Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

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

von

Milica Jaric, geb. Gvozdenac

aus
München

2011

Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 (in der Fassung der vierten Änderungssatzung vom 26. November 2004) von Herrn Prof. Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe bearbeitet.

München, am 21. Januar 2011

.....
Milica Jaric

Dissertation eingereicht am 21.01.2011

1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Manfred Heuschmann

Mündliche Prüfung am 24.02.2011

This work was carried out from August 2007 to January 2011 under the guidance of Prof. Dr. Paul Knochel at the Department Chemie und Pharmazie of the Ludwig-Maximilians-Universität, Munich.

Firstly, I would like to express my appreciation to Prof. Dr. Paul Knochel for giving me the great opportunity to do my Ph.D. in his group and for his guidance and support in the course of my scientific research.

I am also very grateful to Prof. Dr. Manfred Heuschmann for agreeing to be my "Zweitgutachter" as well as Prof. Dr. Heinz Langhals, Prof. Dr. Konstantin Karaghiosoff, Prof. Dr. Hans Rudolf Pfaendler and Prof. Dr. Rudolf Knorr for their interest shown in this manuscript by accepting to be referees.

I really would like to thank Laurin Melzig, Tobias Blümke and Sebastian Bernhardt for the careful correction of this manuscript. Furthermore, I want to thank Silvia Zimdars for her great support in formatting "a lot of stuff".

I would like to thank Benjamin Haag for the successful collaboration in the field of the frustrated Lewis pairs and Andreas Unsinn for the endless discussions. I would like to thank Dr. Vladimir Malakhov and Dr. Shohei Sase for the fruitful collaboration in the field of the arylzinc chemistry and Sophia Manolikakes, as well as Dr. Coura Diène for their great support in the area of the quinine functionalization.

I thank all past and present co-workers I have met in the Knochel group for their kindness and their help. Special thanks to my actual and former lab mates Tobias Blümke, Dr. Stéphanie Duez, Sophia Manolikakes, Dr. Albrecht Metzger, Nadja Barl, Dr. Murthy N. Cheemala, Dr. Yi-Hung Chen and Dr. Shohei Sase for the great time together with good music.

Additional thanks go to Matthias Schade, Andreas Wagner, Klaus Groll, Thomas Kunz, Cora Dunst, Tomke Bresser, Gabriel Monzon, Tobias Thaler, Andreas Steib, Christoph Sämann, Zhihua Peng, Zhi-Liang Shen, Stephanie Seel, Dr. Xavier Mollat du Jourdin, Dr. Alexei Bredihhin and Dr. Christina Despotopoulou for being fantastic colleagues.

I would also like to thank Dr. Vladimir Malakhov, Simon Matthe, Beatrix Cammelade, Renate Schröder and Yulia Tsvik for their help in organizing everyday life in the lab and in the office, as well as the analytical team of the LMU for their invaluable help.

I thank Demetria Dolores Pérez Hernandéz for her contribution to this work in course of her internship in the Knochel group.

Special thanks to my friends Sanela Babic, Borislava Peric, Andreas Latkovic, Danijela Maric, Ljiljana and Nadja Bojic for their backup throughout this time.

I would like to thank my husband Slavko for his love and support.

Very special thank to my parents and my sister for their great support, throughout my studies, my Ph.D and all the other years. I couldn´t have done this without you!

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

S. Sase, **M. Jaric**, A. Metzger, V. Malakhov, P. Knochel: "One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents with Aryl Chlorides, Bromides, and Triflates" *J. Org. Chem.* **2008**, *73*, 7380.

M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel: "Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or Zn- and Mg-TMP-Bases with $BF_3 \cdot OEt_2$" *Angew. Chem. Int. Ed.* **2010**, *49*, 5451 (**hot paper**); *Angew. Chem.* **2010**, *122*, 5582.

M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel: "Selective and Multiple Functionalization of Complex Pyridines and Alkaloids *via* Mg- and Zn-Organometallic Intermediates" *Org. Lett.*, accepted.

Мојим родитељима
којима дугујем 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

Table of Contents

Abbreviations

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
bs	broad singulet
Bn	benzyl
Bu	butyl
*t*Bu	*t*-Butyl
calc.	calculated
conc.	concentrated
Cp*	pentamethylcyclopentadienyl
d	doublet
δ	chemical shifts in parts per million
dba	*trans,trans*-dibenzylideneacetone
dest.	distilled
DMAE	dimethylaminoethanol
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
E	electrophile
EI	electron ionization
ESI	electrospray ionization
EN	electronegativity
equiv	equivalent
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium diisopropylamide
m	multiplet
M	molar
m	*meta*
Me	methyl
Met	metal
min	minute
mmol	millimole
M.p.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidine
o	*ortho*
p	*para*
PG	protecting group
Ph	phenyl
Py	pyridine
q	quartet
R	organic substituents
rt	room temperature
s	singulet
sat.	saturated
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
t	triplet

TBAF	tetrabutylammonium fluoride	TLC	thin layer chromatography
TBDMS	tertbutyldimethylsilyl	TMP	2,2,6,6-tetramethylpiperidyl
*t*Bu	*tert*-butyl	TMPH	2,2,6,6-tetramethylpiperidine
Tf	triflates	TMS	trimethylsilyl
tfp	tris-(2-furyl)phosphine	TP	typical procedure
THF	tetrahydrofuran	Ts	4-toluenesulfonyl
TIPS	triisopropylsilyl		

A. Introduction

1. Overview

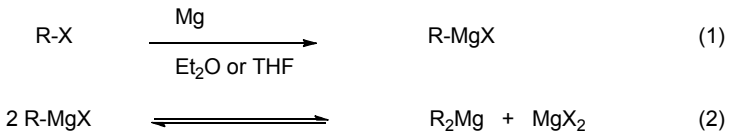
The remarkable flowering of organometallic chemistry begining from the second half of the 20th century up to now has enriched and transformed chemical science and technology to a degree and in ways that have few parallels in the history of the discipline.[1] These include the discovery of radically new types of chemical compounds, novel structures and bonding modes, unprecedent 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.[2] 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.[3,4] Organometallic compounds provide a general approach to complex molecules and numberless applications in total synthesis prove their suitability.[5] A large number of metals was used in synthetic organic chemistry to overcome ongoing problems.[6] Depending on the nature of the carbon-metal bond the reactivity towards numerous electrophiles can be excellent (organolithium compounds)[7] 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.[8]

[1] J. Halpern, *Pure Appl. Chem.* **2001**, *73*, 209.
[2] The Royal Swedish Academy of Science, press Release: **2010**.
[3] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
[4] W. B. Motherwell, D. Chrich, *Free Radical Chain Reaction in Organic Synthesis*, Academic Press, London, **1192**.
[5] K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, **2003**.
[6] (a) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**; (b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed, Wiley-VCH, Weinheim, **2004**.
[7] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[8] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

2. Preparation of Funtionalized 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).[9] 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.[10]



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.[11] In solution, Grignard reagents (RMgX) are in equilibrium (*Schlenk* equilibrium) with R_2Mg and MgX_2 (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.[12]

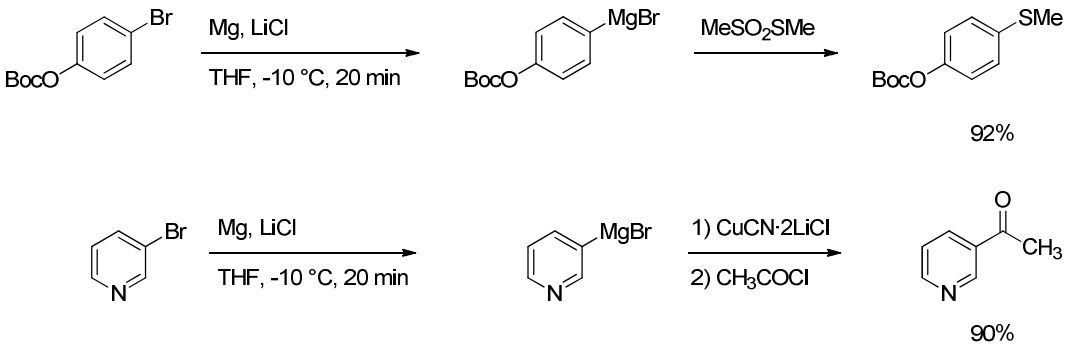
For the formation of organometallic species, such a direct insertion combines several advantages, like atom economy and the low toxicity of magnesium. In addition, magnesium turnings are one of the cheapest reagents in organometal chemistry.

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 $MgCl_2$.[13] This very reactive magnesium species was used for the preparation of different functionalized aryl magnesium reagents at -78 °C.

---

[9] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[10] G. E. Coates, K. Wade, *The Main Group Elementes*, 3rd ed, Methuem, London, **1967**.
[11] (a) M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, **1954**; (b) H. M. Walborsky, *Acc. Chem. Res.* **1990**, *23*, 286; (c) J. F . Garst, *Acc. Chem. Res.* **1991**, *24*, 95.
[12] W. Schlenk, Jr. Schlenk, *Chem. Ber.* **1929**, *62*, 920.
[13] (a) J. Lee, R. Velarde-Ortiz, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; (b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; (c) R. D. Rieke, *Aldrichim. Acta* **2000**, *33*, 52; (d) R. D. Rieke, M. S. Sell, W. R. Klein, T. -A. Chen, J. D. Brown, M. U. Hansen, *Active Metals. Preparation, Characterization, Application*, A. Fürstner, (Ed.), Wiley-VCH, Weinheim, **1996**.

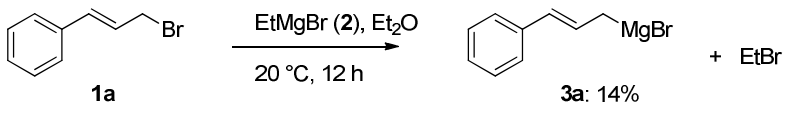
Recently, *Knochel et al.* reported the convenient preparation of various aryl and heteroaryl magnesium reagents from aryl and heteroaryl halides by a direct magnesium insertion in the presence of LiCl.[14] This salt has a fundamental role and serves several purposes. Firstly, it solubililizes the resulting 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.[15] This new method allows the preparation of funtionalized aryl and heteroaryl magnesium reagents which were previously inaccessible due to incompatibility of various functional groups with magnesium (Scheme 2).



Scheme 2: Preparation of functionalized Grignard reagents using magnesium turnings in the presence of LiCl and subsequent quenching with electrophiles.

2.2 The halogen/magnesium exchange reaction

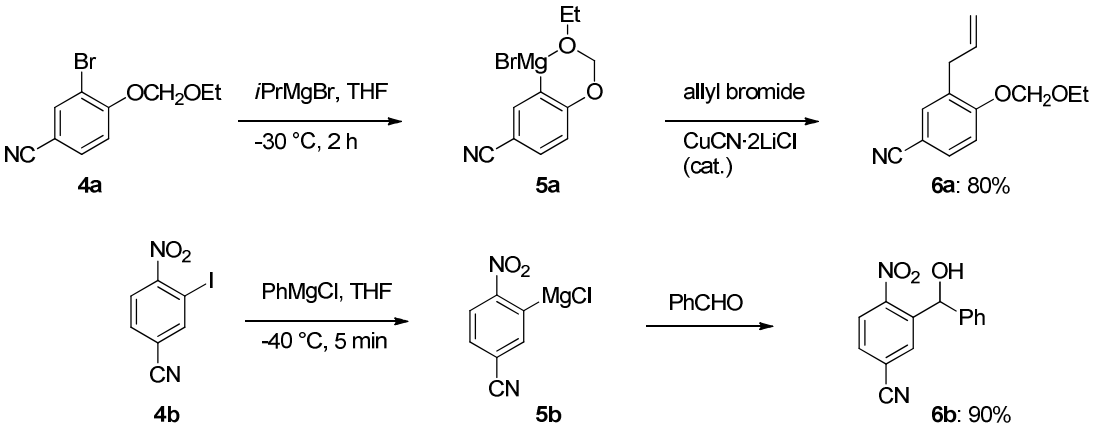
An alternative preparation of organomagnesium reagents consists in the halogen/magnesium exchange reaction. In 1931, *Prévost* reported the first example of a bromine/magnesium exchange by reacting cinnamylmagnesium bromide (**1a**) with ethylmagnesium bromide (**2**) furnishing cinnamylmagnesium bromide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



Scheme 3: First example of a halogen/magnesium exchange reaction.

[14] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[15] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, **2003**, p. 46.
[16] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.

Over the years, this procedure has turned out to be the method of choice for preparing functionalized organometallic compounds of great synthetic utility.[17] The requirement of such a reaction is that the generated magnesium reagent has to be more stable than the exchange reagent ($sp > sp_2(vinyl) > sp_2(aryl) > sp_3(prim.) > sp_3(sec.)$).[18] Moreover, the formation rate of the new Grignard reagent also depends on the electronic properties of both the halogen atom and the organic molecule.[19] 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 *i*PrMgBr 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).

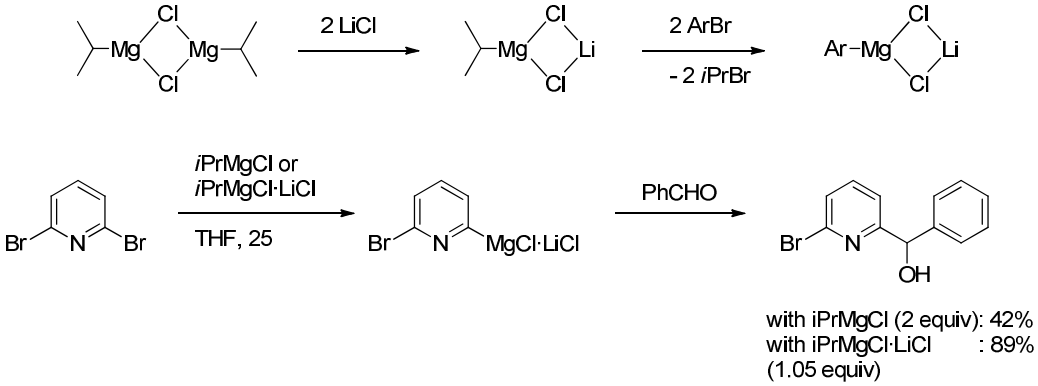


Scheme 4: Examples of halogen/magnesium exchange reaction and trapping with electrophiles.

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

[17] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed*. **2003**, *42*, 4302.
[18] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev*. **2006**, *10*, 733.
[19] C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153.

breaking the aggregates of *i*PrMgCl.[20] The new mixed organometallic *i*PrMgCl·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).



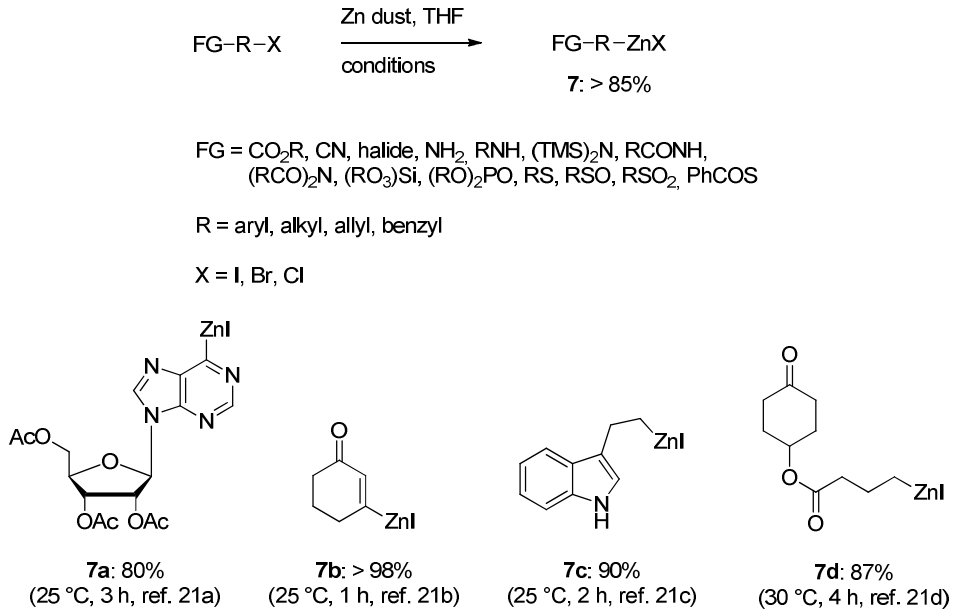
Scheme 5: Rate acceleration of the bromine/magnesium exchange reaction by LiCl.

[20] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

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]

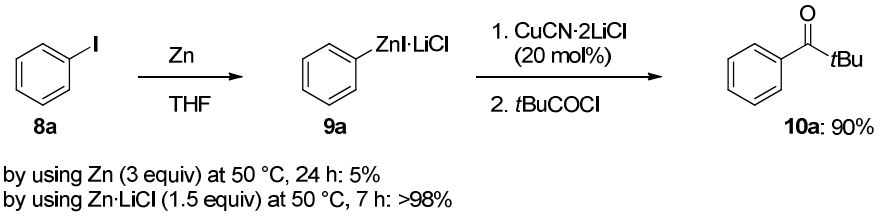


Scheme 6: Preparation of funcionalized organozinc reagents (**7**) by the direct insertion of zinc metal into the corresponsing iodide.

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]

[21] (a) T. M. Stevenson, B. Prasad, J. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375; (b) P. Knochel, C. Janakiram, *Tetrahedron* **1993**, *49*, 29; (c) H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974; (d) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[22] (a) R. D. Rieke, *Science* **1989**, *246*, 1260; (b) M. V. Hanson, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; (c) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; (d) M. V. Hanson, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 1445; (e) R. D: Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.
[23] (a) M. Gaudemar, *Bull. Soc. Chim. Fr.* **1962**, *5*, 974; (b) E. Erdik, *Tetrahedron* **1987**, *43*, 2203.
[24] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

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.

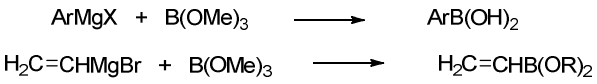
This method allows a convenient and high-yielding access to various alkyl, aryl and heteroarylzinc reagents under mild conditions. Additionally, all reactions proceed within a practical temperature range (25-50 °C) and can be extended to large scale preparation.

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

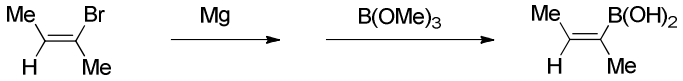
4.1 Alkylation of organomagnesium or lithium reagents with trialkyl borate

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).[25]



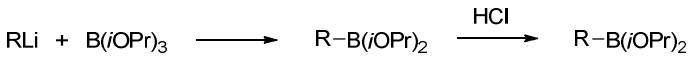
Scheme 8: Preparation of organoboron reagents.

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).[26]



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).[27]

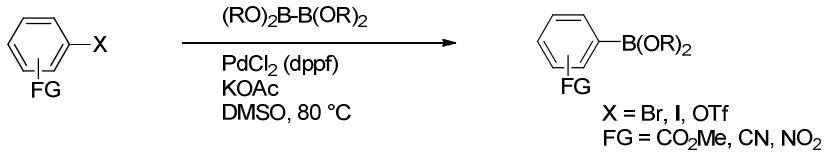


Scheme 10: Preparation of organoboronic esters from organolithium reagents.

[25] (a) W. Gerrard, *The Chemistry of Boron*, Academic, New York, **1961**; (b) E. L. Muetterties, *The Chemistry of Boron and its Compounds*, Wiley, New York; **1967**.
[26] D. S. Matteson, J. D. Liedtke, *J. Am. Chem. Soc.* **1965**, *87*, 1526.
[27] (a) H. C. Brown, T. E. Cole, *Organometallics* **1983**, *2*, 1316; (b) H. C. Brown, N. G. Bhat, M. Srebnik, *Tetrahedron Lett.* **1988**, *29*, 2631; (c) H. C. Brown, M. V. Rangaishenvi, *Tetrahedron Lett.* **1990**, *49*, 7113.

4.2 Pd-catalyzed cross-coupling reaction of aryl halides with bis(pinacolato)diboron

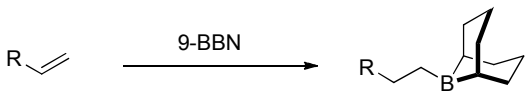
A very efficient route to arylboronic esters tolerating a wide range of functional groups, such as ester, nitrile or acyl groups has been described by *Miyaura et al.* Aryl halides are directly utilized in cross-coupling reactions with (alkoxy)diborons under Pd catalysis (Scheme 11).



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.



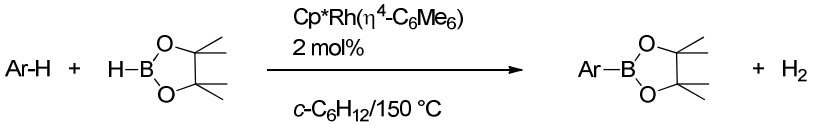
Scheme 12: Hydroboration of 1-alkene to give alkylboron copmpound.

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,

[28] (a) H. C. Brown, *Organic Syntheses via Boranes*, Wiley, New York, **1975**, (b) N. Miyaura, T. Ishiyama, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314.

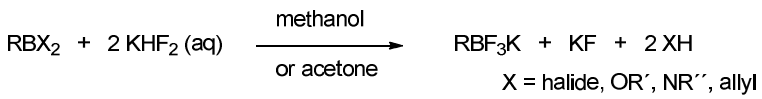
arenes and benzylic positions of alkylarenes by pinacolborane for example, provide alkyl-, aryl-, heteroaryl- and benzylboron compounds, respectively (Scheme 13).[29]



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. Aditionally, they combine economy, efficiency and benignity *inter alia* in the synthesis of complex natural products or other challenging structures.[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).[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.[32] But applications in large scale turn out to be difficult due to the corrosive character of flourine.



Scheme 14: Preparation of potassium organotrifluoroborates.

[29] T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3.
[30] S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
[31] E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020.
[32] G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.

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[33] and amidozincates such as Li[*t*Bu$_2$(tmp)Zn] introduced by *Kondo et al*.[34] 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[35] (**11**), TMPZnCl·LiCl[36] (**12**), TMP$_2$Mg·2LiCl[37] (**13**), TMP$_2$Zn·2MgCl$_2$·2LiCl[38] (**14**) and TMP$_3$Al·3LiCl[39] (**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 atmosophere at ambient temperatures.

[33] (a) P. E. Eaton, R. M. Martin, *J. Org. Chem.* **1988**, *53*, 2728. (b) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc*. **1989**, *111*, 8016. (c) Y. Kondo, Y. Akihiro, T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2331. (d) M. Shilai, Y. Kondo, T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **2001**, 442. (e) M.-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169. (f) P. E. Eaton, M.-X. Zhang, N. Komiya, C. G. Yang, I Steele, R. Gilardi, *Synlett* **2003**, *9*, 1275.

[34] (a) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) T. Imahori, M. Uchiyama, T. Sakamoto, Y. Kondo, *Chem. Commun.* **2001**, 442.

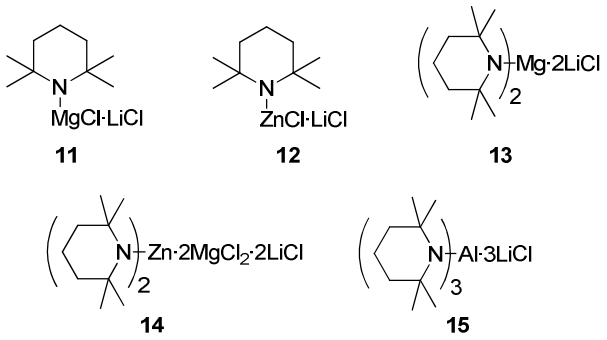
[35] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

[36] (a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. (b) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406. *(c)* M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.

[37] (a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed*. **2007**, *46*, 7681. (b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503. (c) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel *Org. Synth.* **2009**, *86*, 374.

[38] (a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. (b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

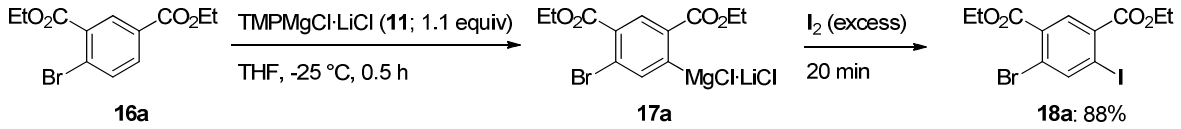
[39] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed*. **2009**, *48*, 1501.



Scheme 15: TMP-derived, mixed metal/Li amide bases.

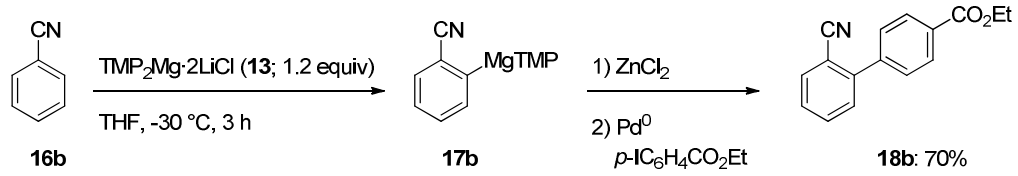
5.2 Magnesium amide bases

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**).

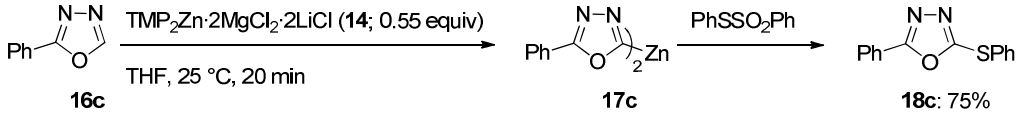
However, for poorly activated substrates such as benzonitriles (**16b**), only a sluggish metalation is observed with TMPMgCl·LiCl (**11**). For this purpose $TMP_2Mg·2LiCl$ (**13**) was developed featuring an improved kinetic basicity. By using the latter, benzonitrile (**16b**) was magnesiated within 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.

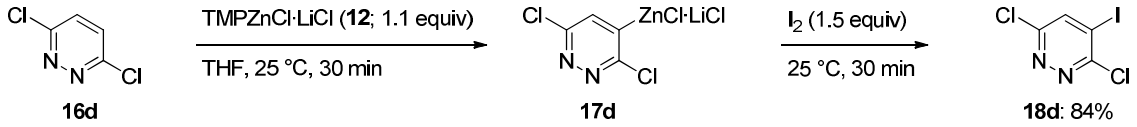
5.3 Zinc amide bases

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.[40] Changing from lithium or magnesium to another metal, namely zinc, enables the metalation at 25 °C without any undesired side reactions.[38a] Thus, **16c** is deprotonated at 25 °C with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**) within 20 min providing the heteroarylzinc compound (**17c**) which furnishes the expected product (**18c**) after quenching with $PhSSO_2Ph$ in 75% yield (Scheme 18).



Scheme 18: Selective zincation of heterocycle **16c** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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 $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**). To address this problem a chemoselective base was developed tolerating sensitive functionalities such as an aldehyde, a nitro group or sensitive heterocycles.[36] Using this new base TMPZnCl·LiCl (**12**) several heteroarenes, like pyridazines[41] and pyrimidines[42] are cleanly zincated 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-dichlorpyrazine (**16d**) using TMPZnCl·LiCl (**12**) and subsequent trapping with I_2.

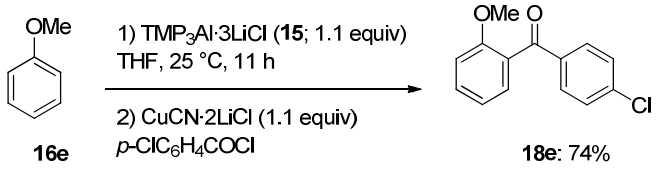
[40] (a) R. G. Micetich, *Can. J. Chem.* **1970**, *48*, 2006; (b) A. I. Meyers, G. N. Knaus, *J. Am. Chem. Soc.* **1973**, *95*, 3408; (c) G. N. Knaus, A. I. Meyers, *J. Org. Chem.* **1974**, *39*, 1189; (d) R. A. Miller, M. R. Smith, B. Marcune, *J. Org. Chem.* **2005**, *70*, 9074; (e) C. Hilf, F. Bosold, K. Harms, M. Marsch, G. Boche, *Chem. Ber./Recl.* **1997**, *130*, 1213.

[41] S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, *47*, 6387.

[42] (a) A. Turck, N. Plé, G. Quéguiner, *Heterocycles* **1990**, *37*, 2149; (b) R. Radinov, C. Chanev, M. Haimova, *J. Org. Chem.* **1991**, *56*, 4793; (c) T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082.

5.4 Aluminum amide bases

Another challenge are electron-rich compounds, which are also very difficult to metalate since aromatic ethers are poor *ortho*-directing groups even for lithiation reactions,[43] not to mention magnesium and zinc amides. However, aluminum amides are powerful reagents for the metalation 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 $TMP_3Al \cdot 3LiCl$ (**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).

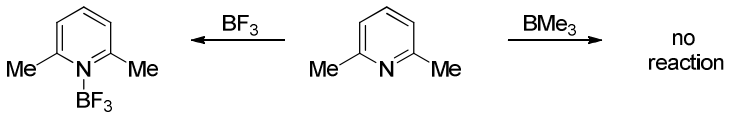


Scheme 20: Selective *ortho*-alumination of anisole (**16e**) with $TMP_3Al \cdot 3LiCl$ (**15**) and subsequent copper-mediated acylation.

[43] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

6. Frustrated Lewis Pairs

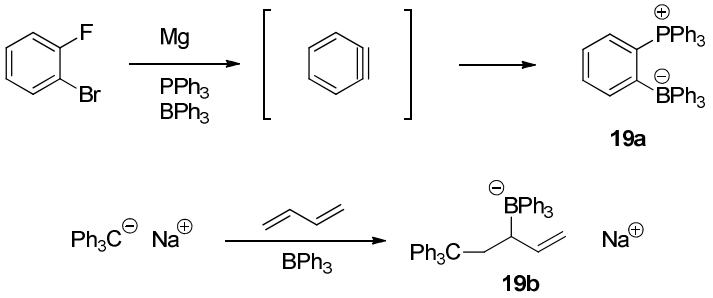
First in 1923 Gilbert N. Lewis proposed a concept whereupon molecules that donate electron-pairs act as bases and conversely those which accept electron-pairs are classified as acids. Thus, combining a simple Lewis acid with a Lewis base results in neutralization similar to the corresponding combination 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 BMe_3 (Scheme 21).[44]



Scheme 21: Treatment of lutidine with BF_3 and BMe_3.

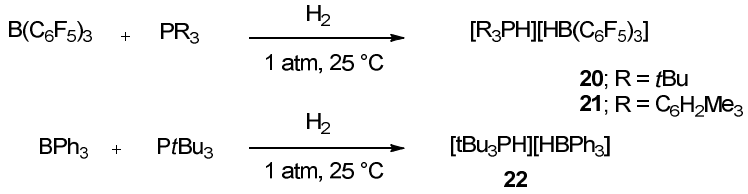
Based on molecular models, this anomal result was attributed to the steric demand of the *ortho*-methyl groups of lutidine. But its impact on subsequent reactivity was not further pursued at that time. In 1950, *Wittig et al.* described that 1,2-didehydrobenzene, generated *in situ* from *o*-fluorobromobenzene, reacts with a mixture of the Lewis base triphenylphosphine and the Lewis acid triphenylboran to give the *o*-phenylenebridged phosphonium-borate **19a** (Scheme 22).[45] 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 BPh_3 to the mixture of butadiene monomer and trityl anion initiator (Scheme 22).[46]

[44] (a) H. C. Brown, H. I. Schlesinger, S. Z. Cardon, *J. Am. Chem. Soc.* **1942**, *64*, 325. (b) H. C. Brown, B. Kanner, *J. Am. Chem. Soc.* **1966**, *88*, 986.
[45] G. Wittig, E. Benz, *Chem. Ber.* **1959**, *92*, 1999.
[46] W. Tochtermann, *Angew. Chem.* **1966,** *78*, 355; *Angew. Chem. Int. Ed.* **1966,** *5*, 351.



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 (PR_3, R = $C_6H_2Me_3$ or *t*Bu) and boranes (BR'_3, R´ = C_6F_5) can easily cleave molecular hydrogen (H_2) in a heterolytic manner under very mild conditions (Scheme 23),[47] and they can undergo addition reactions with olefins as well.[48] Furthermore, compounds of the type R_2P-C_6H_4-BR'_2 have been shown to reversibly activate and liberate H_2[49] and act as effective hydrogenation catalyst for the reduction of C-N multiple bonds.[50]

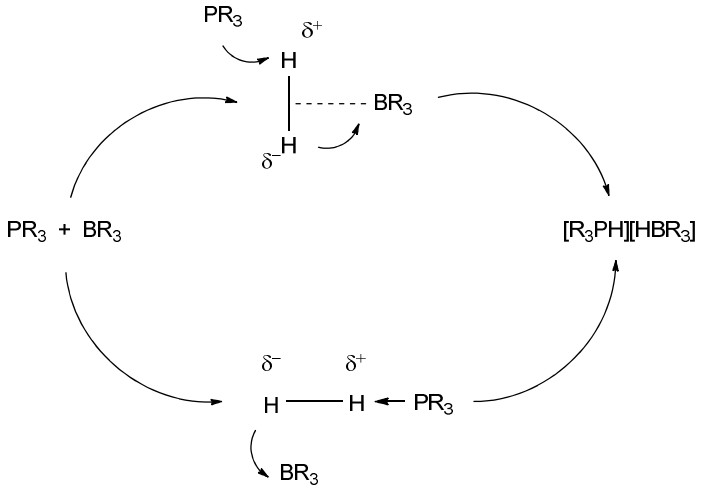


Scheme 23: Heterolytic cleavage of H_2 py phosphine and borane.

By analogy to transition metal chemistry, it is anticipated that a side-on interaction of H_2 with the Lewis acid BR_3 (R = C_6F_5, C_6H_5) results in polarization of H_2, thus facilitating protonation of an approaching phosphine resulting in the formation of **20-22** (Scheme 24). Attempts to observe such a Lewis acid-H_2 interaction were undertaken by treatment by $B(C_6F_5)_3$ with

[47] (a) G. C. Welch, D. W. Stephan, *J. Am. Chem. Soc.* **2007**, *129*, 1880; (b) P. Spies, G. Erker, G. Kehr, K. Bergander, R. Fröhlich, S. Grimme, D. W. Stephan, *Chem. Commun.* **2007**, 5072.
[48] J. S. J. McCahill, G. C. Welch, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 4968.
[49] G. C. Welch, R. R. San Juan, J. D. Masuda, D. W. Stephan, *Science* **2006**, *314*, 1124.
[50] P. A. Chase, G. C. Welch, T. Jurca, D. W. Stephan, *Angew. Chem.* **2007**, *119*, 8196; *Angew. Chem. Int. Ed.* **2007**, *46*, 8050.

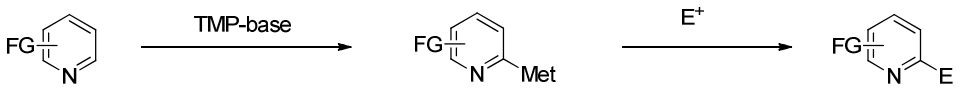
higher pressures of H_2 (4 atm). Monitoring these mixtures by ^{1}H- and ^{19}F-NMR spectroscopy at temperatures as low as 190 K showed resonances attributable to free $B(C_6F_5)_3$. No other species were observed, and thus this experimental evidence suggests that a borane-H_2 adduct is not stable.[47a]



Scheme 24: Suggested mechanisms for heterolytic cleavage of H_2 by phosphine and borane.

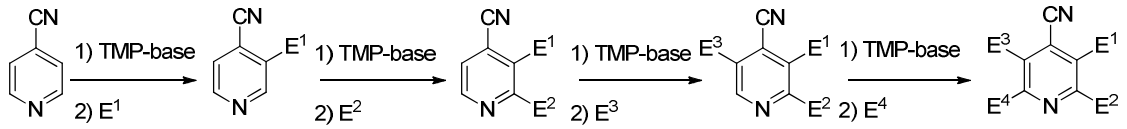
7. Objectives

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).



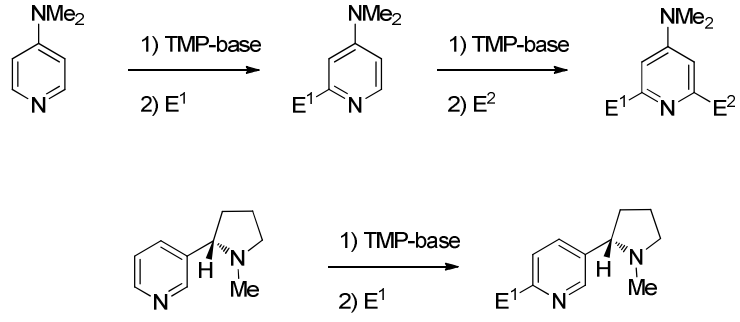
Scheme 25: General pathway for the metalation of poorly activated pyridines.

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).



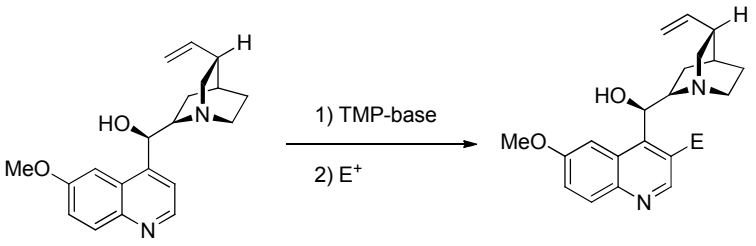
Scheme 26: Multiple regio- and chemoselective functionalizations of the pyridine core *via* directed metalation.

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



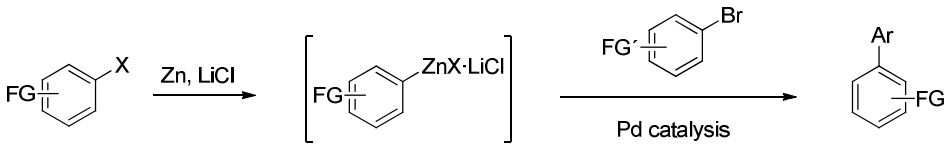
Scheme 27: Regio- and chemoselective functionalization of DMAP and (*S*)-nicotine.

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.

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).



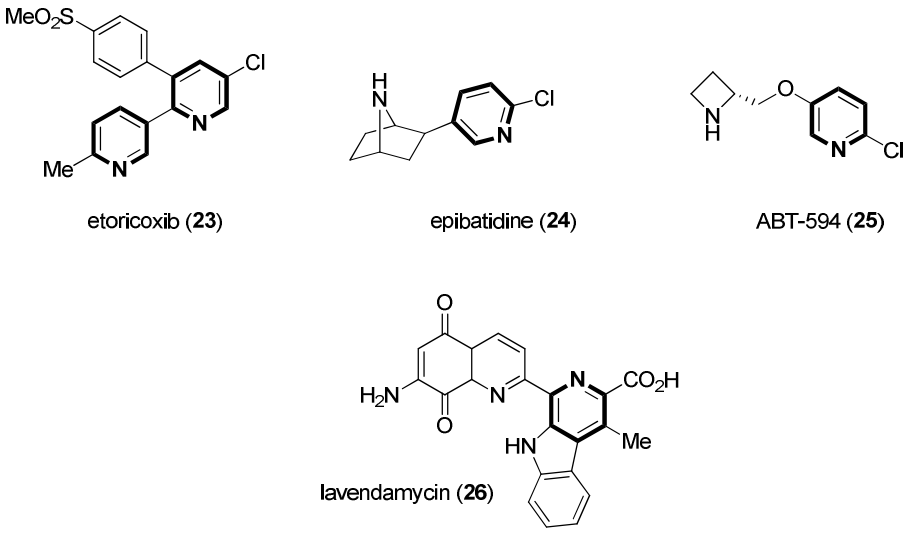
Scheme 29: *In situ* generation of arylzinc reagents followed by Pd-catalyzed cross-coupling reaction.

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 continously. 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.



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

[51] R. W. Friesen, C. Brideau, C. C. Chan, S. Charleson, D. Deschênes, D. Dubé, D. Ethier, R. Fortin, J. Y. Gauthier, Y. Girard, R. Gordon, G. M. Greig, D. Riendeau, C. Savoie, Z. Wang, E. Wong, D. Visco, L. J. Xu, R. N. Young, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2777.
[52] T. F. Spande, H. M. Garaffo, M. W. Edwards, H. J. C. Yeh, L. Pannell, J. W. Daly, *J. Am. Chem. Soc.* **1992**, *114*, 3475.

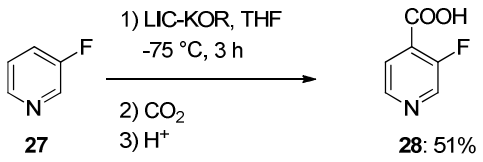
resulting in respiratory paralysis and death.[53] Nonetheless, this alkaloid served as an exciting lead in the search for novel analgesics. However, despite these structural similarities to epibatidine (**24**) ABT-594 (**25**) was discovered accidently during tests against Alzheimer's Disease. It combines namely potent analgesic activity with a highly satisfactory safety profile.[54] Finally, lavendamycin (**26**), a naturally occurring pyridine derivative isolated from the fermentation broth of *Streptomyces lavendulae*, shows antimicrobial and cytotoxic properties. [55] However, its biological interest is limited by its toxicity toward human cells that may be linked to the presence of the quinone moiety.[56]

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.[57] Among metalations, the halogen-metal exchange has proven to be an efficient process.[58] But often the parent halopyridines are not available and therefore a more straightforward route to functional derivatives is offered by direct metalations.[59] 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[60] or LiTMP have been proposed. [61,62] However, equilibrated reactions were observed, implying trapping of

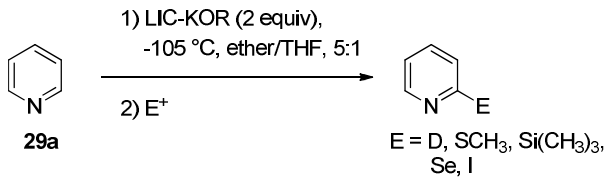
[53] D. W. Bonhaus, K. R. Bley, C. A, Broka, D. J. Fontana, E. Leung, R. Lewis, A. Shieh, E. H. F. Wong, *J. Pharmacol. Exp. Ther.* **1995**, *273*, 1199.
[54] M. W. Holladay, J. T. Wasicak, N.-H. Lin, Y. He, K. B. Ryther, A. W. Bannon, M. J. Buckley, D. J. B. Kim, M. W. Decker, D. J. Anderson, J. E. Campbell, T. A. Kuntzweiler, D. L. Donnelly-Roberts, M. Piattoni-Kaplan, C. A. Briggs, *J. Med. Chem.*, **1998**, *41*, 407.
[55] A. Nourry, S. Legoupy, F. Huet, *Tetrahedron Lett.* **2007**, *48*, 6014.
[56] D. L. Boger, Y. M. Mitscher, S. D. Drake, P. A. Kitos, S. C. Thompson, *J. Med. Chem.* **1987**, *30*, 1918.
[57] G. D. Henry, *Tetrahedron* **2004**, *29*, 6043.
[58] (a) F. Marsais, F. Trecourt, P. Breant, G. Quéguiner, *J. Heterocycl. Chem.* **1988**, *25*, 81; (b) M. A. Peterson, J. R. Mitchell, *J. Org. Chem.* **1997**, *62*, 8237; (c) G. Karig, J. A. Spencer, T. Gallagher, *Org. Lett.* **2001**, *3*, 835; (d) P. C. Gros, F. Elaachbouni, *Chem. Commun.* **2008**, 4813; (e) A. Doudouh, C. Woltermann, P. C. Gros, *J. Org. Chem.* **2007**, *72*, 4978.
[59] P. C. Gros, Y. Fort, *Eur. J. Org. Chem.* **2009**, 4199.
[60] (a) R. R. Fraser, A. Baignée, M. Bresse, K. Hata, *Tetrahedron Letters* **1982**, *23*, 4195. (b) F. Marsais, G. Quéguiner, *Tetrahedron* **1983**, *39*, 2009. (c) A. Hosomi, M. Ando, H. Sakurai, *Chem. Lett.* **1984**, *13*, 1385. (d) D. L. Comins, D. H. LaMunyon, *Tetrahedron Lett.* **1988**, *29*, 773. (e) A. S. Galiano-Roth, Y. J. Kim, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, D. B. Collum, *J. Am. Chem. Soc.* **1991**, *113*, 5053. (f) F. E. Romesberg, D. B. Collum, *J. Am. Chem. Soc.* **1992**, *114*, 2112.
[61] (a) R. R. Fraser, A. Baignée, M. Bresse, K. Hata, *Tetrahedron Lett.* **1982**, *23*, 4195. (b) F. Marsais, G. Quéguiner, *Tetrahedron* **1983**, *39*, 2009. (c) A. Hosomi, M. Ando, H. Sakurai, *Chem. Lett.* **1984**, *13*, 1385. (d) D. L. Comins, D. H. LaMunyon, *Tetrahedron Lett.* **1988**, *29*, 773. (e) A. S. Galiano-Roth, Y. J. Kim, J. H.

lithiated pyridines *in situ*.[63] 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).[64]



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

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.[65] Thus, only few compounds are efficiently accessible by this method (Scheme 32).



Scheme 32: Metalation of pyridine (**29a**) using an excess of superbase.

Gilchrist, A. T. Harrison, D. J. Fuller, D. B. Collum, *J. Am. Chem. Soc.* **1991**, *113*, 5053. (f) F. E. Romesberg, D. B. Collum, *J. Am. Chem. Soc.* **1992**, *114*, 2112.

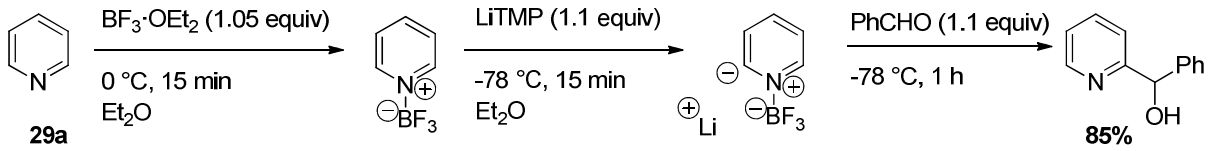
[62] (a) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582. (b) S. L. Taylor, D. Y. Lee, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4156. (c) R. R. Fraser, M. Bresse, T. S. Mansour, *J. Org. Chem.*, *Chem. Commun.* **1983**, 620. (d) P. L. Hall, J. H. Gilchrist, D. B. Collum, *J. Am. Chem. Soc.* **1991**, *113*, 9571. (e) N. Plé, A. Turck, P. Martin, S. Barbey, G. Quéguiner, *Tetrahedron Lett.* **1993**, *34*, 1605.

[63] F. Trecourt, M. Mallet, F. Marsais, G. Quéguiner, *J. Org. Chem.* **1988**, *53*, 1367.

[64] G-Q. Shi, S. Takagishi, M. Schlosser, *Tetrahedron* **1994**, *50*, 1129.

[65] J. Verbeek, L. Brandsma, *J. Org. Chem.* **1984**, *49*, 3857.

An elegant solution has been proposed by *Kessar et al.* who showed that a complexation of pyridine (**29a**) with BF_3 allows a low temperature α-lithiation of **29a** (Scheme 33).[66]

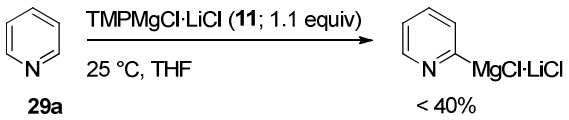


Scheme 33: Metallation of BF_3-complexed pyridine using LiTMP and subsequent reaction with aldehyde.

This procedure is also applicable to tertiary amines affording α-carbanions,[67] which is remarkable since nitrogen does not provide sufficient stabilisation to an adjoining negative charge, unlike phosphorus and sulphur.[68]

1.3 Regio- and chemoselective functionalization of pyridine and its derivatives using TMP-derived bases in the presence of BF_3·OEt_2

Recently, the preparation of various TMP-derived metal/Li-bases has been reported for the directed metalation of sensitive aromatics and heteroaromatics, with a great compatibility with a broad range of functional groups. However, attempts to magnesiate, zincate, or aluminate 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**).

This prompted us to explore the impact of BF_3·OEt_2 in directed metalations using TMP-derived bases (**11-15**) (Scheme 35).

[66] S. V. Kessar, P. Singh, M. Dutt, *J. Chem. Soc., Chem. Commun.* **1991**, 570.
[67] S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, K. N. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568.
[68] (a) D. J. Peterson, *J. Organomet. Chem.* **1967**, *9*, 373. (b) H. Schmidbaur, E. Weiss, B. Zimmermann-Gasser, *Angew. Chem. Int. Ed.* **1979**, *18*, 782.

Scheme 35: Selective metalation of pyridine and its derivatives (**29a-e**) by complexation with BF_3 and subsequent addition of TMPMgCl·LiCl (**11**).

Thus, complexation of pyridine (**29a**) with $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$ and thereupon it reacted with TMPMgCl·LiCl (**11**) for 20 min at -40 °C providing after trapping with I_2 the product (**30b**) in 63% yield. Transmetalation of the intermediate with $ZnCl_2$ enabled a *Negishi* cross-coupling[69] 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 benzoyl 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 zincated at position 3 by using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**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 metalated species ended up in 71% yield (entries 8 and 9). While ethyl isonicotinate[37a] requires the use of $TMP_2Mg \cdot 2LiCl$ 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 BF_3 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). Futhermore, electron-rich substituted pyridines, such as 4-methoxypyridine (**29e**) can be metalated applying this procedure. Thus, after precomplexation with $BF_3 \cdot OEt_2$, **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).

[69] (a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

Table 1: Products obtained by complexation with BF_3 and subsequent addition of the appropriate TMP-base.

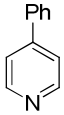
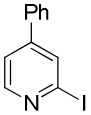
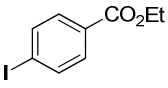
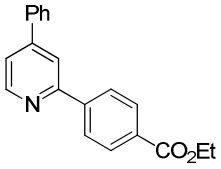
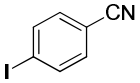
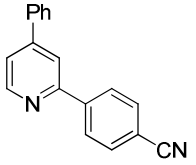
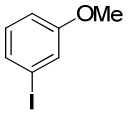
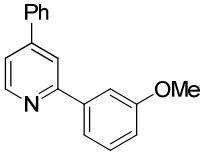
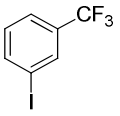
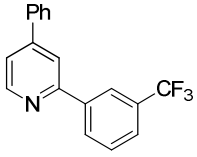
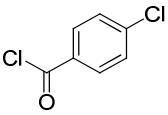
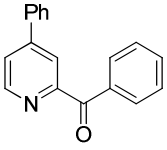
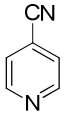
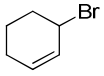
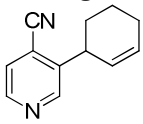
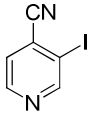
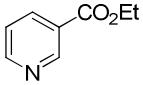
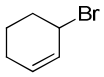
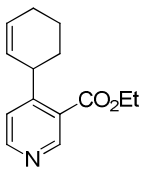
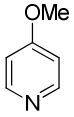
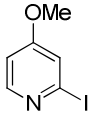
Entry	Substrate	Temperature [°C] / Time [h]	Electrophile	Product	Yield [%][a]
1	 **29a**	-40 / 0.25	I_2	 **30a**	61
2	 **29b**	-40 / 0.3	I_2	 **30b**	63
3	**29b**	-40 / 0.3		 **30c**	84[b]
4	**29b**	-40 / 0.3		 **30d**	82[b]
5	**29b**	-40 / 0.3		 **30e**	81[b]
6	**29b**	-40 / 0.3		 **30f**	75[b]
7	**29b**	-40 / 0.3		 **30g**	77[c]
8	 **29c**	-20 / 3		 **30h**	77[c]
9	**29c**	-20 / 3	I_2	 **30i**	71
10	 **29d**	-40 / 0.5		 **30j**	75[c]

Table 1 continued

11	 **29e**	-20 / 30	I_2	 **30k**	75

[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 $P(2\text{-furyl})_3$. [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 anolog 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 resistent *P. falcipurum* malaria and is also well-tolerated for long-term malaria chemoprophylaxis.[74]

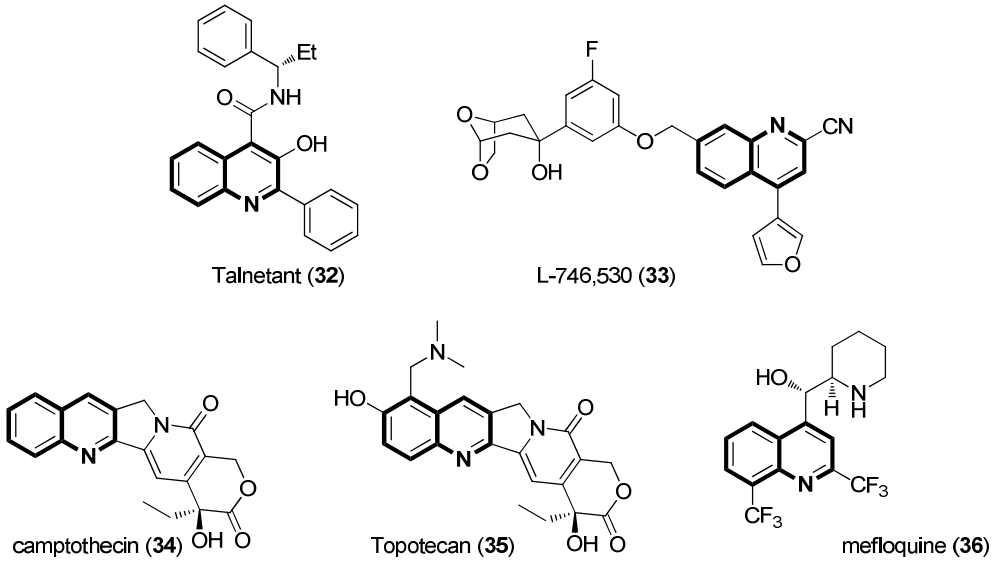
[70] (a) G. A. M. Giardina, L. F. Raveglia, M. Grugni, H. M. Sarau, C. Farina, A. D. Mendhurst, D. Graziani, D. B. Schmidt, R. Rigolio, M. Luttmann, S. Cavagnera, J. J. Foley, V. Vecchietti, D. W. P. Hay, *J. Med. Chem.* **1999**, *42*, 1053; (b) J. M. Elliot, R. W. Carling, M. Chambers, G. C. Chicchi, P. H. Hutson, B. A. Jones, A. MacLeod, R. Marwood, G. Meneses-Lorente, E. Mezzogori, F. Murray, M. Rigby, I. Royo, M. G. N. Russel, B. Sohal, K. L. Tsao, B. Williams, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5748.

[71] D. Dubé, M. Blouin, C. Brideau, C.-C. Chan, S. Desmarais, D. Ethier, J.-P. Falgueyret, R. W. Friesen, M. Girard, J. Guay, D. Riendeau, P. Tagari, R. N. Young, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255.

[72] (a) G. Stork, A. G. Schultz, *J. Am. Chem. Soc.* **1971**, *93***,** 4074; (b) E. Winterfeldt, T. Korth, D. Pike, M. Boch, *Angew. Chem. Int. Ed.* **1972**, *11*, 289.

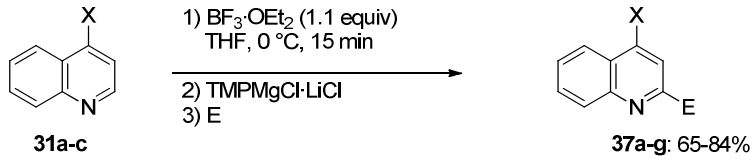
[73] (a) D. Ormrod, C. M. Spencer, *Drugs* **1999**, *58*, 533; (b) T. J. Herzog, *Oncologist* **2002**, *7(Suppl. 5)*, 3; (c) J. M. D. Fortunak, A. R. Mastrocola, M. Mellinger, N. J. Sisti, J. L. Wood, Z.-P. Zhuang, *Tetrahedron Lett.* **1996**, *37*, 5679.

[74] (a) S. Adam, *Tetrahedron* **1991**, *36*, 7609; (b) P. G. Bray, S. A. Ward, (c) J. Wiesner, R. Ortmann, H. Jomaa, M. Schlitzer, *Angew. Chem. Int. Ed.* **2003**, *42*, 5274.



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 $BF_3 \cdot OEt_2$



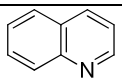
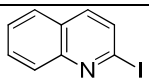
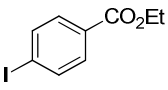
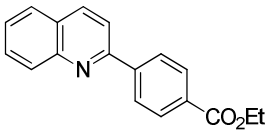
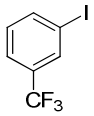
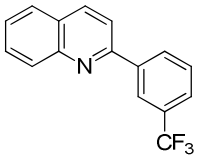
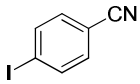
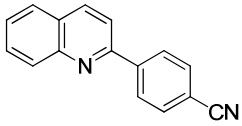
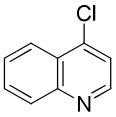
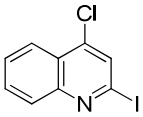
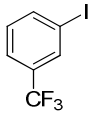
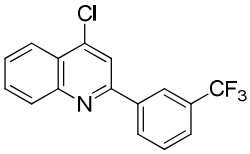
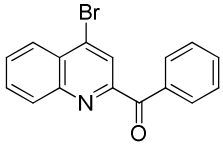
Scheme 37: Selective metalation of quinoline and its derivatives (**31a-c**) by complexation with BF_3 and subsequent addition of TMPMgCl·LiCl (**11**).

Thus, precomplexation with $BF_3 \cdot OEt_2$ (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-iodoquinoline (**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-iodoquinoline (**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 $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) using

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).

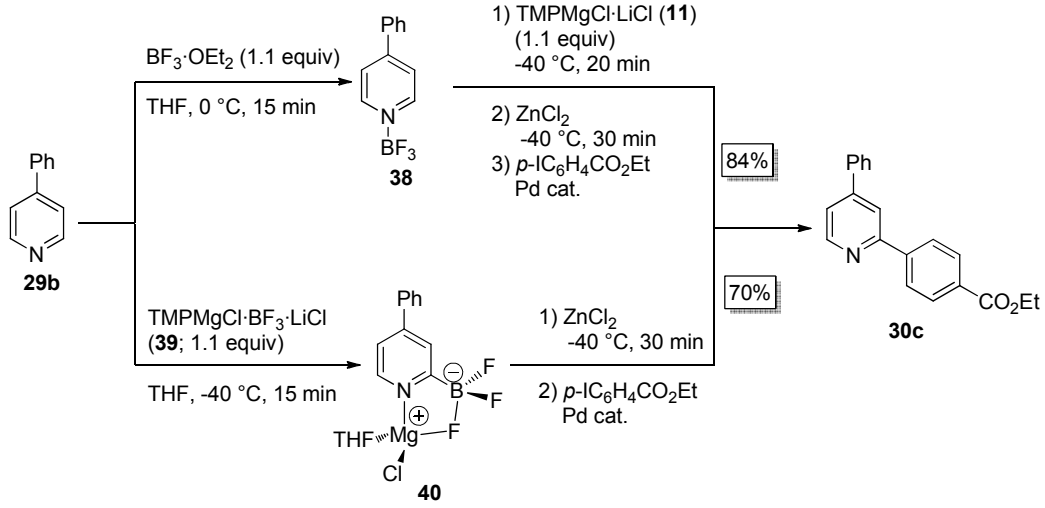
Table 2: Products obtained by complexation with BF_3 and subsequent addition of TMPMgCl·LiCl (**11**).

Entry	Substrate	Temperature [°C] / Time [h]	Electrophile	Product	Yield [%][a]
1	 **31a**	0 / 0.3	I_2	 **37a**	75
2	**31a**	0 / 0.3		 **37b**	80[b]
3	**31a**	0 / 0.3		 **37c**	82[b]
4	**31a**	0 / 0.3		 **37d**	80[b]
5	 **31b**	-10 / 0.2	I_2	 **37e**	65
6	**31b**	-10 / 0.2		 **37f**	70[b]
7	 **31c**	-10 / 0.3	I_2	 **37g**	84[c]

[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 $P(2\text{-furyl})_3$. [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

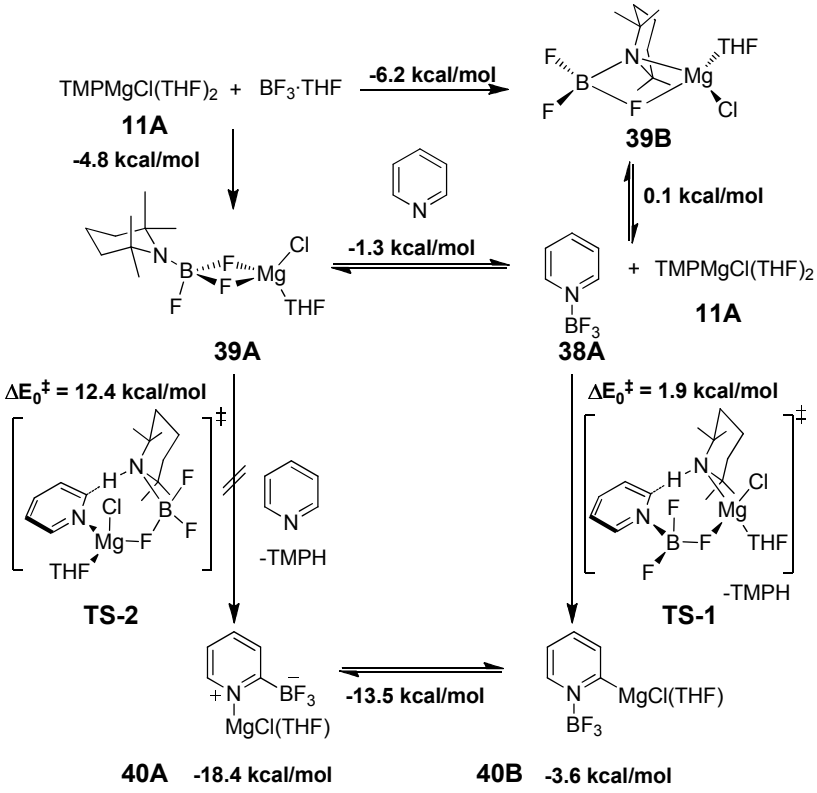
The complexation of 4-phenylpyridine (**29b**) with $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) furnishes the intermediate (**38**). The subsequent addition of TMPMgCl·LiCl (**11**; 1.1 equiv, -40 °C, 20 min) generates a metalated pyridine derivative, which after transmetalation with $ZnCl_2$ and a subsequent *Negishi* cross-coupling with ethyl 4-iodobenzoate affords the product **30c** in 84% yield (Scheme 38).



Scheme 38: Selective BF_3-triggered metalations.

In exploring the scope of this metalation method, we queried the nature of the generated organometallic intermediate in which the strong Lewis acid $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$ (1.1 equiv) and TMPMgCl·LiCl (**11**; 1.1 equiv, -40 °C, 10 min), tentatively written as TMPMgCl·BF_3·LiCl (**39**), and compared the result with the above described two-step metalation with prior complexation with $BF_3 \cdot OEt_2$ and subsequent addition of TMPMgCl·LiCl (**11**) (Scheme 38). An efficient metalation with the reagent **39** occurs within 10 min at -40 °C. Transmetalation with $ZnCl_2$ and a *Negishi* cross-coupling reaction with the aryl iodide provides the 2-arylated pyridine (**30c**) in 70% yield (Scheme 38). This alternative metalation method involves a new frustrated Lewis pair TMPMgCl·BF_3·LiCl (**39**) that is quite reactive for the selective metalation 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.[75] This structure has also been supported by DFT-calculations.[76] 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.[77,78,79] The exact

[75] R. A. Oliveira, R. O. Silva, G. A. Molander, P. H. Menezes, *Magn. Reson. Chem.* **2009**, *47*, 873.

[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).

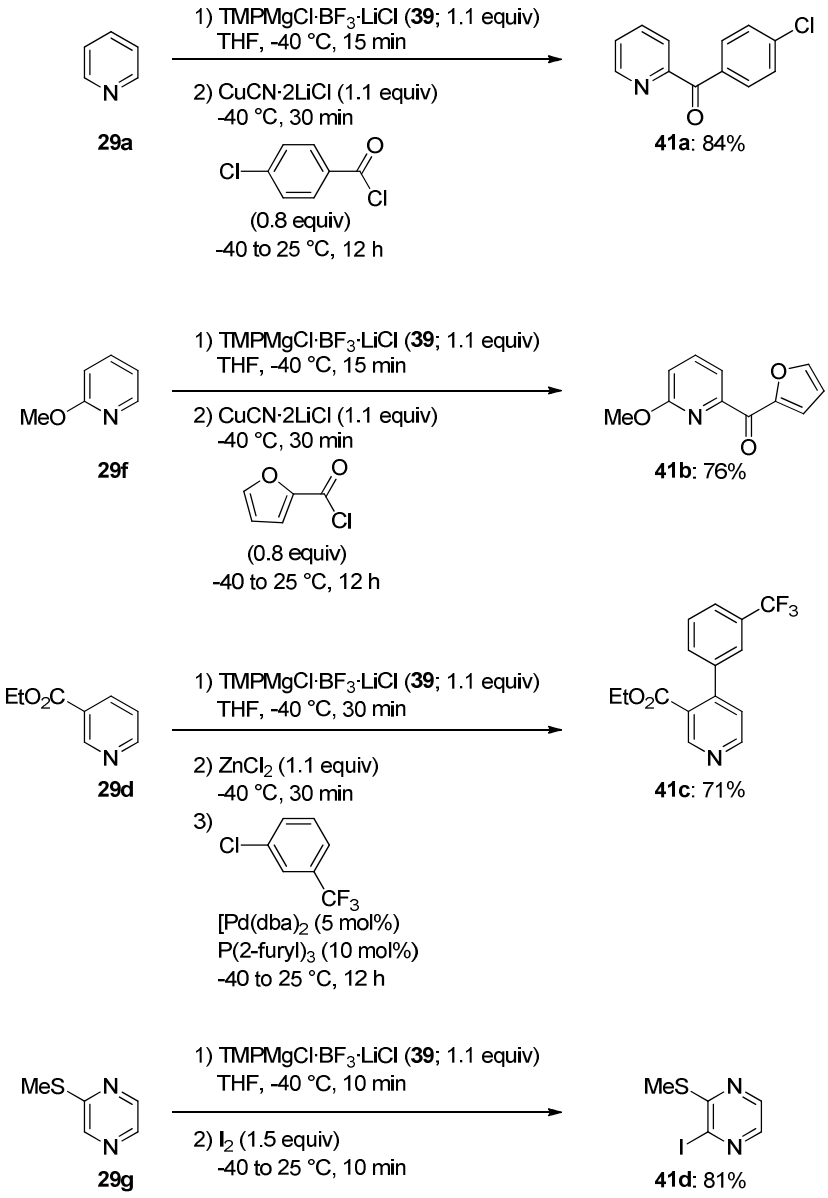
[77] This cross-coupling proceeds less efficiently in the absence of $ZnCl_2$. For details on stability and cross-coupling of potassium α-pyridyltrifluoroborates, see: (a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302. (b) K. Billingsley, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 4773; *Angew. Chem. Int. Ed.* **2008**, *47*, 4695.

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).[80] 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.[81] 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.[82] 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

[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.
[79] For an excellent review, see: G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.
[80] These calculations were done by B. A. Haag and are mentioned here for sake of clarity.
[81] (a) P. Gros, Y. Fort, G. Quéguiner, P. Caubère, *Tetrahedron Lett.* **1995**, *36*, 4791. (b) P. Gros, Y. Fort, P. Caubère, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071.
[82] G. Bentabed-Ababsa, S. Cheikh Sid Ely, S. Hesse, E. Nassar, F. Chevallier, T. Tai Nguyen, A. Derdour, F. Mongin, *J. Org. Chem.* **2010**, *75*, 839.

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).

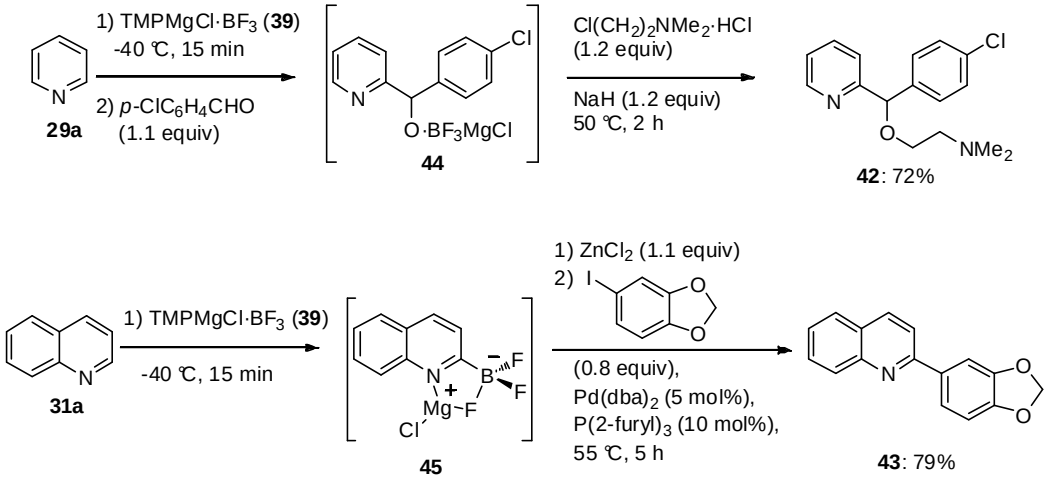


Scheme 40: Regioselective metalation of *N*-heterocycles with the frustrated Lewis pair **39**.

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

[83] This experiment was done by B. A. Haag and is mentioned here for sake of completeness.
[84] (a) B. Garat, C. Landa, O. Rossi Richeri, R. Tracchia, *J. Allergy* **1956**, *27*, 57. (b) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675.
[85] C. M. Melendez Gomez, V. V. Kouznetsov, M. A. Sortino, S. L. Alvarez, S. A. Zacchino, *Bioorg. Med. Chem.* **2008**, *16*, 7908.

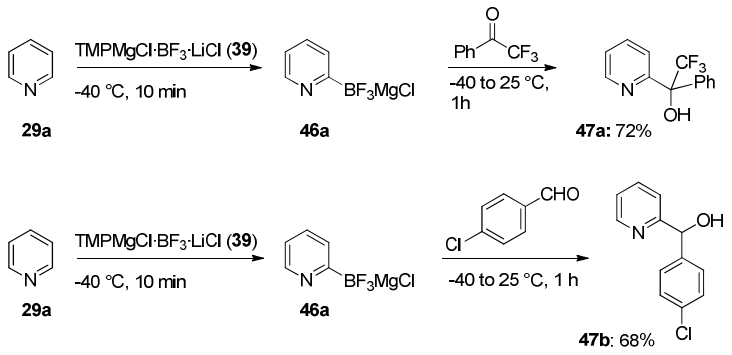
treatment of pyridine (**29a**) with TMPMgCl·BF_3·LiCl (**39**; 1.1 equiv, -40 °C, 15 min) followed by the addition of 4-chlorobenzaldehyde leads to the alcoholate **44**, which was in situ reacted with $Cl(CH_2)_2NMe_2$·HCl (1.2 equiv) and NaH (1.2 equiv, 50 °C, 2 h): this sequence provided carbinoxamine (**42**)[83] 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).



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.[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.

[86] K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169.



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 metalation with prior precomplexation with BF_3·OEt_2 and subsequent addition of TMPMgCl·LiCl (**11**), TMP_2Zn·2$MgCl_2$·LiCl (**14**) or [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**15**) in a second step proves to be more flexible and often results in higher yields.[87] This two-step metalation allows, in a number of cases, a complete switch of regioselectivity by using either TMP-derived bases (**11** – **15**) without BF_3·OEt_2 (metalation procedure A) or metalation of BF_3-precomplexed N-heterocycles (metalation 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 metalation 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 transmetalation 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 metalation with TMPMgCl·LiCl (**11**; 1.1 equiv, –78 °C, 30 min) provides the 4-metalated 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

[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 $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**14**) and furnishes, after a *Negishi* cross-coupling reaction, the 2,3-disubstituted pyridines **48e-f** in 72-85% yield. Precomplexation with $BF_3 \cdot OEt_2$ and zincation 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 $BF_3 \cdot OEt_2$ (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 zincation occurs in position 4 after precomplexation with $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) and subsequent reaction with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**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 $[(t\text{Bu})NCH(i\text{Pr})(t\text{Bu})]_3Al \cdot 3LiCl$ (**15**) which, in the absence of $BF_3 \cdot OEt_2$, is leading after acylation to the 2,3-substituted pyridine **48j** (80% yield; entry 7). Precomplexation with $BF_3 \cdot OEt_2$ 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 $[(t\text{Bu})NCH(i\text{Pr})(t\text{Bu})]_3Al \cdot 3LiCl$ (**15**) in position 5[88] affording after transmetalation with $ZnCl_2$ and a subsequent *Negishi* cross-coupling the 5,6-disubstituted quinoline **48k** in 68% yield whereas a precomplexation with $BF_3 \cdot OEt_2$ using TMPMgCl·LiCl (**11**) leads after a copper-mediated acylation to the 2,6-disubstituted quinoline **49l** (94% yield; entry 8)[89]. The regioselectivity of the metalation in the presence of BF_3 may be best explained by assuming in the case of 3-substituted pyridines that the BF_3-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 $BF_3 \cdot OEt_2$.

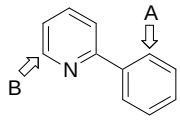
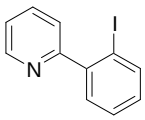
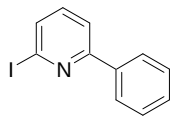
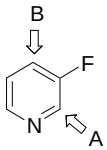
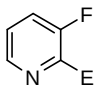
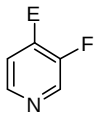
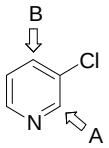
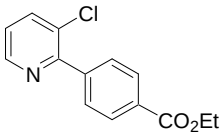
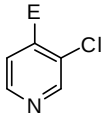
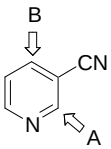
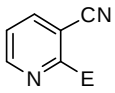
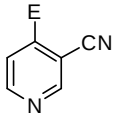
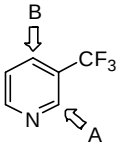
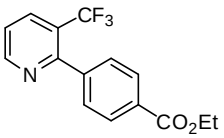
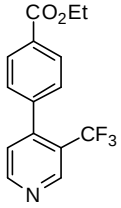
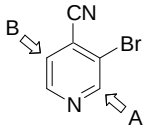
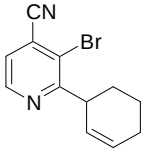
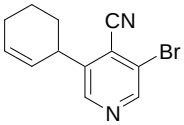
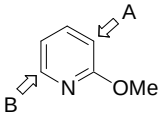
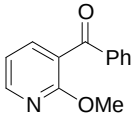
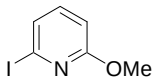
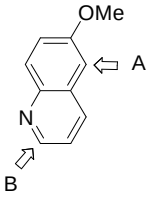
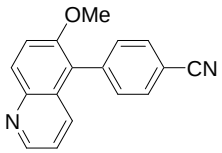
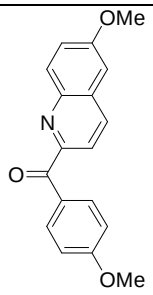
Entry	Substrate	TMP-base metalation (procedure A)[a]	BF_3-triggered metalation (procedure B)[a]
1	 **29h**	 **48a**: 85%	 **49a**:83%
2	 **29i**	 **48b**; E = I: 63% **48c**; E = $pC_6H_4CO_2Et$: 72%[b]	 **49b**; E = I: 56% **49c**; E = $pC_6H_4CO_2Et$: 74%[b]
3	 **29j**	 **48d**: 75%[b]	 **49d**; E = CO(*o*-furyl): 78%[c] **49e**; E = $pC_6H_4CO_2Et$: 95%[b]
4	 **29k**	 **48e**; E = pC_6H_4OMe: 72%[b] **48f**; E = Ph(**C**=CH_2): 85%[b] **48g**; E = cyclohexene: 73%[c]	 **49f**; E = $mC_6H_4CF_3$: 79%[b] **49g**; E = Ph(**C**=CH_2): 70%[b] **49h**; E = I: 77%
5	 **29l**	 **48h**: 69%[b]	 **49i**: 65%[b]
6	 **29m**	 **48i**: 65%[c]	 **49j**: 63%[c]
7	 **29f**	 **48j**: 80%[c]	 **49k**: 75%

Table 3 continued

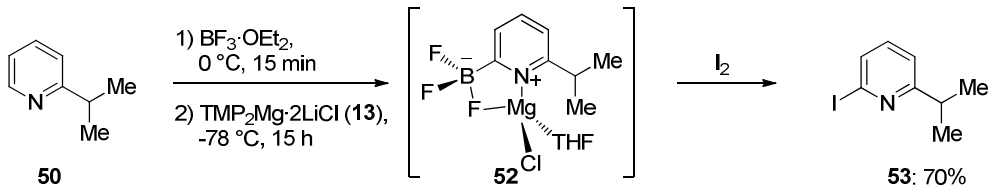
8			
	29n	**48k**: 68%[b]	**49l**: 94%[b]

[a] Yield of analytically pure isolated product. [b] Transmetalation with 1.1 equiv of $ZnCl_2$ and subsequent *Negishi* cross-coupling using $Pd(dba)_2$ and $P(2\text{-furyl})_3$. [c] Transmetalation with 1.1 equiv of CuCN·2LiCl.

4. Regio- and Chemoselective Functionalization of Alkylpyridines

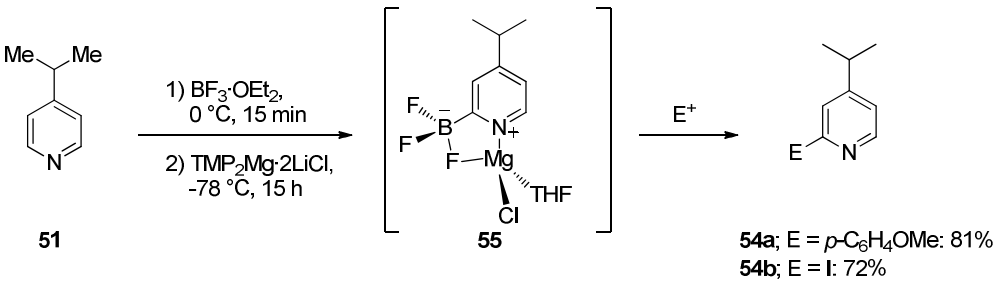
4.1 Isopropylpyridine

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 $BF_3 \cdot OEt_2$. Thus, 2-isopropylpyridine (**50**) was precomplexed with $BF_3 \cdot OEt_2$ (1.1 equiv, 15 min, 0 °C) and in a second step it was selectively metalated with $TMP_2Mg \cdot 2LiCl$ (**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 metalation of 2-isopropylpyridine (**50**).

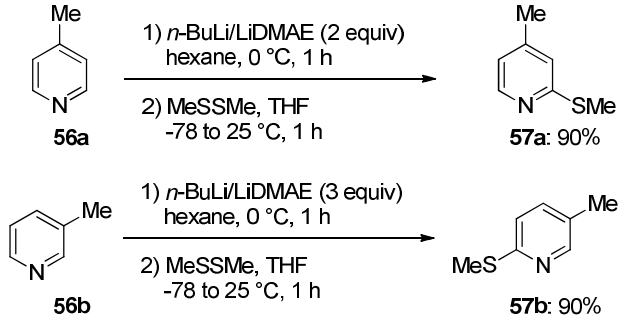
In analogous manner, 4-isopropylpyridine (**51**) was first treated with $BF_3 \cdot OEt_2$ (1.1 equiv, 15 min, 0 °C) and thereafter metalated exclusively at position 2 of the pyridine ring using $TMP_2Mg \cdot 2LiCl$ (**13**) (Scheme 44). After transmetalation with $ZnCl_2$ and a subsequent *Negishi* 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 metalation of 4-isopropylpyridine (**51**).

4.2 Methylpyridine

As the methyl group can be converted into an aldehyde,[90] a carboxylic acid[91] or subjected to olefination for preparing conjugated molecules,[92] 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[93] due to the high acidity of the methyl protons.[94] Thus, using conventional bases, such as LDA or LiTMP affected only the methyl groups.[95] 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,[96] while 3-methylpyridine (**56b**) underwent a *para*-lithiation with *n*-BuLi/LiDMAE (Scheme 45).[97]

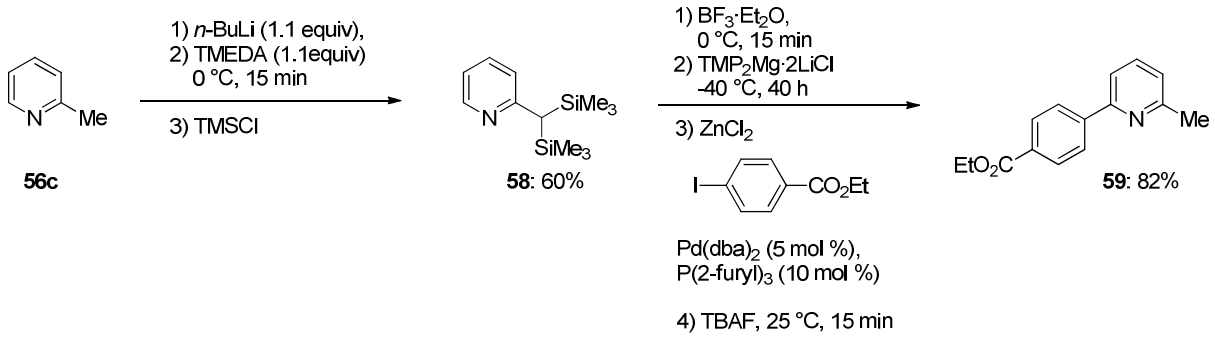


Scheme 45: Ring lithiation of methylpyridines using *n*-BuLi/LiDMAE.

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 $BF_3 \cdot OEt_2$. To overcome this problem, two TMS-substituents at the methyl group were introduced affording **58**, which then could be selectively metalated with $TMP_2Mg \cdot 2LiCl$ (**13**) in the presence of $BF_3 \cdot OEt_2$. Subsequent transmetalation with $ZnCl_2$ and *Negishi* cross-coupling with ethyl 4-iodobenzoate using as catalyst $Pd(dba)_2$ (5 mol%) and

[90] L. F. Frey, K. Marcantonio, D. E. Frantz, J. A. Murry, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Tetrahedron Lett.* **2001**, *42*, 6815.
[91] S. R. L. Fernando, U. S. M. Maharoof, K. D. Deshayes, T. H. Kinstle, M. Y. Ogawa, *J. Am. Chem. Soc.* **1996**, *118*, 5783.
[92] (a) A. Juris, S. Campagna, I. Bidd, J.-M. Lehn, R. Ziessel, *Inorg. Chem.* **1988**, *27*, 4007; (b) M. J. Meyers, K. E. Carlson, J. A. Katzenellenbogen, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3589.
[93] (a) F. Effenberger, A. Krebs, *Chem. Ber.* **1992**, *125*, 1131; (b) G. A. Kraus, J. Malpert, *Synlett* **1997**, *1*, 107; (c) G. Hanan, U. Schubert, D. Volkmer, E. Rivière, J.-M. Lehn, N. Kyritsakas, J. Fisher, *Can. J. Chem.* **1997**, *75*, 169.
[94] R. R. Fraser, T. S. Mansour, S. Savard, *J. Org. Chem.* **1985**, *50*, 3232.
[95] E. W. Kaiser, *Tetrahedron* **1983**, *39*, 2055.
[96] T. Kaminski, P. Gros, Y. Fort, *Eur. J. Org. Chem.* **2003**, 3855.
[97] J. Mathieu, P. Gros, Y. Fort, *Chem. Commun.* **2000**, 951.

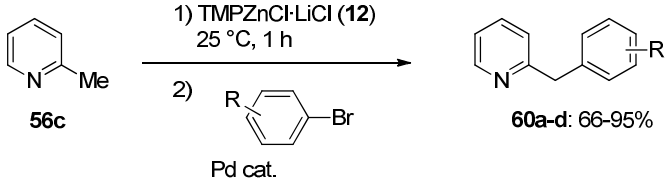
P(2-furyl)$_3$ (10 mol%) furnished the intermediate which after treatment with TBAF led to the 2,6-disubstituted pyridine **59** in 74% yield (Scheme 46).



Scheme 46: Conditions for the metalation of the pyridine ring of 2-methylpyridine (**56c**).

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 $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$/TMPMgCl·LiCl and subsequently quenched with allyl bromide in the presence of CuCN·2LiCl in moderate yield. While exploring the reactivity of the generated organometalic intermediate, we realized that TMPZnCl·LiCl (**12**) without precomplexation with $BF_3 \cdot OEt_2$ leads to better results concerning the reaction conditions and the yields of the isolated products (Scheme 47).[98]



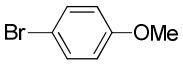
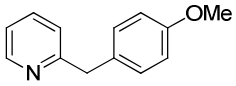
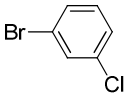
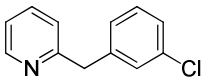
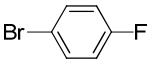
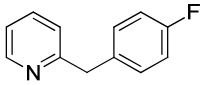
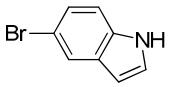
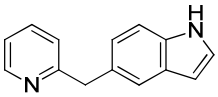
Scheme 47: Arylation of 2-methylpyridine (**56c**) and subsequent cross-coupling reaction.

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-1*H*-indole (**61d**) afforded the compounds **60c** and **60d** in 78-86% yield.

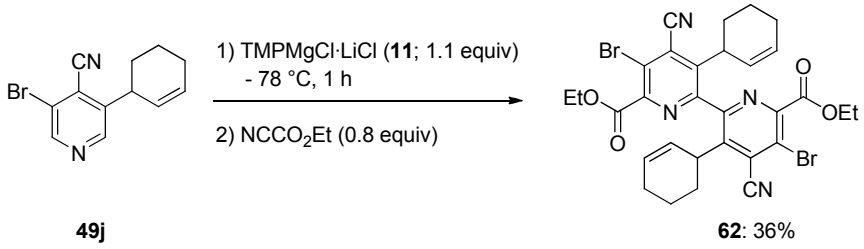
Table 4: Products obtained by the zincation of 2-methylpyridine (**56c**) with TMPZnCl·LiCl (**12**) and subsequent Pd-catalyzed cross-coupling reaction with aromatic bromides.

Entry	Aryl bromide	Conditions	Product	Yield [%][a]
1	 **61a**	Pd_2dba_3 2 mol% SPhos 4 mol% 3 h, 50 °C	 **60a**	95
2	 **61b**	$Pd(OAc)_2$ 2 mol% SPhos 4 mol% 6 h, 50 °C	 **60b**	66
3	 **61c**	$Pd(OAc)_2$ 2 mol% SPhos 4 mol% 6 h, 50 °C	 **60c**	78
4	 **61d**	$Pd(OAc)_2$ 2 mol% SPhos 4 mol% 7 h, 50 °C	 **60d**	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 $BF_3 \cdot OEt_2$

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 $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**14**), in the presence or absence of $BF_3 \cdot OEt_2$. Thus, complexation of 4-cyanopyridine (**29c**) with $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) followed by treatment with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[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 $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) and subsequent addition of $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[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).



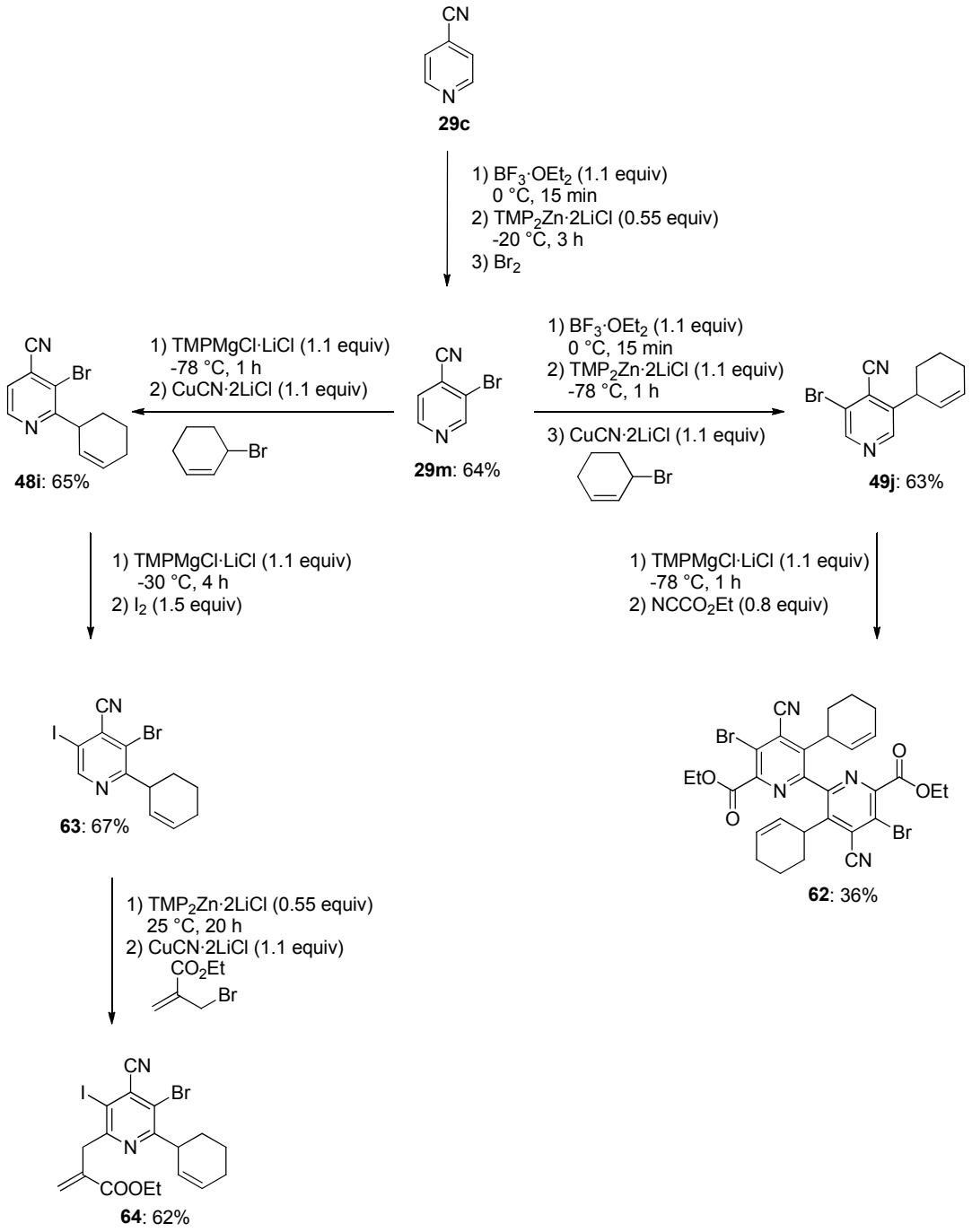
49j **62**: 36%

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 $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ has been omitted for sake of clarity.

be metalated with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[99] (**14**) within 20 h at ambient temperature. Transmetalation with CuCN·2LiCl and trapping with ethyl 2-(bromomethyl)acrylate led to the fully substituted pyridine **64** in 62% yield. Using TMPMgCl·LiCl (**11**), only polymerisation could be detected, even at low temperatures.



Scheme 49: Full functionalization of pyridine starting from 4-cyanopyridine (**29c**).

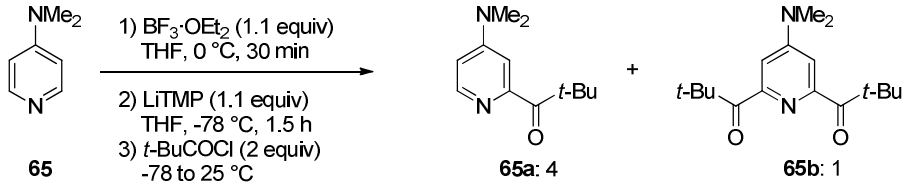
6. Regio- and Chemoselective Functionalization of *N*,*N*-4-Dimethylamino-pyridine (DMAP; 65)

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.[100] 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.[101]

6.2 Functionalization of DMAP (65) using lithium bases

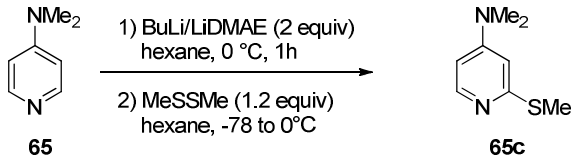
In contrast to this, the functionalization of the pyridine core rather than the side chain appears to be a more challenging task. The literature reveals that for the functionalization of C-2 two lithiation methodologies are known. Analogously to *Kessar´s* strategy with pyridine, **65** was activated by conversion into the BF_3-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).[102]



Scheme 50: Metalation of **65** using LiTMP in the presence of $BF_3 \cdot OEt_2$.

[100] (a) K. Mashima, T. Oshiki, H. Yrata, *J. Organomet. Chem.* **1998**, *569*, 15; (b) Y. Takenaka, K. Osakada, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 129.
[101] (a) S. Wagau, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 7240; (b) J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054; (c) H. Hotsuki, H. Sakai, T. Shinohara, *Synlett* **2000**, 116; (d) A. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave, C. S. Frampton, *J. Chem. Soc., Perkin Trans 1* **2000**, 3460.
[102] E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809.

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).[103]

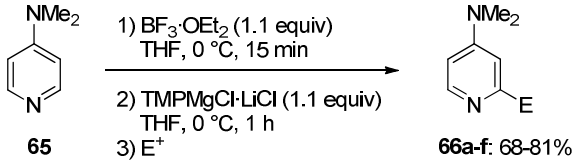


Scheme 51: Metalation of **65** using superbase.

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 $BF_3 \cdot OEt_2$

Using the above described two-step metalation protocol with prior precomplexation with $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$.

Thus, precomplexation of DMAP with $BF_3 \cdot OEt_2$ (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

[103] D. Cuperly, P. Gros, Y. Fort, *J. Org. Chem.* **2002**, *67*, 238.

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 $P(2\text{-furyl})_3$ (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.

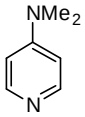
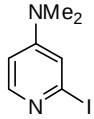
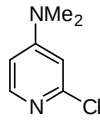
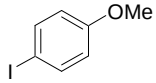
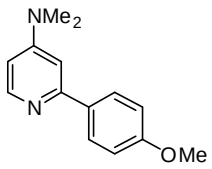
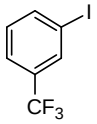
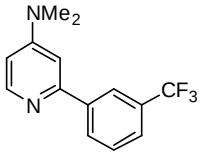
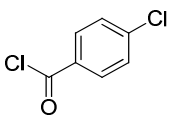
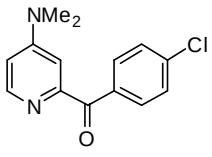
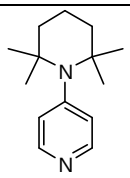
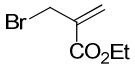
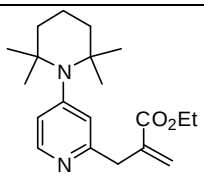
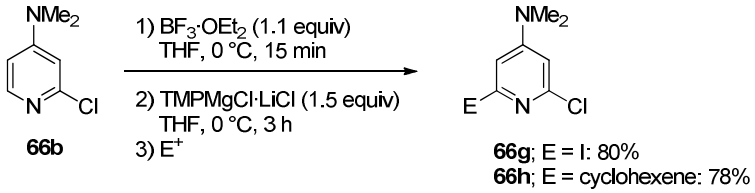
Entry	Substrate	Electrophile	Product (yield)[a]
1	 **65**	I_2	 **66a**: 72%
2	**65**	$C_2Cl_3F_3$	 **66b**: 70%
3	**65**		 **66c**: 81%[b]
4	**65**		 **66d**: 79%[b]
5	**65**		 **66e**: 68%[c]

Table 5 continued

6	 **65d**		 **66f**: 71: %[c]

[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 $P(2\text{-furyl})_3$. [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 $BF_3{\cdot}OEt_2$ (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 $BF_3{\cdot}OEt_2$.

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*,[104] has drawn a lot of interest due to its potential role in therapeutics for central nervous system (CNS) diseases.[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 desease or Tourette´s syndrome along with other CNS related disorders.[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.[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.[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

---

[104] (a) J. W. Gorrod, P. Jacob, III *Analytical Determination of Nicotine and Related Compounds and their Metabolites*; Elsevier: New York, **1999**; (b) M. Pailer, *Tabacco Alkaloids and Related Compounds*; U. S. von Euler, Ed.; Pergamon Press: New York, **1965**.

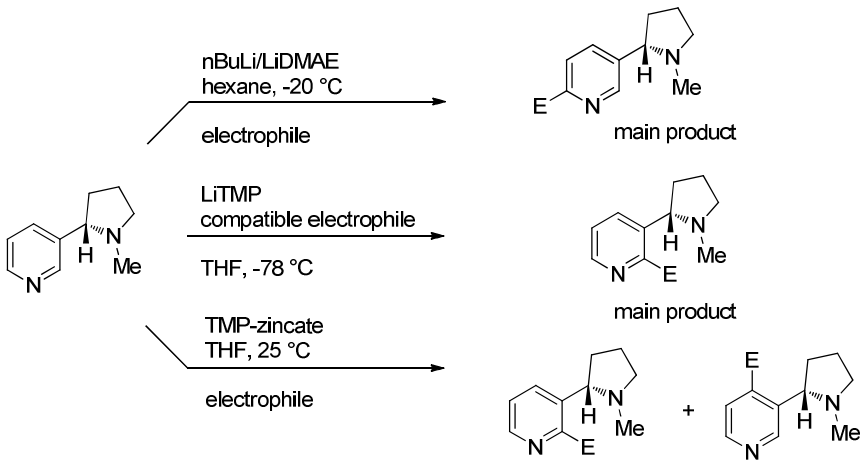
[105] (a) M. K. Holladay, M. J. Dart, J. K. Lynch, *J. Med. Chem.* **1997**, *40*, 4169; (b) E. D. Levin, *J. Neurobiol.* **2002**, *53*, 633; (c) C. Lee, *Pharmacol. Ther.* **2003**, *98*, 143; (d) S. R. Breining, *Curr. Top. Med. Chem.* **2004**, *4*, 609; (e) A. A. Jensen, B. Frölund, T. Liljefors, P. J. Krogsgaard-Larsen, *J. Med. Chem.* **2005**, *48*, 4705.

[106] (a) P. A. Newhouse, M. Kelton, *Pharm. Acta Helv.* **2000**, *74*, 91; (b) E. D. Levin, *J. Neurobiol.* **2002**, *53*, 633.

[107] (a) I. A. McDonald, J.-M. Vernier, N. D. P. Cosford, J. Corey-Naeve, *Curr. Pharm. Des.* **1996**, *2*, 357; (b) N. D. P. Cosford, L. Bleiker, H. Dawson, J. P. Whitten, P. Adams, L. Chavez-Noriega, L. D. Correa, J. H. Crona, L. S. Mahaffy, F. M. Menzaghi, T. S. Rao, R. Reid, A. I. Sacaan, E. Santori, K. Stauderman, K. Whelan, G. K. Lloyd, I. A. McDonald, *J. Med. Chem.* **1996**, *39*, 3235.

[108] K. H. Kim, N. Lin, D. J. Anderson, *Bioorg. Med. Chem.* **1996**, *4*, 2211.

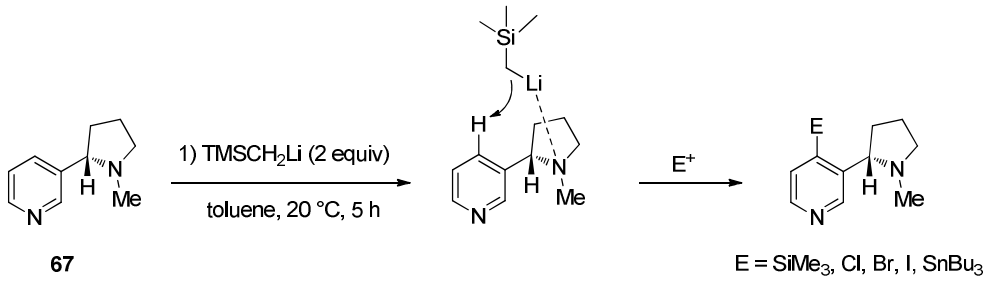
intermediate. Thus, using a mixture of *n*BuLi/LiDMAE enables the lithiation in position 6 of the pyridine ring. Depending on the electrophile, also the formation of the C-2 regioisomer was observed.[109] Selectively functionalizing the C-2 position of the pyridine ring proved to be most challenging 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 achieved the best results concerning regioselectivity. But the functionalization was made possible only by trapping the lithio intermediate with base-compatible electrophiles - nicotine was added to a solution containing both LiTMP and the electrophile. Consequently, this methodology limits the functional group diversity. *Kondo´s* TMP-zincate was also tested but it led to a mixture of C-2- and C-4-substituted nicotine derivatives in very poor yield.[109] Moreover, the metalation did not go to completion even when using 2 equiv of base (Scheme 54).



Scheme 54: Metalations of (*S*)-nicotine (**67**) with different metalating agents.

A clean metalation at position 4 of the pyridine ring could be achieved with $TMSCH_2Li$ at ambient temperature.[110] The reactivity of $TMSCH_2Li$ 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 $TMSCH_2Li$ at the appropriate place to abstract the H-4 proton.

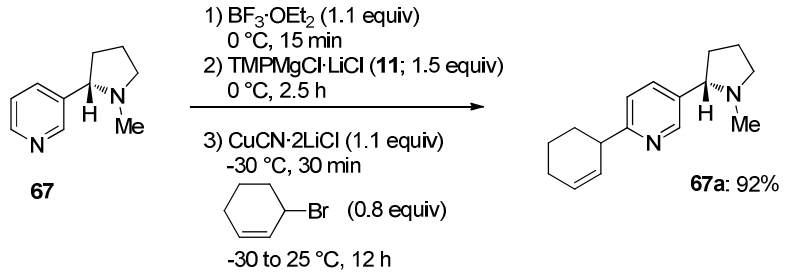
[109] F. C. Février, E. D. Smith, D. L. Comins, *Org. Lett.* **2005**, *7*, 5457.
[110] P. C. Gros, A. Doudouh, C. Woltermann, *Org. Biomol. Chem.* **2006**, *4*, 4331.



Scheme 55: C-4 metalation of **67** using $TMSCH_2Li$.

7.3 Regio- and chemoselective functionalization of (*S*)-nicotine (67) and its derivatives using TMP-derived bases in the presence of $BF_3 \cdot OEt_2$

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 $BF_3 \cdot OEt_2$ and subsequent addition of TMPMgCl·LiCl (**11**) in a second step (Scheme 56).



Scheme 56: Regioselective, BF_3-triggered metalation of **67** and subsequent allylation.

Thus, **67** was first treated with $BF_3 \cdot OEt_2$ (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.[111] More recently, the interest in quinine was driven by the utility as a catalyst or ligand for asymmetric synthesis.[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 resistence 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,[112c] and changes to the carbon skeleton tend to be laborious.[113] A view in the literature reveals that, *inter alia*, C-C bond formation at the vinyl group[114] and functionalization at the C-2 position of the quinoline moiety[115] are possible (Scheme 57).

---

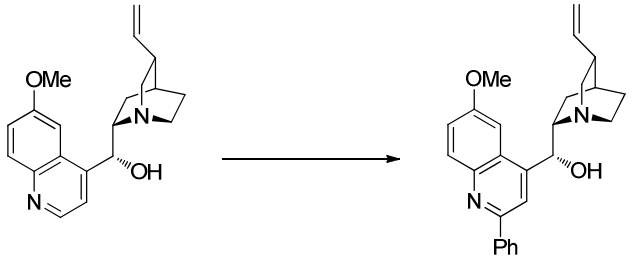
[111] D. Butler, J. Maurice, C. O´Brien, *Nature* **1997**, *386*, 535.

[112] (a) H. Pracejus, *Fortschr. Chem. Forsch.* **1967**, *8*, 493; (b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; (c) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961; (d) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; (e) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[113] (a) H. M. R. Hoffmann, J. Franckenpohl, *Eur. J. Org. Chem.* **2004**, 4293.

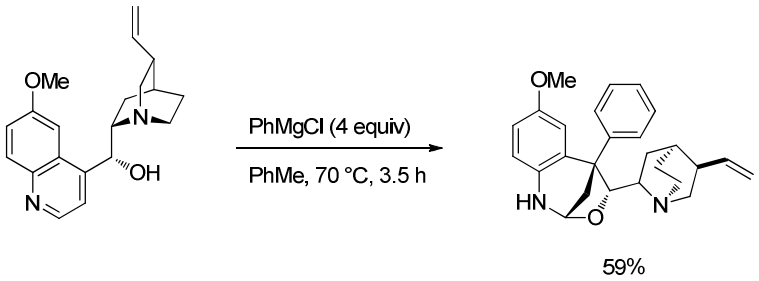
[114] (a) M. P. Arrington, Y. L. Bennani, T. Göbel, P. Walsh, S.-H. Zhao, K. B. Sharpless, *Tetrahedron Lett.* **1993**, *34*, 7375; (b) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229; (c) W. M. Braje, J. Frackenpohl, O. Schrake, R. Wartchow, W. Beil, H. M. R. Hoffmann, *Helv. Chim. Acta* **2000**, *83*, 777; (d) F. Fache, O. Piva, *Tetrahedron Lett.* **2001**, *42*, 5655; (e) M. Lambers, F. H. Beijer, J. M. Padron, I. Toth, J. G. de Vries, *J. Org. Chem.* **2002**, *67*, 5022; (f) A. Merschaert, P. Delbecke, D. Daloze, G. Dive, *Tetrahedron Lett.* **2004**, *45*, 4697.

[115] (a) J. F. Mead, M. M. Rapport, J. B. Koepfli, *J. Am. Chem. Soc.* **1946**, *68*, 2704; (b) E. Ochiai, M. Hamana, Y. Kobayashi, C. Kaneko, *Chem. Pharm. Bull.* **1960**, *8*, 487; (c) E. Ochiai, H. Kataoka, T. Dado, H. Tanida, M. Horiuchi, R. Kido, *Chem. Abstr.* **1961**, 106009; (d) J. P. Yardley, R. E. Bright, L. Rane, R. W. A. Reeks, P. B. Russell, H. Smith, *J. Med. Chem.* **1971**, *14*, 62; (e) W. A. Laurie, D. McHale, K. Saag, J. B. Sheridan, *Tetrahedron* **1988**, *44*, 5905.



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 C_6H_6 to the alkaloid (Scheme 58).[116]

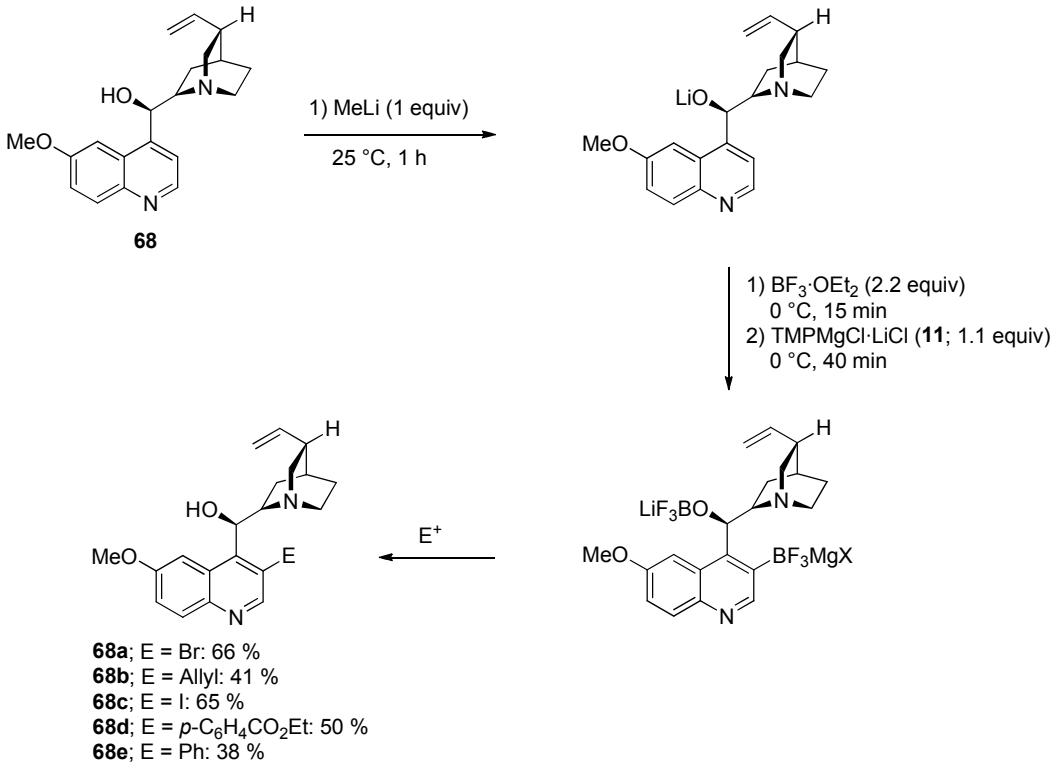


Scheme 58: Reaction of **68** with a Grignard reagent.

8.3 Regio- and chemoselective functionalization of quinine (68) in position 3 using mixed Mg/Li bases in the presence of $BF_3 \cdot OEt_2$

Our metalation protocol has been applied to this more complex scaffold and has allowed for the first time to selectively metalate 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 $BF_3 \cdot OEt_2$ (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 BF_3 with the tertiary amine. However, metalation with TMPMgCl·LiCl (**11**) without previous BF_3-complexation leads to a low conversion and a mixture of isomers which could not be isolated in pure form. Quenching with various electrophiles (iodine, $C_2Cl_4Br_2$, 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).

[116] L. Hintermann, M. Schmitz, U. Englert, *Angew. Chem. Int. Ed.* **2007**, *46*, 5164.

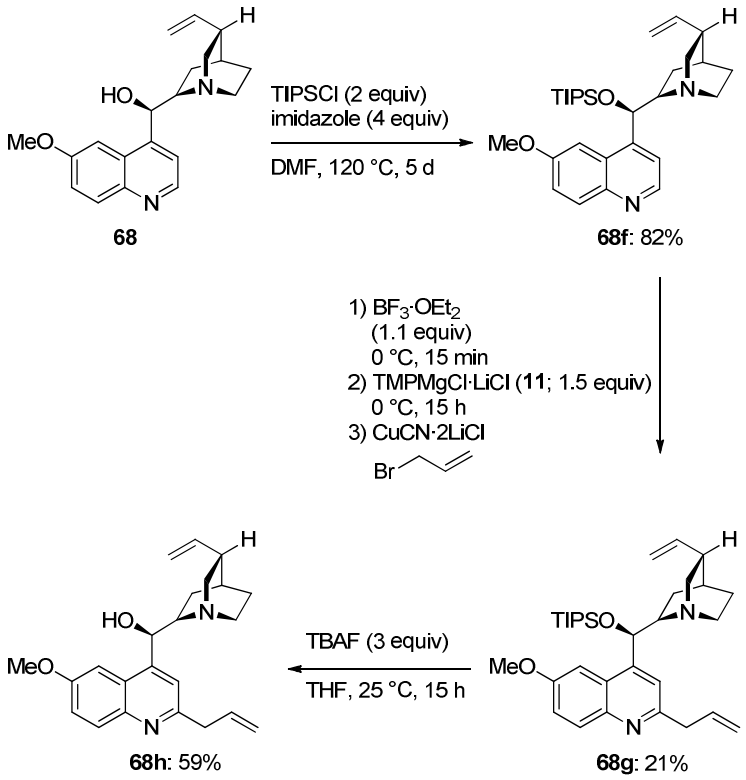


Scheme 59: Functionalization at position 3 of the quinoline ring of quinine (**68**).

8.4 Regio- and chemoselective functionalization of quinine (68) in position 2 using mixed Mg/Li bases in the presence of $BF_3 \cdot OEt_2$

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 $BF_3 \cdot OEt_2$ (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 **68g** in 21% yield. The deprotection with TBAF (3 equiv) leads to the 2-substitued quinine derivative **68h** in 59% yield (Scheme 60).

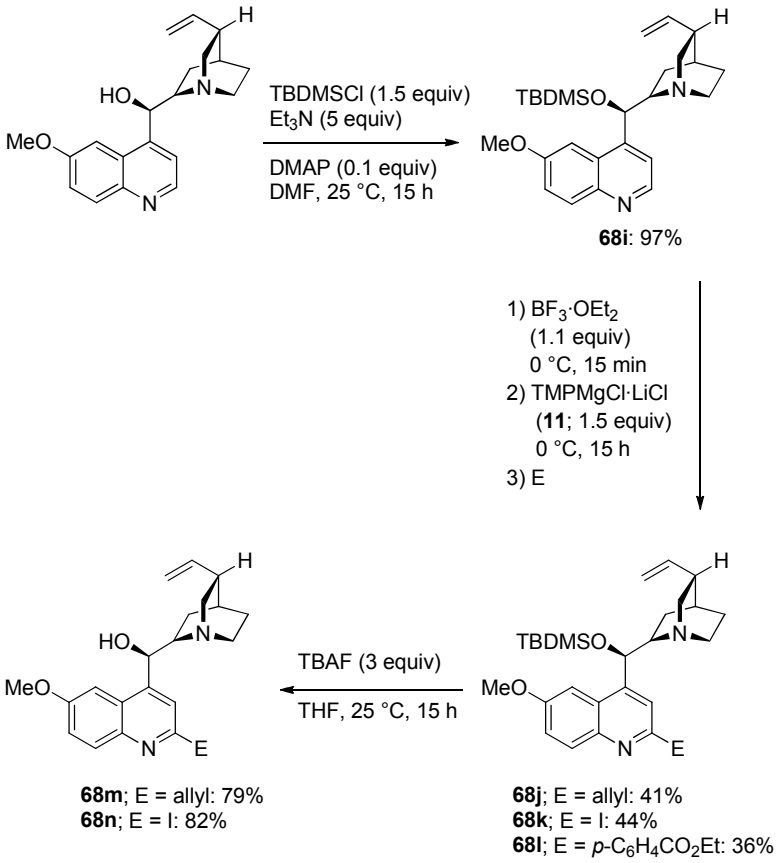
[117] K. K. Ogilvie, E. A. Thompson, M. A. Quilliam, J. B. Westmore, *Tetrahedron Lett.* **1974**, *15*, 2865.



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

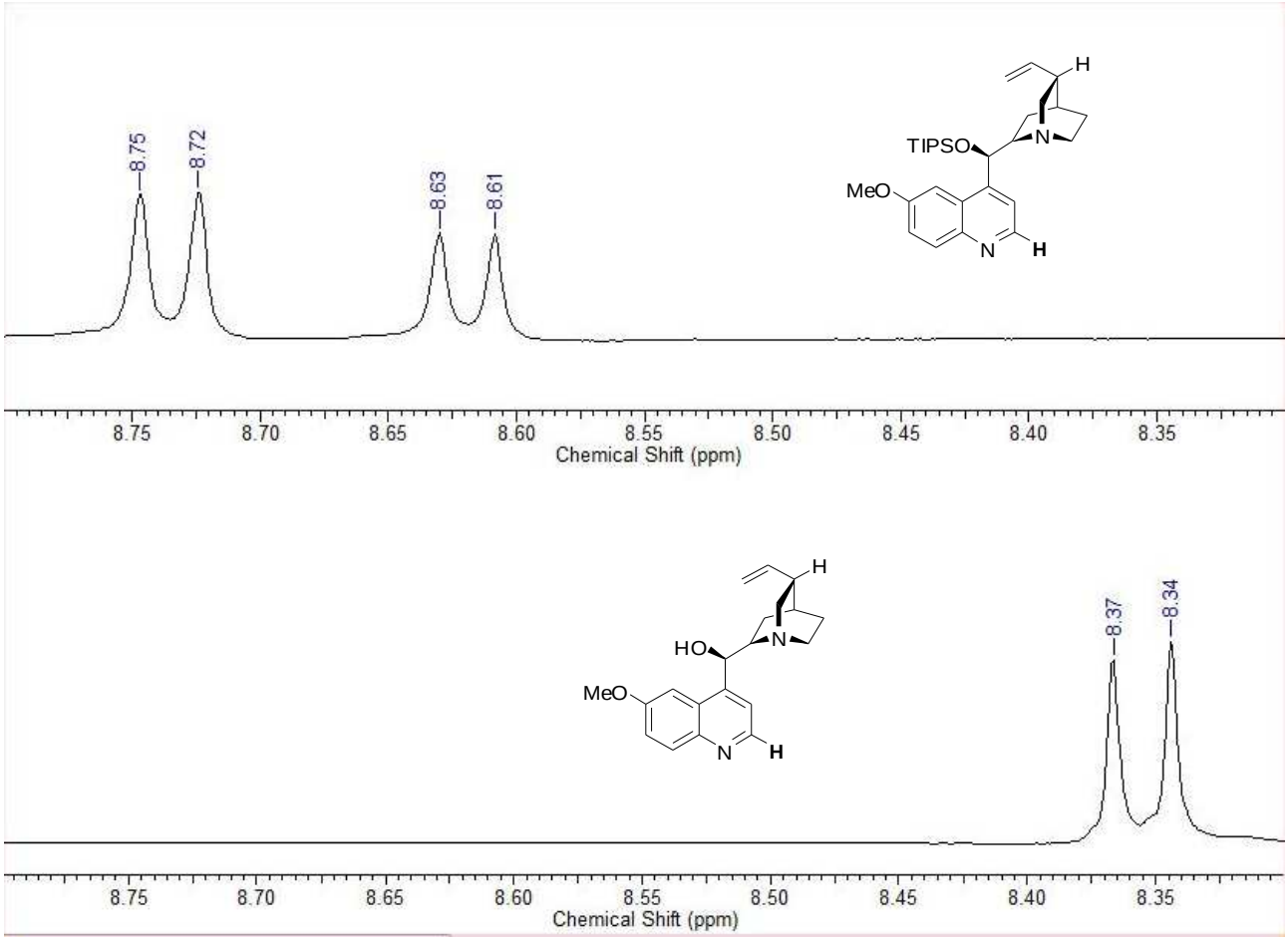
Due to the comparably low yields we changed the protecting group to TBDMS according to the procedure of *Sherrington*[118] furnishing the product **68i** in 97% yield. The two-step metalation of **68i** with $BF_3 \cdot OEt_2$ (1.1 equiv) followed by addition of TMPMgCl·LiCl (**11**; 1.5 equiv, 15 h) 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).

[118] P. Bresenius, P. A. G. Cormack, J. Liu, S. Otto, J. K. M. Sanders, D. C. Sherrington, *Chem. Eur. J.* **2008**, *14*, 9006.



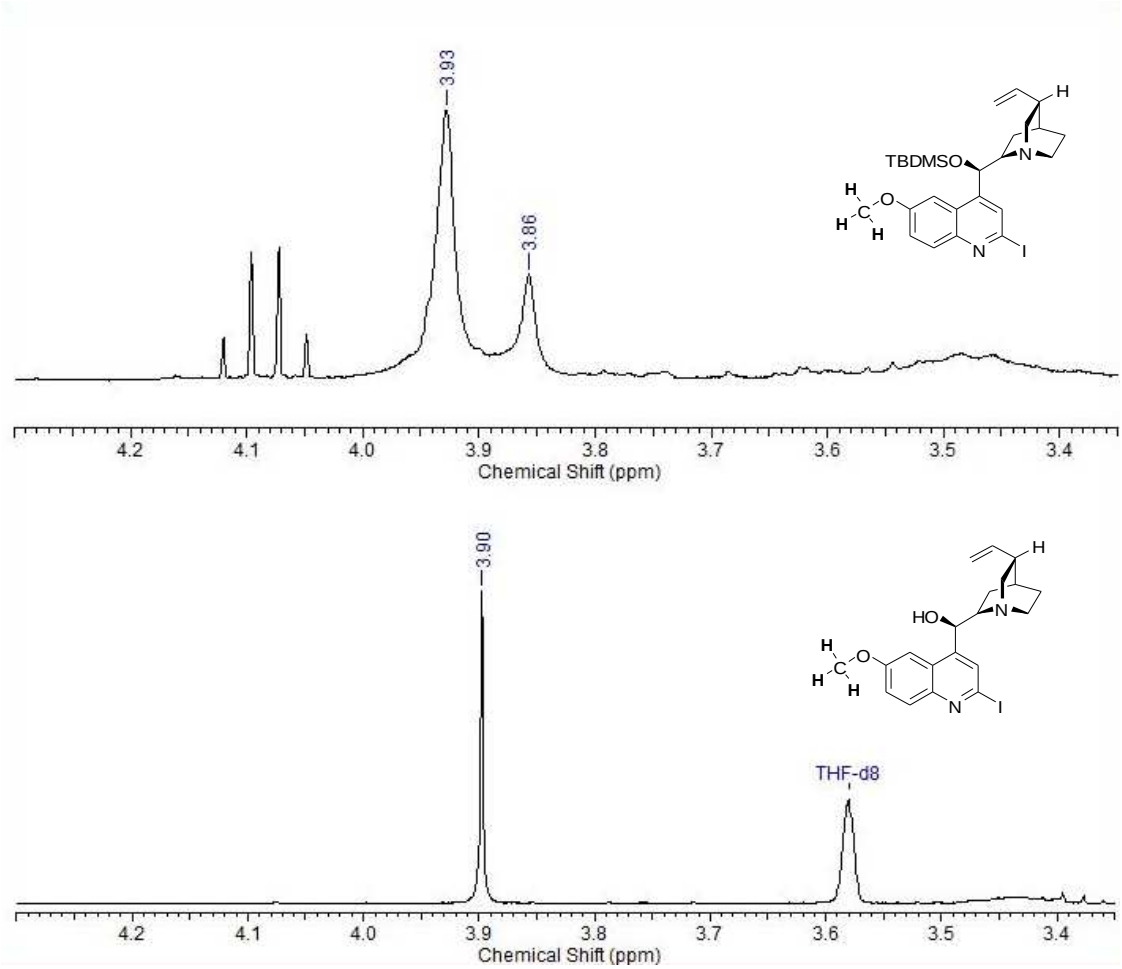
Scheme 61: Functionalization of the TBDMS-protected quinine derivative (**68i**) at position 2 and subsequent deprotection.

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 *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.[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.[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.[121] Especially, the *Suzuki* cross-coupling reaction has been used extensively owing to the air and moisture stability of boronic acids and their derivatives.[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 limitates the presence of functional groups.[123] Alternatively, organozinc reagents display in Pd-catalyzed cross-couplings (*Negishi* cross-coupling) much higher reactivity[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.[125] Recently, a very efficient LiCl-mediated direct insertion of zinc into unsaturated halides was reported.[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,

---

[119] (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed., Wiley-VCH: Weinheim, **2005**; (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijere, F. Diederich, Wiley-VCH: Weinheim, **2004**; (c) *Transition Metals for Organic Synthesis*, M. Beller, C. Bolm, Wiley-VCH: Weinheim, **2004**.

[120] (a) M. Beller, A. Zapf, W. Mägerlein, *Chem. Eng. Technol.* **2001**, *24*, 575; (b) T. Banno, Y. Hayakawa, M. Umeno, *J. Organomet. Chem.* **2002**, *653*, 288.

[121] (a) Handbook of Organopalladium Chemistry for Organic Synthesis; E. Negishi, Wiley: New York, **2002**; (b) J. Tsuji, Palladium Reagents and Catalysts, Innovations in Organic Synthesis, Wiley: New York, **1995**.

[122] (a) Q. B. Song, R. X. Lin, M. Y. Teng, J. Zhang, C. A. Ma, *Synthesis* **2006,** 123. (b) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419. (c) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633. (d) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147. (e) N. Miyaura, *Advances in Metal-Organic Chemistry*; L. S. Liebeskind, JAI: London, **1998**; Vol. 6, pp 187. (f) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

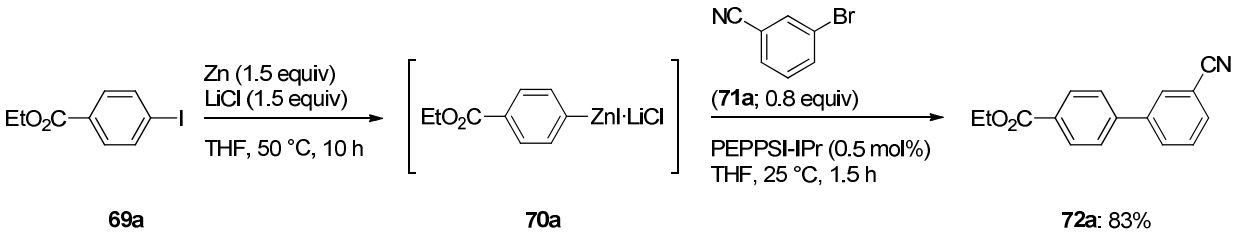
[123] (a) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem,. Int. Ed.* **2001**, *40*, 4544. (b) A. F. Littke, G. C. Fu, *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (c) S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

[124] E. Negishi, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijere, F. Diederich, Eds., Wiley-VCH: Weinheim, **2004**.

[125] (a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117; (b) P. Knochel, M. J. Rozema, C. E. Tucker, C. Retherford, M. Furlong, S. AchyuthaRao, *Pure Appl. Chem.* **1992**, *64*, 361.

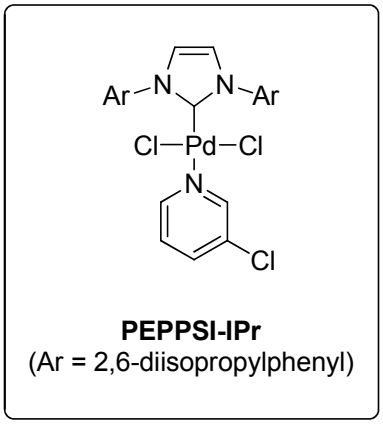
[126] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

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 *without need to remove the excess of zinc powder*.



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.



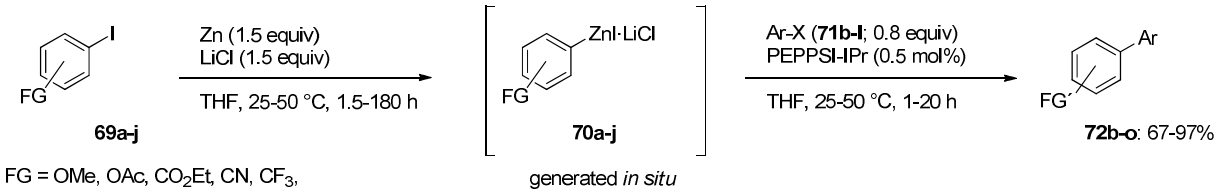
Scheme 65: PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenyl-imidazolium derivative.

[127] PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenyl-imidazolium derivative.

[128] (a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; (b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Eur. J. Chem.* **2006**, *12*, 4749; (c) For the use of PEPPSI-IPr, see also: (i) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443; (ii) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; (iii) G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 1351; (iv) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735.

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

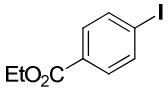
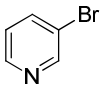
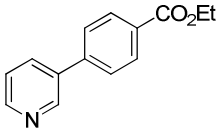
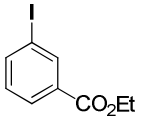
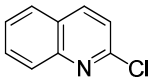
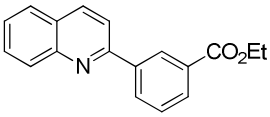
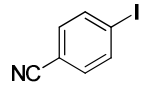
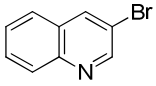
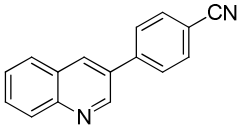
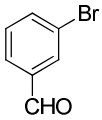
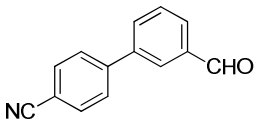
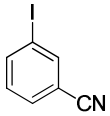
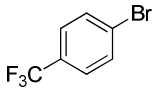
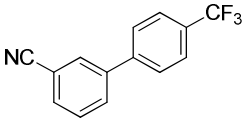
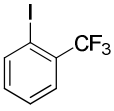
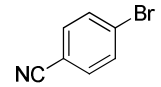
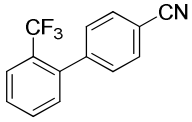
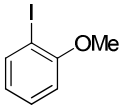
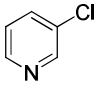
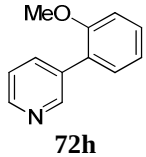
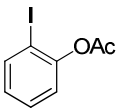
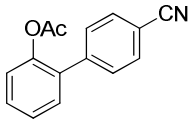
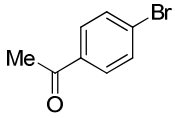
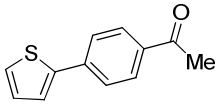
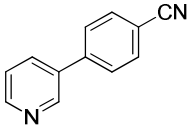
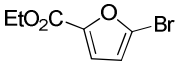
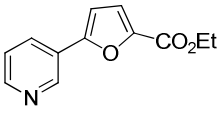
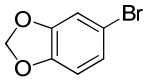
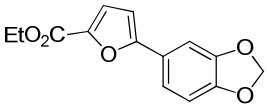
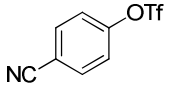
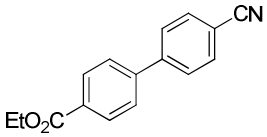
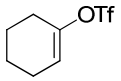
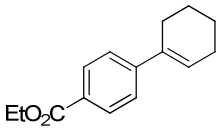
Entry	Aryl iodide, conditions	Electrophile, conditions	Product	Yield [%][a]
1	 **69a** (50 °C, 10 h)	 **71b** (50 °C, 3 h)	 **72b**	86
2	 **69b** (50 °C, 12 h)	 **71c** (40 °C, 20 h)	 **72c**	85
3	 **69c** (50 °C, 8 h)[f]	 **71d** (25 °C, 5 h)	 **72d**	91
4	**69c**	 **71e** (25 °C, 2 h)	 **72e**	80
5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

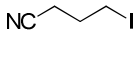
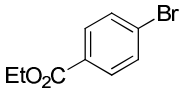
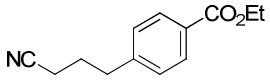
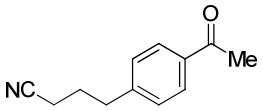
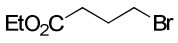
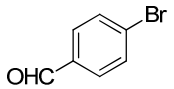
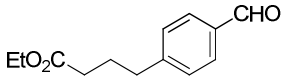
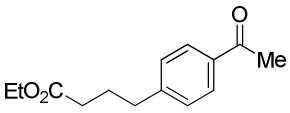
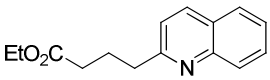
Table 6 continued

9	 **69h** (25 °C, 1.5 h)	 **71i** (25 °C, 1 h)	 **72j**	82
10	 **69i** (50 °C, 12 h)	**71g** (50 °C, 5 h)	 **72k**	75
11	 **69j** (30 °C, 3 h)	**71b** (50 °C, 5 h)	 **72l**	86
12	**69j**	 **71j** (50 °C, 20 h)	 **72m**	91
13	**69a**	 **71k** (25 °C, 4 h)	 **72n**	78
14	**69a**	 **71l** (25 °C, 4 h)	 **72o**	75

[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 *in situ* generated alkylzinc iodides **74a-b** with aromatic bromides and chlorides.

Entry	Aryl iodide, conditions	Electrophile, conditions	Product	Yield [%][a]
1	 **73a** (25 °C, 2 h)	 **71m** (25 °C, 2 h)	 **75a**	86
2	**73a**	**71i** (25 °C, 2 h)	 **75b**	70
3	 **73b** (50 °C, 12 h)[f]	 **71j** (25 °C, 1 h)	 **75c**	87
4	**73b**	**71i** (25 °C, 2 h)	 **75d**	83
5	**73b**	**71c** (50 °C, 15 h)	 **75e**	73

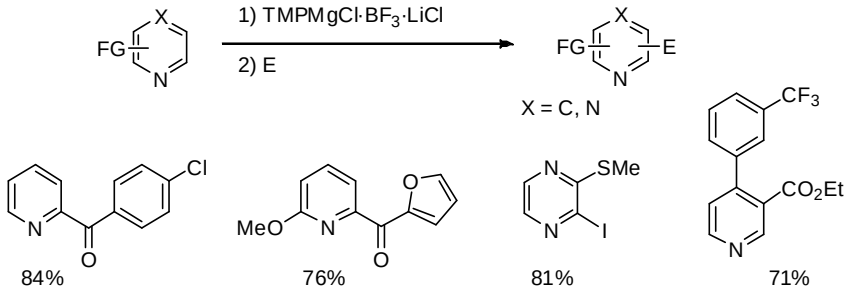
[a] Yield of isolated analytically pure product.

10. Summary and Outlook

In this work, we have reported a new class of frustrated Lewis pairs based on $BF_3 \cdot OEt_2$ 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.

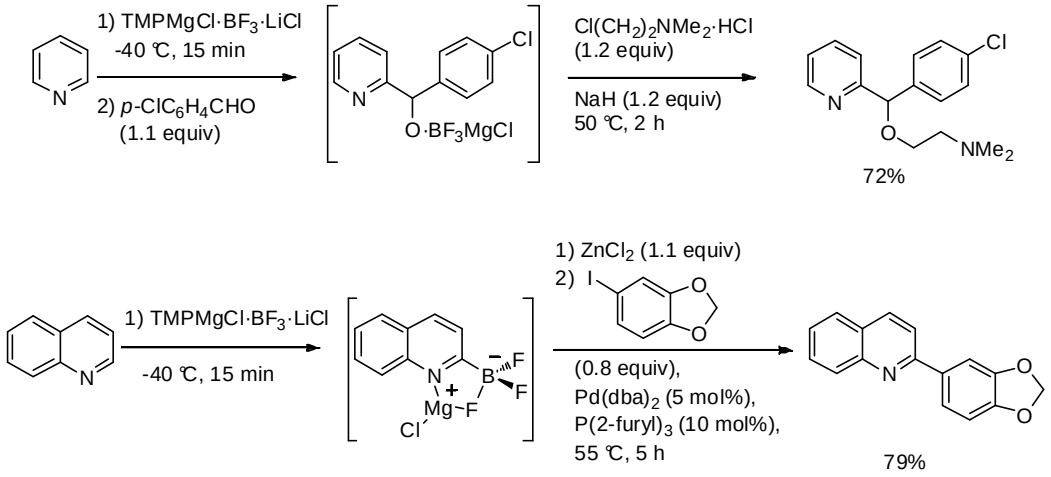
Preparation and use of the new class of frustrated Lewis pairs TMPMgCl·BF_3·LiCl

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).



Scheme 67: Regioselective metalation of N-heterocycles with the frustrated Lewis pair TMPMgCl·BF_3·LiCl.

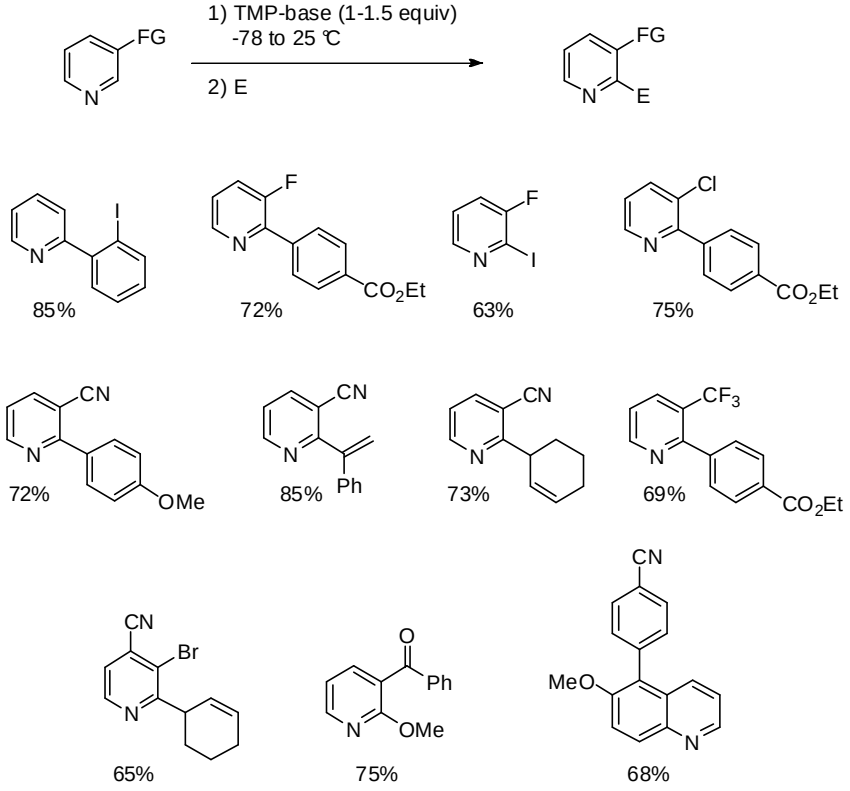
This new protocol was also used for the preparation of two biologically active molecules: the antihistaminic drug, carbinoxamine and the haplophyllum alkaloid, dubamine, in two one-pot procedures.



Scheme 68: One-pot preparation of carbinoxamine and dubamine.

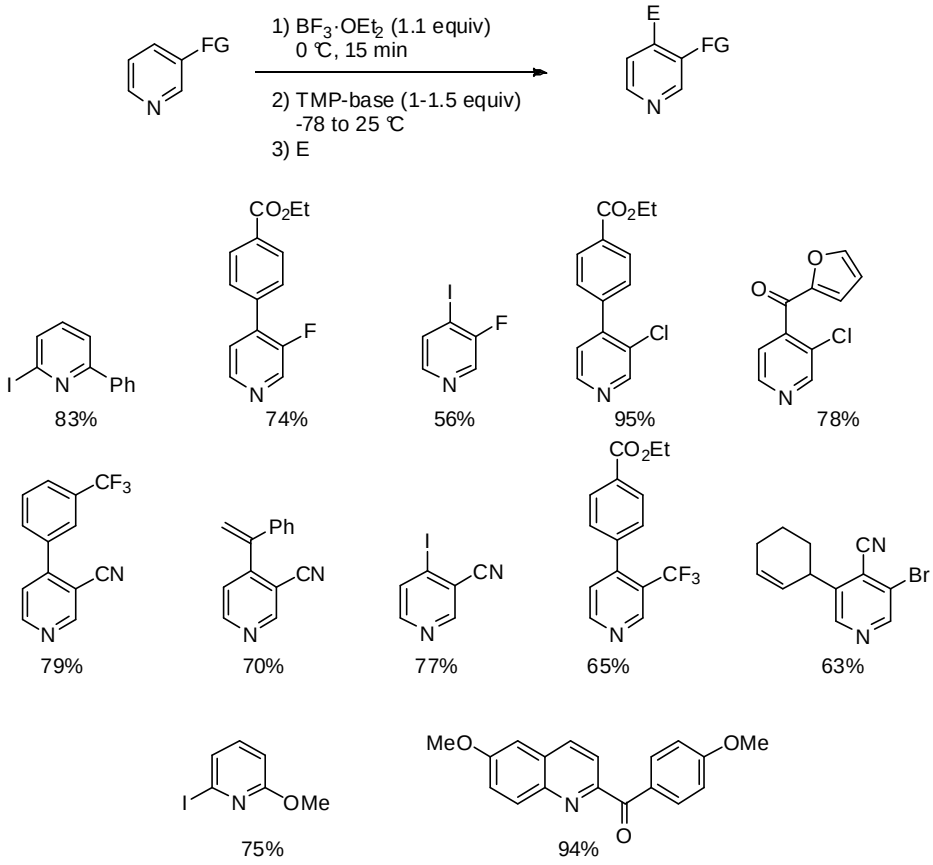
The two-step metalation allows a complete switch of regioselectivity by using either TMP-derived bases without $BF_3 \cdot OEt_2$ (Scheme 69) or metalation of BF_3-precomplexed N-heterocycles (Scheme 70).

- TMP-base metalation:



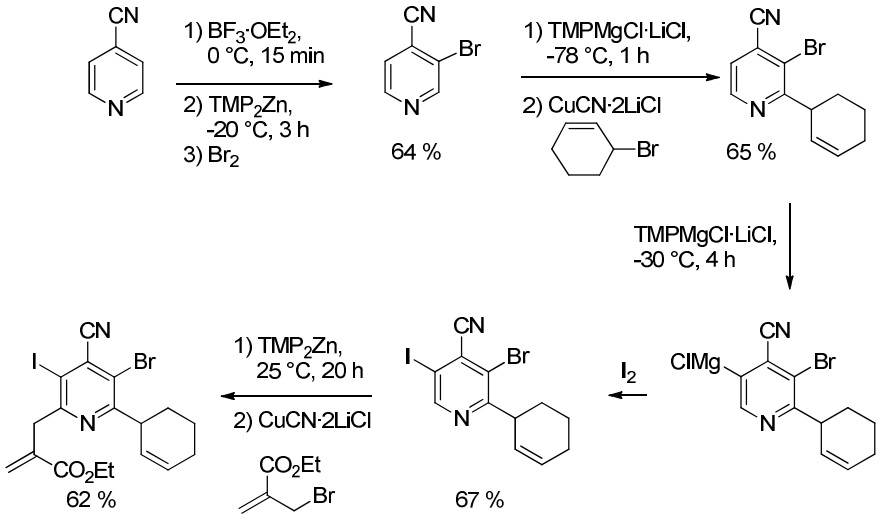
Scheme 69: Regio- and chemoselective functionalization of N-heterocycles with TMP-bases.

- BF_3-triggered metalation:



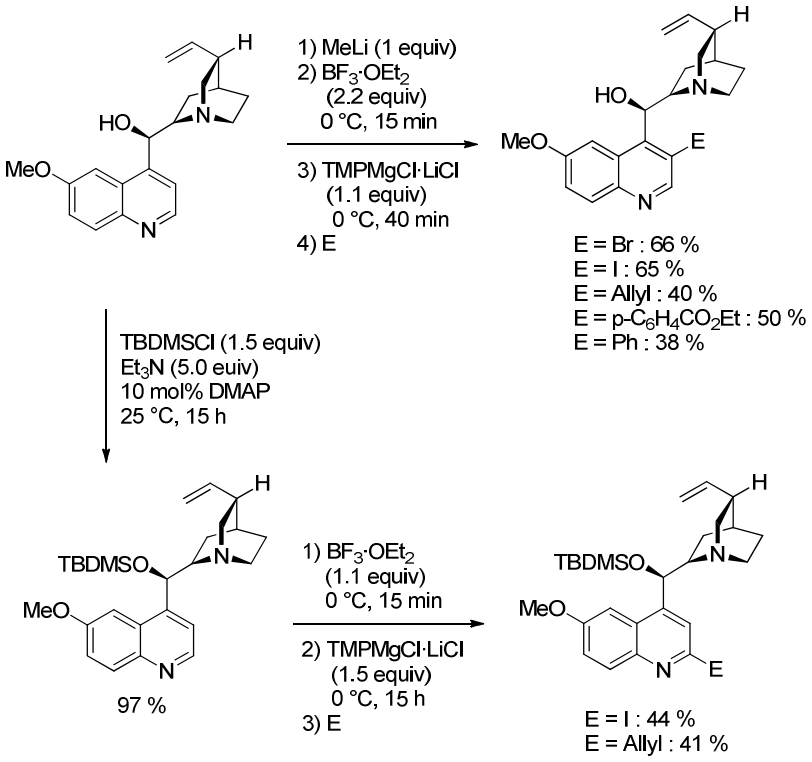
Scheme 70: Regio- and chemoselective functionalization of N-heterocycles using $BF_3{\cdot}OEt_2$ and TMP-bases.

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).



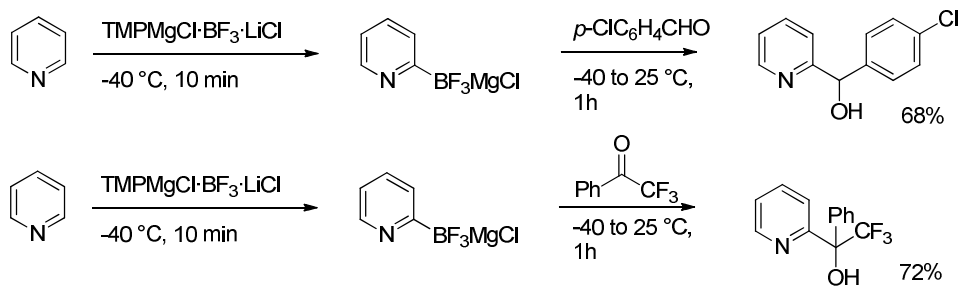
Scheme 71: Full functionalization of the pyridine core.

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).

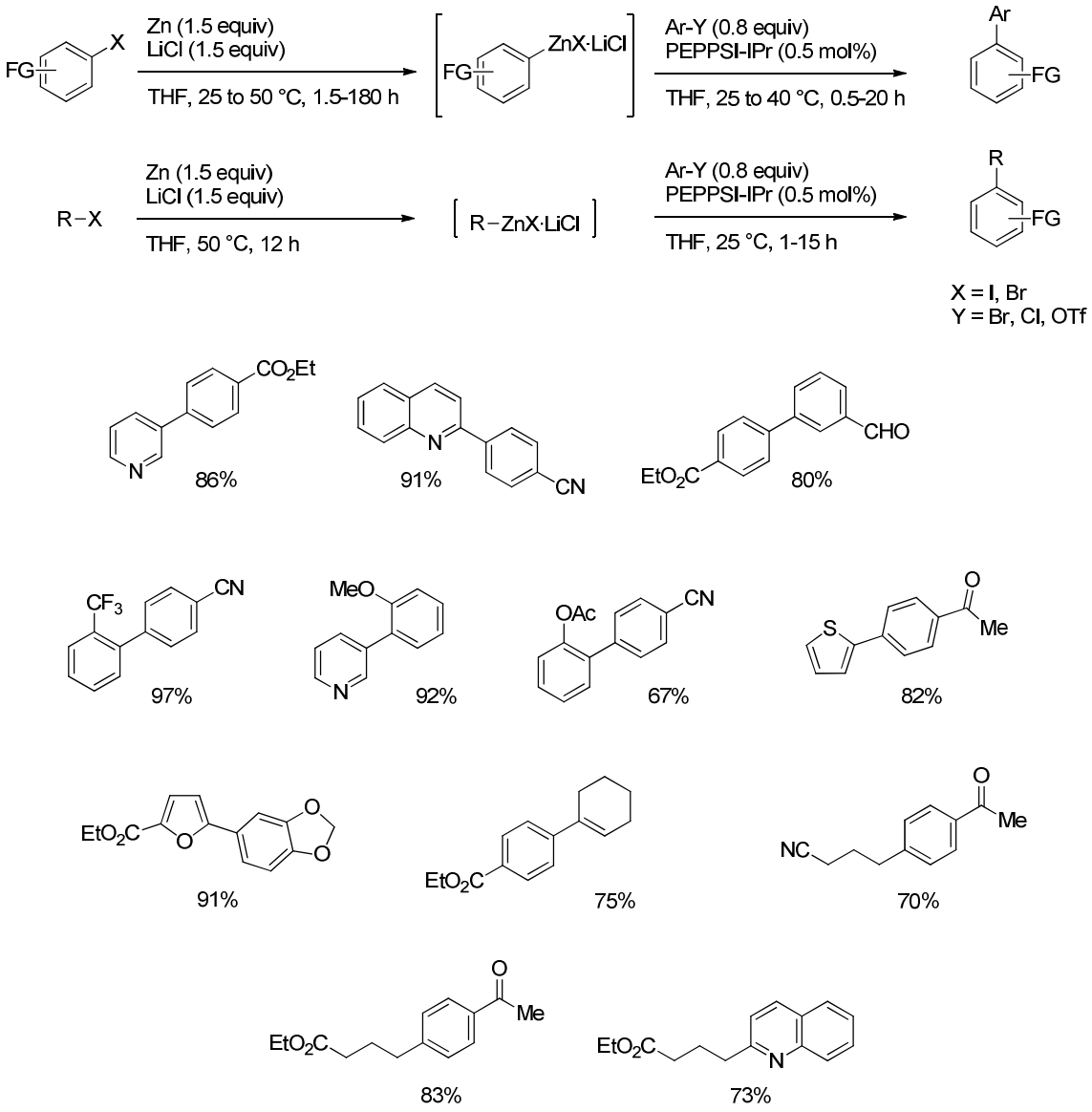


Scheme 73: Addition of magnesium pyridyltrifluoroborates to carbonyl derivatives.

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.

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

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

Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

NMP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

Pyridine was dried over KOH and distilled.

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

Toluene was predried over $CaCl_2$ and distilled from CaH_2.

Triethylamine was dried over KOH and distilled.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

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

***i*-PrMgCl·LiCl** solution in THF was purchased from Chemetall.

***i*-PrMgCl** solution in THF was purchased from Chemetall.

PhMgCl solution in THF was purchased from Chemetall.

***n*-BuLi** solution in hexane was purchased from Chemetall.

TMPMgCl·LiCl was prepared according to a literature procedure (ref.35).

TMP_2Mg·2LiCl was prepared according to a literature procedure (ref.37).

TMPZnCl·LiCl was prepared according to a literature procedure (ref.36).

TMP_2Zn·2$MgCl_2$·2LiCl was prepared according to a literature procedure (ref.38).

[(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl 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.

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (100 mmol, 136 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.

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.

$ZnCl_2$/LiCl solution (1.1/1.5 M) was prepared by drying LiCl (15.9 g, 375 mmol) and $ZnCl_2$ (37.5 g, 275 mmol) under high vacuum (1 mbar) for 5 h at 140 °C. After cooling to 25 °C, dry THF (250 mL) was added and stirring was continued until the salts were dissolved.

1.3 Content and determination of organometallic reagents

Organzinc and organomagnesium reagents were titrated against I_2 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 **$TMP_2Zn·2MgCl_2·2LiCl$** were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

[(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·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 SiO_2 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:

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).

[129] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

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 δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H: 7.25, δ_C: 77.0). For the characterization of the observed signal multiplicities the following appreviations 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 DuraSampl*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.

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. $BF_3 \cdot OEt_2$ (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 "$TMPBF_3 \cdot MgCl \cdot LiCl$" (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. $BF_3 \cdot OEt_2$ (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 BF_3-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 Et_2O) were added dropwise and stirred for 1 h at 25 °C. After cooling to 0 °C $BF_3{\cdot}OEt_2$ (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 $BrCH_2CH_2Br$ (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 T_1. The completion of the insertion reaction was checked by GC analysis of reaction aliquots quenched with sat. aqueous NH_4Cl 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 T_2. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with sat. aqueous NH_4Cl solution), the reaction mixture was quenched with sat. aqueous NH_4Cl 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 $MgSO_4$. 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 $BrCH_2CH_2Br$ (5 mol%), TMSCl (1 mol%), and I_2 (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 NH_4Cl 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 NH_4Cl solution), the reaction mixture was quenched with sat. aqueous NH_4Cl solution (5 mL), followed by filtration with cotton plug. The aqueous phase was extracted with Et_2O or EtOAc, and the combined organic phase was washed with brine and dried over $MgSO_4$. 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 $BF_3 \cdot OEt_2$ and subsequent addition of TMP-base

Synthesis of 3-bromoisonicotinonitrile (29m):

According to **TP2**, a mixture of isonicotinonitrile (**29c;** 208 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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 **$C_6H_3BrN_2$** (181.9480): 181.9483.

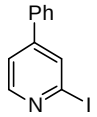
[130] C.-Y. Chang, H.-M. Liu, R.-T. Hsu, *Tetrahedron* **2009**, *65*, 748.

Synthesis of 2-iodopyridine (30a)

According to **TP2**, a mixture of pyridine (**29a**; 158 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**11**; 2.5 mL, 2.2 mmol, 1.2 M in THF) (-40 °C, 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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 10:1) furnished the compound **30a** as colorless oil (250 mg, 61% yield).
The analytical data were found to match literature data.[131]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.55 (m, 1H), 7.70-7.73 (m, 1H), 7.22-7.35 (m, 2H).

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



According to **TP2**, a mixture of 4-phenylpyridine (**29b**; 310 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (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). 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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 10:1) furnished the compound **30b** as yellow oil (354 mg, 63% yield).

[131] A. C. Bissember, M. G. Banwell, *J. Org. Chem.* **2009**, *74*, 4893.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

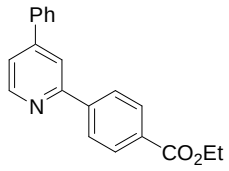
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 150.7, 150.1, 136.3, 132.5, 129.5, 129.1, 126.7, 121.0, 118.8.

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 **$C_{11}H_8IN$** (280.9701): (280.9691).

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



A) Preparation of **30c** via metalation $BF_3{\cdot}OEt_2$-precomplexed 4-phenylpyridine:

A mixture of 4-phenylpyridine (**29b**; 310 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (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 $P(2\text{-furyl})_3$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) were added and the layers were separated followed by extraction using Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the product **30c** as pale yellowish solid (407 mg, 84% yield).

B) Preparation of **30c** via metalation with "$TMPBF_3{\cdot}MgCl{\cdot}LiCl$":

According to **TP3**, $BF_3{\cdot}OEt_2$ (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. $Pd(dba)_2$ (56 mg, 5 mol%) and $P(2\text{-furyl})_3$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) were added and the layers were separated followed by extraction using Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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).

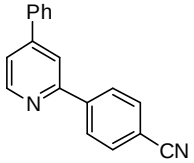
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 166.3, 156.7, 150.0, 149.8, 143.1, 138.1, 130.9, 130.0, 129.3, 129.2, 127.1, 126.9, 121.0, 119.2, 61.1, 14.3.

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 **$C_{20}H_{17}O_2N$** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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).

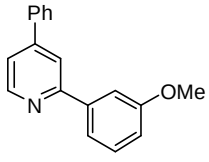
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 155.8, 150.4, 149.7, 143.5, 138.0, 132.5, 129.3, 129.2, 127.5, 127.0, 121.4, 119.1, 118.8, 112.5.

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)

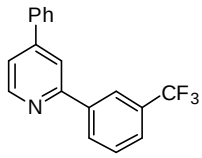


According to **TP2**, a mixture of 4-phenylpyridine (**29b**; 310 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**11**; 2.5 mL, 2.2 mmol, 1.2 M in THF) (-40 °C, 20 min). $ZnCl_2$ (2.2 mmol, 2.2 mL, 1 M in THF) was added dropwise at -40 °C and stirred for 30 min at 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

(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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 6:1) furnished the compound **30e** as yellowish oil (340 mg, 81% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).
^{13}C-NMR (75 MHz, $CDCl_3$): 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) $\tilde{\nu}$ (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 **$C_{18}H_{15}NO$** (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 $BF_3{\cdot}OEt_2$ (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 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 NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in*

vacuo. Flash column chromatographical purification (silica gel, pentane/Et_2O, 7:1) furnished the compound **30f** as yellow oil (180 mg, 75% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

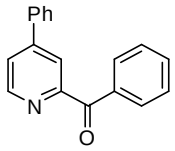
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 156.5, 150.3, 149.7, 140.2 131.2 (q, *J* = 32.4 Hz), 130.2 (q, *J* = 1.2 Hz), 129.2, 129.2, 127.1, 125.6 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.2 Hz), 123.9 (q, *J* = 3.7 Hz), 121.0, 118.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_{18}H_{12}F_3N$** (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 $BF_3{\cdot}OEt_2$ (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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 5:1) furnished the compound **30g** as yellowish solid (399 mg, 77% yield).

M. p. (°C): 66.9-68.4.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

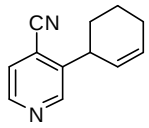
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 194.0, 155.6, 149.6, 149.0, 137.4, 136.3, 132.9, 131.0, 129.5, 129.2, 128.1, 127.0, 123.8, 122.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3052, 2362, 1736, 1652, 1590, 1542, 1464, 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) $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **30h** as brown oil (227 mg, 77% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

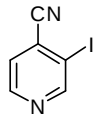
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 150.4, 147.8, 143.3, 131.1, 126.3, 125.5, 120.0, 115.5, 38.4, 31.2, 24.6, 20.6.

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 **$C_{12}H_{12}N_2$** (184.1000): 184.0994.

Synthesis of 3-iodoisonicotinonitrile (30i)



According to **TP2**, a mixture of isonicotinonitrile (**29c**; 208 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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 NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (3 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were driedover Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 9.11 (s, 1H), 8.72 (d, *J* = 4.9 Hz, 1H), 7.52 (d, *J* = 4.9 Hz, 1H).

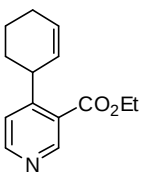
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 158.0, 148.9, 128.0, 127.1, 117.0, 96.3.

IR (Diamand-ATR, neat) $\tilde{\nu}$ (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 **$C_6H_3IN_2$** (229.9341): (229.9314).

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



[132] G. Bentabed-Ababsa, S. C. S. Ely, S. Hesse, E. Nassar, F. Chevallier, T. T. Nguyen, A. Derdour, F. Mongin, *J. Org. Chem.* **2010**, *75*, 839.

According to **TP2**, a mixture of ethyl nicotinate (**29d**; 302 mg, 2.0 mmol) $BF_3 \cdot OEt_2$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **30j** as colorless oil (266 mg, 75% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

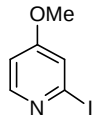
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 166.2, 156.9, 151.8, 151.0, 129.8, 128.3, 125.9, 123.6, 61.3, 37.5, 31.4, 24.9, 20.9, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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)



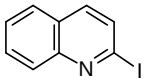
According to **TP2**, a mixture of 4-methoxypyridine (**29e**; 218 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**11**; 2.5 mL, 3.0 mmol, 1.2 M in THF) (-20 °C, 30 h). A solution of iodine (1.0 g, 4.0 mmol) inTHF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were driedover Na_2SO_4 and after filtration

the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **30k** as yellowish oil (353 mg, 75% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.13 (d, *J* = 5.8 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 5.7, 2.8 Hz, 1H), 3.81 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 165.7, 151.0, 120.2, 118.3, 110.5, 55.4.
IR (Diamond-ATR, neat) $\tilde{\nu}$ (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.
MS (70 eV, EI) *m/z* (%): 235 [M^+] (75), 108 (100), 93 (14).
HRMS (EI) for **C_6H_6INO** (234.9494): 234.9491.

4. Preparation of functionalized quinoline derivatives by complexation with BF_3·OEt_2 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 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, 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 NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **37a** as brown solid (384 mg, 75% yield). The analytical data were found to match literature data.[133]

M. p. (°C): 52.1-53.
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.03-8.08 (m, 1H), 7.77-7.81 (m, 1H), 7.73-7.76 (m, 2H), 7.69-7.73 (m, 1H), 7.54-7.60 (m, 1H).

[133] A. C. Bissember, M. G. Banwell, *J. Org. Chem.* **2009**, *74*, 4893.

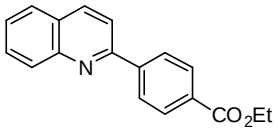
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 149.6, 137.1, 132.0, 130.3, 128.8, 127.8, 127.1, 127.1, 119.0.

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_9H_6IN** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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, $CDCl_3$): δ / (ppm) = 166.4, 156.0, 148.2, 143.6, 136.9, 131.0, 130.0, 129.8, 127.4, 127.4, 126.7, 118.9, 61.0, 14.3.

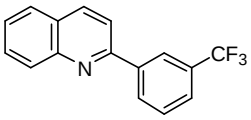
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2984, 2870, 2400, 2274, 1702, 1666, 1616, 1606, 1596, 1576, 1554, 1540, 1512, 1494, 1458, 1444, 1432, 1406, 1394, 1366, 1314, 1268, 1242, 1212,

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 **$C_{18}H_{15}NO_2$** (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 $BF_3{\cdot}OEt_2$ (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 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 NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 10:1) furnished the compound **37c** as yellow solid (224 mg, 82% yield).

M. p. (°C): 79.1-80.9.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

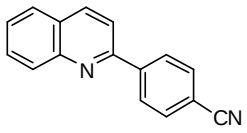
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 155.5, 148.2, 140.4, 137.1, 131.3 (q, *J* = 32.3 Hz), 130.7 (q, *J* = 1.1 Hz), 129.9, 129.8, 129.3, 127.5, 127.4, 126.8, 125.8 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 272.4 Hz), 118.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2362, 2340, 1740, 1598, 1508, 1432, 1350, 1326, 1284, 1268, 1236, 1216, 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 **$C_{16}H_{10}F_3N$** (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 $BF_3 \cdot OEt_2$ (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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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).

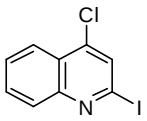
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 154.9, 148.2, 143.7, 137.2, 132.6, 130.1, 129.9, 128.0, 127.5, 127.1, 118.8, 118.6, 112.7.

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)



According to **TP2**, a mixture of 4-chloroquinoline (**31b**; 327 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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).

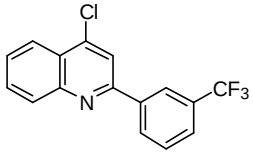
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 149.8, 142.4, 131.2, 131.2, 129.2, 128.0, 125.6, 124.4, 116.9.

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_9H_5ClIN** (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 $BF_3 \cdot OEt_2$ (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. $Pd(dba)_2$ (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-(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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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).

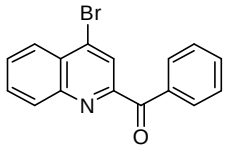
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 155.4, 150.0, 143.6, 139.3, 131.4 (q, *J* = 32.5 Hz), 130.8, 130.6 (q, *J* = 1.2 Hz), 130.2, 129.4, 127.7, 126.3 (q, *J* = 3.7 Hz), 125.5, 124.4 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.6 Hz), 124.0, 118.7.

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 **$C_{16}H_9ClF_3N$** (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 $BF_3{\cdot}OEt_2$ (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, benzoyl 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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) and extracted with Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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.

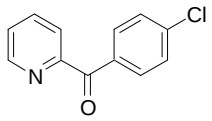
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3308, 3056, 2922, 2416, 1950, 1772, 1666, 1600, 1568, 1548, 1492, 1458, 1444, 1406, 1362, 1316, 1304, 1274, 1262, 1206, 1178, 1158, 1118, 1074, 1024, 1002, 984, 966, 948, 914, 886, 866, 830, 814, 796, 778, 766, 734, 700, 686, 656, 628, 604.

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 **$C_{16}H_9BrClNO$** (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 pyrdine (**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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) and extracted with Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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).

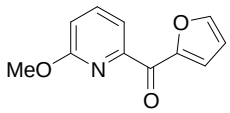
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 192.0, 154.3, 148.2, 139.5, 137.5, 134.4, 132.4, 128.5, 126.5, 124.7.

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 **$C_{12}H_9ON$** (217.0294): 218.0365.

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



According to **TP3**, $BF_3 \cdot OEt_2$ (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 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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) and extracted with Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 5:1) furnished the compound **41b** as yellow solid (124 mg, 76% yield).

M. p. (°C): 60.1-62.9.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

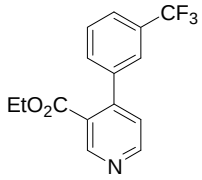
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 178.5, 163.1, 151.2, 151.1, 147.5, 139.2, 123.1, 117.5, 115.1, 112.2, 53.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3126, 3106, 3006, 2950, 2850, 1632, 1612, 1586, 1554, 1470, 1458, 1436, 1422, 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 **$C_{11}H_9O_3N$** (203.0582): 203.0583.

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



According to **TP3**, $BF_3{\cdot}OEt_2$ (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 $P(2\text{-furyl})_3$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) were added and the layers were separated followed by extraction using Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 1:1) furnished the product **41c** as yellow oil (335 mg, 71% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ / (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).

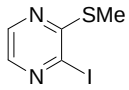
^{13}C-NMR (75 MHz, $CDCl_3$) δ / (ppm): 165.7, 151.2, 150.5, 149.6, 139.2, 131.4 (q, *J* = 1.4 Hz), 130.9 (q, *J* = 32.6 Hz), 128.9, 125.3 (q, *J* = 3.7 Hz), 125.0 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.5 Hz), 61.7, 13.6.

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 **$C_{15}H_{12}O_2NF_3$** (295.0820): 295.0824.

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



According to **TP3**, $BF_3{\cdot}OEt_2$ (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_4Cl solution (5 mL), NH_3 (5 mL, 2 M) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over Na_2SO_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, $CDCl_3$): *δ* / (ppm): 8.30 (d, *J* = 2.4 Hz, 1H), 7.95 (d, *J* = 1.0 Hz, 1H), 2.50 (s, 1H).

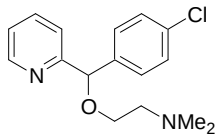
^{13}C-NMR (75 MHz, $CDCl_3$): *δ* / (ppm): 162.7, 142.1, 138.9, 118.6, 15.6.

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 **$C_5H_5IN_2S$** (251.9218): 251.9212.

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



According to **TP3**, $BF_3 \cdot OEt_2$ (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 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 Et_2O (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 Na_2SO_4 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).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

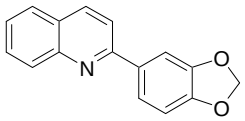
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 161.2, 148.9, 139.6, 136.8, 133.3, 128.4, 128.2, 122.4, 120.5, 84.3, 67.6, 58.8, 45.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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.

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

HRMS (EI) for **$C_{16}H_{20}ClN_2O$** (291.1264): 291.1249.

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



According to **TP3**, $BF_3 \cdot OEt_2$ (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. $Pd(dba)_2$ (28 mg, 5 mol%) and $P(2\text{-furyl})_3$ (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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) were added and the layers were separated followed by extraction using Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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).

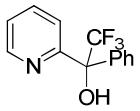
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 156.6, 148.8, 148.4, 148.0, 136.7, 134.0, 129.7, 129.4, 127.4, 127.0, 126.1, 121.8, 118.6, 108.4, 107.9, 101.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_{16}H_{11}O_2N$** (249.0790): 249.0787.

Synthesis of 2,2,2-trifluoro-1-phenyl-1-(pyridin-2-yl)ethanol (47a)



According to **TP3**, $BF_3 \cdot OEt_2$ (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 Na_2SO_4 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%).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

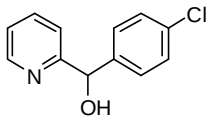
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.0, 147.2, 138.3, 137.4, 128.6, 128.4, 127.0, 125.0 (q, *J* = 286.0 Hz), 124.0, 122.9,

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{13}H_{10}F_3NO$** (253.0714): 253.0722.

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



According to **TP3**, $BF_3 \cdot OEt_2$ (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 Na_2SO_4 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.

^{1}H-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).

^{13}C-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.

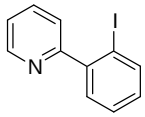
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3142, 2848, 1592, 1572, 1492, 1468, 1438, 1410, 1334, 1192, 1114, 1090, 1056, 1018, 1002, 856, 812, 770, 748, 624.

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 **$C_{12}H_{10}ClNO$** (219.0451): 219.0444.

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

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



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 NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the

solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **48a** as yellowish oil (478 mg, 85% yield).

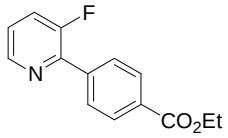
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm): 8.70 (ddd, *J* = 4.9 Hz, 1.8 Hz, 1.0 Hz, 1H), 7.93-7.97 (m, 1H), 7.72-7.81 (m, 1H), 7.38-7.52 (m, 3H), 7.27-7.33 (m, 1H), 7.03-7.11 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 160.6, 149.0, 144.8, 139.7, 136.1, 130.3, 129.7, 128.2, 124.5, 122.5, 96.6 ppm.
IR (Diamond-ATR, neat) $\tilde{\nu}$ (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^+] (100), 155 (11), 154 (87), 153 (12), 128 (16), 127 (50), 126 (12).
HRMS (EI) for **$C_{11}H_8IN$** (280.9701): 280.9682.

Synthesis of 3-fluoro-2-iodopyridine (48b)

According to **TP1**, 3-fluoropyridine (**29i**; 97 mg, 1.0 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_4Cl solution (4.5 mL), NH_3 (conc.) (0.5 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 10:1) furnished the compound **48b** as colorless oil (140 mg, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / (ppm) = 8.21 (d, *J* = 4.3 Hz, 1H), 7.20-7.33 (m, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / (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) $\tilde{\nu}$ (cm^{-1}): 3060, 1580, 1445, 1415, 1265, 1205, 1060, 1045.
MS (70 eV, EI) *m/z* (%): 223 [M^+] (100), 127 (12), 96 (67), 76 (33), 69 (10).
HRMS (EI) for **C_5H_3FIN** (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). $ZnCl_2$ (2.2 mL, 2.2 mmol, 1 M in THF) was added and the mixture was stirred for 30 min at the same temperature. $Pd(dba)_2$ (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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **48c** as yellow oil (282 mg, 72% yield).

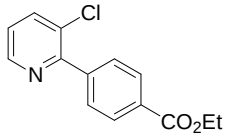
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm): 8.52-8.56 (m, 1H), 8.15-8.17 (m, 1H), 8.12-8.14 (m, 1H), 8.05-8.08 (m, 1H), 8.02-8.05 (m, 1H), 7.48-7.56 (m, 1H), 7.28-7.35 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 ppm (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): 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) $\tilde{\nu}$ (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 **$C_{14}H_{13}FNO_2$ ($M+H^+$)** (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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL)followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 3:1) furnished the compound **48d** as yellow solid (157 mg, 75% yield).

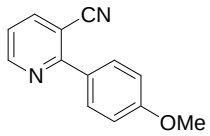
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm): 8.59-8.64 (m, 1H), 8.11-8.18 (m, 2H), 7.76-7.86 (m, 3H), 7.26-7.31 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / (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 $TMP_2Zn·2MgCl_2·2LiCl$ (**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

quenched with sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 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.

^{1}H-NMR (300 MHz, $CDCL_3$): 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).

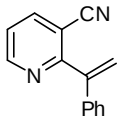
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 161.3, 160.4, 152.5, 141.9, 130.4, 129.5, 120.9, 117.9, 114.1, 106.7, 55.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_{13}H_{10}N_2O$** (210.0793): 210.0790.

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



According to **TP1**, nicotinonitrile (**29k**; 208 mg, 2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 1:1) furnished the product **48f** as yellow oil (280 mg, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.81 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.03 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.23 - 7.42 (m, 7H), 6.02 (s, 1H), 5.76 (s, 1H).

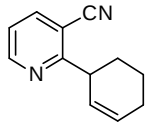
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.4, 152.0, 146.1, 141.5, 138.6, 128.6, 128.5, 127.4, 122.2, 120.7, 116.3, 109.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2228, 1576, 1558, 1496, 1434, 1326, 1160, 1108, 1098, 1064, 1028, 914, 798, 774, 696, 648, 606.

MS (EI, 70 eV): m/z (%) = 206 [M^+] (38), 180 (5), 103 (5), 77 (6).

HRMS (**EI**) for **$C_{14}H_{10}N_2$** (206.0844): (206.0835).

Synthesis of 2-(cyclohex-2-en-1-yl)nicotinonitrile (48g)



According to **TP1**, nicotinonitrile (**29k**; 208 mg, 2.0 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **48g** as colorless oil (216 mg, 73% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

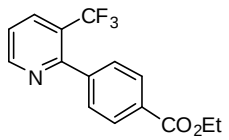
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 168.2, 152.7, 140.7, 129.6, 126.8, 121.1, 116.6, 108.6, 42.7, 29.9, 24.5, 21.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_{12}H_{12}N_2$** (184.1000): 184.0974.

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). $ZnCl_2$ (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 slowly warmed to 55 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 9:1) furnished the compound **48h** as colorless oil (162 mg, 69% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.85 (d, *J* = 4.1 Hz, 1H), 8.07-8.17 (m, 3H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

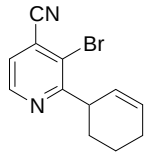
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 157.3 (q, *J* = 1.7 Hz), 151.8, 143.1, 134.9 (q, *J* = 4.8 Hz), 130.8, 129.2, 128.7 (q, *J* = 1.7 Hz), 125.0 (q, *J* = 32.0 Hz), 123.4 (q, *J* = 273.5 Hz), 122.2, 61.1, 14.2.

IR (Diamand-ATR, neat) $\tilde{\nu}$ (cm^{-1}) = 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 **$C_{15}H_{12}F_3NO_2$** (295.0820): 295.0819.

Synthesis of 3-bromo-2-cyclohexylisonicotinonitrile (48i)



According to **TP1**, 3-bromoisonicotinonitrile (**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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 5:1) furnished the compound **48i** as yellowish oil (274 mg, 65% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) 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).

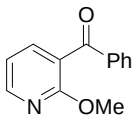
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 148.3, 129.0, 127.1, 124.6, 124.3, 122.2, 115.5, 42.6, 28.4, 24.5, 21.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_{12}H_{11}BrN_2$** (262.0106): 262.0115.

Synthesis of (2-methoxypyridin-3-yl)(phenyl)methanone (48j):



According to **TP1**, 2-methoxypyrdine (**29f**; 218 mg, 2.0 mmol) reacted with [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·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 $ZnCl_2$ (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 benzoyl 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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 5:1) furnished the compound **48j** as white solid (341 mg, 80% yield).

M. p. (°C): 80.2-81.5.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

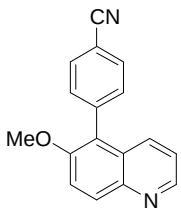
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 194.7, 161.1, 149.2, 138.9, 137.2, 133.3, 129.7, 128.4, 122.7, 116.5, 53.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_{13}H_{11}NO_2$** (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 [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al·3LiCl (**15**; 2.0 mmol, 6.67 mL, 0.3 M in THF) (-78 °C, 1 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 (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_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, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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.

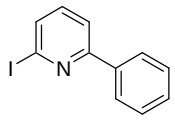
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 2224, 1606, 1596, 1472, 1444, 1426, 1400, 1380, 1372, 1340, 1312, 1234, 1212, 1202, 1188, 1176, 1150, 1122, 1114, 1046, 1026, 988, 964, 918, 882, 850, 836, 798, 784, 770, 744, 660, 642, 604.

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

HRMS (EI) for **$C_{17}H_{12}N_2O$** (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)



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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (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).

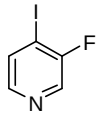
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 159.0, 138.0, 137.7, 133.1, 129.5, 128.8, 126.9, 119.3, 118.2.

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 **$C_{11}H_8NI$** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (4.5 mL), NH_3 (conc.) (0.5 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (ppm) = 8.34 (s, 1H), 8.04 (d, *J* = 4.7 Hz, 1H), 7.72 (t, *J* = 4.9 Hz, 1H).

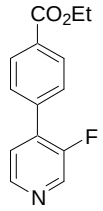
^{13}C-NMR (100 MHz, $CDCl_3$): δ / (ppm) = 160.8, 158.2, 145.9, 145.9, 137.6, 137.3, 134.1, 92.6, 92.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3060, 1570, 1550, 1475, 1415, 1260, 1202, 1050, 1040.

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

HRMS (EI) for **C_5H_3FIN** (222.9294): 222.9283.

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



According to **TP2**, a mixture of 3-fluoropyridine (**29i**; 97 mg, 1.0 mmol) and $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (**11**; 0.92 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 30 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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 3:1) furnished the compound **49c** as yellow solid (145 mg, 74% yield).

M. p. (°C): 60.4-62.9.

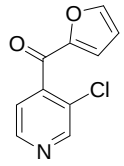
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm): 8.56 (d, *J* = 2.2 Hz, 1H), 8.49 (d, *J* = 4.9 Hz, 1H), 8.10-8.18 (m, 2H), 7.63-7.70 (m, 2H), 7.37-7.45 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): 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.

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 **$C_{14}H_{13}FNO_2$ ($M+H^+$)** (246.0930): 246.0923.

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



According to **TP2**, a mixture of 3-chloropyridine (**29j**; 228 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (ppm): 8.71 (s, 1H), 8.61 (d, *J* = 4.9 Hz, 1H), 7.71 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.37 (dd, *J* = 4.9, 0.7 Hz, 1H), 7.14 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.61 (dd, *J* = 3.7, 0.8 Hz, 1H).

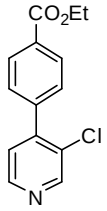
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 179.3, 151.1, 150.0, 148.8, 147.4, 144.6, 128.8, 122.6, 122.1, 113.1.

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 **$C_{10}H_6ClNO_2$** (207.0087): 207.0075.

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 $BF_3 \cdot OEt_2$ (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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 3:1) furnished the compound **49e** as yellow solid (200 mg, 95% yield).

M. p. (°C): 64.9-66.7.

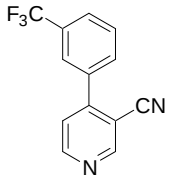
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.70 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.16 (m, *J* = 8.5 Hz, 2H), 7.55 (m, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 4.9 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{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) $\tilde{\nu}$ (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)



According to **TP2**, a mixture of nicotinonitrile (**29k**; 208 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**; 3.1 mL, 2.2 mmol, 0.71 M in THF) (-30 °C, 30 min).). $Pd(dba)_2$ (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 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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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).

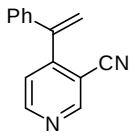
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 154.0, 153.1, 150.7, 136.2, 131.8 (q, *J* = 33.0 Hz), 131.7 (q, *J* = 1.3 Hz), 129.8, 127.0 (q, *J* = 3.7 Hz), 125.3 (q, *J* = 3.8 Hz), 123.7, 123.6 (q, *J* = 272.6 Hz), 116.1, 108.7.

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 **$C_{13}H_7F_3N_2$** (248.0561): 248.0550.

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

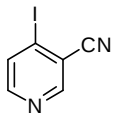


According to **TP2**, a mixture of nicotinonitrile (**29k**; 104 mg, 1 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**14**; 1.6 mL, 1.1 mmol, 0.71 M in THF) (-30 °C, 30 min). $Pd(dba)_2$ (28 mg, 5 mol%) and P(*o*-fur)$_3$ (23 mg, 10 mol%) dissolved in THF (1 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of (1-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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 2:1) furnished the product **49g** as yellowish oil (115 mg, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / 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, $CDCl_3$): δ / 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): $\tilde{\nu}$ / 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 $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (3 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were driedover Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / (ppm) = 8.73 (s, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 7.92 (d, *J* = 5.4 Hz, 1H).

[134] T. Cailly, S. Lemaître, F. Fabis, S. Rault, *Synthesis* **2007**, 3247.

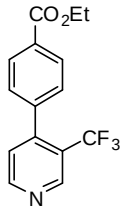
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 153.1, 152.1, 134.0, 118.8, 117.3, 109.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ (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 **$C_6H_3IN_2$** (229.9341): 229.9339.

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



According to **TP2**, a mixture of 3-(trifluoromethyl)pyridine (**29l**; 147 mg, 1.0 mmol) and $BF_3{\cdot}OEt_2$ was reacted with TMPMgCl·LiCl (**11**; 0.8 mL, 1.1 mmol, 1.2 M in THF) (-78 °C, 10 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 slowly warmed to 55 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 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, $CDCl_3$): δ / ppm = 8.98 (s, 1H), 8.10-8.19 (m, 4H), 8.02 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.85-7.95 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).

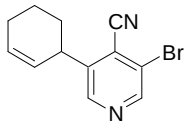
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 159.4 (q, *J* = 1.7 Hz), 146.7 (q, *J* = 3.9 Hz), 141.7, 134.1 (q, *J* = 3.7 Hz), 131.8, 130.1, 127.2, 125.5 (q, *J* = 33.1 Hz), 123.6 (q, *J* = 272.4 Hz), 120.4, 61.2, 14.3.

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 **$C_{15}H_{12}F_3NO_2$** (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 $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 5:1) furnished the compound **49j** as yellowish oil (266 mg, 63% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

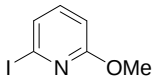
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm): 150.4, 149.7, 148.3, 145.6, 131.3, 125.8, 122.7, 113.9, 38.8, 31.0, 24.6, 20.5.

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 $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**11**; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 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 NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 150:1) furnished the compound **49k** as yellowish solid (353 mg, 75% yield).

M. p. (°C): 49.1-50.3.

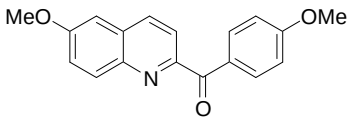
^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm): 7.29 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.13-7.19 (m, 1H), 6.67 (dd, *J* = 8.2, 0.9 Hz, 1H), 3.90 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): 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 **C_6H_7INO ($M+H^+$)** (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 $BF_3 \cdot OEt_2$ (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 NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/EtOAc, 2:1) furnished the compound **49l** as white solid (441 mg, 94% yield).

M. p. (°C): 138.1-139.3.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

^{13}C-NMR (75 MHz, $CDCl_3$): 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.

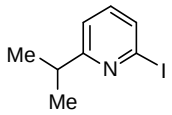
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3006, 2932, 2842, 1646, 1620, 1596, 1512, 1498, 1480, 1434, 1406, 1384, 1344, 1330, 1308, 1292, 1256, 1232, 1186, 1162, 1134, 1120, 1108, 1022, 972, 944, 904, 850, 830, 812, 792, 782, 754, 732, 710, 654, 634, 612.

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 **$C_{18}H_{15}NO_3$** (293.1052): 293.1046.

8. Preparation of the isopropylpyridine derivatives

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

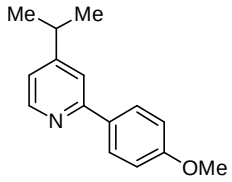


According to **TP2**, a mixture of 2-isopropylpyridine (**50**; 121 mg, 1.0 mmol) and $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (**13**; 2.5 mL, 1.5 mmol, 0.6 M in THF) (-78 °C, 15 h). A solution of iodine (0.5 g, 2 mmol) in THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (4.5 mL), NH_3 (conc.) (0.5 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x20 mL). The combined organic layers were driedover Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 100:1) furnished the compound **53** as colorless oil (173 mg, 70% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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 $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (**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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **54a** as yellow oil (297 mg, 81% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 8.55 (d, *J* = 5.1 Hz, 1H), 7.96 (m, 2H), 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).

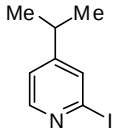
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 160.3, 158.4, 157.0, 149.2, 132.1, 128.2, 119.8, 118.3, 114.0, 55.3, 33.8, 23.1.

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 **$C_{14}H_{16}N_2O$** (228.1263): 228.1333.

Synthesis of 2-iodo-4-isopropylpyridine (54b)

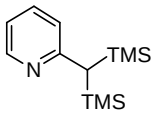


According to **TP2**, a mixture of 4-isopropylpyridine (**51**; 121 mg, 1.0 mmol) and $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) reacted with $TMP_2Mg \cdot 2LiCl$ (**13**; 2.5 mL, 1.5 mmol, 0.6 M in THF) (-78 °C, 40 h). A solution of iodine (0.5 g, 2 mmol) in THF (2 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aqueous NH_4Cl solution (4.5 mL), NH_3 (conc.) (0.5 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x20 mL). The combined organic layers were driedover Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 25:1) furnished the compound **54b** as yellow oil (178 mg, 72% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 160.2, 150.1, 133.3, 121.7, 118.0, 33.3, 22.8.
IR (Diamond-ATR, neat) $\tilde{\nu}$ (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)

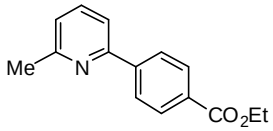


This compound was prepared following the literature procedure.[135] The analytical data were found to match literature data.

^{1}H-NMR (400 MHz, $CDCl_3$): 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).

[135] K. Hassall, C. H. Schiesser, J. M. White, *Organometallics* **2007**, *26*, 3094.

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 $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) reacted with $TMP_2MgCl \cdot 2LiCl$ (**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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_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_2O (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane / Et_2O = 10:1) afforded the product **59** (159 mg, 82%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

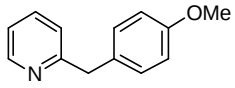
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 166.4, 158.6, 155.6, 143.6, 137.0, 130.5, 129.9, 126.8, 122.4, 118.0, 61.0, 24.6, 14.3.

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

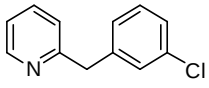
Synthesis of 2-(4-methoxybenzyl)pyridine (60a)



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_4Cl solution (10 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, hexane/Et_2O, 7:3) furnished the compound **60a** as yellow oil (303 mg, 95% yield). The analytical data were found to match literature data.[136]

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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)

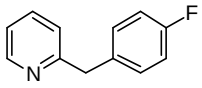


[136] T. Niwa, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2007**, *46*, 2643.

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_4Cl solution (10 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, hexane/Et_2O, 7:3) furnished the compound **60b** as yellow oil (216 mg, 66% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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) $\tilde{\nu}$ (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)

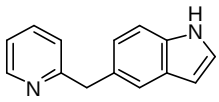


According to **TP1**, 2-methylpyridine (**56c**; 186 mg, 2.0 mmol) was reacted with TMPZn·LiCl (**12**; 2.3 mL, 3.0 mmol, 1.3 M in THF) (25 °C, 1 h). $Pd(OAc)_2$ (9 mg, 2 mol%) and S-Phos (33 mg, 4 mol%) dissolved in THF (2 mL) were then transferred *via* cannula to the reaction mixture, followed by 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_4Cl solution (10 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were

dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 4:1) furnished the compound **60c** as brown oil (234 mg, 78% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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, $CDCl_3$): δ / (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)



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-1*H*-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_4Cl solution (10 mL) followed by extraction with Et_2O (3×30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 6:4) furnished the compound **60d** as red solid (287 mg, 86% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / (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.

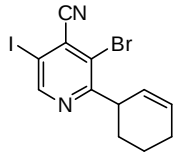
IR (Diamond-ATR, neat) $\tilde{\nu}$ (cm^{-1}): 3116, 3098, 3028, 3004, 2902, 2714, 2360, 2340, 1736, 1592, 1570, 1540, 1474, 1456, 1438, 1366, 1344, 1336, 1316, 1286, 1226, 1218, 1140, 1106, 1094, 1004, 916, 902, 890, 842, 816, 794, 774, 756, 736, 656, 630, 606.

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-iodoisonicotinonitrile (63):



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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane / Et_2O = 10:1) furnished the compound **63** as yellow oil (521 mg, 67%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (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).

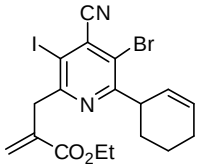
^{13}C-NMR (75 MHz, $CDCl_3$): δ / (ppm) = 164.1, 155.5, 130.9, 129.5, 123.3, 116.7, 93.6, 42.5, 28.5, 24.6, 21.4.

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, 1508, 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).

HRMS (EI) for **$C_{12}H_{10}BrIN_2$** (387.9072): 387.9049.

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 $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, pentane/Et_2O, 20:1) afforded the product **64** as yellow oil (311 mg, 62%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / (ppm) = 6.27-6.32 (m, 1H), 5.77-5.88 (m, 1H), 5.50-5.58 (m, 1H), 5.43-5.46 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.92-4.03 (m, 3H), 2.00-2.12 (m, 2H), 1.90-1.98 (m, 1H), 1.80-1.89 (m, 1H), 1.59-1.75 (m, 2H), 1.14-1.31 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / (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.

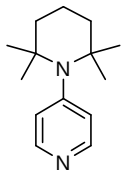
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2934, 2838, 2360, 2340, 1718, 1654, 1646, 1630, 1540, 1522, 1506, 1430, 1414, 1388, 1368, 1338, 1324, 1296, 1258, 1216, 1184, 1148, 1114, 1096, 1044, 1026, 956, 916, 894, 858, 838, 824, 784, 768, 668, 658.

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

HRMS (EI) for **$C_{18}H_{18}BrIN_2O_2$** (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-iodopyrdidine (205 mg, 1.0 mmol). After cooling to -40 °C, *i*PrMgCl·LiCl (0.90 mL, 1.1 mmol, 1.2 M in THF) was added dropwise and stirred for 30 min. $ZnCl_2$ (0.55 mL, 0.55 mmol, 1 M in THF) was added and the mixture was stirred for 30 min at the same temperature. CuCl·2LiCl (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 tetramethylpiperidide (2.0 mmol; prepared by adding *n*BuLi (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. Et_2O (100 mL) was poured into the crude reaction mixture. The organic phase was washed with 2 x 10 mL portions of aqueous NH_4OH (2.0 M) and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatographical purification (Al_2O_3 III, pentane/ether; 1:5) furnished the product **65d** as yellow solid (65 mg, 30%).

M. p. (°C): 52.7-54.7.

^{1}H-NMR (400 MHz, D_6-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).

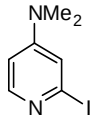
^{13}C-NMR (100 MHz, D_6-DMSO): δ / ppm = 154.1, 149.8, 129.0, 53.6, 41.3, 29.3, 17.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{14}H_{22}N_2$** (218.1783): (218.1775).

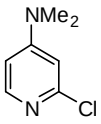
Synthesis of 2-iodo-*N*,*N*-dimethylpyridin-4-amine (66a)



According to **TP2**, a mixture of DMAP (**65**; 244 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_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 **$C_7H_9IN_2$** (247.9810): (247.9808).

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



According to **TP2**, a mixture of DMAP (**65**; 244 mg, 2.0 mmol) and $BF_3 \cdot OEt_2$ (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). $C_2Cl_3F_3$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3x30 mL). The combined organic

layers were dried over Na_2SO_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, $CDCl_3$): δ / 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).

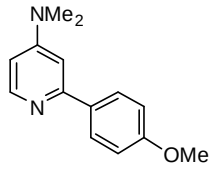
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.0, 152.1, 148.9, 105.8, 105.3, 39.1.

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 **$C_7H_9ClN_2$** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_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.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

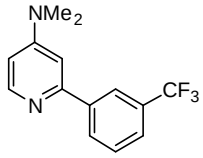
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.3, 156.7, 155.2, 148.4, 132.2, 128.3, 113.9, 105.0, 102.8, 55.3, 39.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{14}H_{16}N_2O$** (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 $BF_3{\cdot}OEt_2$ (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-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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 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.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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).

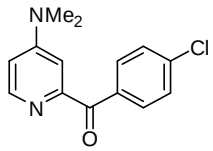
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.0, 151.1, 142.8, 134.9, 131.5 (q, *J* = 32.8 Hz), 130.0, 127.2 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 4.0 Hz), 123.6 (q, *J* = 272.7 Hz), 106.2, 104.7, 40.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{14}H_{13}F_3N_2$** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x40 mL). The combined organic layers were dried over Na_2SO_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, $CDCl_3$): δ / 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).

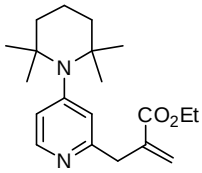
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 193.1, 154.4, 154.4, 148.1, 138.5, 134.7, 132.0, 127.8, 108.1, 106.8, 38.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3088, 2918, 2818, 1918, 1662, 1584, 1540, 1504, 1486, 1430, 1414, 1398, 1376, 1338, 1282, 1264, 1224, 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 **$C_{14}H_{13}ClN_2O$** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and extracted with Et_2O (3x40 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (Al_2O_3 III, pentane/Et_2O, 4:1) afforded the product **66f** (397 mg, 71%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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).

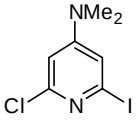
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.7, 159.0, 155.5, 149.2, 138.9, 129.0, 126.9, 126.6, 60.7, 54.1, 41.8, 40.6, 29.6, 18.1, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 2930, 2870, 1716, 1632, 1588, 1542, 1474, 1456, 1446, 1428, 1378, 1364, 1326, 1294, 1272, 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 **$C_{20}H_{30}N_2O_2$** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and sat. aqueous $Na_2S_2O_3$ solution (2 mL) followed by extraction with Et_2O (3x30 mL). The combined organic layers were dried over Na_2SO_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, $CDCl_3$): δ / ppm = 6.84 (d, *J* = 2.2 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 2.98 (s, 6H).

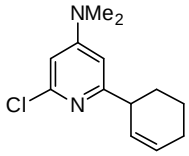
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.1, 150.2, 115.9, 115.7, 105.4, 39.4.

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 **$C_7H_8ClIN_2$** (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 $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) reacted with TMPMgCl·LiCl (**11**; 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_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) and extracted with Et_2O (3x20 mL). The combined organic layers were dried over Na_2SO_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, $CDCl_3$): δ / 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, $CDCl_3$): δ / 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.

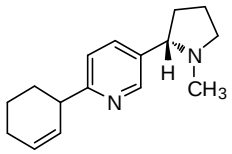
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2928, 2860, 2836, 1662, 1590, 1528, 1504, 1422, 1366, 1326, 1294, 1214, 1184, 1126, 1064, 980, 934, 914, 896, 888, 822, 810, 748, 726, 710.

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 $BF_3 \cdot OEt_2$ (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 NH_4Cl solution (4.5 mL) and NH_3 (conc.) (0.5 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (Al_2O_3 III, pentane / Et_2O = 1:1) afforded the product **67a** (223 mg, 92%) as red oil.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

^{13}C-NMR (75 MHz, $CDCl_3$): 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.

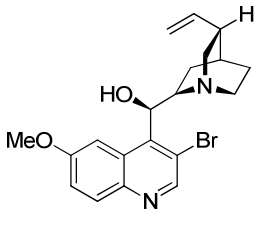
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}): 3018, 2934, 2874, 2858, 2836, 2774, 2720, 2664, 2362, 2340, 1734, 1674, 1616, 1596, 1566, 1480, 1456, 1448, 1420, 1400, 1374, 1344, 1332, 1314, 1288, 1250, 1216, 1210, 1152, 1132, 1116, 1086, 1044, 1026, 988, 966, 922, 902, 886, 838, 788, 764, 722, 688, 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 **$C_{16}H_{22}N_2$** (242.1783): 242.1777.

14. Preparation of functionalized quinine derivatives

Synthesis of (*R*)-(3-bromo-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-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 Et_2O), $BF_3{\cdot}OEt_2$ (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 NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (Al_2O_3 III, hexane/EtOAc, 1:1) furnished the product **68a** as off-white solid (532 mg, 66% yield).

M. p. (°C): 84.2-87.5.

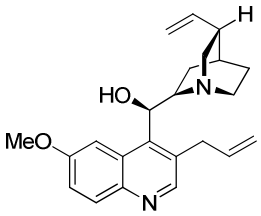
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = : 8.65 (s, 1H), 7.95 (s, br, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.29 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 5.92-5.77 (m, 1H), 5.59 (d, *J* = 8.8 Hz, 1H), 5.02 (s, 1H), 4.98 (d, *J* = 5.6 Hz, 1H), 3.90 (s, 3H), 3.75-3.53 (m, 1H), 3.45-3.25 (m, 1H), 2.99-2.80 (m, 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).

^{13}C-NMR ($CDCl_3$, 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): $\tilde{\nu}$ / 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 **$C_{20}H_{24}BrN_2O_2$ ($M+H^+$)** (403.1016): 403.1014.

Synthesis of (*R*)-(3-allyl-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)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_2O), $BF_3{\cdot}OEt_2$ (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_4Cl solution (14 mL) and NH_3 (conc.) (2 mL) followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (Al_2O_3 III, pentan/EtOAc, 5:1) furnished the compound **68b** as slightly yellow resin (451 mg, 41%).

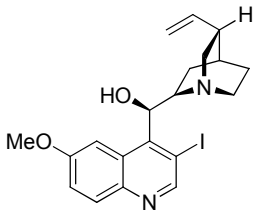
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.42 (s, 1H), 7.91 (d, J = 9.2Hz, 1H), 7.22-7.28 (m, 2H), 5.95-6.10 (m, 1H), 5.77-5.90 (m, 1H), 5.75-5.62 (m, 1H), 5.31-5.44 (m, 1H), 5.04-5.11 (m, 1H), 4.87-5.01 (m, 3H), 3.88 (s, 3H), 3.63-3.73 (m, 1H), 3.51-3.59 (m, 1H), 3.07-3.22 (m, 2H), 2.84-2.83 (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).

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (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 **$C_{23}H_{29}N_2O_2$ ($M+H^+$)** (365.2224): 365.2221.

Synthesis of (*R*)-(3-iodo-6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-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 Et_2O), $BF_3{\cdot}OEt_2$ (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 NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (Al_2O_3 III, hexane/EtOAc, 1:1) furnished the product **68c** as off-white solid (585 mg, 65% yield).

M. p. (°C): 84.8-85.1.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

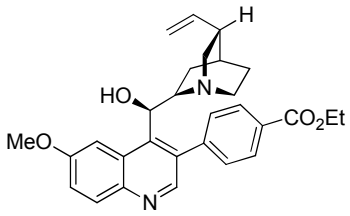
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.8, 154.6, 147.6, 144.3, 141.0, 130.9, 129.1, 121.7, 116.5, 114.6, 104.3, 81.0, 60.0, 55.3, 55.1, 43.1, 39.1, 27.2, 27.1, 24.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{20}H_{23}IN_2O_2$** (450.0804): 450.0932.

Synthesis of ethyl 4-(4-((*R*)-hydroxy((2*S*,4*S*,8*R*)-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 Et_2O), $BF_3{\cdot}OEt_2$ (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 $ZnCl_2$ (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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt_3, 10:1:1) afforded the product **68d** (378 mg, 50%) as yellow resin.

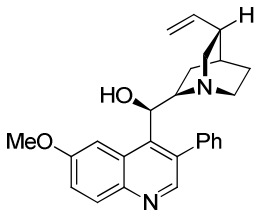
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.31 (s, 1H), 8.05-8.16 (m, 2H), 7.95-8.00 (m, 1H), 7.86-7.92 (m, 1H), 7.34-7.41 (m, 2H), 7.25-7.30 (m, 1H), 5.67-5.78 (m, 1H), 5.21-5.28 (m, 1H), 4.85-4.97 (m, 2H), 4.86 (q, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 3.43-3.53 (m, 1H), 3.06-3.15 (m, 1H), 2.67-2.77 (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).

^{13}C-NMR ($CDCl_3$, 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 **$C_{29}H_{33}N_2O_4$ ($M+H^+$)** (473.2440): 443.2436.

Synthesis of (*R*)-(6-methoxy-3-phenylquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methanol (68e)



According to **TP4**, quinine (**68**; 648 mg, 2.0 mmol) reacted with MeLi (1.2 mL, 2.0 mmol, 1.63 M in Et_2O), $BF_3{\cdot}OEt_2$ (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 $ZnCl_2$ (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 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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *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).

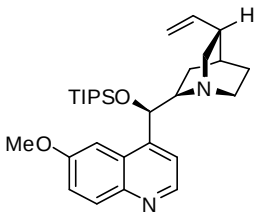
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (ppm) = 157.0, 149.0, 144.3, 143.4, 142.1, 138.5, 135.0, 131.1, 130.0, 128.1, 127.3, 127.0, 121.1, 113.8, 104.9, 72.3, 60.0, 55.6, 55.4, 41.6, 39.7, 27.7, 27.2, 25.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{26}H_{28}N_2O_2$** (400.2151): 400.2148.

Synthesis of (1*S*,4*S*,5*R*)-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 TIPSCl (7.7 g, 40 mmol) in DMF (20 mL) was heated at 120 °C for 5 d. After addition of CH_2Cl_2 (100 mL) the organic layer was washed with sat. aqueous $NaHCO_3$ solution (2x40 mL) and dried over $MgSO_4$. After filtration the solvents were evaporated *in vacuo*. Flash column purification (silica gel, EtOAc/MeOH/NEt_3, 10:1:1) furnished the product **68f** as yellow resin (7.88 g, 82%).

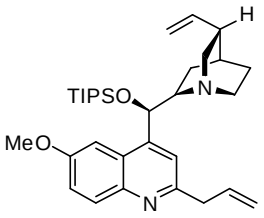
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.73 (d, J = 4.6 Hz, 1 H, major rotamer), 8.62 (d, J = 4.3 Hz, 1 H, minor rotamer), 8.00 (d, J = 9.3 Hz, 1 H, major rotamer), 7.96 (d, J = 9.2 Hz, 1 H, minor rotamer), 7.84 (d, J = 2.8 Hz, 1 H, minor rotamer), 7.56 (d, J = 4.6 Hz, 1 H, major rotamer), 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.

^{13}C-NMR ($CDCl_3$, 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): $\tilde{\nu}$ / 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 **$C_{29}H_{45}N_2O_2Si$ ($M+H^+$)** (481.3245): 481.3241.

Synthesis of (1*S*,4*S*,5*R*)-2-((*R*)-(2-allyl-6-methoxyquinolin-4-yl)((triisopropylsilyl)oxy)methyl)-5-vinylquinuclidine (68g)



According to **TP2**, a mixture of (1*S*,4*S*,5*R*)-2-((*R*)-(6-methoxyquinolin-4-yl)((triisopropylsilyl)oxy)methyl)-5-vinylquinuclidine (**68f**; 962 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (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_4Cl solution (10 mL) and NH_3 (conc.) (2 mL) followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_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%).

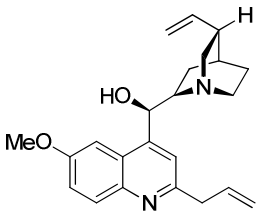
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.96 (d, J = 9.1 Hz, 1 H, major rotamer), 7.92 (d, J = 9.4 Hz, 1 H, minor rotamer), 7.80 (d, J = 3.0 Hz, 1 H, minor rotamer), 7.49 (s, 1 H, major rotamer), 7.35-7.26 (m, 1 H), 7.15 (d, J = 2.8 Hz, 1 H, major rotamer), 7.01 (s, 1 H; minor rotamer), 6.17-6.00 (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 ≈ 0.6/1.

^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ / (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 **$C_{32}H_{49}N_2O_2Si$ ($M+H^+$)** (521.3558): 521.3553.

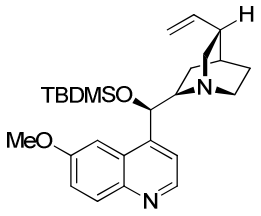
Synthesis of (1*R*)-(2-allyl-6-methoxyquinolin-4-yl)((1*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (68h)



A mixture of (1*S*,4*S*,5*R*)-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 $MgSO_4$. After filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt_3, 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 (1*S*,4*S*,5*R*)-2-((*R*)-((*tert*-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (68i)



A mixture of quinine (**68**; 8.0 g, 24.4 mmol), NEt_3 (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 $NaHCO_3$ solution (3x40 mL) and dried over $MgSO_4$. After filtration the solvents were evaporated *in vacuo*. Flash column purification (silica gel, EtOAc/MeOH/NEt_3, 9:1:1) furnished the product **68i** as orange resin oil (10.4 g, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$, 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,

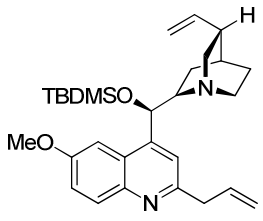
J = 9.3 Hz, 1H, minor rotamer), 8.83 (d, *J* = 2.6 Hz, 1H, minor rotamer), 7.51 (d, *J* = 4.6 Hz, 1H, major rotamer), 7.36 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz 1H, major rotamer), 7.31 (dd, *J* = 9.3 Hz, *J* = 2.6 Hz, 1H, minor rotamer), 7.19 (d, *J* = 2.6 Hz, 1H, major rotamer), 7.10 (d, *J* = 4.2 Hz, 1H,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

^{13}C-NMR ($CDCl_3$, 100 MHz, 25 °C): δ / (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 **$C_{26}H_{39}N_2O_2Si$ ($M+H^+$)** (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 $BF_3{\cdot}OEt_2$ (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_4Cl solution (10 mL) and NH_3 (conc.) (2 mL) followed by extraction with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over Na_2SO_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 **68j** as slightly brown resin oil (379 mg, 41%).

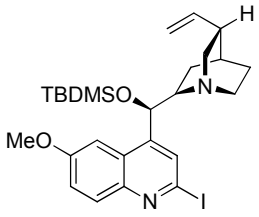
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.00-7.89 (m, 1H), 7.79 (br, 1H, minor rotamer), 7.45 (s, 1H, major rotamer), 7.36-7.25 (m, 1H), 7.17 (br, 1H, major rotamer), 7.03 (s, 1H, minor rotamer), 6.17-6.00 (m, 1H), 5.94-5.54 (m, 2H), 5.23-5.08 (m, 2H), 5.02-4.71 (m, 2H), 3.93 (s, 3H, major 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.

^{13}C-NMR ($CDCl_3$, 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): $\tilde{\nu}$ / 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 **$C_{29}H_{43}N_2O_2Si$ ($M+H^+$)** (479.3088): 479.3084.

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

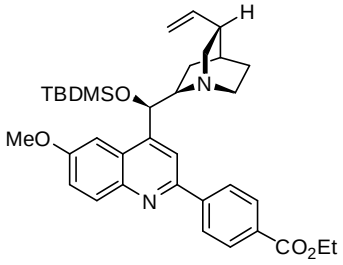


According to **TP2**, a mixture of (1*S*,4*S*,5*R*)-2-((*R*)-((*tert*-butyldimethylsilyl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**68i**; 1.75 g, 4.0 mmol) and $BF_3{\cdot}OEt_2$ (624 mg, 4.4 mmol) reacted with TMPMgCl·LiCl (**11**; 4.8 mL, 6.0 mmol, 1.26 M in THF) (0 °C, 15 h). Iodine (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 NH_4Cl solution (18 mL), NH_3 (conc.) (2 mL) and sat. aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt_3, 50:1:1) furnished the product **68k** as resin (1.00 g, 44%).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.95-7.86 (m, 1H), 7.81 (s, 1H, major rotamer), 7.77 (br, 1H, minor rotamer), 7.42 (s, 1H, minor rotamer), 7.34-7.26 (m, 1H), 7.16 (br, 1H, major rotamer), 5.90-5.56 (m, 2H), 5.00-4.61 (m, 2H), 3.93 (s, 3H, major rotamer), 3.86 (s, 3H, minor rotamer), 3.57-1.36 (m, 11H), 0.96 (s, 9H, major rotamer), 0.80 (s, 9H, minor rotamer), 0.14 (s, 3H, major rotamer), 0.08 (s, 3H, minor rotamer), -0.34 (s, 3H, major rotamer), -0.43 (s, 3H, minor rotamer). Ratio of rotamers determined by NMR ≈ 3/1.
^{13}C-NMR ($CDCl_3$, 75 MHz, 25 °C): δ (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, 25.7, 20.7, 18.0, -3.4, -4.2, -4.6, -5.0, -5.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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, 1004, 952, 944, 912, 880, 870, 834, 804, 776, 726, 710, 672, 646.
HRMS (ESI) for **$C_{26}H_{38}IN_2O_2Si$ ($M+H^+$)** (565.1742): 565.1737.

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



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 $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) reacted with TMPMgCl·LiCl (**11**; 2.5 mL, 3.0 mmol, 1.22 M in THF)

(0 °C, 15 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 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_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_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.

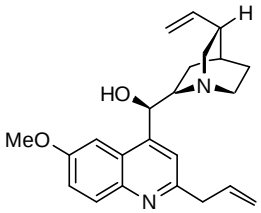
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 8.24-8.13 (m, 4H,), 8.12 (d, J = 9.3 Hz), 8.08-8.04 (m, 1H, major rotamer, 1H, minor rotamer), 7.85 (d, J = 2.7 Hz, 1 H, Minor rotamer), 7.61 (br, 1H, minor rotamer), 7.40 (dd, J = 9.2, 2.7 Hz, 1H, major rotamer), 7.34 (dd, J = 9.2, 2.7 Hz, 1H, minor 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, 3H, major 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 ≈ 3/1.

^{13}C-NMR ($CDCl_3$, 100 MHz, 25 °C): δ / (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 **$C_{35}H_{47}N_2O_4Si$ ($M+H^+$)** (587.3300): 587.3294.

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



A mixture of (1*S*,4*S*,5*R*)-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 $MgSO_4$. After filtration the solvents were evaporated *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt_3, 150:1:1) furnished the product **68m** as yellow solid (461 mg, 79%).

M.p. (°C): Decomp. at 83.0.

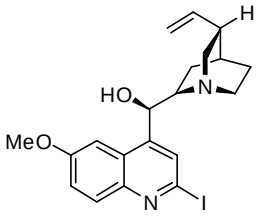
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C): δ / (ppm) = 7.88 (d, J = 9.1 Hz, 1H, minor rotamer), 7.81 (d, J = 9.1 Hz, 1H, minor rotamer), 7.51 (s, 1H, minor rotamer), 7.41 (s, 1H, major rotamer), 7.25-7.15 (m, 1H), 7.12 (d, J = 2.5 Hz, 1H, major rotamer), 7.04 (d, J = 2.7 Hz, 1H, minor rotamer), 6.65-6.40 (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, 2 H), 3.26-2.95 (m, 2H), 2.73-2.57 (m, 2H), 2.33-2.18 (m, 1H), 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.

^{13}C-NMR ($CDCl_3$, 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): $\tilde{\nu}$ / 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 **$C_{23}H_{29}N_2O_2$ ($M+H^+$)** (365.2224): 365.2220.

Synthesis of (1*R*)-(2-iodo-6-methoxyquinolin-4-yl)((1*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (68n)



A mixture of (1*S*,4*S*,5*R*)-2-((*R*)-((*tert*-butyldimethylsilyl)oxy)(2-iodo-6-methoxyquinolin-4-yl)methyl)-5-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 *in vacuo*. Flash column chromatographical purification (silica gel, EtOAc/MeOH/NEt_3, 150:1:1) furnished the product **68n** as white solid (406 mg, 82%).

M.p. (°C): Decomp. at 257.6.

^{1}H-NMR (400 MHz, THF-d8, 25 °C): δ / (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).

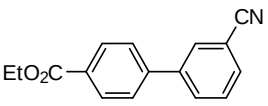
^{13}C-NMR (THF-d8, 100 MHz, 25 °C): δ / (ppm) = 158.9, 152.1, 146.6, 143.4, 131.7, 129.8, 127.1, 122.6, 116.5, 114.1, 103.2, 72.4, 61.9, 57.7, 55.9, 43.6, 41.6, 29.4, 28.7, 22.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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.

HRMS (ESI) for **$C_{20}H_{24}IN_2O_2$ ($M+H^+$)** (451.0877): 451.0873.

15. Preparation of Pd-catalyzed one-pot reaction of aryl- and alkylzinc reagents with aryl halides

Synthesis of 3'-cyano-biphenyl-4-carboxylic acid ethyl ester (72a)



(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 °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 °C for 15 h; *work-up and purification*: extracted with EtOAc (4×10 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 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 °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 °C for 1.5 h; *work-up and purification*: extracted with Et_2O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 5:1) to give **72a** as white solid (167 mg, 83%).

M. p. (°C): 90.7-93.3.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / 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).

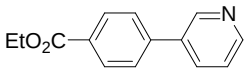
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 166.1, 143.0, 141.3, 131.6, 131.4, 130.8, 130.4, 130.3, 129.8, 127.0, 118.5, 113.2, 61.2, 14.3.

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 °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 °C for 3 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane, Et_2O, 1 : 1) to give **72b** as white solid (156 mg, 86%).

M. p. (˚C): 55.0-56.7.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.86 (brs, 1H), 8.54-8.70 (m, 1H), 8.13 (d, *J* = 7.7 Hz, 2H), 7.83-7.94 (m, 1H), 7.63 (d, *J* = 7.7 Hz, 2H), 7.37 (dd, *J* = 7.8 Hz, *J* = 4.8 Hz, 1H).

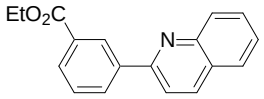
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 149.2, 148.3, 142.1, 135.6, 134.4, 130.3, 130.1, 127.0, 123.6, 61.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{14}H_{13}NO_2$** (227.0946): 227.0945.

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 ˚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 ˚C for 4.5 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 100:18) to give **72c** as pale yellow oil (333 mg, 85%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.78-8.81 (m, 1H), 8.21-8.27 (m, 1H), 8.38-8.45 (m, 1H), 8.16-8.21 (m, 1H), 8.11-8.16 (m, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.80-7.86 (m, 1H), 7.70-7.78 (m, 1H), 7.50-7.64 (m, 3H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).

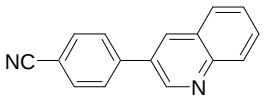
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.5, 156.2, 148.3, 139.9, 137.0, 131.9, 131.1, 130.3, 129.8 (overlapped), 128.9, 128.5, 127.5, 127.3, 126.5, 118.8, 6.13, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{18}H_{15}NO_2$** (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 °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 °C for 5 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 1:2.5) to give **72d** as white solid (334 mg, 91%).

M. p. (°C): 171.5-173.0.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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), 7.85-7.93 (m, 1H), 7.73-7.84 (m, 5H), 7.57-7.65 (m, 1H).

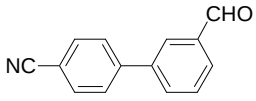
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.1, 147.9, 142.4, 133.9, 132.9, 131.8, 130.2, 129.4, 128.1, 128.0, 127.7, 127.5, 118.6, 111.8.

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*: **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 °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 °C for 2 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 2:1) to give **72e** as white solid (267 mg, 80%).

M. p. (˚C): 129.3-131.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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).

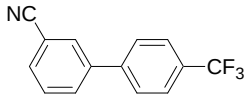
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 191.7, 144.1, 140.1, 137.1, 132.9, 132.8, 131.0, 129.9, 127.9, 122.8, 118.6, 111.8.

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 **$C_{14}H_9NO$** (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_2O, 100:8) to give **72f** as white solid (490 mg, 83%).

M. p. (˚C): 61.6-63.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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).

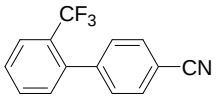
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 142.3, 141.0, 131.6, 130.8, 130.5 (q, *J* = 32.7 Hz), 129.9, 127.5, 126.1 (q, *J* = 272.1 Hz), 118.5, 113.3.

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 **$C_{14}H_8F_3N$** (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 °C for 48 h; *cross-coupling*: **71g** (437 mg, 2.4 mmol), PEPPSI (8.0 mg, 0.012 mmol), T_2 = 25 °C for 15 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 20:1) to give **72g** as white solid (569 mg, 97%).

M. p. (°C): 123.8-125.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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).

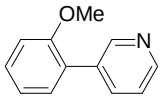
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 144.5, 139.3, 131.6, 131.4, 129.8, 128.3, 127.9 (q, J = 30.9 Hz), 126.3 (q, J = 5.3 Hz), 123.9 (q, 273.9 Hz), 118.6, 111.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{14}H_8F_3N$** (247.0609): 247.0612.

Synthesis of 3-(2-methoxy-phenyl)-pyridine (**72h)**



According to **TP5** – *Zn insertion*: 69**1f** (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 °C for 180 h; *cross-coupling*: **71h** (478 mg, 2.4 mmol), PEPPSI (8.0 mg, 0.012 mmol), T_2 = 25 °C for 2 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 1:1) to give **72h** as yellow oil (380 mg, 92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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).

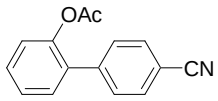
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.4, 150.0, 147.3, 138.3, 135.0, 130.5, 130.0, 126.0, 123.5, 121.1, 111.3, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2832, 1598, 1581, 1565, 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)**



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 (3×5 mL), purified by flash chromatography (silica gel, gradient elution; pentane/Et_2O, 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, $CDCl_3$): δ / 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).

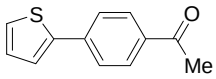
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.0, 147.6, 142.4, 133.1, 132.1, 130.5, 129.7, 129.6, 126.6, 123.1, 118.7, 111.3, 20.8.

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 **$C_{15}H_{11}O_2N$** (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), T_1 = 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), T_2 = 25 °C for 1 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, gradient elution: pentane/Et_2O, 100:10 to 100:15) to give **72j** as white solid (266 mg, 82%).

M. p. (°C): 124.6-126.4.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

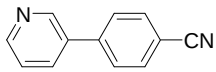
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.2, 142.9, 138.7, 135.7, 129.1, 128.3, 126.4, 125.6, 124.6, 26.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 3006, 1674, 1598, 1423, 1358, 1312, 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 **$C_{12}H_{10}OS$** (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), T_1 = 50 °C for 12 h; *cross-coupling*: **71g** (291 mg, 1.6 mmol), PEPPSI (5.3 mg, 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_2O, 1:1 to Et_2O) to give **72k** as white solid (216 mg, 75%).

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).

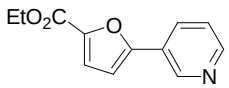
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.7, 148.2, 142.3, 134.7, 134.4, 132.8, 127.1, 123.7, 118.5, 111.9.

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 **$C_{12}H_8N_2$** (180.0687): 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_2O, 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).

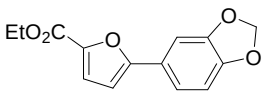
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.5, 154.4, 149.6, 146.2, 144.8, 131.7, 125.7, 123.5, 119.5, 107.9, 61.0, 14.3.

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 **$C_{12}H_8NO_3$** (217.0739): 217.0729.

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 °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 °C for 20 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, graduate elution; pentane/Et_2O, 100:10 to 100:15) to give **72m** as white solid (379 mg, 91%).

M. p. (°C): 97.0-99.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.28 (dd, *J* = 8.1 Hz, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 1.7 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 3.7 Hz, 1H), 5.98 (s, 2H), 4.86 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H).

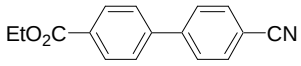
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.8, 157.3, 148.3, 148.1, 143.3, 123.9, 119.9, 108.6, 105.7, 105.3, 101.4, 60.8, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3119, 2992, 2916, 1708, 1472, 1356, 1386, 1303, 1229, 1154, 1034, 966, 932, 864, 813, 758, 686.

MS (EI, 70 eV): m/z (%) = 260 [M^+] (100), 232 (58), 215 (13), 159 (22), 129 (9), 107 (9), 75 (9).

HRMS (EI) for **$C_{14}H_{12}O_5$** (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 °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 °C for

4 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 9:1) to give **72n** as white solid (313 mg, 78%).

M. p. (°C): 118.3-120.4.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

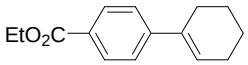
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 144.5, 143.3, 132.7, 130.6, 130.3, 127.9, 127.2, 118.7, 111.8, 61.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{16}H_{13}NO_2$** (251.0946): 251.0930.

Synthesis of 4-Cyclohex-1-enyl-benzoic acid ethyl ester (72o)



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 °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), T_2 = 25 °C for 4 h; *work-up and purification*: extracted with EtOAc (3×5 mL), purified by flash chromatography (silica gel, graduate elution; pentane/Et_2O, 400:1 to 199:1) to give **72o** as white solid (276 mg, 75%).

M. p. (°C): 71.7-73.1.

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

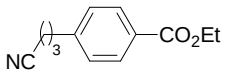
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 147.0, 135.9, 129.5, 128.4, 127.1, 124.7, 60.8, 27.2, 26.0, 22.9, 22.0, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2862, 1708, 1602, 1462, 1410, 1364, 1271, 1188, 1102, 1018, 921, 869, 835, 768, 747, 696.

MS (EI, 70 eV): m/z (%) = 230 [M^+] (99), 185 (45), 157 (100), 129 (84), 115 (26), 91 (24), 77 (10).

HRMS (EI) for **$C_{15}H_{18}O_2$** (230.1307): 230.1305.

Synthesis of 4-(3-cyano-propyl)-benzoic acid ethyl ester (75a)



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), T_1 = 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), T_2 = 25 °C for 2 h; *work-up and purification*: extracted with Et_2O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 2:1) to give **75a** as yellow oil (299 mg, 86%).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

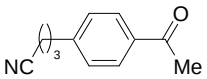
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 144.9, 130.0, 129.0, 128.4, 119.2, 60.9, 34.4, 26.6, 16.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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 **$C_{13}H_{15}NO_2$** (217.1103): 217.1096.

Synthesis of 4-(4-acetyl-phenyl)-butyronitrile (75b)

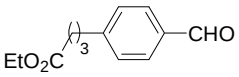


According to **TP6** – *Zn insertion*: **73a** (390 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T_1 = 25 °C for 2 h; *cross-coupling*: **71i** (318 mg,

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 °C for 2 h; *work-up and purification*: extracted with Et_2O (3×5 mL), purified by flash chromatography (silica gel, gradient elution; pentane/Et_2O, 2:1 to 1:2) to give **75b** as yellow oil (210 mg, 70%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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, $CDCl_3$): δ / 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)



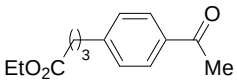
According to **TP6** – *Zn insertion*: **73b** (484 mg, 2.0 mmol), LiCl (127 mg, 3.0 mmol), and Zn (196 mg, 3.0 mmol) in THF (2.0 mL), T_1 = 50 °C for 12 h; *cross-coupling*: **71j** (296 mg, 1.6 mmol), PEPPSI (0.20 mL of a 40 mmol/L solution in THF, 0.008 mmol), DMI (1.0 mL), T_2 = 25 °C for 1 h; *work-up and purification*: extracted with Et_2O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 4:1) to give **75c** as yellow oil (307 mg, 87%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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, $CDCl_3$): δ / 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_1 = 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_2 = 25 °C for 2 h; *work-up and purification*: extracted with Et_2O (3×5 mL), purified by flash chromatography (silica gel, pentane/Et_2O, 5:1) to give **75d** as yellow oil (257 mg, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$): 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).

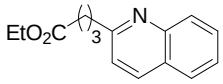
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 197.8, 173.2, 147.2, 135.3, 128.7, 128.6, 60.3, 35.1, 33.5, 26.5, 26.1, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 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_1 = 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 °C for 15 h; *work-up and purification*: extracted with Et_2O (3×5 mL), purified by flash chromatography (silica gel, gradient elution; pentane/Et_2O, 2:1 to 3:2) to give **75e** as yellow oil (285 mg, 73%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / 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 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.90-3.08 (m, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.27-2.07 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / 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.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2979, 2935, 1728, 1600, 1504, 1426, 1374, 1307, 1244, 1178, 1139, 1026, 951, 827, 753, 618.
MS (EI, 70 eV): m/z (%) = 243 [M^+] (15), 198 (67), 170 (100), 156 (26), 143 (32), 128 (25), 115 (19).
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

Sept/1991-June/2000	Gisela-Gymnasium Munich (main subjects: mathematics/french)
Oct/2000-Nov/2006	Studies in Chemistry at LMU Munich
Nov/2006-May/2007	Diploma thesis “Ein neues, effizientes Ein-Topf-Verfahren für die Negishi-Kreuzkupplung“ in the group of Prof. Dr. P. Knochel
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

1.) S. Sase, **M. Jaric**, A. Metzger, V. Malakhov, P. Knochel: "One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents with Aryl Chlorides, Bromides, and Triflates" *J. Org. Chem.* **2008**, *73*, 7380.

2.) **M. Jaric**, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel: "Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or Zn- and Mg-TMP-Bases with $BF_3{\cdot}OEt_2$" *Angew. Chem. Int. Ed.* **2010**, *49*, 5451 (**hot paper**); *Angew. Chem.* **2010**, *122*, 5582.

3.) **M. Jaric**, B. A. Haag, S. M. Manolikakes, P. Knochel: "Selective and Multiple Functionalization of Complex Pyridines and Alkaloids via Mg- and Zn-Organometallic Intermediates" *Org. Lett.*, accepted.

Posters

Milica Gvozdenac, Shohei Sase, Vladimir Malakhov, and Paul Knochel. "A One-Pot Negishi Reaction for Biaryl Synthesis: Pd-catalyzed Cross-Coupling of Arylzinc Iodides with Aryl- and Heteroaryl Halides in the presence of Zinc Dust".
14th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (**OMCOS-14**), Nara, Japan. 2nd-6th, August, **2007**.