Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

Preparation of Functionalized Aromatics, Pyridines and Related Heteroaromatics Using Sterically Hindered Metal Amide Bases in the Presence or Absence of $BF_3 \cdot OEt_2$.

von

Sophia Maria Manolikakes

aus München, Deutschland

2014

Erklärung

Diese Dissertation wurde im Sinne von §7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Paul Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

München, ____ März 2014

.....
Sophia Manolikakes

Dissertation eingereicht am	17. März 2014
1. Gutachter	Prof. Dr. Paul Knochel
2. Gutachter	Prof. Dr. Konstantin Karaghiosoff
Mündliche Prüfung am	29. April 2014

This work was carried out from February 2011 to March 2014 under the guidance of Prof. Dr. Paul Knochel at the Faculty of Chemistry and Pharmacy of the Ludwig-Maximilians Universität, Munich. First, I thank Prof. Dr. Paul Knochel for giving me the opportunity to carry out my PhD thesis in his group. He made it possible for me to perform the research I was interested in and supported me throughout my studies.

I also thank Prof. Dr. Konstantin Karaghiosoff for agreeing to be my "Zweitgutachter" as well as Prof. Dr. Manfred Heuschmann, Prof. Dr. Herbert Mayr, Prof. Dr. Klaus Wanner and Prof. Dr. Heinz Langhals for their interest in this manuscript and for accepting to be referees.

I am also very grateful to Lydia Klier, Annette Frischmuth, Nadja Barl and Trine Petersen for carefully proofreading this manuscript.

Moreover, I thank all my past and present coworkers in the Knochel group for generating a nice atmosphere not only for working and discussing (non-)chemical problems, but also for having a beer or a party (or both). Special thanks goes to my lab mates Dr. Stéphanie Duez, Dr. Tobias Blümke, Dr. Milica Jaric, Nadja Barl, Andreas Steib, Julia Nafe and also Mario Ellwart. You made F2.001b the best lab I could have imagined.

I also thank my cooperation partners: Dr. Stéphanie Duez and Andres Steib for the great work on the benzylic metalations and cross-couplings. Dr. Milica Jaric, Dr. Xavier Mollat du Jourdin, Dr. Aleksei Bredihhin and Dr. Klaus Groll for the cooperation on the BF_3 activation and metalation of heterocycles. Special thanks on this occasion go to Prof. Dr. Konstantin Karaghiosoff for the hundreds of hours he spent on measuring my very instable intermediates and the patience, motivation and interest he showed in this project. For the work on the zinc pivalates I thank Dr. Christos Stathakis, Dr. Sebastian Bernhardt and Mario Ellwart for their excellent work and advice. I also thank the group of Prof. Dr. Robert Mulvey and Prof. Dr. Eva Hevia for their great structural insights they provided on the solid organozinc reagents.

Furthermore, I thank my cooking group Annette Frischmuth and Lydia Klier for always supplying me with tasty food at lunchtime. I also want to thank all the colleagues who helped me through my PhD, also in the more frustrating times there was always someone to talk to and to discuss problems with. Special thanks at this point goes to Nadja Barl, Annette Frischmuth, Pauline Quinio, Julia Nafe and Lydia Klier for always cheering me up and for spending some great time together inside and especially outside the lab. You made the time in this group an awesome experience.

I would also like to thank my bachelor student Philipp Bielec for his great engagement and interest he showed during his internship.

I thank Dr. Vladimir Malakhov, Simon Matthe, Yulia Tsvik and especially Renate Schröder for their help in organizational issues and beyond. I appreciate also the work of the analytical team of the department for their invaluable help.

Last but not least I want to thank my parents, my brothers and the rest of my family for always supporting me through all my studies. I would not have come this far without your help. I also thank Oliviaki for his incredibly profound and sophisticated weekly phone calls.

Parts of this PhD thesis have been published

Communications

1.) Milica Jaric, Benjamin A. Haag, Sophia M. Manolikakes, Paul Knochel "Selective and Multiple Functionalization of Pyridines and Alkaloids *via* Mg- and Zn-Organometallic Intermediates" *Org. Lett.* **2011**, *13*, 2306-2309.

2.) Stéphanie Duez, Andreas K. Steib, Sophia M. Manolikakes, Prof. Dr. Paul Knochel "Lewis Acid Promoted Benzylic Cross-Couplings of Pyridines with Aryl Bromides" *Angew. Chem. Int. Ed.* **2011**, *50*, 7686-7690.

3.) Sophia M. Manolikakes, Milica Jaric, Konstantin Karaghiosoff, Paul Knochel "Metalated N-heterocyclic reagents prepared by the frustrated Lewis pair TMPMgCl·BF_3 and their addition to aromatic aldehydes and activated ketones" *Chem. Commun.* **2013**, *49*, 2124-2126.

4.) Christos I. Stathakis , Sophia M. Manolikakes, Paul Knochel "TMPZnOPiv•LiCl: A New Base for the Preparation of Air-Stable Solid Zinc Pivalates of Sensitive Aromatics and Heteroaromatics" *Org. Lett*, **2013**, *15*, 1302–1305.

5.) Klaus Groll, Sophia M. Manolikakes, Xavier Mollat du Jourdin, Milica Jaric, Aleksei Bredihhin, Konstantin Karaghiosoff, Thomas Carell, Paul Knochel "Regioselective Metalations of Pyrimidines and Pyrazines by Using Frustrated Lewis Pairs of BF_3·OEt_2 and Hindered Magnesium– and Zinc–Amide Bases" *Angew. Chem. Int. Ed.* **2013**, *52*, 6776-6780.

6.) Alberto Hernán-Gómez, Emma Herd, Eva Hevia, Alan R. Kennedy, Paul Knochel, Konrad Koszinowski, Sophia M. Manolikakes, Robert E. Mulvey, Christoph Schnegelsberg "Organozinc Pivalate Reagents: Segregation, Solubility, Stabilization and Structural Insights" *Angew. Chem. Int. Ed.* **2014**, *53*, 2706-2710.

7.) Sophia M. Manolikakes, Mario Ellwart, Christos I. Stathakis, Paul Knochel "Air Stable Solid Aryl and Heteroaryl Organozinc Pivalates: Their Syntheses and Applications in Organic Synthesis" *Chem. Eur. J.* **2014**, manuscript accepted.

Reviews

1.) Paul Knochel, Konstantin Karaghiosoff, Sophia M. Manolikakes "Selective C–H Activations Using Frustrated Lewis Pairs. Applications in Organic Synthesis" *Top. Curr. Chem.* **2013**, *334*, 171-190.

2.) Sophia M. Manolikakes, Nadja M. Barl, Christoph Sämann, Paul Knochel "Regioselective Functionalization of Pyridines using a Directed Metalation or a Halogen/Metal Exchange" *Zeitschr. Nat. Forsch.* **2013**, *68b*, 411-422.

"It's a magical world, Hobbes, ol' buddy...

Let's go exploring!"

Bill Watterson in Calvin & Hobbes

Für meine Familie

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
Alk	alkyl
aq	aqueous
Ar	aryl
Bu	butyl
calc.	calculated
conc.	concentrated
Cy	cyclohexyl
DavePhos	2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	*trans*,*trans*-dibenzylideneacetone
DBE	1,2-dibromoethane
dist.	distilled
DMF	*N*,*N*-dimethylformamide
DMG	Directed metalation group
DMPU	1,3-dimethyl-3,4,5,6-tetra-hydropyrimidine-2(*1H*)-one
DMSO	dimethyl sulfoxide
D*o*M	Directed *ortho* metalation
DreM	Directed remote metalation
δ	chemical shifts in ppm
E	electrophile
EDG	electron-donating group
EI	electron impact ionization
Equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
FLP	frustrated Lewis pair
GC	gas chromatography
h	hour
*i*hexane	*iso*-hexane
HRMS	high resolution mass spectrometry
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
LA	Lewis acid
LB	Lewis base
LDA	lithium di*iso*propylamide
M	molarity
MCR	multi-component reaction
m	*meta*
m.p.	melting point
Me	methyl
Met	metal
min	minute
mmol	millimole
MS	mass spectrometry
MWI	microwave irradiation
NBS	*N*-bromosuccinimide
NEP	*N*-ethyl-2-pyrrolidine
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	*ortho*
Oct	octyl
p	*para*
PEPPSI-*i*Pr	[1,3-bis(2,6-di(*iso*propyl)-phenyl)imidazol-2-ylidene] (3-chloropyridyl)-palladium(II) dichloride
Ph	phenyl
ppm	parts per million
R	organic substituent
RuPhos	2-dicyclohexylphosphino-2’,6’-di(*iso*propoxy)-biphenyl
sat.	saturated
*s*Bu	*sec*-butyl
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
Tf	triflate
TFP	tris-(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	tri(*iso*propylsilyl)

TLC	thin layer chromatography	TMS	trimethylsilyl
TMEDA	*N,N,N',N'*-tetramethylene-diamine	Ts	4-toluenesulfonyl
		X	halide or pseudohalide
TMP	2,2,6,6-tetramethyl-piperidyl	XantPhos	4,5-bis(diphenylphosphino)-9,9'-dimethylxanthene
TMPH	2,2,6,6-tetramethylpiperidine		

A. INTRODUCTION

1. OVERVIEW

In March 2012 the population of earth surpassed seven billion and it is currently estimated that around 7.2 billion people live on earth,[1] meaning that at the beginning of the 21st century the world has more inhabitants than ever before. This huge growth in population, which started with the agricultural and industrial revolution,[2] was (and is) further promoted by technological and scientific achievements like for example improvements in sanitation and medicine.[3] Not only does the world population constantly grow, but more and more developing and emerging countries demand rightfully access to western standard technology, which results in an increased concern about climate change, environmentalism and limited resources. From these facts result the major challenges for the 21st century scientist: To establish technologies for cheap, clean and sustainable energy sources, to reduce the amount of precious raw materials being wasted, to find ways to satisfy the increasing demand of foodstuff and to create new methods and drugs to face problems like increasing antibiotic resistance and rising cancer rates, as well as finding vaccines and cures for diseases like malaria and HIV/AIDS.

Applied to chemistry this means a huge variety of new materials and drugs must be developed, as well as new ways to synthesize these compounds. These processes must be environmentally beneficial, sustainable, cost-efficient and of course energy and resource saving. Therefore chemical reactions not only need to be selective but also high yielding and atom economical to avoid large amounts of materials being wasted. Moreover unnecessary interconversions of functional groups and protection/deprotection steps should be kept at a minimum. Since many of these required materials are organic compounds like pesticides[4] and drugs,[5] as well as semiconductors[6] or organic frameworks,[7] chemists in this field are in great demand.

To achieve these goals there are several different approaches like cascade and multi-component reaction (MCR) to reduce the overall number of steps and purification procedures necessary.[8] But also technologies like high-throughput screenings/reactions[9] gain more and more importance since they make it possible to screen a big set of different reaction conditions in a very short time using rather small amounts of chemicals, thus making it possible to optimize reaction conditions and catalysts for desired

[1] Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, *World Population Prospects. The 2012 Revision*.

[2] G. Caselli, G. Wunsch, J. Vallin, *Demography: Analysis and Synthesis, A Treatise in Population*, Elsevier, Oxford, UK, **2005**.

[3] B. Robinson, *Victorian Medicine - From Fluke to Theory*, BBC, February 1, **2002**, retrieved from http://www.bbc.co.uk on February 5th, 2014.

[4] *Sittig's Handbook of Pesticides and Agricultural Chemicals* (Eds.: S. A. Greene, R. P. Pohanish), William Andrew Publishing, Norwich, **2005**.

[5] M. Negwer, H.-G. Scharnow, *Organic-Chemical Drugs and Their Synonyms, 8th Edition*, Wiley-VCH, Weinheim, **2001**.

[6] D. Yan, H. Wang, B. Du, *Introduction to Organic Semiconductor Heterojunction*, John Wiley&Sons, Singapore, **2010**.

[7] a) J. L.C. Rowsell, O. M. Yaghi, *Microporous Mesoporous Mater.* **2004**, *73*, 3; b) X. Feng, X. Ding, D. Jiang, *Chem. Soc. Rev.* **2012**, *41*, 6010; c) S.-Y. Ding, W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 548; d) H. Furukawa, K. E. Cordova, M. O'Keeffe, O. M. Yaghi, *Science*, **2013**, *341*, 974.

[8] a) K. C. Nicolaou, T. Montagnona, S. A. Snydera, *Chem. Commun.* **2003**, 551; b) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365; c) K. C. Nicolaou, Jason S. Chen, *Chem. Soc. Rev*. **2009**, *38*, 2993; d) M. S. Singh, S. Chowdhury, *RSC Adv*. **2012**, *2*, 4547; e) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442; f) S. Brauch, S. S. van Berkela, B. Westermann, *Chem. Soc. Rev.*, **2013**, *42*, 4948; g) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2013**, *113*, DOI: 10.1021/cr400215u.

[9] a) A. Hagemeyer, P. Strasser, A. F. Volpe Jr., *High-Throughput Screening in Chemical Catalysis: Technologies, Strategies and Application* (Eds. A. Hagemeyer, P. Strasser, A. F. Volpe Jr,) Wiley-VCH, Weinheim, **2004**; b) C. Jäkel, R. Paciello, *Chem. Rev*. **2006**, *106*, 2912; c) D. Farrusseng, *Surf. Sci. Rep.* **2008**, *63*, 487.

compounds fast and efficient.[10] Moreover, it is possible to synthesize a large plethora of different compounds in a rapid and automated way and test them for new applications.[11]

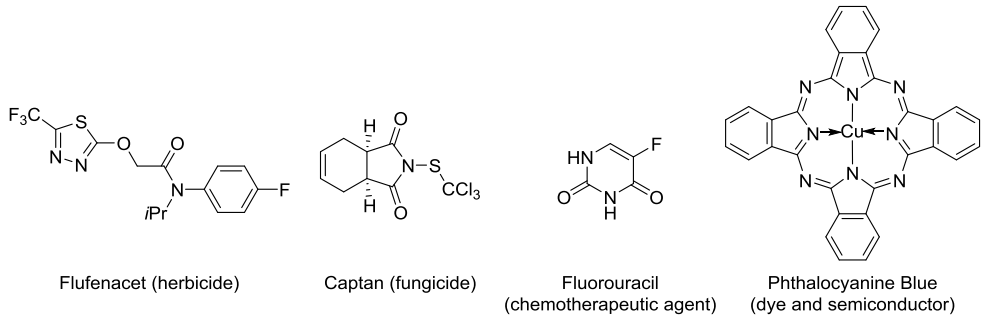


Figure 1: Selected relevant organic molecules.

Organometallic reagents play a special role in organic synthesis since they have a broad scope of developed methods for transformations of chemical structures, mainly due to the variety of metals which can be used.[12] Furthermore, organometallics have proven to be crucial synthetic tools in MCR as catalysts and/or as reagents (Scheme 1),[13] and moreover transition metal catalysts play a key role in high-throughput experimentation.[14] Therefore, organometal-chemists are under pressure to improve the existing methodologies for synthesizing and transforming organometallic compounds, as well as developing new types of reagents and new ways to react these.

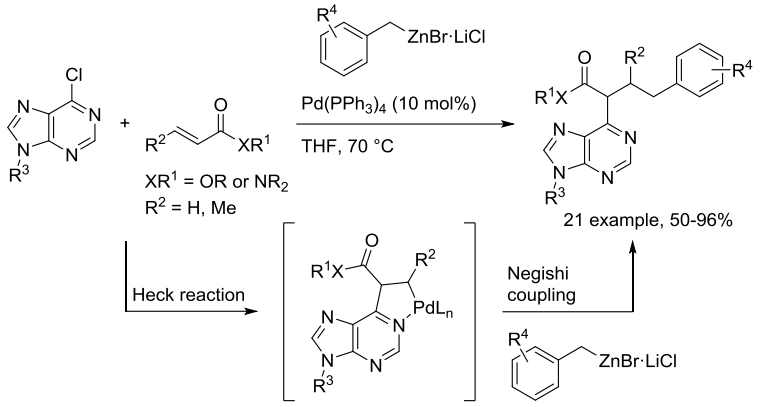
[10] a) M. S. Congreve, C. Jamieson, *Drug Discovery Today* **2002**, *7*, 139; b) J. F. Traverse, M. L. Snapper, *Drug Discovery Today* **2002**, 1002; c) J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, 799; d) R. J. Hendershot, C. M. Snively, J. Lauterbach, *Chem.–Eur. J.* **2005**, *11*, 806.

[11] a) S. Ma, R. Subramanian, *J. Mass Spectrom.* **2006**, *41*, 1121; b) D. C. Webster, *Macromol. Chem. Phys.* **2008**, *209*, 237; c) O. Sharma, A. Kotnala, B. Shrivastva, R. K Singla, *Pharmacologyonline Newsletter* **2011**, *2*, 134.

[12] a) E. Negishi, *Organometallics in Organic Synthesis*, Wiley, New York, **1980**; b) *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

[13] a) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; b) Y. Yoshida, K. Murakami, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.*, **2010**, *132*, 8878; c) M. G. Kamau, L. S. Harikrishnan, H. J. Finlay, J. X. Qiao, J. Jiang, M. A. Poss, M. E. Salvati, R. R. Wexler, R. M. Lawrence, *Tetrahedron* **2012**, *68*, 2696; d) E. Le Gall, Eric Léonel, *Chem.–Eur. J.* **2013**, *19*, 5238; e) L. Zhang, L. Sonaglia, J. Stacey, M. Lautens, *Org. Lett.* **2013**, 2128; f) T. Wakamatsu, K. Nagao, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2013**, 52; g) J. Tsoung, J. Panteleev, M. Tesch, M. Lautens, *Org. Lett.* **2014**, *16*, 110; h) D.-Chao Wang, H.-Y. Niu, M.-S. Xie, G.-R. Qu, H.-X. Wang, H.-M. Guo, *Org. Lett.* **2014**, *16*, 262.

[14] H. Zhang, V. Marin, M. W. M. Fijten, U. S. Schubert, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 1876; J. Le Nôtre, R. Touzani, O. Lavastre, C. Bruneau, P. H. Dixneuf, *Adv. Synth. Catal*. **2005**, *347*, 783; J. Zhang, C. Stanciu, B. Wang, M. M. Hussain, C.-S. Da, P. J. Carroll, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2011**, *133*, 20552; J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, , *J. Am. Chem. Soc.* **2012**, *134*, 13765; For a review see: S. Monfette, J. M. Blacquiere, D. E. Fogg, *Organometallics* **2011**, *30*, 36.



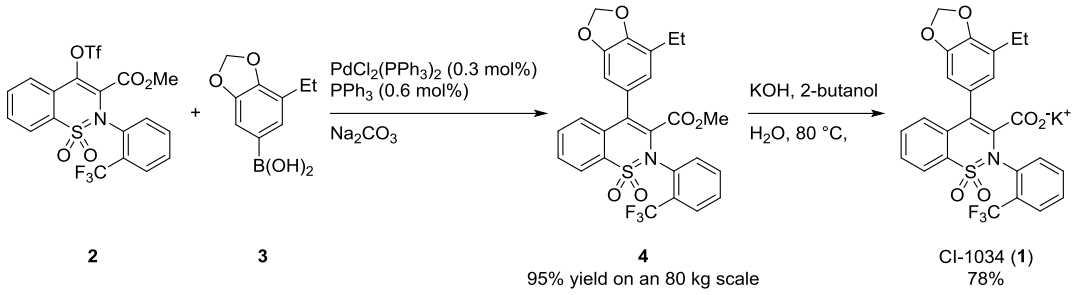
Scheme 1: Three-Component Domino Heck−Negishi Coupling Reaction for the Functionalization of Purines.

2. PREPARATION OF ORGANOMETALLIC REAGENTS

The first organometallic compound ever synthesized[15] is considered to be "*Cadet's fuming liquid*", a mixture of cacodyl $(Me_2As)_2$ and cacodyl oxide $((Me_2As)_2O)$, prepared by the French pharmacist-chemist Louis-Claude Cadet de Gassicourt in 1760.[16] And although the synthesis of yet another organometallic species, *Zeise's Salt* (potassium trichloro(ethene)platinate(II)), was published in 1827,[17] the first "successful" reagent of this class was certainly diethylzinc, first reported by *Frankland* in 1849,[18] which is industrially used until today. However, the final breakthrough for organometallic chemistry was eventually made by the introduction of organomagnesium reagents 50 years later by François Auguste Victor Grignard.[19] Over the course of the 20th century organometallic reagents gained more and more importance and since the millennium alone three Nobel-Prizes were given to contributors in the field of organometallic chemistry.[20] One of the major reasons for the success story of this compound class is the broad latitude of different reagents with a huge variety of transformations possible. This is partly due to the nature of the carbon-metal bond being more reactive, the more electropositive the specific metal is, causing the bond to become more ionic and less covalent. Thus, organolithium, -sodium or -potassium reagents possess a very nucleophilic carbon atom and exhibit an excellent reactivity towards many electrophiles. However, this comes at the expense of a very limited functional group tolerance.[21] At the other end of the spectrum are organoboron or –indium reagents with a very covalent carbon-metal bond which is stable towards most functionalities and even tolerates air and water.[22] Yet, since these reagents are relatively inert, they require either an appropriate catalyst or harsh reaction conditions in order to react with most electrophiles.[12] A maybe even more important role play transition metals. The presence of valence electrons in the d-orbitals significantly differentiates the reactivity of the carbon-transition-metal bond from the carbon-main-group-metal bond. Since the d-orbitals of the transition metals can interact with the bonding to the carbon as well as with other reagents, they allow particular, very selective transformations that would be impossible with main group metals. For this reason they are broadly used as catalysts in organic synthesis. One example for the use of organometallic reagents and catalysts on a large scale is the synthesis of the endothelin antagonist CI-1034 (**1**)[23] by Pfizer. Using a palladium catalyzed Suzuki–Miyaura cross-coupling[24] of the triflate **2** with

[15] C. Eschenbroich, *Organometallchemie*, Wiley-VCH, Weinheim, **2008**.
[16] a) J.J. Berzelius. *Jahresber.* **1839**, *18*, 487; b) J. H. Burns, J. Waser, *J. Am. Chem. Soc.* **1957**, *79*, 859; c) D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[17] a) W. C. Zeise, *Poggendorff's Ann. Phys.* **1827**, *9*, 632; b) W. C. Zeise, *Poggendorff's Ann. Phys.* **1831**, *21*, 497; c) W. C. Zeise, *Poggendorff's Ann. Phys.* **1837**, *40*, 234.
[18] a) E. Frankland, *Ann. Chem.* **1849**, *71*, 171; b) E. Frankland, *Ann. Chem.* **1849**, *71*, 213.
[19] V. Grignard, *Compt. Rend. Acad. Sc. Paris* **1900**, *130*, 1322.
[20] **2001**: Knowles, Noyori, Sharpless; **2005**: Chauvin, Grubbs, Schrock; **2010**: Heck, Negishi, Suzuki.
[21] J. Clayden, *Organolithiums: Selectivity for Synthesis* (Ed. J. E. Baldwin), Pergamon Press, Oxford, **2002**.
[22] a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials* (Ed. D. G. Hall), Wiley-VCH, Weinheim, **2011**; b) Z.-L. Shen, S.-Y. Wang, Y.-K. Chok, Y.-H. Xu, T.-P. Loh, *Chem. Rev.* **2013**, *113*, 271.
[23] S. Motte, K. McEntee, R. Naeije, *Pharmacol. Ther.* **2006**, *110*, 386.
[24] a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437; b) N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.*, **1979**, 866.

the arylboronic acid **3** the precursor **4** was prepared on an 80 kg scale in 95% yield and after an ester saponification the desired CI-1034 (**1**) was obtained in 78% (Scheme 2).[25]



Scheme 2: Large scale synthesis of CI-1034 (**1**) by a Suzuki cross-coupling.

2.1 Oxidative Insertion

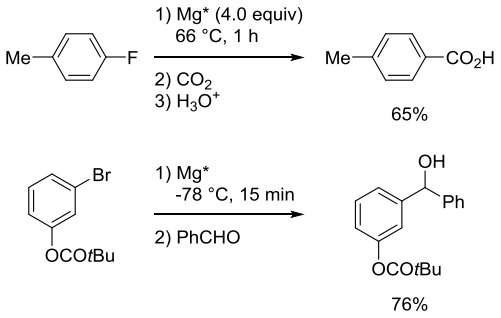
Oxidative insertion of elemental metal into a carbon-halogen bond is by far the oldest method of preparing organometallic reagents. It was first reported by *Frankland***,** who reacted zinc metal with alkyl halides, thus creating the first organozinc compound.[18] Later the first organoaluminum reagent was prepared in a similar way from aluminum and methyl iodide by *Hallwachs* and *Schaferik*.[26] The final breakthrough was made by *Grignard*, who generated the first organomagnesium reagents also *via* insertion of elemental magnesium into a carbon halide bond.[19]

One of the major drawbacks of the first magnesium insertions are the rather harsh reaction conditions, (normally refluxing of the solvent is required), which limit the functional groups that can be tolerated. Another problem is the fact that those reactions normally have an induction period followed by heat evolution since the insertion can be very exothermic, which is especially problematic for large scale syntheses. The first successful approach to overcome these obstacles was made by *Rieke*: By reducing anhydrous metal chlorides with an alkali metal such as lithium, sodium or potassium in THF it is possible to generate highly reactive metal powders. This method enables the preparation of *Grignard* reagents at low temperatures, thus increasing the functional group tolerance. Moreover, is also a feasible way to transform relatively unreactive organohalides, for instance fluorides, into the corresponding magnesium species (Scheme 3).[27]

[25] T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. J. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanninga, G. S. Risedorph, R. E. Seamans, R. Skeean, D. D. Winkle, T. M. Zennie, *Org. Process Res. Dev.* **2004**, *8*, 201.

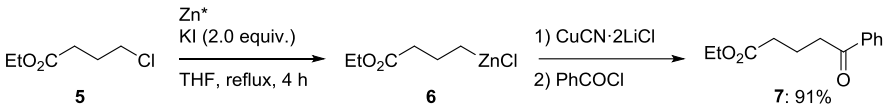
[26] W. Hallwachs, A. Schaferik, *Ann. Chem.* **1859**, *109*, 206.

[27] a) R. D. Rieke, L.-C. Chao, *Syn. React. Inorg. Metal-Org. Chem.* **1974**, *4*, 101; b) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301; c) R. D. Rieke,, *Science* **1989**, *246*, 1260; d) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; R. D. Rieke, M. V. Hanson, *Tetrahedron*, **1997**, *53*, 1925; f) R. D. Rieke, *Aldrichim. Acta* **2000**, *33*, 52; g) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R.Wurst, R. D. Rieke, *J. Org. Chem.* **2000,** *65*, 5428.



Scheme 3: Preparation and reaction of functionalized *Grignard* reagents using *Rieke* magnesium.

This method not only works for magnesium, but is also viablefor the insertion of zinc metal into a carbon-halide bond. The so called *Rieke* zinc is prepared by the reduction of zinc chloride with lithium naphtalenide and reacts readily under mild conditions with a variety of functionalized alkyl- and aryl halides.[27d] By adding 2 equivalents of potassium iodide it was even possible to perform an insertion into the carbon-chlorine bond of the alkyl ester **5** to generate the organozinc compound **6** that underwent a copper mediated acylation[28] to give the desired product **7** in high yield (Scheme 4).



Scheme 4: Preparation and reaction of functionalized zinc reagents using *Rieke* zinc.

A major drawback of this method is however, that the *Rieke* metals always have to be freshly prepared and the functional group tolerance of the magnesium reagents are still limited and require low temperatures. In recent years *Knochel* and coworkers developed a method to generate magnesium and zinc organometallics from commercially available metal turnings or powders. They found, that the addition of lithium chlorides promotes the insertion reaction dramatically, making it possible to prepare a variety of functionalized organozinc and -magnesium reagents in a simple straightforward manner.[29] Several studies show that the LiCl facilitates the metal insertion by lowering the energy of the transition state[30] and, as ESI-measurements imply, the generated metal compounds are existent as ate-species of the general formula $RMetXCl^-Li^+$ (R = alkyl or aryl; Met = Mg, Zn, X = Cl, Br, I).[31] LiCl also increases the solubility of the formed metal reagents.[32] It is believed, that the LiCl thus "cleans up" the metal surface by solubilizing the already generated organometallics and therefore regenerating active metal

[28] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert,. *Tetrahedron Lett.* **1988**, *29*, 2395; c) M. C. P. Yeh, P. Knochel, W. M. Bulter, S. C. Berk, *Tetrahedron Lett.* **1988**, *29*, 6693.

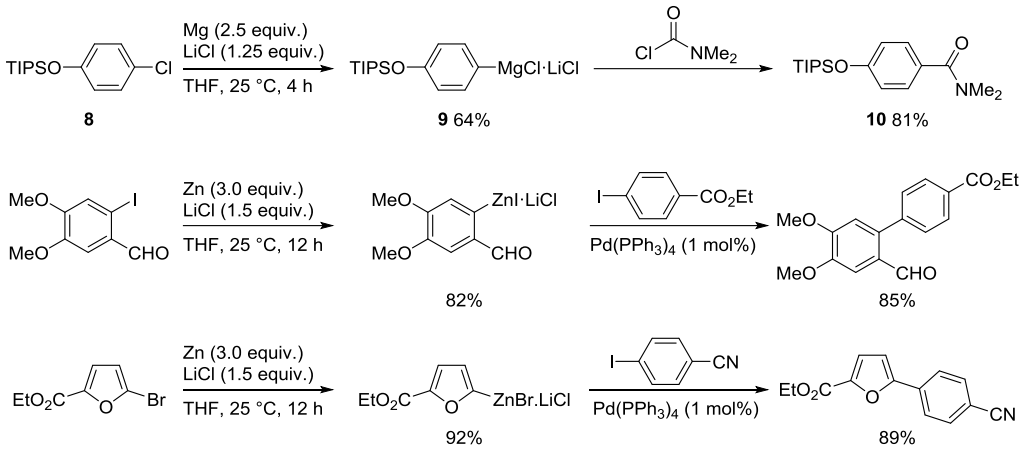
[29] Zn reagents: a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; Mg reagents: d) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802

[30] C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780.

[31] a) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; b) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.

[32] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

surface.[31a] Using this methods various aryl- and heteroarylhalides can be transformed into the corresponding magnesium or zinc species. For instance the electron rich arylchloride **8** was converted into the magnesium species **9** at ambient temperature, which then could be reacted with dimethylcarbamoyl chloride to give the amide **10** in 81% yield (Scheme 5)[33] Using zinc insertion also very sensitive functionalities such as aldehydes or esters can be tolerated and the generated organozinc reagents can undergo a variety of reactions with different electrophiles (Scheme 5).[29a]



Scheme 5: Selected examples for LiCl promoted Mg and Zn insertion.

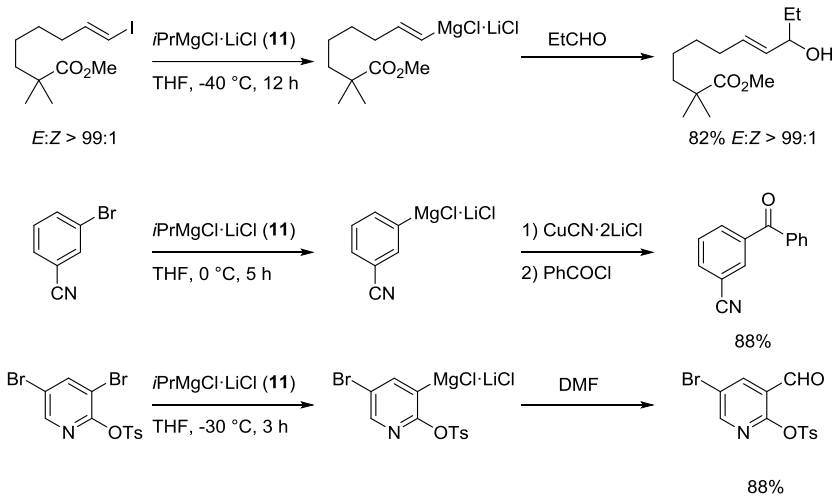
Nevertheless, in some cases the zinc insertion is still very slow and the generated zinc reagents are inert towards many electrophiles. This problem can be overcome by performing a LiCl promoted Mg insertion in the presence of $ZnCl_2$. The magnesium reagent is formed fast and is then instantly transmetalated to zinc creating MgXCl (X = Cl, Br, I) complexed organozinc species of the general formula RZnCl·MgXCl·LiCl. These Mg salt containing zinc compounds react readily with aldehydes, ketones and CO_2, whereas reagents free of MgXCl do not react at all or only in moderate yields.[34]

2.2 Halogen-Metal Exchange Reactions

A different approach for the synthesis of organometallics is the halogen metal exchange which normally starts from an aryl bromide or iodide and an alkyl-metal reagent. In the course of the reaction the more stable organometallic species is formed, thus making it a convenient method for the formation of $C(sp^2)$-metal bonds.[35] The halogen-magnesium exchange was pioneered by *Prévost* in 1931, who used EtMgBr for the generation of allylic magnesium reagents.[36] Another version, developed by *Wittig* and *Gillman* in the same decade, uses lithium compounds like *n*BuLi, *t*BuLi or PhLi.[37] However halogen-lithium exchange reactions always require very low temperatures and carefully controlled reaction conditions,

[33] C. Dunst, P. Knochel, *Synlett* **2011**, *14*, 2064.
[34] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665
[35] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[36] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[37] a) G. Wittig, U. Poeckels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106; c) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1.

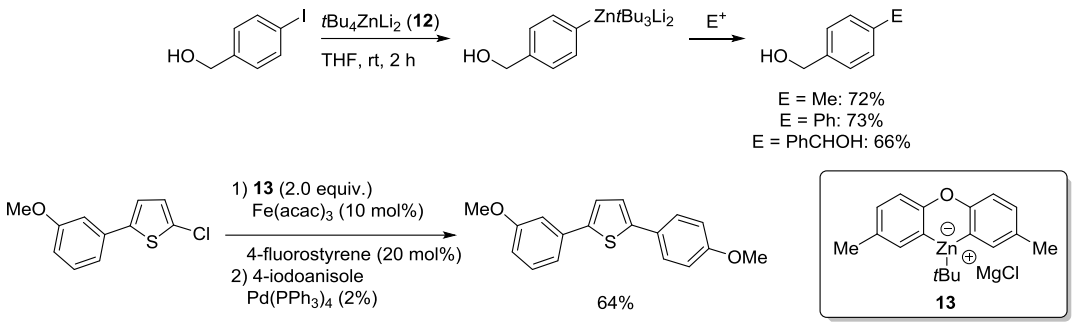
since alkyllithium reagents are prone to undergo side reactions especially when N-heterocycles are involved.[38] Another version of the halogen magnesium exchange was eventually made by *Knochel* and coworkers, who prepared arylmagnesium reagents by treating aryl iodides with *i*PrMgBr or iPr$_2$Mg and in the case of very electron poor aromatics with PhMgCl.[39] This method was further improved by developing the LiCl complexed reagent *i*PrMgCl·LiCl (**11**), the so called "turbo-*Grignard*", that shows an extremely high exchange reactivity towards aryl iodides and bromides.[40] This behavior might be due to the formation of the magnesiate species *i*PrMgCl$_2^-$Li$^+$ and furthermore the LiCl also increases the solubility of the *Grignard* reagent. Due to this enhanced reactivity aryl-, heteraoaryl and vinyl-magnesium reagents can be prepared at low temperatures, making it possible to tolerate sensitive functionalities such as a nitrile or even an ester (Scheme 6).[41]



Scheme 6: Hal/Mg exchange using *i*PrMgCl·LiCl.

Also zinc reagents can be prepared directly *via* exchange reactions. For instance iPr$_2$Zn in the presence of Li(acac) (acac = acetylacetonate) can perform iodine-zinc exchange on various iodinated aromatic and heteroaromatics.[42] By using the dianion-type zincate tBu$_4$ZnLi$_2$ (**12**), *Uchiyama* and coworkers managed to find an exchange protocol that can be applied in the presence of unprotected alcohols (Scheme 7).[43] The magnesium zincate **13**, developed by *Knochel* et al., can even be used to perform a chlorine zinc exchange in the presence of catalytic amounts of Fe(acac)$_3$ or Co(acac)$_2$.[44]

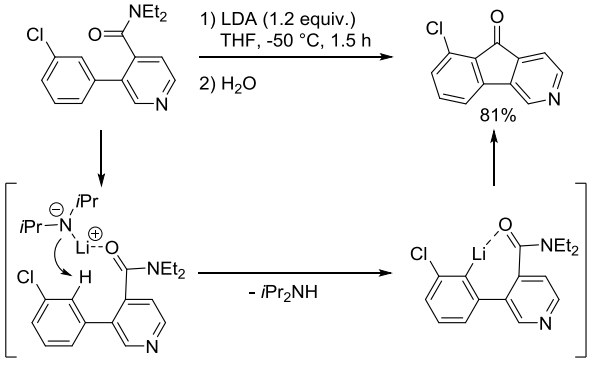
[38] P. Pierrat, P. Gros, Y. Fort, *Synlett* **2004**, 2319.
[39] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.
[40] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[41] H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215; H. Ren, P. Knochel, *Chem. Commun*. **2006**, 726;
[42] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[43] M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8404.
[44] L. Melzig, C. R. Diène, C. J. Rohbogner, P. Knochel, *Org. Lett.* **2011**, *13*, 3174.



Scheme 7: Hal/Zn exchange using lithium or magnesium zincates.

2.3 Metalation

As described above the metal insertion as well as the halogen-metal exchange require a halogen precursor, usually iodine or bromine. This is a serious drawback since halogenated substrates can be expensive, especially iodides, or might not be accessible at all. Therefore, generating a carbon-metal bond from a C-H bond is a feasible route for the preparation of organometallics. The first attempt on metalation of aromatics were made by *Gilman* and *Wittig* who used organolithium compounds like *n*BuLi or PhLi for the directed *ortho*-metalation (D*o*M) next to a methoxy moiety as directing metalation group (DMG).[45] The DMG normally contains a heteroatom with a free electron pair that can coordinate to the lithium reagent and thus the deprotonation occurs in *ortho*-position to this group. Later non-nucleophilic, sterically hindered lithium bases such as lithium di*iso*propylamide (LDA) or TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl)[46] were established and the directed *ortho*-litiation was especially promoted by the work of *Snieckus* and coworkers, who introduced carbamates, amides, and a variety of ethers as convenient DMGs.[47] There is also a modification of the D*o*M where not the carbon next to the DMG is metalated, but a "remote" C-H bond in the molecule is activated. This variation, the directed remote metalation (DreM), is particularly useful in the metalation of biarylic substrates (Scheme 8).[48]



Scheme 8: Example for a directed remote metalation (DreM).

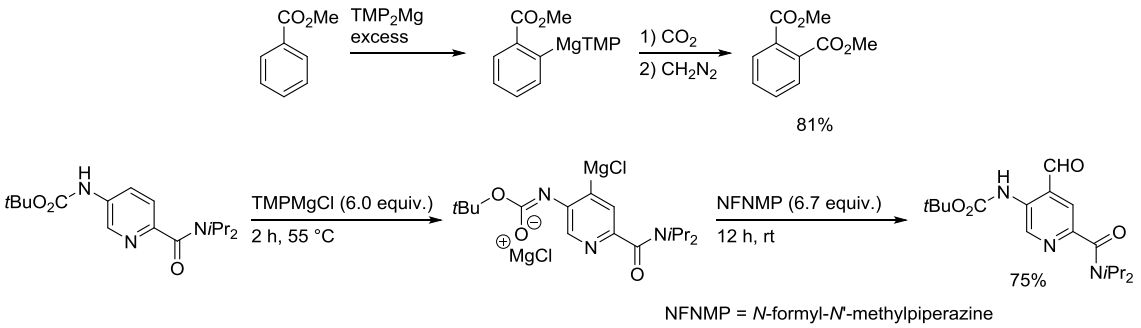
[45] a) H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109; b) G. Wittig, G. Fuhrmann, *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1197.

[46] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.

[47] a) V. Snieckus, *Pure & Appl. Chem.* **1990**, *62*, 2047; b) T. K. Macklin, J. Panteleev, V. Snieckus, *Angew. Chem. Int. Ed.* **2008**, *47*, 2097.

[48] a) M. Alessi, A. L. Larkin, K. A. Ogilvie, L. A. Green, S. Lai, S. Lopez,. V. Snieckus, *J. Org. Chem.* **2007**, *72*, 1588; for a review see: b) D. Tilly, J. Magolan, J. Mortier, *Chem.–Eur. J.* **2012**, *18*, 3804, and references cited therein.

However, the major drawback of the directed lithiation is however, the high reactivity of the bases used and also the generated metal species, which can lead to numerous side reactions like, for instance *Chichibabin* addition.[49] This high reactivity also limits the number of functional groups that are tolerated and in addition, most lithiations require low temperatures (-78 to -100 °C). Therefore, the use of magnesium amide bases is generally preferred when dealing with more sensitive functionalities. Historically, the first magnesium amides were prepared by *Meunier* at the beginning of the 20th century by mixing the recently discovered *Grignard* reagents with various amines. [50] Over 40 years later *Hauser* and coworkers established bases of the type R_2NMgBr for the condensation of esters, referred to from that time on as *Hauser* bases.[51] However, the first application for a directed *ortho* magnesiation was made by *Eaton* et al., who used the sterically demanding amides TMPMgBr and TMP_2Mg for the metalation of aromatic carboxamides and esters (Scheme 9).[52] Further improvement was made by *Mulzer* by applying TMPMgCl for the magnesiation of pyridinecarboxamides and carbamates (Scheme 9).[53] Although, these magnesium amide bases are superior to the lithium derivatives regarding functional group tolerance their general utilization is hampered by low solubility due to aggregation, and the need of large excesses of both base and electrophile.[53]

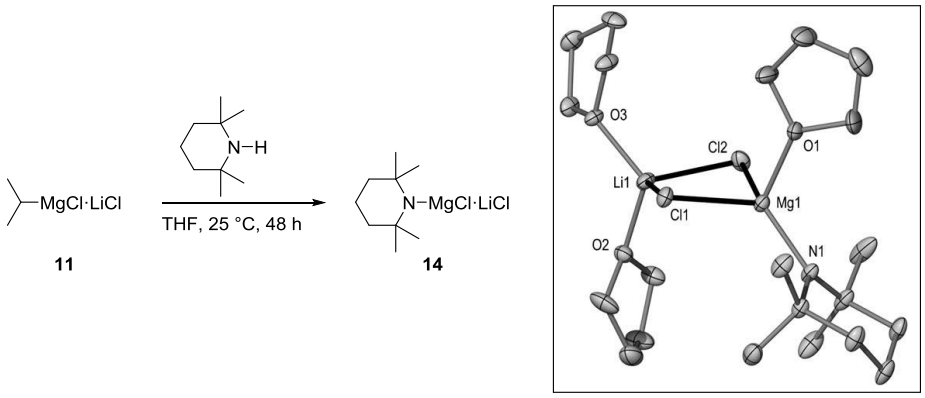


Scheme 9: Early examples of magnesiation by TMP-magnesium amides.

Knochel and coworkers found, that similar to the turbo-*Grignard* reagents the solubility and reactivity of these TMP-magnesium amides could be significantly enhanced by using stoichiometric amounts of LiCl, thus creating the so called turbo-*Hauser* bases with the general formula $R_2NMgCl{\cdot}LiCl$.[54] Especially the sterically hindered TMPMgCl·LiCl (**14**), obtained by mixing turbo-*Grignard* **11** with TMPH, proved to be an excellent reagent to deprotonate a large variety of functionalized aromatic compounds and heterocycles.[55] Studies by the *Mulvey* group imply that the LiCl causes a deaggregation of the magnesium amide, thus TMPMgCl·LiCl (**14**) crystallizes as a monomer (Scheme 10), whereas

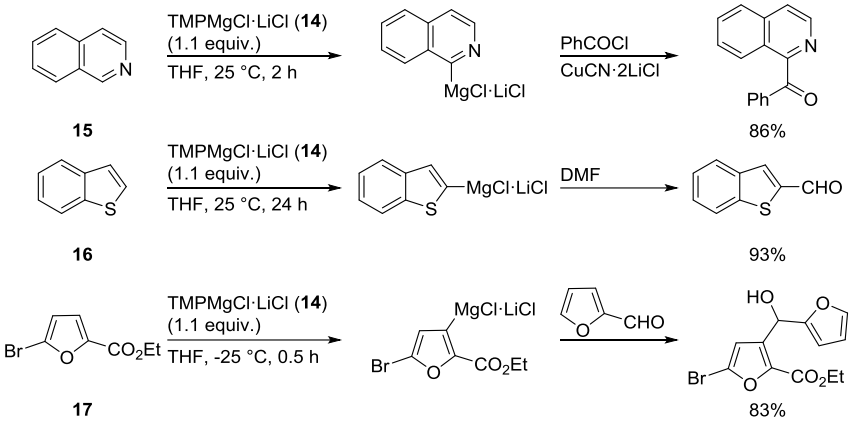
[49] A. E. Chichibabin, O. A. Zeide, *J. Russ. Phys. Chem.* **1914**, *46*, 1216.
[50] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[51] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[52] P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.
[53] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[54] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed*. **2006**, *45*, 2958.
[55] For a review see: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed*. **2011**, *50*, 9794.

TMPMgCl forms a dimer. Although the structure in solution may be different from the crystal, it is reasonable to assume that **14** reacts as a monomeric species.[56]



Scheme 10: Synthesis and crystal structure of TMPMgCl·LiCl (**14**)

The excellent kinetic basicity and high solubility of **14** makes it possible to magnesiate various substrates such as isoquinoline (**15**), benzothiophene (**16**) and even the sensitive disubstituted furan **17** under very mild reaction conditions and using only 1.1 equiv. of base. The generated magnesium species can react with various electrophiles in very good to excellent yields (Scheme 11).[54]



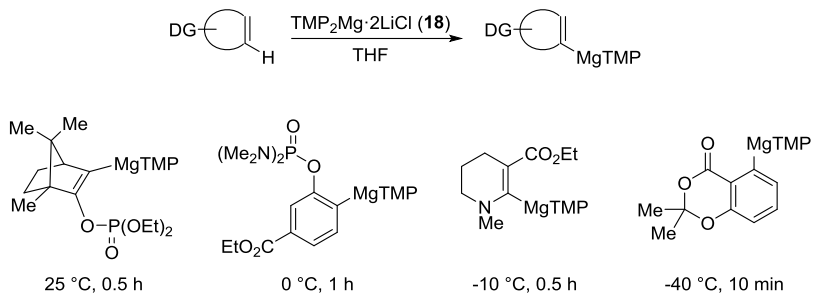
Scheme 11: Deprotonation of various heterocycles with TMPMgCl·LiCl (**14**) and subsequent reactions with electrophiles.

By mixing TMPLi with TMPMgCl·LiCl (**14**) the LiCl activated $TMP_2Mg·2LiCl$ (**18**)[57] can be prepared, which has an enhanced kinetic basicity compared to **14** and can therefore be used for the deprotonation of moderately activated substrates in the cases were **14** is not reactive enough (Scheme 12).[58]

[56] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.

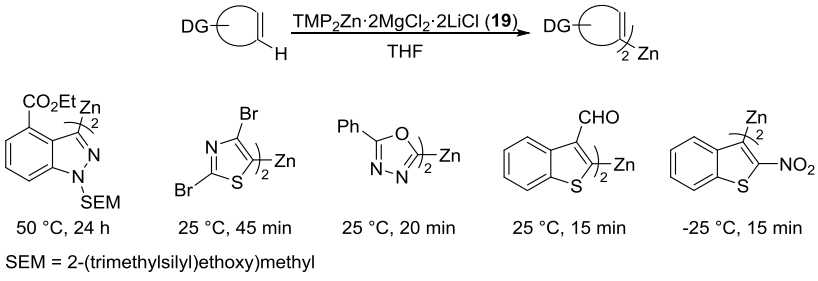
[57] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed*. **2007**, *46*, 7681; b) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374.

[58] C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed*. **2008**, *47*, 1503; F. M. Piller, T. Bresser, M. K. R. Fischer, P. Knochel, *J. Org. Chem.* **2010**, *75*, 7365; T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914;

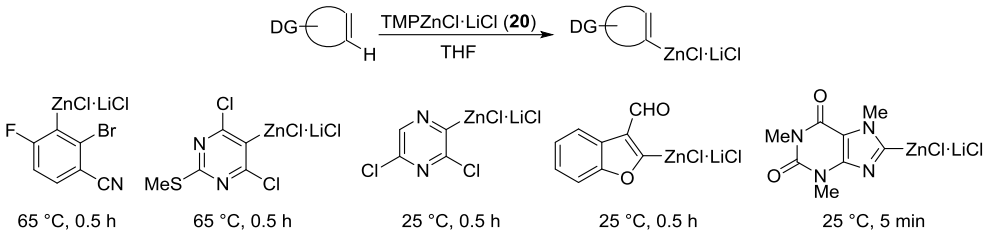


Scheme 12: Magnesiation of various aromatic and non-aromatic substrates by $TMP_2Mg·2LiCl$ (**18**).

Although these magnesium amide bases have an excellent reactivity and can be applied in the presence of nitriles, esters, and aryl ketones, there are still some very sensitive functionalities such as nitro- or aldehyde groups as well as electron poor heterocycles that are not compatible with magnesium reagents. For such substrates the zinc derivatives of **14** and **18** have been established. By transmetalating TMPMgCl·LiCl (**14**) or TMPLi with $ZnCl_2$ the very mild zinc amides $TMP_2Zn·2MgCl_2·2LiCl$ (**19**) [59] and TMPZnCl·LiCl (**20**),[60] respectively, can be readily prepared. These bases can be used for the mild zincation of a variety of sensitive substrates (Scheme 13 and Scheme 14)



Scheme 13: Zincation of various sensitive heterocycles using $TMP_2Zn·2MgCl_2·2LiCl$ (**19**).



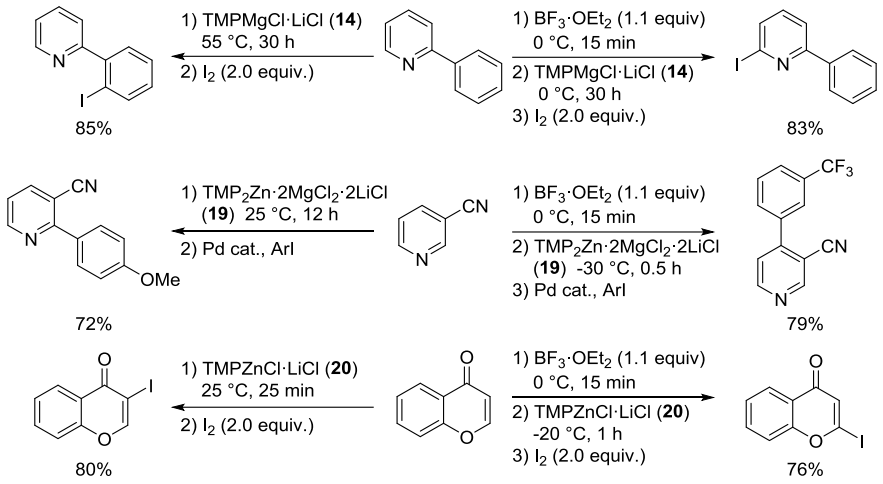
Scheme 14: Zincation of various functionalized aromatics using TMPZnCl·LiCl (**20**).

[59] a) S. H. Wunderlich, P. Knochel, *Angew. Chem., Int. Ed.* **2007**, *46*, 7685, b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; c) M. Mosrin, P. Knochel, *Chem.–Eur. J.* **2009**, *15*, 1468; d) M. Kienle, C. Dunst, P. Knochel, *Org. Lett.* **2009**, *11*, 5158; e) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.

[60] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; b) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615, c) T. Bresser, M. Mosrin, G. Monzon, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686; d) T. Bresser, P. Knochel, *Angew. Chem., Int. Ed.* **2011**, *50*, 1914.

Over the course of the last decades a broad variety of mixed Li/metal amide bases have been developed with Fe, Mn, La, Zr, Cd and Cu.[55]

Kessar discovered that the lithiation of pyridine and related heterocycles can be assisted by pre-mixing pyridine with the Lewis acid (LA) $BF_3 \cdot OEt_2$ before the addition of an appropriate lithium base.[61] Recently *Knochel* and coworkers found that this protocol can also be expanded to magnesium or zinc amide bases, thus generating much milder reaction conditions. This metalation procedure does not only accelerate or facilitate the metalation, but in some cases the regioselectivity of the deprotonation can be orthogonal to the one achieved without the use of $BF_3 \cdot OEt_2$ (Scheme 15).[62]



Scheme 15: Switchable, regioselective metalation of *N*-heterocycles with TMP-bases in the presence or absence of $BF_3 \cdot OEt_2$

It was also found, that the Lewis base TMPMgCl·LiCl (**14**) is compatible with the Lewis acid $BF_3 \cdot OEt_2$ at low temperatures. It is believed that the two compounds form the Lewis pair TMPMgCl·BF_3 (**21**), which is still able to deprotonate various N-heterocycles. This led to the assumption that the Lewis base TMPMgCl·LiCl (**14**) and the Lewis acid $BF_3 \cdot OEt_2$ form a so called frustrated Lewis pair (FLP),[63] where the $BF_3 \cdot OEt_2$ can still act as a Lewis acid and **14** is able to perform the deprotonation, instead of irreversibly forming an acid base adduct that possesses no metalation potential anymore. Therefore it is possible to perform the metalation of 4-phenylpyridine (**22**) by first activating it with $BF_3 \cdot OEt_2$ and then adding the base **14** to give, after a *Negishi* cross-coupling,[64] the product **23** in very good yield. Also pre-

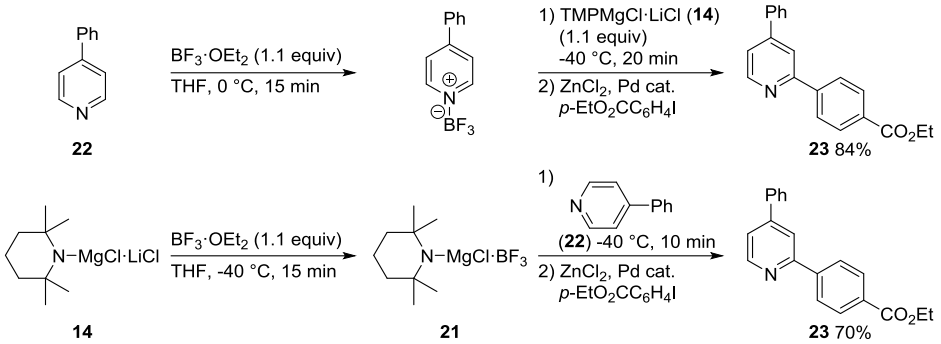
[61] a) S. V. Kessar, P. Singh, K. N. Singh, M. Dutt, *J. Chem. Soc. Chem. Commun.* **1991**, 570; b) S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, K. N. Singh, *J. Chem. Soc. Chem. Commun* **1991,** 568; c) S. V. Kessar, R. Vohra, N. P. Kaur, *Tetrahedron Lett.* **1991**, *32*, 3221; d) S. V. Kessar, P. Singh, K. N. Singh, V. K. Kuul, G. Kumar, *Tetrahedron Lett.* **1995**, *36*, 8481; for a review see: e) S. V. Kessar, P. Singh, *Chem. Rev.* **1997,** *97*, 721.

[62] a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; b) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc*. **2012**, *134*, 13584.

[63] a) G. C. Welch, L. Cabrera, P. A. Chase, E. Hollink; J. D. Masuda, P. Wei, D.W. Stephan, *Dalton Trans*. **2007**, 3407; b) J. D. Masuda, P. Wei, D. W. Stephan, *Dalton Trans.* **2007**, 3407; c) J. S. J. McCahill, G. C. Welch, D.W. Stephan, *Angew. Chem. Int. Ed*. **2007**, *46*, 4968; d) T. A. Rokob, A. Hamza, A. Stirling, T. Soós, I. Pápai, *Angew. Chem. Int. Ed.* **2008**, *47*, 2435; e) D.W. Stephan, *Dalton Trans.* **2009**, 3129; f) S. Grimme, H. Kruse, L. Goerigk, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 1402; for a reaview see: f) D.W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46.

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

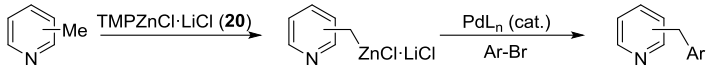
mixing the base **14** with $BF_3{\cdot}OEt_2$ at -40 °C to form the Lewis pair **21** followed by addition of the pyridine **22** leads, after cross-coupling, to the same product **23** in slightly reduced yield (Scheme 16).[62]



Scheme 16: BF_3-mediated deprotonation of 4-phenylpyridine (**22**).

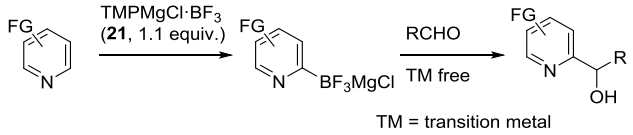
3. OBJECTIVES

The goal of the first project was to expand the metalation of TMPZnCl·LiCl (**20**) to the zincation of the benzylic position of various methylated pyridines and quinolines and the subsequent *Negishi* cross-coupling with various aryl bromides (Scheme 17). So far, palladium-catalyzed arylations of picolines *via* C–H activation[65] have no generality. This might be due to the formation of palladium complexes that are reluctant to undergo reductive elimination.



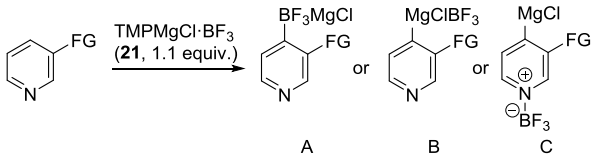
Scheme 17: Benzylic zincation of picolines with TMPZnCl·LiCl (**20**) followed by *Negishi* cross-coupling.

Another aim was to investigate the metalation of pyridines and other N-heterocyles with TMPMgCl·BF_3 (**21**). It is known that when the metalation occurs at the carbon atom adjacent to the nitrogen atom, the resulting species are pyridyl trifluoroborates. In general, the reactivity of pyridyl trifluoroborates towards aldehydes is quite low and a successful addition usually requires a rhodium, nickel or palladium catalyst.[66] Our goal was to develop a transition metal free addition of these borates to aldehydes (Scheme 18).



Scheme 18: Transition metal free addition of pyridyl trifluoroborates to aldehydes.

We also wanted to investigate the structure of the metal intermediate generated by treating 3-substituted pyridine derivatives with **21**. In those cases, the metalation occurs in position 4 of the pyridine scaffold. So far, the structure of the 4-metalated pyridines has not been studied. Therefore, it is not known if they are also pyridyl trifluoroborates (structure A, Scheme 19) or if they are pyridyl magnesium compounds (structures B or C). This would raise the question if the BF_3 coordinates to the pyridyl nitrogen (structure B) or to the *Grignard* reagent (structure C) or if it located somewhere else.

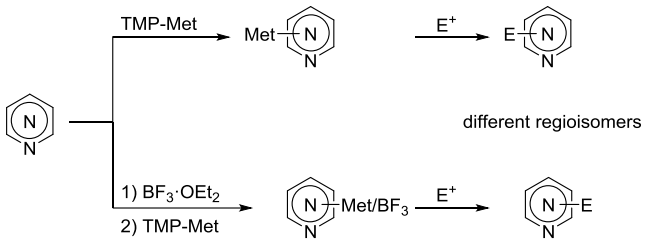


Scheme 19: Possible structure of N-heterocycles metalated by TMPMgCl·BF_3 (**21**).

[65] a) S. Murai, *Activation of Unreactive Bonds and Organic Synthesis*, Springer-Verlag, Berlin Heidelberg, **1999**; b) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; c); d) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439; d) M. Schlosser, F. Mongin, *Chem. Soc. Rev.* **2007**, *36*, 1161; e) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; f) For a special issue on Selective Functionalization of C-H Bonds: *Chem. Rev.* **2010**, *110*, 575.

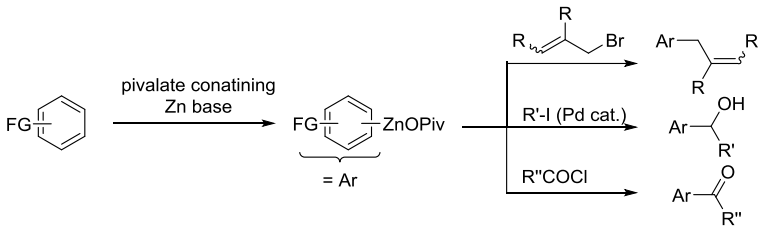
[66] a) M. Pucheault, S. Darses and J.-P. Genet, *Chem. Commun.*, **2005**, 4714; b) F. Sakurai, K. Kondo and T. Aoyama, *Chem. Pharm. Bull.*, **2009**, **57**, 511; c) M. Kuriyama, R, Shimazawa, T. Enomoto and R. Shirai, *J. Org. Chem.*, **2008**, *73*, 6939.

Furthermore, we wanted to expand the regioselective metalations of pyrimidines, pyrazines and other N-heterocycles by using frustrated Lewis pairs of $BF_3 \cdot OEt_2$ and hindered magnesium and zinc amide bases. We also investigated, if a switch in regioselectivity was observed in the presence or absence of the Lewis acid (Scheme 20).



Scheme 20: Switchable regioselectivity in the presence or absence of $BF_3 \cdot OEt_2$.

Recently our group has established solid salt stabilized organozinc reagents, by transmetalation of organomagnesium reagents, obtained by either Hal/Mg exchange or Mg insertion, with $Zn(OPiv)_2 \cdot 2LiCl$ (**24a**). These compounds are obtained as easy-to-handle solids that prove to be stable against air exposure for a certain time.[67] Another route for the preparation of solid organozinc pivalates is the magnesiation of aryls and heteroaryls by TMPMgCl·LiCl (**14**) followed by transmetalation with $Zn(OPiv)_2$ (**24b**).[68] However, for preparing organozinc reagents bearing very sensitive functional groups, such as an aldehyde or a nitro group, those routes are not suitable. Therefore we wanted to prepare a zinc base that would directly generate the desired organozinc pivalate without having an unstable magnesium intermediate and check their reactivity towards various electrophiles (Scheme 21).



Scheme 21: Preparation of organozinc pivalates by directed zincation followed by reaction with various electrophiles.

Since these organozinc pivalates are complex mixtures of three different metals (Li, Mg and Zn) and three different anionic ligands (Cl^-, $OPiv^-$ and Ar^-) they make for highly complex chemistry. Therefore, studies were performed to elucidate the multicomponent compositions and structures of the organozinc pivalate "cocktail".

[67] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed*. **2011**, *50*, 9205.
[68] C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed*. **2012**, *51*, 9428.

B. RESULTS & DISCUSSION

1. Benzylic Zinc Reagents of Pyridines and Quinolines for Cross-Couplings with Aryl Bromides

1.1. Introduction

The functionalization of pyridines and related heterocycles is very important because of their biological properties and relevance to material science.[69] The benzylic arylation of pyridines is, in particular, a challenging synthetic problem. Palladium-catalyzed arylations of 2-picoline involving direct C–H activation [65] have no generality, and only few examples have been reported. Thus, azaarenes bearing electron-withdrawing groups (EWG) may be arylated at 100 °C with a Pd catalyst.[70] Several alternative procedures involving the fragmentation of a 2-(2-pyridyl)ethanol,[71] the arylation of N-oxides,[72] and N-iminopyridinium ylides[73] have been described. These methods, although displaying generality, require modified N-heterocyclic precursors. In addition, whereas 2-picoline (**25a**) can be functionalized in this way, the arylation of 4-picoline (**26a**) has not been described. The difficulty in forming a new carbon–carbon bond with metalated 2-picoline (**27**, or 4-picoline) may be due to the nature of the palladium complexes[74] **28a-c** resulting from the reaction with ArPdX (Scheme 22).We anticipate that all of these possible structures of type **28** are reluctant to undergo a reductive elimination because of the chelation of the heterocyclic nitrogen with the Pd-center. *Hartwig* and co-workers have already shown that

[69] a) M. A. Yurovskaya, A. V. Karchava, *Chem. Heterocycl. Compd.* **1994**, *30*, 1331; b) P. N. W. Baxter, J.-M. Lehn, J. Fischer, M.-T. Youinou, *Angew. Chem. Int. Ed.* **1994**, *33*, 2284; c) K. C. Nicolaou, R. Scarpelli, B. Bollbuck, B. Werschkun, M. M. A. Pereira, M. Wartmann, K.-H. Altmann, D. Zaharevitz, R. Gussio, P. Giannakakou, *Chem. Biol.* **2000**, *7*, 593; d) J.-M. Lehn, *Science* **2002**, *295*, 2400; e) B. Oliva, K. Miller, N. Caggiano, A. J. O´Neill, G. D. Cuny, M. Z. Hoemann, J. R. Hauske, I. Chopra, *Antimicrob. Agents Chemother.* **2003**, *47*, 458; f) A. Bouillon, A. S. Voisin, A. Robic, J.-C. Lancelot, V. Collot, S. Rault, *J. Org. Chem.* **2003**, *68*, 10178; g) E. M. Nolan, J. Jaworski, K.-I. Okamoto, Y. Hayashi, M. Sheng, S. J. Lippard, *J. Am. Chem. Soc.* **2005**, *127*, 16812; h) T. Laird, *Org. Process Res. Dev.* **2006**, *10*, 851; i) A. Hayashi, M. Arai, M. Fujita, M. Kobayashi, *Biol. Pharm. Bull.* **2009**, *32*, 1261; j) X. Chen, K. M. Engle, D.-H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; k) J. Quiroga, J. Trilleras, B. Insuasty, R. Abonia, M. Nogueras, A. Marchal, J. Cobo, *Tetrahedron Lett.* **2010**, *51*, 1107.

[70] P. M. Burton, J. A. Morris, *Org. Lett.* **2010**, *12*, 5359.

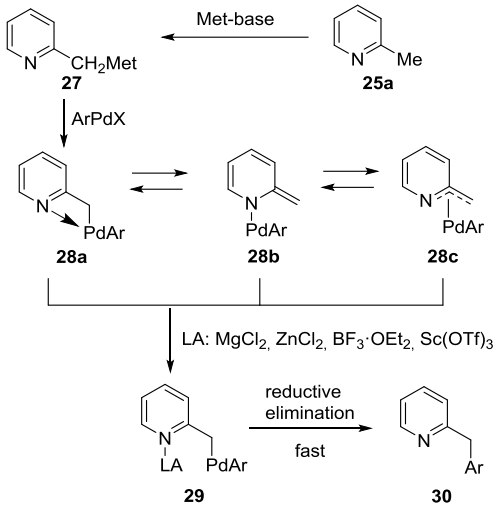
[71] a) T. Niwa, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2007**, *46*, 2643; b) T. Niwa, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 2373.

[72] a) L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266; b) D. J. Schipper, L.-C. Campeau, K. Fagnou, *Tetrahedron* **2009**, *65*, 3155.

[73] J. J. Mousseau, A. Larivée, A. B. Charette, *Org. Lett.* **2008**, *10*, 1641.

[74] For structures of palladium picolyl derivatives, see: a) M. Onishi, K. Hiraki, K. Maeda, T. Itoh, *J. Organomet. Chem.* **1980**, *188*, 245; b) K. Isobe, Y. Nakamura, S. Kawaguchi, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1802; c) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2010**, *132*, 3650.

palladium-catalyzed aminations are accelerated by a LA (BEt_3).[75] *Nolan* and co-workers have also reported that reductive elimination of Pd complexes are accelerated by $AlCl_3$.[76]



Scheme 22: Lewis-acid (LA) promoted benzylic cross-coupling

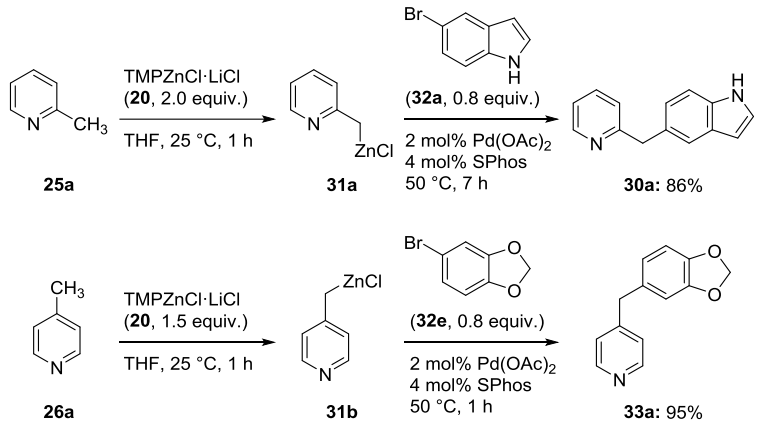
It was envisioned that the presence of an appropriate LA complexing the nitrogen atom of the heterocycle may lead to a new Pd-intermediate such as **29**, which would then undergo fast reductive elimination leading to the desired cross-coupling product **30**. Similar behavior may be expected for the arylation of 4-picoline (**26a**). The beneficial effect of Lewis acids in the additions of 2-picoline (**25a**) to imines and enones has already been demonstrated.[77] The kinetically highly active LiCl-solubilized TMP-base: TMPZnCl·LiCl (**20**) displays a high chemoselectivity in various directed zincations of arenes and heterocycles.[60] Besides, **20** proved to be an excellent base for the preparation of nitrile and ester enolates.[78,79] We have also demonstrated that **20** is compatible with additional strong Lewis acids ($MgCl_2$, $BF_3{\cdot}OEt_2$) and forms frustrated Lewis pairs.[62a,63] Herein, we report that Lewis acids such as $ZnCl_2$, $MgCl_2$, $BF_3{\cdot}OEt_2$, and $Sc(OTf)_3$ in combination with TMPZnCl·LiCl efficiently promote the *Negishi* cross-coupling[64] of various methyl-substituted N-heterocycles.

1.2. Preparation and Cross-Coupling of Benzylic Pyridyl Zinc Reagents

First the zincation of 2-methylpyridine (**25a**) with TMPZnCl·LiCl (**20,** 2.0 equiv.) was performed to give the zincated picoline **31a** after 1 h at room temperature. It was possible to perform a cross-coupling

[75] Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc*. **2007**, *129*, 7734.
[76] J. Huang, C. M. Haar, S. P. Nolan, *Organometallics* **1999**, *18*, 297.
[77] a) B. Qian, S. Guo, C. Xia, H. Huang, *Adv. Synth. Catal*. **2010**, *352*, 3195; b) M. Rueping, N. Tolstoluzhsky, *Org. Lett*. **2011**, *13*, 1095, c) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, *Org. Lett*. **2011**, *13*, 1706.
[78] a) M. L. Hlavinka, J. R. Hagadorn, *Tetrahedron Lett.* **2006**, *47*, 5049; b) M. L. Hlavinka, J. R. Hagadorn, *Organometallics* **2007**, *26*, 4105.
[79] S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690.

with 5-bromoindole (**32a**, 0.8 equiv.) using 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos[80] (50 °C, 7 h) which afforded the desired pyridine **30a** in 86% yield (Scheme 23). Such cross-coupling reactions could be extended to various substituted aryl bromides (**32b-d**) leading to products **30b-d** in 66 to 95% yield (Table 1, entries 1-3). Also, pyridines bearing a substituent at the benzylic position such as **25b-c** were readily metalated using TMPZnCl·LiCl (**20**) under the similar conditions and provided, after cross-coupling with 4-bromoanisole (**32b**), the desired products (**30e-f**) in excellent yields (92 to 99%, entries 4-5).



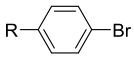
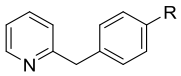
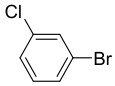
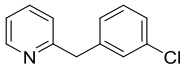
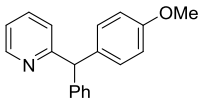
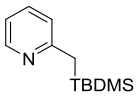
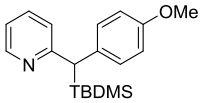
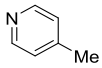
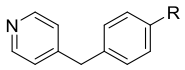
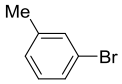
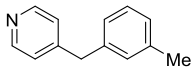
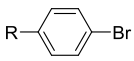
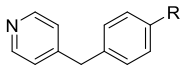
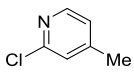
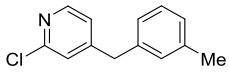
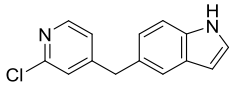
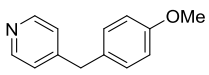
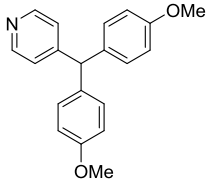
Scheme 23: Palladium-catalyzed direct cross-coupling of 2-picoline (**25a**) and 4-picoline (**26a**).

Also the zincation of **26a** with **20** (1.5 equiv.) proceeded readily within 1 h at 25 °C and after a palladium-catalyzed cross-coupling of the generated zinc reagent **31b** with the bromide **32e** the desired product **33a** was obtained in 95% yield (Scheme 23). This is remarkable, since to our knowledge, no arylation of 4-picoline (**26a**) in the bezylic postion has previously been reported in the literature. Various other aryl bromides (**32b, 32f-i**) reacted under similar conditions and furnished the 4-substituted pyridines **33b-f** in 70 to 98% yield (Table 1, entries 6–10). 2-Chloro-4-methylpyridine (**26b**) reacted similarly and produced, after cross-coupling with the bromides **32f** and **32a**, the arylated products **33g** and **33h** in 69% yield (Table 1, entries 11 and 12). Finally, the substitiuted 4-picoline **33b** could be further metalated and cross-coupling with 4-bromoanisole (**32b**) furnished the desired product (**33i**) in high yield (entry 13). These smooth cross-couplings may be explained by the the fact that the generated $ZnCl_2$ acts as a Lewis acid. Interestingly, the use of TMPZnCl·$MgCl_2$·2LiCl (**19**)[59] led to even faster cross-couplings (at least six times faster). However, the yield was significantly diminished by increased amounts of diarylation[81] making the general use of this base unattractive.

[80] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; c) R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115; d) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

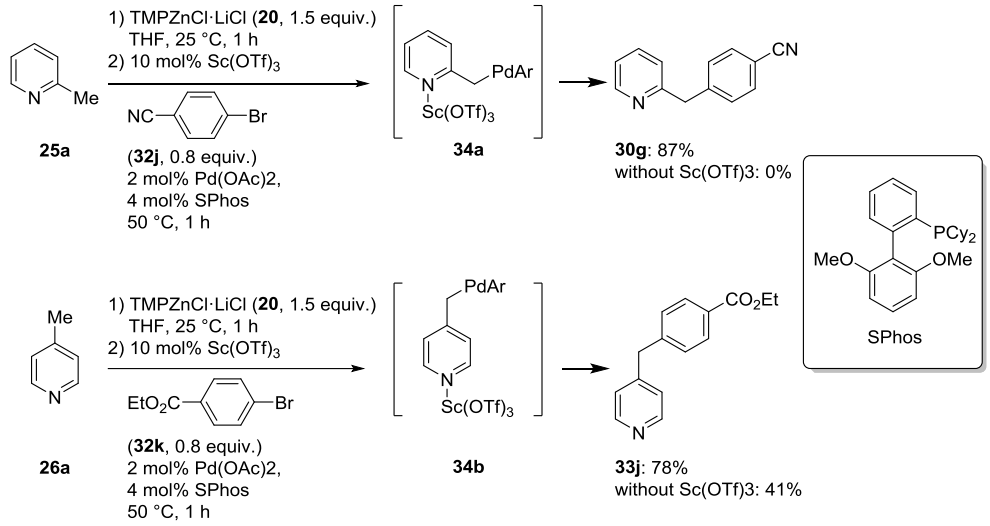
[81] The palladium-catalyzed arylation of 2-picoline (**25a**) with 3-chlorobromobenzene (**32d**) proceeds in 1 h in the presence of TMPZnCl·$MgCl_2$·LiCl (**19**) instead of in 6 h in the presence of TMPZnCl·LiCl (**20**) but led to less product **30d** (61%) owing to the formation of 17% of diarylated product.

Table 1: Direct benzylic cross-coupling of 2- and 4-picoline derivatives.

Entry	Picoline[a]	Electrophile	Product	Yield[b] [%]
				
1	**25a** (3)	**32b**: R = OMe	**30b**: R = OMe	95
2	**25a** (6)	**32c**: R = F	**30c**: R = F	78
				
3	**25a** (6)	**32d**	**30d**	66
				
4	**25b** (20)	**32b**	**30e**	99
				
5	**25c**[d] (20)	**32b**	**30f**	92
				
6	**26a** (1)	**32b**	**33b**: R = OMe	98[c]
				
7	**26a** (1)	**32f**	**33c**	82
				
8	**26a** (1)	**32g**: R = NMe_2	**33d**: R = NMe_2	70
9	**26a** (1)	**32h**: R = OH	**33e**: R = OH	84[c]
10	**26a** (1)	**32i**: R = OPiv	**33f**: R = OPiv	81[c]
				
11	**26b** (1)	**32f**	**33g**	69[e]
				
12	**26b** (1)	**32a**	**33h**	69
				
13	**33b** (3)	**32b**	**33i**	93

[a] Reaction time (h) for the arylation in brackets. [b] Yield of isolated, analytically pure product. [c] $Pd(O_2CCF_3)_2$ was used instead of $Pd(OAc)_2$. [d] TBDMS=tert-butyldimethylsilyl. [e] 2 mol% $Pd(OAc)_2$, 4 mol% PCy_3 were used

A further hint showing the importance of Lewis acids for the tentative Pd intermediate of type **29** (Scheme 22) is found in the cross-coupling reaction of picolines (**25a** or **26a**) with electron deficient aryl bromides. Substrates like 4-bromobenzonitrile (**32j**) and ethyl 4-bromobenzoate (**32k**) gave disappointing results in the presence of either $ZnCl_2$ or $MgCl_2$ as Lewis acids. Therefore, other alternative Lewis acids[82] such as $ScCl_3$, $Sc(OTf)_3$,[83] $Yb(OTf)_3$,[84] and $Y(OTf)_3$[82] were screened. It was found, that the direct cross-coupling of zincated 2-picoline (**31a**) with 4-bromobenzonitrile (**32j**) proceeded readily in the presence of 10 mol% $Sc(OTf)_3$ and afforded the coupling product **30g** in 87% yield (Scheme 24). Without the Lewis acid, no product was obtained (even after additional ligands for the Pd catalyst were screened). Similarly, the cross-coupling of the metalated 4-picoline (**31b**) with the ester **32k** proceeded only in 41% yield in the absence of $Sc(OTf)_3$, but the yield of the desired product **33j** could be increased to 78% after addition of 10 mol% $Sc(OTf)_3$ (Scheme 24).



Scheme 24: $Sc(OTf)_3$ catalyzed cross-coupling of 2-picoline (**25a**) and 4-picoline (**26a**) with electron-withdrawing substituted aryl bromides (**32j-k**).

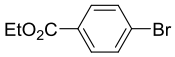
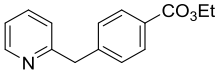
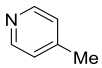
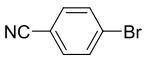
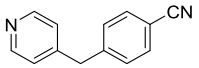
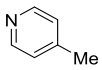
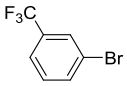
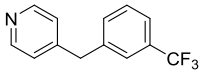
The effect of $Sc(OTf)_3$ may best be explained by an acceleration of the reductive elimination step in the cross-coupling as a result of the complexation of $Sc(OTf)_3$ to the heterocyclic nitrogen (see **34a**,**b**, Scheme 24). It is anticipated that electron-withdrawing substituents lead to Pd-intermediates of type **28** (Scheme 22) which are especially reluctant to undergo reductive elimination. We found the effect of a strong Lewis acid to be crucial in these cases. For instance the cross-couplings of picolines **25a** and **26a** with various electron-deficient aryl bromides (**32j–l**) are dramatically improved by the presence of 10 mol% $Sc(OTf)_3$ and the cross-coupling products **30h** and **33k–l** are obtained in 75–85% yield. In the absence of $Sc(OTf)_3$, the yields of the cross-coupling are between 0 and 51% (Table 2, entries 1–3)

[82] a) S. Kobayashi, *Lanthanides: Chemistry and Use in Organic Synthesis*, Springer, Berlin, **1999**; b) M. Shibasaki, S. Matsunaga, N. Kumagai, *Acid Catalysis in Modern Organic Synthesis, Vol. 2*, Wiley-VCH, Weinheim, 2008, 635.

[83] a) S. Kobayashi, I. Hachiya, M. Araki, H. Ishitani, *Tetrahedron Lett.* **1993**, *34*, 3755; b) S. Kobayashi, *Lewis Acids in Organic Synthesis, Vol. 2*, Wiley-VCH, Weinheim, **2000**, 883; c) C. Ogawa, Y. Gu, M. Boudou, S. Kobayashi, *Acid Catalysis in Modern Organic Synthesis, Vol. 2*, Wiley-VCH,Weinheim, **2008**, 589.

[84] a) S. Kobayashi, *Transition Metals for Organic Synthesis, Vol. 1*, Wiley, Weinheim, **1998**, 285; b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227.

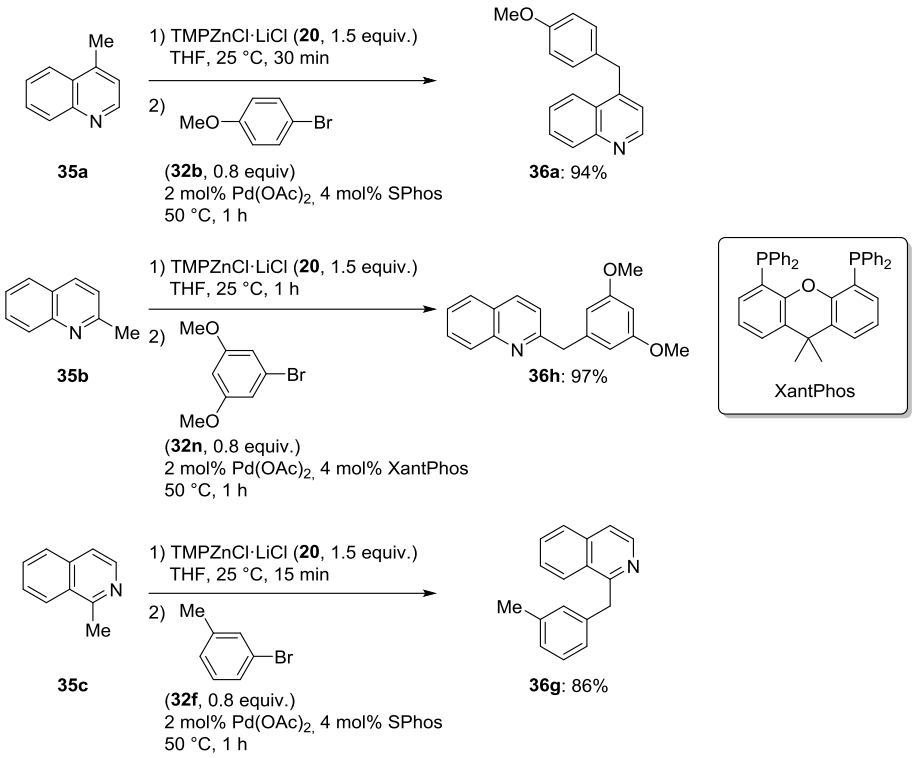
Table 2: Effect of $Sc(OTf)_3$ on the benzylic cross-coupling of 2- (**25a**) and 4-picoline (**26a**) with electron-deficient electrophiles

Entry	Picoline	Electrophile[a]	Product	Yield[b] [%]
1	 **25a** (3)	 **32k**	 **30h**	85 (31)
2	 **26a** (1)	 **32j**	 **33k**	75 (0)
3	 **26a** (1)	 **32l**	 **33l**	78 (51)

[a] Cross-coupling conditions: 50 °C, 1 h. [b] Yield of isolated, analytically pure product, in parenthesis: isolated yield of reaction performed without $Sc(OTf)_3$.

1.3. Preparation and Cross-Coupling of Benzylic Quinolyl Zinc Reagents

The metalation and cross-coupling protocol could also be expanded to 2- and 4-methylquinoline (**35a**,**b**) and 1-methylisoquinoline (**15c**). For all three compounds the zincation, using TMPZnCl·LiCl (**20**, 1.5 equiv.), proceeded readily at room temperature within 15 to 60 min and also cross-coupling reactions worked well with an appropriate catalyst system. Therefore, **35a** was zincated and could be cross-coupled with 4-bromoanisole (**32b**) in the presence of 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos to yield the arylated quinoline derivative **36a** in 94% (Scheme 25). The cross-coupling could be performed using various aryl bromides (**32g-h**,**j**,**l**,**m**) and gave the desired 4-substituted quinolines **36b-f** in very good to excellent yields (Table 3, entries 1-5). In case of *Negishi* cross-couplings with aryl bromides bearing an acidic proton (**32h**,**m**), the use of $Pd(O_2CCF_3)_2$ introduced by *Oshima* and *Yorimitsu*[71] was advantageous and ensured high yields and fast cross-couplings (entries 4 and 5).

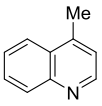
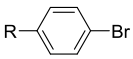
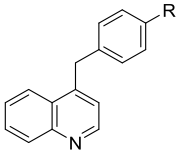
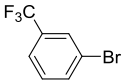
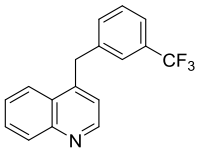
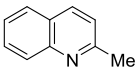
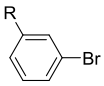
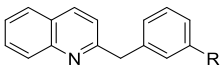
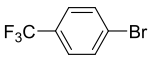
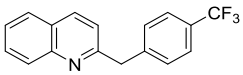
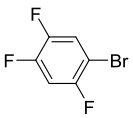
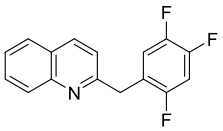
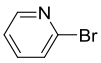
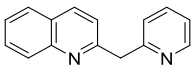


Scheme 25: Benzylic cross-coupling of quinoline derivatives (**35a-c**) with different aryl bromides.

Also the isoquinoline **35c** could be cross-coupled with the bromide **32f** using the $Pd(OAc)_2$/SPhos system and furnished the functionalized derivative **36g** in 86% yield (Scheme 25). For the arylation of 2-methylquinoline (**35b**), the XantPhos[85] ligand proved to be best, since the formation of double arylation by products could be avoided. Thus, the arylation of **35b** with the dimethoxysubstituted bromide **32n** using 2 mol% $Pd(OAc)_2$ and 2 mol% XantPhos provided the desired arylated quinoline **36h** in 97% yield. Similar to the 4-methylquinoline (**35a**) the cross-coupling of **35b** could be performed with various different arylbromides (**32f**,**o-r**) to provide the 2-substituted quinolines **36i-m** in 68 to 96% yield (Table 3, entries 6-10).

[85] P.W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741.

Table 3: Benzylic cross-couplings of quinoline derivatives with various aryl bromides.

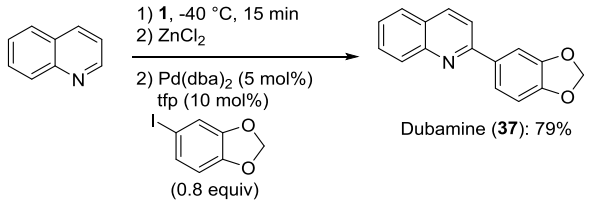
Entry	Quinoline	Electrophile[a]	Product	Yield[b] [%]
				
1	**35a**	**32g**: R = NMe_2 (1)	**36b**: R = NMe_2	93
2	**35a**	**32j**: R = CN (1)	**36c**: R = CN	66
3	**35a**	**32h**: R = OH (2)	**36d**: R = OH	76[c]
4	**35a**	**32m**: R = NH_2 (2)	**36e**: R = NH_2	74[c]
				
5	**35a**	**32l** (1)	**36f**	72
				
6	**35b**	**32f**: R = Me (1)	**36i**: R = Me	96
7	**35b**	**32o**: R = F (1)	**36j**: R = F	95
				
8	**35b**	**32p** (1)	**36k**	86
				
9	**35b**	**32q** (1)	**36l**	78
				
10	**35b**	**32r** (1)	**36m**	68

[a] Cross-coupling conditions: 50 °C, reaction time in brackets. [b] Yield of isolated, analytically pure product. [c] 2.0 equiv. of TMPZnCl·LiCl, 2 mol% $Pd(O_2CCF_3)_2$ and 4 mol% SPhos were used.

2. METALATING N-HETEROCYCLES USING THE FRUSTRATED LEWIS PAIR TMPMGCL·BF_3 FOLLOWED BY ADDITION TO AROMATIC ALDEHYDES AND ACTIVATED KETONES

2.1. Introduction

The metalation of pyridines is an important reaction since it is a convenient way of functionalization.[47a,86] The preparation of polyfunctional pyridines can be achieved by ring metalation,[65d 87] radical functionalization[88] or C-H activation.[89] Recently *Knochel* and coworkers showed, that the combination of the hindered base TMPMgCl·LiCl (**14**) in the presence of BF_3·OEt_2 allows the regioselective metalation of various electron-poor N-heterocycles. It was found that the base **14** is compatible with the strong Lewis acid BF_3·OEt_2 at temperatures below -20 °C.[62a] This frustrated Lewis pair **21**, tentatively written as TMPMgCl·BF_3 (**21**), resulting from TMPMgCl·LiCl (**14**) and BF_3·OEt_2 allowed a smooth activation of pyridine and related heterocycles and could readily be applied in a straightforward one-pot synthesis of the haplophyllum alkaloid dubamine (**37**, Scheme 26).[90]



Scheme 26: One-pot synthesis of dubamine (**37**).

Amino substituted alcaloids could be functionalized using similar reaction conditions.[91] Remarkably the activation with BF_3·OEt_2 happens without interference of the amino substituents and no competitive complexation of the BF_3 group was observed. Thus, nicotine (**38**) was metallated and further allylated at the 6 position of the pyridine moiety (Scheme 27). Quinine (**39**) was also magnesiated, after *in situ* protection of the alcohol group with MeLi, at the 3 position of the quinoline scaffold and could be reacted with various electrophiles.

[86] a) 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; b) F. Mongin, G. Quéguiner, *Tetrahedron*, 2001, **57**, 4059.

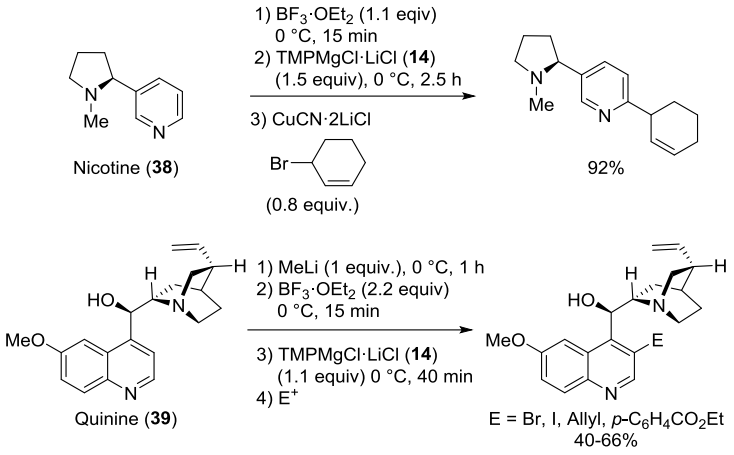
[87] a) D. L. Comins, D. H. LaMunyon, *Tetrahedron Lett.* **1988**, *29*, 773; b) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; c) G. Karig, J. A. Spencer, T. Gallagher, *Org. Lett.* **2001**, *3*, 835; d) M. Schlosser, *Angew. Chem., Int. Ed.* **2005**, *44*, 376; e) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem., Int. Ed.* **2007**, *46*, 3802; f) P.C. Gros, Y. Fort, *Eur. J. Org. Chem.* **2009**, 4199; g) H. K. Khartabil, P. C. Gros, Y. Fort, M. F. Ruiz-López, *J. Am. Chem. Soc.* **2010**, *132*, 2410.

[88] a) F. Minisci, F. Fontana, E. J. Vismara, *Heterocycl. Chem.* **1990**, *27*, 79; b) D. C. Harrowven, B. J. Sutton, *Prog. Heterocycl. Chem.* **2004**, *16*, 27; c) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194; d) J. A. Joule, K. Mills, *Heterocyclic Chemistry, Vol. 5*, Wiley-Blackwell, Chichester, **2010**.

[89] a) X. Chen, K. M. Engle, D.-H. Wang, J-Q. Yu, *Angew. Chem., Int. Ed.* **2009**, *48*, 5094; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) B. Li, Z-H. Wu, Y-F. Gu, C.-L. Sun, B-Q. Wang, Z.-J. Shi, *Angew. Chem., Int. Ed.* **2011**, *50*, 1109; d) H. Prokopcová, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel, B. U. W. Maes, *Chem.–Eur. J.* **2010**, *16*, 13063.

[90] C. M. Melendez Gomez, V. V. Kouznetsov, M. A. Sortino, S. L. Alvarez, S. A. Zacchino, *Bioorg. Med. Chem.* **2008**, *16*, 7908.

[91] M. Jaric, B. A. Haag, S. M. Manolikakes, Paul Knochel, *Org. Lett.* **2011**, *13*, 2306.



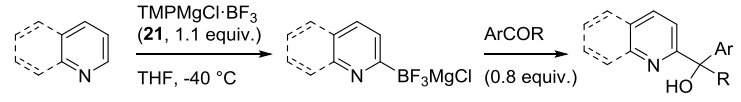
Scheme 27: Functionalization of nicotine (**38**) and quinine (**39**) using TMPMgCl·LiCl (**14**) and $BF_3{\cdot}OEt_2$.

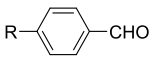
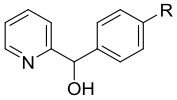
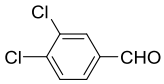
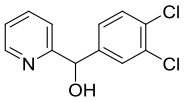
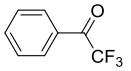
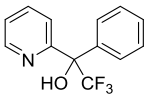
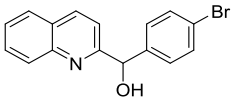
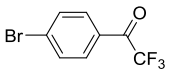
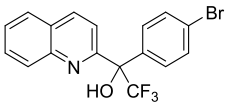
2.2. Addition to Aromatic Aldehydes and Activated Ketones

The organometallic reagent produced by the treatment of pyridine (**40a**) with the Lewis pair **21** is the pyridyl trifluoroborate **41a**, as shown by a $^2J_{19F\text{-}13C}$ coupling between C2 of **41a** and the fluorine atoms (Table 4, Scheme).[62] In general, the reactivity of pyridyl trifluoroborates towards aldehydes is quite low and a successful addition usually requires a rhodium, nickel or palladium catalyst.[66] However, we have found that magnesium 2-pyridyl trifluoroborates such as **41a** reacted readily with various aldehydes and activated ketones providing the pyridyl alcohols of type **42**. Thus, the reaction of pyridine (**40a**) with the Lewis pair **21** (1.1 equiv.), prepared by mixing TMPMgCl·LiCl (**14**, 1.1 equiv.) with $BF_3{\cdot}OEt_2$ (1.1 equiv.) at -40 °C for 10 min, gave after further 15 min at -40 °C the trifluoroborate **41a** which reacted with 4-cyanobenzaldehyde (**43a**, 0.8 equiv., -40 to 25 °C, 2 h) leading to the desired pyridyl alcohol **42a** in 73% yield (Table 4, entry 1). Similarly, the substituted benzaldehydes **43b-d** reacted in the same way (-40 to 25 °C, 2-4 h) providing the alcohols **42b-d** in 66-68% yield (entries 2-4). Interestingly, the pyridyl intermediate **41a** also added smoothly to the ketone $PhCOCF_3$ (**43e**) affording the tertiary alcohol **42e** in 72% yield (Table 1, entry 5).[92] The metalation of quinoline (**40b**) with the Lewis pair **21** (1.1 equiv.) proceeded readily under similar conditions (-40 °C, 40 min). The resulting trifluoroborate **41b** added smoothly to 4-bromobenzaldehyde (**43c**) and the trifluoromethyl ketone (**43f**) providing the quinolyl alcohols **42f-g** in 65% yield (entries 6-7).

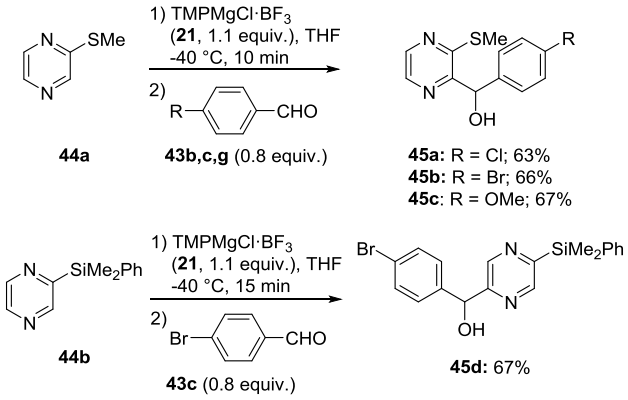
[92] The use of aliphatic aldehydes leads only to decomposition and no product could be isolated.

Table 4: Addition of 2-pyridyl trifluoroborates to aromatic aldehydes or activated ketones.



Entry	Substrate	Carbonyl Compound	Product	Yield[a] [%]
				
1	**40a**	**43a**: R = CN	**42a**: R = CN	73
2	**40a**	**43b**: R = Cl	**42b**: R = Cl	68
3	**40a**	**43c**: R = Br	**42c**: R = Br	67
				
4	**40a**	**43d**	**42d**	66
				
5	**40a**	**43e**	**42e**	72
				
6	**40b**	**43c**	**42f**	65
				
7	**40b**	**43f**	**42g**	65

[a] Yield of isolated, analytically pure product.



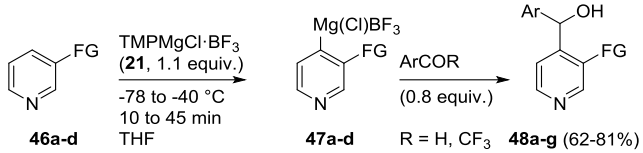
Scheme 28: Metalation of monosubstituted pyrazines followed by trapping with aromatic aldehydes.

The 2-pyrazine **44a** could also be metalated using 1.1 equivialents of TMPMgCl·BF_3 (**21**, -40 °C, 10 min). The deprotonation occurred next to the thiomethyl group and after the addition to the substituted benzaldehydes **43b,c,g** the expected carbinols **45a-c** were obtained in 63-67% yield (Scheme 28). The silylsubstituted pyrazine **44b** was also readily metalated using **21** (-40 °C, 15 min), this time however, the deprotonation took place opposite to the bulky $SiMe_2Ph$ group. It can be assumed that due to the steric hinderance of the silyl group the base coordinates to the less hindered nitrogen atom of the pyrazine ring and then abstracts the less hindered proton in position 5.[93] Therefore, after addition to 4-bromobenzaldehyde (**43c**), the 2,5-disubstituted pyrazine derivative **45d** is obtained in 67% yield.

Then, we examined various 3-substituted pyridines (**46a-d**) and found that their treatment with TMPMgCl·BF_3 (**21**) at -40 °C or -78 °C afforded metalated species of type **47** which reacted readily with several aromatic aldehydes (Table 5). Thus, the treatment of ethyl nicotinate (**46a**) with **21** (1.1 equiv., -40 °C, 30 min) provided after the addition to 4-bromobenzaldehyde (**43c**) or benzaldehyde (**43h**, 0.8 equiv. -40 °C to 25 °C, 4 h), respectively, and cyclization the lactones **48a-b** in 62-72% yield (entries 1 and 2). It was also possible to react the intermediate **47a** with the ketone **43e** to yield the lactone **48c** in 65% (entry 3). Similarly, the 3-fluoro and 3-chloro substituted pyridines **46b** and **46c** were readily metalated in position 4 by TMPMgCl·BF_3 (**21**, 1.1 equiv.) at -78 °C within 10 min. After quenching **47b** with the aldehyde **43c** the carbinol **48d** could be isolated in 81% (entry 4). Quenching the metalated species of **46c** with either 4-chloro- or 4-bromobenzaldehyde (**43b**,**c**) furnished the alcohols **48e** and **48f** in 71% yield each (entries 5 and 6). Finally, diethyl nicotinamide (**46d**) was metalated under the same conditions providing after addition to 3,4-dichlorobenzaldehyde (**43d**) the desired product **48g** in 81% yield (entry 7).

[93] K. Groll, S. M. Manolikakes, X. mollat du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776.

Table 5: Metalation of 3-substituted pyridines followed by trapping with aromatic aldehydes.



Entry	Substrate	Carbonyl Compound	Product	Yield[a] [%]
1	**46a**	**43c**	**48a:** Ar = *p*-C_6H_4Br	72
2	**46a**	**43h**	**48b**	62
3	**46a**	**43e**	**48c**	65
4	**46b**	**43c**	**48d:** Ar = *p*-C_6H_4Br	81
5	**46c**	**43b**	**48e:** Ar = *p*-C_6H_4Cl	71
6	**46c**	**43c**	**48f:** Ar = *p*-C_6H_4Br	71
7	**46d**	**43d**	**48g:** Ar = 3,4-C_6H_3Cl	81

[a] Yield of isolated, analytically pure product.

2.3. Unraveling the Structures of the Intermediates

As studies have already shown, the intermediates of type **41** are indeed pyridyl trifluoroborates that display a noticeable $^{2}J_{19F\text{-}13C}$ coupling of 14.7 Hz between C2 of **41** and the fluorine atoms.[62a,94] This is also reasonable since the C-B bond is thermodynamically favoured over the C-Mg bond, due to the higher electronegativity of the boron atom. However, the nature of the 4-metalated pyridines of type **47** could not be so easily evaluated. This is also due to the fact, that the intermediates **47b-d** are only stable for a limited time at -78 °C, which makes NMR-studies extremely difficult. Luckily, the intermediate **47a** proved to be stable at -60 °C over a longer period of time, so that extensive ^{1}H-, ^{11}B-, ^{13}C- and ^{19}F-NMR experiments could be performed. Contrary to the 2-metalated species of type **41** where a $^{2}J_{19F\text{-}13C}$ between C2 and the fluorine atoms was observed in the ^{13}C-NMR spectrum, such couplings could not be found for the 4-metalated species **47a**, clearly indicating, that the transmetalation from Mg to B does not occur in position 4 of the pyridine scaffold, thus excluding the formation of an arylic trifluoroborate of structure **47aa** (Figure 2). Also, no $^{3}J_{19F\text{-}13C}$ coupling between C2 or C6 and fluorine could be observed, suggesting that no, or only a very weak, complexation of BF_3 at the pyridyl nitrogen occurs (see complex **47ab**).[95] This would implicate that the structure of the intermediates of type **47** is a pyridylmagnesium derivative like **47ac**. However, this leaves the question open to where the BF_3 group is located, if not on the pyridyl nitrogen.

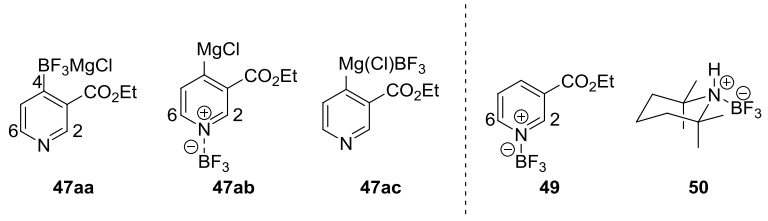
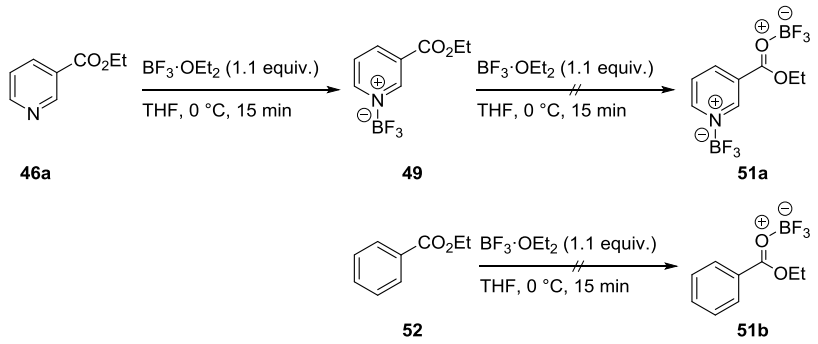


Figure 2: Possible structure of N-heterocycles metalated by TMPMgCl·BF_3 (**21**) and BF_3 complexes.

Therefore, several control experiments were performed: First, **46a** was treated with $BF_3{\cdot}OEt_2$ (1.1 equiv., 0 °C, 15 min) in THF-d_8 resulting in the pyridinium complex **49** (Scheme 29), where the complexation of BF_3 with the pyridine nitrogen resulted in a distinct shift and splitting of the C2 and C6 in the ^{13}C-NMR spectrum ($^{3}J_{19F\text{-}13C}$ = 2.2 Hz).[95] In another control experiment the TMPH-BF_3 complex (**50**, Figure 2) was prepared by reacting TMPH with $BF_3{\cdot}OEt_2$ (1.1 equiv., 0 °C, 15 min) in THF-d_8. The complexation of the BF_3 through the nitrogen was again confirmed *via* NMR-spectroscopy.[95] When evaluating the ^{13}C-NMR spectra of **47a** complex **50** is not observed and therefore is not formed during the metalation process, thus the BF_3 group must be located somewhere else. The BF_3 could also be coordinated to the carbonyl of the ethyl nicotinate (**47a**). To evaluate this possibility the pyridinium complex **49** was treated with second equivalent of $BF_3{\cdot}OEt_2$ to see if the signal of the carbonyl group would show any significant shift in the ^{13}C-NMR spectrum implying the formation of a complex tentatively depicted as **51a** (Scheme 29). No such shift was observed, but instead a low field shift of the THF-d_8 signal in the ^{13}C-NMR from 66.7 to 69.4 ppm and 24.4 to 25.5 ppm, respectively, clearly

[94] M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed*. **2010**, *49*, 8520.
[95] See: C. Experimental Section and D. Appendix

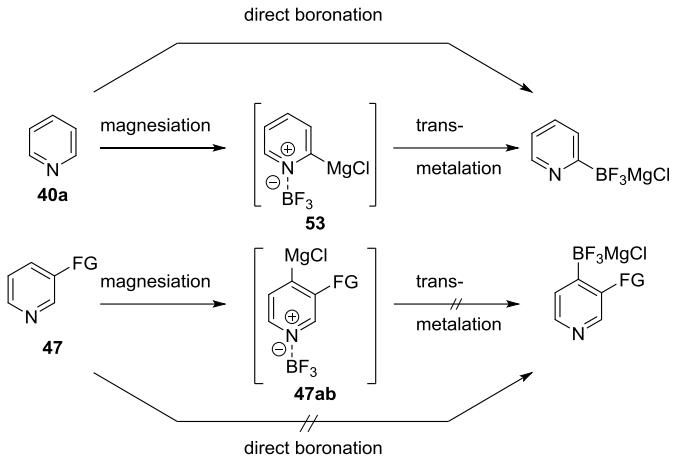
indicated a coordination of the BF_3 to the THF-d_8.[95] The same effect was observed when ethyl benzoate (**52**) was treated in the same way, which means that the structures **51a-b** were not formed, since the THF is the stronger ligand. However, in the ^{13}C-NMR spectrum of **47a** no solvent signal shift was observed, meaning there must be a stronger complexing ligand present in the reaction mixture.



Scheme 29: Reaction of ethyl nicotinate (**46a**) and ethyl benzoate (**52**) with $BF_3{\cdot}OEt_2$.

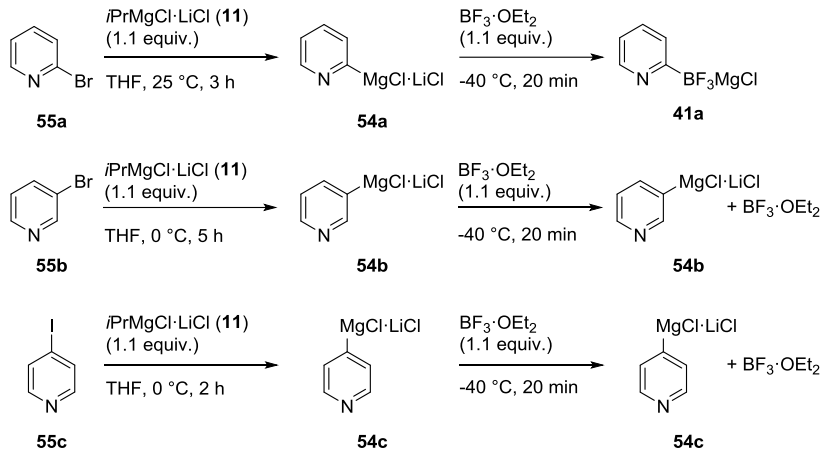
The experiments described above clearly show, that in the case of **47a** the BF_3 coordinates neither to TMPH nor to THF. It is also reasonable to conclude that the BF_3 does not coordinate to the ester group of the metalated ethyl nicotinate (**47a**). Unfortunately, the ^{13}C-NMR signals of the metalated species **47a** are broad ($\Delta_{1/2}$ ca. 5 Hz) and do not show any evidence for a splitting due to $^3J_{19F\text{-}13C}$ coupling, which is in the region of ca. 2 Hz and therefore probably not visible. Thus it can only be assumed that there might be a weak coordination of BF_3 to the pyridine nitrogen atom as depicted in structure **47ab** (since the BF_3 group does not seem to be located anywhere else), however there is no direct evidence for this fact.

Another remarkable result is the fact, that a C-B bond is formed only when the metalation takes place next to the nitrogen but not when the 4 position of the pyridine ring is deprotonated. The question arises if the transmetalation from Mg to B is generally hindered and in the case of pyridine (**40a**) and quinoline (**40b**) a direct boronation occurs, whereas in the case of the C4 metalation, a magnesiation takes place (Scheme 30). Another possibility would be that in both cases the first step is a magnesiation and the transmetalation is generally hindered at low temperatures and that the pyridyl nitrogen coordinates to the BF_3 group (as the studies described above suggest). In the case of the pyridine (**40a**) this would bring the boron atom in direct vicinity to the C-Mg bond (see structure **53**), thus making an intramolecular transmetalation possible, while in the intermediate **47ab** the boron and the magnesium atom are simply too far away from each other to make a transmetalation possible.



Scheme 30: Possible metalation pathways for position 2 and 4 of the pyridine scaffold.

To elucidate the reaction pathway the 2-, 3- and 4-magnesiated pyridine derivatives **54a-c** were generated separately *via* halogen magnesium exchange using *i*PrMgCl·LiCl (**11**, 1.1 equiv., 0 to 25 °C, 2-5 h), starting from 2- or 3-bromo- or 4-iodopyridine (**55a-c**), respectively (Scheme 31). The reagents **54a-c** were examined using ^{1}H- and ^{13}C-NMR spectroscopy before the reaction mixtures were cooled to -40 °C and 1.1 equiv. of $BF_3{\cdot}OEt_2$ were added. The resulting mixtures were investigated *via* ^{1}H- and ^{13}C-, ^{11}B- and ^{19}F-NMR spectroscopy.



Scheme 31: Reactions of pyridyl magnesium reagents with $BF_3{\cdot}OEt_2$.

The magnesium species **54a-c**, in the absence of $BF_3{\cdot}OEt_2$, proved to be mixtures of two or more reagents, which is not surprising since organomagnesium reagents are known to undergo *Schlenk* equilibria in THF.[96] Interestingly, when $BF_3{\cdot}OEt_2$ was added to the reagent **54a** there only one metalated species could be observed in the ^{13}C-NMR, namely the same species **41a** which was also obtained by metalating pyridine (**40a**) with the base TMPMgCl·BF_3 (**21**), showing the same $^{2}J_{19F\text{-}13C}$ coupling of 14.5 Hz between C2 and the fluorine atoms.[95] When the magnesium was located in position 3 or 4 of

[96] W. Schlenk, W. Schlenk jun., *Chem. Ber.* **1929**, *62*, 920.

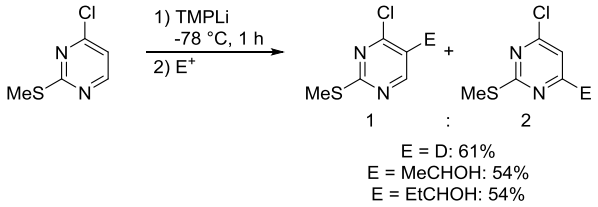
the pyridine residue however, no carbon fluorine coupling could be observed and also the *Schlenk* equilibria did not change significantly.

These results indicate that for the pyridine metalation, the magnesiation/transmetalation pathway is definitely possible, although the direct boronation pathway cannot be completely excluded. As for the 4-substituted magnesium reagents of type **47 , 54b** and **54c** a transmetalation to boron does not occur.

3. Regioselective Metalations of Pyrimidines by Using Frustrated Lewis Pairs of $BF_3 \cdot OEt_2$ and Hindered Magnesium and Zinc Amide Bases

3.1. Introduction

The functionalization of pyrimidines is of great importance, since this class of heterocycles is represented in numerous natural products, pharmaceuticals, and agrochemicals.[97] They also have various applications in materials science and polymer chemistry.[98] As described in A2.3 the directed metalation and further functionalization of electron-deficient N-heterocycles can be realized with different sterically hindered metal amides. So far, the C-H activation of diazines has been accomplished by ate bases[99] and Li amides.[100] However, due to the low stability of the generated lithiated intermediates, low temperatures and carefully designed reaction conditions are required. Moreover, some of these metalations provide the desired products only in low yields or furnish mixtures of different regioisomers (Scheme 32).[101]



Scheme 32: Metalation of a pyrimidine derivative with TMPLi.

The previously discussed LiCl-solubilized TMP metal bases give access to several metalated diazines[60a,102]and purines.[103] As already mentioned in A2.3 and B2 it was also found that various N-heterocycles can be activated by strong Lewis acids like $BF_3 \cdot OEt_2$, which proved to be compatible with the metallic amide bases. Thus, the reactivity of the sterically hindered TMP base is not quenched by $BF_3 \cdot OEt_2$, but on the contrary, a synergetic effect is observed (dual activation). This effect allows a regioselective metalation of various non-activated substituted pyridines and derivatives,[62a,91] which is not possible without the use of this Lewis pair combination.

.

[97] T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles, 2nd ed.*, Wiley-VCH, Weinheim, **2003**, Chap. 6.

[98] a) K.-T. Wong, T. S. Hung, Y. Lin, C.-C. Wu, G.-H. Lee, S.-M. Peng, C. H. Chou, Y. O. Su, *Org. Lett.* **2002**, *4*, 513; b) N. Hebbar, C. Foil-Petit, Y. Ramondenc, G. Plé, N. Plé, *Tetrahedron* **2011**, *67*, 2287.

[99] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b)W. Clegg, S. H. Dale, A. M. Drummond, E. Hevia, G.W. Honeyman, R. E. Mulvey, *J. Am. Chem. Soc.* **2006**, *128*, 7434; c) W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia,G.W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, 45, 2374; d) A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem.* **2007**, *72*, 6602; e) J.-M. L'Helgoual'ch, G. Bentabed-Ababsa, F. Chevallier, M. Yonehara, M. Uchiyama, A. Derdour, F. Mongin, *Chem. Commun.* **2008**, 5375.

[100] For reviews see: a) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, 57, 4489; b) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595.

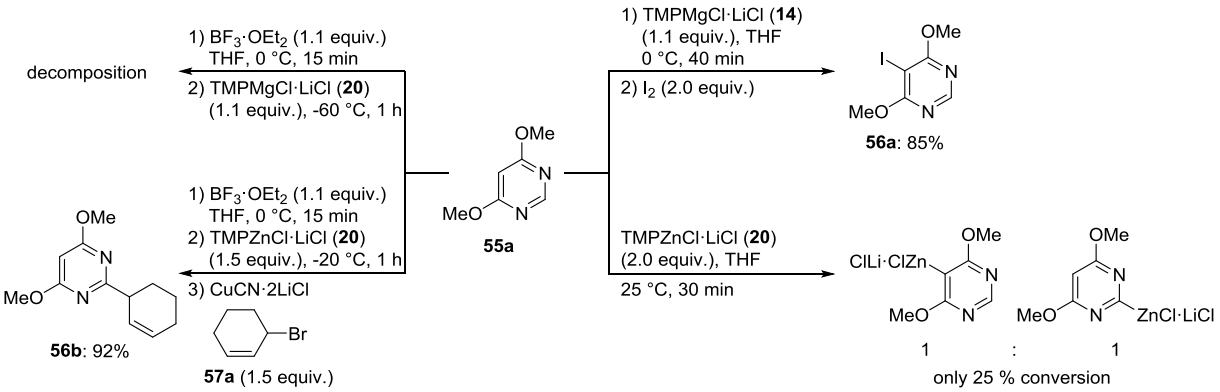
[101] N. PIé A. Turck, P. Martin, S. Barbey, G. Quéguiner, *Tetrahedron Lett.* **1993**, *34*, 1605

[102] a) M. Mosrin, P. Knochel, *Org. Lett*. **2008**, *10*, 2497; b) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237; c) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128.

[103] S. Zimdars, X. M. du Jourdin, F. Crestey, T. Carrell, P. Knochel, *Org. Lett.* **2011**, *13*, 792.

3.2. Effect of Different TMP-Metal Bases and BF_3·OEt_2 on the Metalation of Pyrimidines

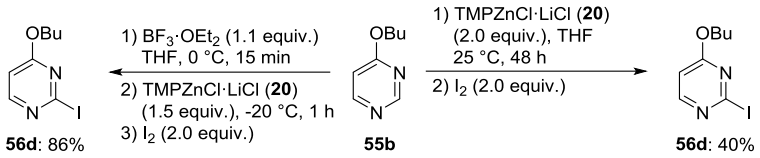
We found that the use of BF_3·OEt_2 allowed the orthogonal metalation of the pyrimidine scaffold. Treating 4,6-dimethoxypyrimidine (**55a**) with TMPMgCl·LiCl (**14**, 1.1 equiv., 0 °C, 40 min) provided a regioselective magnesiation at position 5 (Scheme 33). After iodolysis, the expected iodide **56a** was isolated in 85% yield. In contrast, the reaction of the pyrimidine **55a** with BF_3·OEt_2 (1.1 equiv.; 0 °C, 15 min) followed by the addition of TMPZnCl·LiCl (**20**, 1.5 equiv., -20 °C, 1 h) led to a quantitative metalation at position 2. After a copper-mediated allylation with 3-bromocyclohexene (**57a**), the desired 2-functionalized pyrimidine **56b** was isolated in 92% yield (Scheme 33). This behavior might be explained by an increased acidity at position 2 owing to the complexation of BF_3 with the pyrimidine ring allowing a complete switch of regioselectivity. In the absence of BF_3·OEt_2 no zincation of **55a** was observed at -20 °C (under 5% conversion).[104] However, the use of 2.0 equiv of TMPZnCl·LiCl (**20**) at 25 °C for 30 min affords an unselective metalation (1:1) and only 25% conversion. The combination of BF_3·OEt_2 with TMPMgCl·LiCl (**14**, 1.1 equiv.) mostly led to decomposition of **55a** at low temperature and only 20% of the 2-metalated pyrimidine derivative was detected by GC-analysis. The zincated intermediate of **55a** also underwent a smooth palladium catalyzed *Negishi* cross-coupling[64] with 4-iodoanisole (**57b**) affording the 2-arylated pyrimidine **56c** in 89% yield (Table 6, entry 1)



Scheme 33: Reactivity of 4,6-dimethoxypyrimidine (55a) towards metalation in the presence or absence of BF_3·OEt_2.

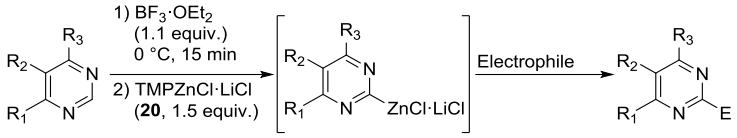
4-Butoxypyrimidine (**55b**) could also be selectively metalated in position 2 by pre-treating it with BF_3·OEt_2 (1.1 equiv.; 0 °C, 15 min) and using TMPZnCl·LiCl (**20**, 1.5 equiv., -20 °C, 1 h). After iodolysis the disubstituted pyrimine **56d** was obtained in 86% yield (Scheme 34). In the absence of BF_3·OEt_2 the zincation also occured regioselective at position 2, however the conversion was low, even when an excess of base was used and the reaction time was extended to 48 h. Thus, after iodolysis, the compound **56d** was only isolated in 40% yield. Treating **55b** with TMPMgCl·LiCl (**14**) in the presence or absence of BF_3·OEt_2 only led to decomposition of the starting material.

[104] The conversion was determined by GC-analysis.



Scheme 34: Metalation of 4-butoxypyrimidine (**55b**) in the presence or absence of $BF_3 \cdot OEt_2$.

Table 6: Regioselective zincation of pyrimidine derivatives **55** in position 2.

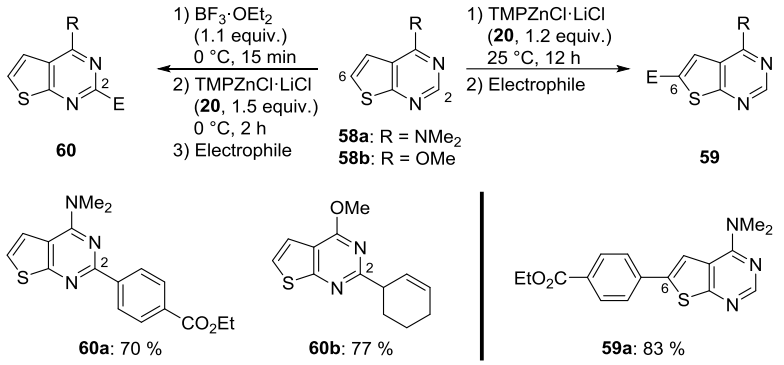


Entry	Substrate	Electrophile	Product	Yield[a] [%]
1	**55a**	**57b**	**56c**	89[b]
2	**55b**	**57c**	**56e**	66[b]
3	**55c**	**57b**	**56f**	70[b]
4	**55c**	**57d**	**56g**	69[b]
5	**55c**	**57a**	**56h**	71[c]
6	**55d**	I_2	**56i**	92
7	**55e**	I_2	**56j**	82
8	**55f**	I_2	**56k**	77
9	**55f**	**57d**	**56l**	67[b]

[a] Yield of isolated, analytically pure product. [b] 3 mol% of $Pd(dba)_2$ and 6 mol% of TFP were used. [c] Obtained by Cu-mediated allylation.

The zincated pyrimidine **55b** could also be cross-coupled with 1-iodo-3-(trifluoromethyl)benzene (**57c**) to yield the desired biaryl **56e** in 66% (Table 6, entry 2). This regioselectivite metalation is quite general and independent of the substitution pattern, as also the pyrimidines **55c-f** are all selectively zincated in position 2. After allylation, iodolysis or Pd-catalyzed cross-coupling the expected 2-functionalized pyrimidines **56f-l** are obtained in 67-92% yield (entries 3-9).

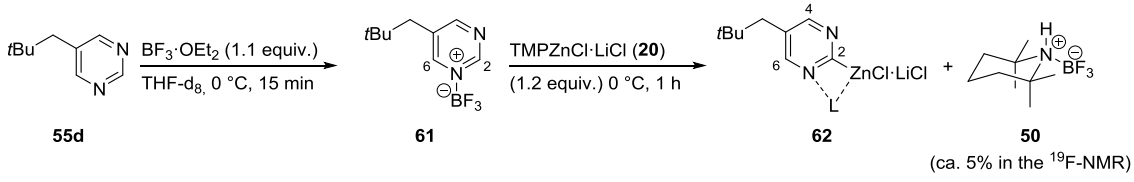
It was also possible to perform a regioselectivity switch at the condensed thienopyrimidines **58a-b** (Scheme 35). Thus, the treatment of **58a** (R = NMe_2) with TMPZnCl·LiCl (**20**) led to a smooth deprotonation of the most acidic proton of **58a** (i.e. position 6) giving after *Negishi* cross-coupling with **57d** the 6-arylated product **59a** in 83% yield. Alternatively, addition of BF_3·OEt_2 to **58a-b** followed by TMPZnCl·LiCl (**20**) leads to a regioselective zincation at position 2 (>10:1) of the pyrimidine ring. Pd-catalyzed cross-coupling or a Cu-mediated allylation furnishes the 2-functionalized thienopyrimidines **60a-b** in 70-77% yield.



Scheme 35: Switchable, regioselective metalation of the thienopyrimidines **58a** and **58b**.

3.3. NMR-Studies of BF_3-Activated Pyrimidine 55d

To gain some structural information of the BF_3-activated and zincated pyrimidines we decided to investigate the metalation of the pyrimidine **55d** *via* NMR-spectroscopy. Therefore the pyrimidine **55d** was treated with 1.1 equiv. of BF_3·OEt_2 in deuterated THF and the resulting aduct **61** was subjected to ^{1}H-, ^{11}B-, ^{13}C- and ^{19}F-NMR spectroscopy (Scheme 36). The coordination of the BF_3 group to the pyrimidyl nitrogen atom could easily be verified in the ^{13}C-NMR spectrum, where the C2 and the C6 carbon atoms show a distinct coupling to the fluorine atoms ($^{3}J_{19F\text{-}13C}$ = 2.8 and 2.0 Hz).



Scheme 36: BF_3-activation and zincation of pyrimidine **55d**.

The base **20** was added and the formed zincated species **62** was investigated *via* NMR spectroscopy. The metalated reagent definitely proved to be a zinc species, since there was no detectable interaction

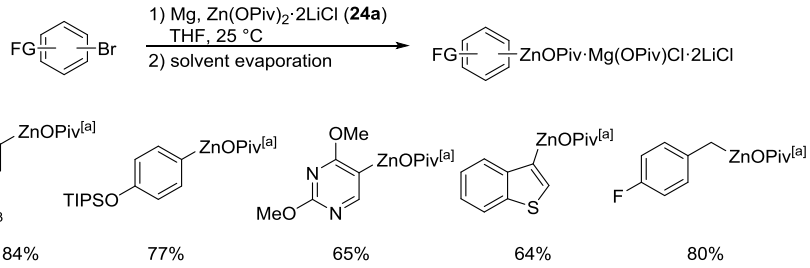
between the pyrimidine moiety and the BF_3 group, which clearly indicates that there is no transmetalation from zinc to boron, although the C-B would be thermodynamically favored being slightly more covalent.[105] Moreover, the zinc species **62** proved to be nonsymmetrical, *i.e* the hydrogen and carbon atoms at position 4 and 6 exhibit different chemical shifts. This indicates that some ligand coordinates to the zinc reagent making it unsymmetrical. The nature of this ligand could not be completely clarified, but a BF_3 coordination could be excluded, since no evidence for this was visible in the NMR spectra. Remarkably, what could be detected were small amounts of the TMPH-BF_3 adduct **50** (see B2.3), however this does not seem to be the major BF_3 species.

[105] Electronegativity (according to the Pauling-scale): Zn: 1.65; B: 2.04; C: 2.55 from L. Pauling, *The Nature of the Chemical Bond and the Structure of molecules and Crystals: An Introduction to Modern Structural Chemistry, 3rd ed.*, Cornell University Press, New York, **1960**, Chapter 3.

4. TMPZnOPiv·LiCl: A New Base for the Preparation of Air-Stable Solid Zinc Pivalates of Sensitive Aromatics and Heteroaromatics

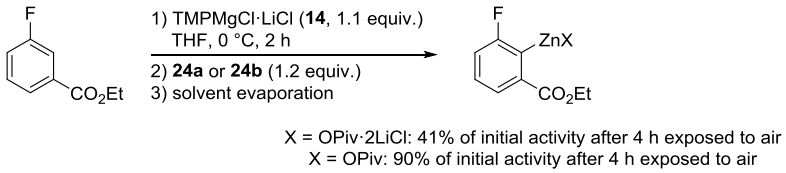
4.1. Introduction

Organozinc reagents hold a special position among organometallics due to their compatibility with a wide range of sensitive functional groups.[12b,106] In addition, they are valuable synthetic tools in C-C bond formation reactions, *via* transition-metal catalyzed transformations.[28a,64,107] However, a major drawback is their instability when exposed to air and the pyrophoric properties of some of the smaller alkylic derivatives. *Knochel* and coworkers recently described the preparation of aryl- and heteroaryl-zinc pivalates which are easy-to-handle solids with exceptional stability when exposed to air.[67,68] These zinc reagents have been prepared *via*, either Mg insertion in the presence of $Zn(OPiv)_2$·2LiCl (**24a**, Scheme 37)[67] or directed metalation using TMPMgCl·LiCl (**14**) and subsequent transmetalation to zinc (Scheme 38).[68]



Scheme 37: Preparation of solid functionalized zinc pivalates from *via* Mg insertion. [a] Complexed Mg(OPiv)Cl and LiCl are omitted for clarity

When the transmetalation of the magnesiated species was performed using the LiCl-free $Zn(OPiv)_2$ (**24b**) instead of **24a** this stability towards air is further improved, since LiCl is known to be highly hygroscopic.



Scheme 38: Preparation of aryl zinc pivalate by metalation with **14** followed by transmetalation with **24a** or **24b**

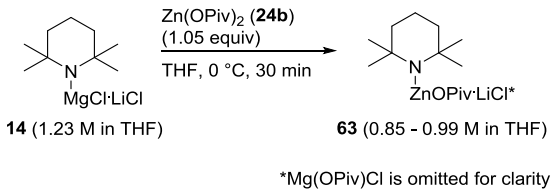
However, none of the methods above can be applied efficiently when sensitive functionalities, such as an aldehyde, a nitro group or other electron-withdrawing groups, are present. To overcome this limitation, we envisioned the use of a milder zinc amide base, as these are known to provide zinc

[106] a) P. Knochel, J. Almena, P. Jones, *Tetrahedron* **1998**, *54*, 8275; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem., Int. Ed.* **2000**, *39*, 4115.
[107] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.

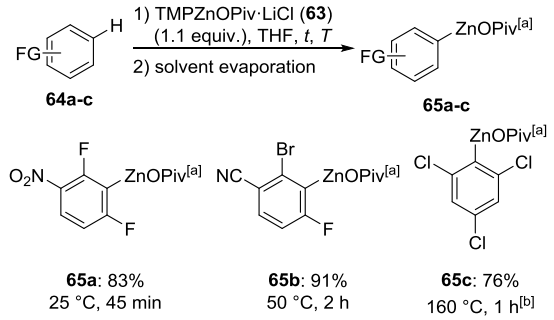
reagents which are compatible with most functionalities. The zinc base would have to contain the stabilizing pivalate salt since a transmetalation cannot be performed.

4.2. Preparation of Air-Stable Solid Zinc Pivalates using TMPZnOPiv·LiCl

We were able to prepare a new mild zinc amide base TMPZnOPiv·Mg(OPiv)Cl·LiCl (**63**)[108] which was compatible with functionalities like nitro groups, aldehydes or sensitive heteroaromatic rings. In addition, we showed that the new base **63** provided fast and efficient access, after removal of the solvent, to solid zinc pivalates, which exhibit significant tolerance towards hydrolysis or oxidation after air-exposure. TMPZnOPiv·LiCl (**63**) is prepared by addition of solid $Zn(OPiv)_2$ (1.05 equiv., 0 °C) to a solution of TMPMgCl·LiCl (**14**, 1.23 M in THF) and subsequent dilution with dry THF until a clear solution arises (final concentration: 0.85 – 0.99 M, Scheme 39).



Scheme 39: Preparation of the new zinc amide base TMPZnOPiv·LiCl (**63**) from TMPMgCl·LiCl (**14**).



Scheme 40: Preparation of aromatic zinc pivalates **65a-c** using TMPZnOPiv·LiCl (**63**). [a] OPiv = $Cl·Mg(OPiv)_2·LiCl$ see also B5. [b] MWI was used.

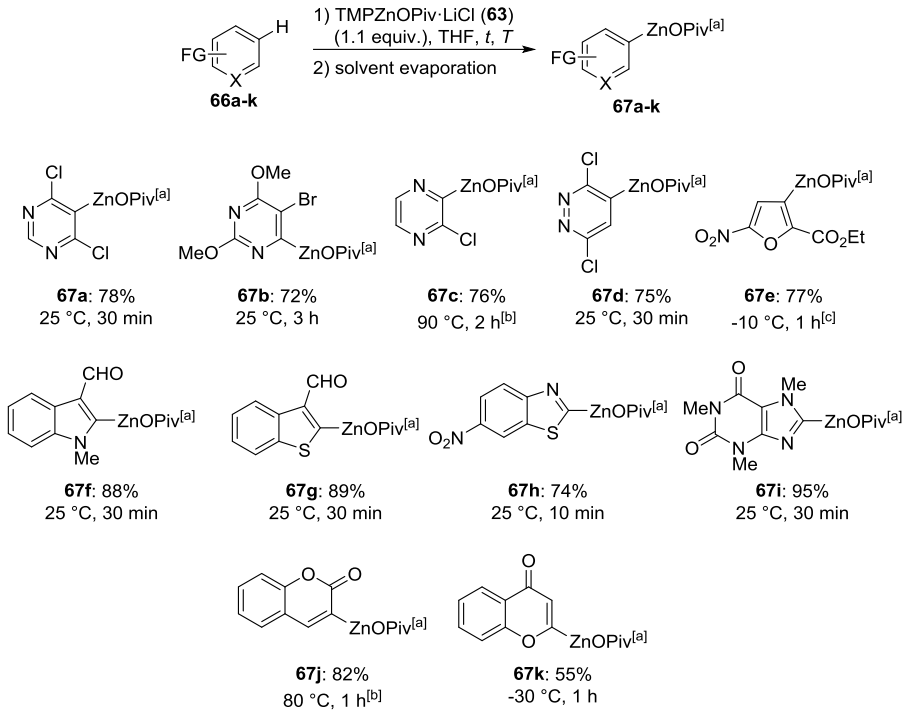
The new zinc amide base **63** was tested for the metalation of a broad range of aromatic and heteroaromatic substrates bearing sensitive functionalities and of heteroaromatics prone to fragmentation. In most cases, the metalation proceeded with excellent regio- and chemo-selectivity, in short reaction times (< 2 h), using 1.1 to 2.0 equiv. of the base at 25 °C or by mild heating to 50 °C. After removal of the solvent under high vacuum (0.1 mbar, 3 h), the zinc reagents were obtained as fine powders.[109] In this way, the aromatic compounds **64a-c** could be readily transformend into the

[108] For the detailed structure of the generated zinc reagnets see B5

[109] Typical titration via iodolysis was not possible for most of the solid zinc pivalates due to their deep red or brown color. In these cases the content of active zinc species was determined by GC-analysis and calculation of the iodinated compound derived by iodolysis of a certain amount of zinc pivalate, based on a calibration curve using an external standard. See C. Experimental Section.

corresponding zinc pivalates **65a-c** in 76 to 91% yield (Scheme 40). Remarkably, the base **63** could also be used under very harsh conditions. Thus the trichlorobenzene **65c** was metalated using microwave irradiation (MWI) at 160 °C to give the desired zinc pivalate in good yield.

The zincation of heteraromatic substrates proved to be quite general and could be performed under mild conditions and the solid zinc reagents were obtained in good yields (Scheme 41). Thus, the diazines **66a-d** were zincated by **63** (1.1 equiv.) at 25 °C or, using MWI, at 90 °C within 0.5 – 3 h to give the heteroaromatic zinc reagents **67a-d** in 72-76% yield. Also the sensitive ethyl 5-nitrofuran-2-carboxylate (**66e**) could be metalated using 2.0 equiv. of TMPZnCl·LiCl (**63**) at -10 °C within 1 h to yield the zincated furan **67e** in 77% yield. The zincation also worked at ambient temperature on the aldehydes **66f** and **66g**, as well as on 6-nitrobenzothiazole (**66h**) and caffeine (**66i**). Coumarin (**66j**) was deprotonated using MWI at 80 °C for 1 h to give the zincated product **67j** in 82% yield. Finally, also chromone (**66k**) could be regioselectively metalated with TMPZnOPiv·LiCl (**63**), exclusively at the *beta*-position to the carbonyl group (-30 °C, 1 h), after preactivation with $BF_3{\cdot}OEt_2$.[62b]

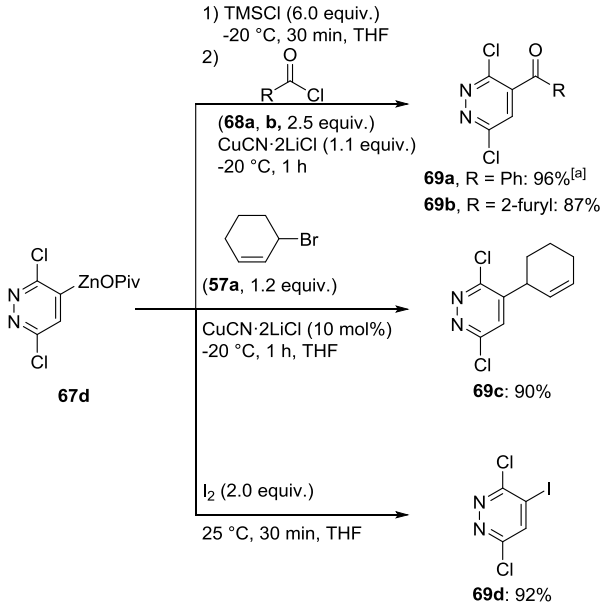


Scheme 41: Preparation of heteroaromatic zinc pivalates **67a-k** using TMPZnOPiv·LiCl (**63**). [a] OPiv = $Cl{\cdot}Mg(OPiv)_2{\cdot}LiCl$ see also B5. [b] MWI was used [c] 2.0 equiv. of **63** were used.

4.3. Reactions of Air-Stable Solid Zinc Pivalates

The reactivity of the thus obtained zinc reagents was then studied in various reactions with electrophiles, such as *Negishi* cross-coupling, copper mediated allylation[110] or acylation reactions.[28a,111] While cross-couplings and copper catalyzed allylation reactions proceeded readily (vide infra), copper mediated acylation reactions proved to be problematic. Thus, the reactions with various acyl chlorides did only work in certain cases (Scheme 42 and Scheme 43), depending on the zinc reagent and/or the acyl chloride, and seemed not to be general. We assumed that the acyl chlorides might form a mixed anhydride with the pivalate anion $PivO^-$ which is significantly less reactive than the acyl chloride itself and therefore in some cases no or only very slow conversion to the desired products was observed. This obstacle could be overcome by the addition of an excess of TMSCl (6.0 equiv.). We assume that by addition of TMSCl the free $PivO^-$ is trapped in the form of the silylester PivOTMS which does not undergo the mixed anhydride formation anymore.

Thus, in the presence of TMSCl (6.0 equiv.) and stoichiometric amounts of CuCN·2LiCl the pyridazine **67d** reacted readily with benzoylchloride (**68a**) and 2-furoyl chloride (**68b**) to the desired ketones **69a** and **69b** in 96 and 87% yield, respectively (Scheme 42). The allylation reaction of **67d** with 3-bromocyclohex-1-ene (**57a**, 1.2 equiv.) in the presence of catalytic amounts of CuCN·2LiCl gave the allylated product **69c** in 90% yield. Finally, iodolysis of **67d** gave the trihalogenated diazine **67d** in 92% yield.

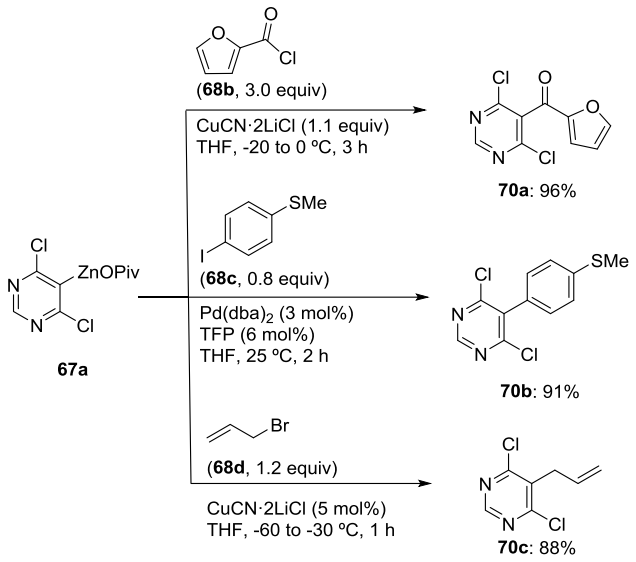


Scheme 42: Reactions of functionalized organozinc reagent **67d** with various electrophiles. [a] In the absence of TMSCl only trace amounts of **69a** were observed.

[110] a) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379; b) F. Dübner, P. Knochel *Tetrahedron*, **2000**, *41*, 9233; c) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.*, **2001,** *3*, 1169; d) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765; e) K. Geurts, S. P. Fletcher, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Pure Appl. Chem.*, **2008**, *5*, 1025; f) E. Erdik, M. Koçoğlu, *J. Organomet. Chem.* **2009**, *694*, 1890.

[111] a) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1982**, *106*, 3368; b) P. Knochel, S. A. Rao, *J. Am. Chem. Soc.* **1990**, *112*, 6146.

Remarkably, the zincated pyrimidine **67a** underwent the acylation reaction with 2-furoyl chloride (**68b**) also in the absence of TMSCl to give the ketone **70a** in 96% yield (Scheme 43). Also a *Negishi* cross-coupling with 4-iodothioanisole (**68c**) could be performed using $Pd(dba)_2$ (3 mol%) and TFP (6 mol%) (dba = dibenzylideneacetone, TFP = Tri(2-furyl)phosphine)[112] to yield the biaryl **70b** in 91%. A copper catalyzed allylation reaction with allylbromide (**68d**) furnished the desired product **70c** in 88% yield.

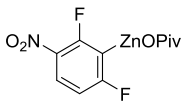
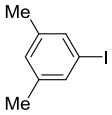
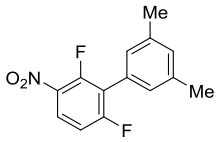
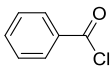
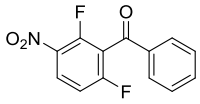
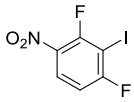
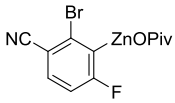
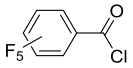
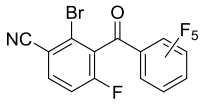
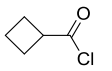
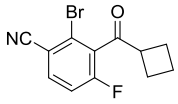
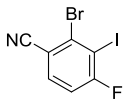
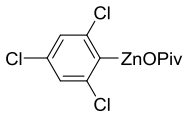
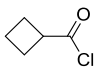
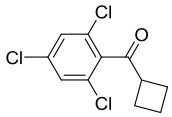
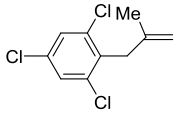


Scheme 43: Reactivity of **67a** towards various electrophiles.

The reactivity of the aromatic zinc pivalates **65a-c** towards various electrophiles proved to be excellent (Table 7). Therefore, it was possible to perform a Pd-catalyzed cross-coupling of **65a** with 1-iodo-3,5-dimethylbenzene (**68e**) as well as a copper mediated acylation with benzoylchloride (**68a**) and a iodolysis to give the products **71a-c** in 59 to 98% yields (entries 1-3). Also **65b** could be readily acylated in the presence of an excess of TMSCl and stoichiometric amounts of CuCN·2LiCl yielding after reaction with the perfluorated acyl chloride **68f** or cyclobutoylchloride (**68g**) the desired ketones **71d-e** in 95% each (entries 4-5). Iodolyis of **65b** gave the tetrasubstituted benzene **71f** in 91% (entry 6). The trichlorobenze derivative **65c** could also be acylated with cyclobutoylchloride (**68g**) or allylated using 2-methyl-allylbromide (**68h**) and the desired functionalized aromatics **71g-h** wre obtained in excellent yields (entries 7-8)

[112] a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585; b) I. Klement, M. Rottlander, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

Table 7: Reactions of aromatic organozinc pivalates **65a-c** with various electrophiles.

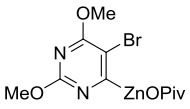
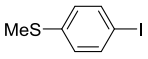
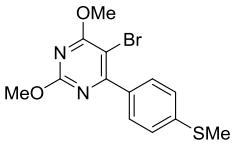
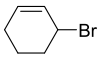
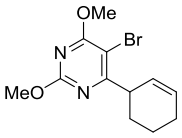
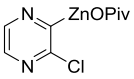
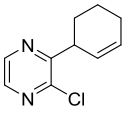
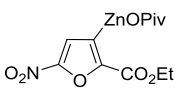
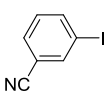
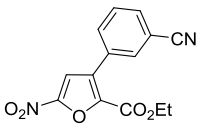
Entry	Substrate	Electrophile	Product	Yield[a] [%]
				
1	**65a**	**68e**	**71a**	98[b]
				
2	**65a**	**68a**	**71b**	59[c]
				
3	**65a**	I_2	**71c**	98
				
4	**65b**	**68f**	**71d**	95[c]
				
5	**65b**	**68g**	**71e**	95[c]
				
6	**65b**	I_2	**71f**	91
				
7	**65c**	**68g**	**71g**	95
				
8	**65c**	**68h**	**71h**	94

[a] Isolated yield of analytically pure product. [b] Obtained by cross-coupling in the presence of $Pd(dba)_2$ (3 mol%) and TFP (6 mol%). [c] 1.1 equiv. CuCN·2LiCl and 6.0 equiv. TMSCl were used. [d] 10 mol% CuCN·2LiCl were used.

Also, the heteroaromatic zinc reagents **67b-c,e-k** proved to be excellent nucleophiles in various reactions. Thus, the zincated pyrimidine **67b** underwent a smooth Pd-catalyzed cross-coupling with 4-iodothioanisol (**68c**) and a copper catalyzed allylation reaction with 3-bromocyclohexene (**57a**) to furnish the desired full functionalized pyrimidines **72a** and **72b** in 81 and 89%, respectively (Table 8, entries 1-2). The zincated chloropyrazine **67c** could also be allylated using **57a** or iodinated to give the

disubstituted derivative **72c** and **72d** in excellent yields (entries 3-4). The furan derivative **67e** and the indole **67f** both could be cross-coupled with 3-iodobenzonitrile (**68i**) and ethyl 4-iodobenzoate (**57d**), respectively, and the biaryls **72e** and **72g** were obtained in 66 to 91% (entries 5 and 7). CuCN·2LiCl-catalyzed allylation of the furan **67e** and the aldehydes **67f** and **67g** with 3-bromocyclohexene (**57a**) furnished the desired alkenes **72f,h,i** in70-98% yield (entries 6, 8 and 9). Iodolysis of the benzothiophene **67g** provided the disubstituted product **72j** in 89% (entry 10). A Pd-catalyzed cross coupling of the benzothiazole **67h** with the *E*-alkenyl iodide **68j**[113] furnished the product **72k** in 95% yield and with complete retention of the double-bond configuration (entry 11). Addition of 2-bromomethylpropene (**68h**) to **67h**, in the presence of 10 mol% CuCN·2LiCl, led to the allylated derivative **72l** in 88% yield (entry 12). The copper mediated acylation in the presence of an excess of TMSCl of the zincated caffeine (**67i**) with 3,4-difluorobenzoyl chloride (**68k**) afforded the ketone **72m** in 73% (entry 13) and after copper catalyzed allylation allylation of **67i** with 2-bromomethylpropene (**68h**) the alkene **72n** was obtained in 94% yield (entry 14).The zincated coumarin **67j** was cross-coupled with the iodide **57c** allylated with allylbromide (**68d**) and iodinated and the desired 3-substituted coumarin derivatives **72o-q** were isolated in 92 to 98% yield (entries 15-17). Finally, cross-coupling of the chromone **67k** with the iodide **68l** and acylation with cyclohexanoyl chloride (**68m**) furnished the biaryl **72r** and the ketone **72s** in 70 and 78% yield, respectively (entries 18-19).

Table 8: Reactions of heterocyclic zinc pivalates of with various electrophiles.

Entry	Substrate	Electrophile	Product	Yield[a] [%]
1	 **67b**	 **68c**	 **72a**	81[b]
2	**67b**	 **57a**	 **72b**	89[c]
3	 **67c**	**57a**	 **72c**	91[c]
4	**67c**	I_2	 **72d**	93
5	 **67e**	 **68i**	 **72e**	66[b]

[113] Alkenyl iodide **68j** was prepared in 87% yield according to the procedure described in: V. R. Krishnamurthy, A. Dougherty, C. A. Haller, E. L. Chaikof, *J. Org. Chem.* **2011**, *76*, 5543.

Table 8 continued.

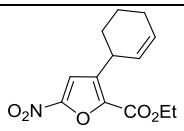
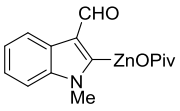
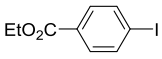
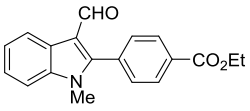
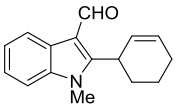
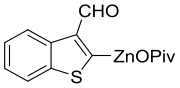
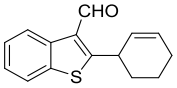
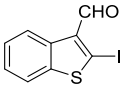
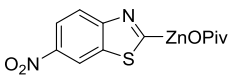
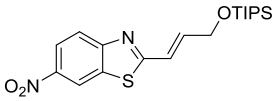
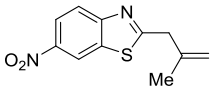
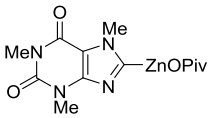
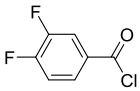
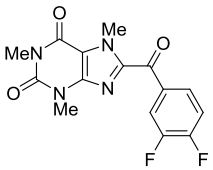
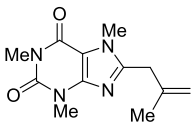
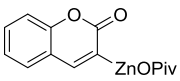
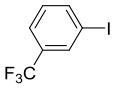
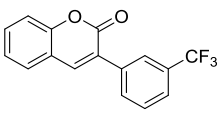
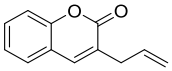
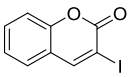
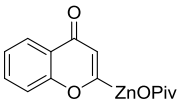
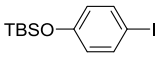
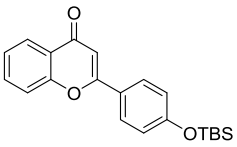
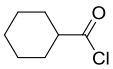
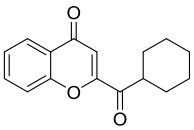
Entry	Substrate	Electrophile	Product	Yield[a] [%]
6	 **67e**	**57a**	 **72f**	70[c]
7	 **67f**	 **57d**	 **72g**	91[b]
8	 **67f**	**57a**	 **72h**	98[c]
9	 **67g**	**57a**	 **72i**	95[c]
10	**67g**	I_2	 **72j**	89
11	 **67h**	**68j** (> 99% *E*)	 **72k** (> 99% *E*)	95[b]
12	**67h**	 **68h**	 **72l**	88[c]
13	 **67i**	 **68k**	 **72m**	73[d]
14	**67i**	 **68h**	 **72n**	94[c]
15	 **67j**	 **57c**	 **72o**	96[b]

Table 8 continued.

Entry	Substrate	Electrophile	Product	Yield[a] [%]
16	**67j**		 **72p**	98[c]
17	**67j**	I_2	 **72q**	92
18	 **67k**	 **68l**	 **72r**	78[b]
19	**67k**	 **68m**	 **72s**	70[d]

[a] Yield of isolated, analytically pure product. [b] Obtained by cross-coupling in the presence of $Pd(dba)_2$ (3 mol%) and TFP (6 mol%). [c] 10 mol% CuCN·2LiCl were used [d] 1.1 equiv. CuCN·2LiCl and 6.0 equiv. TMSCl were used.

4.4. Air-Stability of the Solid Zinc Pivalates

The vast majority of the organozinc pivalates tested exhibited exceptional air-stability. For instance, after 4 h air exposure the aromatic zinc pivalates **65a** and **65b** still showed 97 and 86%, respectively, of their initial activity (Table 9, entry 1-2).[109] Also the heterocyclic reagents **67a,b,d-j,k** were tested for their stability towards air exposure (entries 3-11). Most of the heteroaromatic zinc pivalates showed an activity loss of less than five percent after being exposed for 4 h to air (entries 3, 5-8). Moreover, the zinc reagents **67f,h.j,k** even showed some remaining activity after 24 h of air exposure (42-52% of initial activity, entries 7, 9-11). When leaving the pyrimidine derivatives **67a,b** in air for 24 h even 69 and 72%, respectively, of the original concentrations of active zinc species were obtained (entries 3-4).

Table 9: Stability studies of organozinc reagents towards air.

	Time in air [h]	0	1	2	4	24
Entry	Zinc reagent	Percentage of the active aryl- or heteroarylzinc species[109]				
1	**65a**	100	100	98	97	-[a]
2	**65b**	100	95	92	86	-[a]
3	**67a**	100	99	97	95	69
4	**67b**	100	100	97	94	72
5	**67d**	100	99	97	95	-[a]
6	**67e**	100	97	96	95	-[a]
7	**67f**	100	99	98	96	48
8	**67g**	100	99	98	95	-[a]
9	**67h**	100	100	96	94	52
10	**67j**	100	93	91	88	51
11	**67k**	100	98	95	90	42

[a] After 24 h the organozinc compound had become a sticky/oily substance which could not be weighted properly and was therefore not titrated again.

5. Structural Insights on Organozinc Pivalate Reagents

5.1. Introduction

As already described in A2, salt additives can activate but also deactivate organometallic compounds.[34,114] Metal halides like LiCl and $MgCl_2$ can enhance the reactivity of organometallic compounds within their THF solutions as examplified in $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**19**). And as described in B4 the magnesium-zinc pivalate systems "RZnOPiv·Mg(OPiv)X·nLiCl (R = aryl, heteroaryl or benzyl; X = Cl, Br or I) show a high stability towards attack by air and moisture, especially when isolated as solids (Table 9).[67,68] Rapid decomposition is the normal outcome when such organometallic compounds are exposed to these antagonists since Met-C bonds are generally thermodynamically unstable with respect to the Met-O bonds that form as a result, making inert atmosphere protocols mandatory. While synthetic applications of these salt-stabilized organo zinc compounds in a variety of C-C bond formation reactions have been demonstrated (vide supra) their multicomponent heterotrimetallic-heterotrianionic compositions make for highly complicated chemistry. To begin unravelling this complexity the goal was to elucidate the structures and roles of the compounds generated in these challenging pivalate mixtures.

5.2. Elucidating the Structure and Role of the Existing Compounds [115]

The first question that was pursued was what the exact nature of the organozinc pivalates, formed by transmetalation of the RMgX species with $Zn(OPiv)_2{\cdot}nLiCl$ (**24**), was. Usually, the formed reagents are represented by the general formula RZnOPiv·Mg(OPiv)Cl·nLiCl (vide supra) implying the formation of a mixed Mg salt and two distinct pivalate anions (Equation 1). This transmetalation was tested by investigating the arylester reagent $EtO_2C(p\text{-}C_6H_4)MgCl{\cdot}LiCl$ (**73**) and zinc pivalate (**24b**) in THF solution by NMR spectroscopy.

$$RMgCl + Zn(OPiv)_2 \xrightarrow{LiCl} RZn(OPiv) + Mg(OPiv)Cl \quad (1)$$

Surprisingly, ^{1}H-NMR and COSY spectra of this mixture revealed only one pivalate signal and two distinct sets of aryl signals, in contrast to the two pivalate and one set of aryl signals expected from the transmetalation.[116] ^{1}H-DOSY-NMR[117] experiments implied the presence of two major species of which one could be identified as ethyl benzoate, presumably from partial hydrolysis of the zinc reagent due to

[114] a) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc*. **2006**, 128, 9998; b) M. Hatano, K. Ishihara in *Acid Catalysis in Modern Organic Synthesis* Vol. 1, (Eds.: H. Yamamoto, K. Ishihara), Wiley-VCH, Weinheim, **2008**, pp. 175 c) L. Jin, C. Liu, J. Liu, F. Hu, Y. Lan, A. S. Batsanov, J. A. K. Howard, T. D. Marder, A. Lei, *J. Am. Chem. Soc.* **2009**, 131, 16656; d) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *Chem. Commun.* **2010**, 46, 2674; e) M. Hatano, S. Suzuki, K. Ishihara, *Synlett*, **2010**, 321; f) E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2011**, 50, 6448.

[115] The NMR experiments and X-ray crystal-structures described in this chapter have been performed by the *Mulvey/Hevia* group at the University of Strathclyde, Glasgow; for more detailed information check: A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, DOI: 10.1002/anie.201309841.

[116] See D Appendix 1

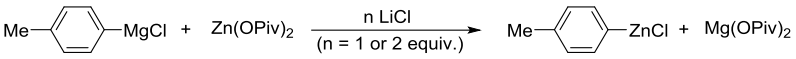
[117] For DOSY reviews, see: a) D. Li, I. Keresztes, R. Hopson, P. Williard, *Acc. Chem. Res.* **2009**, *42*, 270; b) A. Macchioni, G. Ciancaleoni, C. Zuccaccia, D. Zuccaccia, *Chem. Soc. Rev.* **2008**, *37*, 479; c) B. Antalek, *Concepts Magn. Reson. Part A* **2007**, *30*, 219.

prolonged storage of the sample prior to the NMR studies. Supporting this assumption was the crystallization of a mixed cluster that can be formalized as $[\{Mg(OPiv)_2\}_5\{Mg(OH)_2\}(MgO)\cdot 4THF]$[115] from the THF solution. Apart from the OH^- and O^{2-} incorporation the 1:2 stoichiometry of Mg/OPiv is the most telling feature, since from Equation 1 a Mg/OPiv ratio of 1:1 would be expected. These results indicate two things: The Mg pivalate produced in the reaction could act as a moisture/oxygen scavenger and the transmetalation process seems to go beyond the monopivalate Mg(OPiv)Cl to the bispivalate $Mg(OPiv)_2$ (**74**). To investigate these assumptions attempts were made to prepare $Mg(OPiv)_2$ (**74**) by an alternative method by deprotonating pivalic acid with Bu_2Mg (Equation 2).

$$2\ PivOH + MgBu_2 \longrightarrow \underset{\textbf{74'}}{[\{Mg_6(OPiv)_{12}\}(MgO)_2]} \qquad (2)$$

X-ray crystallography however showed, that the product was not the desired product **74** but the O^{2-} contaminated product **74'**. It turned out that the O^{2-} contamination came from the commercially purchased Bu_2Mg. The desired $Mg(OPiv)_2$ (**74**) was eventually prepared by using self-prepared $Mg(CH_2SiMe_3)_2$ under strict anhydrous and oxygen free conditions. This result suggests that $Mg(OPiv)_2$ (**74**) could be functioning as a decontaminating agent mopping up any OH^- or related ions by trapping them in clusters, thus protecting the zinc organometallic species.

Then the transmetalation was monitored at the less sensitive *p*-tolyl derivative (Scheme 44). For comparison the spectra of the separately prepared compounds Me(*p*-C_6H_4)MgCl·LiCl (**75**) and Me(*p*-C_6H_4)ZnCl·LiCl (**76a**) were also recorded. Most informatively ^{13}C NMR spectra revealed well separated C_{ipso} resonances for **75** (165.8 ppm) and **76a** (153.0 ppm) (Figure 4).



Scheme 44: Transmetalation of *p*-tolylMgCl with $Zn(OPiv)_2$ an in the presence of LiCl.

Most striking is the fact that the mixture of Me(*p*-C_6H_4)MgCl (**75**) and $Zn(OPiv)_2\cdot n$LiCl (n = 1 or 2) shows only aromatic resonances matching those of Me(*p*-C_6H_4)ZnCl·LiCl (**76a**) and none corresponding to the magnesium species **75**. Also, the ^{1}H-DOSY-NMR spectrum of the reaction mixture revealed that the aromatic resonances and pivalate resonance belong to distinct molecules.[116]

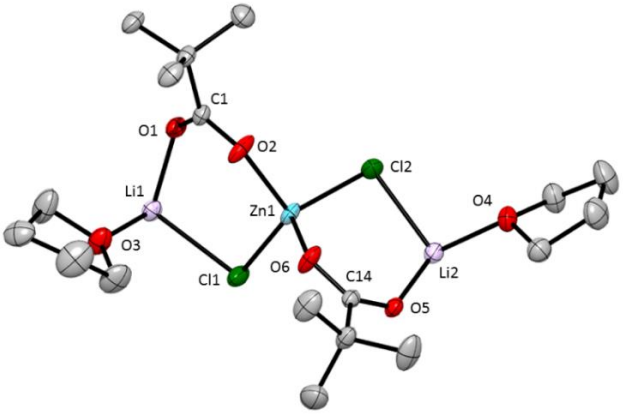


Figure 3: Molecular structure of $[(THF)_2Li_2(\mu\text{-}Cl)_2(\mu\text{-}OPiv)_2Zn]$ (**24c**). Ellipsoids set at 50% probability; hydrogen atoms omitted for clarity.[115]

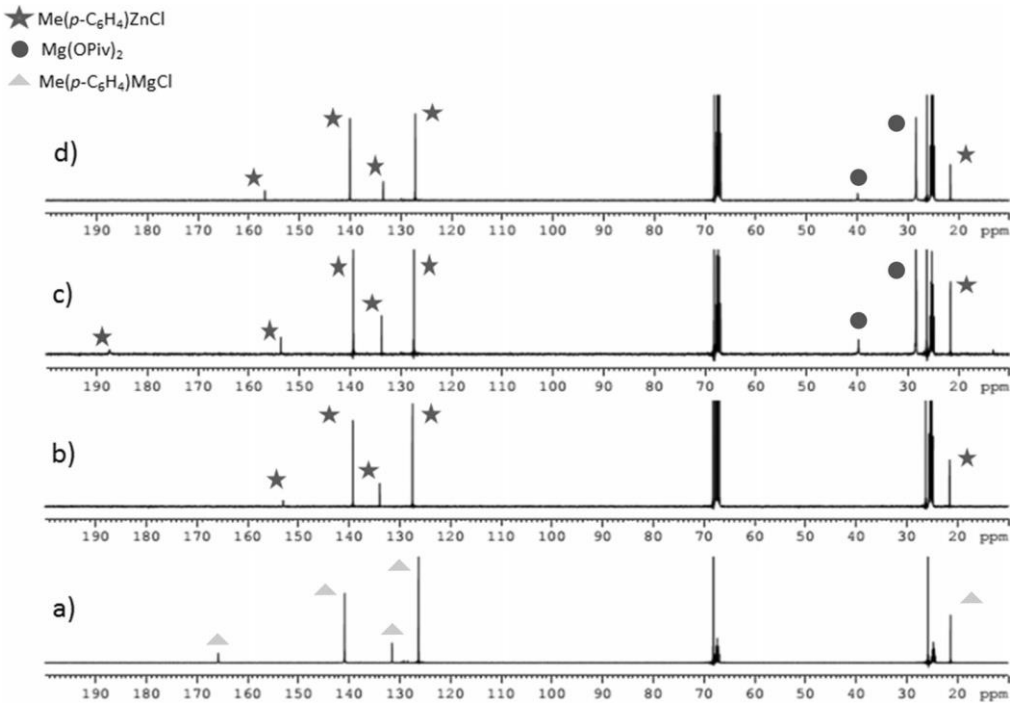


Figure 4: From bottom to top: ^{13}C-NMR spectrum of a) Me(*p*-C_6H_4)MgCl·LiCl (**75**), b) Me(*p*-C_6H_4)ZnCl·LiCl (**76a**), c) Zn(OPiv)$_2$·LiCl (**24c**) and Me(*p*-C_6H_4)MgCl (**75**), and d) Zn(OPiv)$_2$·2LiCl (**24a**) and Me(*p*-C_6H_4)MgCl in THF-d_8 at 25 °C.

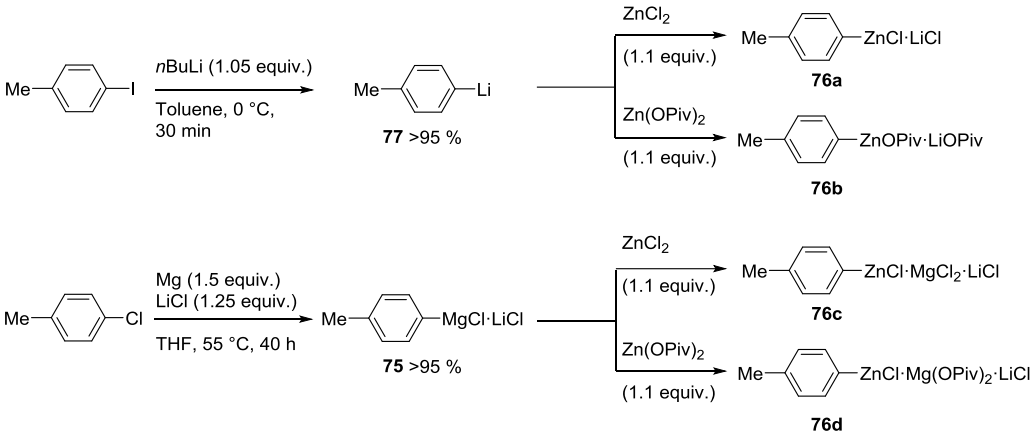
These observations indicate strongly that there is indeed a complete transmetalation of Zn(OPiv)$_2$ (**24b**) to Mg(OPiv)$_2$ (**74**) with Zn receiving the aryl and the Cl ligands. This assumption was further reinforced by the trapping of this Zn heteroleptic complex as its TMEDA solvate, (TMEDA)ZnMe(*p*-C_6H_4)Cl, by adding TMEDA to the original reaction mixture of Me(*p*-C_6H_4)ZnCl·LiCl (**76a**) and Mg(OPiv)$_2$ (**74**).[115]

Next the solubilizing effect of LiCl on the Zn(OPiv)$_2$ (**24b**) was investigated. The salt **24b** alone barely dissolves in THF, however when one equivalent of LiCl is added a clear solution forms within ca. 15 min. Crystals deposited from this solution turned out to be [(THF)$_2$Li$_2$(μ-Cl)$_2$(μ-OPiv)$_2$Zn] (**24c**, Figure 3). It can be assumed, that the enhanced solubility can be led back to the formation of this complex since the LiCl completes the coordination of the Lewis basic OPiv moiety and the Lewis acidic Zn atom.

5.3. Reactivity of Different Salts Containing *p*-Tolylzinc Reagents

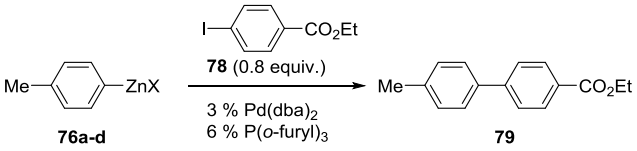
Next, we checked whether in addition to its stabilizing role Mg(OPiv)$_2$ (**74**) had any appreciable effect on the *Negishi* cross-coupling capability of the Me(*p*-C_6H_4)ZnX (X = Cl·LiCl, Cl·MgCl$_2$·LiCl, OPiv·LiOPiv, or Cl·Mg(OPiv)$_2$·LiCl) reagents. For this purpose we prepared (*p*-C_6H_4Me)MgCl·LiCl (**75**) *via* Mg insertion from 4-chlorotoluene and (*p*-C_6H_4Me)Li (**77**) from 4-iodotoluene *via* I/Li exchange (Scheme 45). These reagents were then each transmetalated using either ZnCl$_2$ or Zn(OPiv)$_2$ providing the zinc reagents **76a-d** (Scheme 45).

These organozinc compounds were then compared with respect to their reactivity in a cross-coupling reaction using ethyl 4-iodobenzoate (**78**) as electrophile and $Pd(dba)_2$ (3 mol%) and TFP (6 mol%) as catalyst system. As shown in Table 10 all cross-coupling reactions proceeded very fast at ambient temperature giving the biphenyl **79** in comparable yields of 89-94%.



Scheme 45: Preparation of (p-C_6H_4Me)ZnX with X = Cl·LiCl (**76a**), OPiv·LiOPiv (**76b**), Cl·$MgCl_2$·LiCl (**76c**), Cl·$Mg(OPiv)_2$·LiCl (**76d**).

Table 10: Reactivity of zinc reagents **76a-d** towards cross-coupling with ethyl 4-iodobenzoate (**78**).



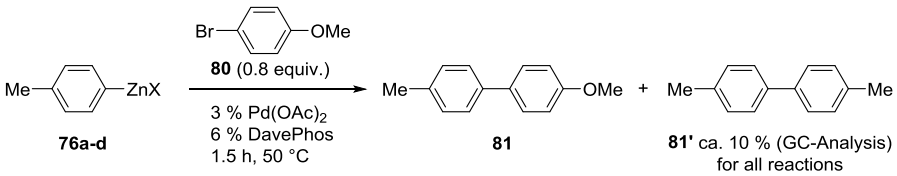
Entry	X	Reaction conditions	Isolated yield of **79** [%]
1	Cl·LiCl (**76a**)	25 °C, 30 min	94
2	OPiv·LiOPiv (**76b**).	25 °C, 30 min	93
3	Cl·$MgCl_2$·LiCl (**76c**)	25 °C, 30 min	91
4	Cl·$Mg(OPiv)_2$·LiCl (**76d**)	25 °C, 30 min	89

Since the reaction with ethyl 4-iodobenzoate showed no significant difference neither in reaction time nor in product yield, the reactivity was further studied with a less reactive electrophile such as 4-bromoanisole (**80**) to see if longer reaction times and higher temperatures lead to any significant differences in the reaction outcome. Also, the influence of the more polar solvent EtOAc was investigated and the effect of air on the cross-coupling capability. The cross-couplings with **80** (0.8 equiv.) in the presence of 3 mol% $Pd(OAc)_2$ and 6 mol% of DavePhos[118] in THF under argon gave the biphenyl **81** in 82 to 86% yield (Table 11, entries 1, 5, 9 and 13). Then the cross-couplings were performed in air in non-dried glassware but in dry THF. For the pivalate-free reactions the yield dropped slightly from 86 to 81% for reagent **76a** and from 85 to 77% for reagent **76c**, respectively (entries 2 and

[118] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc*. **1998**, *120*, 9722.

10). For the pivalate-containing reagents **76b** and **76d** however, the yield increased from 82 to 88% for both reagents (entries 6 and 14). When the cross-couplings were carried out in EtOAc and under argon the yields for the magnesium salt containing reagents **76c** and **76d** increased to 91% and to 85%, respectively (entries 11 and 15). However, the yield dropped slightly for both reagents when the reactions were performed in air in non-dried glassware (entries 12 and 16). Remarkably, when no magnesium salt was present, the cross-coupling in EtOAc did not work at all no matter if it was performed under argon or open to air (entries 3, 4, 7 and 8). GC-samples quenched with iodine showed that the metal species **76a** and **76b** did not decompose when the reaction was performed under argon, and the amount of electrophile did also not decrease significantly. Longer reaction time and a higher catalyst loading did not lead to any improvements. However, for the reactions carried out in air a slow decomposition of the metal species could be observed.

Table 11: Reactivity of zinc reagents **76a-d** towards cross-coupling with ethyl 4-bromoanisole (**80**).

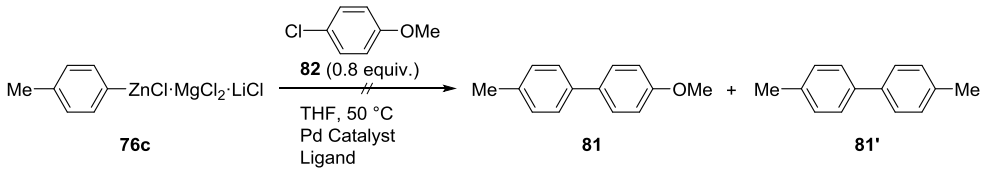


Entry	X	Solvent	Reaction Conditions	Isolated yield of **81** [%]
1	Cl·LiCl (**76a**)	THF	under Argon	86
2	Cl·LiCl (**76a**)	THF	in air	81
3	Cl·LiCl (**76a**)	EtOAc[a]	under Argon	only traces of **81**[b,c]
4	Cl·LiCl (**76a**)	EtOAc[a]	in air	only traces of **81**[b,c]
5	OPiv·LiOPiv (**76b**)	THF	under Argon	82
6	OPiv·LiOPiv (**76b**)	THF	in air	88
7	OPiv·LiOPiv (**76b**)	EtOAc[a]	under Argon	only traces of **81**[b,c]
8	OPiv·LiOPiv (**76b**)	EtOAc[a]	in air	only traces of **81**[b,c]
9	Cl·$MgCl_2$·LiCl (**76c**)	THF	under Argon	85
10	Cl·$MgCl_2$·LiCl (**76c**)	THF	in air	77
11	Cl·$MgCl_2$·LiCl (**76c**)	EtOAc[a]	under Argon	91
12	Cl·$MgCl_2$·LiCl (**76c**)	EtOAc[a]	in air	78
13	Cl·$Mg(OPiv)_2$·LiCl (**76d**)	THF	under Argon	82
14	Cl·$Mg(OPiv)_2$·LiCl (**76d**)	THF	in air	88
15	Cl·$Mg(OPiv)_2$·LiCl (**76d**)	EtOAc[a]	under Argon	85
16	Cl·$Mg(OPiv)_2$·LiCl (**76d**)	EtOAc[a]	in air	81

[a] EtOAc was purchased from Fluka as analytical grade reagent (99.9%) which was stored open to air and used without further drying. [b] GC-analysis of hydrolyzed/iodolyzed reaction aliquots was performed, no product was isolated. [c] The reaction was also performed with 6 mol% $Pd(OAc)_2$ and 12 mol% DavePhos and the reaction time was elongated to 24 h.

We also briefly examined the cross-coupling of Me(*p*-C_6H_4)ZnCl·$MgCl_2$·LiCl (**76c**) with the even less reactive electrophile 4-chloroanisole (**82**). However, we were unable to find a catalyst system where more than trace amounts of the desired product **81** could be observed using GC-analysis. In all cases the undesired side product **81'** was the major product (Table 12).

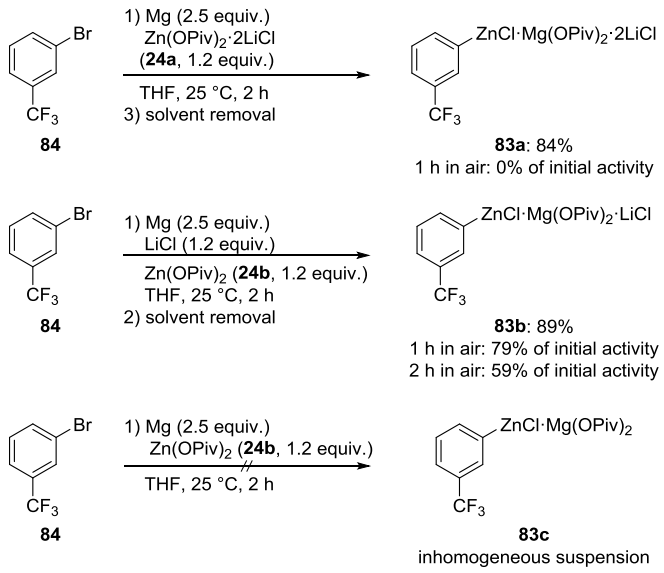
Table 12: Reactivity of zinc reagent **76c** towards cross-coupling with ethyl 4-chloroanisole (**82**).



Entry	Pd/Ligand	Reaction Time	Results[a]
1	$Pd(OAc)_2$ (3 mol%) SPhos (6 mol%)	45 h	only trace amounts of **81** ca. 25% of **81'**
2	$Pd(OAc)_2$ (3 mol%) DavePhos (6 mol%)	45 h	ca. 15% of **81** ca. 20% of **81'**
3	$Pd(OAc)_2$ (3 mol%) XPhos (6 mol%)	45 h	only trace amounts of **81** ca. 30% of **81'**
4	PEPPSI™-IPr	45 h	no reaction

[a] *via* GC-analysis of hydrolyzed reaction aliquots.

Next, the air stability of the zinc reagents **83a-c**, containing different amounts of LiCl was briefly investigated (Scheme 46). Therefore, Mg insertion reactions were performed on 1-bromo-3-(trifluoromethyl)benzene (**84**) in the presence of $Zn(OPiv)_2 \cdot 2LiCl$ (**24a**),[67] $Zn(OPiv)_2$ (**24b**) and 1.2 equivalents of LiCl or $Zn(OPiv)_2$ (**24b**) in the absence of LiCl. While the yield of the two LiCl containing reagents **83a** and **83b** was comparable, the Mg insertion in the absence of LiCl was very sluggish and did not go to full conversion due to the bad solubility of the reactants and **83c** could only be obtained as an inhomogeneous suspension.



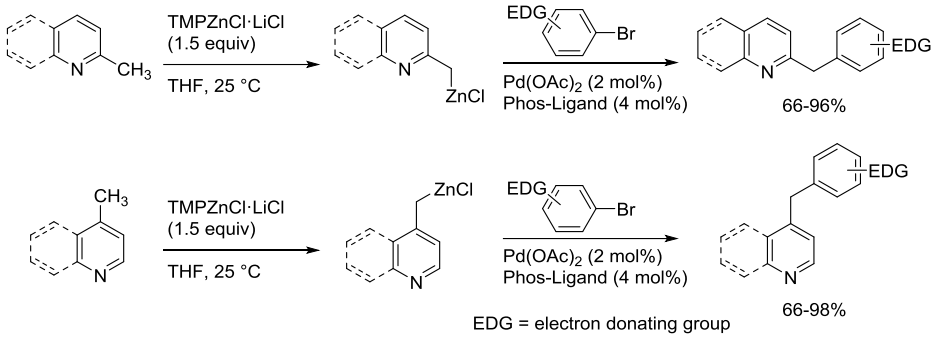
Scheme 46: Comparison of air stability of the organozinc species **83a-c**.

Remarkably, the stability towards air exposure increases drastically by reducing the amount of LiCl from two to one equivalents. Thus, when the reagent **84a** was exposed to air for one hour no active metalating species could be detected while the zinc reagent **84b** still exhibited 79% of its initial activity and after 2 h in air 59% of the original concentration was preserved. These results clearly indicate, that on the one hand the presence of LiCl is necessary for the solubility and reactivity of the organozinc pivalates, but that on the other hand the hygroscopic nature of LiCl diminishes the stability of the generated zinc reagents and therefore the amount should be kept at a minimum.

6. SUMMARY

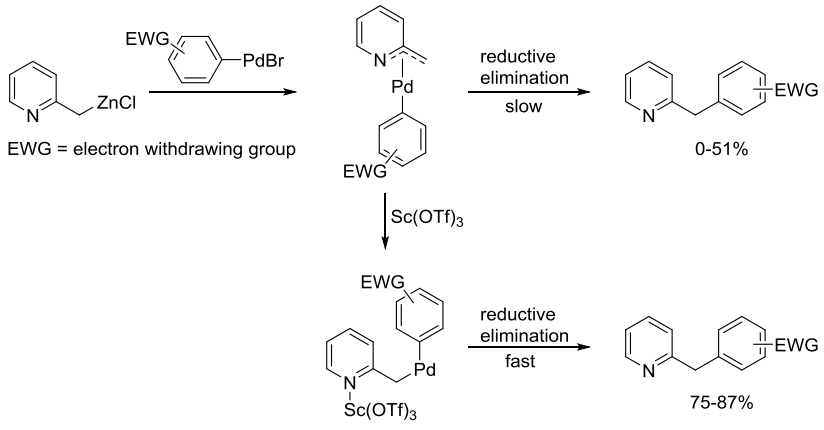
6.1. Benzylic Zinc Reagents of Pyridines and Quinolines for Cross-Couplings with Aryl Bromides

The very mild zinc base TMPZnCl·LiCl was successfully used for the regioselective benzylic metalation of a variety of methyl substituted pyridines and quinolines at ambient temperature. The resulting zinc reagents underwent smooth *Negishi* cross-coupling reactions with a plethora of electron rich aryl bromides using $Pd(OAc)_2$ or $Pd(O_2CCF_3)_2$ and an appropriate Phos-type ligand in good to excellent yields (Scheme 47).



Scheme 47: *Negishi* cross-coupling of benzyilic pyridyl zinc reagents with electron rich aryl bromides.

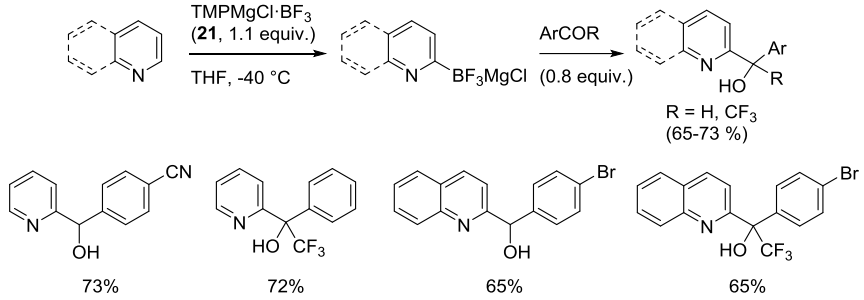
The cross-coupling reaction with electron poor aryl bromides proved to be difficult due to a hampered reductive elimination step of the intermediate palladium complex. This problem was overcome by the addition of catalytic amounts of $Sc(OTf)_3$, since this Lewis acid can complex to the pyridyl nitrogen and thus promote the reductive elimination. In the presence of $Sc(OTf)_3$ the cross-coupling of benzylic zinc reagents with electron poor aryl bromides proceeded readily to the desired products (Scheme 48).



Scheme 48: $Sc(OTf)_3$-promoted cross-coupling of benzyilic pyridyl zinc reagents with electron poor aryl bromides.

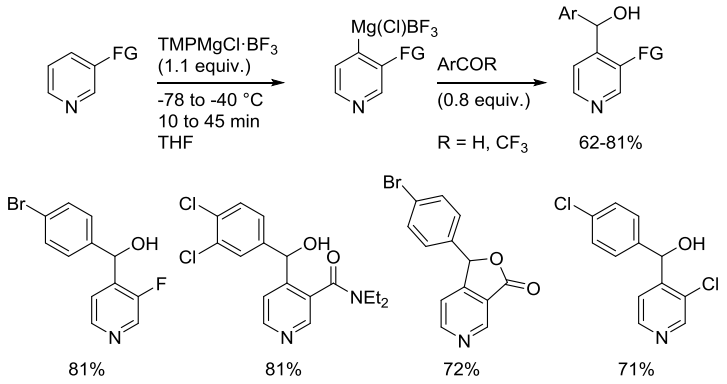
6.2. Metalating N-Heterocycles using the Frustrated Lewis Pair TMPMgCl·BF_3 Followed by Addition to Aromatic Aldehydes and Activated Ketones

The Lewis pair TMPMgCl·BF_3 has successfully been used for the deprotonation of pyridine, quinoline and pyrazine derivatives. The generated trifluoroborates could be added to various aromatic aldehydes and activated ketones in good yields without the need of a transition metal catalyst (Scheme 49).



Scheme 49: Addition of N-heteroaryl trifluoroborates to aldehydes and activated ketones.

Several 3-substituted pyridine derivatives were metalated by TMPMgCl·BF_3 in position 4 of the pyridine scaffold. The metalated intermediates reacted readily with a range of benzaldehyde derivatives to give the desired carbinoles in very good yields (Scheme 50).

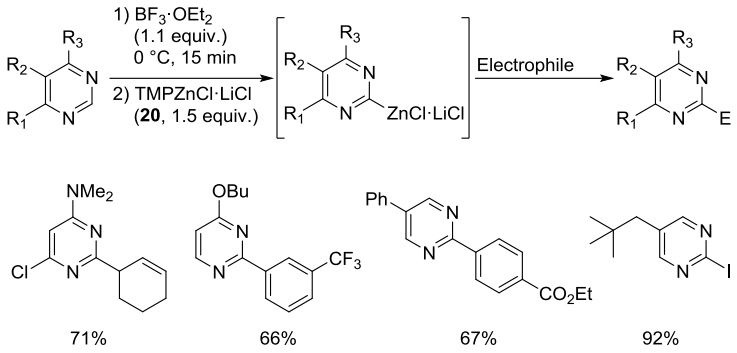


Scheme 50: Metalation of 3-substituted pyridines followed by trapping with aromatic aldehydes.

The structure of the metalated intermediate was investigated *via* ^{1}H-, ^{11}B-, ^{13}C- and ^{19}F-NMR studies. It turned out to be a magnesium species and not, as for the 2-metalated pyridines, a trifluoroborate, since there was no evidence pointing towards a C-B bond. The location of the BF_3-group could not be completely clarified, but it is assumed that it is coordinating to the pyridyl nitrogen or to the magnesium (as depicted in Scheme 50).

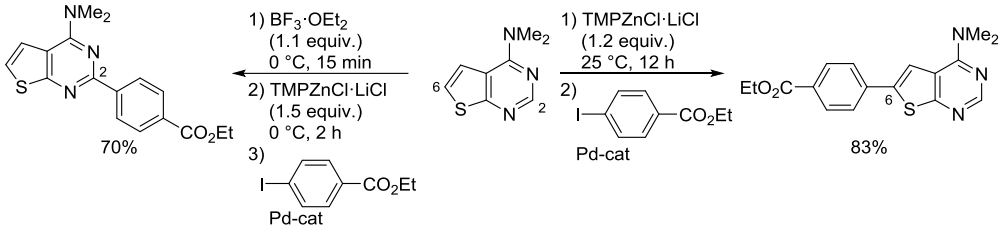
6.3. Regioselective Metalations of Pyrimidines Using Frustrated Lewis Pairs of BF_3·OEt_2 and Hindered Magnesium and Zinc Amide Bases

A range of pyrimidine derivatives could be regioselectively deprotonated at position 2 of the pyrimidine scaffold under mild conditions by activating the heterocycle with BF_3·OEt_2 prior to adding the base TMPZnCl·LiCl. The zincated pyrimidines underwent various cross-coupling reactions as well as allylation reactions (Scheme 51).

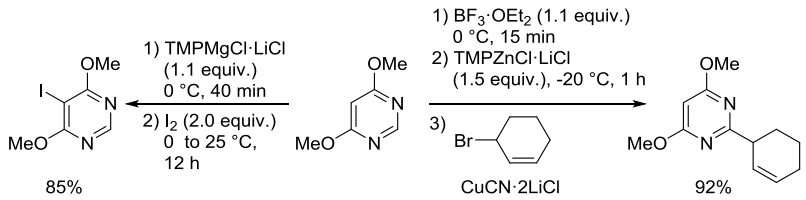


Scheme 51: Regioselective zincation of pyrimidine derivatives in position 2.

A switch of reagioselectivity could be performed in the presence or absence of BF_3·OEt_2, thus making it possible to deprotonate benzothiophenes in the absence of the Lewis acid in position 6. When BF_3·OEt_2 was present however, the zincation took place at the position 2 (Scheme 52). A similar effect could be observed at 4,6-dimethoxypyrimidine: Using TMPMgCl·LiCl in the absence of BF_3·OEt_2 magnesiated the pyrimidine at position 5, whereas when BF_3·OEt_2 was present the base TMPZnCl·LiCl deprotonated the carbon at position 2 (Scheme 53).



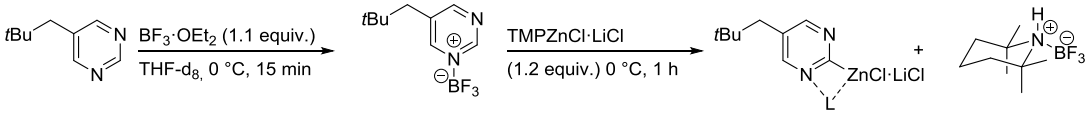
Scheme 52: Switchable, regioselective metalation of 4-(*N*,*N*-dimethylamaino)thienopyrimidine.



Scheme 53: Switchable, regioselective metalation of 4,6-dimethoxypyrimidine.

Moreover, the structure of the intermediates have been studied *via* NMR spectroscopy. The activation with BF_3OEt_2 results from a coordination of the Lewis acid to the nitrogen atom of the pyridine ring.

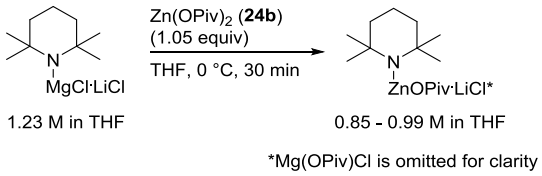
The addition of the base TMPZnCl·LiCl results in the formation of a non-symmetrical pyrimidyl zinc species and a TMPH-BF_3 adduct (Scheme 54).



Scheme 54: BF_3-activation and zincation of 5-neopentylpyrimidine.

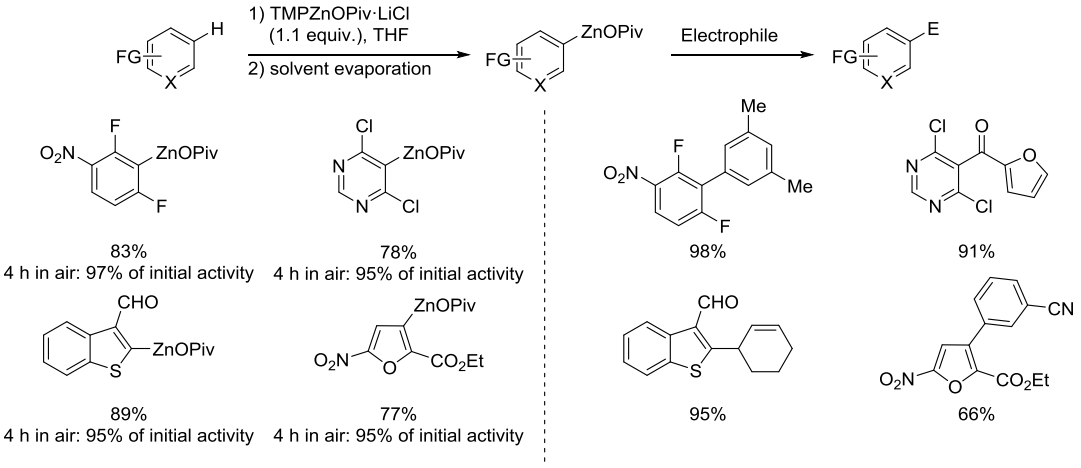
6.4. TMPZnOPiv·LiCl: A New Base for the Preparation of Air-Stable Solid Zinc Pivalates of Sensitive Aromatics and Heteroaromatics

By adding $Zn(OPiv)_2$ to a solution of TMPMgCl·LiCl in THF the new base TMPZnOPiv·LiCl was prepared as a clear solution that proved to be stable for several month under argon (Scheme 55). This base proved to have a similar metalation capability as TMPZnCl·LiCl with the advantage that it allowed to prepare solid organozinc reagents without going through a magnesiated intermediate.



Scheme 55: Preparation of the new zinc amide base TMPZnOPiv·LiCl.

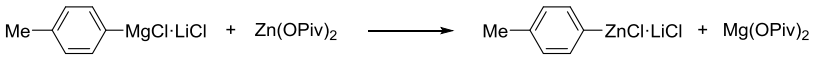
Using this base it was possible to transform sensitive aromatic and heteroaromatic substrates bearing a nitro or an aldehyde group into the corresponding solid zinc pivalates. The generated solid organozinc reagents exhibited an exceptional stability towards air. Thus, most of the formed zinc reagents lost less than five percent of their initial activity after 4 h of air exposure. Moreover, the solid organozinc reagents proved to be excellent nucleophiles for *Negishi* cross-coupling, acylation and allylation reactions (Scheme 56).



Scheme 56: Preparation of solid organozinc pivalates and subsequent reactions with electrophiles.

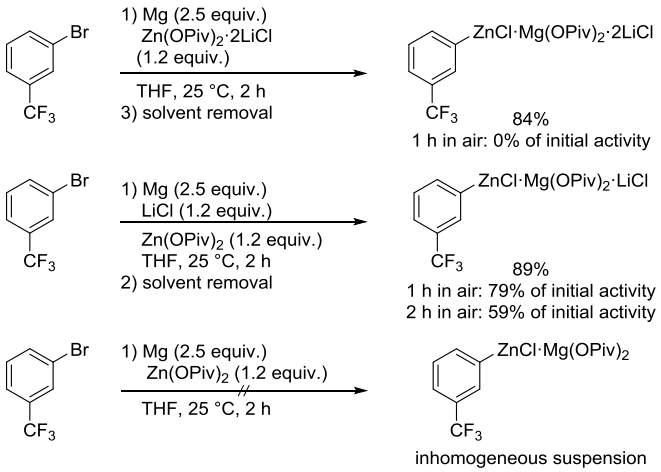
6.5. Structural Insights into Organozinc Pivalate Reagents

Several studies have been performed to elucidate the structure of the zinc reagents formed by transmetalation of a magnesium species RMgCl with $Zn(OPiv)_2 \cdot nLiCl$ (n = 1 or 2). The first thing that was found out is that the pivalate anions are completely transmetalated to magnesium thus generating RZnCl and Mg(OPiv). Therefore, when *p*-tolyMgCl·LiCl is treated with $Zn(OPiv)_2$ the corresponding *p*-tolylZnCl·LiCl is formed alongside with $Mg(OPiv)_2$ (Scheme 57).



Scheme 57: Transmetalation of *p*-tolylMgCl·LiCl with $Zn(OPiv)_2$.

Another striking insight is the fact that $Mg(OPiv)_2$ was easily contaminated by O^{2-} and OH^- ions thus generating structures of the type as $[\{Mg(OPiv)_2\}_5\{Mg(OH)_2\}(MgO)\cdot 4THF]$ or $[\{Mg_6(OPiv)_{12}\}(MgO)_2]$. This might explain the excellent air stability of the generated zinc reagents since the $Mg(OPiv)_2$ could mop up OH^- and O^{2-} ions and thus capture and hold on to H_2O molecules making them less accessible for the hydrolysis of the C-Zn bond. Also the role of the LiCl has been investigated. It was found that by adding LiCl the otherwise insoluble $Zn(OPiv)_2$ could be dissolved in THF, whereupon crystals of the formula $[(THF)_2Li_2(\mu\text{-}Cl)_2(\mu\text{-}OPiv)_2Zn]$ deposited from this solution. It can therefore be assumed that the LiCl enhanced solubility can be led back to the formation of this complex, since the LiCl completes the coordination of the Lewis basic OPiv moiety and the Lewis acidic Zn atom. This assumption was reinforced by the fact, that when no LiCl is present a clean transmetalation from MgCl to $Zn(OPiv)_2$ is not possible due to the low solubility of the reactants. Another remarkable result is the fact that too much LiCl drastically diminishes the air stability of the organozinc pivalate. Thus, when two equivalents of LiCl are present the organozinc reagent decomposes completely within one hour in air, while zinc reagents with only one equivalent of LiCl still exhibit rather high activity, even after being exposed to air for two hours. Removing the LiCl completely is not possible however, since the solubility of the reactants was to low to give satisfactory yields (Scheme 58).



Scheme 58: Comparison of air stability of different organozinc species.

Moreover, the cross-coupling capability of different salt containing *p*-tolylZnX (X = Cl·LiCl, Cl·$MgCl_2$·LiCl, OPiv·LiOPiv, Cl·$Mg(OPiv)_2$·LiCl) derivatives was tested. The *Negishi* cross-coupling with 4-bromoanisole under argon atmosphere in THF gave comparable yields of the desired biaryl. When performing the cross-coupling in air the pivalate-free zinc reagents gave somewhat lower yields than the reagents containing zinc pivalate. The influence of the more polar solvent EtOAc was also studied. While the cross-coupling proceeded well with the magnesium salt containing zinc reagents, it did not work at all in the absence of magnesium salts, *i.e.* *p*-tolylZnX with X = Cl·LiCl and OPiv·LiOPiv.

C. EXPERIMENTAL SECTION

1. General Considerations

If not otherwise stated, all reactions have been carried out using standard *Schlenk*-techniques in flame-dried glassware under nitrogen or argon. Prior to use, syringes and needles have been purged with the respective inert gas.

1.1. Solvents

Solvents needed for moisture sensitive reactions were dried according to the following standard procedures via distillation over drying agents and stored under an inert gas atmosphere:

DME (1,2-dimethoxyethane) was predried over $CaCl_2$ and distilled from Na/benzophenone ketyl under argon.

DMF was refluxed over CaH_2 (14 h), distilled from CaH_2 and stored over 4 Å molecular sieve under an Ar atmosphere.

DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) was predried over CaH_2 (4 h) and distilled off.

Et_2O was predried over $CaCl_2$ and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

NEP (*N*-ethylpyrrolidinone) was refluxed over CaH_2 and distilled from CaH_2.

NMP (*N*-methylpyrrolidinone) was refluxed over CaH_2 and distilled from CaH_2.

Pyridine was dried over KOH and distilled.

THF (tetrahydrofuran) was continuously refluxed and freshly distilled from Na/benzophenone ketyl under nitrogen and stored over 4 Å molecular sieve under an Ar atmosphere..

Toluene was predried over $CaCl_2$, distilled from CaH_2 and stored over 4 Å molecular sieve under an Ar atmosphere.

Triethylamine was dried over KOH and distilled.

Solvents for reaction workup and for column chromatography were distilled prior to use.

1.2. Reagents

Commercially available reagents were used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use.

BF_3·OEt_2 was distilled under Ar prior to use.

TMPH was distilled under Ar prior to use.

CuCN·2LiCl solution was prepared by drying CuCN (8.96 g, 100 mmol) and LiCl (8.48 g, 200 mmol) in a *Schlenk*-flask under high vacuum for 5 h at 140 °C. After cooling to 25 °C, dry THF (100 mL) was added and the mixture was stirred for 24 h.

$ZnCl_2$ solution was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) in a *Schlenk*-flask under high vacuum for 6 h at 140 °C. After cooling to 25 °C, dry THF (500 mL) was added and the mixture was stirred until all salts were dissolved.

$Zn(OPiv)_2$ (24b): Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL three-necked round-bottom flask, equipped with a magnetic stirring bar, a septum and a pressure equalizer, and was dissolved in dry THF (120 mL). The mixture was cooled at 0 °C, and a solution of Et_2Zn (13.0 g, 10.8 mL, 105 mmol) in dry THF (120 mL) was cannulated to it over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring continued at 25 °C for one additional hour at which point bubbling was ceased (a thick slurry was formed). The solvent was removed *in vacuo* and the solid residue was dried for at least 4 h longer. $Zn(OPiv)_2$ was received in quantitative yield, as a puffy amorphous white solid.

***i*PrMgCl·LiCl** was purchased as a solution in THF from Rockwood Lithium GmbH.

***n*BuLi** was purchased as a solution in hexane from Rockwood Lithium GmbH.

TMPMgCl·LiCl (14): A dry and argon flushed 250 mL flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*PrMgCl·LiCl[119] (100 mL, 1.2 M in THF, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH) (19.8 g, 126 mmol, 1.05 equiv) was added dropwise at room temperature. The reaction mixture was stirred at 25 °C until gas evolution was completed (ca. 48 h).

TMPZnCl·LiCl (20): A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (10.2 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to -40 °C and *n*BuLi (2.4 M in hexane, 25 mL, 60 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was added dropwise and the resulting solution was stirred for 30 min at -10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl (**20**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.30 M in THF was obtained.

TMPZnOPiv·LiCl (63): A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar, was charged with a solution of TMPMgCl·LiCl (**14**, 87.7 mL, 100 mmol) and cooled at 0 °C. Then, solid $Zn(OPiv)_2$ (28.1 g, 105 mmol, dried *in vacuo* at 400 °C prior to use) was added in one portion and the mixture was allowed to slowly warm up to 25 °C over ca. 1.5 h. Then THF (ca. 10-

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

20 mL) was added to give **63** as a bright yellow solution. The freshly prepared TMPZnOPiv·LiCl was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.85 to 0.99 M in THF was obtained.

1.3. Analytical Data

Gas chromatography was performed with machines of type *Hewlett-Packard* 6890 or 5890 series II, using a column of type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm; film thickness: 0.25 µm). The detection was accomplished by using a flame ionization detector. The carrier gas was nitrogen. Alkanes like dodecane or tetradecane were used as internal standards.

Infrared spectra were recorded from 4000-400 cm^{-1} on a Perkin 281 IR spectrometer. Samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands are reported in wave numbers (cm^{-1}).

Mass spectra were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.

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

NMR spectra were recorded on *Varian* Mercury 200, *Bruker* AC 300, WH 400, or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak, i.e. chloroform-d (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR), DMSO-D_6 (δ 2.50 ppm for ^{1}H-NMR and δ 39.5 ppm for ^{13}C-NMR) THF-d_8 (δ 1.73 and 3.58 ppm for ^{1}H NMR and δ 25.4 and 67.6 ppm for ^{13}C-NMR) . For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), m (multiplet), q (quartet), quint (quintet), sxt (sextet), oct (octet), as well as br (broad).

1.4. Chromatography

Thin layer chromatography (TLC) was performed using aluminum plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV-light or by staining of the TLC plate with the solution below followed by heating if necessary:

- Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12.0 mL) in water (230 mL).
- Iodine absorbed on silica gel.
- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh) from Merck.

2. Benzylic Zinc Reagents of Pyridines and Quinolines for Cross-Couplings with Aryl Bromides

Note: The Lewis acid screening and the Pd-salt/Ligand screening for the picoline metalation mentioned in B1 were performed by Andreas Steib and Dr. Stéphanie Duez.

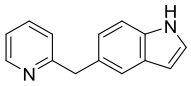
2.1. Typical Procedure

Typical Procedure for the Metalation of pyridines and related N-heterocycles with TMPZnCl·LiCl (20) (TP1):

In a dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar and a septum, the methylated N-heterocycle (1.30 mmol, 1.00 equiv.) was dissolved in dry THF (2 mL). Then, TMPZnCl·LiCl (**20**, 1.50 mL, 1.30 M in THF, 1.95 mmol) was added dropwise and the reaction mixture was stirred for the indicated time at the indicated temperature. The completion of the zincation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

2.2. Preparation and Cross-coupling of Benzylic Pydridyl Zinc Reagents

Synthesis of 5-(pyridine-2-ylmethyl)-1*H*-indole (30a):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 2.00 mL, 2.60 mmol) was added to a solution of 2-methylpyridine (**25a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 5-bromoindole (**32a**, 196 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 7 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 3:2) furnished 5-(pyridine-2-ylmethyl)-1*H*-indole (**30a**, 180 mg, 86%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (d, *J* = 4.9 Hz, 1H), 8.22 (s, 1H), 7.57 (dt, *J* = 7.6, 1.9 Hz, 1H), 7.57 – 7.56 (m, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.21 (t, *J* = 3.0 Hz, 1H), 7.16 – 7.09 (m, 3H), 6.53 – 6.51 (m, 1H), 4.29 (s, 2H).

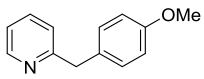
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 162.1, 149.1, 136.5, 134.7, 130.8, 128.2, 124.4, 123.5, 123.1, 121.0, 120.9, 111.1, 102.5, 44.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3114, 3097, 3028, 2852, 2361, 1739, 1592, 1474, 1344, 1218, 1138, 1093, 998, 889, 793, 755, 736, 655.

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

HRMS for **$C_{14}H_{12}N_2$** (208.1000): 208.0933 (M^+).

Synthesis of 2-(4-methoxybenzyl)pyridine (30b):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**25a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**32b**, 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 20:3) furnished 2-(4-methoxybenzyl)pyridine (**30b**, 190 mg, 95%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 5.8, 1.9 Hz, 1H), 7.54 (dt, *J* = 7.5, 2.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.08 (s, 2H), 3.76 (s, 3H).

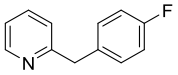
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 161.4, 158.2, 149.3, 136.5, 131.6, 130.1, 123.0, 121.1, 114.0, 55.2, 43.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2951, 2931, 2833, 1737, 1609, 1587, 1508, 1470, 1433, 1300, 1243, 1175, 1032, 993, 850, 841, 805, 781, 748, 725.

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

HRMS for **$C_{13}H_{13}NO$** (199.0997): 199.0975 (M^+).

Synthesis of 2-(4-fluorobenzyl)pyridine (30c):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**25a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-4-fluorobenzene (**32c**, 175 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 6 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 4:1) furnished 2-(4-fluorobenzyl)pyridine (**30c**, 147 mg, 78%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (dd, *J* = 4.6, 1.9 Hz, 1H), 7.58 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.22 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.13 – 7.09 (m, 2H), 6.98 (d, *J* = 8.7, 5.6 Hz, 2H), 4.12 (s, 2H).

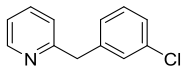
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 161.5 (J_{CF} = 253 Hz), 160.8, 149.4, 136.6, 135.2, 130.4 (J_{CF} = 7.9 Hz), 123.0, 121.3, 115.3 (J_{CF} = 21 Hz), 43.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3008, 2924, 2362, 1892, 1738, 1600, 1588, 1570, 1506, 1472, 1434, 1298, 1098, 994, 846, 790, 748, 628.

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

HRMS for **$C_{12}H_{10}FN$** (187.0797): 187.0742 (M^+).

Synthesis of 2-(3-chlorobenzyl)pyridine (30d):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**25a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-chlorobenzene (**32d**, 191 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 6 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 7:3) furnished 2-(3-chlorobenzyl)pyridine (**30d**, 134 mg, 66%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.61 (dt, *J* = 7.4, 2.0 Hz, 1H), 7.28 – 7.12 (m, 6H), 4.14 (s, 2H).

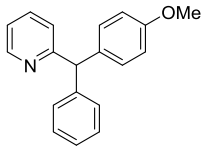
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 160.1, 149.5, 141.5, 136.6, 134.3, 129.8, 129.2, 127.3, 126.6, 123.1, 121.5, 44.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2924, 1737, 1668, 1588, 1568, 1471, 1428, 1303, 1077, 994, 865, 775, 769, 694, 681.

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

HRMS for **$C_{12}H_{10}ClN$** (203.0502): 203.0471 (M^+).

Synthesis of 2-((4-methoxyphenyl)(phenyl)methyl)pyridine (30e):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-(benzyl)pyridine (**25b**, 220 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**32b**, 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 20 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 7:3) furnished 2-((4-methoxyphenyl)(phenyl)methyl)pyridine (**30e**, 272 mg, 99%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.62 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.62 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.34 – 7.05 (m, 9H), 6.86 (dt, *J* = 8.8, 3.0 Hz, 2H), 5.67 (s, 1H), 3.80 (s, 3H).

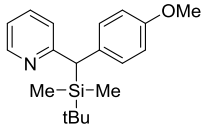
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 163.6, 158.2, 149.5, 143.1, 136.4, 135.0, 130.3, 129.3, 128.6, 126.4, 123.7, 121.3, 113.8, 58.6, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2951, 2931, 2876 1737, 1609, 1587, 1504, 1465, 1427, 1300, 1241, 1177, 1032, 993, 850, 841, 805, 781, 748, 725.

MS (EI, 70 eV): *m/z* (%) = 275 [M^+] (100), 260 (31), 243 (8), 230 (12), 197 (32), 167 (23), 153 (23).

HRMS for **$C_{19}H_{17}NO$** (275.1310): 275.1305 (M^+).

Synthesis of 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)methyl)pyridine (30f):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-(*tert*-butyldimethylsilyl)pyridine (**25c**, 269 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**32b**, 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 20 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 95:5) furnished 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)methyl)pyridine (**30f**, 288 mg, 92%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.47 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.42 (dt, *J* = 8.7, 2.2 Hz, 2H), 7.16 (dt, *J* = 7.8, 2.1 Hz, 1H), 6.98 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.80 (dt, *J* = 8.7, 2.2 Hz, 2H), 3.78 (s, 4H), 0.72 (s, 9H), 0.05 (s, 6H).

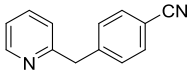
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 163.6, 157.4, 148.9, 135.9, 134.2, 129.9, 123.2, 120.0, 113.5, 55.2, 45.0, 27.0, 17.8, -6.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2948, 2927, 2852, 1583, 1504, 1465, 1427, 1240, 1181, 1031, 869, 857, 824, 807, 778, 692.

MS (EI, 70 eV): *m/z* (%) = 313 [M^+] (14), 298 (9), 256 (100), 242 (10), 225 (23), 212 (11), 198 (10), 182 (11), 167 (13), 154 (8), 120 (3), 73 (42).

HRMS for **$C_{19}H_{27}NOSi$** (313.1862): 313.1855 (M^+).

Synthesis of 4-(pyridin-2-ylmethyl)benzonitrile (30g):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**25a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv.) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromobenzonitrile (**32j**, 183 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished 4-(pyridin-2-ylmethyl)benzonitrile (**30g**, 170 mg, 87%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (ddd, *J* = 4.8, 1.9, 0.8 Hz, 1H), 7.65 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.60 (dt, *J* = 8.6, 2.1 Hz, 2H), 7.39 (dt, *J* = 8.6, 2.1 Hz, 2H), 7.21 – 7.14 (m, 2H), 4.22 (s, 2H).

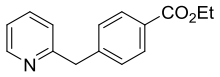
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.2, 149.6, 145.0, 136.9, 132.3, 129.8, 123.3, 121.8, 118.9, 110.4, 44.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3044, 3005, 2932, 2226, 1737, 1670, 1585, 1504, 1470, 1433, 1310, 1153, 1048, 994, 865, 809, 774, 749, 691.

MS (EI, 70 eV): *m/z* (%) = 194 [M^+] (23), 193 (100), 166 (4), 140 (2), 89 (3).

HRMS (ESI) for **$C_{13}H_{11}N_2$** (195.0922): 195.0916 ([M+H]$^+$).

Synthesis of ethyl 4-(pyridin-2-ylmethyl)benzoate (30h):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**25a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv.) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and ethyl 4-bromobenzoate (**32k**, 227 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished ethyl 4-(pyridin-2-ylmethyl)benzoate (**30h**, 206 mg, 85%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.57 (d, *J* = 5.1 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.61 (dt, *J* = 7.7, 1.9 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.18 – 7.11 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.23 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

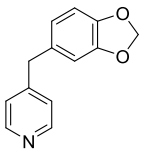
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.5, 160.0, 149.5, 144.7, 136.7, 129.9, 129.1, 128.7, 123.2, 121.5, 60.8, 44.6, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2904, 1710, 1709, 1585, 1472, 1434, 1415, 1366, 1270, 1176, 1100, 1020, 752, 702.

MS (EI, 70 eV): *m/z* (%) = 241 [M^+] (32), 240 (100), 212 (26), 196 (15), 167 (41).

HRMS (ESI) for **$C_{15}H_{16}NO_2$** (242.1181): 242.1175 ([M+H]$^+$).

Synthesis of 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyridine (33a):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 5-bromobenzo[1,3]dioxol (**32e**, 199 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification

by flash-chromatography (CH_2Cl_2 / MeOH = 99:1) furnished 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyridine (**33a**: 203 mg, 95%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.51 (d, *J* = 6.1 Hz, 2H), 7.11 (d, *J* = 6.1 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.68 – 6.65 (m, 2H), 5.95 (s, 2H), 3.89 (s, 2H).

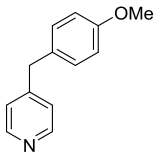
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 149.9, 147.9, 146.3, 132.6, 124.0, 122.0, 109.4, 108.4, 101.0, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 3024, 2982, 2854, 1596, 1485, 1440, 1413, 1244, 1186, 1109, 1033, 925, 868, 814, 799, 767, 728, 713.

MS (EI, 70 eV): *m/z* (%) = 213 [M^+] (100), 183 (17), 154 (22), 135 (36), 127 (10), 77 (11).

HRMS for **$C_{13}H_{11}NO_2$** (213.0790): 213.0784 (M^+).

Synthesis of 4-(4-methoxybenzyl)pyridine (33b):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(O_2CCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**32b**, 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished 4-(4-methoxybenzyl)pyridine (**33b**, 195 mg, 98%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.50 (d, *J* = 5.5 Hz, 2H), 7.13 – 7.08 (m, 4H), 6.88 (dt, *J* = 8.7, 3.1 Hz, 2H), 3.98 (s, 2H), 3.81 (s, 3H).

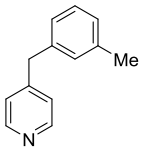
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.4, 150.5, 149.8, 130.9, 130.0, 124.1, 114.1, 55.3, 40.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 3027, 2954, 2907, 2834, 1737, 1598, 1509, 1413, 1245, 1176, 1152, 1107, 1030, 993, 796, 759.

MS (EI, 70 eV): *m/z* (%) = 199 [M^+] (100), 184 (23), 168 (17), 154 (11), 121 (54).

HRMS for **$C_{13}H_{13}NO$** (199.0997): 199.0977 (M^+).

Synthesis of 4-(3-methylbenzyl)pyridine (33c):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-methylbenzene (**32f**, 169 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1→2:3) furnished 4-(3-methylbenzyl)pyridine (**33c**, 150 mg, 82%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (d, *J* = 5.5 Hz, 2H), 7.25 – 6.97 (m, 6H), 3.95 (s, 2H), 2.35 (s, 3H).

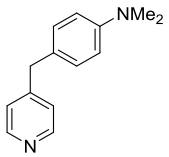
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 149.8, 138.8, 138.4, 129.8, 128.6, 127.4, 126.0, 124.2, 41.2, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2920, 2854, 1737, 1720, 1597, 1558, 1490, 1413, 1284, 1247, 1217, 1110, 993, 800, 778, 750, 698.

MS (EI, 70 eV): *m/z* (%) = 183 [M^+] (100), 168 (58), 152 (4), 141 (5), 128 (4), 115 (5), 105 (6), 91 (7).

HRMS for $C_{13}H_{13}N$ (183.1048): 183.1047 (M^+).

Synthesis of *N*,*N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (33d):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromo-*N*,*N*-dimethylaniline (**32g**, 199 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1→2:3) furnished *N*,*N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (**33d**, 149 mg, 70%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.49 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.12 (d, *J* = 6.0 Hz, 2H), 7.06 (dt, *J* = 9.3, 2.4 Hz, 2H), 6.71 (dt, *J* = 9.3, 2.4 Hz, 2H), 3.89 (s, 2H), 2.95 (s, 6H).

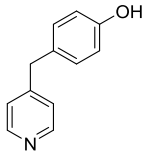
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 151.1, 149.7, 149.4, 129.7, 126.7, 124.1, 112.9, 40.7, 40.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2894, 2808, 2338, 2360, 1739, 1611, 1597, 1518, 1484, 1445, 1420, 1410, 1346, 1230, 1170, 111, 1065, 945, 914, 827, 787, 720.

MS (EI, 70 eV): *m/z* (%) = 212 [M^+] (100), 195 (4), 167 (14), 134 (60), 118 (14).

HRMS for **$C_{14}H_{16}N_2$** (212.1313): 212.1323 (M^+).

Synthesis of 4-(pyridin-4-ylmethyl)phenol (33e):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 2.00 mL, 2.60 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(O_2CCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromo-phenol (**32h**, 172 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (CH_2Cl_2 / MeOH = 97:3) furnished 4-(pyridin-4-ylmethyl)phenol (**33e**, 155 mg, 84%) as a colorless oil.

^{1}H-NMR (300 MHz, DMSO-d_6): δ / ppm = 9.24 (s, 1H), 8.43 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.19 (dd, *J* = 4.3, 1.7 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 2H).

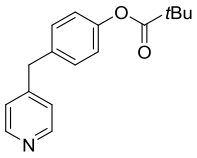
^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 156.2, 151.1, 149.9, 130.2, 130.0, 124.3, 115.7, 39.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2997, 2925, 2883, 2794, 2673, 2594, 2360, 2339, 1602, 1513, 1455, 1420, 1430, 1380, 1245, 1217, 1205, 1007, 919, 845, 804.

MS (EI, 70 eV): *m/z* (%) = 185 [M^+] (100), 167 (8), 156 (9), 128 (7), 107 (43), 77 (14).

HRMS for **$C_{12}H_{11}NO$** (185.0841): 185.0840 (M^+).

Synthesis of 4-(pyridin-4-ylmethyl)phenyl pivalate (33f):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(O_2CCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromophenyl pivalate (**32i**, 256 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 2:3) furnished 4-(pyridin-4-ylmethyl)phenyl pivalate (**33f**, 218 mg, 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 5.8, 1.6 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 5.8 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 3.98 (s, 2H), 1.36 (s, 9H).

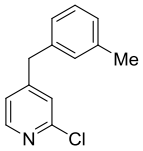
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 177.1, 149.9, 149.8, 149.7, 135.1, 129.9, 124.1, 121.7, 40.6, 39.1, 27.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 3033, 3017, 2933, 2973, 2872, 1741, 1595, 1505, 1477, 1411, 1277, 1294, 1112, 1030, 899, 806, 760.

MS (EI, 70 eV): *m/z* (%) = 269 [M^+] (26), 226 (4), 185 (100), 156 (12), 128 (10), 107 (11), 85 (8), 57 (50).

HRMS for **$C_{17}H_{19}NO_2$** (269.1416): 269.1425 (M^+).

Synthesis of 2-chloro-4-(3-methylbenzyl)pyridine (33g):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-chloro-4-methylpyridine (**26b**, 165 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), PCy_3 (12 mg, 4 mol%) and 1-bromo-3-methylbenzene (**32f**, 169 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced

pressure. Purification by flash-chromatography (*i*-hexane / ether = 4:1) furnished 2-chloro-4-(3-methylbenzyl)pyridine (**33g**, 150 mg, 69%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.26 (d, *J* = 5.1 Hz, 1H), 7.22 (t, *J* = 7.2, 1H), 7.14 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 5.1 Hz, 1H), 6.98 – 6.95 (m, 2H), 3.91 (s, 2H), 2.33 (s, 3H).

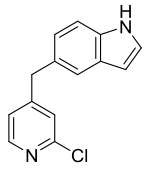
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 153.6, 151.7, 149.5, 138.6, 137.9, 129.8, 128.8, 127.7, 126.0, 124.4, 123.0, 40.9, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 2920, 2863, 1740, 1720, 1589, 1558, 1490, 1413, 1381, 1284, 1247, 1217, 1110, 1084, 993, 800, 745, 750, 715, 698.

MS (EI, 70 eV): *m/z* (%) = 217 [M^+] (100), 202 (42), 182 (32), 166 (35), 152 (9), 139 (10).

HRMS (ESI) for **$C_{13}H_{13}ClN$** (218.0737): 218.0732 ([M+H]$^+$).

Synthesis of 5-((2-chloropyridine-4-yl)methyl)-1*H*-indole (33h):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-chloro-4-methylpyridine (**26b**, 165 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 5-bromoindole (**32a**, 195 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 3:2) furnished 5-((2-chloropyridine-4-yl)methyl)-1*H*-indole (**33h**, 167 mg, 69%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.23 (d, *J* = 5.3 Hz, 1H), 8.16 (s, 1H), 7.42 (s, 1H), 7.34 (dd, *J* = 8.4 Hz, 1H), 7.23 – 7.14 (m, 2H), 7.06 (d, *J* = 5.1 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.51 – 6.49 (m, 1H), 4.04 (s, 2H).

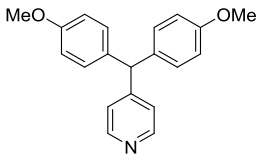
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 155.2, 151.4, 149.1, 134.8, 129.2, 128.3, 124.8, 125.6, 123.2, 123.1, 121.0, 111.5, 102.5, 41.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 3022, 2920, 2863, 1740, 1589, 1545, 1464, 1381, 1216, 1119, 1084, 989, 835, 785, 745, 715, 697.

MS (EI, 70 eV): *m/z* (%) = 242 [M^+] (100), 205 (21), 178 (10), 151 (8), 130 (79).

HRMS (ESI) for $\mathbf{C_{14}H_{12}ClN_2}$ (243.0689): 243.0683 ($[M+H]^+$).

Synthesis of 4-(bis(4-methoxyphenyl)methyl)pyridine (33i):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-(4-methoxybenzyl)pyridine (**33b**, 259 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**32b**, 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 7:3) furnished 4-(bis(4-methoxyphenyl)methyl)pyridine (**33i**, 283 mg, 93%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.06 – 6.99 (m, 6H), 6.89 – 6.83 (m, 4H), 5.42 (s, 1H), 3.81 (s, 6H).

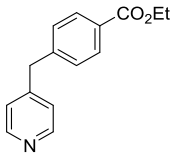
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.4, 153.4, 149.8, 134.6, 130.2, 124.3, 113.9, 55.3, 54.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 3032, 2995, 2833, 1608, 1594, 1581, 1506, 1491, 1457, 1441, 1412, 1303, 1240, 1177, 1111, 1030, 819.

MS (EI, 70 eV): *m/z* (%) = 305 [M^+] (61), 274 (23), 227 (100), 212 (6), 198 (7), 169 (7), 154 (14).

HRMS for $\mathbf{C_{20}H_{19}NO_2}$ (305.1416): 305.1411 (M^+).

Synthesis of ethyl 4-(pyridin-4-ylmethyl)benzoate (33j):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv.) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and ethyl 4-bromobenzoate (**32k**, 227 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated

aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished ethyl 4-(pyridin-4-ylmethyl)benzoate (**33j**, 188 mg, 78%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.49 (dd, *J* = 4.5, 1.7 Hz, 2H), 7.97 (dt, *J* = 8.4, 1.9 Hz, 2H), 7.26 – 7.05 (m, 4H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

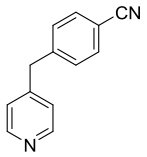
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.3, 149.7, 149.5, 143.8, 130.0, 130.0, 129.0, 124.2, 60.9, 41.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2981, 2931, 1710, 1597, 1413, 1365, 1270, 1177, 1100, 1020, 994, 870, 786, 754, 704.

MS (EI, 70 eV): *m/z* (%) = 241 [M^+] (31), 213 (32), 196 (100), 167 (43), 139 (10), 115 (8).

HRMS (ESI) for **$C_{15}H_{16}NO_2$** (242.1181): 242.1173 ([M+H]$^+$).

Synthesis of 4-(pyridin-4-ylmethyl)benzonitrile of (33k):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv.) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromobenzonitrile (**32j**, 183 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished 4-(pyridin-4-ylmethyl)benzonitrile (**33k**, 146 mg, 75%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (dd, *J* = 4.6, 2.0 Hz, 2H), 7.60 (dt, *J* = 8.3, 1.9 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.12 (d, *J* = 6.1 Hz, 2H), 4.05 (s, 2H).

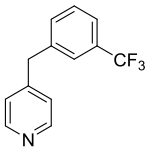
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 149.8, 148.5, 144.2, 132.5, 129.8, 124.2, 119.6, 110.9, 41.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3016, 226, 1739, 1597, 1554, 1506, 1496, 1414, 1426, 1223, 993, 927, 865, 840, 783, 722.

MS (EI, 70 eV): *m/z* (%) = 194 [M^+] (100), 166 (9), 140 (9), 116 (10), 89 (7), 63 (5).

HRMS (ESI) for **$C_{13}H_{10}N_2$** (195.0922): 195.0916 ([M+H]$^+$).

Synthesis of 4-(3-(trifluoromethyl)benzyl)pyridine (33l):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**26a**, 121 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv.) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-(trifluoromethyl)benzene (**32l**, 224 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 2:3) furnished 4-(3-(trifluoromethyl)benzyl)pyridine (**33l**, 185 mg, 78%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (dd, *J* = 6.2, 1.7 Hz, 2H), 7.55 – 7.36 (m, 4H), 7.11 (d, *J* = 6.2, 2H), 4.05 (s, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 148.8, 139.8, 132.4, 131.1 (J_{CF} = 32 Hz), 129.2, 125.7 (J_{CF} = 3.8 Hz), 124.1, 124.0 (J_{CF} = 272 Hz), 123.6 (J_{CF} = 3.8 Hz), 40.9.

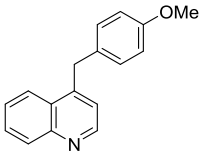
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3028, 2992, 1737, 1673, 1598, 1449, 1414, 1327, 1160, 117, 1071, 919, 880, 791, 701, 663.

MS (EI, 70 eV): *m/z* (%) = 237 [M$^+$] (100), 218 (6), 167 (18), 159 (7), 139 (3).

HRMS for **$C_{13}H_{10}F_3N$** (237.0765): 237.0760 (M$^+$).

2.3. Preparation and Cross-coupling of Benzylic Quinolyl Zinc Reagents

Synthesis of 4-(4-methoxybenzyl)quinoline (36a):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylquinoline (**35a**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**32b**, 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished 4-(4-methoxybenzyl)quinoline (**36a**, 234 mg, 94%) as a white solid.

M.p. (°C): 78.0-80.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.84 (d, *J* = 4.5 Hz, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.73 (dt, d, *J* = 7.6, 1.5 Hz, 1H), 7.56 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.17 – 7.10 (m, 3H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.41 (s, 2H), 3.81 (s, 3H).

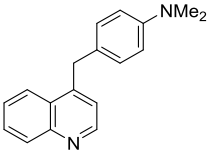
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.4, 150.1, 148.1, 147.3, 130.5, 130.0, 129.9, 129.2, 127.6, 126.6, 123.9, 121.7, 114.2, 55.3, 37.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3030, 3006, 2967, 2911, 2839, 1737, 1610, 1588, 1569, 1588, 1509, 1449, 1461, 1443, 1525, 1298, 1246, 1170, 1103, 1030, 929, 846, 837, 758, 751, 730.

MS (EI, 70 eV): *m/z* (%) = 249 [M^+] (100), 234 (50), 217 (31), 204 (28), 121 (27).

HRMS for **$C_{17}H_{15}NO$** (249.1154): 249.1143 (M^+).

Synthesis of *N*,*N*-dimethyl-4-(quinolin-4-ylmethyl)aniline (36b):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylquinoline (**35a**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromo-*N*,*N*-dimethylaniline (**32g**, 199 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction

mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished *N*,*N*-dimethyl-4-(quinolin-4-ylmethyl)aniline (**36b**, 245 mg, 93%) as a yellow solid.

M.p. (°C): 115.7-117.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.82 (d, *J* = 4.5 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.71 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.57 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.17 (d, *J* = 4.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5, 2H), 4.38 (s, 2H), 2.94 (s, 6H).

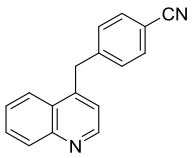
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.0, 149.4, 148.1, 147.9, 129.8, 129.6, 129.2, 127.7, 126.5, 126.2, 124.0, 121.6, 113.0, 40.7, 37.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2890, 2800, 2361, 2337, 1737, 1610, 1589, 1518, 1478, 1441, 1343, 1324, 1218, 1139, 1124, 1057, 941, 931, 843, 835, 806, 767.

MS (EI, 70 eV): *m/z* (%) = 262 [M^+] (100), 245 (4), 217 (20), 204 (4), 189 (4), 134 (61), 118 (12).

HRMS (ESI) for **$C_{18}H_{19}N_2$** (263.1548): 263.1541 ([M+H]$^+$).

Synthesis of 4-(quinolin-4-ylmethyl)benzonitrile (36c):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylquinoline (**35a**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromobenzonitrile (**32j**, 183 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished 4-(quinolin-4-ylmethyl)benzonitrile (**36c**, 161 mg, 66%) as a white solid.

M.p. (°C): 148.0-149.0 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.88 (d, *J* = 4.5 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.93 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.56 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 4.5 Hz, 1H), 4.52 (s, 2H).

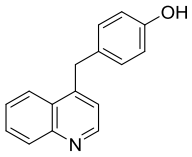
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 148.3, 144.9, 144.2, 132.6, 130.3, 129.7, 129.6, 127.3, 127.0, 123.5, 122.0, 118.7, 110.8, 38.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3001, 2361, 2335, 2225, 1737, 1590, 1508, 1424, 1395, 1237, 933, 868, 861, 761, 748.

MS (EI, 70 eV): *m/z* (%) = 244 [M^+] (82), 243 (100), 229 (6), 214 (7), 190 (5).

HRMS (ESI) for **$C_{17}H_{13}N_2$** (245.1079): 245.1071 ([M+H]$^+$).

Synthesis of 4-(quinolin-4-ylmethyl)phenol (36d):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 2.00 mL, 2.60 mmol) was added to a solution of 4-methylquinoline (**35a**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP1**. $Pd(O_2CCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromophenol (**32h**, 171 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (CH_2Cl_2 / MeOH, 99:→98:2) furnished 4-(quinolin-4-ylmethyl)phenol (**36d**, 179 mg, 76%) as a white solid.

M.p. (°C): 229.3-232.8 °C.

^{1}H-NMR (300 MHz, DMSO-d_6): δ / ppm = 9.24 (s, 1H), 8.80 (d, *J* = 4.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.72 (dt, *J* = 7.6, 1.50 Hz, 1H), 7.58 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.29 (d, *J* = 4.5 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 4.34 (s, 2H).

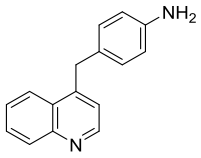
^{13}C-NMR (75 MHz, DMSO-d_6): δ = 156.2, 150.8, 148.3, 147.8, 130.2, 130.0, 129.6, 129.5, 127.4, 126.9, 124.9, 122.1, 115.8, 36.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2670, 2339, 2360, 1737, 1591, 1508, 1440, 1376, 1268, 1245, 1231, 1169, 1100, 841, 817, 771, 749, 724.

MS (EI, 70 eV): *m/z* (%) = 235 [M^+] (100), 217 (18), 204 (14), 129 (9), 107 (16).

HRMS (ESI) for **$C_{16}H_{14}NO$** (236.1075): 236.1069 ([M+H]$^+$) .

Synthesis of 4-(quinolin-4-ylmethyl)aniline (36e):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 2.00 mL, 2.60 mmol) was added to a solution of 4-methylquinoline (**35a**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP1**. $Pd(O_2CCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoaniline (**32m,** 171 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (CH_2Cl_2 / MeOH = 99:1→98:2) furnished 4-(quinolin-4-ylmethyl)aniline (**36e,** 173 mg, 74%) as a orange solid.

M.p. (°C): 139.3-141.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.82 (d, *J* = 4.5 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.73 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.56 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.17 (d, *J* = 4.5 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 4.36 (s, 2H), 3.40 (s, 2H).

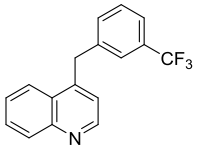
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 149.8, 148.2, 147.7, 145.0, 129.8, 129.7, 129.3, 128.2, 127.7, 126.6, 123.9, 121.6, 115.4, 37.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3411, 3300, 3191, 3057, 3021, 2897, 2844, 2360, 1736, 1625, 1590, 1568, 1513, 1507, 1444, 1307, 1277, 1234, 1171, 1141, 942, 915, 818, 812, 770, 748, 723.

MS (EI, 70 eV): *m/z* (%) = 234 [M^+] (100), 217 (17), 204 (7), 116 (7), 106 (41).

HRMS (ESI) for **$C_{16}H_{15}N_2$** (235.1235): 235.1228 ([M+H]$^+$).

Synthesis of 4-(3-(trifluoromethyl)benzyl)quinoline (36f):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylquinoline (**35a**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-(trifluoromethyl)benzene (**32l**, 224 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate

(3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / ether = 1:1) furnished 4-(3-(trifluoromethyl)benzyl)quinoline (**36f**, 207 mg, 72%) as a slightly yellow solid.

M.p. (°C): 79.1-80.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.86 (d, *J* = 4.7 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.60 – 7.33 (m, 5H), 7.15 (d, *J* = 4.7, 1H), 4.52 (s, 2H).

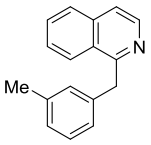
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.2, 148.3, 145.6, 139.5, 132.2, 131.1 (J_{CF} = 32 Hz), 130.2, 129.4, 129.2, 127.4, 126.9, 125.6 (J_{CF} = 3.7 Hz), 124.0 (J_{CF} = 271 Hz), 123.6 (J_{CF} = 3.7 Hz), 123.5, 121.8, 37.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3032, 2925, 2359, 2338, 1737, 1591, 1569, 1508, 1451, 1427, 1327, 1317, 1205, 1159, 1119, 1073, 938, 831, 809, 747, 704.

MS (EI, 70 eV): *m/z* (%) = 287 [M^+] (100), 268 (7), 217 (53), 189 (8).

HRMS (ESI) for **$C_{17}H_{13}F_3N$** (288.1000): 288.0991 ([M+H]$^+$).

Synthesis of 1-(3-methylbenzyl)isoquinoline (36g):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 1-methylisoquinoline (**35c**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), XantPhos (12 mg, 2 mol%) and 1-bromo-3-methylbenzene (**32f**, 169 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O = 2:1) furnished 1-(3-methylbenzyl)isoquinoline (**36g**, 200 mg, 86%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.50 (d, *J* = 5.9 Hz, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.65 (m, 1H), 7.50 – 7.57 (m, 2H), 7.05 – 7.16 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 1H), 4.64 (s, 2H), 2.27 (s, 3H).

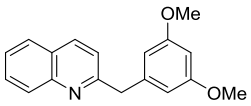
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2, 141.8, 139.2, 138.1, 136.6, 129.9, 129.3, 128.4, 127.3, 127.2, 127.2, 127.0, 125.9, 125.6, 119.8, 41.9, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3049, 3016, 2916, 2861, 2360, 2334, 1772, 1621, 1605, 1585, 1559, 1500, 1487, 1459, 1436, 1383, 1353, 1339, 1241, 1169, 1154, 1134, 1091, 1073, 1039, 1018, 999, 952, 930, 880, 866, 822, 797, 776, 748, 737, 723, 693, 673.

MS (70 eV, EI): *m/z* (%): 233 (M^+, 31), 232 (100), 217 (29), 116 (5), 109 (6).

HRMS for **$C_{17}H_{15}N$** (233.1204): 233.1163 (M^+).

Synthesis of 2-(3,5-dimethoxybenzyl)quinoline (36h):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylquinoline (**35b**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), XantPhos (12 mg, 2 mol%) and 1-bromo-3,5-dimethoxybenzene (**32n**, 215 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / Et_2O = 4:1) furnished 2-(3,5-dimethoxybenzyl)-quinoline (**36h**, 271 mg, 97%) as a pale beige oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.09 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.72 (m, 1H), 7.45 – 7.51 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 2.2 Hz, 2H), 6.33 (d, *J* = 2.3 Hz, 1H), 4.27 (s, 2H), 3.73 (s, 6H).

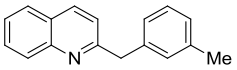
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.9, 160.9, 147.7, 141.4, 136.5, 129.4, 128.9, 127.5, 126.8, 126.0, 121.4, 107.3, 98.5, 55.2, 45.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2998, 2935, 2835, 1592, 1564, 1504, 1458, 1425, 1345, 1322, 1313, 1288, 1262, 1219, 1203, 1147, 1114, 1063, 1055, 1016, 992, 972, 940, 916, 820, 792, 762, 734, 694, 679.

MS (70 eV, EI): *m/z* (%): 279 [M^+] (81), 278 (100), 264 (30), 249 (16), 204 (15).

HRMS (ESI) for **$C_{18}H_{18}NO_2$** (280.1332): 280.1329 ([M+H^+]).

Synthesis of 2-(3-methylbenzyl)quinoline (36i):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylquinoline (**35b**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), XantPhos (12 mg, 2 mol%) and 1-bromo-3-methylbenzene (**32f**, 169 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a

mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / Et_2O, 5:1) furnished 2-(3-methylbenzyl)quinoline (**36i**, 224 mg, 96%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.82 (m, 2H), 7.49 – 7.57 (m, 1H), 7.20 – 7.30 (m, 2H), 7.05 – 7.18 (m, 3H), 4.36 (s, 2H), 2.35 (s, 3H).

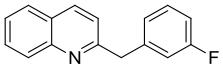
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.3, 147.8, 139.1, 138.2, 136.4, 130.0, 129.4, 129.0, 128.5, 127.5, 127.2, 126.7, 126.2, 125.9, 121.5, 45.5, 21.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3040, 3014, 2949, 2917, 2862, 1933, 1617, 1598, 1563, 1504, 1488, 1458, 1424, 1374, 1309, 1219, 1170, 1140, 1114, 1090, 1039, 1015, 952, 869, 831, 799, 781, 757, 737, 728, 692.

MS (70 eV, EI): *m/z* (%): 233 [M^+] (56), 232 (100), 217 (35), 116 (11), 44 (53).

HRMS for **$C_{17}H_{15}N$** (233.1204): 233.1189 (M^+).

Synthesis of 2-(3-fluorobenzyl)quinoline (36j):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylquinoline (**35b**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-fluorobenzene (**32o**, 174 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / Et_2O = 2:1) furnished 2-(3-fluorobenzyl)quinoline (**36j**, 225 mg, 95%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.13 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.77 (m, 1H), 7.50 – 7.57 (m, 1H), 7.22 – 7.33 (m, 2H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.02 – 7.08 (m, 1H), 6.90 – 6.98 (m, 1H), 4.37 (s, 2H).

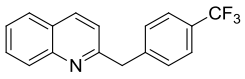
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.9 (d, J_{CF} = 246 Hz), 160.3, 147.8, 141.7 (d, J_{CF} = 7.1 Hz), 136.6, 130.0 (d, J_{CF} = 8.3 Hz), 129.6, 129.0, 127.5, 126.8, 126.1, 124.8 (d, J_{CF} = 2.9 Hz), 121.4, 116.0 (d, J_{CF} = 21 Hz), 113.4 (d, J_{CF} = 21 Hz), 45.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2917, 2348, 1930, 1615, 1598, 1588, 1564, 1504, 1485, 1447, 1425, 1373, 1311, 1265, 1245, 1219, 1137, 1114, 1074, 1015, 971, 946, 926, 916, 883, 865, 829, 797, 781, 761, 741, 730, 683, 670.

MS (70 eV, EI): *m/z* (%): 237 [M^+] (41), 236 (100), 118 (4). 101 (3).

HRMS for **$C_{16}H_{12}FN$** (237.0954): 237.0931 (M^+).

Synthesis of 2-(4-(trifluoromethyl)benzyl)quinoline (36k):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylquinoline (**35b**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), XantPhos (12 mg, 2 mol%) and 1-bromo-4-(trifluoromethyl)benzene (**32p**, 223 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O = 2:1) furnished 2-(4-(trifluoromethyl)benzyl)quinoline (**36k**, 247 mg, 86%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.02 – 8.11 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.74 (m, 1H), 7.48 – 7.58 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 1H), 4.39 (s, 2H).

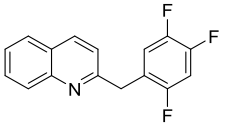
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.0, 147.9, 143.3 (q, J_{CF} = 1.4 Hz), 136.8, 129.6, 129.4, 129.0, 128.8 (q, J_{CF} = 32 Hz), 127.5, 126.8, 126.2, 125.5 (q, J_{CF} = 3.7 Hz), 124.2 (q, J_{CF} = 272 Hz), 121.4, 45.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2358, 2340, 1925, 1738, 1617, 1598, 1564, 1504, 1426, 1418, 1321, 1220, 1161, 1114, 1104, 1065, 1018, 953, 933, 885, 855, 816, 791, 766, 742, 710, 676.

MS (70 eV, EI): *m/z* (%): 287 [M^+] (45), 286 (100), 216 (10), 128 (14), 109 (17), 77 (11).

HRMS for **$C_{17}H_{12}F_3N$** (287.0922): 287.0903 (M^+).

Synthesis of 2-(2,4,5-trifluorobenzyl)quinoline (36l):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylquinoline (**35b**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), XantPhos (12 mg, 2 mol%) and 1-bromo-2,4,5-trifluorobenzene (**32q**, 211 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched

with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane / Et_2O = 2:1) furnished 2-(2,4,5-trifluorobenzyl)quinoline (**36l**, 213 mg, 78%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.15 – 8.04 (m, 2H), 7.80 (ddd, *J* = 8.1, 1.6, 0.6 Hz, 1H), 7.73 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.20 – 7.08 (m, 1H), 6.96 (ddd, *J* = 10.1, 9.1, 6.6 Hz, 1H), 4.32 (s, 2H).

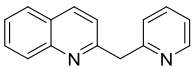
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.8, 155.7 (ddd, J_{CF} = 244, 9.3, 2.7 Hz), 148.8 (ddd, J_{CF} = 250, 15, 12 Hz), 147.9, 146.7 (ddd, J_{CF} = 245, 13, 3.7 Hz), 136.9, 129.7, 129.0, 127.5, 126.9, 126.3, 122.5 (ddd, J_{CF} = 18, 5.6, 4.2 Hz), 121.1, 118.8 (ddd, J_{CF} = 19, 5.7, 1.3 Hz), 105.3 (ddd, J_{CF} = 29, 21, 0.8 Hz), 37.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 1737, 1631, 1619, 1598, 1565, 1516, 1504, 1422, 1365, 1333, 1311, 1228, 1208, 1149, 1114, 1095, 1016, 954, 935, 876, 840, 819, 795, 765, 746, 738, 709, 682, 660.

MS (70 eV, EI): *m/z* (%): 273 [M^+] (85), 254 (100), 233 (3), 128 (4), 101 (3), 44 (3).

HRMS for **$C_{16}H_{10}F_3N$** (273.0765): 273.0755 (M^+).

Synthesis of 2-(pyridin-2-ylmethyl)quinoline (36m):



TMPZnCl·LiCl (**20**, 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylquinoline (**35b**, 186 mg, 1.30 mmol, 1.00 equiv.) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), XantPhos (12 mg, 2 mol%) and 2-bromopyridine (**32r**, 158 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/EtOAc = 1:1) furnished 2-(pyridin-2-ylmethyl)quinoline (**36m**, 150 mg, 68%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.57 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.03 – 8.13 (m, 2H), 7.77 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.65 – 7.73 (m, 1H), 7.59 (td, *J* = 7.7, 1.9 Hz, 1H), 7.45 – 7.53 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.34 (m, 1H), 7.13 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 4.55 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.7, 159.1, 149.3, 147.8, 136.6, 136.6, 129.5, 128.9, 127.5, 126.9, 126.1, 123.7, 121.8, 121.6, 48.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 3010, 1681, 1618, 1596, 1586, 1568, 1502, 1466, 1426, 1397, 1382, 1324, 1306, 1283, 1243, 1214, 1194, 1148, 1123, 1118, 1081, 1050, 1016, 995, 972, 952, 928, 853, 821, 785, 755, 718, 704, 700, 686.

MS (70 eV, EI): *m/z* (%): 220 [M^+] (36), 219 (100), 218 (11), 207 (3), 192 (5), 76 (2), 44 (24).

HRMS for $\mathbf{C_{15}H_{12}N_2}$ (220.1000): 220.0940 (M^+).

3. Metalating N-Heterocycles using the Frustrated Lewis Pair TMPMgCl·BF_3 Followed by Addition to Aromatic Aldehydes and Activated Ketones

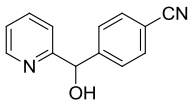
3.1. Typical Procedure

Typical Procedure for the metalation with "TMPMgCl·BF_3·LiCl"(21) (TP2):

A dry and argon flushed 20 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 m in THF) and cooled to the indicated temperature. BF_3·OEt_2 (312 mg, 2.2 mmol) was added dropwise and the resulting mixture was stirred for 10 min before the corresponding *N*-heteroarene (2.0 mmol) dissolved in dry THF (10 mL) was added. The reaction mixture was stirred at the given temperature 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.

3.2. Addition to Aromatic Aldehydes and Activated Ketones

Synthesis of 4-[hydroxy(pyridin-2-yl)methyl]benzonitrile (42a):



According to **TP2**, pyridine (**40a**, 158 mg, 2.0 mmol) reacted with BF_3·OEt_2 (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 4-Cyanobenzaldehyde (**43a**, 1.6 mmol, 288 mg) was added and the mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:2) furnished **42a** as pale yellow oil (246 mg, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm: 8.58 (d, J = 6.0 Hz, 1H), 7.62 – 7.70 (m, 3H), 7.52 (d, J = 8.0 Hz, 2H), 7.20 – 7.26 (m, 1H), 7.18 (d, J = 6.0 Hz, 1H) 5.81 (s, 1H).

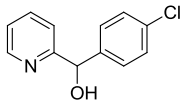
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm: 159.4, 148.3, 148.0, 137.0, 132.2, 127.4, 122.8, 121.0, 118.5, 111.4, 74.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3192, 3062, 2872, 2228, 1738, 1724, 1668, 1608, 1592, 1572, 1502, 1472, 1436, 1406, 1312, 1196, 1114, 1056, 870, 810, 780, 750, 616.

MS (70 eV, EI): *m/z* (%) = 210 [M^+] (100), 192 (15), 130 (17), 108 (42), 102 (18), 80 (18), 79 (91), 51 (20).

HRMS (EI) for **$C_{13}H_{10}N_2O$** (210.0793): 210.0791 (M^+).

Synthesis of (4-chlorophenyl)(pyridin-2-yl)methanol (42b):



According to **TP2**, pyridine (**40a**, 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 4-Chlorobenzaldehyde (**43b**, 1.6 mmol, 225 mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 2:1) furnished **42b** as pale yellow solid (239 mg, 68%).

M. p. (°C): 96.3-97.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm: 8.59 (d, J = 4.5 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.15 – 7.44 (m, 6H), 5.95 (br, 1H), 5.84 (s, 1H).

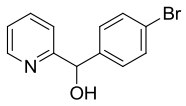
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm: 160.2, 146.8, 141.2, 138.2, 133.8, 128.8, 128.4, 122.9, 121.8, 73.8.

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* (%) =219 [M^+] (100), 217 (41), 201 (47), 188 (46), 139 (40), 111 (25), 108 (40), 79 (94).

HRMS (EI) for **$C_{12}H_{10}ClNO$** (219.0451): 219.0444 (M^+).

Synthesis of (4-bromophenyl)(pyridin-2-yl)methanol (42c):



According to **TP2**, pyridine (**40a**, 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 4-Bromobenzaldehyde (**43c**, 1.6 mmol, 296 mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 2:1) furnished **42c** as pale white solid (282 mg, 67%).

M.p. (°C): 97.5-99.1.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56 (dt, *J* = 5.0, 1.6 Hz, 1H), 7.66 (td, *J* = 7.6, 1.6 Hz, 1H), 7.42 – 7.50 (m, 2H), 7.19 – 7.31 (m, 3H), 7.13 – 7.18 (m, 1H), 5.74 (s, 1H), 5.12 (br s, 1H).

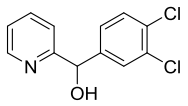
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.3, 147.6, 142.1, 137.2, 131.6, 128.7, 122.7, 121.8, 121.3, 74.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = cm-1, 3136, 2919, 2896, 2848, 1738, 1591, 1570, 1489, 1469, 1438, 1404, 1333, 1232, 1215, 1190, 1154, 1112, 1072, 1056, 1014, 1001, 946, 855, 846, 831, 808, 769, 745, 714, 682.

MS (EI, 70 eV): m/z (%) = 264 [M+H$^+$] (16), 166 (6), 108 (31), 79 (100), 52 (10).

HRMS (EI) for **$C_{12}H_{11}BrNO$** (264.0019): 263.9923 ([M+H]$^+$).

Synthesis of (3,4-dichlorophenyl)(pyridin-2-yl)methanol (42d):



According to **TP2**, pyridine (**40a**, 158 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 3,4-Dichlorobenzaldehyde (**43d**, 1.6 mmol, 280 mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:1) furnished **42d** as pale yellow oil (268 mg, 66%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56 (dt, *J* = 4.7, 1.7 Hz, 1H), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.14 – 7.26 (m, 3H), 5.70 (s, 1H).

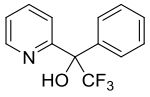
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.7, 148.0, 143.4, 137.1, 132.6, 131.7, 130.5, 128.9, 126.3, 122.8, 121.2, 73.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3178, 1738, 1593, 1571, 1466, 1435, 1416, 1385, 1312, 1257, 1230, 1216, 1190, 1148, 1129, 1099, 1045, 1029, 1002, 908, 895, 847, 811, 787, 748, 720, 706, 678.

MS (EI, 70 eV): m/z (%) = 253 [M$^+$] (33), 111 (12), 108 (38), 79 (100), 52 (11).

HRMS (EI) for **$C_{12}H_9Cl_2NO$** (253.0061): 253.0052 (M$^+$).

Synthesis of 2,2,2-trifluoro-1-phenyl-1-(pyridin-2-yl)ethanol (42e):



According to **TP2**, pyridine (**40a**, 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 2,2,2-Trifluoro-1-phenylethanone (**43e**, 1.6 mmol, 279mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:1) furnished **42e** as yellow oil (292 mg, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 – 8.63 (m, 1H), 7.73 – 7.79 (m, 1H), 7.64 – 7.69 (m, 2H), 7.50 (dq, *J* = 8.0, 1.0 Hz 1H), 7.30 – 7.40 (m, 4H), 6.02 (s, br, 1H).

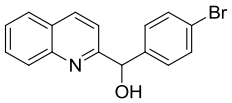
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.0, 147.2, 138.3, 137.4, 128.6, 128.4, 127.8 (q, J_{CF} = 10 Hz) 127.0 (q, J_{CF} = 2.0 Hz), 125.0 (q, J_{CF} = 286 Hz), 124.0, 122.9 (q, J_{CF} = 2.0 Hz).

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), 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 (M^+).

Synthesis of (4-bromophenyl)(quinolin-2-yl)methanol (42f):



According to **TP2**, quinoline (**40b**, 302 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 40 min. 4-Bromobenzaldehyde (**43c**, 1.6 mmol, 296 mg) was added and the reaction mixture was slowly warmed to -20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **42f** as white solid (325 mg, 65%).

M.p. (°C): 118.9-120.0.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (d, *J* = 9.6 Hz, 1H), 8.08 (d, *J* 0 8.5 Hz, 1H), 7.74 – 7.84 (m, 2H), 7.55 – 7.60 (m, 1H), 7.45 – 7.50 (m, 2H), 7.27 – 7.33 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 5.84 (s, 1H).

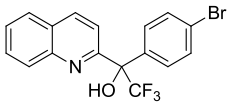
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 145.9, 141.8, 137.2, 131.7, 130.1, 129.1, 128.7, 127.6, 127.5, 126.8, 122.0, 119.0, 74.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2360, 2334, 1738, 1729, 1665, 1585, 1565, 1502, 1480, 1459, 1427, 1392, 1316, 1293, 1274, 1248, 1230, 1209, 1179, 1165, 1109, 1067, 1045, 1008, 967, 958, 923, 858, 846, 830, 794, 770, 741, 720, 693.

MS (EI, 70 eV): m/z (%) = 313 [M^+] (100), 298 (11), 217 (14), 158 (48), 129 (93), 77 (11).

HRMS (EI) for **$C_{16}H_{12}BrNO$** (313.0102): 313.0089 (M^+).

Synthesis of 1-(4-bromophenyl)-2,2,2-trifluoro-1-(quinolin-2-yl)ethanol (42g):



According to **TP2**, quinoline (**40b**, 302 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 40 min. 1-(4-Bromophenyl)-2,2,2-trifluoroethanone (**43f**, 1.6 mmol, 405 mg) was added and the reaction mixture was slowly warmed to 0 °C and stirred for 19 h at this temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) furnished **42g** as colorless viscous oil (325 mg, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.23 (d, *J* = 8.9 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.79 – 7.86 (m, 1H), 7.48 – 7.68 (m, 6H).

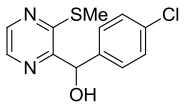
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.0 (q, J_{CF} = 0.8 Hz), 145.2, 138.0, 137.1, 131.6, 130.6, 128.8 (q, J_{CF} = 2.0 Hz), 128.8, 127.9, 127.8, 127.5, 124.8 (q, J_{CF} = 286 Hz), 123.0, 119.4 (q, J_{CF} = 2.6 Hz), 77.7 (q, J_{CF} = 29 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3264, 3065, 2353, 2323, 2155, 1738, 1620, 1596, 1573, 1504, 1489, 1470, 1454, 1398, 1380, 1306, 1278, 1259, 1218, 1191, 1158, 1153, 1124, 1084, 1010, 989, 941, 932, 870, 823, 809, 787, 776, 754, 736, 712, 665.

MS (EI, 70 eV): m/z (%) = 381 [M^+] (16), 314 (35), 256 (10), 226 (21), 204 (12), 128 (100).

HRMS (EI) for **$C_{17}H_{11}BrF_3NO$** (380.9976): 380.9973 (M^+).

Synthesis of (4-chlorophenyl)(3-(methylthio)pyrazin-2-yl)methanol (45a):



According to **TP2**, 2-(methylthio)pyrazine (**44a**, 252 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40°C for 10 min. 4-Chlorobenzaldehyde (**43b**, 1.6 mmol, 225 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **45a** as yellow solid (268 mg, 63%).

M.p. (°C): 123.6-124.7.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 (s, 2H), 7.33 (s, 4H), 5.78 (s, 1H), 2.55 (s, 3H).

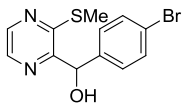
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.4, 150.8, 141.9, 141.4, 140.6, 133.9, 128.9, 128.1, 73.1, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3292, 2357, 2333, 1738, 1730, 1591, 1502, 1488, 1466, 1454, 1411, 1378, 1371, 1366, 1334, 1324, 1284, 1276, 1268, 1233, 1217, 1195, 1112, 1092, 1070, 1029, 1016, 960, 928, 901, 872, 842, 823, 771, 732, 702, 690.

MS (EI, 70 eV): m/z (%) = 266 [M^+] (100), 250 (32), 139 (37), 127 (73), 111 (23), 77 (27), 43 (36).

HRMS (EI) for **$C_{12}H_{11}ClN_2OS$** (266.0281): 266.0276 (M^+).

Synthesis of (4-bromophenyl)(3-(methylthio)pyrazin-2-yl)methanol (45b):



According to **TP2**, 2-(methylthio)pyrazine (**44a**, 252 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40°C for 10 min. 4-Bromobenzaldehyde (**43c**, 1.6 mmol, 296 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **45b** as yellow solid (329 mg, 66%).

M.p. (°C): 129.8-131.4.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (d, *J* = 1.7 Hz, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 7.45 – 7.50 (m, 2H), 7.24 – 7.29 (m, 2H), 5.77 (s, 1H), 2.55 (s, 3H).

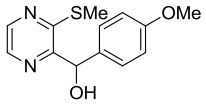
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.5, 150.7, 141.9, 141.4, 141.1, 131.8, 128.4, 122.1, 73.2, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3288, 2931, 2872, 2360, 1738, 1589, 1574, 1503, 1483, 1464, 1406, 1333, 1293, 1282, 1265, 1234, 1192, 1112, 1072, 1065, 1028, 1011, 961, 928, 900, 871, 840, 818, 769, 731, 725, 699, 668.

MS (EI, 70 eV): m/z (%) = 228 [M+H$^+$] (3), 127 (20), 77 (9), 61 (16), 45 (13), 43 (100).

HRMS (EI) for **$C_{12}H_{12}BrN_2OS$** (310.9848): 310.9771 ([M+H]$^+$).

Synthesis of (4-methoxyphenyl)(3-(methylthio)pyrazin-2-yl)methanol (45c):



According to **TP2**, 2-(methylthio)pyrazine (**44a**, 252 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –40°C for 10 min. 4-Methoxybenzaldehyde (**43g**, 1.6 mmol, 218 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **45c** as yellow solid (282 mg, 67%).

M.p. (°C): 65.7-67.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 (s, 2H), 7.22 – 7.31 (m, 2H), 6.82 – 6.29 (m, 2H), 5.74 (s, 1H), 3.76 (s, 3H), 3.66 (br, s, 1H), 2.53 (s, 3H).

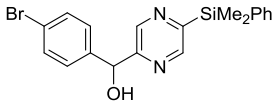
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.4, 155.8, 151.6, 142.0, 141.2, 134.3, 128.1, 114.1, 73.4, 55.2, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3266, 3017, 2928, 1738, 1607, 1586, 1508, 1461, 1440, 1428, 1366, 1352, 1337, 1305, 1286, 1242, 1228, 1205, 1181, 1133, 1116, 1057, 1025, 970, 960, 932, 895, 871, 838, 828, 787, 755, 738, 709, 666.

MS (EI, 70 eV): m/z (%) = 262 [M$^+$] (68), 154 (17), 137 (100), 135 (72), 121 (29), 77 (26).

HRMS (EI) for **$C_{13}H_{14}N_2O_2S$** (262.0776): 262.0770 (M$^+$).

Synthesis of (4-bromophenyl)(5-(dimethyl(phenyl)silyl)pyrazin-2-yl)methanol (45d):



According to **TP2**, 2-(dimethyl(phenyl)silyl)pyrazine (**44b**, 107 mg, 0.5 mmol) reacted with $BF_3 \cdot OEt_2$ (78 mg, 0.55 mmol) and TMPMgCl·LiCl (**14**, 0.49 mL, 0.55 mmol, 1.13 M in THF) at −40°C for 15 min. 4-Bromobenzaldehyde (**43c**, 0.6 mmol, 111 mg) was added and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 9:1) furnished **45d** as yellow oil (133 mg, 67%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.72 (d, *J* = 1.7 Hz, 1H), 8.53 (d, *J* = 1.7 Hz, 1H), 7.56 – 7.68 (m, 2H), 7.46 – 7.51 (m, 2H), 7.34 – 7.45 (m, 3H), 7.26 – 7.31 (m, 2H), 5.79 (s, 1H), 0.65 (s, 6H).

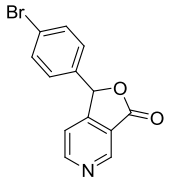
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.7, 147.2, 146.0, 144.1, 140.9, 135.6, 134.1, 131.9, 129.8, 128.5, 128.1, 122.2, 73.2, -3.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = cm-1, 3067, 3047, 2958, 2854, 1665, 1585, 1564, 1500, 1486, 1462, 1428, 1397, 1316, 1277, 1247, 1220, 1190, 1175, 1154, 1111, 1068, 1034, 1011, 998, 930, 920, 869, 834, 807, 786, 775, 756, 749, 737, 699, 680, 667, 655.

MS (EI, 70 eV): m/z (%) = 398 [M^+] (71), 397 (100), 385(24), 383 (28), 381 (28), 213 (21), 182 (32), 145 (19), 137 (23), 135 (63), 61 (18), 43 (81).

HRMS (EI) for **$C_{19}H_{18}BrN_2OS$** (397.0377): 397.0369 ([M-H]$^+$).

Synthesis of 1-(4-bromophenyl)furo[3,4-c]pyridin-3(1*H*)-one (48a):



According to **TP2**, ethyl nicotinate (**46a**, 302 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 30 min. 4-Bromobenzaldehyde (**43c**, 1.6 mmol, 296 mg) was added and the reaction mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:1) furnished **48a** as white solid (416 mg, 72%).

M.p. (°C): 155.5-157.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.24 (s, 1H), 8.86 (d, *J* = 5.3 Hz, 1H), 7.50 – 7.58 (m, 2H), 7.34 (d, *J* = 5.3 Hz, 1H), 7.11 – 7.19 (m, 2H), 6.39 (s, 1H).

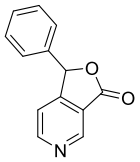
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.1, 157.3, 153.6, 148.1, 133.7, 132.5, 128.4, 124.1, 121.8, 117.8, 81.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1758, 1606, 1590, 1487, 1421, 1410, 1334, 1301, 1241, 1212, 1201, 1149, 1110, 1068, 1028, 1014, 984, 957, 944, 904, 862, 833, 824, 794, 762, 728, 695, 664.

MS (EI, 70 eV): m/z (%) = 289 [M^+] (90), 210 (43), 183 (34), 166 (100), 139 (26), 133 (21), 105 (51).

HRMS (EI) for **$C_{13}H_8BrNO_2$** (288.9738): 288.9732 (M^+).

Synthesis of 1-phenylfuro[3,4-c]pyridin-3(1*H*)-one (48b):

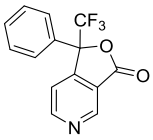


According to **TP2**, ethyl nicotinate (**46a**, 302 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 30 min. Benzaldehyde (**43h**, 1.6 mmol, 212 mg) was added and the reaction mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. The crude product was recrystallized from a mixture of EtOAc/EtOH to give **48b** as white solid (165 mg, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.15 (d, *J* = 1.2 Hz, 1H), 8.75 (d, *J* = 6.2 Hz, 1H), 7.32 (dd, *J* = 1.4, 6.1 Hz, 1H), 7.25 – 7.48 (m, 5H), 6.61 (s, 1H)

The analytical data was found to match the literature.[120]

Synthesis of 1-phenyl-1-(trifluoromethyl)furo[3,4-*c*]pyridin-3(1*H*)-one (48c):



According to **TP2**, ethyl nicotinate (**46a**, 302 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 30 min. 2,2,2-Trifluoro-1-phenylethan-1-one (**43e**, 1.6 mmol, 296 mg) was added and the reaction mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **48c** as slightly yellow solid (295 mg, 65%).

[120] S. Broussy, V. Bernardes-Génisson, H. Gornitzka, J. Bernadou, B. Meuniera *Org. Biomol. Chem.* **2005**, *3*, 666.

M.p. (°C): 92.8-94.4.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.26 (s, 1H), 9.02 (d, *J* = 5.2 Hz, 1H), 7.88 (d, *J* = 5.2 Hz, 1H), 7.65 – 7.80 (m, 2H), 7.37 – 7.53 (m, 3H).

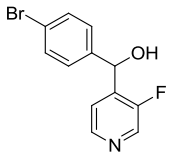
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.0, 154.4, 148.9, 137.4, 130.8, 130.4, 126.3 (q, J_{CF} = 1.5 Hz), 123.4, 122.6 (q, J_{CF} = 284 Hz), 121.7, 118.7, 85.5 (q, J_{CF} = 33 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3043, 2984, 2360, 1795, 1754, 1722, 1604, 1592, 1493, 1451, 1427, 1368, 1313, 1282, 1257, 1228, 1188, 1166, 1150, 1113, 1093, 1070, 1042, 1023, 1000, 965, 946, 916, 847, 835, 822, 784, 762, 746, 720, 710, 695, 672, 655.

MS (EI, 70 eV): m/z (%) = 279 [M^+] (21), 211 (50), 210 (100), 127 (29), 105 (25), 77 (39), 51 (18), 42 27).

HRMS (EI) for **$C_{14}H_8F_3NO_2$** (279.0507): 279.0497 (M^+).

Synthesis of (4-bromophenyl)(3-fluoropyridin-4-yl)methanol (48d):



According to **TP2**, 3-fluoropyridine (**46b**, 194 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at –78 °C for 10 min. 4-Bromobenzaldehyde (**43c**, 1.6 mmol, 296 mg) was added and the reaction mixture was stirred for 45 min at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:2) furnished **48d** as white solid (364 mg, 81%).

M.p. (°C): 161.6-163.2.

^{1}H-NMR (400 MHz,THF-d_8): δ / ppm = 8.36 (d, *J* = 4.9 Hz, 1H), 8.32 (s, 1H), 7.59 (t, *J* = 4.9 Hz, 1H), 7.48 – 7.82 (m, 2H), 7.30 – 7.36 (m, 2H), 6.00 (d, *J* = 2.6 Hz, 1H), 5.50 (d, *J* = 3.5 Hz, 1H).

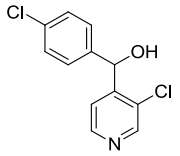
^{13}C-NMR (100 MHz, THF-d_8): δ / ppm = 157.7 (d, J_{CF} = 254 Hz), 147.2 (d, J_{CF} = 5 Hz), 143.6 (d, J_{CF} = 0.8 Hz), 141.2 (d, J_{CF} = 11 Hz), 138.5 (d, J_{CF} = 23 Hz), 132.4, 129.4 122.4, 122.3, 68.6 (d, J_{CF} = 2 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3124, 2854, 2682, 2351, 2199, 1973, 1754, 1738, 1729, 1715, 1612, 1588, 1494, 1482, 1470, 1462, 1453, 1446, 1434, 1413, 1401, 1378, 1372, 1332, 1313, 1275, 1240, 1227, 1194, 1184, 1166, 1151, 1103, 1069, 1052, 1010, 960, 909, 875, 840, 825, 795, 754, 738, 714, 676.

MS (EI, 70 eV): m/z 281 (M^+, 68%), 202 (100), 187 (25), 157 (18), 124 (71), 97 (20), 77 (22).

HRMS (EI) for **$C_{12}H_9BrFNO$** (280.9852): 280.9842 (M^+).

Synthesis of (4-chlorophenyl)(3-chloropyridin-4-yl)methanol (48e):



According to **TP2**, 3-chloropyridine (**46c**, 227 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at −78 °C for 45 min. 4-Chlorobenzaldehyde (**43b**, 1.6 mmol, 225 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:2) furnished **48e** as white solid (293 mg, 71%).

M.p. (°C): 139.9-140.7.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (d, *J* = 5.0 Hz, 1H), 8.43 (s, 1H), 7.66 (d, *J* = 5.0 Hz, 1H), 7.31 (s, 4H), 6.09 (s, 1H).

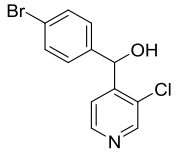
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.5, 149.2, 148.0, 139.2, 134.3, 130.0, 128.9, 128.5, 121.9, 71.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3116, 2846, 2359, 1908, 1590, 1488, 1475, 1434, 1403, 1331, 1314, 1288, 1269, 1216, 1180, 1165, 1104, 1092, 1064, 1041, 1013, 982, 960, 868, 856, 836, 825, 808, 750, 732, 714, 692.

MS (EI, 70 eV): m/z (%) = 253 [M^+] (100), 218 (85), 139 (84), 111 (37), 77 (47).

HRMS (EI) for **$C_{12}H_9Cl_2NO$** (253.0061): 253.0060 (M^+).

Synthesis of (4-bromophenyl)(3-chloropyridin-4-yl)methanol (48f):



According to **TP2**, 3-chloropyridine (**46c**, 227 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at −78 °C for 45 min. 4-Bromobenzaldehyde (**43c**, 1.6 mmol, 225 mg) was added and the reaction mixture was stirred for 3 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:1) furnished **48f** as white solid (339 mg, 71%).

M.p. (°C): 148.9-151.2

^{1}H-NMR (400 MHz, THF-d_8): δ / ppm = 8.39 – 8.53 (m, 2H), 7.68 (d, *J* = 5.0 Hz, 1H), 7.41 – 7.49 (m, 2H), 7.23 – 7.37 (m, 2H), 6.00 (d, *J* = 3.4 Hz, 1H), 5.54 (d, *J* = 3.8 Hz, 1H).

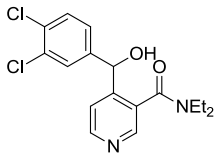
^{13}C-NMR (100 MHz, THF-d_8): δ / ppm = 151.5, 150.2, 149.3, 142.9, 132.4, 130.0, 123.1, 122.3, 108.5, 71.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =cm-1, 3112, 3027, 2970, 2845, 2360, 2337, 1739, 1729, 1588, 1574, 1485, 1470, 1462, 1445, 1434, 1415, 1400, 1366, 1332, 1313, 1286, 1267, 1228, 1217, 1210, 1180, 1166, 1104, 1094, 1064, 1041, 1009, 982, 959, 867, 855, 836, 823, 804, 746, 730, 711, 676.

MS (EI, 70 eV): m/z (%) = 297 [M$^+$] (57), 218 (100), 187 (46), 183 (15), 159 (17), 157 (20), 140 (74), 115 (16), 77 (28), 61 (19), 43 (68).

HRMS (EI) for **$C_{12}H_9BrClNO$** (296.9556): 296.9544 (M$^+$).

Synthesis of 4-((3,4-dichlorophenyl)(hydroxy)methyl)-*N*,*N*-diethylnicotinamide (48g):



According to **TP2**, *N*,*N*-diethylnicotinamide (**46d**, 366 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (**14**, 1.95 mL, 2.2 mmol, 1.13 M in THF) at −78 °C for 10 min. 3,4-Dichlorobenzaldehyde (**43d**, 280 mg, 1.6 mmol) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) 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*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:5) furnished **48g** as white solid (360 mg, 80%).

M.p. (°C): 108.8-110.0.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.64 (d, *J* = 5.0 Hz, 1H), 8.44 (s, 1H), 7.35 – 7.48 (m, 3H), 7.09 – 7.16 (m, 1H), 5.75 (s, 1H), 3.24 – 3.53 (m, 2H), 2.68 – 3.01 (m, 2H), 0.37 – 0.84 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.8, 151.2, 150.1, 147.0, 142.0, 132.5, 131.7, 130.6, 130.2, 128.7, 128.5, 126.0, 77.2, 43.3, 39.4, 13.7, 12.2.

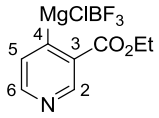
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3075, 3063, 2996, 2975, 2877, 2838, 1628, 1597, 1566, 1504, 1462, 1437, 1408, 1396, 1375, 1364, 1348, 1339, 1318, 1308, 1295, 1274, 1244, 1227, 1215, 1200,

1183, 1151, 1126, 1103, 1082, 1066, 1057, 1029, 998, 981, 957, 944, 902, 882, 869, 849, 834, 808, 792, 776, 748, 734, 701, 678.

HRMS (ESI) for $\mathbf{C_{17}H_{19}C_{l2}N_2O_2^+}$ (353.0818): 353.0815 ($[M+H]^+$).

3.3. Synthesis and Spectra of the Intermediates

Low temperature NMR-studies of the metalated intermediate 47a



In order to provide structural information on the 4-metalated pyridines of type **47** we investigated the metalation of ethyl nicotinate (**46a**) with TMPMgCl·BF_3 (**21**) at -40 °C (the metalation of the other 3-substituted pyridines **46b-d** could not be examined due to the low stability of the metalated intermediates). Therefore 0.55 mmol (0.49 mL, 1.13 M in THF) of TMPMgCl·LiCl (**14**) were put in a dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar. The solvent was removed *in vacuo* to give TMPMgCl·LiCl (**14**) as a light brown slurry. The base was redissolved in THF-d_8 (ca. 0.5 mL) and reacted with BF_3·OEt_2 (0.55 mmol, 78 mg, see **TP2**). Ethyl nicotinate (**46a**, 0.5 mmol, 75.6 mg), dissolved in 1.5 mL THF-d_8, was slowly added at -40 °C and the reaction was stirred for 30 min. Then the Schlenk-tube was cooled down to -50 °C and ca. 0.7 mL of the reaction mixture were cannulated in a dry, argon flushed NMR-tube, which was cooled at -78 °C. Then several NMR studies were performed at -50 °C, including ^{1}H-, ^{13}C- ^{11}B and ^{19}F-NMR. The spectra showed in addition to the characteristic signals of the BF_3-complex **47a** also the signals of free TMPH and BF_3·OEt_2 in addition the BF_3 complex **49**.

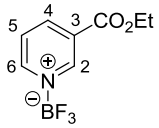
^{1}H-NMR (400 MHz, THF-d_8): δ / ppm: 8.68 (s, 2-H, 1H), 8.42 (d, J_{56} = 4.0 Hz, 6-H, 1H), 8.18 (d, J_{56} 4.0 Hz, 5-H, 1H), 4.43 (q, J_{CH2CH3} = 6.8 Hz, CH_2, 2H), 1.46 (t, J_{CH2CH3} = 6.8 Hz, CH_3, 3H).

^{13}C-NMR (100 MHz, THF-d_8): δ / ppm: 223.0 (4-C), 173.6 (C=O), 137.2 (6-C), 137.0 (2-C), 136.6 (5-C), 135.9 (3-C), 63.8 (CH_2), 13.7 (CH_3).

^{11}B-NMR (128 MHz, THF-d_8): δ / ppm: -0.5.

^{19}F-NMR (376 MHz, THF-d_8): δ / ppm: -151.64 (^{10}B isotopomer), -151.71 (^{11}B isotopomer).

Synthesis and NMR-studies of (3-(ethoxycarbonyl)pyridin-1-ium-1-yl)trifluoroborate (49)



A dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with 45 mg ethyl nicotinate (**46a**, 0.3 mmol) in 0.6 mL THF-d_8 and cooled to 0 °C. $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. The complex **49** was then transferred in a dry, argon flushed NMR-tube which was cooled at -50 °C, and characterized with ^{1}H-, ^{13}C- ^{11}B and ^{19}F-NMR. The spectra showed in addition to the characteristic signals of the BF_3-complex **49** also the signals of free $BF_3 \cdot OEt_2$.

^{1}H-NMR (400 MHz, THF-d_8): δ / ppm: 9.14 (s, 2-H, 1H), 9.00 (d, J_{56} = 5.6 Hz, 6-H, 1H), 8.94 (dt, J_{45} = 8.0 Hz, J_{46} 1.6 Hz, 4-H, 1H), 8.12 (dd, J_{45} = 8.0 Hz, J_{56} = 5.6 Hz, 5-H, 1H), 4.44 (q, J_{CH2CH3} = 7.2 Hz, CH_2, 2H), 1.43 (t, J_{CH2CH3} = 7.2 Hz, CH_3, 3H).

^{13}C-NMR (100 MHz, THF-d_8): δ / ppm: 162.4 (C=O), 146.8 (q, J_{CF} 2.0 Hz, 6-C), 144.0 (4-C), 143.9 (q, J_{CF} 2.2 Hz, 2-C), 129.5 (3-C), 127.1 (5-C), 62.4 (CH_2), 13.6 (CH_3).

^{11}B-NMR (128 MHz, THF-d_8): δ / ppm: -0.4.

^{19}F-NMR (376 MHz, THF-d_8): δ / ppm: -151.15 (^{10}B isotopomer), -151.22 (^{11}B isotopomer).

When complex **49** was treated with another equivalent of $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) at 0 °C in THF-d_8, no shift change for the carbonyl group could be observed in the ^{13}C-NMR indicating that the ester group coordinates to the excess Lewis acid. However, what can be observed is a coordination of the BF_3 to the THF-d_8 resulting in a low field shift in the ^{13}C-NMR from 66.7 to 69.4 ppm and 24.4 to 25.5 ppm, respectively (see Figure 5 and Figure 6).

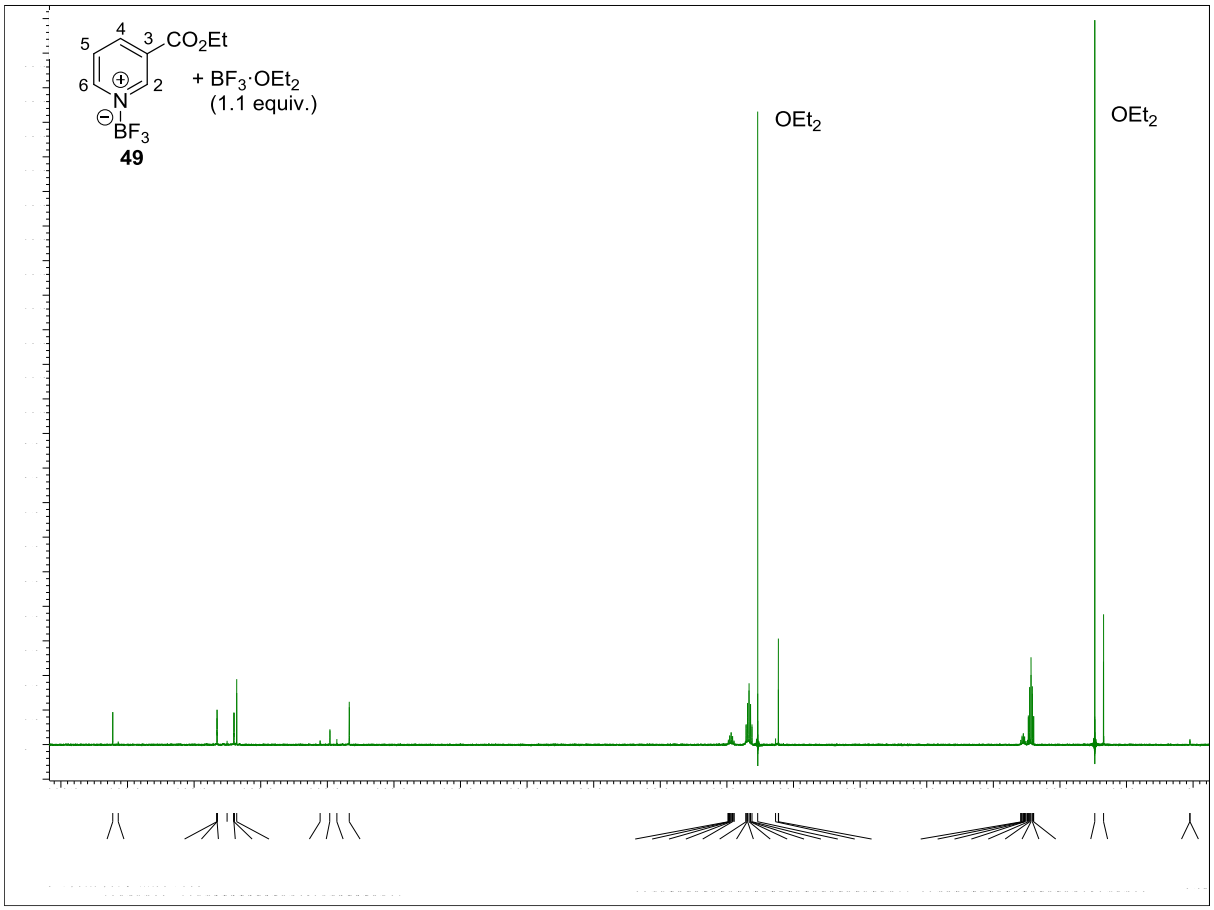


Figure 5: ^{13}C-NMR spectrum of complex **49** with another 1.1 equivalents of $BF_3{\cdot}OEt_2$ in THF-d_8 at -50 °C.

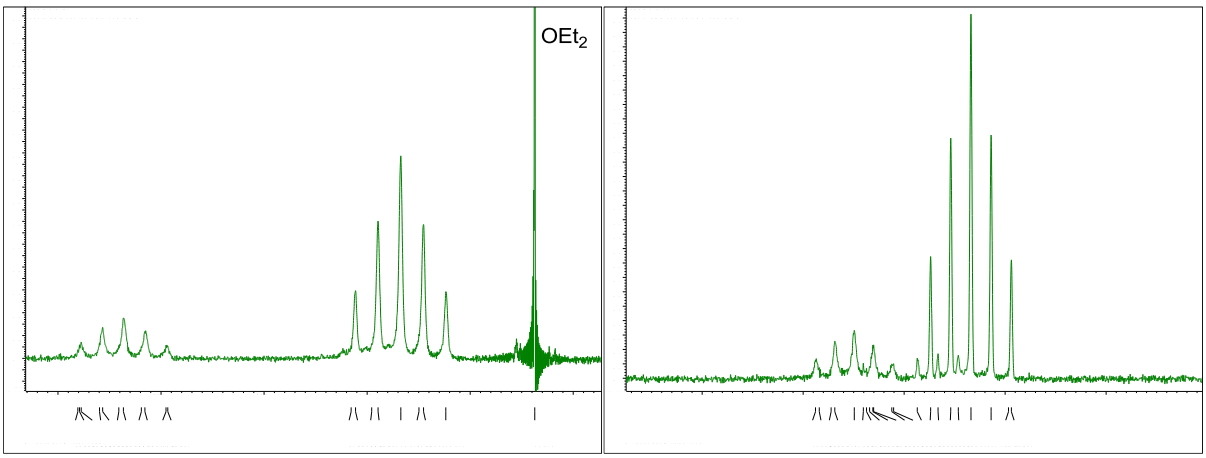


Figure 6: Expansion of the THF-d_8 signals of Figure 5.

The same effect can be observed, when ethyl benzoate (**52**, 45 mg, 0.3 mmol) is treated with 1.1 equivalents of $BF_3{\cdot}OEt_2$ (47 mg, 0.33 mmol) in THF-d_8 (0.6 mL) under the same conditions (Figure 7 and Figure 8).

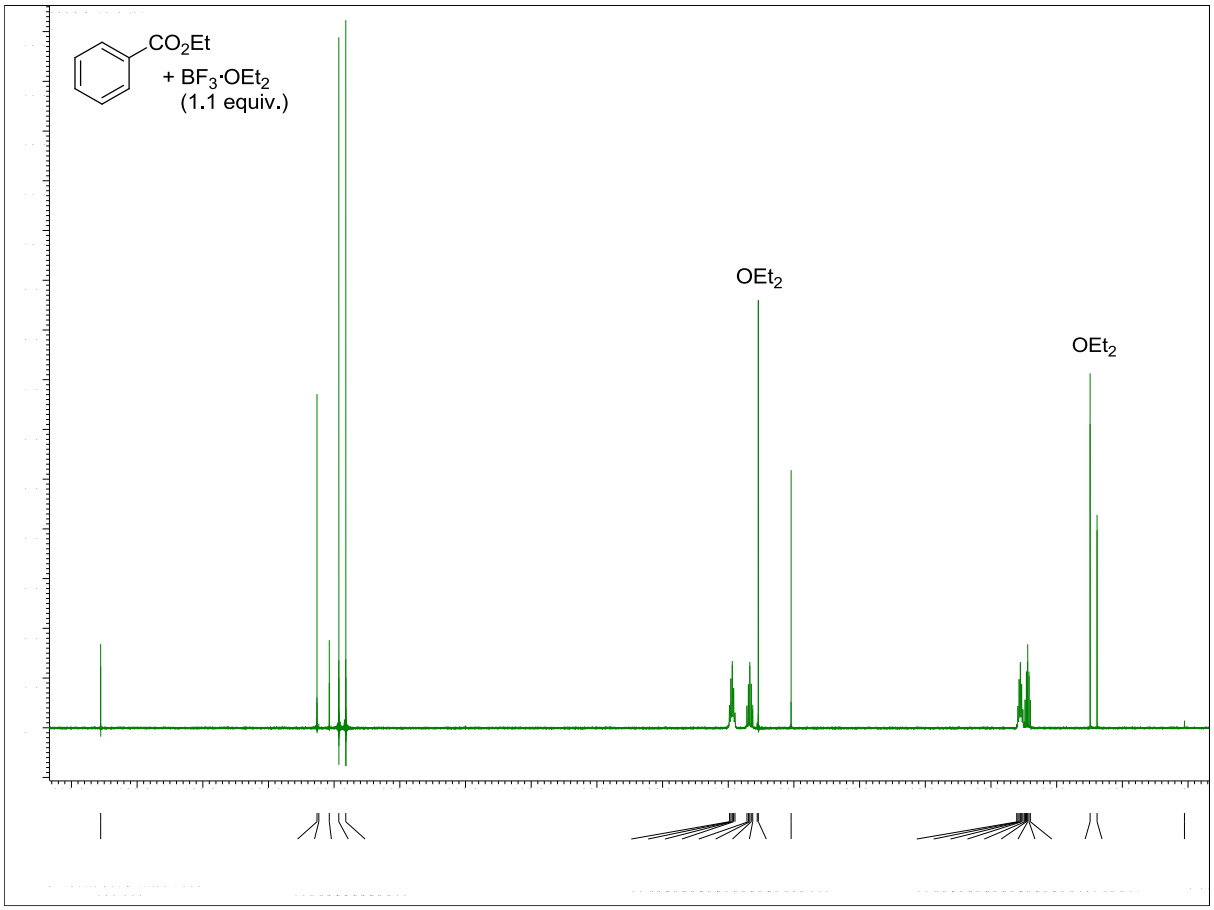


Figure 7: ^{13}C-NMR spectrum of ethyl benzoate with 1.1 equivalents of $BF_3 \cdot OEt_2$ in THF-d_8 at -50 °C.

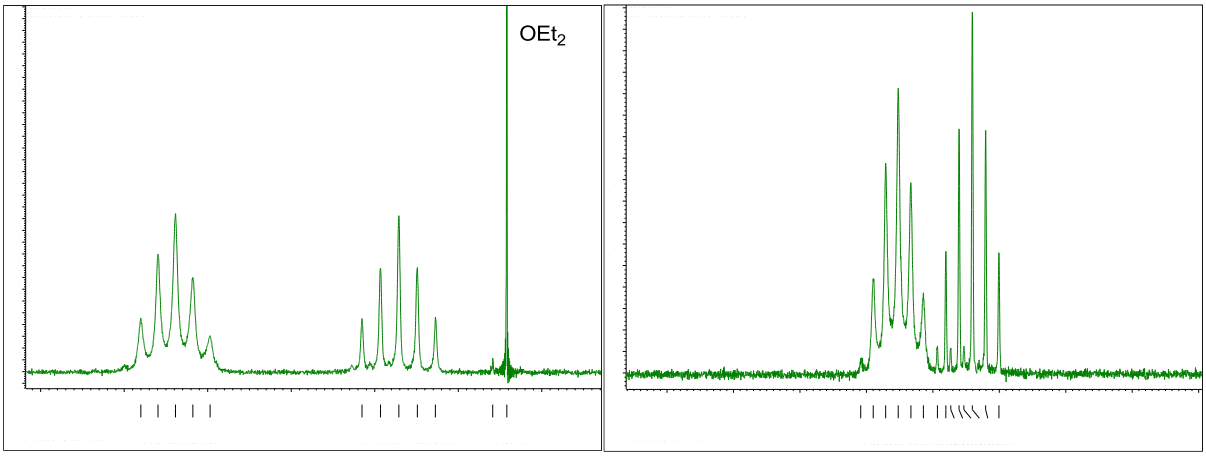
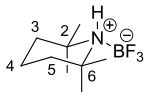


Figure 8: Expansion of the THF-d_8 signals of Figure 7.

Synthesis and NMR-studies of trifluoro(2,2,6,6-tetramethylpiperidin-1-ium-1-yl)borate (50)



A dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with 42 mg 2,2,6,6-tetramethylpiperidine (0.3 mmol) in 0.6 mL THF-d_8 and cooled to 0 °C. $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. The solution of complex **50** was then transferred in a dry, argon flushed NMR-tube which was cooled at -50 °C, and characterized. The spectra showed in addition to the characteristic signals of the BF_3-complex **12** also the signals of free TMPH and $BF_3 \cdot OEt_2$. Due to superposition of those signals in the ^{1}H-NMR spectrum no clear assignment for the ^{1}H-NMR signals was possible.

^{13}C-NMR (100 MHz, THF-d_8): δ / ppm: 58.1 (2-C, 6-C), 40.6 (3-C, 5-C), 31.5 (q, J_{CF} = 4.4 Hz, CH_3), 22.2 (q, J_{CF} = 3.2 Hz, CH_3), 16.5 (4-C).

^{11}B-NMR (128 MHz, THF-d_8): δ / ppm: -0.5 (q, J_{BF} = 20.8 Hz).

^{19}F-NMR (376 MHz, THF-d_8): δ / ppm: -132.35 (d, J_{BF} = 20.3 Hz, ^{10}B isotopomer), -132.46 (d, J_{BF} = 20.3 Hz, ^{11}B isotopomer).

The experiments described above show clearly, that in the case of **47a** the BF_3 is bonded neither to TMPH nor to THF. It is also reasonable to conclude, that the BF_3 does not coordinate to the ester group of the metalated ethyl nicotinate (**47a**). Unfortunately the ^{13}C-NMR signals of the metalated species **47a** are broad ($\Delta_{1/2}$ ca. 5 Hz) and do not show any evidence for a splitting due to coupling with fluorine. Thus we have no evidence for the coordination of BF_3 to the pyridine nitrogen atom.

4. Regioselective Metalations of Pyrimidines by Using Frustrated Lewis Pairs of $BF_3 \cdot OEt_2$ and Hindered Magnesium and Zinc Amide Bases

4.1. Typical Procedures

Typical Procedure for Metalations with TMP-Metal Bases (TP3):

A dry argon flushed Schlenk-flask was charged with a solution of the N-heterocycle (1.0 equiv) in dry THF. After cooling to the given temperature, a THF-solution of the indicated metal TMP-amide base was added dropwise and the reaction mixture was stirred for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF.

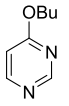
Typical Procedure for BF3-directed Metalations (TP4):

A dry argon flushed Schlenk-flask was charged with a solution of the N-heterocycle (1.0 equiv) in dry THF. After cooling to 0 °C, $BF_3 \cdot OEt_2$ (1.1 equiv.) was added dropwise and the mixture was stirred for 15 min at this temperature. Then, the reaction mixture was cooled to the given temperature followed by dropwise addition of a THF-solution of the indicated metal TMP-amide base and stirred for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF.

4.2. Synthesisof Pyrimidines of Type 55

*Note: The starting materials **55b**, **55c** and **55f** were prepared by Drs. Aleksei Bredihhin and Xavier Mollat du Jourdin.*

Synthesis of 4-butoxypyrimidine (55b):



To a stirred solution of 4,6-dichloropyrimidine (1.56 g, 10.5 mmol) in *n*-butanol (20 mL) sodium butanolate (5.04 g, 10.5 mmol) was added at 25 °C. The reaction mixture was stirred at this temperature till completion. The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) followed by extraction with EtOAc (3 × 40 mL). After drying (Na_2SO_4), the solvents were removed in vacuo. The crude product was redissolved in DCM (50 mL) and nondissolved solids were removed by filtration. Dichloromethane was evaporated *in vacuo* to give the crude 4-butoxy-6-chloropyrimidine (1.95 g, 10.5 mmol) which was used without further purification. To a stirred solution of crude 4-butoxy-6-chloropyrimidine (1.95 g, 10.5 mmol) in MeOH (20 mL), Pd/C (400 mg, 10% active Pd, 0.38 mmol, 4 mol%) and NH_4HCO_2 (2.65 g, 42.0 mmol) were added successively at 40 °C. The reaction mixture was stirred at 40 °C for 1 h and then filtered over celite. The celite was washed with MeOH and the filtrate concentrated in vacuo. The crude product was redissolved in DCM (50 mL) and nondissolved solids were removed by filtration. Dichloromethane was evaporated *in vacuo* to give without further purification the desired 4-butoxypyrimidine (**55b**, 1.43 g, 89%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.75 (s, 1H), 8.40 (d, *J* = 5.89 Hz, 1H), 6.71 (dt, *J* = 5.88, 0.59 Hz, 1H), 4.36 (t, *J* = 6.66 Hz, 2H), 1.68 – 1.81 (m, 2H), 1.38 – 1.53 (m, 2H), 0.96 (t, *J* = 7.36 Hz, 3H).

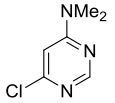
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.2, 158.2, 156.5, 108.7, 66.4, 30.7, 19.1, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3049, 2960, 2935, 2874, 1715, 1579, 1559, 1532, 1480, 1463, 1399, 1376, 1301, 1266, 1225, 1168, 1119, 1062, 1002, 986, 962, 895, 833, 808, 774, 739, 672.

MS (EI, 70 eV): m/z (%) = 152 $[M]^+$ (1), 123 (16), 98 (6), 97 (100), 96 (24), 80 (15), 79 (15), 68 (7).

HRMS for **$C_8H_{12}N_2O$** (152.0950): 152.0980 (M^+).

Synthesis of 6-chloro-*N*,*N*-dimethylpyrimidin-4-amine (55c):



To a stirred solution of 4,6-dichloropyrimidine (1.00 g, 6.70 mmol) in THF (7.0 mL) dimethylamine (1.51 g, 13.4 mmol) was added at 25 °C and stirred for 1 h. The reaction was quenched with brine (50 mL) followed by extraction with EtOAc (3 × 50 mL). After drying (Na_2SO_4), the solvents were removed *in vacuo* to give without further purification the desired 6-chloro-*N*,*N*-dimethylpyrimidin-4-amine (**55c**, 1.01 g, 96%) as a white solid.

M.p. (°C): 106-107.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.34 (s, 1H), 6.39 (s, 1H), 3.09 (s, 6H).

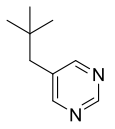
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.7, 159.4, 157.7, 100.9, 37.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 3854, 3746, 3079, 2920, 2873, 2362, 2338, 1718, 1616, 1576, 1560, 1541, 1522, 1506, 1498, 1458, 1431, 1417, 1396, 1343, 1298, 1262, 1217, 1200, 1183, 1106, 1068, 987, 965, 857, 815, 760, 744, 738.

MS (EI, 70 eV): m/z (%) = 157 $[M]^+$ (26), 142 (34), 128 (38), 58 (28), 44 (100), 42 (22).

HRMS for **$C_6H_8ClN_3$** (157.0407): 157.0402 (M^+).

Synthesis of 5-neopentylpyrimidine (55d):



To a stirred solution of neopentyllithium (26 mL, 12.5 mmol, 0.48 M in hexane) in a dry and argon flushed Schlenk-flask 12.5 mmol of $ZnCl_2$ (1 M in THF) were added ad 25 °C. After stirring this mixture for 20 min at the same temperature $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), SPhos (82 mg, 0.2 mmol) and 5-bromopyrimidine (1.59 g, 10 mmol) were added successively. After stirring for 2.5 h at 25 °C the reaction mixture was quenched with aq. NH_4Cl-solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / Et_2O = 1:1) furnished **55d** as off-white solid (1.28 g, 85%)

M.p. (°C): 53.9-55.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.05 (s, 1H), 8.51 (s, 2H), 2.45 (s, 2H), 0.90 (s, 9H).

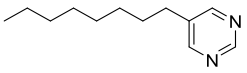
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.8, 156.5, 132.7, 44.4, 31.6, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 2957, 2950, 2937, 2918, 2866, 2851, 1582, 1560, 1476, 1438, 1405, 1364, 1327, 1235, 1206, 1170, 1150, 1139, 1112, 1050, 1032, 988, 920, 900, 832, 806, 764, 744, 730, 652.

MS (EI, 70 eV): m/z (%) = 150 [M^+] (5), 135 (10), 94 (100), 66 (5), 57 (44), 41 (16).

HRMS for **$C_9H_{14}N_2$** (150.1157): 150.1150 (M^+).

Synthesis of 5-octylpyrimidine (55e):



To a stirred solution of OctylMgBr (25.3 mL, 20 mmol, 0.89 M in THF) in a dry and argon flushed Schlenk-flask 20 mmol of $ZnCl_2$ (1 M in THF) were added ad 0 °C. After stirring this mixture for 20 min at the same temperature $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), SPhos (82 mg, 0.2 mmol) and 5-bromopyrimidine (2.54 g, 16 mmol) were added successively. The solution was slowly brought to 25 °C and after stirring for 2.5 h at this temperature the reaction mixture was quenched with aq. NH_4Cl-solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, *iso*-hexane / Et_2O = 1:1) furnished **55e** as colorless oil (1.37 g, 71%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.04 (s, 1H), 8.55 (s, 2H), 2.67 – 2.49 (m, 2H), 1.71 – 1.51 (m, 2H), 1.40 – 1.14 (m, 10H), 0.89 – 0.78 (m, 3H).

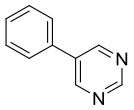
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.6, 156.4, 135.5, 31.7, 30.6, 30.4, 29.20, 29.1, 29.0, 22.6, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 3045, 3020, 2955, 2925, 2855, 1582, 1559, 1465, 1436, 1409, 1378, 1232, 1195, 1169, 1127, 1046, 903, 829, 797, 728.

MS (EI, 70 eV): m/z (%) = 192 [M^+] (10), 135 (21), 121 (15), 107 (100), 94 (84), 66 (15), 57 (19), 43 (23), 41 (24).

HRMS for **$C_{12}H_{20}N_2$** (192.1626): 192.1628 (M^+).

Synthesis of 5-Phenylpyrimidine (55f):

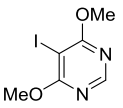


A solution of PhMgCl (17.0 mL, 30.0 mmol, 1.76 M in THF) was cooled at 0 °C. $ZnCl_2$ (33 mmol, 33 mL, 1.0 M in THF) was added and the mixture was stirred for 15 min at the same temperature. Then, a suspension of 5-bromopyrimidine (4.77 g, 30 mmol), $Pd(dba)_2$ (517 mg, 0.90 mmol) and PPh_3 (944 mg, 3.6 mmol) in THF (10 mL) was added and the suspension was heated at 60 °C for 3 h. The reaction was quenched with brine (40 mL), NH_3 (conc., 20 mL) and water (20 mL) followed by extraction with EtOAc (4 × 100 mL) and DCM (1 × 100 mL). After drying ($MgSO_4$), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / EtOAc / NEt_3 = 2:1:0.15) the desired 5-phenylpyrimidine (**55f**, 4.27 g, 91%) was obtained as a colorless liquid.

The analytical data were found to match the literature data.[121]

4.3. Preparation of Pyrimidines of Type 56

Synthesis of 5-iodo-4,6-dimethoxypyrimidine (56a):



According to **TP3**, a mixture of 4,6-dimethoxypyrimidine (**55a**, 140 mg, 1.0 mmol) in dry THF (2.0 mL) reacted with TMPMgCl·LiCl (**14**, 0.96 mL, 1.1 mmol, 1.15 M in THF) for 40 min at 0 °C. Then, a solution of iodine (508 mg, 2.0 mmol) in THF (2.0 mL) was added at the same temperature. The reaction mixture was allowed to warm to 25 °C over 30 min, sat. aq. NaS_2O_3 (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography (silica gel, *iso*-hexane / DCM = 1:1) afforded the desired product **56a** (225 mg, 85%) as a white solid.

M. p. (°C): 155-156.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.26 (s, 1H), 4.03 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.4, 156.6, 62.1, 55.3.

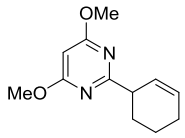
[121] T. Mino, Y. Shirae, M. Sakamoto, T. Fujita, *J. Org. Chem*. **2005**, *70*, 2191.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3011, 2992, 2956, 2926, 2855, 1928, 1890, 1571, 1548, 1522, 1466, 1443, 1407, 1382, 1299, 1283, 1259, 1207, 1175, 1108, 1036, 1023, 967, 893, 826, 776.

MS (EI, 70 eV): m/z (%) = 267 $[M-H]^+$ (100), 237 (14), 109 (12), 82 (20), 42 (17).

HRMS (EI) for **$C_6H_7IN_2O_2$** (265.9552): 265.9547 (M^+).

Synthesis of 2-(cyclohex-2-en-1-yl)-4,6-dimethoxypyrimidine (56b):



According to **TP4**, 4,6-dimethoxypyrimidine (**55a**, 280 mg, 2.0 mmol) in dry THF (2.0 mL) reacted with $BF_3 \cdot OEt_2$ (312 mg, 0.27 mL, 2.2 mmol) and TMPZnCl·LiCl (**20**, 2.25 mL, 2.2 mmol, 0.98 M in THF) at -20 °C for 1 h. The reaction mixture was cooled to -40 °C and CuCN·2LiCl (1.1 mL, 1.1 mmol, 1.0 M in THF) was added. After stirring for 15 min at this temperature, 3-bromocyclohexene (**57a**, 580 mg, 0.42 mL, 3.6 mmol) was added dropwise and the reaction mixture was slowly warmed to 25 °C. The reaction was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying ($MgSO_4$), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 10:1) the desired product **56b** (407 mg, 92%) was obtained as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 5.90 – 6.01 (m, 1H), 5.75 – 5.90 (m, 2H), 3.92 (s, 6H), 3.43 – 3.59 (m, 1H), 2.02 – 2.16 (m, 3H), 1.83 – 2.01 (m, 2H), 1.58 – 1.75 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 172.5, 171.4, 128.3, 127.7, 86.4, 53.8, 44.3, 27.8, 24.9, 21.4.

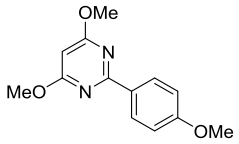
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2988, 2950, 2934, 2862, 2838, 1678, 1582, 1564, 1460, 1390, 1372, 1296, 1280, 1258, 1242, 1214, 1186, 1158, 1094, 1054, 988, 958, 936, 864, 828, 798, 748, 724, 660, 620.

MS (EI, 70 eV): m/z (%) = 220 [M^+] (50), 219 (20), 205 (40), 191 (100), 179 (23), 154 (18), 77

(19), 68 (17).

HRMS for **$C_{12}H_{16}N_2O_2$** (220.1212): 220.1198 (M^+).

Synthesis of 4,6-dimethoxy-2-(4-methoxyphenyl)pyrimidine (56c):



According to **TP4**, 4,6-dimethoxypyrimidine (**55a**, 280 mg, 2.0 mmol) in dry THF (2.0 mL) reacted with $BF_3 \cdot OEt_2$ (312 mg, 0.27 mL, 2.2 mmol) and TMPZnCl·LiCl (**20**, 2.25 mL, 2.2 mmol, 0.98 M in THF) at -20 °C for 1 h. $Pd(dba)_2$ (35 mg, 0.06 mmol, 3 mol%), TFP (28 mg, 0.12 mmol, 6 mol%) and 1-iodo-4-methoxybenzene (**57b**, 468 mg, 2.0 mmol) were added successively and the reaction mixture was stirred at 25 °C for 15 h. The reaction was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying ($MgSO_4$), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 1:5) the desired product **56c** (437 mg, 89%) was obtained as a yellow solid.

M.p. (°C): 90-92.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.42 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 5.92 (s, 1H), 4.04 (s, 6H), 3.88 (s, 3H).

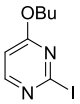
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 171.4, 163.1, 161.8, 130.1, 129.9, 113.5, 87.0, 55.3, 53.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 3024, 2998, 2952, 2938, 2842, 1592, 1564, 1554, 1512, 1492, 1458, 1440, 1418, 1384, 1372, 1304, 1292, 1266, 1250, 1188, 1158, 1130, 1104, 1050, 1030, 988, 918, 898, 842, 814, 790, 778, 732, 696, 678, 668, 634, 620.

MS (EI, 70 eV): m/z (%) = 246 (100), 217 (14), 201 (14), 148 (25), 134 (62), 90 (10), 68 (27).

HRMS for **$C_{13}H_{15}N_2O_3$** (247.1077): 247.1075 ($[M+H]^+$).

Synthesis of 4-butoxy-2-iodopyrimidine (56d):



According to **TP4**, 4-butoxypyrimidine (**55b**, 159 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with $BF_3 \cdot OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 0.89 mL, 1.2 mmol, 1.35 M in THF) at -20 °C for 1 h. Then, a solution of iodine (508 mg, 2.0 mmol) in THF (2.0 mL) was added at the same temperature. The reaction mixture was allowed to warm to 25 °C over 30 min, sat. aq. NaS_2O_3 (5 mL) and NH_3 (conc., 1 mL) were added and the aqueous layer was extracted with EtOAc (3 × 10 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / EtOAc = 9:1) the desired product **56d** (239 mg, 86%) was obtained as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.10 (d, *J* = 5.80 Hz, 1H), 6.68 (d, *J* = 5.6 Hz, 1H), 4.36 (t, *J* = 6.6 Hz, 2H), 1.69 – 1.81 (m, 2H), 1.39 – 1.54 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

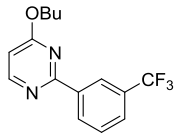
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.3, 157.7, 127.5, 108.0, 67.4, 30.5, 19.0, 13.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2932, 2872, 1562, 1531, 1465, 1437, 1382, 1312, 1267, 1210, 1165, 1147, 1122, 1071, 1059, 1018, 1002, 976, 962, 912, 880, 868, 829, 771, 763, 739, 695.

MS (EI, 70 eV): m/z (%) = 278 [M^+] (3), 222 (100), 206 (7), 194 (6), 56 (5), 41 (12).

HRMS (EI) for **$C_8H_{11}IN_2O$** (277.9916): 277.9909 (M^+).

Synthesis of 4-butoxy-2-(3-(trifluoromethyl)phenyl)pyrimidine (56e):



According to **TP4**, 4-butoxypyrimidine (**55b**, 159 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 0.89 mL, 1.2 mmol, 1.35 M in THF) at -20 °C for 1 h. $Pd(dba)_2$ (17 mg, 0.03 mmol, 3 mol%), TFP (14 mg, 0.06 mmol, 6 mol%) and 1-iodo-3-(trifluoromethyl)benzene (**57c**, 385 mg, 1.4 mmol) were added successively and the reaction mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 4:1) the desired product **56e** (190 mg, 66%) was obtained as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.72 (s, 1H), 8.63 (d, *J* = 7.3 Hz, 1H), 8.52 (d, *J* = 5.7 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 5.7 Hz, 1H), 4.52 (t, *J* = 6.6 Hz, 2H), 1.77 – 1.90 (m, 2H), 1.45 – 1.61 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.5, 162.8, 157.4, 138.4, 131.3 (q, *J* = 1 Hz), 130.9 (q, *J* = 32 Hz), 128.9, 127.1 (q, *J* = 4 Hz), 125.0 (q, *J* = 4 Hz), 124.2 (q, *J* = 272 Hz), 107.0, 66.4, 30.8, 19.2, 13.8.

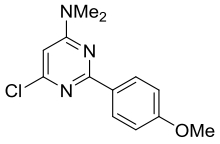
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2876, 1616, 1597, 1572, 1559, 1491, 1461, 1435, 1392, 1324, 1294, 1272, 1256, 1225, 1164, 1122, 1113, 1091, 1069, 1019, 1001, 987, 973, 921, 832, 814, 802, 785, 724, 709, 694, 668.

MS (EI, 70 eV): m/z (%) = 296 [M^+] (11), 267 (25), 253 (36), 240 (83), 223 (52), 212 (41), 172 (100), 69 (90), 41 (19).

HRMS for **$C_{15}H_{15}F_3N_2O$** (296.1136): 296.1129 (M^+).

Synthesis of 6-chloro-2-(4-methoxyphenyl)-*N*,*N*-dimethylpyrimidin-4-amine (56f):

Note: This example was performed by Dr. Xavier Mollat du Jourdin.



According to **TP4**, 6-chloro-*N*,*N*-dimethylpyrimidin-4-amine (**55c**, 157 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with $BF_3 \cdot OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 1.11 mL, 1.5 mmol, 1.35 M in THF) at -20 °C for 1 h. $Pd(dba)_2$ (17 mg, 0.03 mmol, 3 mol%), TFP (14 mg, 0.06 mmol, 6 mol%) and 1-iodo-4-methoxybenzene (**57b**, 397 mg, 1.7 mmol) were added successively and the reaction mixture was slowly warmed to 25 °C. The reaction was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 1:1→1:4) the desired product **56f** was obtained as a pale brown solid (185 mg, 70%).

M.p. (°C): 141-143.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.37 (d, J = 9.2 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.28 (s, 1H), 3.87 (s, 3H), 3.17 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.4, 163.0, 161.8, 159.9, 130.0, 129.9, 113.5, 98.0, 55.3, 37.2.

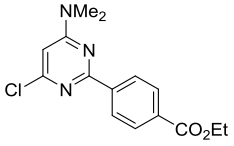
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3010, 2961, 2932, 2833, 1716, 1607, 1588, 1572, 1512, 1492, 1461, 1451, 1430, 1421, 1415, 1384, 1366, 1303, 1271, 1246, 1199, 1176, 1166, 1144, 1105, 1095, 1066, 1030, 994, 968, 944, 850, 814, 800, 772, 728, 696, 672.

MS (EI, 70 eV): m/z (%) = 263 [M^+] (83), 248 (65), 234 (100), 219 (14), 185 (18), 134 (48), 115

(13), 80 (14).

HRMS for **$C_{13}H_{15}ClN_3O$** (264.0898): 264.0896 ([M+H]$^+$).

Synthesis of ethyl 4-(4-chloro-6-(dimethylamino)pyrimidin-2-yl)benzoate (56g):



According to **TP4**, 6-chloro-*N*,*N*-dimethylpyrimidin-4-amine (**55c**, 157 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with $BF_3 \cdot OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 1.11 mL, 1.5 mmol, 1.35 M in THF) at -20 °C for 1 h. $Pd(dba)_2$ (17 mg, 0.03 mmol, 3 mol%), TFP (14 mg, 0.06 mmol, 6 mol%) and ethyl 4-iodobenzoate (**57d**, 483 mg, 1.7 mmol) were added successively and

the reaction mixture stirred for 2.5 h, without additional cooling. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 1:1→1:4) the desired product **56g** (212 mg, 69%) was obtained as a pale brown solid.

M.p. (°C): 102-103.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.46 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 6.36 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.19 (br s, 6H), 1.42 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 163.0, 162.7, 160.1, 141.3, 132.1, 129.4, 128.2, 99.3, 61.0, 37.3, 14.3.

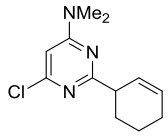
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3521, 2981, 2942, 2931, 2909, 2870, 1716, 1681, 1610, 1585, 1571, 1543, 1493, 1480, 1441, 1434, 1418, 1407, 1389, 1366, 1302, 1276, 1197, 1142, 1123, 1109, 1101, 1074, 1023, 992, 968, 872, 835, 823, 802, 789, 751, 705, 694, 666.

MS (EI, 70 eV): m/z (%) = 305 [M^+] (76), 290 (45), 276 (100), 260 (24), 176 (21), 148 (25), 130

(15), 102 (15), 80 (19).

HRMS for **$C_{15}H_{17}ClN_3O_2$** (306.1004): 306.1002 ([M+H]$^+$).

Synthesis of 6-chloro-2-(cyclohex-2-en-1-yl)-*N*,*N*-dimethylpyrimidin-4-amine (56h):



According to **TP4**, 6-chloro-*N*,*N*-dimethylpyrimidin-4-amine (**55c**, 157 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 1.11 mL, 1.5 mmol, 1.35 M in THF) at -20 °C for 1 h. The reaction mixture was cooled to -45 °C and CuCN·2LiCl (0.10 mL, 0.10 mmol, 1.0 M in THF) and 3-bromocyclohexene (**57a**, 274 mg, 1.7 mmol) were added successively. After stirring for 3 h at the same temperature the reaction mixture was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 1:4) the desired product **56h** (169 mg, 71%) was obtained as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.24 (s, 1H), 5.87 – 5.98 (m, 1H), 5.76 – 5.86 (m, 1H), 3.44 – 3.56 (m, 1H), 3.10 (s, 6H), 1.97 – 2.19 (m, 3H), 1.81 – 1.96 (m, 2H), 1.57 – 1.75 (m, 1H).

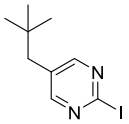
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 172.8, 163.1, 159.7, 128.2, 127.8, 98.0, 44.6, 37.1, 28.2, 24.8, 21.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2931, 2862, 1576, 1545, 1496, 1456, 1448, 1424, 1391, 1340, 1297, 1218, 1194, 1157, 1129, 1062, 1049, 987, 971, 936, 920, 897, 825, 809, 786, 734, 723, 668.

MS (EI, 70 eV): m/z (%) = 237 [M^+] (79), 222 (45), 208 (100), 39 (171), 95 (32), 80 (22).

HRMS for **$C_{12}H_{17}ClN_3$** (238.1106): 238.1104 ([M+H]$^+$).

Synthesis of 2-iodo-5-neopentylpyrimidine (56i)



According to **TP4**, 5-neopentylpyrimidine (**55d**, 300 mg, 2.0 mmol) in dry THF (8.0 mL) reacted with BF_3·OEt_2 (312 mg, 0.27 mL, 2.2 mmol) and TMPZnCl·LiCl (**20**, 1.62 mL, 2.4 mmol, 1.48 M in THF) at 0 °C for 1 h. A solution of iodine (1.65 g, 6.5 mmol) in dry THF (5.0 mL) was dropwise added and the reaction mixture was stirred for 5 min at the same temperature. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (18 mL) and NH_3 (conc, 2 mL) followed by extraction with Et_2O (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / Et_2O = 5:1) the desired product **56i** (510 mg, 92%) was obtained as a white solid.

M.p. (°C): 76.6-78.2

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.23 (s, 2H), 2.40 (s, 2H), 0.91 (s, 9H).

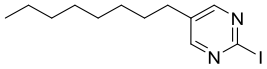
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.6, 132.0, 126.4, 43.8, 31.6, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2910, 2866, 1564, 1532, 1474, 1444, 1379, 1363, 1320, 1249, 1234, 1202, 1135, 1106, 1043, 951, 930, 903, 837, 808, 762, 740, 670.

MS (EI, 70 eV): m/z (%) = 276 [M^+] (29), 220 (100), 59 (10), 57 (83), 44 (11), 41 (23).

HRMS (EI) for **$C_9H_{13}IN_2$** (276.0123): 276.0118 (M^+).

Synthesis of 2-iodo-5-octylpyrimidine (56j)



According to **TP4**, 5-octylpyrimidine (**55e**, 192 mg, 1.0 mmol) in dry THF (4.0 mL) reacted with BF_3·OEt_2 (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 0.86 mL, 1.2 mmol, 1.39 M in THF) at 0 °C for 30 min. A solution of iodine (508 g, 2.0 mmol) in dry THF (2.0 mL) was dropwise added and the reaction mixture was stirred for 5 min at the same temperature. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (9 mL) and NH_3 (conc, 1 mL) followed by extraction with Et_2O (3 × 10 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography

(silica gel, *iso*-hexane / Et_2O = 10:1) the desired product **56j** (261 mg, 86%) was obtained as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.29 (s, 2H), 2.54 (d, *J* = 7.7 Hz, 2H), 1.54 – 1.68 (m, 2H), 1.20 – 1.37 (m, 10H), 0.84 – 0.92 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.6, 135.0, 125.9, 31.7, 30.5, 29.7, 29.2, 29.1, 29.0, 22.6, 14.0.

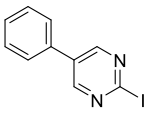
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3017, 2954, 2923, 2854, 2493, 2411, 1568, 1534, 1464, 1380, 1242, 1227, 1165, 1112, 1040, 928, 831, 799, 757, 722, 655.

MS (EI, 70 eV): m/z (%) = 318 [M^+] (6), 220 (35), 191 (100), 107 (10), 93 (18).

HRMS (EI) for **$C_{12}H_{19}IN_2$** (318.0593): 318.0576.

Synthesis of 2-iodo-5-phenylpyrimidine (56k):

Note: This example was performed by Dr. Aleksei Bredihhin



According to **TP4**, 5-phenylpyrimidine (**55f**, 781 mg, 5.0 mmol) in dry THF (5.0 mL) reacted with $BF_3{\cdot}OEt_2$ (780 mg, 0.68 mL, 5.5 mmol) and TMPZnCl·LiCl (**20**, 4.60 mL, 5.5 mmol, 1.13 M in THF) at -20 °C for 1 h. A solution of iodine (1.65 g, 6.5 mmol) in dry THF (5.0 mL) was dropwise added and the reaction mixture was stirred for 5 min at the same temperature. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (18 mL) and NH_3 (conc, 2 mL) followed by extraction with DCM (3 × 100 mL). After drying ($MgSO_4$), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / EtOAc / NEt_3 = 2:1:0.15) the desired product **56k** (1.09 g, 77%) was obtained as a white solid.

M.p. (°C): 164-166.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.66 (s, 2H), 7.42 – 7.60 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.5, 133.7, 133.0, 129.5, 129.4, 127.3, 126.8.

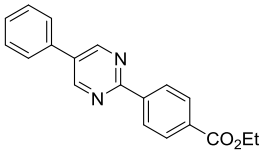
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 3042, 2682, 2496, 1904, 1578, 1564, 1516, 1444, 1380, 1370, 1324, 1302, 1284, 1238, 1160, 1116, 1082, 1064, 1034, 1002, 946, 924, 876, 858, 782, 766, 754, 700, 636, 614.

MS (EI, 70 eV): m/z (%) = 282 $[M]^+$ (71), 155 (100), 128 (18), 103 (26), 102 (16), 77 (21).

HRMS for **$C_{10}H_7IN_2$** (281.9654): 281.9638 (M^+)

Synthesis of ethyl 4-(5-phenylpyrimidin-2-yl)benzoate (56l):

Note: This example was performed by Dr. Aleksei Bredihhin.



According to **TP4**, 5-phenylpyrimidine (**55f**, 312 mg, 2.0 mmol) in dry THF (4.0 mL) reacted with $BF_3 \cdot OEt_2$ (312 mg, 0.27 mL, 2.2 mmol) and TMPZnCl·LiCl (**20**, 2.25 mL, 2.2 mmol, 0.98 M in THF) at -20 °C for 1.5 h. $Pd(dba)_2$ (35 mg, 0.06 mmol, 3 mol%), TFP (28 mg, 0.12 mmol, 6 mol%) and ethyl 4-iodobenzoate (**57d**, 552 mg, 2.0 mmol) were added subsequently and the reaction mixture was heated to 50 °C for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying ($MgSO_4$), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM / NEt_3 = 5:1:0.5) the desired product **56l** (407 mg, 67%) was obtained as an off-white solid.

M.p. (°C): 172.6-173.7.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.04 (s, 2H), 8.57 (d, *J* = 8.2 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.69 (m, 2H), 7.42 – 7.58 (m, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 162.4, 155.2, 141.1, 134.2, 132.2, 132.2, 129.8, 129.4, 128.9, 128.0, 126.8, 61.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 3028, 2972, 1956, 1828, 1720, 1582, 1534, 1450, 1436, 1406, 1390, 1374, 1364, 1314, 1302, 1280, 1246, 1182, 1168, 1128, 1120, 1106, 1096, 1078, 1018, 970, 954, 914, 870, 854, 808, 790, 756, 692, 656, 632.

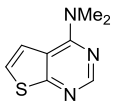
MS (EI, 70 eV): m/z (%) = 305 (22), 304 [M^+] (90), 276 (39), 260 (24), 259 (100), 231 (32), 102

(48).

HRMS for **$C_{19}H_{16}N_2O_2$** (304.1212): 304.1207 (M^+).

4.4. Preparation of Thienopyrimidines

Synthesis of *N*,*N*-Dimethylthieno[2,3-*d*]pyrimidin-4-amine (58a):



To a stirred solution of 4-chlorothieno[2,3-*d*]pyrimidine (850 mg, 5.0 mmol) in THF (5.0 mL) dimethylamine (2.25 g, 20.0 mmol) was added at 25 °C and stirred for 3 h. The reaction mixture was quenched with brine (50 mL) followed by extraction with EtOAc (3 × 50 mL). After drying (Na_2SO_4),

the solvents were removed *in vacuo*. Flash column chromatography (silica gel, *iso*-hexane / EtOAc = 1:2) furnished the desired *N*,*N*-dimethylthieno[2,3-*d*]pyrimidin-4-amine (**58a**, 877 mg, 98%) as an off-white solid.

M.p. (°C): 86-88.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.44 (s, 1H), 7.46 (d, *J* = 6.1 Hz, 1H), 7.18 (d, *J* = 6.1 Hz, 1H), 3.38 (s, 6H).

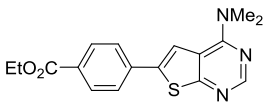
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.9, 158.4, 152.9, 121.4, 120.3, 115.9, 40.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3751, 3108, 2924, 2362, 1559, 1522, 1500, 1480, 1457, 1418, 1402, 1388, 1331, 1279, 1246, 1212, 1188, 1140, 1088, 1063, 1002, 980, 874, 853, 803, 790, 700.

MS (EI, 70 eV): m/z (%) = 179 [M^+] (68), 164 (45), 149 (100), 135 (45), 109 (29).

HRMS for **$C_8H_9N_3S$** (179.0517): 179.0513 (M^+).

Synthesis of ethyl 4-(4-(dimethylamino)thieno[2,3-*d*]pyrimidin-6-yl)benzoate (59a):



According to **TP3**, *N*,*N*-dimethylthieno[2,3-*d*]pyrimidin-4-amine (**58a**, 179 mg, 1.0 mmol) in dry THF (2.0 mL) reacted with TMPZnCl·LiCl (**20**, 1.11 mL, 1.5 mmol, 1.35 M in THF) at 25 °C for 12 h. $Pd(dba)_2$ (17 mg, 0.03 mmol, 3 mol%), TFP (14 mg, 0.06 mmol, 6 mol%) and ethyl 4-iodobenzoate (**57d**, 483 mg, 1.7 mmol) were added successively and the reaction mixture stirred for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / EtOAc = 1:1 to 1:4) the desired product **59a** (274 mg, 83%) was obtained as an off-white solid.

M.p. (°C): 142-145.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.44 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.63 – 7.75 (m, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.44 (s, 6H), 1.42 (t, *J* = 7. Hz, 3H).

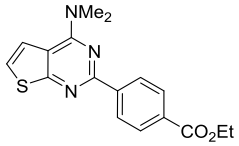
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.9, 166.0, 158.1, 153.2, 137.9, 136.5, 130.2, 129.9, 125.7, 118.3, 117.2, 61.1, 40.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1}= 3121, 2984, 2940, 2901, 1703, 1663, 1620, 1603, 1565, 1503, 1477, 1451, 1441, 1406, 1363, 1336, 1327, 1313, 1271, 1242, 1228, 1181, 1137, 1123, 1109, 1063, 1020, 1007, 972, 953, 913, 867, 853, 835, 764, 692, 654.

MS (EI, 70 eV): m/z (%) = 327 [M^+] (88), 312 (21), 298 (100), 284 (18), 270 (21).

HRMS for **$C_{17}H_{17}N_3O_2S$** (327.1041): 327.1036 (M^+).

Synthesis of ethyl 4-(4-(dimethylamino)thieno[2,3-*d*]pyrimidin-2-yl)benzoate (60a):



According to **TP4**, *N*,*N*-dimethylthieno[2,3-*d*]pyrimidin-4-amine (**58a**, 179 mg, 1.0 mmol) in dry THF (2.0 mL) reacted with $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) and TMPZnCl·LiCl (**20**, 1.11 mL, 1.5 mmol, 1.35 M in THF) at 0 °C for 2 h. $Pd(dba)_2$ (17 mg, 0.03 mmol, 3 mol%), TFP (14 mg, 0.06 mmol, 6 mol%) and ethyl 4-iodobenzoate (**57d**, 483 mg, 1.7 mmol) were added subsequently and the reaction mixture stirred for 3 h. The reaction mixture wasquenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / EtOAc = 3:1) the desired product **60a** (230 mg, 70%) was obtained as an off-white solid.

M.p. (°C): 143-147.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 6.2 Hz, 1H), 7.19 (d, *J* = 6.2 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.45 (s, 6H), 1.43 (t, *J* = 7.1 Hz, 3H).

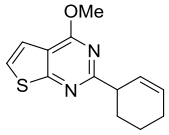
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.1, 166.6, 158.3, 157.7, 142.5, 131.3, 129.4, 128.0, 121.5, 120.7, 114.6, 60.9, 40.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2977, 2898, 1710, 1609, 1578, 1550, 1510, 1502, 1468, 1413, 1404, 1385, 1364, 1347, 1299, 1263, 1246, 1186, 1171, 1158, 1122, 1108, 1098, 1059, 1018, 1006, 888, 866, 858, 852, 819, 796, 773, 763, 716, 698, 676, 666.

MS (EI, 70 eV): m/z (%) = 327 [M^+] (54), 298 (100), 284 (10), 270 (16), 255 (25), 211 (16), 109 (11).

HRMS for **$C_{17}H_{18}N_3O_2S$** (328.1114): 328.1112 ([M+H]$^+$)

Synthesis of 2-(cyclohex-2-en-1-yl)-4-methoxythieno[2,3-*d*]pyrimidine (60b):



According to **TP4**, 4-methoxythieno[2,3-*d*]pyrimidine (**58b**, 332 mg, 2.0 mmol) in dry THF (7.0 mL) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 0.27 mL, 2.2 mmol) and TMPZnCl·LiCl (**20**, 1.7 mL, 2.2 mmol, 1.27 M in THF) at -40 °C for 1 h. CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.0 M in THF) and 3-bromocyclohexene (**57a**, 419 mg, 0.30 mL, 2.6 mmol) were added subsequently and the reaction mixture was slowly

warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (9 mL) and NH_3 (conc., 1 mL) followed by extraction with DCM (3 × 20 mL). After drying (Na_2SO_4), removal of the solvents *in vacuo* and flash column chromatography (silica gel, *iso*-hexane / DCM = 1:5) the desired product **60b** (374 mg, 77%) was obtained as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.23 – 7.34 (m, 2H), 5.94 – 6.07 (m, 1H), 5.84 – 5.95 (m, 1H), 4.12 (s, 3H), 3.68 – 3.79 (m, 1H), 2.07 – 2.25 (m, 3H), 1.87 – 2.05 (m, 2H), 1.62 – 1.82 (m, 1H).

13C-NMR (75 MHz, CDCl3): δ / ppm = 169.1, 168.7, 164.0, 128.3, 128.0, 123.3, 118.2, 116.7, 53.6, 44.7, 28.8, 24.9, 21.6.

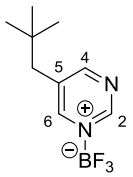
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 3024, 2931, 2860, 2835, 1573, 1535, 1468, 1410, 1368, 1346, 1318, 1270, 1249, 1218, 1194, 1174, 1153, 1135, 1092, 1038, 1008, 953, 929, 892, 874, 851, 800, 794, 787, 696.

MS (EI, 70 eV): m/z (%) = 246 [M$^+$] (82), 245 (24), 231 (53), 218 (20), 217 (100), 205 (17), 203 (16), 180 (24).

HRMS for **$C_{13}H_{14}N_2OS$** (246.0827): 246.0812 (M$^+$).

4.5. Synthesis and Spectra of the Intermediates

Synthesis and NMR-studies of (5-(neopenthyl)pyrimidin-1-ium-1-yl)trifluoroborate (61)



A dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with 38 mg 5-neopentylpyrimidine (**55d**, 0.25 mmol) in 1.0 mL THF-d_8 and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (39 mg, 0.275 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. The complex **61** was then transferred in a dry, argon flushed NMR-tube which was cooled at -20 °C, and characterized with ^{1}H-, ^{13}C- ^{11}B and ^{19}F-NMR. The spectra showed in addition to the characteristic signals of the BF_3-complex **49** also the signals of free $BF_3{\cdot}OEt_2$.

^{1}H-NMR (400 MHz, THF-d_8): δ / ppm: 9.36 (s, 2-H, 1H), 9.12 (d, J = 2.5 Hz, 6-H, 1H), 8.86 (s, 4-H, 1H), 2.75 (s, CH_2, 2H), 0.94 (s, CH_3, 9H).

^{13}C-NMR (100 MHz, THF-d_8): δ / ppm: 164.3 (4-C), 157.4 (q, $^3J_{C\text{-}F}$ = 2.0 Hz, 6-C), 151.3 (q, $^3J_{C\text{-}F}$ = 2.8 Hz, 2-C), 135.0 (5-C), 42.9 (CH_2), 31.6 ($\underline{C}_q(CH_3)_3$), 28.0 (CH_3).

^{11}B-NMR (128 MHz, THF-d_8): δ / ppm: -0.45.

^{19}F-NMR (376 MHz, THF-d_8): δ / ppm: 150.64 (^{10}B isotopomer), 150.68 (^{11}B isotopomer).

The two carbons at position 2 and six display a distint $^{3}J_{C\text{-}F}$ coupling which can be seen in Figure 9.

^{13}C-NMR expansion of **61**

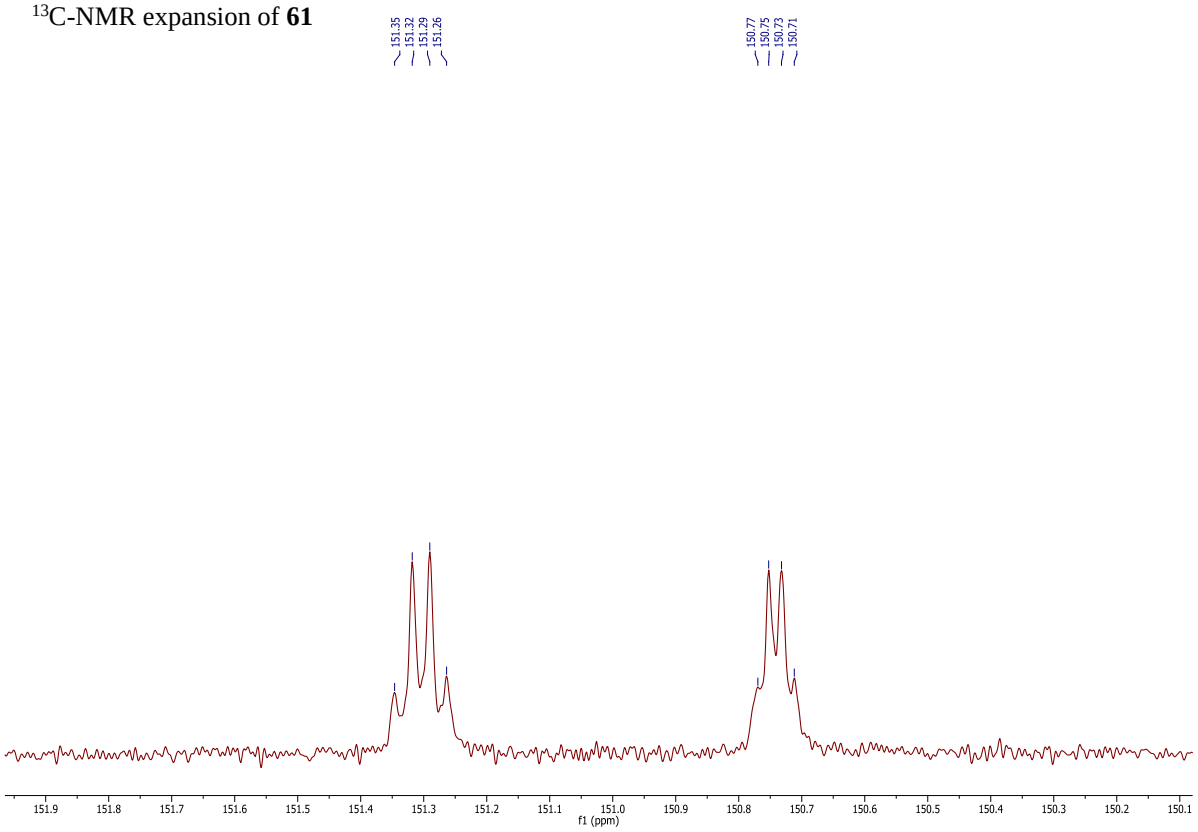
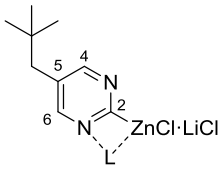


Figure 9: Signals of 2-C (left) and and 6-C (right) of **61**.

NMR-studies of the zinc species 62 in the presence of BF_3·OEt_2



A dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with 38 mg 5-neopentylpyrimidine (**55d**, 0.25 mmol) in 1.0 mL THF-d_8 and cooled to 0 °C. BF_3·OEt_2 (39 mg, 0.275 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. Then 0.3 mmol of TMPZnCl·LiCl (**20**, 0.2 mL, 1.5 M in THF-d_8) were added and the mixture was stirred at 0 °C for 45 min. The solution was then transferred in a dry, argon flushed NMR-tube which was cooled at -20 °C, and characterized with ^{1}H-, ^{13}C- ^{11}B and ^{19}F-NMR. The spectra showed in addition to the characteristic signals of zinc species **62** also the signals of free BF_3·OEt_2, free TMPH the BF_3 complex **61** and the TMPH-BF_3 adduct **50**.

^{1}H-NMR (400 MHz, THF-d_8): δ / ppm: 9.08 (s, 6-H, 1H), 8.86 (s, 4-H, 1H), 7.74 (s, CH_2, 2H), 0.91 (s, CH_3, 9H).

^{13}C-NMR (100 MHz, THF-d_8): δ / ppm: 194.6 (2-C), 159.4 (6-C), 151.4 (4-C), 132.1 (5-C), 42.6 (CH_2), 31.6 ($\underline{C}_q(CH_3)_3$), 28.0 (CH_3).

5. TMPZnOPiv·LiCl: A New Base for the Preparation of Air-Stable Solid Zinc Pivalates of Sensitive Aromatics and Heteroaromatics

5.1. Titration and Stability Studies of Solid Zinc Pivalates

Titration of organozinc reagents using GC-analysis:

First of all, the iodinated compounds of all organic zinc pivalates (**65** and **67**) were isolated. Stock solutions of the iodides (0.1 M) and of an internal standard (0.1 M) were prepared. As internal standard for all calibration curves *n*-octadacane was used, with exception of **67e** where *n*-tetradecane was used, since the iodinated product had the same GC-retention time as *n*-octadecane. For each iodinated compound GC-samples of different iodide/internal standard ratios were prepared and measured (at least eight for each iodide) and these ratios were plotted against the area ratios of the corresponding GC-analysis to give a linear graph with a determined equation. With these equations the amount of iodinated substance of the organozinc pivalates could be calculated.

Stability studies of organozinc reagents towards air:

To evaluate the stability of organozinc reagents towards air, accurately weighted aliquots of the solid organo-zinc pivalate were placed at 25 °C in open *Schlenk*-flasks. After exposure to air for a given time, the flasks were closed, evacuated, filled with argon and the organozinc pivalate was dissolved in dry THF. Then, an excess of iodine was added and the solution stirred for 10 min at 25 °C followed by addition of 100 µL of a 0.1 M stock-solution of *n*-octadecane in toluene (*n*-tetradecane for 6d). An aliquot (ca. 0.1 mL) of this reaction mixture was then quenched with sat. aqueous $Na_2S_2O_3$ solution (ca. 0.5 mL) and extracted with EtOAc (ca. 1 mL). The molar *n*-octadecane/iodinated heteroarene ratio was determined via GC-analysis.

5.2. Typical Procedures

Typical Procedure for the metalation of heteroaromatics with TMPZnOPiv·Mg(OPiv)Cl·LiCl (63) (TP5):

A dry and argon flushed 20-mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with a 0.5 M solution of the corresponding *N*-heteroarene in dry THF. The solution was brought to the given temperature followed by dropwise addition of TMPZnOPiv·Mg(OPiv)Cl·LiCl (**63**, 0.85 M in THF, 1.1 – 2.0 equiv.) and 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 tetradecane as internal standard. The solvent was carefully removed *in vacuo* and the content of active zinc species was determined as described above.

Typical Procedure for the BF_3·OEt_2-triggered metalation of heteroaromatics with TMPZnOPiv·Mg(OPiv)Cl·LiCl (63) (TP6):

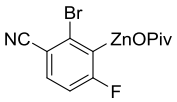
A dry and argon flushed 20-mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with a solution of the corresponding heteroarene (1.0 mmol) in dry THF (2 mL) and cooled to -20 °C. BF_3·OEt_2 (156 mg, 1.1 mmol) was slowly added and stirred for 30 min at the same temperature. The reaction mixture was cooled down to -30 °C and after dropwise addition of TMPZnOPiv·Mg(OPiv)Cl·LiCl (**63**, 0.85 m in THF, 1.1 equiv.) the mixture was stirred for 1 h at -30 °C.

5.3. Praparation of the Solid Organozinc Pivalates of Type 65 and 67

Synthesis of (2,6-difluoro-3-nitrophenyl)zinc pivalate (65a):

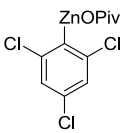
According to **TP5** 2,4-difluoro-1-nitrobenzene (**64a**, 318 mg, 2.0 mmol) in 4 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 M, 2.2 mmol) at 25 °C and stirred at this temperature for 45 min. After solvent removal *in vacuo* **65a** (2.05 g) was obtained as a light brown solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.81 mmol/g, which corresponds to a yield of 83%.

Synthesis of (2-bromo-3-cyano-6-fluorophenyl)zinc pivalate (65b):



According to **TP5** 2-bromo-4-fluorobenzonitrile (**64b**, 600 mg, 3.0 mmol) in 6 mL dry THF reacted with TMPZnOPiv·LiCl (**63,** 3.8 mL, 0.86 M, 3.3 mmol) at 50 °C (oil bath) and for 2 h. After solvent removal *in vacuo* **65b** (3.49 g) was obtained as an orange solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.78 mmol/g, which corresponds to a yield of 91%.

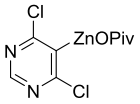
Synthesis of (2,4,6-trichlorophenyl) zinc pivalate (65c):



According to **TP5** 1,3,5-trichlorobenzene (**64c**, 544 mg, 3.0 mmol) in 3 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 5.5 mL, 0.81 M, 4.5 mmol) at 160 °C (microwave) for 1 h. After solvent removal

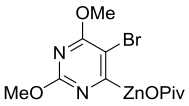
in vacuo **65c** (3.33 g) was obtained as an slightly orange solid. A titration with iodine[67] gave a concentration of the active zinc species of 0.68 mmol/g, which corresponds to a yield of 76%.

Synthesis of 5-(4,6-Dichloropyrimidinyl)zinc pivalate (67a):



According to **TP5** 4,6-dichloropyrimidine (**66a**, 298 mg, 2.0 mmol) in 4 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 m, 2.2 mmol) at 25 °C and stirred at this temperature for 0.5 h. After solvent removal *in vacuo* **67a** (2.06 g) was obtained as a yellow solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.81 mmol/g, which corresponds to a yield of 78%.

Synthesis of (5-bromo-2,6-dimethoxypyrimidin-4-yl)zinc pivalate (67b):

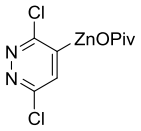


According to **TP5** 5-bromo-2,4-dimethoxypyrimidine (**66b**, 438 mg, 2.0 mmol) in 4 mL THF reacted with TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 m, 2.2 mmol) at 25 °C and stirred at this temperature for 3 h. After solvent removal *in vacuo* **67b** (1.83 g) was obtained as an orange-brown solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.79 mmol/g, which corresponds to a yield of 72%.

Synthesis of (3-chloropyrazin-2-yl)zinc pivalate (67c):

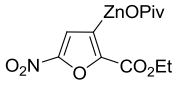
According to **TP5** 2-chloropyrazine (**66c**, 345 mg, 3.0 mmol) in 3 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 3.8 mL, 0.86 M, 3.3 mmol) at 90 °C (microwave) for 2 h. After solvent removal *in vacuo* **67c** (2.68 g) was obtained as an orange solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.85 mmol/g, which corresponds to a yield of 75%.

Synthesis of (3,6-dichloropyridazin-4-yl)zinc pivalate (67d):



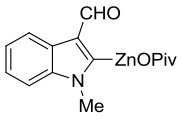
According to **TP5** 3,6-dichloropyridazine (**66d**, 745 mg, 5.0 mmol) in 10 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 6.4 mL, 0.86 M, 5.5 mmol) at 25 °C for 0.5 h. After solvent removal *in vacuo* **67d** (4.81 g) was obtained as a yellow solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.74 mmol/g, which corresponds to a yield of 75%.

Synthesis of 3-(2-ethoxycarbonyl-5-nitrofuranyl)zinc pivalate (67e)



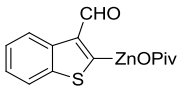
According to **TP5** ethyl 5-nitrofuran-2-carboxylate (**66e**, 370 mg, 2.0 mmol) in 4 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 4.7 mL, 0.85 M, 4.0 mmol) at -10 °C and stirred at this temperature for 1 h. After warming to 25 °C and solvent removal *in vacuo* **67e** (2.04 g) was obtained as a dark red-brown solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.75 mmol/g, which corresponds to a yield of 77%.

Synthesis of (3-formyl-1-methyl-1*H*-indol-2-yl)zinc pivalate (67f):



According to **TP5** 1-methyl-1*H*-indole-3-carbaldehyde (**66f**, 318 mg, 2.0 mmol) in 4 mL THF reacted with TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 M, 2.2 mmol) at 25 °C and stirred at this temperature for 0.5 h. After solvent removal *in vacuo* **67f** (2.06 g) was obtained as a yellow solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.85 mmol/g, which corresponds to a yield of 88%.

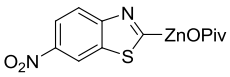
Synthesis of (3-formylbenzo[*b*]thiophen-2-yl)zinc pivalate (67g):



According to **TP5** benzo[*b*]thiophene-3-carbaldehyde (**66g**, 486 mg, 3.0 mmol) in 6 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 3.84 mL, 0.86 M, 3.3 mmol) at 25 °C for 0.5 h. After solvent removal *in*

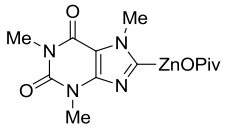
vacuo **67g** (3.12 g) was obtained as a yellow solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.86 mmol/g, which corresponds to a yield of 89%

Synthesis of (6-nitrobenzo[*d*]thiazol-2-yl)zinc pivalate (67h)



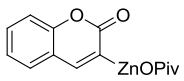
According to **TP5** ethyl 6-nitrobenzothiazol (**66h**, 360 mg, 2.0 mmol) in 4 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 m, 2.2 mmol) at 25 °C and stirred at this temperature for 10 min. After solvent removal *in vacuo* **67h** (1.98 g) was obtained as a dark red-brown solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.75 mmol/g, which corresponds to a yield of 74%.

Synthesis of (1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)zinc pivalate (67i):



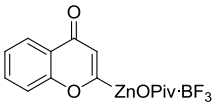
According to **TP5** caffeine (**66i**, 583 mg, 3.0 mmol) in 6 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 3.84 mL, 0.86 M, 3.3 mmol) at 25 °C for 0.5 h. After solvent removal *in vacuo* **67i** (3.68 g) was obtained as a yellow solid. A titration with iodine gave a concentration of the active zinc species of 0.77 mmol/g, which corresponds to a yield of 95%.

Synthesis of (2-oxo-2*H*-chromen-3-yl)zinc pivalate (67j):



According to **TP5** coumarin (**66j**, 438 mg, 2.0 mmol) in 4 mL dry THF reacted with TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 m, 2.2 mmol) at 25 °C and stirred at 80 °C in the microwave for 1 h. After cooling to 25 °C and solvent removal *in vacuo* **67j** (2.23 g) was obtained as a orange solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 1.11 mmol/g, which corresponds to a yield of 82%.

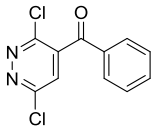
Synthesis of (4-oxo-4*H*-chromen-2-yl) zinc pivalate (67k)



According to **TP6** chromone (**66k**, 292 mg, 2.0 mmol) in 4 mL THF reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPZnOPiv·LiCl (**63**, 2.6 mL, 0.85 m, 2.2 mmol). After solvent removal *in vacuo* **67k** (1.89 g) was obtained as a dark red solid. GC-analysis of an iodinated sample (see above) gave a concentration of the active zinc species of 0.60 mmol/g, which corresponds to a yield of 55%. However, when used as a solution overall yields higher than 55% were obtained, indicating, that the BF_3 containing zinc pivalate **67k** decomposes during the solvent removal. Therefore all yields are referring over two steps (metalation and reaction with electrophile).

5.4. Preparation of the Compounds Type 69-72

Synthesis of (3,6-dichloropyridazin-4-yl)(phenyl)methanone (69a):



(3,6-Dichloropyridazin-4-yl)zinc-pivalate (**67d**, 676 mg, 0.74 mmol/g, 0.5 mmol) dissolved in 1.5 mL dry THF was cooled down to -20 °C. TMSCl (0.4 mL, 2.8 mmol) was added followed by 30 min stirring. Then CuCN·2LiCl (0.5 mL, 1 M, 0.5 mmol) and benzoyl chloride (**68a**, 165 mg, 1.2 mmol) were added subsequently. The reaction mixture was stirred for 1 h at -20 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 5:1) afforded the product **69a** (114 mg, 96%) as a white solid.

M.p. (°C): 98.9-100.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.71 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.54 (tt, *J* = 7.8, 1.7 Hz, 2H), 7.51 (s, 1H).

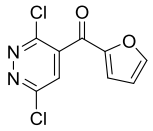
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 189.0, 156.2, 151.7, 140.0, 135.5, 133.9, 130.0, 129.3, 127.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 1666, 1614, 1591, 1575, 1501, 1487, 1444, 1404, 1382, 1325, 1307, 1290, 1247, 1239, 1222, 1173, 1167, 1156, 1135, 1103, 1070, 1052, 1024, 999, 982, 968, 932, 902, 853, 821, 799, 756, 714, 700, 682, 653.

MS (EI, 70 eV): m/z (%) = 254 (7), 252 [M^+] (11), 106 (8), 105 (100), 77 (51), 44 (7).

HRMS (EI) for **$C_{11}H_6Cl_2N_2O$** (251,9857): 251.9842 (M^+).

Synthesis of (3,6-dichloropyridazin-4-yl)(phenyl)methanone (69b):



(3,6-Dichloropyridazin-4-yl)zinc-pivalate (**67d**, 1.22 g, 0.74 mmol/g, 0.9 mmol) dissolved in 3 mL dry THF was cooled down to -20 °C. TMSCl (0.7 mL, 5.4 mmol) was added followed by 30 min stirring. Then CuCN·2LiCl (1 mL, 1 M, 1 mmol) and 2-furoylchloride (**68b**, 294 mg, 2.3 mmol) were added subsequently. The reaction mixture was stirred for 1.5 h at -20 °C and for 15 h at 0 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated in vacuo. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 1:1) afforded the product **69b** (189 mg, 87%) as a white solid.

M.p. (°C): 131.4-132.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.57 (s, 1H), 7.33 (dd, *J* = 3.7, 0.7 Hz, 1H), 6.69 (dd, *J* = 3.7, 1.7 Hz, 1H).

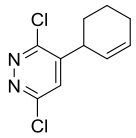
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.7, 156.1, 151.8, 150.5, 149.5, 138.5, 127.9, 122.5, 113.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3114, 3044, 1658, 1558, 1505, 1462, 1392, 1354, 1319, 1283, 1242, 1223, 1202, 1166, 1151, 1119, 1082, 1037, 981, 929, 911, 883, 861, 802, 791, 780, 768, 740, 709, 697, 683, 658.

MS (EI, 70 eV): m/z (%) = 242 [M^+] (100), 96 (28), 84 (21), 67 (13), 43 (17).

HRMS (EI) for **$C_9H_4Cl_2N_2O_2$** (241.9650): 241.9638 (M^+).

Synthesis of 3,6-dichloro-4-(cyclohex-2-en-1-yl)pyridazine (69c)



5-(4,6-Dichloropyrimidinyl)zinc-pivalate (**67d**, 624 mg, 0.74 mmol/g, 0.5 mmol) dissolved in 1.5 mL dry THF was cooled down to -20 °C. CuCN·2LiCl (0.05 mL, 1 M, 0.05 mmol) and 3-bromocyclohexene (**57a**, 89 mg, 0.6 mmol) were added subsequently. The reaction mixture was stirred for 1 h at the same temperature. After quenching with a aqueous NH_4Cl/NH_3(conc.) (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 4:1) afforded the product **69c** (95 mg, 90%) as a colorless liquid.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.37 (d, *J* = 0.6 Hz, 1H), 6.13 (dq, *J* = 9.9, 2.0 Hz, 1H), 5.56 (dq, *J* = 10.0, 2.5 Hz, 1H), 3.70 – 3.77 (m, 1H), 2.17 – 2.10 (m, 3H), 1.71 – 1.47 (m, 3H).

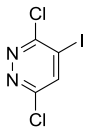
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 156.6, 156.1, 147.7, 132.60, 128.8, 124.8, 37.3, 28.3, 24.7, 19.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2931, 2862, 2837, 1652, 1560, 1447, 1432, 1394, 1356, 1342, 1313, 1293, 1276, 1252, 1192, 1128, 1101, 1059, 1048, 1038, 996, 922, 910, 881, 864, 852, 815, 764, 754, 724, 686, 667.

MS (EI, 70 eV): m/z (%) = 230 (67), 228 [M^+] (100), 214 (27), 193 (47), 174 (41), 102 (22), 81 (48), 77 (21), 67 (23), 54 (32), 41 (33).

HRMS (EI) for **$C_{10}H_{10}Cl_2N_2$** (228.0221): 228.0206 (M^+).

Synthesis of 3,6-dichloro-4-iodopyridazine (69d):



To a solution of (3,6-dichloropyridazin-4-yl)zinc pivalate (**67d**, 1.35 g, 0.74 mmol/g, 1.0 mmol) in THF (3 mL) iodine (508 mg, 2 mmol) was added at 25 °C and the reaction mixture was stirred at 25 °C for 1 h. After quenching with a saturated aqueous $Na_2S_2O_3$ solution (4 mL) the mixture was extracted with ethyl acetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / DCM = 2:1) afforded the product **69d** (252 mg, 92%) as a white solid

M.p. (°C): 142.2-143.0.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.04 (s, 1H).

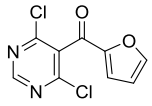
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.7, 153.9, 139.7, 105.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3093, 2247, 2191, 2156, 2024, 1965, 1794, 1490, 1464, 1381, 1331, 1296, 1276, 1234, 1154, 1130, 1061, 1044, 994, 900, 812, 796, 730, 722, 698,659.

MS (EI, 70 eV): m/z (%) = 276 (29), 274 [M^+] (45), 121 (35), 119 (55), 84 (31), 61 (19), 43 (100).

HRMS (EI) for **$C_4HCl_2IN_2$** (273.8561): 273.8561 (M^+).

Synthesis of (4,6-dichloropyrimidin-5-yl)(furan-2-yl)methanone (70a):



A solution of 5-(4,6-dichloropyrimidinyl)zinc pivalate (**67a**, 1.23 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1.0 m in THF) was added dropwise. After stirring at this temperature for 20 min, 2-furoyl chloride (**68b**, 392 mg, 3.0 mmol) was added and the mixture was left to reach 0 °C and stirred there for 3 h. Then, sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) were used to quench the reaction, followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 12:1) afforded the product **70a** (233 mg, 96%) as brown solid.

M.p. (°C): 143.6-145.4.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.87 (s, 1H), 7.69 (d, *J* = 0.9 Hz, 1H), 7.28 (br, s, 1H), 6.65 (dd, *J* = 3.7, 1.7 Hz, 1H).

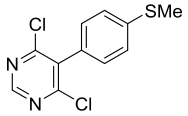
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 175.6, 158.8, 158.4, 150.9, 149.0, 130.9, 121.4, 113.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3133, 2969, 2359, 2340, 1738, 1636, 1558, 1540, 1512, 1450, 1403, 1375, 1361, 1297, 1230, 1216, 1168, 1123, 1083, 1032, 956, 904, 888, 878, 815, 789, 781, 746, 738, 668, 626, 615, 609.

MS (EI, 70 eV): m/z (%) = 242 [M^+] (48), 167 (49), 95 (100), 58 (21), 43 (33).

HRMS (EI) for **$C_9H_4Cl_2N_2O_2$** (241.9650): 241.9653 (M^+).

Synthesis of 4,6-dichloro-5-(4-(methylthio)phenyl)pyrimidine (70b):



To a solution of 5-(4,6-dichloropyrimidinyl)zinc pivalate (**67a**, 1.23 g, 1.0 mmol) in THF (3 mL) $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and 4-iodothioanisole (**68c**, 200 mg, 0.8 mmol) were added subsequently at 25 °C. The reaction mixture was stirred at 25 °C for 2 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 15:1) afforded the product **70b** (197 mg, 91%) as white solid.

M.p. (°C): 88.7-90.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.76 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 2.54 (s, 3H).

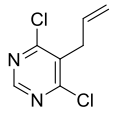
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.5, 156.6, 140.8, 133. 6, 129.5, 128.8, 125.9, 15.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = cm-1, 3050, 2992, 2925, 1916, 1713, 1652, 1594, 1552, 1539, 1504, 1434, 1424, 1406, 1398, 1389, 1372, 1362, 1346, 1322, 1296, 1270, 1230, 1215, 1204, 1189, 1163, 1114, 1093, 1020, 994, 969, 959, 951, 824, 801, 796, 780, 732, 721, 704.

MS (EI, 70 eV): m/z (%) = 271 [M^+] (32), 257 (20), 255 (30), 192 (16), 173 (15), 91 (16), 61 (20), 43 (100).

HRMS (EI) for **$C_{11}H_9Cl_2N_2S$** (270.9858): 270.9860 ([M+H]$^+$).

Synthesis of 5-allyl-4,6-dichloropyrimidine (70c):



A solution of 5-(4,6-dichloropyrimidinyl)zinc pivalate (**67a**, 1.23 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C and CuCN·2LiCl (0.05 mmol, 0.05 mL, 1.0 m in THF) was added. After stirring for 20 min the mixture was cooled further at -60 °C and allyl bromide (**68d**, 145 mg, 1.2 mmol) was added. The reaction mixture was allowed to warm to up to -30 °C over 1 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 10:1) afforded the product **70c** (166 mg, 88%) as colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.62 (s, 1H), 5.84 (ddd, *J* = 16.5, 11.1, 6.0 Hz, 1H), 5.27 – 4.95 (m, 2H), 3.63 (dd, *J* = 6.2, 1.5 Hz, 2H).

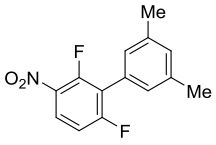
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.0, 155.8, 130.9, 130.6, 118.1, 34.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2969, 2360, 1739, 1639, 1539, 1513, 1435, 1406, 1375, 1348, 1313, 1290, 1200, 1162, 1129, 1090, 989, 929, 906, 839, 777, 687, 668, 627, 621, 616.

MS (EI, 70 eV): m/z (%) = 188 [M^+] (70), 125 (22), 117 (44), 90 (59), 64 (35), 49 (43), 41 (100).

HRMS (EI) for **$C_7H_6Cl_2N_2$** (187.9908): 187.9913 (M^+).

Synthesis of 2,6-difluoro-3',5'-dimethyl-3-nitro-1,1'-biphenyl (71a):



To a solution of (2,6-difluoro-3-nitrophenyl)zinc pivalate (**65a**, 1.23 g, 1.0 mmol) in THF (3 mL) $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and 1-iodo-3,5-dimethylbenzene (**68e**, 185 mg, 0.8 mmol) were added subsequently at 25 °C. The reaction mixture was stirred at 25 °C over 3 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 20:1) afforded the product **71a** (206 mg, 98%) as off-white solid.

M.p. (°C): 71.8-72.8

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.09 (ddd, *J* = 9.26, 8.13, 5.61 Hz, 1H), 6.99 – 7.20 (m, 4H), 2.40 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.8 (dd, *J* = 259, 6 Hz), 153.9 (dd, *J* = 259, 9 Hz), 138.2, 134.7, 131.0, 127.7 (t, *J* = 2 Hz), 126.6, 125.7 (dd, *J* = 11, 2 Hz), 121.5 (dd, *J* = 21, 19 Hz), 111.9 (dd, *J* = 25, 4 Hz), 21.25.

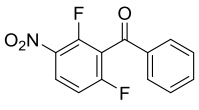
^{19}F-NMR (254 MHz, $CDCl_3$): δ / ppm = -115.20 (dddt, $^4J_{FF}$ = 14.6, $^4J_{HF}$ = 8.0, $^5J_{HF}$ = 1.6, $^5J_{HF}$ = 1.4 Hz, 1F, 2-F), -100.84 (dddt, $^4J_{FF}$ = 14.6, $^3J_{HF}$ = 8.1, $^4J_{HF}$ = 5.6, $^5J_{HF}$ = 1.4 Hz, 1F, 6-F).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 2949, 2916, 2863, 1863, 1618, 1602, 1586, 1526, 1479, 1447, 1416, 1378, 1347, 1304, 1278, 1219, 1204, 1173, 1147, 1106, 1032, 996, 975, 941, 919, 908, 892, 859, 830, 820, 766, 731, 699, 674.

MS (EI, 70 eV): m/z (%) = 263 [M^+] (55), 202 (20), 70 (10), 61 (14), 43 (100).

HRMS (EI) for **$C_{14}H_{11}F_2NO_2$** (263.0758): 263.0752 (M^+).

Synthesis of (2,6-difluoro-3-nitrophenyl)(phenyl)methanone (71b):



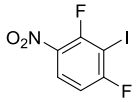
A solution of (2,6-difluoro-3-nitrophenyl)zinc pivalate (**65a**, 1.23 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1.0 m in THF) was added dropwise. After stirring at this temperature for 20 min, benzoyl chloride (**68a**, 281 mg, 2.0 mmol) was added and the mixture was warmed up slowly to reach 25 °C and stirred there for 2 h. The reaction was quenched using sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were

evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 10:1) afforded the product **71b** (156 mg, 59%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (td, *J* = 8.77, 5.55 Hz, 1H), 7.87 (dd, *J* = 7.84, 0.60 Hz, 2H), 7.64 - 7.75 (m, 1H), 7.48 - 7.61 (m, 2H), 7.11 - 7.23 (m, 1H).

The physical and spectroscopical data of compound **71b** were in perfect agreement with the one reported in the literature.[60a]

Synthesis of 1,3-difluoro-2-iodo-4-nitrobenzene (71c):

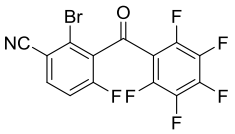


A solution of (2,6-difluoro-3-nitrophenyl)zinc pivalate (**65a**, 1.23 g, 1.0 mmol) in THF (3 mL) was cooled down to 0 °C and I_2 (380 mg, 1.5 mmol) was added. The stirred reaction mixture was allowed to come to 25 °C (over 30 min) and then quenched with a sat. aqueous $Na_2S_2O_3$ solution (9 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 12:1) afforded the product **71c** (278 mg, 98%) as an off-white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (ddd, *J* = 9.24, 8.17, 5.61 Hz, 1H), 7.07 (ddd, *J* = 9.24, 6.38, 1.88 Hz, 1H).

The physical and spectroscopical data of compound **71c** were in perfect agreement with the one reported in the literature. [60a]

Synthesis of 2-bromo-4-fluoro-3-(perfluorobenzoyl)benzonitrile (71d):



(2-Bromo-3-cyano-6-fluorophenyl)-zinc-pivalate (**65b**, 1.17 g, 0.78 mmol/g, 0.9 mmol) dissolved in 2 mL dry THF was cooled down to -20 °C. TMSCl (0.7 mL, 5.4 mmol) was added followed by 30 min stirring. After this CuCN·2LiCl (1 mL, 1 M, 1 mmol) and 2,3,4,5,6-pentafluorobenzoyl chloride (**68f**, 524 mg, 231 g/mol, 2.3 mmol) were added subsequently. The reaction mixture was stirred for 30 min at -20 °C and for 15 h at 0 °C. After quenching with queous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 4:1) afforded the product **71d** (337 mg, 95%) as a off-white solid.

M.p. (°C): 100.1-100.9.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.81 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.31 (t, *J* = 8.5 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 180.4, 161.3 (d, *J* = 264 Hz), 145.8 (d, *J* = 250 Hz), 144.5 (d, *J* = 266 Hz), 137.8 (d, *J* = 260 Hz), 137.3 (d, *J* = 10 Hz), 135.5 (d, *J* = 10 Hz), 131.5 (d, *J* = 20 Hz) 123.7, 116.6 (d, *J* = 23 Hz), 115.9 (d, *J* = 24 Hz), 113.9.

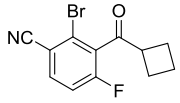
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -103.12 (ddt, *J* = 7.6, 5.3, 2.1 Hz, 1F), -139.48 – (-139.95) (m, 2F), -144.16 (tt, *J* = 25, 6.2 Hz, 1F), -159.06 – (-159.27) (m, 2F).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2239, 1693, 1653, 1575, 1523, 1497, 1456, 1409, 1393, 1365, 1320, 1278, 1246, 1228, 1212, 1177, 1163, 1144, 1136, 1122, 1045, 1030, 984, 958, 911, 898, 852, 830, 805, 781, 742, 711, 685, 667.

MS (EI, 70 eV): m/z (%) = 395 (49), 393 [M^+] (58), 228 (95), 226 (100), 200 (16), 198 (14), 195 (86), 119 (25), 43 (12).

HRMS (EI) for **$C_{14}H_2BrF_6NO$** (392,9224): 392.9231 (M^+).

Synthesis of 2-bromo-3-(cyclobutanecarbonyl)-4-fluorobenzonitrile (71e):



(2-Bromo-3-cyano-6-fluorophenyl)-zinc-pivalate (**65b**, 1.3 g, 0.78 mmol/g, 1.1 mmol) dissolved in 2 mL dry THF was cooled down to -20 °C. TMSCl (0.8 mL, 6.3 mmol) was added followed by 30 min stirring. After this CuCN·2 LiCl (1.2 mL, 1 M, 1.2 mmol) and cyclobutanecarbonyl chloride (**68g**, 311 mg, 2.6 mmol) were added subsequently. The reaction mixture was stirred for 30 min at -20 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 4:1) afforded the product **71e** (280 mg, 95%) as colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.69 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.21 (dd, *J* = 8.7, 8.0 Hz, 1H), 3.70 (quintt, *J* = 8.5, 1.2 Hz, 1H), 2.44 (quint, *J* = 9.2 Hz, 2H), 2.28 – 2.13 (m, 2H), 2.11 – 1.85 (m, 2H).

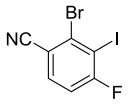
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.1, 184.6, 160.5 (d, *J* = 259 Hz), 140.0 (d, *J* = 10 Hz), 132.6 (d, *J* = 24 Hz), 123.2 (d, *J* = 6.8 Hz), 116.2 (d, *J* = 24 Hz), 113.5 (d, *J* = 3.8 Hz), 46.3, 27.0, 17.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3087, 2949, 2871, 2237, 1701, 1576, 1483, 1457, 1414, 1388, 1367, 1344, 1279, 1249, 1198, 1166, 1136, 1105, 1068, 984, 918, 885, 827, 798, 729, 692, 677.

MS (EI, 70 eV): m/z (%) = 281 [M^+] (3), 255 (10), 253 (10), 228 (98), 227 (11), 226 (100), 200 (11), 198 (11), 119 (21).

HRMS (EI) for **$C_{12}H_9BrFNO$** (280.9852): 280.9836 (M^+).

Synthesis of 2-bromo-4-fluoro-3-iodobenzonitrile (71f):



To a solution of (2-bromo-3-cyano-6-fluorophenyl)-zinc-pivalate (**65b**, 1.3 g, 0.78 mmol/g, 1.1 mmol) in 2 mL dry THF iodine (558 mg, 2.2 mmol) was added at 25 °C and the reaction mixture was stirred for 0.5 h at this temperature. After quenching with a saturated aqueous $Na_2S_2O_3$ solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 9:1) afforded the product **71f** (325 mg, 91%) as a white solid.

M.p. (°C): 102.7-103.3.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.68 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.12 (dd, *J* = 8.6, 6.8 Hz, 1H).

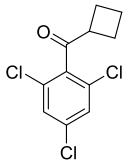
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.7 (d, *J* = 256 Hz), 135.4 (d, *J* = 9 Hz), 134.9 (d, *J* = 2 Hz), 116.6 (d, *J* = 2 Hz), 114.7 (d, *J* = 26 Hz), 112.8 (d, *J* = 4 Hz), 92.9 (d, *J* = 29 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3067, 2237, 1914, 1779, 1660, 1571, 1555, 1444, 1357, 1310, 1292, 1258, 1248, 1223, 1213, 1138, 1076, 959, 920, 897, 826, 756, 741, 690, 661.

MS (EI, 70 eV): m/z (%) = 327 (100), 325 [M^+] (92), 200 (18), 198 (20), 119 (40), 43 (75).

HRMS (EI) for **C_7H_2BrFIN** (324.8399): 324.8396 (M^+).

Synthesis of cyclobutyl(2,4,6-trichlorophenyl)methanone (71g):



(2,4,6-Trichlorophenyl) zinc pivalate (**65c**, 1.53 g, 0.68 mmol/g, 1.0 mmol) dissolved in 2 mL dry THF was cooled to -20 °C. TMS-Cl (0.8 mL, 6.3 mmol) was added followed by 30 min stirring. After this CuCN·2 LiCl (1.1 mL, 1 M, 1.1 mmol) and cyclobutanecarbonyl chloride (**68g**, 307 mg, 2.5 mmol) were added subsequently. The reaction mixture was stirred for 30 min at -20 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane) afforded the product **71g** (250 mg, 95%) as yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.32 (s, 2H), 3.71 (quintt, *J* = 8.5, 1.0 Hz, 1H), 2.56 – 2.37 (m, 2H), 2.29 – 2.11 (m, 2H), 2.09 – 1.83 (m, 2H).

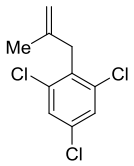
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 202.9, 138.0, 135.5, 131.4, 128.2, 46.2, 25.0, 18.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = cm-1, 3077, 2986, 2946, 2866, 1705, 1574, 1543, 1435, 1378, 1365, 1344, 1260, 1246, 1204, 1183, 1155, 1105, 1086, 1050, 1016, 965, 919, 894, 853, 814, 797, 748, 718, 691, 678.

MS (EI, 70 eV): m/z (%) = 361 [M$^+$] (2), 211 (31), 209 (94), 207 (100), 61 (14), 55 (26), 45 (12), 43 (81).

HRMS (EI) for **$C_{11}H_9Cl_3O$** (261.9719): 261.9721 (M$^+$).

Synthesis of 1,3,5-trichloro-2-(2-methylallyl)benzene (71h):



(2,4,6-Trichlorophenyl)zinc pivalate (**65c**, 1.44 g, 0.68 mmol/g, 0.9 mmol) dissolved in 2 mL dry THF was cooled down to -20 °C. After this CuCN·2LiCl (0.2 mL, 1 M, 0.2 mmol) and 3-bromo-2-methylpropene (**68h**, 159 mg 1.2 mmol) were added. The reaction mixture was stirred for 45 min at -20 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane) afforded the product **71h** (216 mg, 94%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.33 (s, 2H), 4.77 – 4.81 (m, 1H), 4.31 – 4.35 (m, 1H), 3.57 (s, 2H), 1.81 – 1.84 (m, 3H).

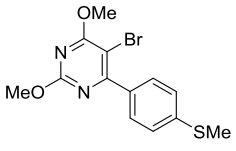
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 140.9, 136.5, 134.6, 132.6, 128.0, 111.0, 38.2, 23.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 2973, 2920, 2851, 1791, 1721, 1652, 1581, 1567, 1548, 1442, 1424, 1390, 1373, 1330, 1283, 1265, 1229, 1208, 1164, 1133, 1098, 1071, 1038, 1020, 925, 915, 890, 855, 812, 784, 766, 693, 673, 662.

MS (EI, 70 eV): m/z (%) = 234 [M$^+$] (8), 201 (7), 194 (6), 164 (5), 73 (5), 70 (12), 61 (15), 45 (14), 43 (100), 42 (5), 41 (6).

HRMS (EI) for **$C_{10}H_9Cl_3$** (233.9770): 233.9761 (M$^+$).

Synthesis of 5-bromo-2,4-dimethoxy-6-(4-(methylthio)phenyl)pyrimidine (72a):



To a solution of (5-bromo-2,6-dimethoxypyrimidin-4-yl)zinc pivalate (**67b**, 1.27 g, 1.0 mmol) in THF (3 mL) $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and 4-iodothioanisole (**68c**, 200 mg, 0.8 mmol) were added subsequently at 25 °C. The reaction mixture was stirred at 25 °C over 12 h and then quenched with sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 5:1) afforded the product **72a** (276 mg, 81%) as white solid.

M.p. (°C): 121.6-123.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.75 (d, J = 8.50 Hz, 2H), 7.31 (d, J = 8.43 Hz, 2H), 4.10 (s, 3H), 4.02 (s, 3H), 2.53 (s, 3H).

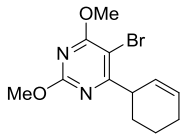
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.1, 165.2, 163.4, 141.2, 134.0, 129.8, 125.2, 96.5, 55.3, 55.2, 15.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3021, 2988, 2953, 2882, 2211, 1596, 1562, 1535, 1499, 1477, 1448, 1420, 1401, 1383, 1350, 1324, 1301, 1240, 1196, 1151, 1111, 1092, 1034, 1020, 1011, 977, 964, 949, 934, 900, 887, 863, 828, 814, 786, 736, 727, 681, 661.

MS (EI, 70 eV): m/z (%) = 342 [^{81}Br, M$^+$] (100), 340 [^{79}Br, M$^+$] (92), 231 (29), 174 (11), 43 (14).

HRMS (EI) for **$C_{13}H_{13}{}^{79}BrN_2O_2S$** (339.9881): 339.9857.

Synthesis of 5-bromo-4-(cyclohex-2-en-1-yl)-2,6-dimethoxypyrimidine (72b):



A solution of (5-bromo-2,6-dimethoxypyrimidin-4-yl)zinc pivalate (**67b**, 1.27 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C. CuCN·2LiCl (0.1 mmol, 0.1 mL, 1 m in THF) and 3-bromocyclohexene (**57a**, 242 mg, 1.5 mmol) were added subsequently. The reaction mixture was allowed to warm up to 25 °C over 12 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 10:1) afforded the product **72b** (266 mg, 89%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 5.82 – 5.93 (m, 1H), 5.57 – 7.70 (m, 1H), 4.04 (s, 3H), 3.95 – 4.02 (m, 4H) 1.61 – 2.17 (m, 6H).

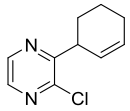
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 172.7, 167.1, 163.5, 128.5, 126.9, 97.6, 55.0, 54.9, 41.6, 27.3, 24.6, 21.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2989, 2940, 2867, 2836, 1563, 1546, 1479, 1452, 1381, 1352, 1299, 1285, 1258, 1239, 1200, 1156, 1138, 1109, 1084, 1069, 1042, 1026, 997, 956, 943, 926, 896, 885, 864, 854, 791, 761, 743, 722, 700, 680, 658.

MS (EI, 70 eV): m/z (%) = 298 [M^+] (72), 271 (100), 259 (18), 234 (37), 219 (40), 72 (17), 43 (16).

HRMS (EI) for **$C_{12}H_{15}BrN_2O_2$** (298.0317): 298.0314.

Synthesis of 2-chloro-3-(cyclohex-2-en-1-yl)pyrazine (72c):



(3-Chloropyrazin-2-yl)zinc-pivalate (**67c**, 976 mg, 0.63 mmol/g, 0.62 mmol) dissolved in 1.2 mL dry THF was cooled down to -20 °C. After this CuCN·2LiCl (0.12 mL, 1 M, 0.12 mmol) and 3-bromocyclohexene (**57a**, 119 mg, 161 g/mol, 0.7 mmol) were added. The reaction mixture was stirred for 15 h at -20 °C. After quenching with a aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 9:1) afforded the product **72c** (109 mg, 91%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.46 (d, J = 2.4 Hz, 1H), 8.20 (d, J = 2.4 Hz, 1H), 6.03 – 5.96 (m, 1H), 5.75 – 5.69 (m, 1H), 4.09 – 4.00 (m, 1H), 2.18 – 2.09 (m, 3H), 1.91 – 1.79 (m, 1H), 1.78 – 1.61 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.0, 148.7, 142.4, 141.3, 129.4, 126.8, 40.0, 28.2, 24.6, 21.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3266, 3027, 2934, 2861, 2836, 1681, 1552, 1519, 1446, 1433, 1394, 1378, 1344, 1328, 1298, 1284, 1247, 1194, 1146, 1132, 1085, 1055, 1039, 987, 964, 934, 889, 854, 809, 782, 753, 721, 661.

MS (EI, 70 eV): m/z (%) = 194 [M^+] (46), 193 (25), 179 (15), 167 (33), 166 (31), 165 (100), 159 (32), 153 (14), 130 (16), 128 (40), 77 (11), 67 (21).

HRMS (EI) for **$C_{10}H_{11}ClN_2$** (194.0611): 194.0590 (M^+).

Synthesis of 2-chloro-3-iodopyrazine (72d):

To a solution of (3-Chloropyrazin-2-yl)zinc-pivalate (**67c**, 1.61 g, 1.0 mmol/g, 0.62 mmol) in 2 mL dry THF iodine (508 mg, 2.0 mmol) was added at 25 °C and the reaction mixture was stirred for 0.5 h at

this temperature. After quenching with sat. aqueous $Na_2S_2O_3$ solution (4 mL) the mixture was extracted with ethyl acetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 10:1) afforded the product **72d** (223 mg, 93%) as a white solid.

M.p. (°C): 141.0-142.2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.29 (d, *J* = 1.4 Hz, 1H), 8.27 (d, *J* = 1.4 Hz, 1H).

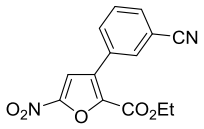
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.6, 142.6, 141.9, 119.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2963, 2925, 2854, 1932, 1821, 1723, 1531, 1494, 1423, 1409, 1335, 1312, 1259, 1228, 1181, 1169, 1138, 1091, 1056, 1016, 858, 796, 778, 746, 702, 692.

MS (EI, 70 eV): m/z (%) = 240 [M^+] (28), 72 (39), 69 (38), 57 (79), 55 (60), 43 (57), 43 (100), 41 (42).

HRMS (EI) for **$C_4H_2ClIN_2$** (239.8951): 239.8953 (M^+).

Synthesis of ethyl 3-(3-cyanophenyl)-5-nitrofuran-2-carboxylate (72e):



To a solution of 3-(2-ethoxycarbonyl-5-nitrofuranyl)zinc pivalate (**67e**, 1.33 g, 1.0 mmol) in THF (3 mL) at 25 °C $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and 3-iodobenzonitrile (**68i**, 183 mg, 0.8 mmol) were added subsequently. The reaction mixture was stirred for 6 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 8:1) afforded the product **72e** (189 mg, 66%) as off-white solid.

M.p. (°C): 133.9-136.5

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.86 (td, *J* = 1.8, 0.6 Hz, 1H), 7.81 (ddd, *J* = 7.9, 1.8, 1.2 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.62 (td, *J* = 7.9, 0.6 Hz, 1H), 7.36 (s, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

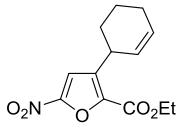
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.7, 157.7, 143.6, 133.7, 133.3, 132.8, 129.8, 129.6, 125.3, 120.4, 117.8, 113.2, 62.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 3066, 2997, 2910, 2238, 1746, 1612, 1591, 1532, 1509, 1481, 1463, 1447, 1420, 1398, 1362, 1348, 1336, 1324, 1301, 1262, 1244, 1224, 1186, 1180, 1155, 1123, 1111, 1096, 1011, 968, 934, 925, 891, 870, 848, 820, 799, 767, 744, 692, 680, 665.

MS (EI, 70 eV): m/z (%) = 286 [M^+] (100), 241 (18), 213 (32), 200 (39), 172 (37), 139 (32), 130 (20), 127 (59).

HRMS (ESI) for **$C_{14}H_{10}N_2O_5$** (286.0590): 286.0585 (M^+).

Synthesis of ethyl 3-(cyclohex-2-enyl)-5-nitrofuran-2-carboxylate (72f):



A solution of 3-(2-ethoxycarbonyl-5-nitrofuranyl)zinc pivalate (**67e**, 1.33 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C. CuCN·2LiCl (0.1 mmol, 0.1 mL, 1 m in THF) and 3-bromocyclohexene (**57a**, 242 mg, 1.5 mmol) were added subsequently. The reaction mixture was allowed to warm to 25 °C over 12 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 10:1) afforded the product **72f** (187 mg, 70%) as reddish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.20 (d, J = 0.5 Hz, 1H), 5.97 (dtd, J = 9.8, 3.7, 2.2 Hz, 1H), 5.64 – 5.54 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.14 (ddd, J = 10.6, 5.5, 2.7 Hz, 1H), 2.17 – 1.99 (m, 3H), 1.77 – 1.64 (m, 2H), 1.61 – 1.48 (m, 1H), 1.40 (t, J = 7.1 Hz, 3H).

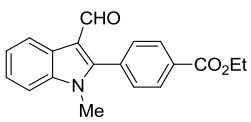
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.2, 147.9, 143.0, 134.0, 130.5, 126.4, 119.9, 62.3, 32.3, 29.1, 24.7, 20.6, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3127, 3025, 2984, 2936, 2864, 2838, 1737, 1724, 1629, 1595, 1532, 1502, 1475, 1465, 1447, 1433, 1402, 1390, 1367, 1337, 1286, 1251, 1226, 1197, 1156, 1140, 1106, 1092, 1015, 981, 965, 932, 883, 851, 818, 764, 746, 725, 671.

MS (EI, 70 eV): m/z (%) = 265 [M^+] (2), 248 (100), 231 (49), 220 (15), 146 (20), 91 (19), 77 (16).

HRMS (ESI) for **$C_{13}H_{15}NO_5$** (265.0950): 265.0943 (M^+).

Synthesis of ethyl 4-(3-formyl-1-methyl-1*H*-indol-2-yl)benzoate (72g):



To a solution of (3-formyl-1-methyl-1*H*-indol-2-yl)zinc pivalate (**67f**, 1.18 g, 1.0 mmol) in THF (3 mL) at 25 °C $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and ethyl 4-iodobenzoate (**57d**, 220 mg, 0.8 mmol) were added subsequently. The reaction mixture was stirred at 25 °C over 3 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether (3 ×

10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 1:1) afforded the product **72g** (281 mg, 91%) as off-white solid.

M.p. (°C): 161.4-163.0.

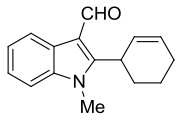
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.75 (s, 1H), 8.44 (d, *J* = 5.73 Hz, 1H), 8.18 – 8.30 (m, 2H), 7.49 – 7.72 (m, 2H), 7.30 – 7.52 (m, 3H), 4.46 (q, *J* = 7.06 Hz, 2H), 3.69 (s, 3H), 1.45 (t, *J* = 7.17 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 186.0, 165.7, 149.7, 137.5, 133.0, 131.8, 130.9, 129.7, 125.1, 124.3, 123.4, 122.2, 116.0, 109.8, 61.4, 31.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3034, 2988, 2978, 2886, 2803, 2770, 2730, 1712, 1649, 1608, 1578, 1567, 1537, 1507, 1467, 1442, 1416, 1371, 1366, 1339, 1327, 1313, 1289, 1280, 1255, 1183, 1155, 1128, 1107, 1082, 1072, 1049, 1028, 1018, 990, 977, 951, 901, 884, 874, 861, 848, 812, 760, 741, 714, 700, 694, 682, 662**.**

HRMS (ESI) for **$C_{19}H_{18}NO_3$** (308.1281): 308.1280 ([M+H]$^+$).

Synthesis of 2-(cyclohex-2-en-1-yl)-1-methyl-1*H*-indole-3-carbaldehyde (72h):



A solution of (3-formyl-1-methyl-1*H*-indol-2-yl)zinc pivalate (**67f**, 1.18 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C. CuCN·2LiCl (0.1 mmol, 0.1 mL, 1 m in THF) and 3-bromocyclohexene (**57a**, 242 mg, 1.5 mmol) were added subsequently. The reaction mixture was allowed to warm to 25 °C over 12 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 2:1) afforded the product **72h** (234 mg, 98%) as orange resin.

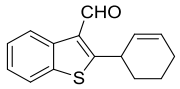
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.34 (s, 1H), 8.35 (s, 1H), 7.25 – 7.40 (m, 3H), 5.96 – 6.05 (m, 1H), 5.80 – 5.88 (m, 1H), 4.22 – 4.37 (m, 1H), 3.80 (s, 3H), 2.11 – 2.26 (m, 3H), 1.74 – 2.04 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 185.2, 153.7, 137.2, 129.4, 127.5, 125.7, 123.3, 123.0, 121.6, 114.3, 109.2, 34.0, 30.7, 27.0, 24.6, 22.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 3024, 2932, 2862, 1713, 1641, 1612, 1580, 1513, 1468, 1446, 1413, 1393, 1372, 1336, 1322, 1291, 1246, 1223, 1186, 1126, 1082, 1048, 1016, 980, 933, 890, 859, 818, 801, 746, 729, 701, 683, 671.

HRMS (ESI) for **$C_{16}H_{18}NO$** (240.1383): 240.1383 ([M+H]$^+$).

Synthesis of 2-(cyclohex-2-en-1-yl)benzo[*b*]thiophene-3-carbaldehyde (72i):



A solution of (3-formylbenzo[*b*]thiophen-2-yl)zinc pivalate (**67g**, 1.16 g, 1.0 mmol) in THF (2 mL) was cooled to -20 °C. CuCN·2LiCl (0.1 mmol, 0.1 mL, 1 m in THF) and 3-bromocyclohexene (**57a**, 242 mg, 1.5 mmol) were added subsequently. The reaction mixture was allowed stirred at -20 °C for 12 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 10:1) afforded the product **72i** (230 mg, 95%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.42 (s, 1H), 8.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.46 (ddd, *J* = 8.0, 7.2, 1.3 Hz, 1H), 7.42 – 7.32 (m, 1H), 6.07 – 5.96 (m, 1H), 5.88 – 5.78 (m, 1H), 4.44 – 4.58 (m, 1H), 2.32 – 2.09 (m, 3H), 1.96 – 1.65 (m, 3H).

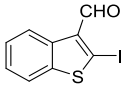
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 184.2, 168.9, 137.6, 137.1, 130.5, 128.9, 128.0, 125.8, 125.0, 124.0, 121.7, 35.5, 33.1, 24.7, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 3023, 2930, 2857, 2834, 2742, 1664, 1591, 1557, 1509, 1461, 1444, 1433, 1398, 1356, 1326, 1294, 1275, 1260, 1224, 1176, 1155, 1146, 1080, 1052, 1020, 968, 942, 900, 889, 863, 838, 817, 800, 754, 731, 698, 656.

MS (EI, 70 eV): m/z (%) = 242 [M$^+$] (100), 225 (27), 213 (41), 187 (21), 185 (25), 171 (15), 147 (16).

HRMS (EI) for **$C_{15}H_{14}OS$** (242.0765): 242.076 (M$^+$).

Synthesis of 2-iodobenzo[*b*]thiophene-3-carbaldehyde (72j):

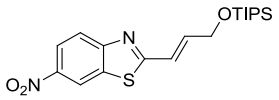


To a solution of (3-formylbenzo[*b*]thiophen-2-yl)zinc pivalate (**67g**, 1.16 g, 1.0 mmol) in THF (2 mL) iodine (508 mg, 2.0 mmol) was added and the reaction mixture was allowed stirred at 25 °C for 30 min. After quenching with sat. aqueous $Na_2S_2O_3$ solution (4 mL) the mixture was extracted with ethyl acetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 10:1) afforded the product **72j** (256 mg, 89%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.99 (s, 1H), 8.88 – 8.60 (m, 1H), 7.84 – 7.64 (m, 1H), 7.54 – 7.31 (m, 2H).

The physical and spectroscopical data of compound **72j** were in perfect agreement with the one reported in the literature.[59a]

Synthesis of (*E*)-6-nitro-2-(3-(triisopropylsilyloxy)prop-1-enyl)benzo[*d*]thiazole (72k):



To a solution of (6-nitrobenzo[*d*]thiazol-2-yl)zinc pivalate (**67h**, 1.33 g, 1.0 mmol) in THF (3 mL) at 25 °C $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and (*E*)-(3-iodoallyloxy)triisopropylsilane (**68j**, 272 mg, 0.8 mmol) were added subsequently. The reaction mixture was stirred for 2 h and then quenched with a sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 25:1) afforded the product **72k** (298 mg, 95%) as orange crystals.

M.p. (°C): 50.5-52.6.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.76 (dd, *J* = 2.3, 0.5 Hz, 1H), 8.32 (dd, *J* = 9.0, 2.3 Hz, 1H), 8.04 (dd, *J* = 9.0, 0.4 Hz, 1H), 7.11 (dt, *J* = 15.6, 2.2 Hz, 1H), 6.96 (dt, *J* = 15.6, 3.4 Hz, 1H), 4.56 (dd, *J* = 3.4, 2.2 Hz, 2H), 1.24 – 1.13 (m, 3H), 1.13 – 1.07 (m, 18H).

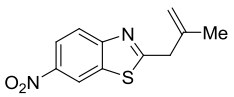
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.6, 157.5, 144.8, 143.1, 134.7, 122.9, 122.1, 121.8, 118.0, 62.7, 18.0, 11.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3112, 2957, 2942, 2890, 2864, 2839, 2718, 1646, 1601, 1567, 1514, 1491, 1462, 1440, 1411, 1384, 1371, 1335, 1290, 1278, 1270, 1261, 1238, 1136, 1126, 1120, 1096, 1073, 1046, 1016, 994, 964, 949, 919, 908, 882, 846, 824, 816, 793, 781, 764, 751, 716, 687, 663.

MS (EI, 70 eV): m/z (%) = 392 [M$^+$] (7), 349 (100), 173 (27), 103 (11), 75 (14), 43 (38).

HRMS (ESI) for **$C_{19}H_{28}N_2O_3SSi$** (392.1590): 392.1584 (M$^+$).

Synthesis of 2-(2-methylallyl)-6-nitrobenzo[*d*]thiazole (72l):



A solution of (6-nitrobenzo[*d*]thiazol-2-yl)zinc pivalate (**67h**, 1.33 g, 1.0 mmol) in THF (3 mL) was cooled to -40 °C. CuCN·2LiCl (0.1 mmol, 0.1 mL, 1 m in THF) and 3-bromo-2-methylpropene (**68h**, 162 mg, 1.2 mmol) were added subsequently. The reaction mixture was stirred for 45 min at the same temperature and then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) and allowed to warm up to 25 °C (prolonged reaction time or quenching at higher temperature led to partial migration of the double bond to conjugation) followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 15:1) afforded the product **72l** (205 mg, 88%) as orange solid.

M.p. (°C): 88.5-90.1.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.78 (dd, *J* = 2.3, 0.4 Hz, 1H), 8.33 (dd, *J* = 9.0, 2.3 Hz, 1H), 8.07 (dd, *J* = 9.0, 0.3 Hz, 1H), 5.07 – 5.04 (m, 1H), 5.04 – 5.02 (m, 1H), 3.88 (d, *J* = 1.0 Hz, 2H), 1.84 (t, *J* = 1.1 Hz, 3H).

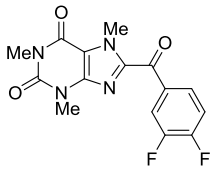
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 176.6, 157.1, 144.8, 140.8, 136.0, 123.0, 121.5, 118.1, 115.6, 43.3, 22.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 3063, 3002, 2980, 2933, 2906, 1944, 1833, 1812, 1738, 1650, 1601, 1567, 1511, 1447, 1418, 1384, 1366, 1344, 1335, 1328, 1310, 1277, 1246, 1196, 1131, 1113, 1047, 1022, 976, 914, 896, 845, 754, 743, 723, 681, 654.

MS (EI, 70 eV): m/z (%) = 234 [M^+] (23), 219 (29), 194 (15), 70 (15), 61 (18), 44 (17), 43 (100).

HRMS (ESI) for **$C_{11}H_{10}N_2O_2S$** (234.0463): 234.0458 (M^+).

Synthesis of 8-(3,4-difluorobenzoyl)-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (72m):



(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)zinc pivalate (**67i**, 1.30 g, 1.0 mmol) dissolved in 2 mL dry THF was cooled to -20 °C. TMSCl (0.75 mL, 6.0 mmol) was added followed by 30 min stirring. After this CuCN·2 LiCl (1.1 mL, 1 M, 1.1 mmol) and 3,4-difluorobenzoyl chloride (**68k**, 441 mg, 2.5 mmol) were added subsequently. The reaction mixture was stirred for 18 h at -20 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / EtOAc = 4:1) afforded the product **72m** (245 mg, 73%) as white solid.

M.p. (°C): 176.9-178.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.29 (ddd, *J* = 11.1, 7.8, 2.1 Hz, 1H), 8.20 (dddd, *J* = 8.7, 4.4, 2.1, 1.3 Hz, 1H), 7.30 (ddd, *J* = 9.6, 8.7, 7.6 Hz, 1H), 4.37 (s, 3H), 3.62 (s, 3H), 3.43 (s, 3H).

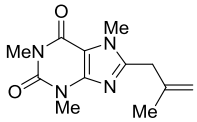
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 180.8 (dd, *J* = 2.0, 1.0 Hz), 155.7, 154.1 (dd, *J* = 259, 13 Hz), 151.4, 149.9 (dd, *J* = 250, 13 Hz), 146.4, 143.4, 133.0 (dd, *J* = 5.2, 3.5 Hz), 128.3 (dd, *J* = 7.5, 3.6 Hz), 120.5 (dd, *J* = 19, 1.9 Hz), 117.3 (dd, *J* = 17.8, 0.5 Hz), 110.5, 35.1, 29.9, 28.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 1704, 1664, 1600, 1542, 1526, 1509, 1478, 1454, 1410, 1388, 1372, 1342, 1286, 1264, 1241, 1229, 1216, 1182, 1128, 1102, 1044, 988, 972, 942, 900, 870, 850, 831, 805, 779, 772, 764, 746, 738, 720, 689.

MS (EI, 70 eV): m/z (%) = 334 [M^+] (100), 248 (11), 141 (33), 113 (23), 82 (14), 67 (33).

HRMS (EI) for **$C_{15}H_{12}F_2N_4O_3$** (334.0877): 334.0870 (M^+).

Synthesis of 1,3,7-trimethyl-8-(2-methylallyl)-3,7-dihydro-1*H*-purine-2,6-dione (72n):



(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)zinc pivalate (**67i**, 1.30 g, 1.0 mmol) dissolved in 2 mL dry THF was cooled to -20 °C. CuCN·2 LiCl (0.1 mL, 1 M, 0.1 mmol) and 3-bromo-2-methylpropene (**68h**, 162 mg, 1.2 mmol) were added subsequently. The reaction mixture was stirred for 1 h at -20 °C. After quenching with aqueous NH_4Cl/NH_3 (8:1) solution (4 mL) the mixture was extracted with ethylacetate (5 × 8 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / EtOAc = 9:1) afforded the product **72n** (248 mg, 94%) as white solid.

M.p. (°C): 122.6-124.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.92 (quint, J = 1.3 Hz, 1H), 4.55 – 4.60 (m, 1H), 3.87 (s, 3H), 3.56 (s, 3H), 3.47 – 3.50 (m, 2H), 3.38 (s, 3H), 1.76 – 1.79 (m, 3H).

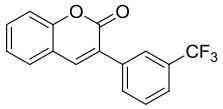
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 155.3, 151.6, 151.4, 147.8, 139.6, 113.4, 107.7, 35.7, 31.9, 29.7, 27.8, 22.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = cm-1, 2973, 2940, 1698, 1694, 1659, 1606, 1544, 1494, 1450, 1422, 1400, 1373, 1341, 1291, 1250, 1220, 1140, 1068, 1037, 976, 966, 951, 909, 795, 758, 741, 706, 679.

MS (EI, 70 eV): m/z (%) = 248 [M^+] (81), 233 (32), 208 (35), 193 (19), 190 (10), 82 (19), 70 (11), 67 (30), 61 (14), 45 (13), 43 (100).

HRMS (EI) for **$C_{12}H_{16}N_4O_2$** (248.1273): 248.1273 (M^+).

Synthesis of 3-(3-(trifluoromethyl)phenyl)-2*H*-chromen-2-one (72o):



To a solution of (2-oxo-2*H*-chromen-3-yl)zinc pivalate (**67j**, 0.91 g, 1.0 mmol) in THF (3 mL) at 25 °C, $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and 1-iodo-3-(trifluoromethyl)benzene (**57c**, 217 mg, 0.8 mmol) were added successively. The reaction mixture was stirred at 25 °C for 1.5 h and then quenched with sat. aqueous NH_4Cl solution (9 mL) followed by extraction with diethyl ether

(3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 5:1) afforded the product **72o** (226 mg, 96%) as white solid.

M.p. (°C): 122.9-124.4.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.90 – 8.01 (m, 2H), 7.89 (s, 1H), 7.64 – 7.73 (m, 1H), 7.58 (t, *J* = 7.36 Hz, 3H), 7.28 – 7.45 (m, 2H).

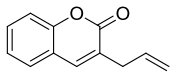
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2, 153.7, 140.7, 135.4, 132.0, 131.9 (q, *J* = 1.3 Hz), 131.0 (q, *J* = 32.5 Hz), 128.9, 128.1, 126.9, 125.5 (q, *J* = 3.8 Hz), 125.2 (q, *J* = 3.8 Hz), 124.7, 123.9 (q, *J* = 272 Hz), 119.3, 116.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3038, 2979, 2889, 1710, 1658, 1608, 1567, 1508, 1492, 1458, 1430, 1400, 1356, 1343, 1332, 1289, 1285, 1261, 1232, 1180, 1165, 1150, 1108, 1076, 1026, 1001, 986, 968, 956, 940, 924, 904, 859, 808, 774, 758, 736, 691, 654.

MS (EI, 70 eV): m/z (%) = 290 [M^+] (100), 262 (88), 233 (9), 165 (29), 43 (10)..

HRMS (EI) for **$C_{16}H_9F_3O_2$** (290.0555): 290.0548 (M^+).

Synthesis of 3-allyl-2*H*-chromen-2-one (72p):



A solution of (2-oxo-2*H*-chromen-3-yl)zinc pivalate (**67j**, 0.91 g, 1.0 mmol) in THF (3 mL) was cooled to -20 °C. CuCN·2LiCl (0.1 mmol, 0.1 mL, 1.0 M in THF) and allyl bromide (**68d**, 182 mg, 1.5 mmol) were added subsequently. The reaction mixture was allowed to warm to 25 °C over 12 h and was then quenched with a sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 4:1) afforded the product **72p** (182 mg, 98%) as a white solid.

M.p. (°C): 41.4-45.9.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.38 – 7.61 (m, 3H), 7.16 – 7.37 (m, 2H), 5.80 – 6.14 (m, 1H), 5.04 – 5.43 (m, 2H), 3.32 (d, *J* = 6.77 Hz, 2H)

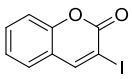
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.5, 153.1, 138.8, 133.7, 130.7, 128.0, 127.2, 124.2, 119.4, 118.1, 116.4, 34.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3016, 2976, 2905, 1707, 1633, 1608, 1578, 1568, 1508, 1484, 1472, 1457, 1429, 1416, 1400, 1382, 1363, 1326, 1291, 1282, 1253, 1232, 1185, 1150, 1124, 1082, 1050, 1026, 1006, 946, 932, 901, 864, 844, 787, 754, 744, 727, 712, 702, 682, 662.

MS (EI, 70 eV): m/z (%) = 186 [M^+] (49), 171 (20), 157 (24), 131 (23), 61 (19), 43 (100).

HRMS (ESI) for **$C_{12}H_{10}O_2$** (186.0681): 186.0674 (M^+).

Synthesis of 3-Iodo-2*H*-chromen-2-one (72q):



A solution of oxo(2-oxo-2*H*-chromen-3-yl)zinc pivalate (**67j**, 0.91 g, 1.0 mmol) in THF (3 mL) was cooled down to 0 °C and I_2 (380 mg, 1.5 mmol) was added. The stirred reaction mixture was allowed to come to 25 °C (over 30 min) and then quenched with a sat. aqueous $Na_2S_2O_3$ solution (9 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 4:1) afforded the product **72q** (250 mg, 92%) as a white solid.

M.p. (°C): 90.2-91.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.36 (s, 1H), 7.52 – 7.63 (m, 1H), 7.44 (d, J = 7.67 Hz, 1H), 7.27 – 7.37 (m, 2H).

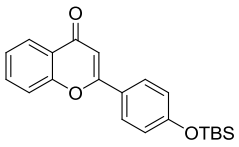
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.4, 153.9, 152.1, 132.3, 126.8, 124.7, 120.1, 116.8, 86.2.

R (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 3047, 3027, 1720, 1706, 1687, 1669, 1602, 1564, 1553, 1508, 1483, 1448, 1440, 1418, 1400, 1363, 1350, 1342, 1329, 1274, 1245, 1212, 1157, 1132, 1119, 1083, 1049, 1026, 986, 958, 948, 934, 913, 860, 802, 782, 763, 750, 724, 700, 682**.**

MS (EI, 70 eV): m/z (%) = 272 [M^+] (100), 244 (29), 145 (44), 89 (61), 63 (28), 43 (18).

HRMS (EI) for **$C_9H_5IO_2$** (271.9334): 271.9333 (M^+).

Synthesis of 2-(4-(tert-butyldimethylsilyloxy)phenyl)-4*H*-chromen-4-one (72r):



According to **TP6** chromone (**66k**, 146 mg, 1.0 mmol) in 2 mL THF reacted with $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) and TMPZnOPiv·LiCl (**63**, 1.3 mL, 0.85 M, 1.1 mmol) to give (4-oxo-4*H*-chromen-2-yl)zinc pivalate (**67k**) as a deep red solution. To this solution $Pd(dba)_2$ (17 mg, 3 mol%), P(*o*-fur)$_3$ (14 mg, 6 mol%) and tert-butyl(4-iodophenoxy)dimethylsilane (**68l**, 267 mg, 0.8 mmol) were added subsequently at 25 °C. The reaction mixture was stirred for 2 h and then quenched with sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 25:1) afforded the product **72r** (218 mg, 78%) as red-brown solid.

M.p. (°C): 94.7-96.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.23 (ddd, *J* = 7.9, 1.7, 0.4 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.73 – 7.65 (m, 1H), 7.55 (ddd, *J* = 8.4, 1.1, 0.4 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.00 – 6.92 (m, 2H), 6.78 (s, 1H), 1.00 (s, 9H), 0.25 (s, 6H).

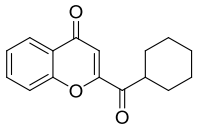
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 178.5, 163.6, 159.1, 156.2, 133.6, 128.0, 125.7, 125.1, 124.5, 123.8, 120.6, 117.9, 106.2, 25.6, 18.3, -4.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2955, 2928, 2857, 2769, 2703, 2641, 1642, 1632, 1620, 1600, 1576, 1509, 1467, 1420, 1376, 1337, 1298, 1274, 1252, 1226, 1176, 1133, 1114, 1043, 1017, 1009, 918, 908, 873, 836, 823, 806, 771, 752, 733, 726, 716, 673.

MS (EI, 70 eV): m/z (%) = 253 [M^+] (76), 297 (22), 296 (100), 295 (20), 175 (11), 121 (29).

HRMS (ESI) for **$C_{21}H_{24}O_3Si$** (352.1495): 352.1494 (M^+).

Synthesis of 2-(cyclohexanecarbonyl)-4*H*-chromen-4-one (72s):



According to **TP6** chromone (**66k**, 146 mg, 1.0 mmol) in 2 mL THF reacted with $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) and TMPZnOPiv·LiCl (**63**, 1.3 mL, 0.85 M, 1.1 mmol) to give (4-oxo-4*H*-chromen-2-yl)zinc pivalate (**67k**) as a deep red solution. This solution was cooled to -20 °C and CuCN·2LiCl (1.1 mmol, 1.1 mL, 1 m in THF) was added. After stirring for 20 min at this temperature, cyclohexanecarbonyl chloride (**68m**, 292 mg, 2.0 mmol) were added dropwise and the reaction mixture was warmed to 25 °C and stirred there for 2 h. Then sat. aqueous NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) were added followed by extraction with ethyl acetate (3 × 10 mL). The combined organic layers were washed with a 15% w/w aqueous solution K_2CO_3 (2×20 mL) and brine (1×20 mL) dried over Na_2SO_4. After filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / ethyl acetate = 15:1) afforded the product **72s** (179 mg, 70%) as colourless crystals.

M.p. (°C): 137.3-140.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (ddd, *J* = 8.0, 1.7, 0.4 Hz, 1H), 7.75 (ddd, *J* = 8.8, 7.1, 1.7 Hz, 1H), 7.58 (ddd, *J* = 8.5, 1.0, 0.4 Hz, 1H), 7.45 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.97 (s, 1H), 3.27 (tt, *J* = 11.2, 3.3 Hz, 1H), 1.95 (dd, *J* = 14.3, 1.3 Hz, 2H), 1.91 – 1.81 (m, 2H), 1.81 – 1.70 (m, 1H), 1.44 (dtdd, *J* = 19.3, 16.0, 9.7, 3.3 Hz, 4H), 1.33 – 1.22 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 197.9, 178.6, 156.5, 155.56, 134.7, 125.9, 125.8, 124.5, 118.6, 112.0, 45.6, 28.4, 25.7, 25.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 2923, 2852, 1693, 1642, 1616, 1570, 1464, 1450, 1398, 1367, 1352, 1331, 1315, 1294, 1272, 1254, 1240, 1224, 1190, 1169, 1148, 1136, 1114, 1103, 1084, 1075, 1057, 1040, 1030, 1020, 996, 962, 924, 896, 878, 866, 839, 784, 771, 755, 744, 721, 676.

MS (EI, 70 eV): m/z (%) = 256 [M^+] (37), 83 (17), 70 (15), 61 (17), 55 (21), 43 (100).

HRMS (ESI) for **$C_{16}H_{16}O_3$** (256.1099): 256.1085 (M^+).

6. Structural Insights on Organozinc Pivalate Reagents

Note: The experiments carried out in C6.1. and C6.2 were performed by the group of Prof. Mulvey and Prof. Hevia at the University of Strathclyde in Glasgow.

6.1. Preparation of the Magnesium and Zinc Pivalate Complexes

X-ray crystallographic studies:

Single-crystal X-ray diffraction data were measured with Oxford Diffraction (now Agilent Technologies) Xcalibur or Gemini diffractometers using MoKα (λ = 0.71073) or Cu-Kα (λ = 1.54180) radiation. The structures were solved by direct methods and refined against all unique F^2 values using programs from the SHELX suit.[122] Refinement of CCDC-953398 ([{Mg(OPiv)$_2$}$_5${Mg(OH)$_2$}(MgO)·4THF]), 953399 ([{Mg$_6$(OPiv)$_{12}$}(MgO$_2$)]·C$_7$H$_8$), 953400 ((TMEDA)ZnMe(*p*-C$_6$H$_4$)Cl) and 953401 ([(THF)$_2$Li$_2$(μ-Cl)$_2$(μ-OPiv)$_2$Zn] (**24c**)) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of [{Mg$_6$(OPiv)$_{12}$}(MgO$_2$)]·C$_7$H$_8$:

MgBu$_2$ (4 mL of a 1 M solution in heptane, 4 mmol) was added to a solution cooled at -30°C of pivalic acid (0.817 g, 8 mmol) in THF (10 mL) and the resulting yellow pale solution was stirred at room temperature for 1 h. The solvent was then removed in vacuo and toluene (10 mL) was added affording a suspension. Gentle heating gave a clear solution which was left to slow cooling, resulted in the formation of colourless crystals (0.23 g, yield 32% based on MgBu$_2$).

^{1}H-NMR (400 MHz, THF-d$_8$): δ / ppm = 7.20 – 7.08 (m, 5H, C$_6$*H*$_5$, Toluene), 2.30 (s, 3H, *Me*, Toluene), 1.14 (s, 36H, C*Me*$_3$,.Pivalate), 1.13 (s, 18H, C*Me*$_3$,.Pivalate), 1.11(s, 54H, C*Me*$_3$,.Pivalate).

^{13}C-NMR (100 MHz, THF-d$_8$): δ / ppm = 193.3, 187.8, 186.9 (O$_2$*C*CMe$_3$, Pivalate), 138.6, 129.7, 128.9, 126.0 (*C*$_6$H$_4$, Toluene), 40.0 (O$_2$C*C*Me$_3$, Pivalate), 28.5, 28.4, 28.1 (O$_2$CC*Me*$_3$, Pivalate), 21.5 (*Me*, Toluene)

6.2. Reaction of Zn(OPiv)$_2$·nLiCl (n=1, 2) with p-tolylMgX

To a solution of Zn(Opiv)$_2$·nLiCl (2 mmol) in 10 mL of THF was added Me(*p*-C$_6$H$_4$)MgCl offering a colourless solution. After stirring the mixture at 25°C for one hour, determination of the contents for the mixture by NMR spectroscopy was carried out.

[122] G. M. Sheldrick, *Acta Crystallogr.* A64, **2008**, 112

Table 13: NMR data in THF-d_8 at 25°C

	^{1}H/δppm	^{13}C/ δ ppm
Me(*p*-C_6H_4)MgCl·LiCl	7.46 (d, *J* = 7.4 Hz, 2H, Me(*p*-C_6H_4)), 6.68 (d, *J* = 7.4 Hz, 2H, Me(*p*-C_6H_4)) 2.06 (s, 3H, *Me*(*p*-C_6H_4))	165.1, 140.1, 130.8, 125.5 Me(*p*-C_6H_4), 20.6 *Me*(*p*-C_6H_4)
Me(*p*-C_6H_4)ZnCl·LiCl	7.37 (d, *J* = 7.4 Hz, 2H, Me(*p*-C_6H_4)), 6.82 (d, *J* = 7.4 Hz, 2H, Me(*p*-C_6H_4)) 2.14 (s, 3H, *Me*(*p*-C_6H_4))	153.0, 139.3, 134.0, 127.5 Me(*p*-C_6H_4), 21.6 *Me*(*p*-C_6H_4)
Me(*p*-C_6H_4)MgCl + $Zn(OPiv)_2$·LiCl	7.39 (d, *J* = 7.6 Hz, 2H, Me(*p*-C_6H_4)), 6.81 (d, *J* = 7.6 Hz, 2H Me(*p*-C_6H_4)) 2.14 (s, 3 H, *Me*(*p*-C_6H_4)), 1.08 (s, 18 H, CO_2CCH_3)	187.5 (CO_2CCH_3), 153.7, 139.4, 133.8, 127.4 Me(*p*-C_6H_4), 39.7 (CO_2CCH_3), 28.4 (CO_2CCH_3), 21.6 *Me*(*p*-C_6H_4)
Me(*p*-C_6H_4)MgCl + $Zn(OPiv)_2$·2LiCl	7.57 (d, *J* = 7.6 Hz, 2H, Me(*p*-C_6H_4)), 6.81 (d, *J* = 7.6 Hz, 2H, Me(*p*-C_6H_4)) 2.15 (s, 3H, *Me*(*p*-C_6H_4)), 1.06 (s, 18H, CO_2CCH_3)	Not detected (CO_2CCH_3), 156.8, 140.1, 133.5, 127.2 Me(*p*-C_6H_4), 39.9 (CO_2CCH_3), 28.4 (CO_2CCH_3), 21.6 *Me*(*p*-C_6H_4)

6.3. Preparation of the *p*-tolylZnX reagents 76a-d

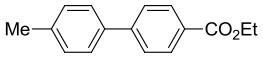
Me(*p*-C_6H_4)MgCl·LiCl (**75**) and Me(*p*-C_6H_4)Li (**77**) were prepared according to literature procedures.[123] The reagents Me(*p*-C_6H_4)ZnX **76a-d** were generated by adding 1.1 equivalents of $ZnCl_2$ (as 1 M solution in THF) and $Zn(OPiv)_2$ (as a neat solid), respectively, to solutions of Me(*p*-C_6H_4)MgCl·LiCl (**75**) and Me(*p*-C_6H_4)Li (**77**) in THF at room temperature. These mixtures were stirred for further 15 min at this temperature until a clear solution formed. The concentration of the active zinc species was determined by titration against a stoichiometric amount of iodine (100 mg) in THF (2 mL). To get comparable reactivities all zinc reagents were then diluted to a concentration of ca. 0.35 mol/L.

6.4. Reaction conditions for the Negishi cross-coupling

When the reactions were performed under argon the reaction flasks were flame dried in vacuum prior to use, while the reactions in air were carried out in non-dried glassware. The EtOAc used in the cross-coupling reactions was purchased from Fluka in analytical grade (99.9%) and was stored in air and used without further drying.

[123] a) M. P. R. Spee, J. Boersma, M. D. Meijer, M. Q. Slagt, G. van Koten, J. W. Geus, *J. Org. Chem.* **2001**, *66*, 1647; b) A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem., Int. Ed.* **2011**, 50, 3303.

Cross-coupling with ethyl 4-iodobenzoate (78)

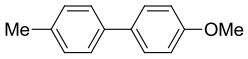


To a solution of Me(*p*-C_6H_4)ZnX (2.86 mL, 1 mmol, 0.35 M in THF) 17.3 mg $Pd(dba)_2$ (0.03 mmol), 14.0 mg P(o-furyl)$_3$ (0.06 mmol) and 221 mg ethyl 4-iodobenzoate (0.8 mmol) were added subsequently ad 25 °C. The reaction was stirred for 30 min at this temperature and then quenched with a sat. aqueous NH_4Cl solution (10 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 20:1) afforded the product **79** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.17 – 7.34 (m, 4H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.28 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).

The analytical data were in accordance with the literature data.[124]

Cross-coupling with 4-bromoanisole (81) in THF

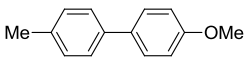


To a solution of Me(*p*-C_6H_4)ZnX (2.86 mL, 1 mmol, 0.35 M in THF) 6.74 mg $Pd(OAc)_2$ (0.03 mmol), 23.6 mg DavePhos (0.06 mmol) and 150 mg 4-bromoanisole (0.8 mmol) were added subsequently ad 25 °C. The reaction was stirred for 1.5 h at 50 °C and then quenched with a sat. aqueous NH_4Cl solution (10 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 100:1) afforded the product **81** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 – 7.58 (m, 4H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.40 (s, 3H).

The analytical data were in accordance with the literature data.[124]

Cross-coupling with 4-bromoanisole (81) in EtOAc



The corresponding solutions of Me(*p*-C_6H_4)ZnX (2.86 mL, 1 mmol, 0.35 M in THF) were dried in high vacuum (<0.1 mbar) to give the THF-free zinc reagents **76a** and **76c** as yellowish slurry and the reagents **76b** and **76d** as off white solids. The reagents were then dissolved in EtOAc (2.5 mL) and 6.74 mg

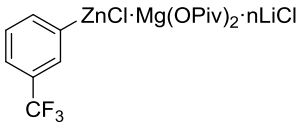
[124] N. Liu, L. Wang, Z.-X. Wang, *Chem. Commun.* **2011**, 47, 1598.

$Pd(OAc)_2$ (0.03 mmol), 23.6 mg DavePhos (0.06 mmol) and 150 mg 4-bromoanisole (0.8 mmol) were added subsequently ad 25 °C. The reaction was stirred for 1.5 h at 50 °C and then quenched with a sat. aqueous NH_4Cl solution (10 mL) followed by extraction with diethyl ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash chromatography (silica gel, *iso*-hexane / Et_2O = 100:1) afforded the product **81** as a white solid.

6.5. Synthesis and Stability Studies of (3-(trifluoromethyl)-phenyl)ZnCl·Mg(OPiv)$_2$·nLiCl (n=0, 1, 2)

The stability studies of the reagents **83a** and **83b** were carried out as described in C5.1. The determination of the active zinc reagent was determined by titration against iodine.[67,68]

Synthesis of (3-(trifluoromethyl)phenyl)ZnCl·Mg(OPiv)$_2$·nLiCl (n=0, 1, 2):

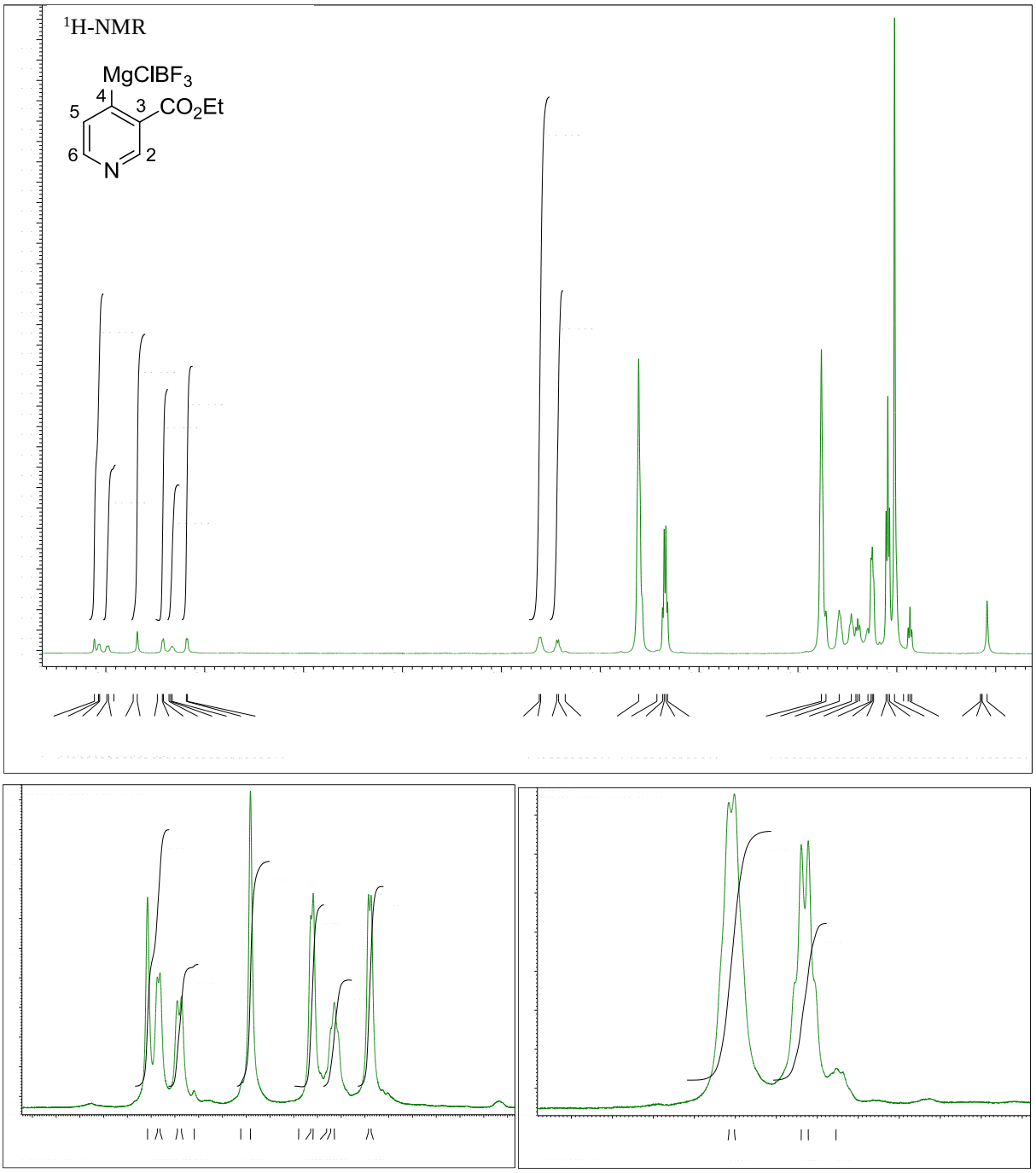


To a suspension of anhydrous LiCl (0, 2.4, 4.8 mmol) in THF (4 mL) was added $Zn(OPiv)_2$ (**24b**, 642 mg, 2.4 mmol) at room temperature. The mixture was stirred at this temperature for 30 min before 1-bromo-3-(trifluoromethyl)benzene (**84**, 450 mg, 2.0 mmol) and Mg turnings (122 mg, 5.0 mmol) were added subsequently. After stirring the reaction mixture for 2 h at 25 °C the THF was removed *in vacuo* to give the reagents (3-(trifluoromethyl)phenyl)ZnCl·Mg(OPiv)$_2$·2LiCl (**83a**, 1.49 g) and (3-(trifluoromethyl)phenyl)ZnCl·Mg(OPiv)$_2$·LiCl (**83b**, 1.50 g) as white solids. The content of active zinc species was determined by titration of the reagents with a stock solution of iodine (0.25 M in THF). A concentration of 1.13 mmol/g was obtained for **83a** which corresponds to a yield of 84%. For **83b** a concentration of 1.19 mmol/g was obtained which corresponds to a yield of 89%. The LiCl-free reagent **83c** did not furnish a homogeneous solid, but a sticky and inhomogeneous slurry and was therefore not titrated.

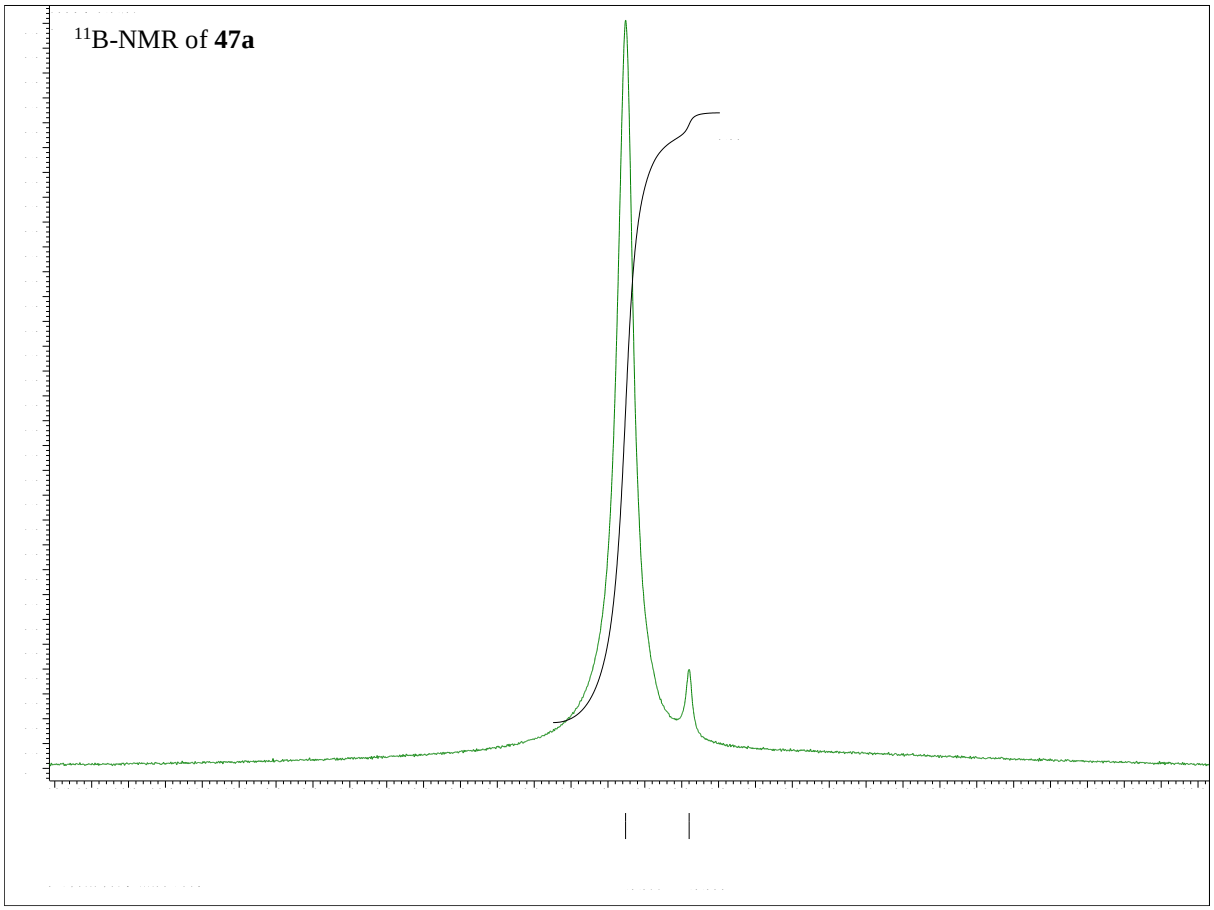
D. APPENDIX

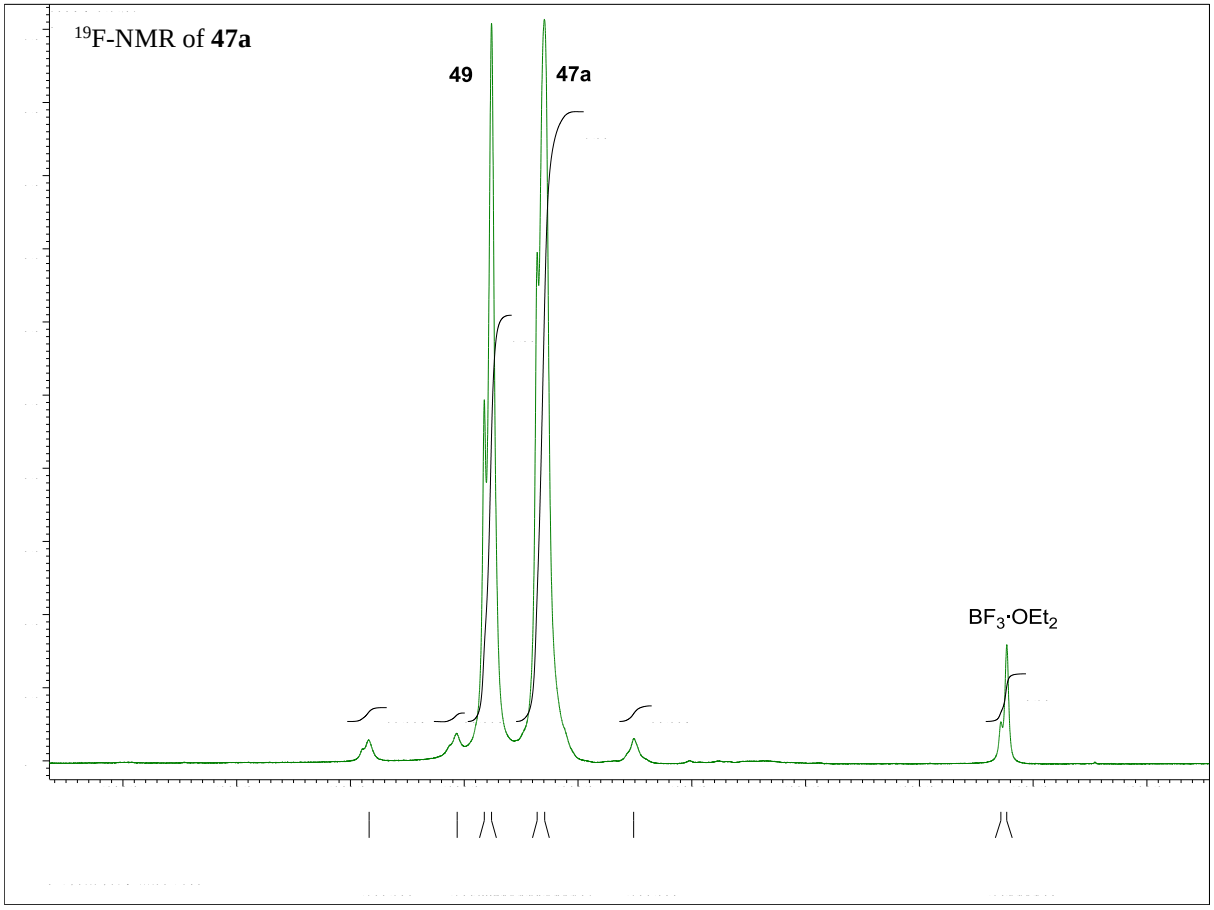
1. NMR-Spectra BF_3 Complexes and Metalated Intermediates

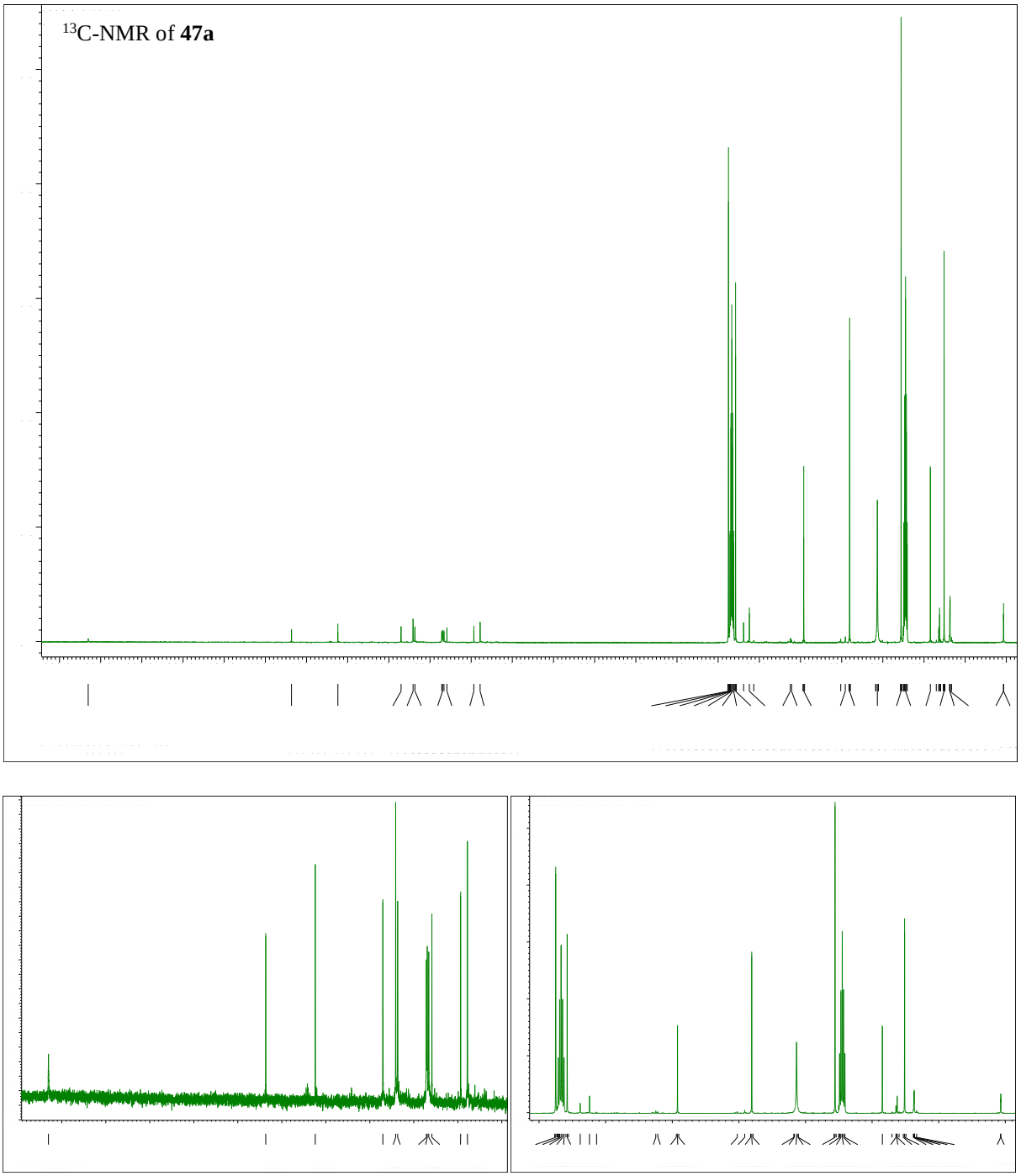
1.1. Metalated intermediate 47a



^{1}H-NMR expansions of intermediate **47a** of the aromatic region (left) and the CH_2 signal region (right).

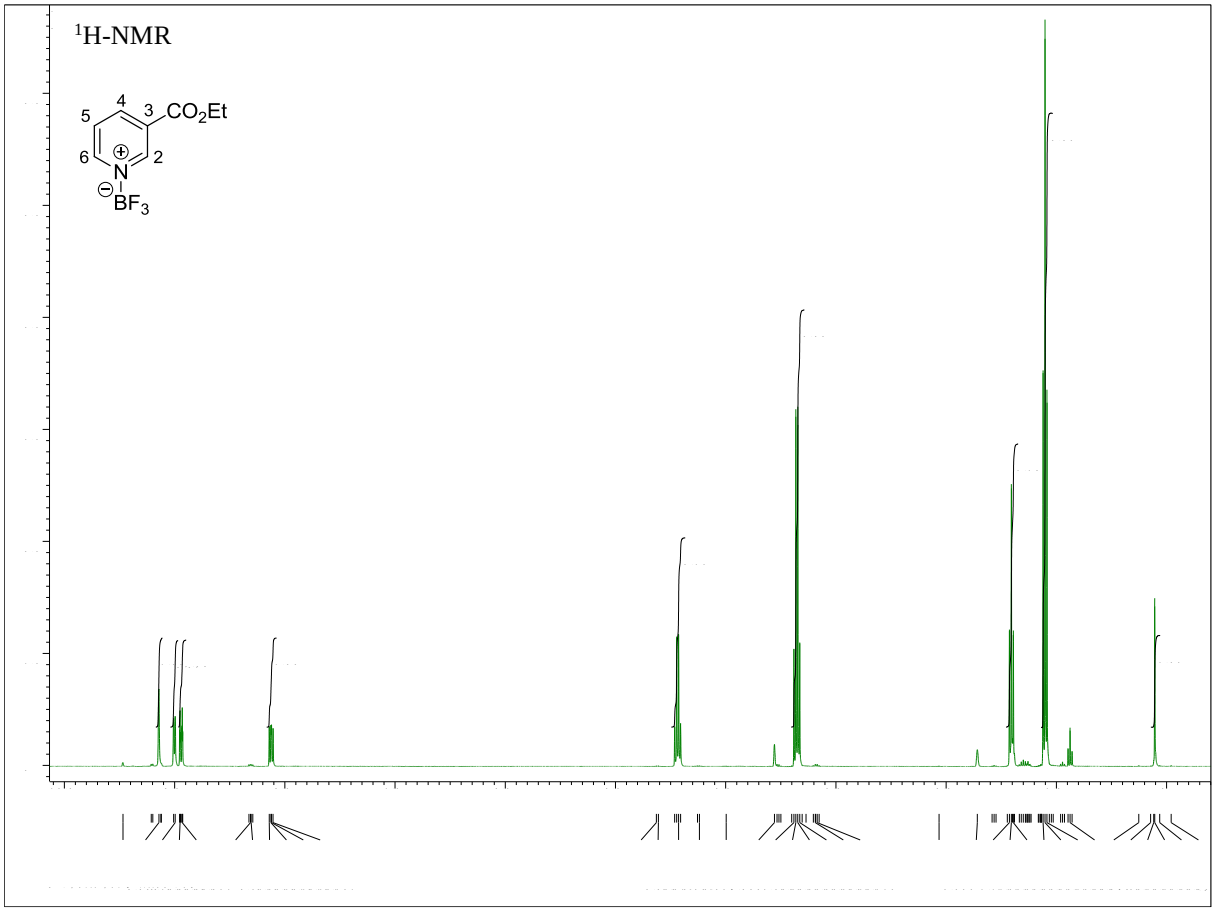

^{11}B-NMR of **47a**

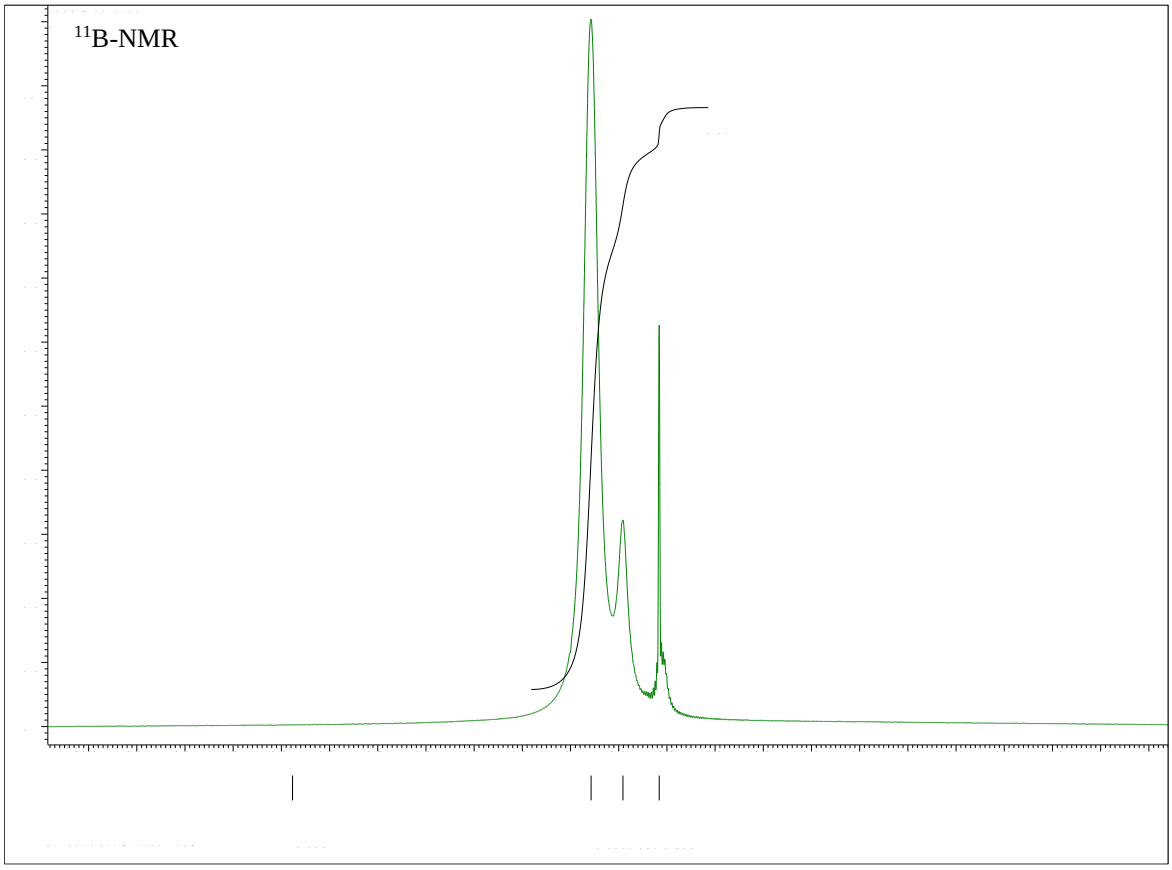

^{19}F-NMR of **47a**
49
47a
$BF_3{\cdot}OEt_2$

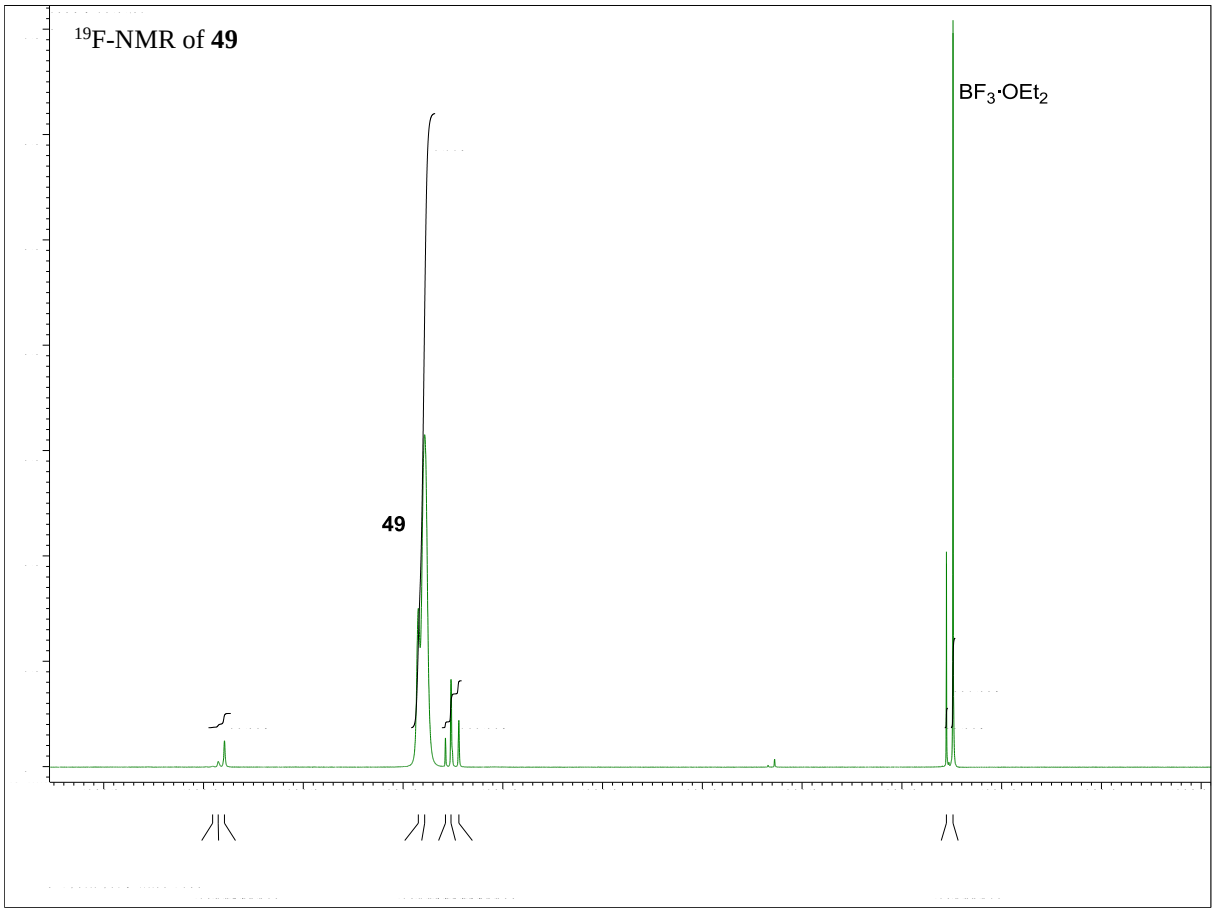


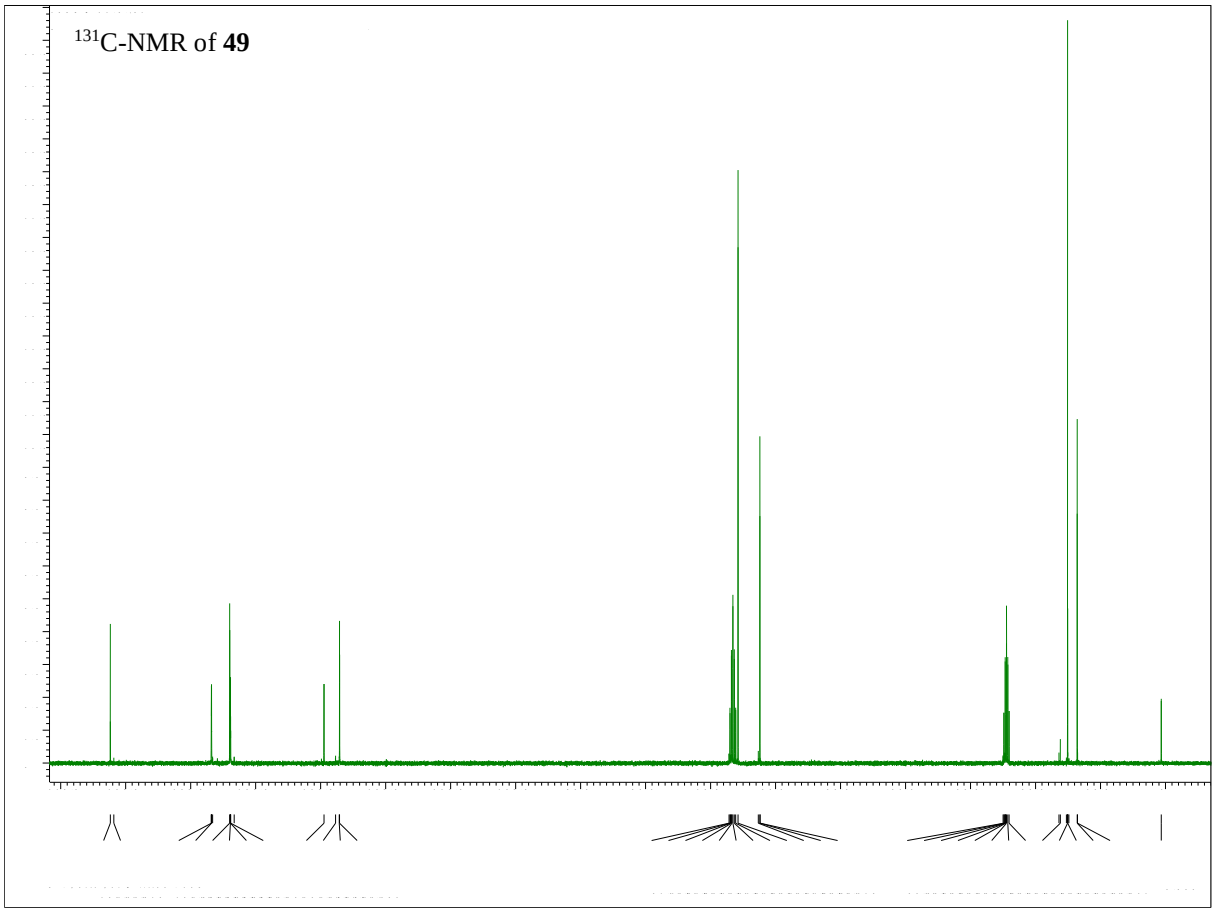
^{13}C-NMR expansions of the intermediate **47a** of the aromatic region (120-230 ppm, left) and the alliphatic region (0-70 ppm) right).

1.2. (3-(ethoxycarbonyl)pyridin-1-ium-1-yl)trifluoroborate (49)

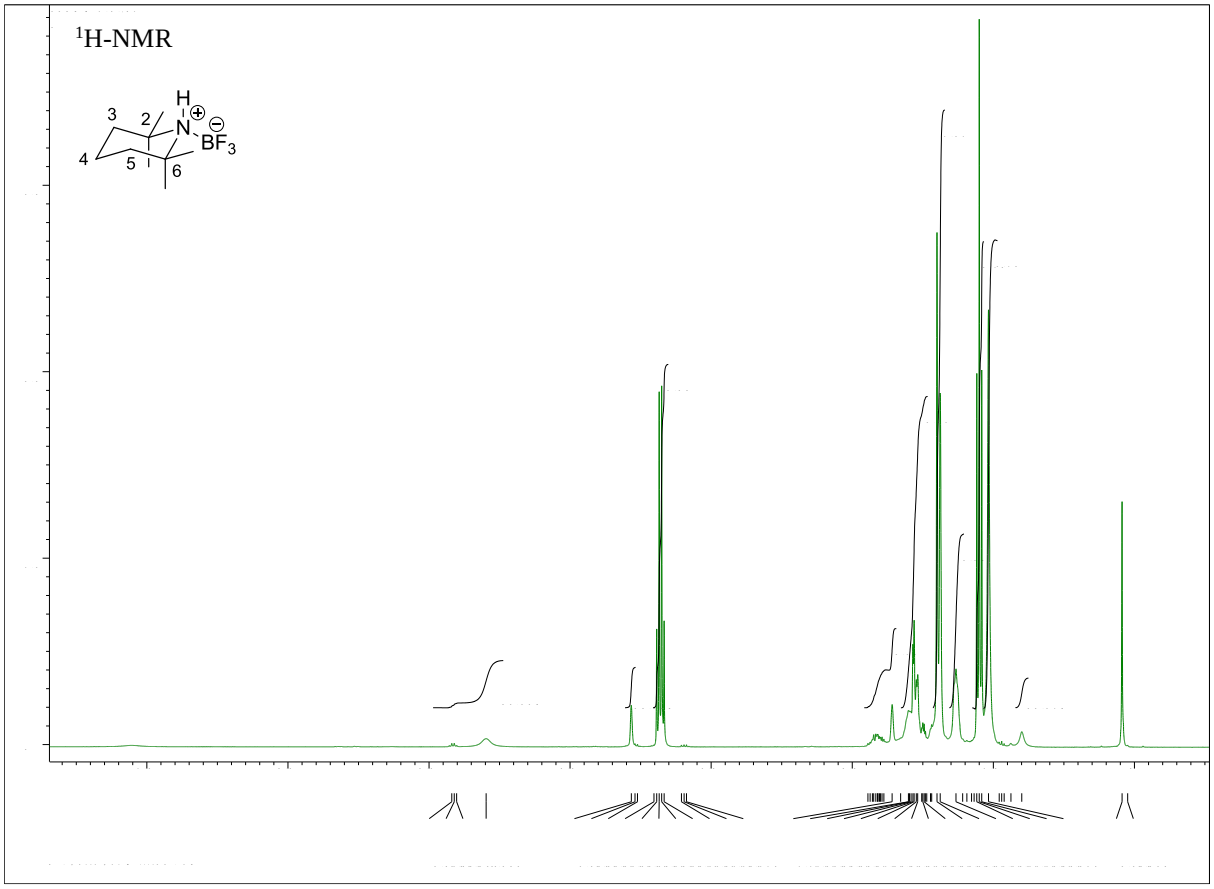


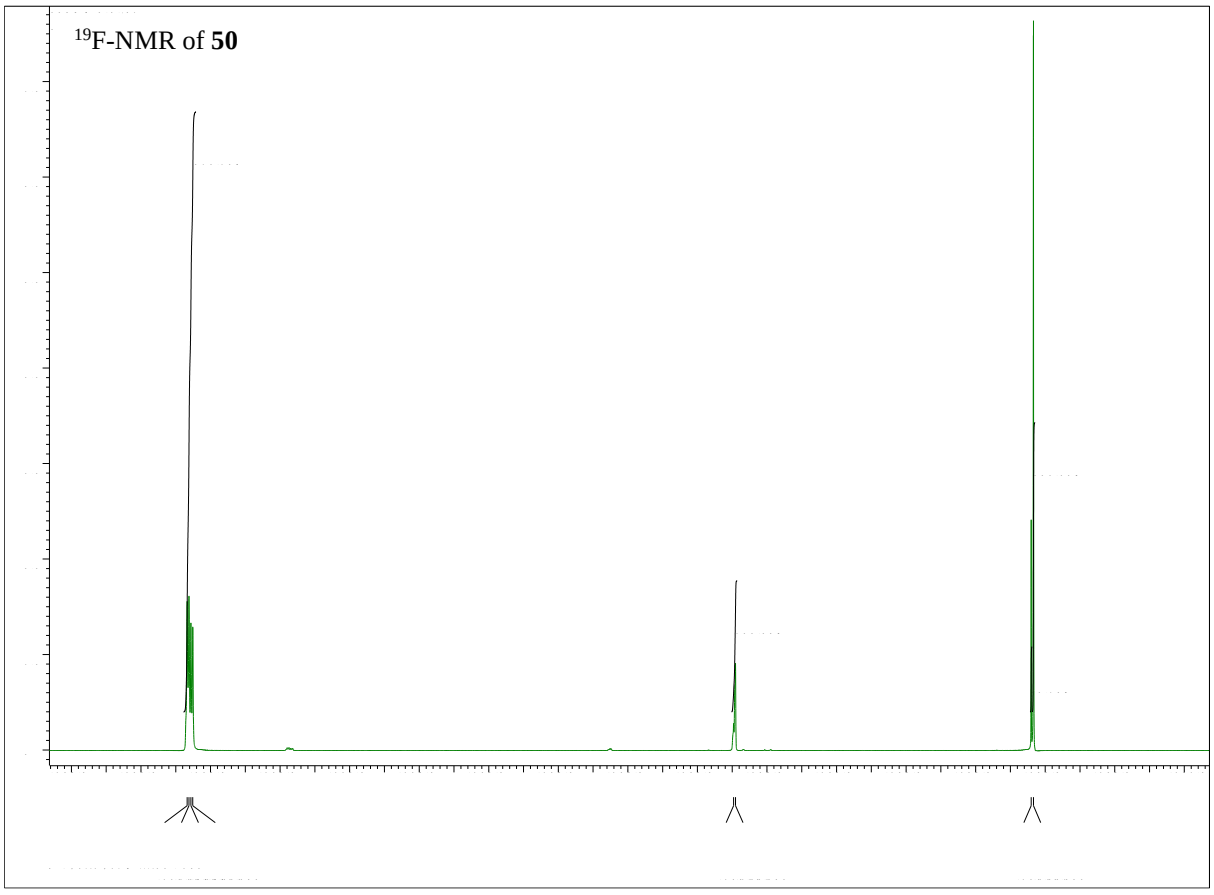


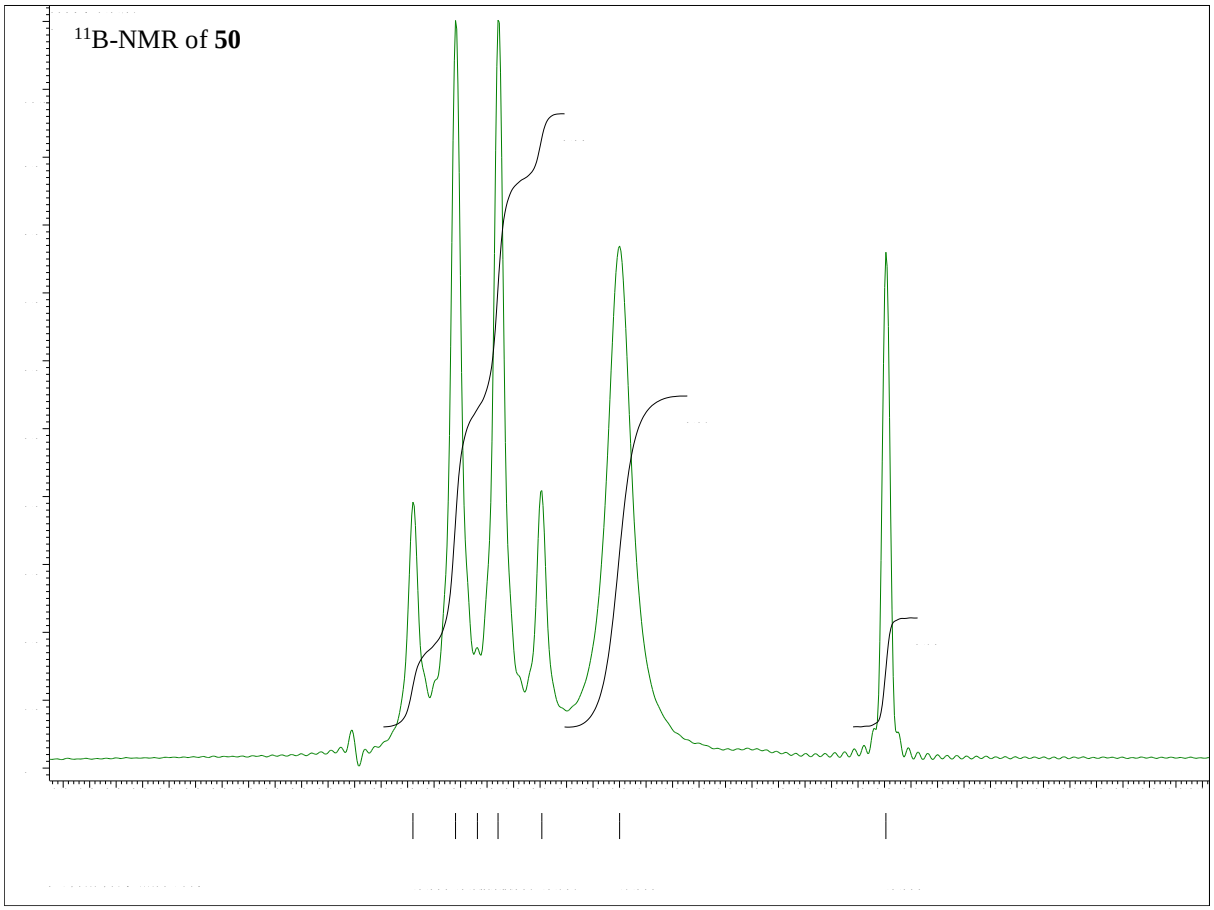

^{19}F-NMR of **49**
$BF_3{\cdot}OEt_2$
49

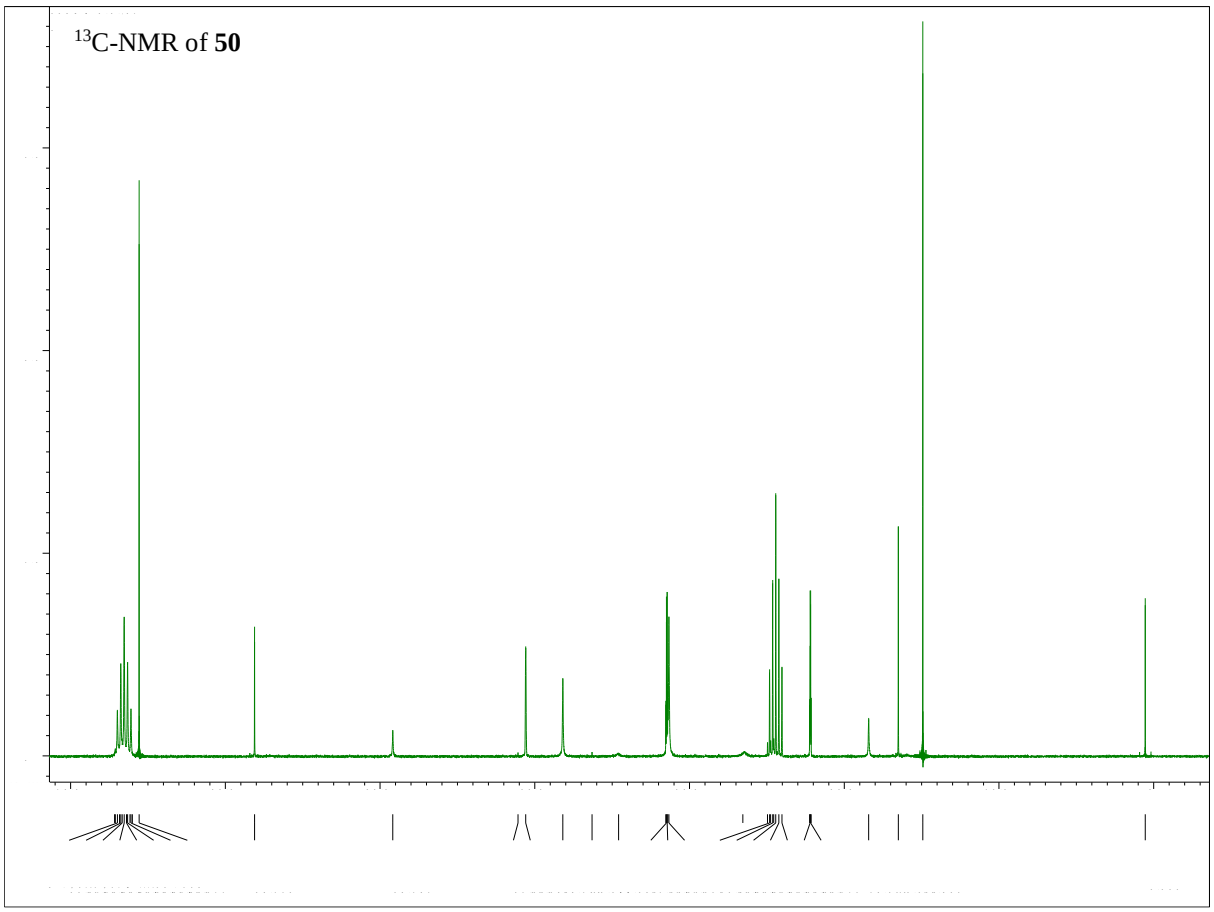

^{131}C-NMR of **49**

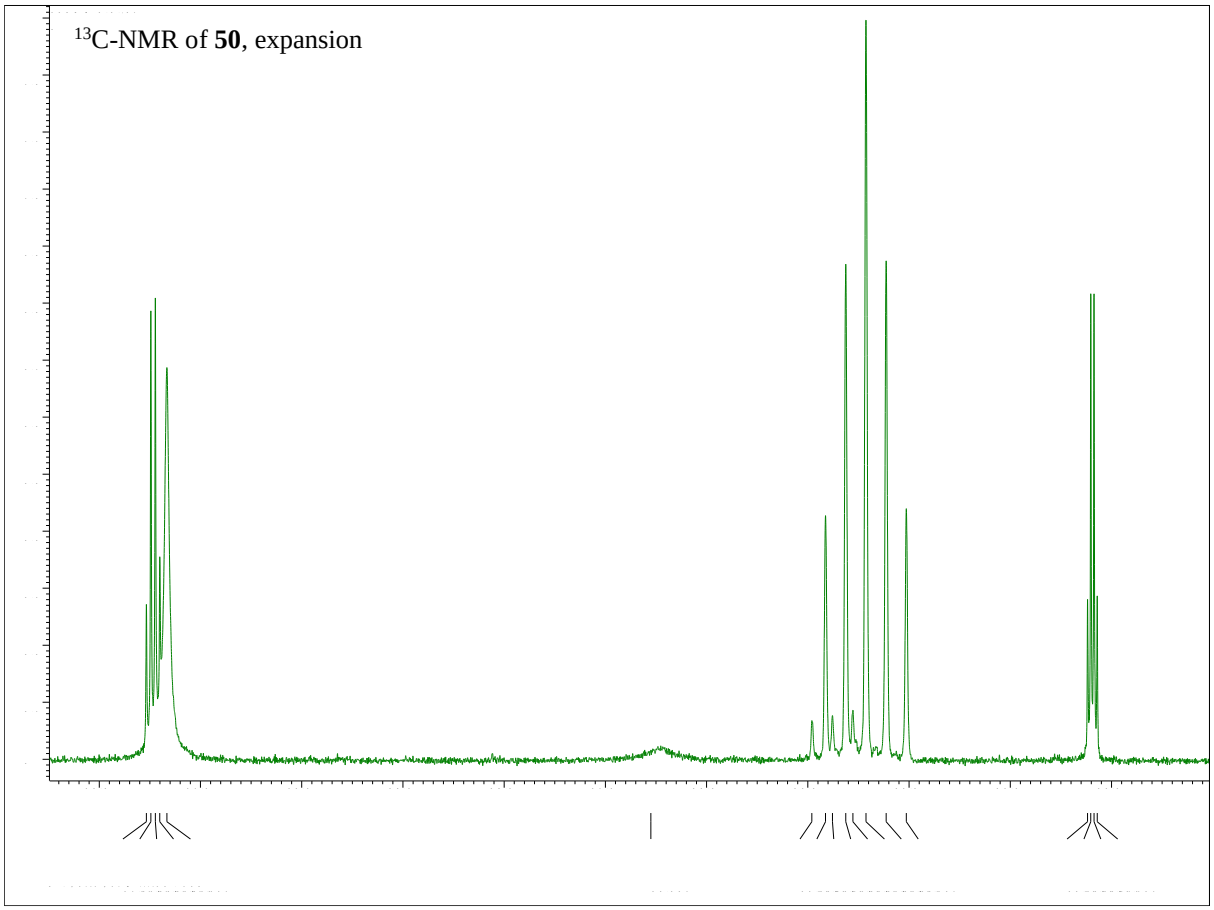
1.3. Trifluoro(2,2,6,6-tetramethylpiperidin-1-ium-1-yl)borate (50)





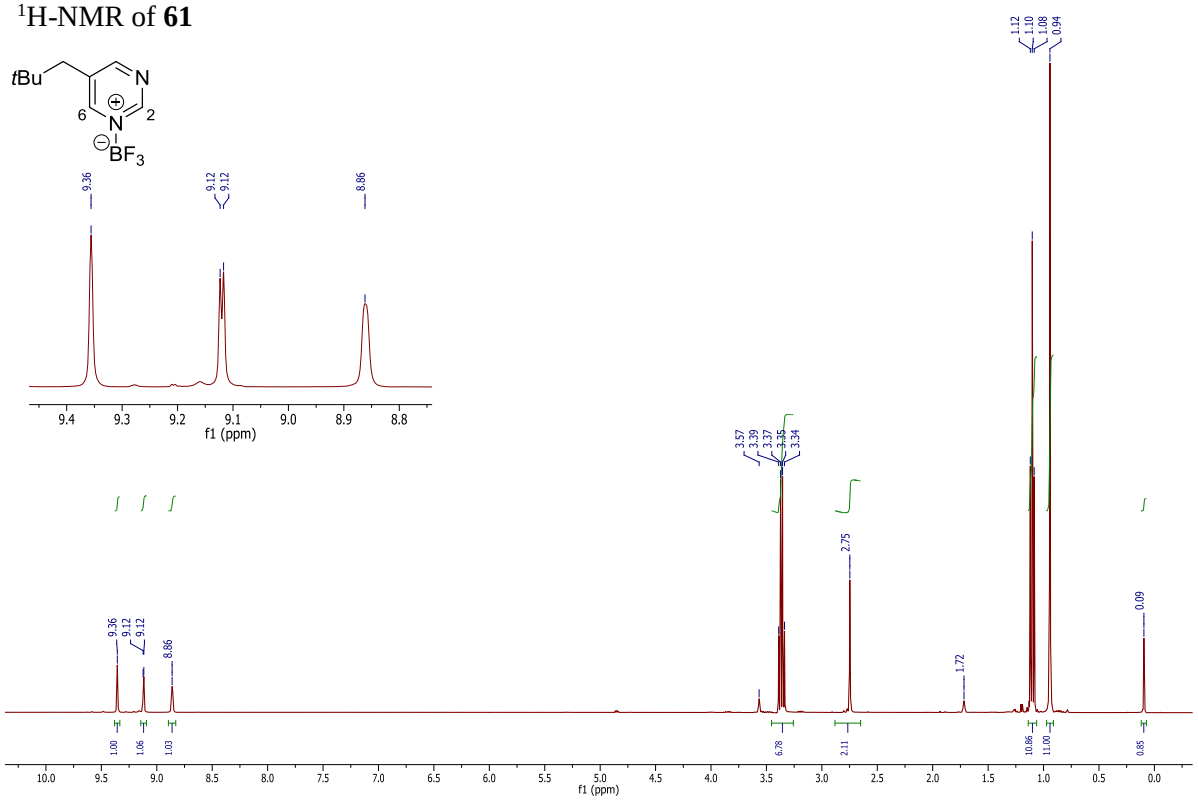

^{11}B-NMR of **50**


^{13}C-NMR of **50**

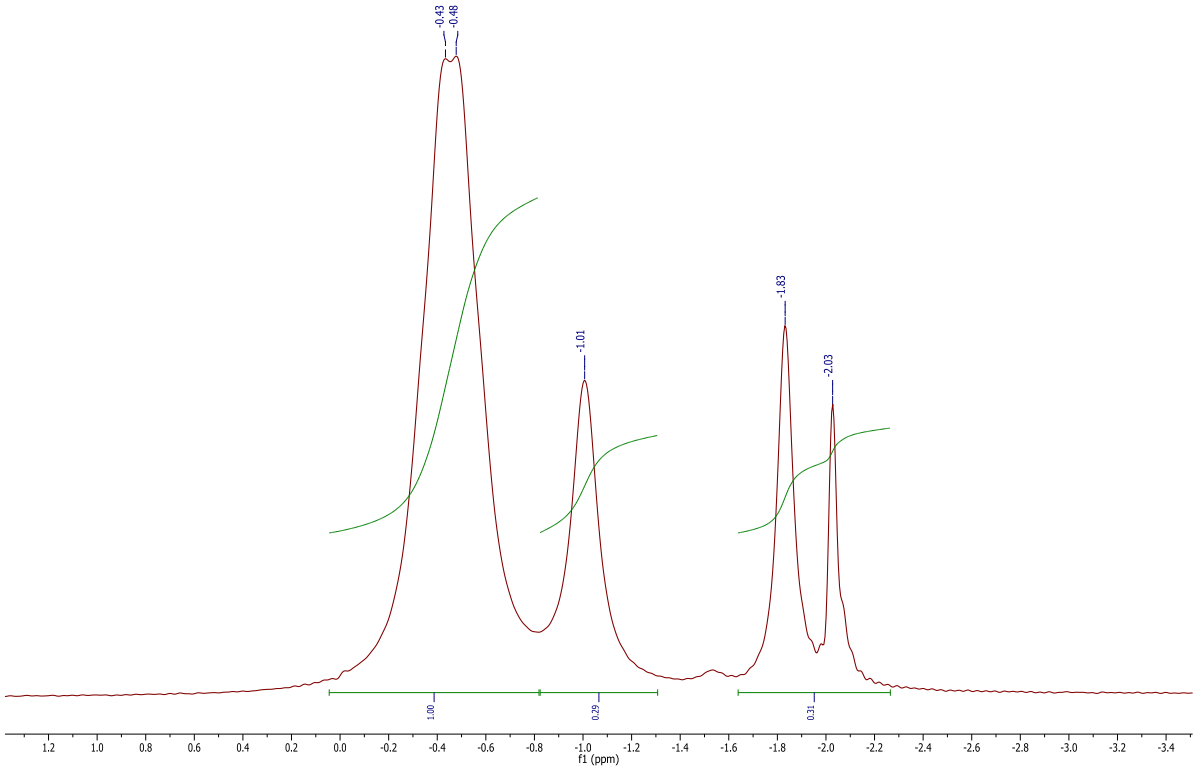

^{13}C-NMR of **50**, expansion

1.4. (5-(neopenthyl)pyrimidin-1-ium-1-yl)trifluoroborate (61)

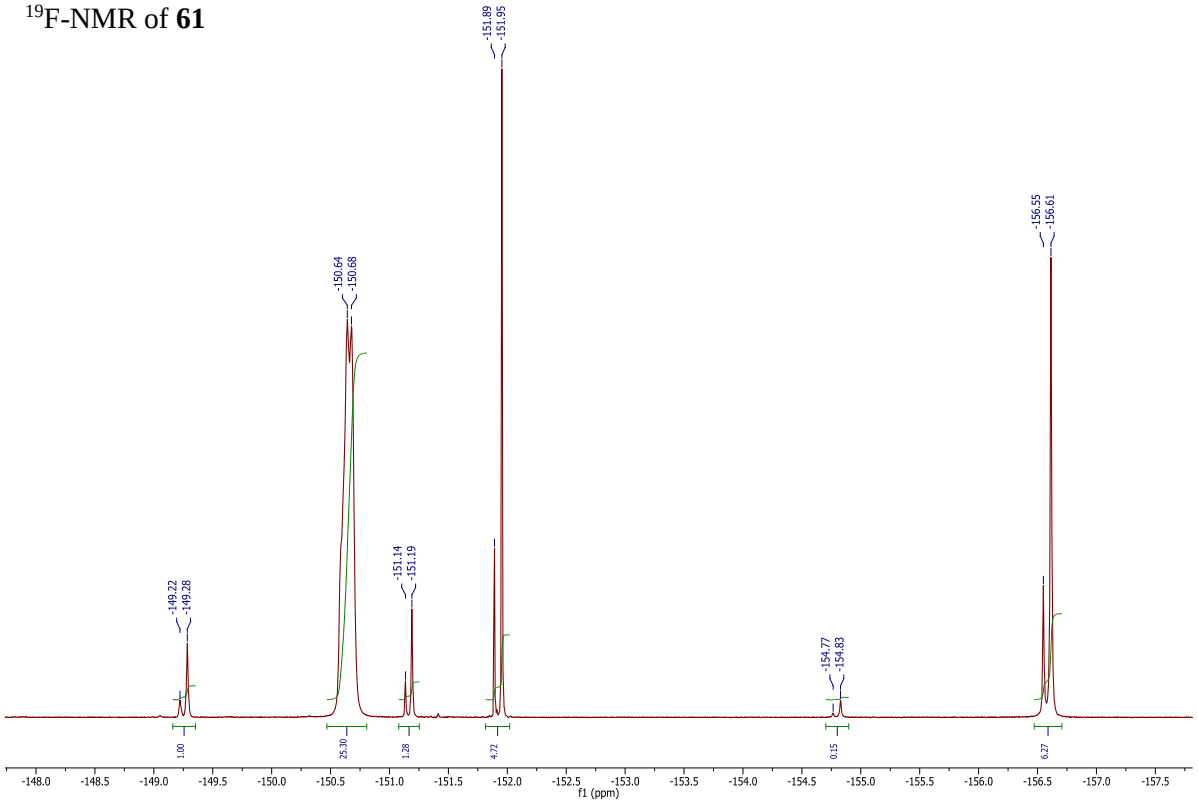
^{1}H-NMR of **61**



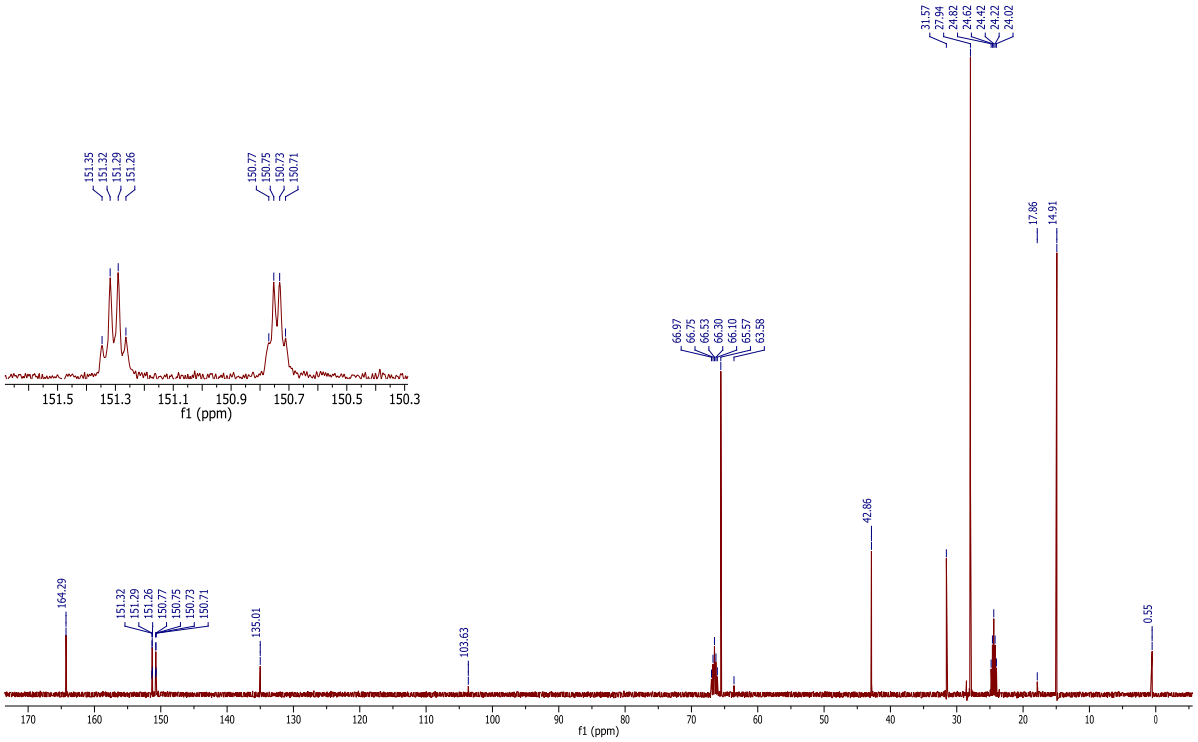
^{11}B-NMR of **61**



^{19}F-NMR of **61**

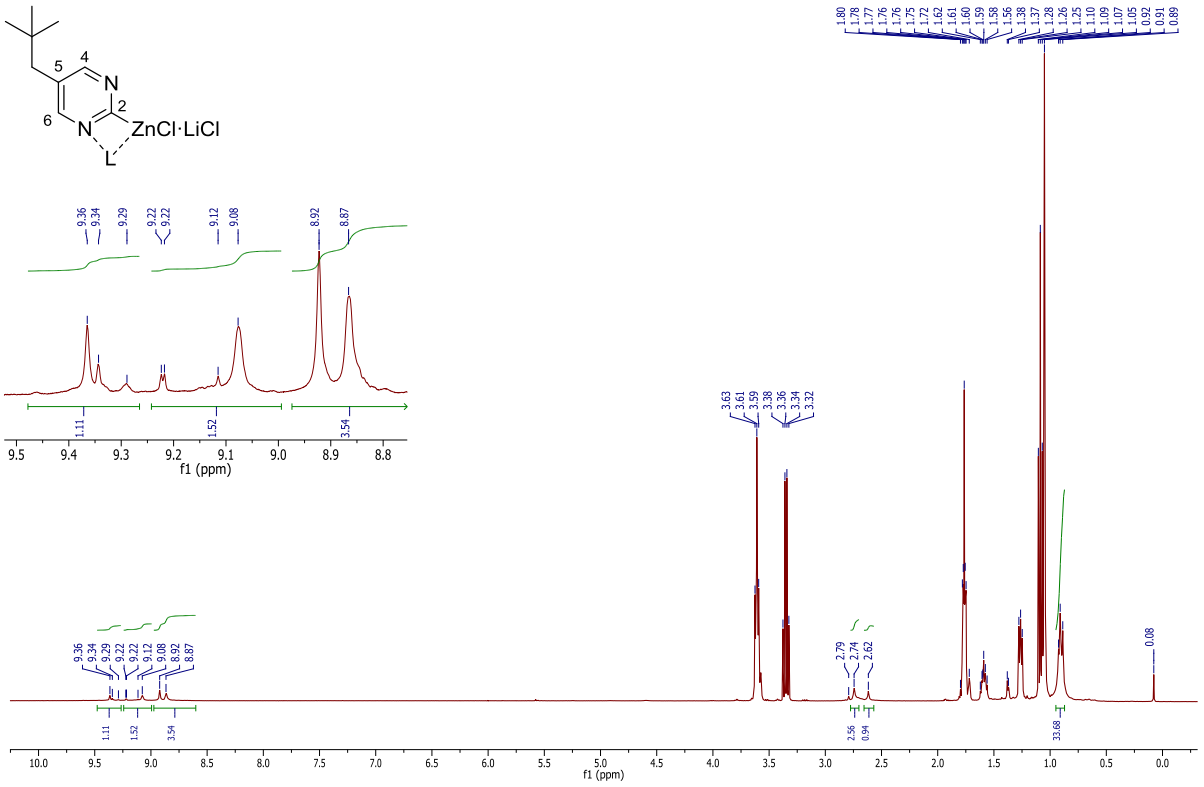


^{13}C-NMR of **61**

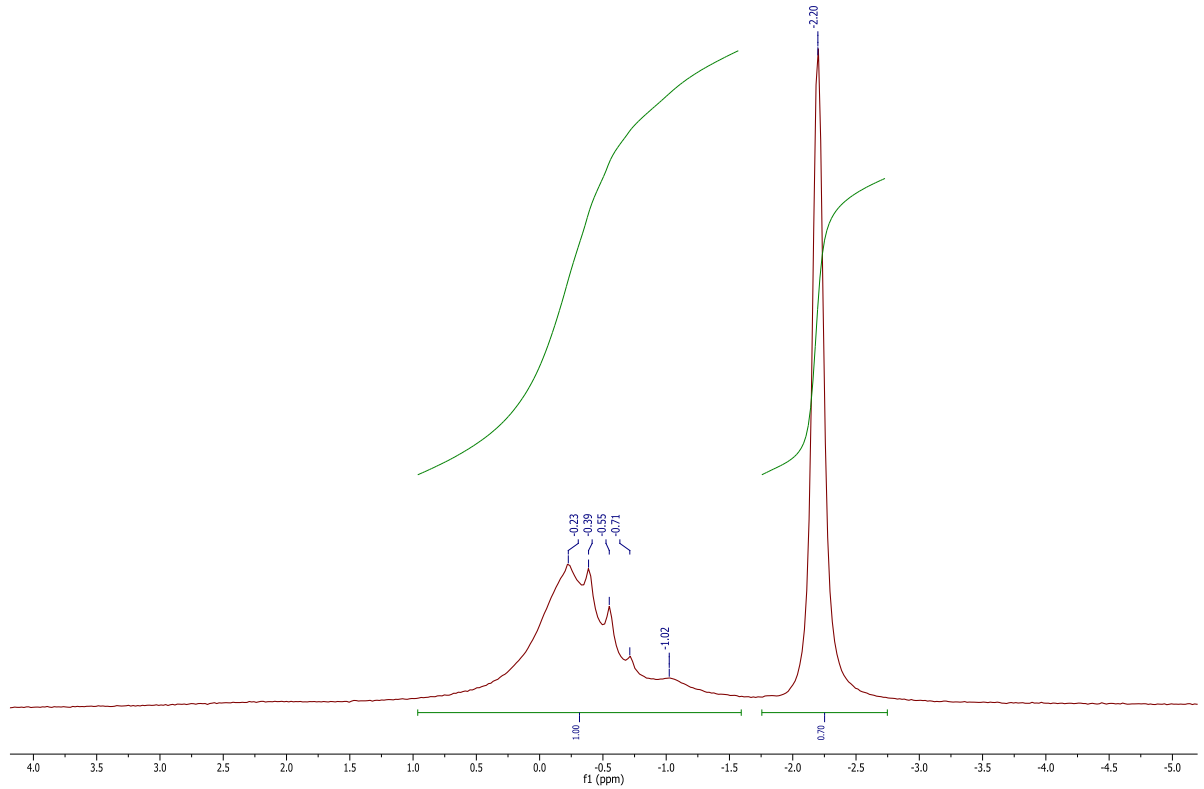


1.5. Zinc Intermediate 62

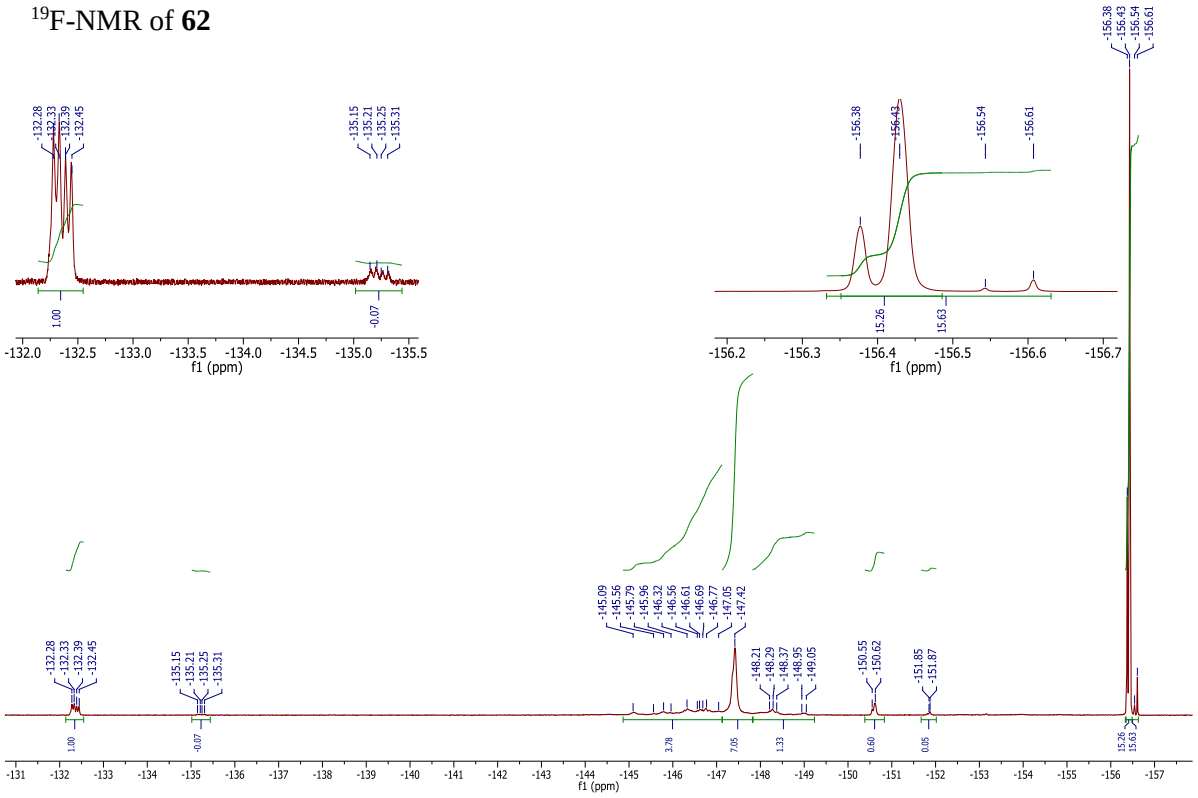
^{1}H-NMR of **62**



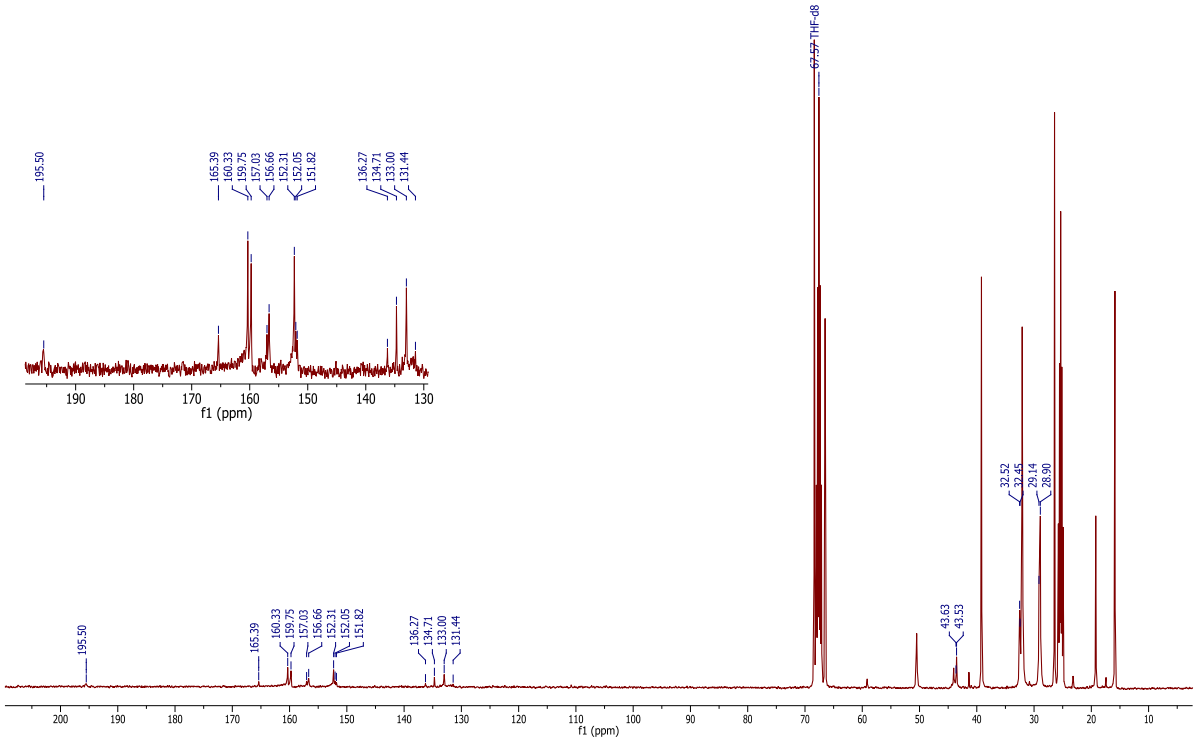
^{11}B-NMR of **61**



^{19}F-NMR of **62**



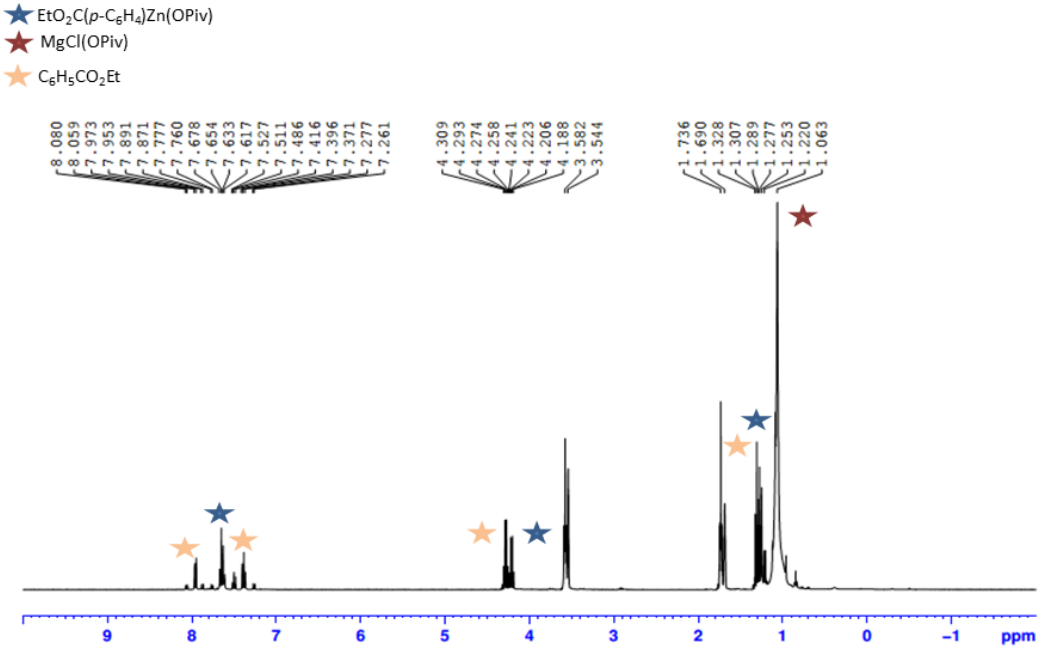
^{13}C-NMR of **62**



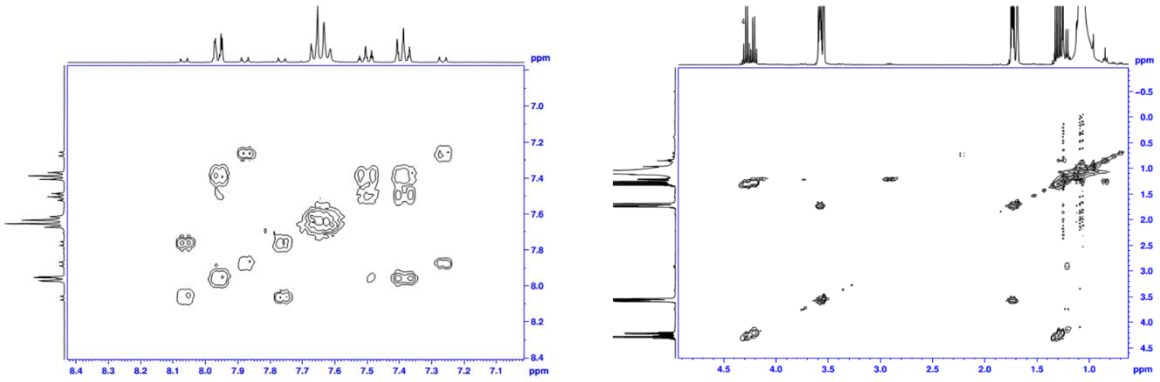
2. Transmetalation Studies of RMgX and Zn(OPiv)$_2$·nLiCl

2.1. Transmetallation study of the mixture of the arylester reagent EtO$_2$C(*p*-C$_6$H$_4$)MgCl·LiCl and Zn(OPiv)$_2$

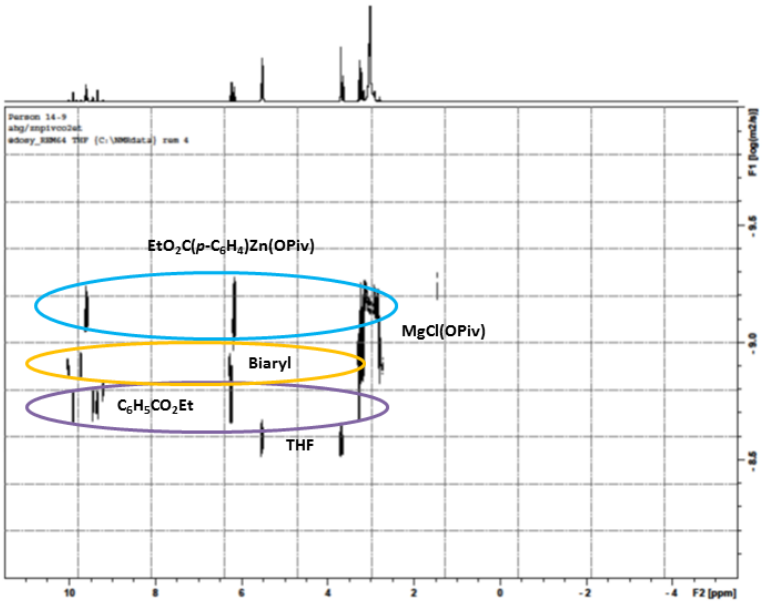
^{1}H NMR in THF-d$_8$ at 25°C:



COSY NMR in THF-d$_8$ at 25°C:



^{1}H DOSY NMR in THF-d_8 at 25°C



2.2. Transmetallation study of the mixture of the arylester reagent *p*-TolylMgCl·LiCl and $Zn(OPiv)_2$

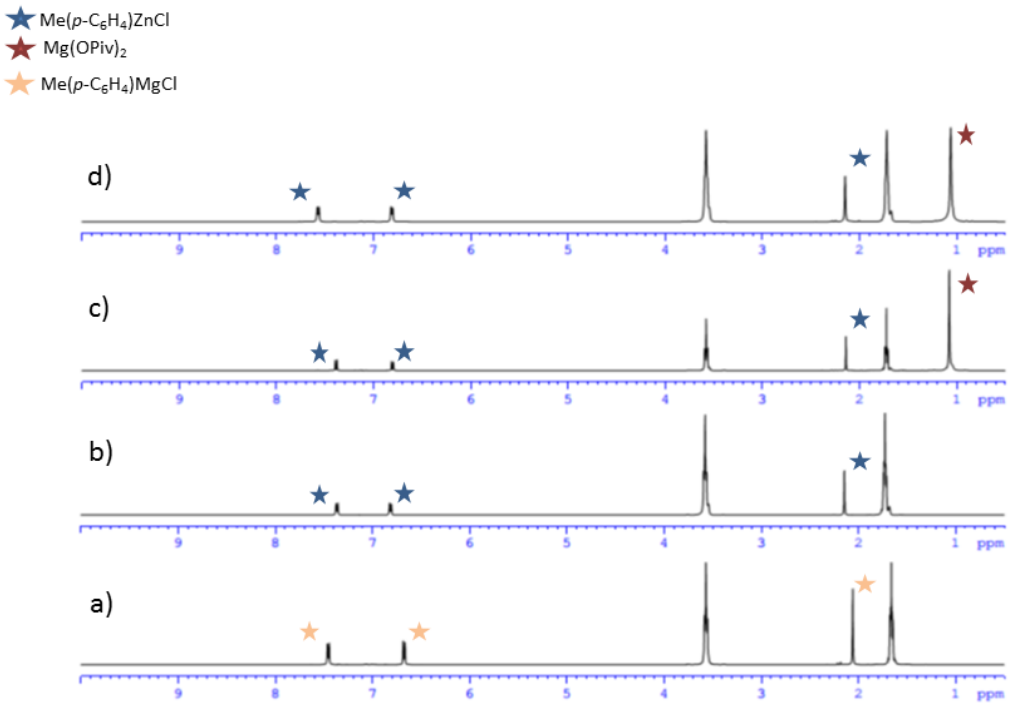


Figure 10: ^{1}H NMR spectrum of a) Me(*p*-C_6H_4)MgCl·LiCl; b) Me(*p*-C_6H_4)ZnCl·LiCl; c) $Zn(OPiv)_2$·LiCl and Me(*p*-C_6H_4)MgCl; d) $Zn(OPiv)_2$·2LiCl and Me(*p*-C_6H_4)MgCl in THF-d_8 at 25°C.

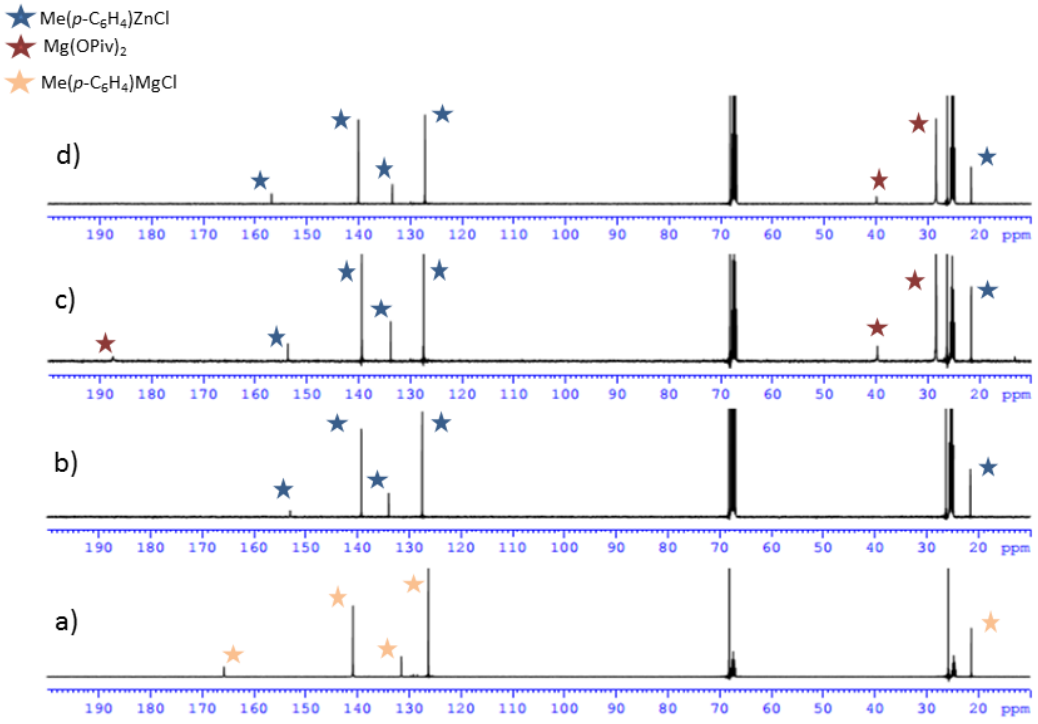


Figure 11: ^{13}C NMR spectrum of a) Me(*p*-C_6H_4)MgCl·LiCl; b) Me(*p*-C_6H_4)ZnCl·LiCl; c) $Zn(OPiv)_2$·LiCl and Me(*p*-C_6H_4)MgCl; d) $Zn(OPiv)_2$·2LiCl and Me(*p*-C_6H_4)MgCl in THF-d_8 at 25°C.

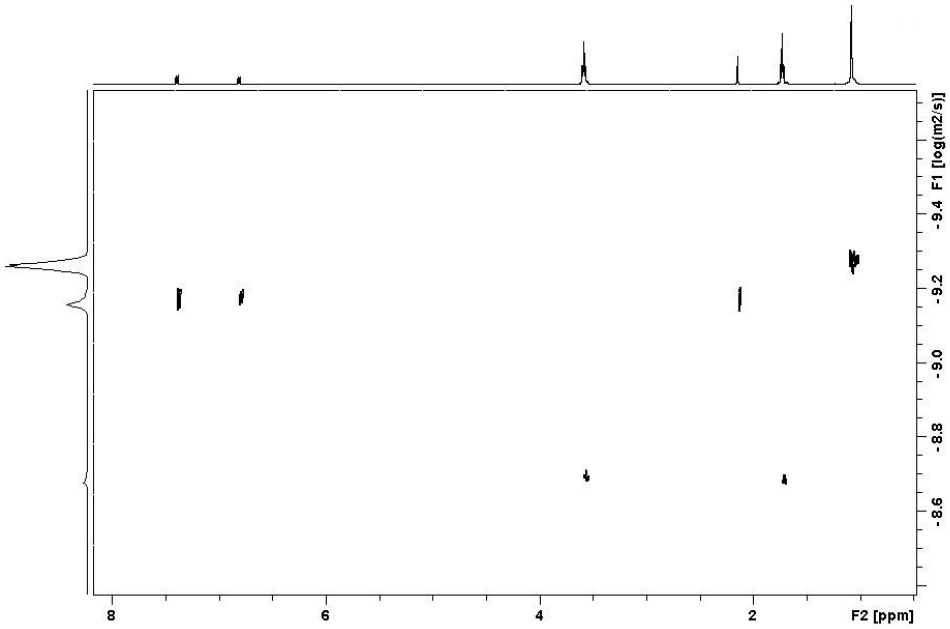


Figure 12: ^{1}H DOSY NMR spectrum of Zn(OPiv)$_2$·LiCl and Me(*p*-C$_6$H$_4$)MgCl in THF-d$_8$ at 25°C

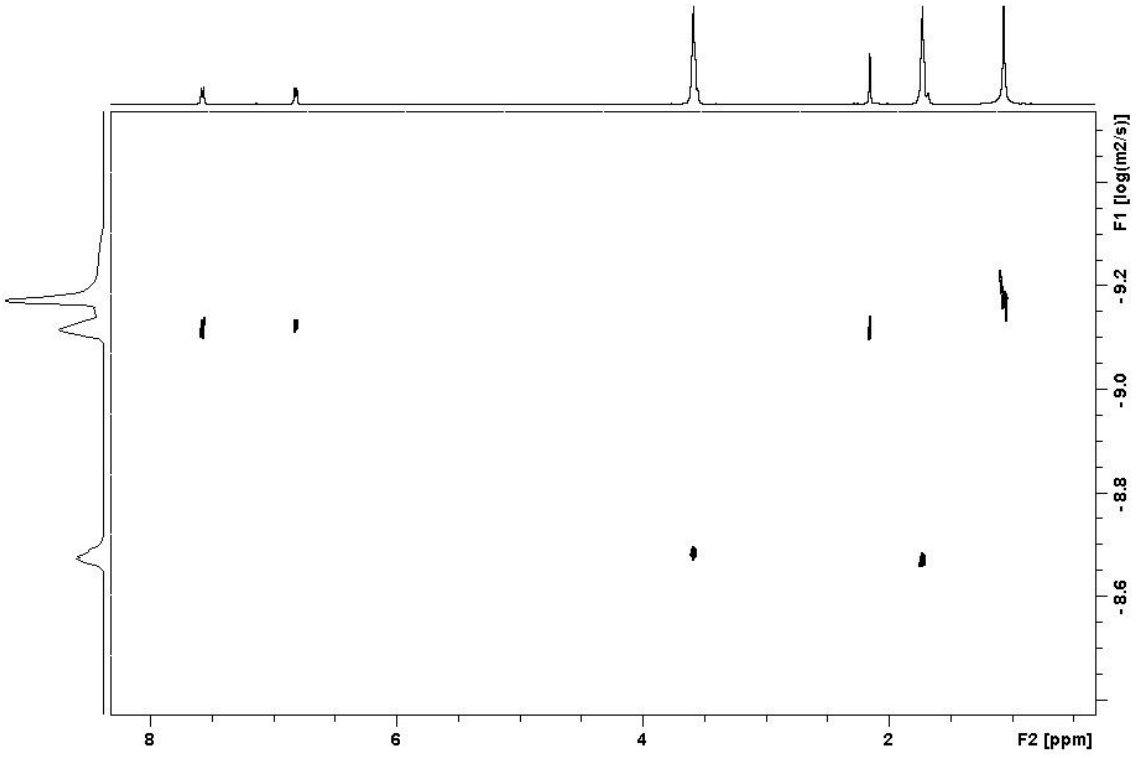
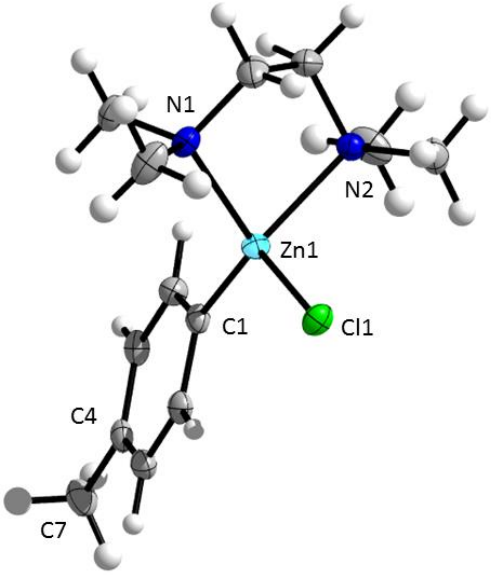


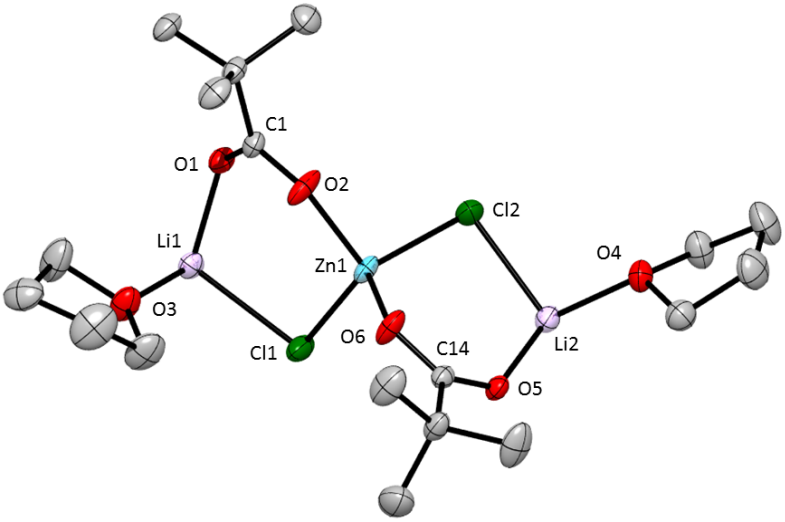
Figure 13: ^{1}H DOSY NMR spectrum of Zn(OPiv)$_2$·2LiCl and Me(*p*-C$_6$H$_4$)MgCl in [D$_8$]THF at 25°C.

2.3. Crystal Structures of the Mg and Zn Pivalate Complexes

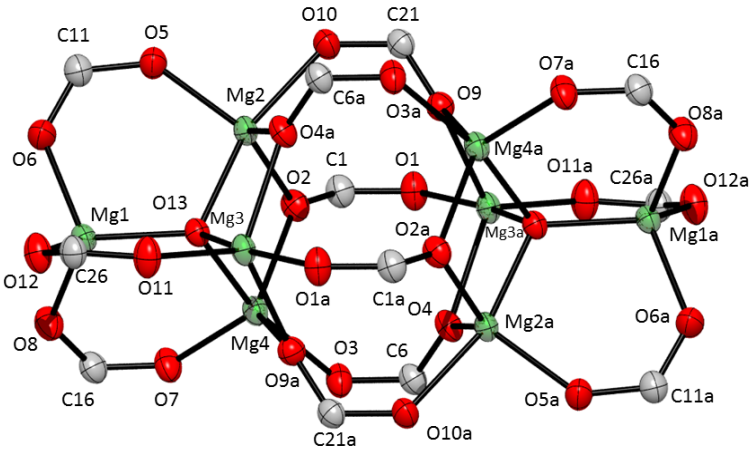
Molecular structure of (TMEDA)ZnMe(*p*-C_6H_4)Cl:



Molecular structure of [$(THF)_2Li_2(\mu\text{-}Cl)_2(\mu\text{-}OPiv)_2Zn$] (24c) with H atoms omitted for clarity:



X-ray crystallographic structure of $[\{Mg_6(OPiv)_{12}\}(MgO)_2]\cdot C_7H_8$ with hydrogen atoms, solvent molecule, *tert*-butyl substituent and disorder omitted for clarity:



Crystallographically derived structure of the $[\{Mg(OPiv)_2\}_5\{Mg(OH)_2\}(MgO)\cdot 4THF]$ core with hydrogen atoms, solvent molecule, *tert*-butyl substituent and disorder omitted for clarity (this Mg_7 species cocrystallizes with the isostructural Mg_6Zn species in a 4:1 ratio):

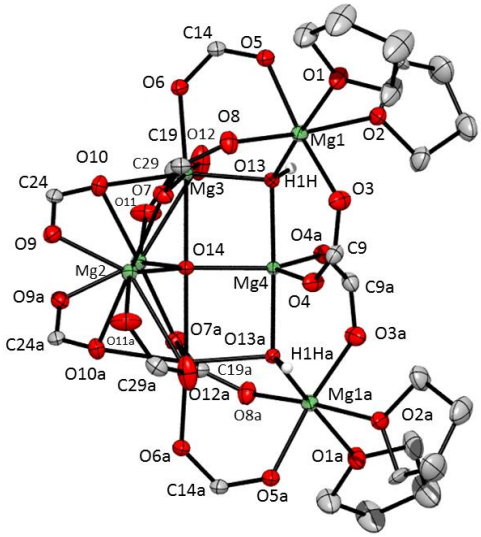


Table 14: Selected crystallographic data for compounds:

	(TMEDA)ZnMe(*p*-C_6H_4)Cl	[$(THF)_2Li_2(\mu\text{-}Cl)_2(\mu\text{-}OPiv)_2Zn$] (**24c**)	[{$Mg_6(OPiv)_{12}$}$(MgO)_2$]·C_7H_8	[{$Mg(OPiv)_2$}$_5${$Mg(OH)_2$}(MgO)·4THF]
Empirical formula	$C_{13}H_{23}Cl_1N_2Zn_1$	$C_{18}H_{34}Cl_2Li_2O_6Zn_1$	$C_{74}H_{124}Mg_8O_{26}$	$C_{68.64}H_{129.28}Mg_{6.75}O_{27.66}Zn_{0.25}$
Molecular Weight	308.17	496.6	1624.21	1577.76
Temperature (K)	123(2)	123(2)	123(2)	123(2)
Wavelenght (Å)	0.71073	0.71073	1.54180	0.71073
Crystal system,	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	Pbca	$P2_1/c$	C2cb
a (Å)	9.9500(3)	14.9325(3)	13.1072(2)	19.2990(6)
b (Å)	11.8823(3)	17.9451(5)	15.5468(3)	24.0340(7)
c (Å)	12.6338(4)	18.2119(4)	23.2630(4)	18.7974(6)
α (°)	90	90	90	90
β (°)	95.329(3)	90	105.827(2)	90
γ (°)	90	90	105.827(2)	90
Cell volume (Å^3)	1487.22(8)	4880.2(2)	90	8718.8(5)
Z	4	8	2	4
ρ_{calc} (g.cm^{-3})	1.376	1.352	1.183	1.204
μ (mm^{-1})	1.813	1.253	1.207	0.200
2θ max(°)	60.50	58.00	147.02	58.00
Index ranges	-14≤*h*≤14 -16≤*k*≤16 -16≤*l*≤17	-19≤*h*≤18 -23≤*k*≤20 -24≤*l*≤14	-16≤*h*≤15 -19≤*k*≤19 -26≤*l*≤28	-16≤*h*≤26 -32≤*k*≤32 -25≤*l*≤18
Reflections collected	14826	29165	36435	21834
Reflections unique	4064	6343	9049	8210
Reflections obs.	3349	4693	6967	6661
R_{int}	0.0400	0.0401	0.0597	0.0378
No. Parameters	159	268	508	533
Goodnes-of-fit-on F^2 (*GOF*)	1.032	1.098	1.053	1.063
Final *R* indices [$I>2\sigma(I)$]	0.0329	0.0399	0.0636	0.0582
R indices (all data)	0.081	0.0911	0.193	0.1557
Largest diff. peak and hole (e Å^{-3})	0.629 and -0.456	0.628 and -0.353	1.021 and -0.620	0.796 and -0.276