ppm) = 164.3, 149.0, 135.7, 135.2, 135.1, 128.8, 128.7, 121.7, 68.7, 68.6, 56.0, 43.7, 40.3, 35.0, 30.6, 24.9, 22.5, 21.1, 21.1.

IR (Diamond-ATR, neat): ν (cm⁻¹): 3018, 2934, 2874, 2858, 2836, 2774, 2720, 2664, 2362, 2340, 1734, 1674, 1616, 1596, 1566, 1480, 1456, 1448, 1420, 1400, 1374, 1344, 1332, 1314, 1288, 1250, 1216, 1210, 1152, 1132, 1116, 1086, 1044, 1026, 988, 966, 922, 902, 886, 838, 788, 764, 722, 688, 642, 610.

MS (70 eV, EI) m/z (%): 242 [M⁺] (63), 213 (30), 185 (16), 156 (8), 133 (15), 84 (100), 42 (9).

HRMS (EI) for C₁₆H₂₂N₂ (242.1783): 242.1777.
14. Preparation of functionalized quinine derivatives

Synthesis of (R)-(3-bromo-6-methoxyquinolin-4-yl)(2S,4S,8R)-8-vinylquinuclidin-2-yl) methanol (68a)

According to TP4, quinine (68; 648 mg, 2.0 mmol) reacted with MeLi (1.23 mL, 2.0 mmol, 1.63 M in Et₂O), BF₃·OEt₂ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (11; 1.85 mL, 2.2 mmol, 1.19 M in THF). 1,2-Dibromo-1,1,2,2-tetrachloroethane (781 mg, 2.4 mmol) was added and the reaction mixture was stirred for 15 h at 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL), NH₃ (conc.) (1 mL) and extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (Al₂O₃ III, hexane/EtOAc, 1:1) furnished the product 68a as off-white solid (532 mg, 66% yield).

M. p. (°C): 84.2-87.5.

¹H-NMR (300 MHz, CDCl₃, 25 °C): δ / (ppm) = : 8.65 (s, 1H), 7.95 (s, br, 1H), 7.88 (d, J = 9.2 Hz, 1H), 7.29 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 5.92-5.77 (m, 1H), 5.59 (d, J = 8.8 Hz, 1H), 5.02 (s, 1H), 4.98 (d, J = 5.6 Hz, 1H), 3.90 (s, 3H), 3.75-3.53 (m, 1H), 3.45-3.25 (m, 1H), 2.99-2.80 (m, 1H), 2.71-2.45 (m, 2H), 2.32-2.18 (m, 1H), 1.94-1.83 (m, 1H), 1.76-1.56 (m, 2H), 1.57-1.36 (m, 2H).

¹³C-NMR (CDCl₃, 75 MHz, 25 °C): δ / (ppm) = 157.4, 149.6, 144.3, 143.9, 141.8, 131.4, 128.8, 121.5, 119.6, 114.3, 104.2, 75.8, 60.0, 55.7, 55.4, 42.8, 39.6, 27.8, 27.3, 25.8.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3134, 3076, 2932, 2864, 2362, 1736, 1618, 1576, 1558, 1500, 1464, 1452, 1418, 1388, 1380, 1356, 1322, 1286, 1262, 1226, 1184, 1158, 1112, 1094, 1028, 988, 950, 938, 912, 886, 870, 858, 830, 810, 784, 774, 746, 714, 686, 668, 648, 610.

HRMS (ESI) for C₂₀H₂₄BrN₂O₂ (M+H⁺) (403.1016): 403.1014.
Synthesis of \((R)-(3\text{-}allyl\text{-}6\text{-}methoxyquinolin\text{-}4\text{-}yl})(2S,4S,8R\text{-}8\text{-}vinylquiuclidin\text{-}2\text{-}yl)\text{methanol (68b)}\)

According to TP4, quinine (68; 973 mg, 3.0 mmol) reacted with MeLi (1.84 mL, 3.0 mmol, 1.63 M in Et<sub>2</sub>O), BF<sub>3</sub>-OEt<sub>2</sub> (937 mg, 6.6 mmol) and TMPMgCl·LiCl (11; 2.77 mL, 3.3 mmol, 1.19 M in THF). CuCN·2LiCl (3.3 mL, 3.3 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for 15 min at 0 °C. After addition of allylbromide (436 mg, 3.6 mmol) the reaction was stirred for 1.5 h at 25 °C. The reaction mixture was quenched with sat. aqueous NH<sub>4</sub>Cl solution (14 mL) and NH<sub>3</sub> (conc.) (2 mL) followed by extraction with CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (Al<sub>2</sub>O<sub>3</sub> III, pentan/EtOAc, 5:1) furnished the compound 68b as slightly yellow resin (451 mg, 41%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, 25 °C): \(\delta / (ppm) = 8.42\ (s, 1H), 7.91\ (d, J = 9.2Hz, 1H), 7.22-7.28\ (m, 2H), 5.95-6.10\ (m, 1H), 5.77-5.90\ (m, 1H), 5.75-5.62\ (m, 1H), 5.31-5.44\ (m, 1H), 5.04-5.11\ (m, 1H), 4.87-5.01\ (m, 3H), 3.88\ (s, 3H), 3.63-3.73\ (m, 1H), 3.51-3.59\ (m, 1H), 3.07-3.22\ (m, 2H), 2.84-2.83\ (m, 1H), 2.61-2.71\ (m, 1H), 2.45-2.54\ (m, 1H), 2.18-2.27\ (m, 1H), 1.87-1.93\ (m, 1H), 1.60-1.76\ (m, 3H), 1.45-1.53\ (m, 1H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz, 25 °C): \(\delta / (ppm) = 157.7, 147.4, 144.2, 144.1, 142.0, 131.3, 130.2, 127.1, 121.5, 120.5, 116.2, 114.1, 101.0, 71.4, 60.4, 55.8, 55.3, 51.1, 42.3, 39.8, 37.6, 35.1, 30.4.

IR (Diamond-ATR, neat): \(\tilde{\nu} / cm^{-1} = 3150, 3076, 2934, 2866, 1738, 1668, 1636, 1620, 1592, 1508, 1466, 1452, 1434, 1422, 1388, 1380, 1362, 1324, 1260, 1228, 1186, 1174, 1130, 1090, 1062, 1030, 992, 912, 884, 872, 858, 830, 808, 754, 730, 694, 666, 644, 610.

HRMS (ESI) for C<sub>23</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> (M+H<sup>+</sup>) (365.2224): 365.2221.
Synthesis of (R)-(3-iodo-6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methanol (68c)

According to TP4, quinine (68; 648 mg, 2.0 mmol) reacted with MeLi (1.23 mL, 2.0 mmol, 1.63 M in Et₂O), BF₃·OEt₂ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (11; 1.85 mL, 2.2 mmol, 1.19 M in THF). Iodine (761 mg, 3 mmol) was added and the reaction mixture was warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (9 mL), NH₃ (conc.) (1 mL) and extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (Al₂O₃ III, hexane/EtOAc, 1:1) furnished the product 68c as off-white solid (585 mg, 65% yield).

M. p. (°C): 84.8-85.1.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.80 (s, 1H), 8.10 (s, br, 1H), 7.83 (d, J = 9.3 Hz, 1H), 7.27 (dd, J = 8.9 Hz, 2.9 Hz, 1H), 5.82-5.73 (m, 1H), 5.51-5.44 (m, 1H), 5.00 (d, J = 1.4 Hz, 1H), 4.98 (dt, J = 7.2 Hz, 1.3 Hz, 1H), 3.89 (s, 3H), 3.59-3.48 (m, 1H), 2.94-2.86 (m, 1H), 2.68-2.61 (m, 2H), 2.31-2.25 (m, 1H), 1.90-1.83 (m, 2H), 1.77-1.69 (m, 2H), 1.55-1.48 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 156.8, 154.6, 147.6, 144.3, 141.0, 130.9, 129.1, 121.7, 116.5, 114.6, 104.3, 81.0, 60.0, 55.3, 55.1, 43.1, 39.1, 27.2, 27.1, 24.6.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3110, 2936, 2858, 2418, 2382, 2350, 2160, 2048, 1736, 1686, 1616, 1542, 1498, 1462, 1452, 1412, 1284, 1260, 1226, 1214, 1180, 1164, 1156, 1130, 1110, 1038, 1026, 986, 948, 908, 884, 874, 828, 808, 786, 766, 744, 734, 712, 674, 654, 640, 622, 612.

MS (EI, 70 eV): 450 [M⁺] (2), 323 (17), 136 (100), 81 (7), 61 (12), 43 (16).

HRMS for C₂₀H₂₃IN₂O₂ (450.0804): 450.0932.
Synthesis of ethyl 4-((4-((R)-hydroxy((2S,4S,8R)-8-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-3-yl)benzoate (68d)

According to TP4, quinine (68; 648 mg, 2.0 mmol) reacted with MeLi (1.2 mL, 2.0 mmol, 1.63 M in Et2O), BF3·OEt2 (624 mg, 4.4 mmol) and TMPMgCl-LiCl (1; 1.8 mL, 2.2 mmol, 1.19 M in THF). The reaction mixture was cooled to -30 °C and ZnCl2 (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature Pd(dba)2 (56 mg, 5 mol%) and P(o-fur)3 (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (442 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH4Cl solution (9 mL) and NH3 (conc.) (1 mL) followed by extraction with Et2O (3×20 mL). The combined organic layers were dried over Na2SO4 and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt3, 10:1:1) afforded the product 68d (378 mg, 50%) as yellow resin.

**1H-NMR** (300 MHz, CDCl3, 25 °C): δ / (ppm) = 8.31 (s, 1H), 8.05-8.16 (m, 2H), 7.95-8.00 (m, 1H), 7.86-7.92 (m, 1H), 7.34-7.41 (m, 2H), 7.25-7.30 (m, 1H), 5.67-5.78 (m, 1H), 5.21-5.28 (m, 1H), 4.85-4.97 (m, 2H), 4.86 (q, J = 6.9 Hz, 2H), 3.87 (s, 3H), 3.43-3.53 (m, 1H), 3.06-3.15 (m, 1H), 2.67-2.77 (m, 1H), 2.19-2.43 (m, 3H), 2.07-2.17 (m, 1H), 1.69-1.76 (m, 1H), 1.18-1.41 (m, 6H).

**13C-NMR** (CDCl3, 75 MHz, 25 °C): δ / (ppm) = 177.1, 166.3, 157.1, 148.7, 144.5, 143.4, 141.4, 133.9, 131.0, 129.3, 127.1, 121.5, 114.2, 110.9, 105.1, 71.7, 61.0, 58.2, 55.4, 55.1, 41.8, 39.2, 29.5, 27.2, 27.1, 25.1.

**IR (Diamond-ATR, neat):** $\tilde{\nu}$ / cm$^{-1}$ = 3074, 2950, 2930, 2884, 1714 (s), 1622, 1608, 1552 (w), 1502 (m), 1462, 1422, 1396, 1390, 1366, 1352, 1308, 1264, 1230, 1176, 1102, 1072, 1028, 1020, 1004, 938, 912, 862, 852, 834, 804, 776, 732, 708, 672.

**HRMS (ESI)** for C$_{29}$H$_{33}$N$_2$O$_4$ (M+H$^+$) (473.2440): 443.2436.
Synthesis of \((R)-(6\text{-methoxy-3-phenylquinolin-4-yl})(2S,4S,8R)-8\text{-vinylquinclidin-2-yl})\text{methanol (68e)}

According to TP4, quinine (68; 648 mg, 2.0 mmol) reacted with MeLi (1.2 mL, 2.0 mmol, 1.63 \text{M in Et}_2\text{O}), BF\text{3-}\text{OEt}_2 (624 mg, 4.4 mmol) and TMPMgCl-LiCl (I; 1.8 mL, 2.2 mmol, 1.19 \text{M in THF}). The reaction mixture was cooled to -30 °C and \text{ZnCl}_2 (2.2 mmol, 2.2 mL, 1 \text{M in THF}) was added dropwise. After stirring for 30 min at the same temperature Pd(dba)$_2$ (56 mg, 5 mol\%) and P(o-fur)$_3$ (46 mg, 10 mol\%) dissolved in THF (2 mL) were then transferred \textit{via} cannula to the reaction mixture, followed by the addition of iodobenzene (326 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with \text{Et}_2\text{O} (3\times20 \text{mL}). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated \textit{in vacuo}. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt$_3$, 10:1:1) afforded the product 68e (240 mg, 38\%) as yellow resin.

$^1$H-NMR (300 MHz, CDCl$_3$, 25 °C): δ / (ppm) = 8.33-8.39 (m, 1H), 8.00 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 9.4 Hz, 1H), 7.21-7.37 (m, 6H), 5.71-5.87 (m, 1H), 5.17 (d, J = 9.7 Hz, 1H), 4.86-5.00 (m, 2H), 3.90 (s, 3H), 3.54-3.65 (m, 1H), 2.63-2.75 (m, 1H), 2.27-2.36 (m, 1H), 1.99-2.20 (m, 4H), 1.68-1.75 (m, 1H), 1.22-1.39 (m, 3H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz, 25 °C): δ / (ppm) = 157.0, 149.0, 144.3, 143.4, 142.1, 138.5, 135.0, 131.1, 130.0, 128.1, 127.3, 127.0, 121.1, 113.8, 104.9, 72.3, 60.0, 55.6, 55.4, 41.6, 39.7, 27.7, 27.2, 25.9.

IR (Diamond-ATR, neat): \text{υ} / \text{cm}^{-1} = 3126, 3077, 2934, 2863, 2362, 2340, 1736, 1619, 1577, 1554, 1540, 1503, 1456, 1416, 1364, 1319, 1261, 1226, 1179, 1164, 1134, 1104, 1049, 1013, 914, 884, 872, 833, 809, 757, 704, 691, 668, 654, 636.

MS (EI, 70 eV): 400 [M$^+$] (32), 265 (88), 248 (63), 137 (68), 136 (100).

HRMS (EI) for C$_{26}$H$_{28}$N$_2$O$_2$ (400.2151): 400.2148.
Synthesis of (1S,4S,5R)-2-((R)-(6-methoxyquinolin-4-yl)((triisopropylsilyl)oxy)methyl)-5-vinylquinuclidine (68f)

A mixture of quinine (68; 6.5 g, 20.0 mmol), imidazole (5.5 g, 80 mmol) and TIPSCI (7.7 g, 40 mmol) in DMF (20 mL) was heated at 120 °C for 5 d. After addition of CH₂Cl₂ (100 mL) the organic layer was washed with sat. aqueous NaHCO₃ solution (2x40 mL) and dried over MgSO₄. After filtration the solvents were evaporated in vacuo. Flash column purification (silica gel, EtOAc/MeOH/NEt₃, 10:1:1) furnished the product 68f as yellow resin (7.88 g, 82%).

¹H-NMR (400 MHz, CDCl₃, 25 °C): δ / (ppm) = 8.73 (d, J = 4.6 Hz, 1 H, major rotamer), 8.62 (d, J = 4.3 Hz, 1 H, minor rotamer), 8.00 (d, J = 9.3 Hz, 1 H, major rotamer), 7.96 (d, J = 9.2 Hz, 1 H, minor rotamer), 7.84 (d, J = 2.8 Hz, 1 H, minor rotamer), 7.56 (d, J = 4.6 Hz, 1 H, major rotamer), 7.33 (dd, J = 9.3 Hz, J = 2.7 Hz, 1 H, major rotamer), 7.29 (dd, J = 9.2 Hz, J = 2.8 Hz, 1 H, minor rotamer), 7.17 (d, J = 2.7 Hz, 1 H, major rotamer), 7.09 (d, J = 4.3 Hz, 1 H, minor rotamer), 5.91-5.80 (m, 1 H, major rotamer), 5.75-5.62 (m, 1 H, major rotamer, 1 H, minor rotamer), 5.01-4.80 (m, 2 H, major rotamer, 3 H, minor rotamer), 3.90 (s, 3 H, major rotamer), 3.87 (s, 3 H, minor rotamer), 3.66-1.40 (m, 11 H), 1.05-0.78 (m, 21 H).

Ratio of rotamers determined by NMR ≈ 0.7/1.

¹³C-NMR (CDCl₃, 100 MHz, 25 °C): δ (ppm) = 157.7, 156.5, 148.9, 147.4, 147.4, 147.2, 145.4, 144.2, 142.3, 142.1, 131.8, 131.5, 127.0, 126.6, 121.5, 121.3, 121.2, 181.9, 114.1, 114.0, 104.4, 100.5, 79.6, 72.6, 62.5, 60.9, 57.3, 56.0, 55.5, 55.2, 43.2, 41.2, 44.4, 39.9, 28.1, 27.9, 27.7, 26.8, 22.7, 18.1, 18.0, 17.8, 17.7, 12.8, 12.4, 12.3.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3074, 2942, 2892, 2866, 2730, 1726, 1656, 1620, 1598, 1554, 1502, 1462, 1432, 1408, 1390, 1360, 1322, 1302, 1254, 1240, 1228, 1184, 1172, 1130, 1102, 1074, 1030, 1004, 978, 952, 940, 912, 874, 832, 802, 776, 716, 704, 670, 642, 630, 612.

HRMS (ESI) for C₂₉H₄₅N₂O₂Si (M+H⁺) (481.3245): 481.3241.
Synthesis of \( (1S,4S,5R)-2-((R)-(2-allyl-6-methoxyquinolin-4-yl)((triisopropylsilyl)oxy)methyl)-5-vinylquinuclidine \) (68g)

According to TP2, a mixture of \( (1S,4S,5R)-2-((R)-(6-methoxyquinolin-4-yl)((triisopropylsilyl)oxy)methyl)-5-vinylquinuclidine \) (68f; 962 mg, 2.0 mmol) and BF\(_3\)-OEt\(_2\) (312 mg, 2.0 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 3.0 mmol, 1.22 M in THF) (0 °C, 15 h). CuCN-2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min at 0 °C. After addition of allylbromide (387 mg, 3.2 mmol) the reaction was stirred for 4 h at 25 °C. The reaction mixture was quenched with sat. aqueous NH\(_4\)Cl solution (10 mL) and NH\(_3\) (conc.) (2 mL) followed by extraction with CH\(_2\)Cl\(_2\) (3x20 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentan/EtOAc/NEt\(_3\), 20:1:1) furnished the compound 68g as slightly brown honey like oil (219 mg, 21%).

\(^1\)H-NMR (300 MHz, CDCl\(_3\), 25 °C): \( \delta \) / ppm = 7.96 (d, \( J = 9.1 \) Hz, 1 H, major rotamer), 7.92 (d, \( J = 9.4 \) Hz, 1 H, minor rotamer), 7.80 (d, \( J = 3.0 \) Hz, 1 H, minor rotamer), 7.49 (s, 1 H, major rotamer), 7.35-7.26 (m, 1 H), 7.15 (d, \( J = 2.8 \) Hz, 1 H, major rotamer), 7.01 (s, 1 H; minor rotamer), 6.17-6.00 (m, 1 H), 5.94-5.62 (m, 2 H), 5.23-5.08 (m, 2 H), 5.02-4.82 (m, 2 H), 3.90 (s, 3 H, major rotamer), 3.87 (s, 3 H, minor rotamer), 3.73-1.39 (m, 13 H), 1.11 – 0.80 (m, 21 H). Ratio of rotamers determined by NMR \( \approx 0.6/1 \).

\(^{13}\)C-NMR (CDCl\(_3\), 75 MHz, 25 °C): \( \delta \) / ppm = 157.4, 157.2, 156.8, 156.2, 149.1, 147.7, 145.2, 144.0, 142.4, 142.2, 135.9, 135.6, 131.3, 131.0, 125.6, 125.1, 121.7, 121.2, 121.1, 119.1, 116.9, 116.6, 114.1, 114.0, 104.6, 100.8, 80.2, 73.0, 62.4, 60.8, 57.4, 56.2, 55.6, 55.3, 46.2, 43.7, 43.3, 43.2, 41.2, 40.5, 40.0, 38.5, 31.5, 28.2, 28.0, 27.8, 27.0, 22.3, 18.1, 17.9, 12.9, 12.5, 11.6.

IR (Diamond-ATR, neat): \( \tilde{\nu} \) / cm\(^{-1}\) = 3074, 2942, 2892, 2866, 2730, 1726, 1656, 1620, 1598, 1554, 1502, 1462, 1436, 1410, 1378, 1356, 1320, 1304, 1260, 1232, 1166, 1104, 1066, 1034, 1012, 996, 968, 910, 882, 832, 796, 768, 734, 678, 652.

HRMS (ESI) for C\(_{32}\)H\(_{49}\)N\(_2\)O\(_2\)Si (M+H\(^+\)) (521.3558): 521.3553.
Synthesis of (1R)-(2-allyl-6-methoxyquinolin-4-yl)((1S,4S,5R)-5-vinylquinuclidin-2-yl)methanol (68h)

A mixture of (1S,4S,5R)-2-((R)-(2-allyl-6-methoxyquinolin-4-yl)((triisopropylsilyl)oxy)methyl)-5-vinylquinuclidine (68g; 219 mg, 0.4 mmol) and TBAF (397 mg, 1.3 mmol) in THF (3 mL) was stirred at 25 °C for 12 h. After addition of EtOAc (5 mL) the organic layer was washed with sat. aqueous NaCl solution (3x10 mL) and dried over MgSO₄. After filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt₃, 150:1:1) furnished the product 68h as yellow solid (86 mg, 59%).

The analytical data (NMR, IR, HRMS (ESI)) match with 68m.

Synthesis of (1S,4S,5R)-2-((R)-(tert-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (68i)

A mixture of quinine (68; 8.0 g, 24.4 mmol), NEt₃ (17 mL, 122 mmol), DMAP (300 mg, 2.5 mmol) and TBDMSCl (5.6 g, 37.0 mmol) in DMF (40 mL) was stirred at 25 °C for 15 h. After addition of toluene (50 mL) the organic layer was washed with sat. aqueous NaHCO₃ solution (3x40 mL) and dried over MgSO₄. After filtration the solvents were evaporated in vacuo. Flash column purification (silica gel, EtOAc/MeOH/NEt₃, 9:1:1) furnished the product 68i as orange resin oil (10.4 g, 97%).

¹H-NMR (400 MHz, CDCl₃, 25 °C): δ / (ppm) = 8.72 (d, J = 4.5 Hz, 1H, major rotamer), 8.63 (d, J = 4.3 Hz, 1H, minor rotamer), 8.02 (d, J = 9.2 Hz, 1H, major rotamer), 7.97 (d,
C. Experimental Section

$J = 9.3 \text{ Hz, } 1\text{H, minor rotamer}$, 8.83 ($d, J = 2.6 \text{ Hz, } 1\text{H, minor rotamer}$), 7.51 ($d, J = 4.6 \text{ Hz, } 1\text{H, major rotamer}$), 7.36 ($dd, J = 9.3 \text{ Hz, } J = 2.7 \text{ Hz } 1\text{H, major rotamer}$), 7.31 ($dd, J = 9.3 \text{ Hz, } J = 2.6 \text{ Hz, } 1\text{H, minor rotamer}$), 7.19 ($d, J = 2.6 \text{ Hz, } 1\text{H, major rotamer}$), 7.10 ($d, J = 4.2 \text{ Hz, } 1\text{H, minor rotamer}$), 5.91-5.81 ($m, 1\text{H, minor rotamer}$), 5.70-5.57 ($m, 2\text{H, major rotamer}$), 5.01-4.74 ($m, 2\text{H}$), 3.93 ($s, 3\text{H, major rotamer}$), 3.89 ($s, 3\text{H, minor rotamer}$), 3.57-3.41 ($m, 1\text{H}$), 3.06 ($dd, J = 14 \text{ Hz, } J = 10 \text{ Hz, } 1\text{H}$), 2.94-2.85 ($m, 1\text{H}$), 2.72-2.55 ($m, 1\text{H}$), 2.27-2.17 ($m, 1\text{H}$), 1.88-1.33 ($m, 5\text{H}$), 0.96 ($s, 9\text{H, major rotamer}$), 0.90 ($s, 9\text{H, minor rotamer}$), 0.12 ($s, 3\text{H, minor rotamer}$), 0.07 ($s, 3\text{H, major rotamer}$), -0.39 ($s, 3\text{H, major rotamer}$), -0.47 ($s, 3\text{H, minor rotamer}$).

Ratio of rotamers determined by NMR $\approx 2/1$.

$^{13}\text{C-NMR}$ (CDCl$_3$, 100 MHz, 25 °C): $\delta$/ (ppm) = 157.9, 148.1, 147.3, 147.3, 147.2, 144.3, 142.2, 142.1, 131.8, 131.4, 129.0, 126.2, 121.5, 121.5, 121.1, 118.7, 114.2, 114.1, 104.4, 100.5, 80.1, 77.2, 72.7, 61.2, 60.8, 57.5, 56.1, 55.8, 55.3, 43.2, 41.2, 40.2, 39.9, 28.2, 27.9, 27.9, 27.8, 27.2, 25.9, 25.7, 25.7, 25.7, 21.1, 18.1, 18.0, 14.2, -3.4, -4.2, -4.7, -5.1, -5.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm$^{-1}$ = 3076, 2998, 2948, 2930, 2884, 2858, 1916, 1620, 1592, 1574, 1508, 1472, 1462, 1432, 1408, 1390, 1360, 1322, 1302, 1254, 1240, 1228, 1184, 1172, 1130, 1102, 1074, 1030, 1004, 978, 952, 940, 912, 874, 832, 802, 776, 716, 704, 670, 642, 630, 612.

HRMS (ESI) for C$_{26}$H$_{39}$N$_2$O$_2$Si (M+H$^+$) (439.2775): 439.2772.

Synthesis of (1$S$,4$S$,5$R$)-2-((R)-(2-allyl-6-methoxyquinolin-4-yl)((tert-butyldimethylsilyl)oxy)methyl)-5-vinylquinuclidine (68j)

According to TP2, a mixture of (1$S$,4$S$,5$R$)-2-((R)-((tert-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (68i; 877 mg, 2.0 mmol) and BF$_3$·OEt$_2$ (312 mg, 2.0 mmol) reacted with TMPMgCl·LiCl (11; 2.5 mL, 3.0 mmol, 1.22 M in THF) (0 °C, 15 h). CuCN·2LiCl (2.2 mL, 2.2 mmol, 1 M in THF) was added and the reaction mixture was stirred for 15 min at 0 °C. After addition of allylbromide (387 mg, 3.2 mmol) the reaction was stirred for 4 h at 25 °C. The reaction mixture was quenched with sat. aqueous...
NH₄Cl solution (10 mL) and NH₃ (conc.) (2 mL) followed by extraction with CH₂Cl₂ (3x20 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, pentan/EtOAc/NEt₃, 20:1:1) furnished the compound 68j as slightly brown resin oil (379 mg, 41%).

**¹H-NMR** (300 MHz, CDCl₃, 25 °C): δ / (ppm) = 8.00-7.89 (m, 1H), 7.79 (br, 1H, minor rotamer), 7.45 (s, 1H, major rotamer), 7.36-7.25 (m, 1H), 7.17 (br, 1H, major rotamer), 7.03 (s, 1H, minor rotamer), 6.17-6.00 (m, 1H), 5.94-5.54 (m, 2H), 5.23-5.08 (m, 2H), 5.02-4.71 (m, 2H), 3.93 (s, 3H, major rotamer), 3.88 (s, 3H, minor rotamer), 3.72-1.28 (m, 13H), 0.96 (s, 9H, major rotamer), 0.80 (s, 9H, minor rotamer), 0.13 (s, 3H, major rotamer), 0.07 (s, 3H, minor rotamer), -0.40 (s, 3H, major rotamer), -0.48 (s, 3H, minor rotamer). Ratio of rotamers determined by NMR ≈ 3/1.

**¹³C-NMR** (CDCl₃, 75 MHz, 25 °C): δ / (ppm) = 157.6, 157.2, 144.0, 142.2, 135.6, 131.2, 124.7, 121.3, 118.9, 117.0, 114.3, 114.1, 100.7, 77.2, 72.7, 61.1, 57.5, 55.8, 43.7, 43.3, 40.2, 39.8, 28.0, 27.8, 25.9, 25.7, 20.7, 18.0, -4.2, -5.2.

**IR** (Diamond-ATR, neat): ν / cm⁻¹ = 3076, 2998, 2948, 2930, 2884, 2858, 1916, 1620, 1592, 1574, 1508, 1472, 1436, 1410, 1378, 1356, 1320, 1304, 1260, 1232, 1166, 1104, 1066, 1034, 1012, 996, 968, 910, 882, 832, 796, 768, 734, 678, 652.

**HRMS** (ESI) for C₂₉H₄₃N₂O₂Si (M+H⁺) (479.3088): 479.3084.

**Synthesis of (1S,4S,5R)-2-((R)-(tert-butyldimethylsilyl)oxy)(2-iodo-6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (68k)**

According to TP2, a mixture of (1S,4S,5R)-2-((R)-(tert-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (68i; 1.75 g, 4.0 mmol) and BF₃·OEt₂ (624 mg, 4.4 mmol) reacted with TMPMgCl-LiCl (11; 4.8 mL, 6.0 mmol, 1.26 M in THF) (0 °C, 15 h). Iodine (2.03 g, 8 mmol) was added and the reaction mixture was stirred for 1 h at
25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution (18 mL), NH₃ (conc.) (2 mL) and sat. aqueous Na₂S₂O₃ solution (10 mL) and extracted with CH₂Cl₂ (3x30 mL). The combined organic layers were dried over Na₂SO₄ and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt₃, 50:1:1) furnished the product **68k** as resin (1.00 g, 44%).

**1H-NMR** (300 MHz, CDCl₃, 25 °C): \(\delta / \text{ppm} = 7.95-7.86 \text{ (m, 1H)}, 7.81 \text{ (s, 1H, major rotamer)}, 7.77 \text{ (br, 1H, minor rotamer)}, 7.42 \text{ (s, 1H, minor rotamer)}, 7.34-7.26 \text{ (m, 1H)}, 7.16 \text{ (br, 1H, major rotamer)}, 5.90-5.56 \text{ (m, 2H)}, 5.00-4.61 \text{ (m, 2H)}, 3.93 \text{ (s, 3H, major rotamer)}, 3.86 \text{ (s, 3H, minor rotamer)}, 3.57-1.36 \text{ (m, 11H)}, 0.96 \text{ (s, 9H, major rotamer)}, 0.80 \text{ (s, 9H, minor rotamer)}, 0.14 \text{ (s, 3H, major rotamer)}, 0.08 \text{ (s, 3H, minor rotamer)}, -0.34 \text{ (s, 3H, major rotamer)}, -0.43 \text{ (s, 3H, minor rotamer)}. Ratio of rotamers determined by NMR \(\approx 3/1\).

**13C-NMR** (CDCl₃, 75 MHz, 25 °C): \(\delta / \text{ppm} = 158.3, 156.9, 149.0, 145.7, 142.1, 131.1, 130.8, 129.6, 126.3, 125.4, 122.3, 122.0, 115.3, 114.6, 114.1, 104.8, 101.0, 79.3, 77.2, 61.1, 60.6, 57.1, 56.1, 56.0, 55.3, 54.7, 43.1, 41.2, 39.8, 28.1, 27.7, 27.2, 25.9, 25.7, 20.7, 18.0, 3.4, 4.2, 4.6, 5.0, 5.3.

**IR** (Diamond-ATR, neat): \(\nu / \text{cm}^{-1} = 3070, 3000, 2948, 2930, 2882, 2858, 2362, 2328, 1738, 1618, 1576, 1548, 1502, 1470, 1462, 1432, 1404, 1388, 1362, 1322, 1284, 1256, 1232, 1092, 1030, 952, 944, 912, 880, 870, 834, 804, 776, 726, 710, 672, 646.

**HRMS (ESI)** for C₂₆H₃₈IN₂O₂Si (M+H⁺) (565.1742): 565.1737.

**Synthesis of ethyl 4-(4-((1R)-(tert-butyldimethylsilyl)oxy)((1S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinolin-2-yl)benzoate (68l)**

According to **TP2**, a mixture of (1S,4S,5R)-2-((R)-(tert-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (68i; 877 mg, 2.0 mmol) and BF₃·OEt₂ (312 mg, 2.2 mmol) reacted with TMPMgCl-LiCl (11; 2.5 mL, 3.0 mmol, 1.22 M in THF)
The reaction mixture was cooled to -30 °C and ZnCl$_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise. After stirring for 30 min at the same temperature Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (442 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH$_4$Cl solution (9 mL) and NH$_3$ (conc.) (1 mL) followed by extraction with CH$_2$Cl$_2$ (3×20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and after filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt$_3$, 150:1:1) afforded the product 68l (428 mg, 36%) as colorless resin.

$^1$H-NMR (400 MHz, CDCl$_3$, 25 °C): $\delta$ / (ppm) = 8.24-8.13 (m, 4H, major rotamer), 8.12 (d, $J = 9.3$ Hz, minor rotamer), 8.08-8.04 (m, 1H, major rotamer), 7.85 (d, $J = 2.7$ Hz, 1H, major rotamer), 7.61 (br, 1H, major rotamer), 7.40 (dd, $J = 9.2$, 2.7 Hz, 1H, minor rotamer), 7.34 (dd, $J = 9.2$, 2.7 Hz, 1H, minor rotamer), 7.23 (br, 1H, major rotamer), 5.96-5.59 (m, 2H, 5.03-4.80 (m, 2H), 4.41 (q, $J = 7.1$ Hz, 2H, major rotamer), 4.11 (q, $J = 7.1$ Hz, 2H, minor rotamer), 3.97 (s, 3H, major rotamer), 3.92 (s, 3H, minor rotamer), 3.63-1.47 (m, 11H), 1.42 (t, $J = 7.1$ Hz, 2H, major rotamer), 1.42 (t, $J = 7.1$ Hz, 2H, minor rotamer), 1.24 (t, $J = 7.1$ Hz, 3H, minor rotamer), 1.01 (s, 9H, major rotamer), 0.83 (s, 9H, minor rotamer), 0.17 (s, 3H, major rotamer), 0.12 (s, 3H, minor rotamer), -0.35 (s, 3H, major rotamer), -0.43 (s, 3H, minor rotamer). Ratio of rotamers determined by NMR $\approx$ 3/1.

$^{13}$C-NMR (CDCl$_3$, 100 MHz, 25 °C): $\delta$ / (ppm) = 166.5, 158.3, 152.9, 148.2, 144.5, 143.9, 142.2, 141.9, 132.3, 131.9, 130.6, 130.0, 129.9, 127.2, 126.9, 125.5, 122.0, 121.9, 118.9, 116.4, 114.4, 114.1, 104.4, 100.5, 77.2, 72.8, 61.1, 61.0, 60.8, 57.3, 56.2, 55.9, 55.4, 43.2, 41.3, 40.1, 39.9, 28.2, 27.9, 27.8, 27.8, 27.2, 26.0, 25.7, 21.0, 20.9, 18.1, 18.1, 14.3, 14.2, 1.0, -4.1, -5.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3074, 2950, 2930, 2884, 2858, 1714, 1622, 1608, 1578, 1552, 1502, 1472, 1462, 1422, 1396, 1390, 1366, 1352, 1308, 1264, 1230, 1176, 1102, 1072, 1028, 1020, 1004, 952, 938, 912, 862, 852, 834, 804, 776, 732, 708, 672, 646.

HRMS (ESI) for C$_{35}$H$_{47}$N$_2$O$_4$Si (M+H$^+$) (587.3300): 587.3294.
C. Experimental Section

Synthesis of (1R)-(2-allyl-6-methoxyquinolin-4-yl)((1S,4S,5R)-5-vinylquinuclidin-2-yl)methanol (68m)

A mixture of (1S,4S,5R)-2-((R)-(2-allyl-6-methoxyquinolin-4-yl)((tert-butyldimethylsilyl)oxy)methyl)-5-vinylquinuclidine (68j; 747 mg, 1.6 mmol) and TBAF (1.5 g, 4.8 mmol) in THF (10 mL) was stirred at 25 °C for 12 h. After addition of EtOAc (10 mL) the organic layer was washed with sat. aqueous NaCl solution (3x15 mL) and dried over MgSO4. After filtration the solvents were evaporated in vacuo. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt3, 150:1:1) furnished the product 68m as yellow solid (461 mg, 79%).

M.p. (°C): Decomp. at 83.0.

^1H-NMR (300 MHz, CDCl3, 25 °C): δ / (ppm) = 7.88 (d, J = 9.1 Hz, 1H, minor rotamer), 7.81 (d, J = 9.1 Hz, 1H, minor rotamer), 7.51 (s, 1H, minor rotamer), 7.41 (s, 1H, major rotamer), 7.25-7.15 (m, 1H), 7.12 (d, J = 2.5 Hz, 1H, major rotamer), 7.04 (d, J = 2.7 Hz, 1H, minor rotamer), 6.65-6.40 (m, 1H), 6.09-5.94 (m, 1H), 5.75-5.60 (m, 1H), 5.55-5.46 (m, 1H), 5.15-5.02 (m, 1H), 4.97-4.83 (m, 1H), 3.82 (s, 3H, major rotamer), 3.80 (s, 3H, minor rotamer), 3.65-3.44 (m, 2H), 3.26-2.95 (m, 2H), 2.73-2.57 (m, 2H), 2.33-2.18 (m, 2H), 1.83-1.66 (m, 3H), 1.61-1.32 (m, 2H), 1.14-0.71 (m, 1H). Ratio of rotamers determined by NMR ≈ 3/2.

^13C-NMR (CDCl3, 75 MHz, 25 °C): δ / (ppm) = 157.4, 157.3, 157.2, 153.6, 148.0, 147.7, 143.8, 143.7, 141.6, 135.6, 135.6, 132.1, 131.5, 130.9, 125.2, 124.9, 121.2, 121.1, 118.5, 116.8, 115.8, 101.3, 101.3, 71.5, 71.4, 59.9, 59.9, 56.9, 56.8, 55.6, 55.6, 43.4, 43.3, 43.2, 39.8, 39.8, 27.8, 27.4, 21.2, 21.0, 18.4.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3076, 2998, 2970, 2932, 2872, 2864, 2838, 1744, 1734, 1658, 1620, 1598, 1566, 1554, 1530, 1502, 1476, 1462, 1452, 1434, 1414, 1378, 1352, 1260, 1232, 1164, 1120, 1100, 1032, 994, 966, 910, 862, 830, 808, 788, 744, 692, 666, 644, 612.

HRMS (ESI) for C_{23}H_{29}N_{2}O_{2} (M+H⁺) (365.2224): 365.2220.
Synthesis of \((1R)-(2\text{-iodo-6-methoxyquinolin-4-yl})((1S,4S,5R)-5\text{-vinylquinuclidin-2-yl})\text{methanol (68n)}\)

A mixture of \((1S,4S,5R)-2-((R)-((\text{tert}-\text{butyldimethylsilyl})\text{oxy})(2\text{-iodo-6-methoxyquinolin-4-yl})\text{methyl})-5\text{-vinylquinuclidine (68k; 600 mg, 1.1 mmol})\) and TBAF (1.0 g, 3.2 mmol) in THF (10 mL) was stirred at 25 °C for 12 h. After addition of EtOAc (5 mL) the organic layer was washed with sat. aqueous NaCl solution (3x10 mL) and dried over MgSO\(_4\). After filtration the solvents were evaporated \textit{in vacuo}. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt\(_3\), 150:1:1) furnished the product \textbf{68n} as white solid (406 mg, 82%).

\textbf{M.p. (°C):} Decomp. at 257.6.

\textbf{\textsuperscript{1}H-NMR} (400 MHz, THF-d\(_8\), 25 °C): \(\delta / (\text{ppm}) = 7.83\) (s, 1H), 7.82 (d, \(J = 9.1\) Hz, 1H), 7.41 (d, \(J = 2.7\) Hz, 1H), 7.30 (dd, \(J = 9.1, 2.7\) Hz, 1H), 5.87-5.77 (m, 1 H), 5.34 (br, 1 H), 4.99-4.84 (m, 3H), 3.90 (s, 3H), 3.49-3.36 (m, 1H), 3.11-2.98 (m, 2H), 2.66-2.53 (m, 4H), 2.27-2.19 (m, 1H), 1.84-1.76 (m, 1H), 1.66-1.55 (m, 1H), 1.52-1.42 (m, 1H).

\textbf{\textsuperscript{13}C-NMR} (THF-d\(_8\), 100 MHz, 25 °C): \(\delta / (\text{ppm}) = 158.9, 152.1, 146.6, 143.4, 131.7, 129.8, 127.1, 122.6, 116.5, 114.1, 103.2, 72.4, 61.9, 57.7, 55.9, 43.6, 41.6, 29.4, 28.7, 22.5.

\textbf{IR (Diamond-ATR, neat):} \(\tilde{\nu} / \text{cm}^{-1} = 3070, 3012, 2984, 2950, 2934, 2914, 2898, 2868, 2562, 1752, 1622, 1570, 1546, 1502, 1462, 1452, 1380, 1352, 1304, 1258, 1240, 1202, 1188, 1168, 1144, 1134, 1102, 1088, 1056, 1040, 1004, 996, 966, 946, 910, 884, 876, 854, 822, 800, 762, 696, 666, 648, 636, 606.

\textbf{HRMS (ESI) for C\textsubscript{20}H\textsubscript{24}IN\textsubscript{2}O\textsubscript{2} (M+H\textsuperscript{+})} (451.0877): 451.0873.

15. Preparation of Pd-catalyzed one-pot reaction of aryl- and alkylzinc reagents with aryl halides

Synthesis of \(3'\text{-cyano-biphenyl-4-carboxylic acid ethyl ester (72a)}\)
C. Experimental Section

(a) using Pd(PPh$_3$)$_4$: According to TP5 – Zn insertion: 69a (1.38 g, 5 mmol), LiCl (635 mg, 15 mmol), and Zn (981 mg, 15 mmol) in THF (10 mL), $T_1 = 50 ^\circ$C for 3 h; Cross-coupling: 71a (728 mg, 4 mmol) in THF (2 mL), Pd(PPh$_3$)$_4$ (14 mg, 0.012 mmol), $T_2 = 25 ^\circ$C for 15 h; work-up and purification: extracted with EtOAc (4×10 mL), purified by flash chromatography (silica gel, pentane/Et$_2$O, 3:1) to give 72a (791 mg, 79%).

(b) using PEPPSI: According to TP5 – Zn insertion: 69a (276 mg, 1 mmol), LiCl (64 mg, 1.5 mmol), and Zn (98 mg, 1.5 mmol) in THF (2 mL), $T_1 = 50 ^\circ$C for 10 h; cross-coupling: 71a (0.8 mmol) in THF (0.5 mL), PEPPSI (0.20 mL of 20 mmol/L solution in THF, 0.004 mmol), $T_2 = 25 ^\circ$C for 1.5 h; work-up and purification: extracted with Et$_2$O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et$_2$O, 5:1) to give 72a as white solid (167 mg, 83%).

M. p. (˚C): 90.7-93.3.

$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ / ppm = 8.11-8.16 (m, 2H), 7.87-7.89 (m, 1H), 7.81-7.85 (m, 1H), 7.65-7.68 (m, 1H), 7.60-7.64 (m, 2H), 7.57 (t, $J = 7.7$ Hz, 1H), 4.41 (q, $J = 7.2$ Hz, 2H), 1.41 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (151 MHz, CDCl$_3$): $\delta$ / ppm = 166.1, 143.0, 141.3, 131.6, 131.4, 130.8, 130.4, 130.3, 129.8, 127.0, 118.5, 113.2, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3403, 2980, 2230 1706, 1610, 1466, 1398, 1370, 1270, 1186, 1098, 1020, 906, 861, 796, 764, 687.

MS (EI, 70eV): m/z (%) = 251 [M$^+$] (57), 223 (44), 206 (100), 175 (23).

HRMS (EI) for C$_{16}$H$_{13}$NO$_2$ (251.0946): 251.0943.

Synthesis of 4-pyridin-3-yl-benzoic acid ethyl ester (72b)

According to TP5 – Zn insertion: 69a (276 mg, 1 mmol), LiCl (64 mg, 1.5 mmol), and Zn (98 mg, 1.5 mmol) in THF (2 mL), $T_1 = 50 ^\circ$C for 10 h; cross-coupling: 71b (126 mg, 0.80 mmol), PEPPSI (0.20 mL of a 20 mmol/L solution in THF, 0.004 mmol), $T_2 = 50 ^\circ$C for 3 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane, Et$_2$O, 1:1) to give 72b as white solid (156 mg, 86%).
**M. p. (°C):** 55.0-56.7.

**\(^1\)H-NMR** (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.86 \text{ (brs, 1H)}, 8.54-8.70 \text{ (m, 1H)}, 8.13 \text{ (d, } J = 7.7 \text{ Hz, 2H}), 7.83-7.94 \text{ (m, 1H)}, 7.63 \text{ (d, } J = 7.7 \text{ Hz, 2H}), 7.37 \text{ (dd, } J = 7.8 \text{ Hz, } J = 4.8 \text{ Hz, 1H}).

**\(^{13}\)C-NMR** (75 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 166.2, 149.2, 148.3, 142.1, 135.6, 134.4, 130.3, 130.1, 127.0, 123.6, 61.1, 14.3.

**IR** (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 3052, 2985, 1700, 1608, 1473, 1366, 1285, 1275, 1124, 1102, 1022, 1000, 856, 814, 765, 699, 615.

**MS** (EI, 70 eV): m/z (%) = 227 [M\(^+\)] (87), 199 (31), 182 (100), 154 (19), 127 (14).

**HRMS (EI)** for \(\text{C}_{14}\text{H}_{13}\text{NO}_2\) (227.0946): 227.0945.

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**Synthesis of 3-quinolin-2-yl-benzoic acid ethyl ester (72c)**

According to **TP5 – Zn insertion: 69b** (552 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (4 mL), \(T_1 = 50 \degree \text{C for 12 h; cross-coupling: 71c} \) (262 mg, 1.6 mmol) in THF (2 mL), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), \(T_2 = 40 \degree \text{C for 4.5 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/EtO, 100:18) to give 72c as pale yellow oil (333 mg, 85%).}

**\(^1\)H-NMR** (300 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 8.78-8.81 \text{ (m, 1H)}, 8.21-8.27 \text{ (m, 1H)}, 8.38-8.45 \text{ (m, 1H)}, 8.16-8.21 \text{ (m, 1H)}, 8.11-8.16 \text{ (m, 1H)}, 7.92 \text{ (d, } J = 8.6 \text{ Hz, 1H}), 7.80-7.86 \text{ (m, 1H)}, 7.70-7.78 \text{ (m, 1H)}, 7.50-7.64 \text{ (m, 3H)}, 4.44 \text{ (q, } J = 7.1 \text{ Hz, 2H)}, 1.44 \text{ (t, } J = 7.1 \text{ Hz, 3H}).

**\(^{13}\)C-NMR** (75 MHz, CDCl\(_3\)): \(\delta / \text{ppm} = 166.5, 156.2, 148.3, 139.9, 137.0, 131.9, 131.1, 130.3, 129.8 \text{ (overlapped), 128.9, 128.5, 127.5, 127.3, 126.5, 118.8, 6.13, 14.4.}

**IR** (Diamond-ATR, neat): \(\tilde{\nu} / \text{cm}^{-1} = 3060, 2980, 1713, 1597, 1556, 1556, 1506, 1431, 1366, 1296, 1253, 1230, 1172, 1104, 1080, 1018, 830, 814, 761, 691.

**MS** (EI, 70 eV): m/z (%) = 277 [M\(^+\)] (42), 205 (100), 176 (5), 102 (7).

**HRMS (EI)** for \(\text{C}_{18}\text{H}_{15}\text{NO}_2\) (277.1103): 277.1085.
Synthesis of 4-quinolin-3-yl-benzonitrile (72d)

According to TP5 – Zn insertion: 69c (458 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (4 mL), $T_1 = 50 \, ^\circ\text{C}$ for 8 h; cross-coupling: 71d (333 mg, 1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), $T_2 = 25 \, ^\circ\text{C}$ for 5 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et$_2$O, 1:2.5) to give 72d as white solid (334 mg, 91%).

M. p. (°C): 171.5-173.0.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 9.15 (d, $J = 2.0$ Hz, 1H), 8.32 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.65-7.69 (m, 1H), 7.30-7.33 (m, 5H), 7.16-7.24 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 149.1, 147.9, 142.4, 133.9, 132.9, 131.8, 130.2, 129.4, 128.1, 128.0, 127.7, 127.5, 118.6, 111.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3062, 2227, 1606, 1492, 1436, 1365, 1186, 1124, 952, 908, 832, 786, 752, 637, 558.

MS (EI, 70 eV): m/z (%) = 230 [M$^+$] (100), 175 (3), 115 (2).

HRMS (EI) for C$_{16}$H$_{10}$N$_2$ (230.0844): 230.0830.

Synthesis of 3'-formyl-biphenyl-4-carbonitrile (72e)

According to TP5 – Zn insertion: 69e (458 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (4 mL), $T_1 = 50 \, ^\circ\text{C}$ for 8 h; cross-coupling: 71e (296 mg, 1.6 mmol) in THF (0.5 mL), PEPPSI (0.10 mL of a 80 mmol/L solution in THF, 0.008 mmol), $T_2 = 25 \, ^\circ\text{C}$ for 2 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et$_2$O, 2:1) to give 72e as white solid (267 mg, 80%).
C. Experimental Section

**M. p. (°C):** 129.3-131.2.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 10.1 (s, 1H), 8.05-8.14 (m, 1H), 7.89-7.96 (m, 1H), 7.81-7.88 (m, 1H), 7.61-7.80 (m, 5H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 191.7, 144.1, 140.1, 137.1, 132.9, 132.8, 131.0, 129.9, 127.9, 122.8, 118.6, 111.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3040, 2840, 2233, 2221, 1696, 1585, 1512, 1457, 1381, 1296, 1182, 1010, 876, 838, 793, 712, 688.

MS (EI, 70 eV): m/z (%) = 207 [M$^+$] (100), 178 (43), 151 (27), 103 (9).

HRMS (EI) for C$_{14}$H$_9$NO (207.0684): 207.0677.

**Synthesis of 4'-trifluoromethyl-biphenyl-3-carbonitrile (72f)**

According to TP5 – Zn insertion: 69d (687 mg, 3.0 mmol), LiCl (191 mg, 4.5 mmol), and Zn (294 mg, 4.5 mmol) in THF (6.5 mL), $T_1 = 50$ °C for 8 h; cross-coupling: 71f (540 mg, 2.4 mmol), PEPPSI (8.0 mg, 0.012 mmol), $T_2 = 25$ °C for 4.5 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et$_2$O, 100:8) to give 72f as white solid (490 mg, 83%).

**M. p. (°C):** 61.6-63.8.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.88-7.92 (m, 1H), 7.82 (dt, $J = 7.8$ Hz, $J = 1.6$ Hz), 7.63-7.77 (m, 5H), 7.55-7.62 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 142.3, 141.0, 131.6, 130.8, 130.5 (q, $J = 32.7$ Hz), 129.9, 127.5, 126.1 (q, $J = 272.1$ Hz), 118.5, 113.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2233, 2228, 1615, 1583, 1573, 1397, 1320, 1182, 1174, 1111, 1097, 1067, 1017, 905, 855, 845,834, 804, 794, 742, 705, 688, 636, 616.

MS (EI, 70 eV): m/z (%) = 247 [M$^+$] (100), 228 (8), 197 (5), 178 (6), 151 (4).

HRMS (EI) for C$_{14}$H$_8$F$_3$N (247.0609): 247.0584.
Synthesis of 2’-trifluoromethyl-biphenyl-4-carbonitrile (72g)

According to TP5 – Zn insertion: 69e (816 mg, 3.0 mmol), LiCl (191 mg, 4.5 mmol), and Zn (294 mg, 4.5 mmol) in THF (6.0 mL), \( T_1 = 25 ^\circ C \) for 48 h; cross-coupling: 71g (437 mg, 2.4 mmol), PEPPSI (8.0 mg, 0.012 mmol), \( T_2 = 25 ^\circ C \) for 15 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et₂O, 20:1) to give 72g as white solid (569 mg, 97%).

M. p. (°C): 123.8-125.6.

\( ^1H \)-NMR (300 MHz, CDCl₃): \( \delta / ppm = 7.74-7.79 \) (m, 1H), 7.66-7.72 (m, 2H), 7.49-7.64 (m, 2H), 7.40-7.46 (m, 2H), 7.26-7.32 (m, 1H).

\( ^{13}C \)-NMR (75 MHz, CDCl₃): \( \delta / ppm = 144.5, 139.3, 131.6, 131.4, 129.8, 128.3, 127.9 \) (q, \( J = 30.9 \) Hz), 126.3 (q, \( J = 5.3 \) Hz), 123.9 (q, 273.9 Hz), 118.6, 111.8.

IR (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 2228, 1602, 1577, 1446, 1308, 1296, 1260, 1169, 1164, 1105, 1071, 1033, 1005, 959, 842, 776, 762, 691, 647. \)

MS (EI, 70 eV): m/z (%) = 247 [M⁺] (100), 226 (10), 208 (4), 177 (4).

HRMS (EI) for C₁₄H₈F₃N (247.0609): 247.0612.

Synthesis of 3-(2-methoxy-phenyl)-pyridine (72h)

According to TP5 – Zn insertion: 69If (702 mg, 3.0 mmol), LiCl (191 mg, 4.5 mmol), and Zn (294 mg, 4.5 mmol) in THF (6.0 mL), \( T_1 = 25 ^\circ C \) for 180 h; cross-coupling: 71h (478 mg, 2.4 mmol), PEPPSI (8.0 mg, 0.012 mmol), \( T_2 = 25 ^\circ C \) for 2 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et₂O, 1:1) to give 72h as yellow oil (380 mg, 92%).
C. Experimental Section

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 8.92 (dd, $J$ = 2.2 Hz, $J$ = 0.7 Hz, 1H), 8.67 (dd, $J$ = 5.1 Hz, $J$ = 1.6 Hz, 1H), 7.95 (dt, $J$ = 7.9 Hz, $J$ = 1.9 Hz, 1H), 7.34-7.44 (m, 2H), 7.30 (dd, $J$ = 7.5 Hz, $J$ = 1.8 Hz, 1H), 7.05 (td, $J$ = 7.5 Hz, $J$ = 1.1 Hz, 1H), 7.00 (dd, $J$ = 8.3 Hz, $J$ = 0.7 Hz, 1H), 3.79 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 156.4, 150.0, 147.3, 138.3, 135.0, 130.5, 130.0, 126.0, 123.5, 121.1, 111.3, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2832, 1598, 1581, 1496, 1461, 1450, 1435, 1413, 1405, 1265, 1237, 1122, 1023, 998, 801, 750, 737, 712, 701, 653.

MS (EI, 70 eV): m/z (%) = 185 [M$^+$] (100), 170 (37), 142 (4), 115 (12).

HRMS (EI) for C$_{12}$H$_{11}$NO (185.0841): 185.0848.

Synthesis of acetic acid 4’-cyano-biphenyl-2-yl ester (72i)

![Acetate and cyanide groups](image)

According to TP5 – Zn insertion: 69g (786 mg, 3.0 mmol), LiCl (191 mg, 4.5 mmol), and Zn (294 mg, 4.5 mmol) in THF (7.0 mL), $T_1$ = 25 °C for 48 h; cross-coupling: 71g (437 mg, 2.4 mmol), PEPPSI (8.0 mg, 0.012 mmol), $T_2$ = 25 °C for 0.5 h; work-up and purification: extracted with EtOAc ($3 \times 5$ mL), purified by flash chromatography (silica gel, gradient elution; pentane/Et$_2$O, 10:1 to 5:1) to give 72i as white solid (370 mg, 67%).

M. p. (˚C): 115.7-117.2.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.67-7.72 (m, 2H), 7.50-7.55 (m, 2H), 7.31-7.47 (m, 3H), 7.14-7.18 (m, 1H), 2.09 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 169.0, 147.6, 142.4, 133.1, 132.1, 130.5, 129.7, 129.6, 126.6, 123.1, 118.7, 111.3, 20.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2225, 1748, 1608, 1481, 1443, 1398, 1365, 1215, 1182, 1154, 1112, 1104, 1046, 1007, 914, 841, 835, 828, 773, 682.

MS (EI, 70 eV): m/z (%) = 237 [M$^+$] (7), 195 (100), 166 (5), 140 (5), 43 (9).

HRMS (EI) for C$_{15}$H$_{11}$O$_2$N (237.0709): 237.0765.
Synthesis of 1-(4-thiophen-2-yl-phenyl)-ethanone (72j)

According to TP5 – Zn insertion: 69h (420 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T1 = 25 °C for 0.5 h; cross-coupling: 71i (318 mg, 1.6 mmol), PEPPSI (0.10 mL of a 80 mmol/L solution in THF, 0.008 mmol), T2 = 25 °C for 1 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, gradient elution: pentane/Et2O, 100:10 to 100:15) to give 72j as white solid (266 mg, 82%).

M. p. (˚C): 124.6-126.4.

1H-NMR (300 MHz, CDCl3): δ / ppm = 7.89-8.01 (m, 2H), 7.62-7.73 (m, 2H), 7.42 (dd, J = 3.6 Hz, J = 1.2 Hz, 1H), 7.36 (dd, J = 5.1 Hz, J = 1.2 Hz, 1H), 7.11 (dd, J = 5.1 Hz, J = 3.6 Hz, 1H), 2.60 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ / ppm = 197.2, 142.9, 138.7, 135.7, 129.1, 128.3, 126.4, 125.6, 124.6, 26.5.

IR (Diamond-ATR, neat): ν / cm⁻¹ = 3074, 3006, 1598, 1423, 1358, 1259, 1186, 1116, 954, 850, 824, 713, 652, 592.

MS (EI, 70 eV): m/z (%) = 202 [M⁺] (62), 187 (100), 159 (20), 115 (49), 79 (9), 42(20).

HRMS (EI) for C12H10OS (202.0452): 202.0449.

Synthesis of 4-pyridin-3-yl-benzonitrile (72k)

According to TP5 – Zn insertion: 69i (410 mg, 2.0 mmol), LiCl (254 mg, 6.0 mmol), and Zn (392 mg, 6.0 mmol) in THF (2.0 mL), T1 = 50 °C for 12 h; cross-coupling: 71g (291 mg, 1.6 mmol), PEPPSI (5.3 mg, 0.008 mmol), T2 = 50 °C for 5 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, graduate elution; pentane/Et2O, 1:1 to Et2O) to give 72k as white solid (216 mg, 75%).
C. Experimental Section

M. p. (°C): 103.0-104.3.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / ppm = 8.84 (d, $J = 2.4$ Hz, 1H), 8.65 (dd, $J = 4.7$ Hz, $J = 1.5$ Hz, 1H), 7.83-7.92 (m, 1H), 7.71-7.80 (m, 2H), 7.63-7.71 (m, 2H), 7.34-7.45 (m, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / ppm = 149.7, 148.2, 142.3, 134.7, 134.4, 132.8, 127.1, 123.7, 118.5, 111.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3059, 3040 (2), 2224, 1608, 1473, 1392, 1187, 1024, 964, 850, 810, 714, 624, 565.

MS (EI, 70 eV): m/z (%) = 180 [M$^+$] (100), 153 (16), 127 (18), 100 (6), 76 (5), 63 (4).

HRMS (EI) for C$_{12}$H$_8$N$_2$: 180.0675.

Synthesis of 5-pyridin-3-yl-furan-2-carboxylic acid ethyl ester (72l)

According to TP5 – Zn insertion: 69j (438 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), $T_1 = 30$ °C for 3 h; cross-coupling: 71b (253 mg, 1.6 mmol), PEPPSI (0.10 mL of an 80 mmol/L solution in THF, 0.008 mmol), $T_2 = 50$ °C for 5 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, graduate elution; pentane/Et$_2$O, 1:1 to ether) to give 72l as pale yellow solid (301 mg, 86%).

M. p. (°C): 48.4-49.9.

$^1$H-NMR (300 MHz, CDCl$_3$): δ / ppm = 8.91-9.03 (m, 1H), 8.50-8.60 (m, 1H), 7.99-8.11 (m, 1H), 7.28-7.38 (m, 1H), 7.23 (d, $J = 3.7$ Hz, 1H), 6.81 (d, $J = 3.7$ Hz, 1H), 4.86 (q, $J = 7.1$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ / ppm = 158.5, 154.4, 149.6, 146.2, 144.8, 131.7, 125.7, 123.5, 119.5, 107.9, 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 3121, 2983, 1716, 1566, 1470, 1414, 1372, 1302, 1281, 1226, 1150, 1018, 964, 920, 805, 757, 712.

MS (EI, 70 eV): m/z (%) = 217 [M$^+$] (100), 189 (4), 172 (50), 145 (28), 116 (31), 89 (10), 63 (12).

HRMS (EI) for C$_{12}$H$_8$NO$_3$: 217.0739: 217.0729.
C. Experimental Section

Synthesis of 5-benzo[1,3]dioxol-5-yl-furan-2-carboxylic acid ethyl ester (72m)

According to TP5 – Zn insertion: 69j (438 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), \( T_1 = 30 \, ^\circ\text{C} \) for 3 h; cross-coupling: 71j (367 mg, 1.6 mmol), PEPPSI (0.10 mL of a 80 mmol/L solution in THF, 0.008 mmol), \( T_2 = 50 \, ^\circ\text{C} \) for 20 h; work-up and purification: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, graduate elution: pentane/Et\(_2\)O, 100:10 to 100:15) to give 72m as white solid (379 mg, 91%).

\[ \text{M. p. (}\, ^\circ\text{C}\text{): 97.0-99.2.} \]

\(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 7.28 \) (dd, \( J = 8.1 \, \text{Hz}, J = 1.7 \, \text{Hz}, 1\text{H} \)), 7.21 (d, \( J = 1.7 \, \text{Hz}, 1\text{H} \)), 7.18 (d, \( J = 3.6 \, \text{Hz}, 1\text{H} \)), 6.83 (d, \( J = 8.1 \, \text{Hz}, 1\text{H} \)), 6.56 (d, \( J = 3.7 \, \text{Hz}, 1\text{H} \)), 5.98 (s, 2H), 4.86 (q, \( J = 7.3 \, \text{Hz}, 2\text{H} \)), 1.37 (t, \( J = 7.3 \, \text{Hz}, 3\text{H} \)).

\(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 158.8, 157.3, 148.3, 148.1, 143.3, 123.9, 119.9, 108.6, 105.7, 105.3, 101.4, 60.8, 14.4. \)

\( \text{IR}\) (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 3119, 2992, 2916, 1708, 1472, 1356, 1386, 1303, 1229, 1154, 1034, 966, 932, 864, 813, 758, 686. \)

\( \text{MS}\) (EI, 70 eV): m/z (%) = 260 [M\(^+\)] (100), 232 (58), 215 (13), 159 (22), 129 (9), 107 (9), 75 (9).

\( \text{HRMS (EI) for C}_{14}\text{H}_{12}\text{O}_{5}\) (260.0685): 260.0676.

Synthesis of 4'-Cyano-biphenyl-4-carboxylic acid ethyl ester (72n)

According to TP5 – Zn insertion: 69a (552 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), \( T_1 = 50 \, ^\circ\text{C} \) for 10 h; cross-coupling: 71k (402 mg, 1.6 mmol), PEPPSI (0.10 mL of a 80 mmol/L solution in THF, 0.008 mmol), \( T_2 = 25 \, ^\circ\text{C} \) for
4 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et₂O, 9:1) to give 72n as white solid (313 mg, 78%).

**M. p. (°C):** 118.3-120.4.

**¹H-NMR** (300 MHz, CDCl₃): δ / ppm = 8.16 (d, J = 8.4 Hz, 2H), 7.63-7.79 (m, 6H), 4.43 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H).

**¹³C-NMR** (75 MHz, CDCl₃): δ / ppm = 166.1, 144.5, 143.3, 132.7, 130.6, 130.3, 127.9, 127.2, 118.7, 111.8, 61.2, 14.3.

**IR** (Diamond-ATR, neat): ν / cm⁻¹ = 2989, 2222, 1705, 1605, 1495, 1470, 1396, 1364, 1312, 1265, 1180, 1098, 1020, 1005, 872, 834, 770, 729, 698.

**MS** (EI, 70 eV): m/z (%) = 251 [M⁺] (43), 223 (36), 206 (100), 178 (24), 151 (22), 44 (8).

**HRMS** (EI) for C₁₆H₁₃NO₂ (251.0946): 251.0930.

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**Synthesis of 4-Cyclohex-1-enyl-benzoic acid ethyl ester (72o)**

![Chemical Structure](image)

According to **TP5 – Zn insertion**: 69a (552 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T₁ = 50 °C for 10 h; *cross-coupling*: 71l (368 mg, 1.6 mmol), PEPPSI (0.10 mL of a 80 mmol/L solution in THF, 0.008 mmol), T₂ = 25 °C for 4 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, graduate elution; pentane/Et₂O, 400:1 to 199:1) to give 72o as white solid (276 mg, 75%).

**M. p. (°C):** 71.7-73.1.

**¹H-NMR** (300 MHz, CDCl₃): δ / ppm = 8.00 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 6.25-6.28 (m, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.40-2.48 (m, 2H), 2.21-2.30 (m, 2H), 1.76-1.87 (m, 2H), 1.64-1.75 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H).

**¹³C-NMR** (75 MHz, CDCl₃): δ / ppm = 166.6, 147.0, 135.9, 129.5, 128.4, 127.1, 124.7, 60.8, 27.2, 26.0, 22.9, 22.0, 14.4.

**IR** (Diamond-ATR, neat): ν / cm⁻¹ = 2927, 2862, 1708, 1602, 1462, 1410, 1364, 1271, 1188, 1102, 1018, 921, 869, 835, 768, 747, 696.
C. Experimental Section

**MS** (EI, 70 eV): m/z (%) = 230 [M⁺] (99), 185 (45), 157 (100), 129 (84), 115 (26), 91 (24), 77 (10).


**Synthesis of 4-(3-cyano-propyl)-benzoic acid ethyl ester (75a)**

![Chemical Structure](image)

According to **TP6 – Zn insertion:** 73a (390 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T₁ = 25 °C for 2 h; **cross-coupling:** 71m (367 mg, 1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), DMI (1.0 mL), T₂ = 25 °C for 2 h; **work-up and purification:** extracted with Et₂O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et₂O, 2:1) to give 75a as yellow oil (299 mg, 86%).

**¹H-NMR** (300 MHz, CDCl₃): δ / ppm = 7.94-8.02 (m, 2H), 7.20-7.29 (m, 2H), 4.36 (q, J = 7.0 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H), 2.37-2.27 (m, 2H), 1.93-2.06 (m, 2H), 1.38 (t, J = 7.0 Hz, 3H).

**¹³C-NMR** (75 MHz, CDCl₃): δ / ppm = 166.4, 144.9, 130.0, 129.0, 128.4, 119.2, 60.9, 34.4, 26.6, 16.5, 14.3.

**IR** (Diamond-ATR, neat): ν / cm⁻¹ = 2982, 2934, 2247, 1710, 1611, 1447, 1417, 1367, 1272, 1178, 1101, 1021, 861, 761, 704.

**MS** (EI, 70 eV): m/z (%) = 217 [M⁺] (7), 189 (9), 172 (100), 149 (6), 135 (5), 91 (5).

**HRMS (EI)** for C₁₃H₁₅NO₂ (217.1103): 217.1096.

**Synthesis of 4-(4-acetyl-phenyl)-butyronitrile (75b)**

![Chemical Structure](image)

According to **TP6 – Zn insertion:** 73a (390 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T₁ = 25 °C for 2 h; **cross-coupling:** 71i (318 mg,
1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), DMI (1.0 mL), $T_2 = 25 \, ^\circ C$ for 2 h; *work-up and purification*: extracted with Et$_2$O (3×5 mL), purified by flash chromatography (silica gel, gradient elution; pentane/Et$_2$O, 2:1 to 1:2) to give $75b$ as yellow oil (210 mg, 70%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 7.84-7.92 (m, 2H), 7.21-7.30 (m, 2H), 2.82 (t, $J = 7.4$ Hz, 2H), 2.56 (s, 3H), 2.32 (t, $J = 7.4$ Hz, 2H), 1.98 (quint, $J = 7.4$ Hz, 2H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 197.6, 145.3, 135.6, 128.7, 128.6, 119.2, 34.3, 26.5, 26.4, 16.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2931, 2246, 1678, 1606, 1414, 1358, 1266, 1183, 1114, 1017, 956, 836, 802, 690, 599.

MS (EI, 70 eV): m/z (%) = 187 [M$^+$] (54), 173 (100), 144 (20), 131 (17), 116 (39), 103 (19), 91 (20).

HRMS (EI) for C$_{12}$H$_{13}$NO (187.0997): 187.0984.

**Synthesis of 4-(4-formyl-phenyl)-butyric acid ethyl ester (75c)**

According to **TP6 – Zn insertion**: $73b$ (484 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), $T_1 = 50 \, ^\circ C$ for 12 h; *cross-coupling*: $71j$ (296 mg, 1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), DMI (1.0 mL), $T_2 = 25 \, ^\circ C$ for 1 h; *work-up and purification*: extracted with Et$_2$O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et$_2$O, 4:1) to give $75c$ as yellow oil (307 mg, 87%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ / ppm = 9.96 (s, 1H), 7.76-7.83 (m, 2H), 7.30-7.37 (m, 2H), 4.12 (q, $J = 7.3$ Hz, 2H), 2.68-2.77 (m, 2H), 2.32 (t, $J = 7.4$ Hz, 2H), 1.91-2.05 (m, 2H), 1.24 (t, $J = 7.3$ Hz).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ / ppm = 191.9, 173.1, 148.9, 134.7, 130.0, 129.2, 60.4, 35.3, 33.5, 26.1, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm$^{-1}$ = 2951, 1725, 1676, 1609, 1575, 1426, 1320, 1290, 1255, 1172, 1019, 934, 859, 760, 696.
MS (EI, 70 eV): m/z (%) = 220 [M+](100), 175 (18), 147 (23), 133 (90), 117 (7), 105 (10), 91 (17).

HRMS (EI) for C_{13}H_{16}O_{3} (220.1099): 220.1071.

Synthesis of 4-(4-acetyl-phenyl)-butyric acid ethyl ester (75d)

According to TP6 – Zn insertion: 73b (484 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T<sub>1</sub> = 50 °C for 12 h; cross-coupling: 71i (318 mg, 1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), DMI (1.0 mL), T<sub>2</sub> = 25 °C for 2 h; work-up and purification: extracted with Et<sub>2</sub>O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et<sub>2</sub>O, 5:1) to give 75d as yellow oil (257 mg, 83%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ / ppm = 7.83-7.91 (m, 2H), 7.21-7.30 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.64-2.75 (m, 2H), 2.57 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 1.92-2.02 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ / ppm = 197.8, 173.2, 147.2, 135.3, 128.7, 128.6, 60.3, 35.1, 33.5, 26.5, 26.1, 14.2.

IR (Diamond-ATR, neat): ν / cm<sup>-1</sup> = 2981, 2937, 1729, 1680, 1606, 1571, 1413, 1358, 1266, 1181, 1146, 1018, 956, 843, 806, 597, 572.

MS (EI, 70 eV): m/z (%) = 234 [M+](100), 219 (33), 189 (22), 118 (6), 90 (7).

HRMS (EI) for C_{14}H_{18}O_{3} (234.1256): 234.1255.

Synthesis of 4-quinolin-2-yl-butyric acid ethyl ester (75e)

According to TP6 – Zn insertion: 73b (484 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T<sub>1</sub> = 50 °C for 12 h; cross-coupling: 71c (327 mg,
1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), DMI (1.0 mL), 

\( T_2 = 50 \, ^\circ\text{C} \) for 15 h; work-up and purification: extracted with Et\(_2\)O (3×5 mL), purified by flash chromatography (silica gel, gradient elution; pentane/Et\(_2\)O, 2:1 to 3:2) to give 75e as yellow oil (285 mg, 73%).

\(^1\text{H-NMR}\) (300 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 7.98-8.10 \) (m, 2H), 7.74-7.79 (m, 1H), 7.62-7.72 (m, 1H), 7.43-7.52 (m, 1H), 7.30 (d, \( J = 8.5 \, \text{Hz} \), 1H), 4.11 (q, \( J = 7.1 \, \text{Hz} \), 2H), 2.90-3.08 (m, 2H), 2.41 (t, \( J = 7.5 \, \text{Hz} \), 2H), 2.27-2.07 (m, 2H), 1.23 (t, \( J = 7.1 \, \text{Hz} \), 3H).

\(^{13}\text{C-NMR}\) (75 MHz, CDCl\(_3\)): \( \delta / \text{ppm} = 173.4, 161.7, 147.9, 136.3, 129.4, 128.9, 127.5, 126.8, 125.8, 121.3, 60.3, 38.3, 33.8, 24.9, 14.2.\n
\textbf{IR} (Diamond-ATR, neat): \( \tilde{\nu} / \text{cm}^{-1} = 3058, 2979, 2935, 1728, 1600, 1504, 1426, 1374, 1307, 1244, 1178, 1139, 1026, 951, 827, 753, 618.\n
\textbf{MS} (EI, 70 eV): m/z (%) = 243 [M\(^{+}\)] (15), 198 (67), 170 (100), 156 (26), 143 (32), 128 (25), 115 (19).

\textbf{HRMS (EI)} for C\(_{15}\)H\(_{17}\)NO\(_2\) (243.1259): 243.1215.
D. Appendix
1. Curriculum Vitae

Personal Informations

Name: Milica Jaric (née: Gvozdenac)
Date of Birth: 19.01.1981
Place of Birth: Munich
Citizenship: Bosnian
Marital Status: married since Aug/2007

Education

Since June/2007: PhD thesis in the group of Prof. Dr. P. Knochel on “The Frustrated Lewis Pair Concept Applied to the Functionalization of N-Heterocycles”

Languages

German: native speaker
Bosnian: native speaker
English: fluently
French: fluently
Spanish: basic proficiency
Italian: basic proficiency

Hobbies

reading, skiing, tennis
**Publications**


**Posters**