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der Fakultät für Chemie und Pharmazie
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$TMP_2Mg \cdot 2LiCl$ and Related Bases for the Metalation of Unsaturated Substrates and the Role of the Phosphorodiamidate Directing Group.
A new Cobalt-Catalyzed Sulfonate/Copper-Exchange.

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aus

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Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 der Promotionsordnung vom 29. Januar 1998 von Professor Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbstständig, ohne unerlaubte Hilfe erarbeitet.

München, den 01.03.2010

……..

Christoph Josef Rohbogner

Dissertation eingereicht am

1. Gutachter:	Prof. Dr. Paul Knochel
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Supporting information for this work is available free of charge on the following pages.

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

C. J. Rohbogner, S. Wirth, P. Knochel **"Phosphorodiamidate-Directed Metalation of *N*-Heterocycles Using Mg- and Zn-TMP Bases"**, *Org. Lett.* **2010**, *ASAP*, **DOI:** 10.1021/ol100453x.

S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel **"Scaleable Preparation of Functionalized Organometallics *via* Directed *ortho*-Metalation Using Mg- and Zn-Amide Bases"**, *Org. Process Res. Dev.* **2010**, *14*, 339-345.

C. J. Rohbogner, C. R. Diène, T. J. Korn, P. Knochel **"A Cobalt-Catalyzed Sulfonate/Copper-Exchange for the Preparation of Highly Functionalized Electron-Deficient Arylcopper Reagents"**, *Angew. Chem. Int. Ed.* **2010**, *49*, 1874-1877; *Angew. Chem.* **2010**, *122*, 1918-1921.

C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel **"Magnesiation of Poorly Activated Substrates Using $TMP_2Mg·2LiCl$. Synthesis of *tert*-butyl ethyl phthalate"**, *Org. Synth.* **2009**, *86*, 374-384.

C. J. Rohbogner, S. H. Wunderlich, G. C. Clososki, P. Knochel **"New Mixed Li/Mg- and Li/Mg/Zn-Amides for the Chemoselective Metallation of Arenes and Heteroarenes"**
Eur. J. Org. Chem. **2009**, 1781-1795. *(special issue dedicated to Prof. Alain Krief)*

C. J. Rohbogner, G. C. Clososki, P. Knochel **"A General Method for *meta*- and *para*-Functionalization of Aromatics Using $TMP_2Mg·2LiCl$"**, *Angew. Chem. Int. Ed.* **2009**, *47*, 1503-1507, *Angew. Chem.* **2009**, *120*, 1526-1530.

G. C. Clososki, C. J. Rohbogner, P. Knochel **"Direct Magnesiation of Polyfunctionalized Arenes and Heteroarenes Using $TMP_2Mg·2LiCl$"**, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684; *Angew. Chem.* **2007**, *119*, 7825-7828. Highlighted in *Nachr. Chem.* **2008**, *56*, 280.

Reviews and Book Chapters :

T. Thaler, H. Ren, N. Gommermann, G. C. Clososki, C. J. Rohbogner, S. H. Wunderlich, P. Knochel **"New Catalytic Cu-, Pd- and Stochiometric Mg- and Zn-Mediated Bond Activations"** in *Activating Unreactive Substrates: The Role of Secondary Interactions* (Eds. C. Bolm, F. E. Hahn), Wiley-VCH, Weinheim (Germany), **2009**, 359-375.

P. Knochel, P. Appukkuttan, A. Gavryshin, G. Manolikakes, A. Metzger, M. Mosrin, F. M. Piller, C. J. Rohbogner, M. A. Schade, S. H. Wunderlich **"Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents"**, *Pfizer In-House Journal Synthon*, **2008**.

Patent Application:

P. Knochel, G. C. Clososki, A. Krasovskiy, V. Krasovskaya, C. J. Rohbogner **“Preparation and use of Magnesium Amides”**, *Eur. Pat. Appl.* **2007** Nr. 07703987.3

to my family

» Success is the ability to go from one failure to another with no loss of enthusiasm. «

-Sir Winston Churchill-

Table of contents

Abbreviations:

Ac	acetyl
aq.	aqueous
Ar	aryl
An	anisyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
CDI	*N*,*N*'-carbonyldiimidazole
DA	*N*,*N*-diisopropylamide
dba	*trans*,*trans*-dibenzyledenacetone
Dma	dimethylaniline
DMG	directing metalation group
DMSO	dimethyl sulfoxide
DMPU	*N*,*N*'-dimethyl *N*,*N*'-propylene urea
equiv	equivalent
EI	electron-impact
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HMDS	hexamethyldisilazane
hex	hexyl
HRMS	high resolution mass spectrospcopy
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
LDA	Lithium *N*,*N*-diisopropylamide
M	molarity
m	meta
Me	methyl
min	minute
m.p.	melting point

MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	ortho
p	para
Pent	pentyl
Ph	phenyl
R	organic substituent
sat.	saturated
S-PHOS	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Ru-PHOS	2-dicyclohexylphosphino-2',6'-diisopropyloxybiphenyl
*t*Bu	*tert*-butyl
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetrametyhlethylendiamine
TMP-H	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TP	typical procedure
Ts	4-toluenesulfonyl
µW	microwave
X	halogen (Cl, Br, I)

1. GENERAL INTRODUCTION

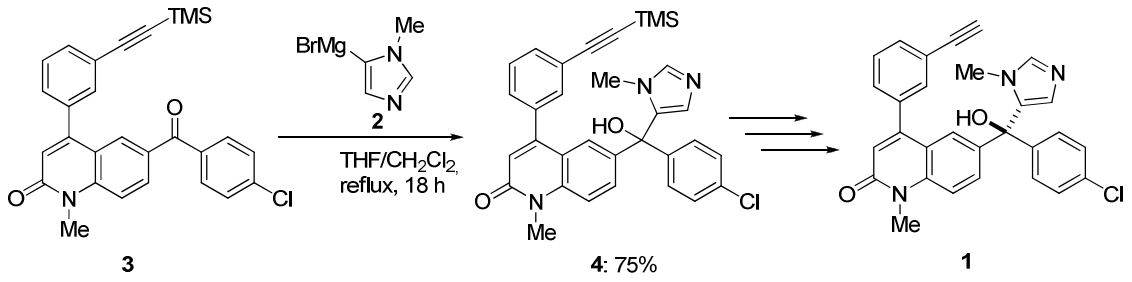
1.1. Overview

Since *Wöhler's* synthesis of Urea in 1828 which is also the "official" birth of organic chemistry, the formation of C-C bonds has become the most important mission in this field of science. *Kolbe* was the first chemist achieving this goal, when he synthesized acetic acid in 1845.[1] Only three years later, *Frankland*[2] managed to produce the first organometallic reagent, diethyl zinc by the reaction of zinc dust with ethyl iodide. This breaktrough discovery would emerge to the most powerful tool to form C-C and C-Heteroatom bonds during the next 150 years. Today one can hardly speak about modern organic chemistry without mentioning the milestones set by *Grignard, Wittig* or *Grubbs,* for instance.[3] In the last 25 years of the 20th century, organic chemistry was characterized by the assembly of complex framworks.[1,3] Like a perpetuum mobile, this work was influenced by the development of new synthetic methods and influenced itself the evolution of new techniques often implementing organometallic reagents or catalysts. The new reagents should fulfill demands which are at first glance contrary: they are asked to be highly reactive, highly selective and highly tolerant towards sensitive functionalities and also be as environmetally friendly as possible and – of course – economically at the same time.[4] The still ongoing development ensures that nearly every metal in the periodic table can be used for either the preparation of (new) organometallic reagents or in catalytic processes.

The origin of the variety in the properties of organometallics can be explained by the difference in the polarity of the carbon-metal bond. Very polar bonds as they are found in organolithium reagents ensure high reactivity towards electrophiles even at low temperatures. At the same time this ionic character of the formed intermediates is the reason for the limited tolerance towards sensitive functional groups. Reagents with a more covalent character of the carbon-metal bond can be found in organozinc or organotin reagents. These compositions offer a wider range of tolerance towards susceptible groups. However, these molecules are often characterized by a lack of reactivity towards electrophiles. This gap can be brigded by transmetalation (Sn or B → Li) or the use of transition-metals as catalysts (Pd, Co, Ni, Cu). Organomagnesium and organocopper compounds play a special role in this context. Showing a good reactivity when intercepted with electrophiles, they possess at the same time, a

[1] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[2] a) E. Frankland, *Liebigs Ann. Chem.* **1848-9**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848-9**, *2*, 263.
[3] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
[4] a) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259; b) C.-J. Li, B. M. Trost, *Proc. Nat. Acad. Sci.* **2008**, *105*, 13197.

remarkable tolerance of a broad range of functional groups. They can also be easily transmetalated to access other organometallic reagents. Therefore, these reagents represent formidable and flexible tools for organic synthesis.[5] *Grignard* reagents are often found in total syntheses, even embedded in process chemistry, as for example in the synthesis of a Farnesyl Transferase Inhibitor **1** by Pfizer, where a heteroaryl magnesium reagent **2** adds to the ketone **3** leading to the alcohol **4** (Scheme 1).[6]



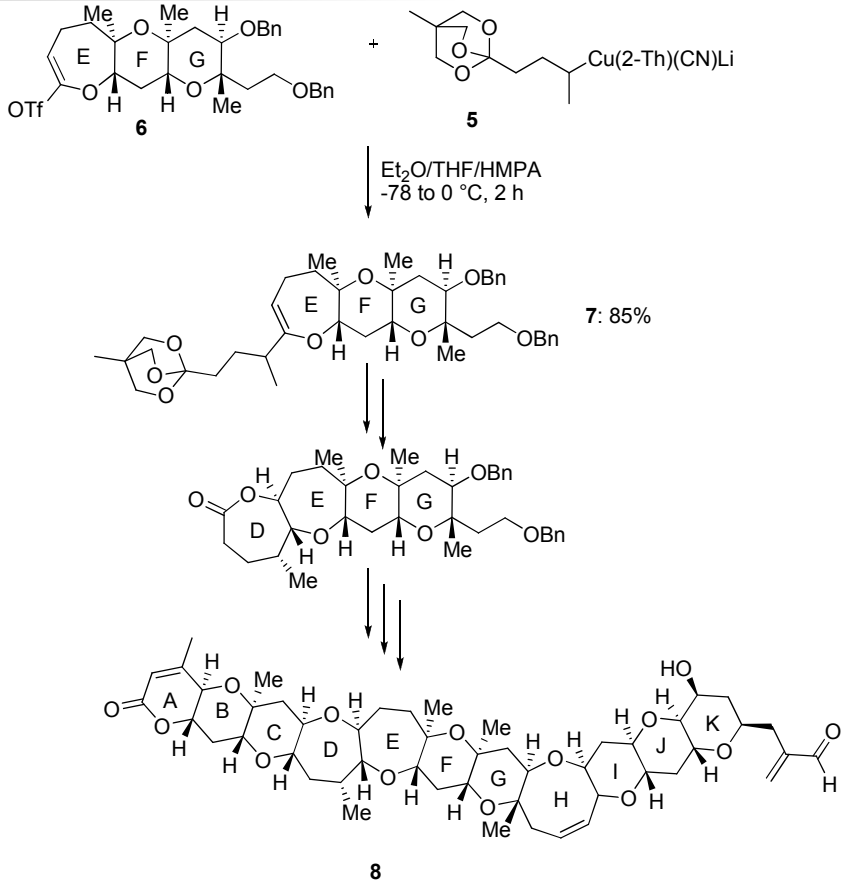
Scheme 1: *Grignard* reagent in the Synthesis of a Farnesyl Transferase Inhibitor.

An example for the use of organocopper reagents in total synthesis is shown in Scheme 2. The assembly of the D ring in the complex natural product Brevetoxin B is supported by the use of the copper reagent **5**, which is brought onto the EFG ring system **6** leading to the substructural unit **7** in good yield. The residue of **5** is used in the following steps to construct the D ring of Brevetoxin B (**8**).[7]

[5] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4415; b) *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

[6] B. M. Andresen, M. Couturier, B. Cronin, M. D'Occhio, M. D. Ewing, M. Guinn, J. M. Hawkins, V. J. Jasys, S. D. LaGreca, J. P. Lyssikatos, G. Moraski, K. Ng, J. W. Raggon, A. M. Stewart, D. L. Tickner, J. L. Tucker, F. J. Urban, E. Vasquez, L. Wei, *Org. Process Res. Dev.* **2004**, *8*, 643.

[7] K. C. Nicolaou, E. A. Theodorakis, F. P. J. T Rutjes, M. Sato, J. Tiebes, X. Y. Xiao, C. K. Hwang, M. E. Duggan, Z. Yang, E. A. Couladouros, F. Sato, F. Shin, H. M. He, T. Bleckman, *J. Am. Chem. Soc.* **1995**, *117*, 10239.

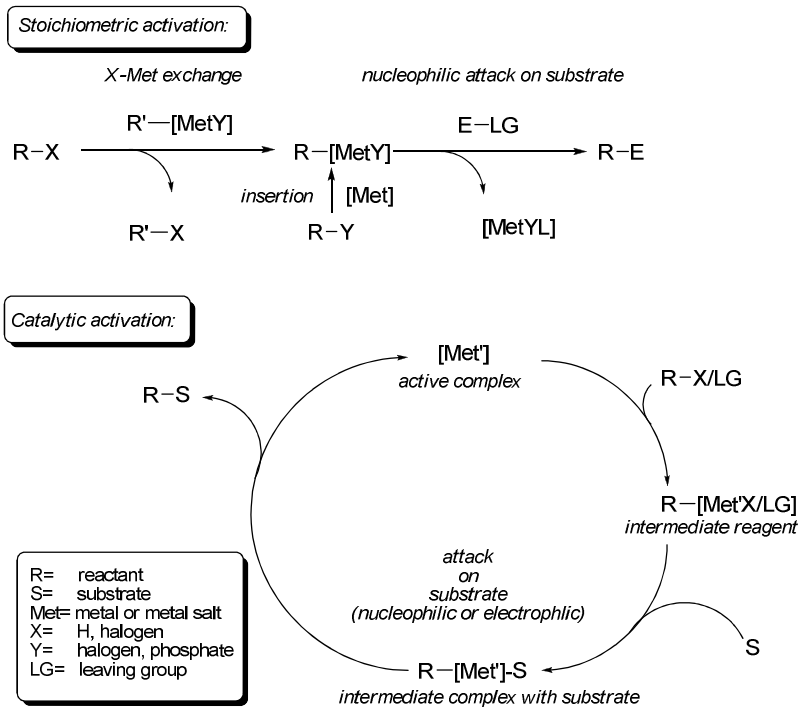


Scheme 2: Organocopper compounds in the synthesis of Brevetoxin B.

1.2. Preparation and Use of Organomagnesium and Organocopper Compounds

1.3. Introduction

A C-H or a C-X/LG (LG: leaving group e.g. OTs, OTf, X: halogen e.g. Cl, Br, I) bond in organic chemistry can basically be activated in catalytical or stoichoimetrical way.



Scheme 3: Simplified mechanisms of the stoichiometric and catalytic bond activations.

In both pathways, the reactive species R-[Met'] / R-[MetY] are obtained by the interaction of the metallic reagent with the reactant R-X/LG / R-Y (Scheme 3). The catalytic activation is especially well-suited for domino-reactions.[8] The catalytic use of an active metal species [Met'] also facilitates enantioselective reactions. These catalytic activations mostly involve the use of expensive and/or toxic transition metals and it is therefore important to minimize the necessary amount of the catalyst. In the stoichiometric activation pathway, [Met] and [R'-MetY] have to be used in stoichiometric amounts and are quantitatively consumed during the

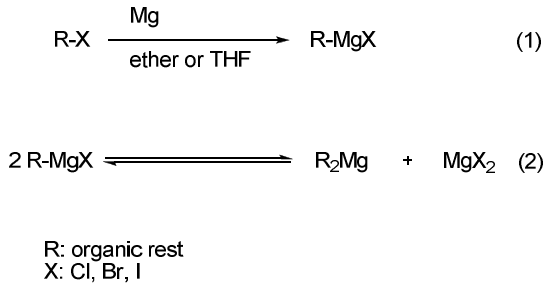
[8] a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; b) A. de Meijere, P. v. Zerschwitz, H. Nuske, B. Stulgies, *J. Org. Chem.* **2002**, *653*, 129; c) S.-I. Ikeda, *Acc. Chem. Res.* **2000**, *33*, 511.

reaction and therefore entail large amounts of chemical waste. That is why inexpensive and readily available metal species have to be used. The following chapters will give an brief overview into historic and current developments in organometallic C-H and C-X/L bond activations by highlighting recent research results in this field. Different approaches, including exchange- as well as catalyzed reactions, for the generation of organomagnesium-, organocopper-, and organozinc reagents will be lit up.

1.4. Stoichiometric Bond Activations for the Preparation of Organomagnesium and Organocopper Reagents

1.4.1. Halogen Metal Interconversion

In 1900, *Grignard* reported for the first time the oxidative insertion of magnesium metal into a carbon-halogen bond.[9] Until now, this reaction is the most commonly used protocol for the synthesis of these so called *Grignard* reagents (Scheme 4, Eq. 1).



Scheme 4: Synthesis of *Grignard* reagents and *Schlenk* equilibrum.

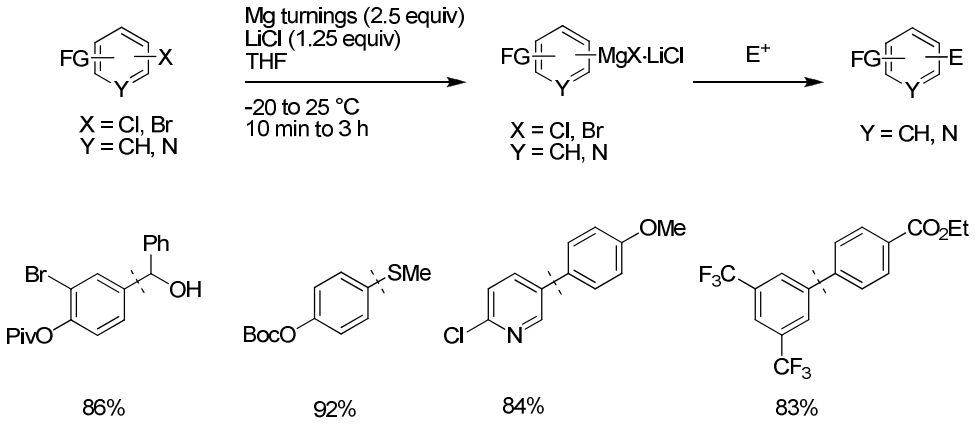
The mechanism of this reaction is not fully clarified, but it is generally assumed that radicals are involved in this transformation.[10] In solution, *Grignard* reagents are in equilibrium with R_2Mg and MgX_2, the so called *Schlenk*-equilibrium (Scheme 4, Eq. 2). This state is influenced by the solvent, the temperature as well as the counterion. Organomagensium reagents are also prone to form dimers or oligomers, which is influenced by the

[9] a) V. Grignard, *C. R. Acad. Sci.* **1900**, *130*, 1322 ; b) *Handbook of Grignard Reagents* (Ed.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1966**; c) *Grignard Reagents, New Developments* (Ed.: H. G. Richey, Jr.), Wiley, New York, **2000**, p. 185.

[10] a) M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, **1954**; b) H. M. Walborsky, *Acc. Chem. Res.* **1990**, *23*, 286; c) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95.

concentration.[11]

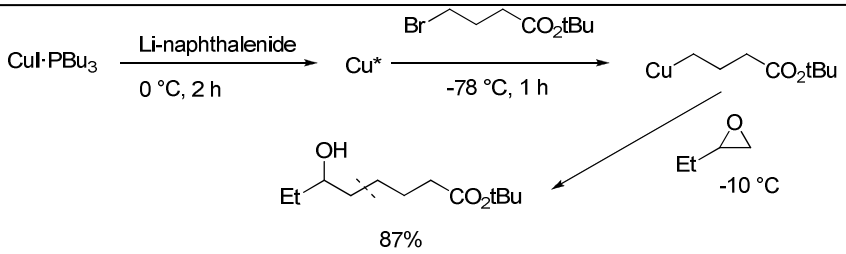
Although this method is a convenient way for the preparation of organomagnesium compounds, it suffers from drawbacks concerning the functional group tolerance. Exothermic conditions during the insertion as well as often necessary activation of the passivated metal surface are an explanation for this limitation.[12] A Mg insertion at cryogenic temperatures using highly active magnesium metal was developed by *Rieke*.[13] Recently, an improved protocol for the Mg-insertion was developed by *Knochel*. The addition of LiCl to the reaction mixture allows the insertion of magnesium into C-X bonds (X: Cl, Br, I) at room temperature or below, improving functional group tolerance in insertion reactions significantly (Scheme 5).[14]



Scheme 5: LiCl faciliated Mg-insertion by *Knochel*.

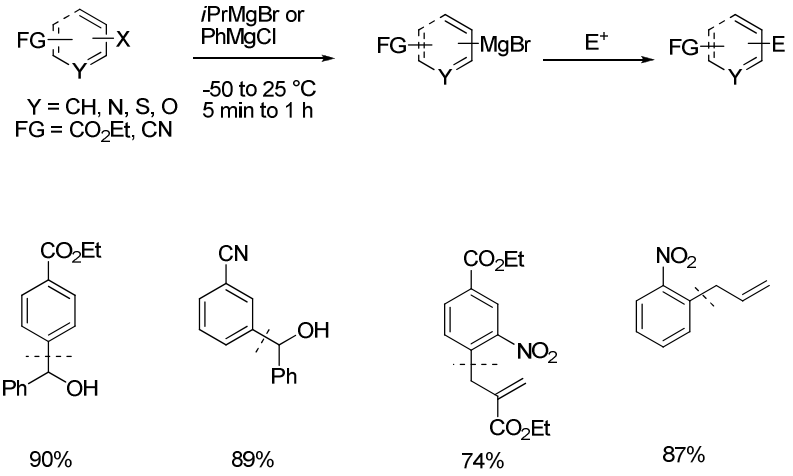
The insertion of copper metal into a carbon halogen bond was developed by *Rieke* in 1984.[15] The use of lithium naphthalenide to generate highly reactive copper metal allows the conversion of organic bromides or iodides into the corresponding copper reagents as shown in Scheme 6.

[11] W. Schlenk, W. Schlenk Jr., *Chem. Ber.* **1929**, *62*, 620.
[12] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
[13] R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.
[14] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun*. **2008**, 5824.
[15] a) R. D. Rieke, G. W. Ebert, *J. Org. Chem.* **1984**, *49*, 5280; b) R. D. Rieke, R. M. Wehmeyer, T.-C. Wu, G. W. Ebert, *Tetrahedron* **1988**, *45*, 443; c) G. W. Ebert, J. W. Cheasty, S. S. Tehrani, E. Aouad, *Organometallics* **1992**, *11*, 1560; d) G. W. Ebert, D. R. Pfenning, S. D. Suchan, T. A. Donovan Jr., *Tetrahedron Lett.* **1993**, *34*, 2279.



Scheme 6: Cu-insertion by *Rieke*.

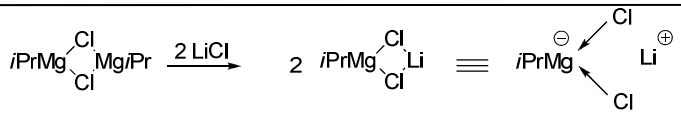
Another convenient way for the preparation of organomagnesium or organocopper compounds with high functional group tolerance is the halogen/magnesium- or iodine/copper-exchange reaction. Based on the work of *Prévost*[16] and *Villeras*[17], *Knochel* demonstrated the feasibility of the iodine/magnesium exchange on substrates bearing sensitive functionalities in 1998 (Scheme 7).[18]



Scheme 7: I/Mg-exchange.

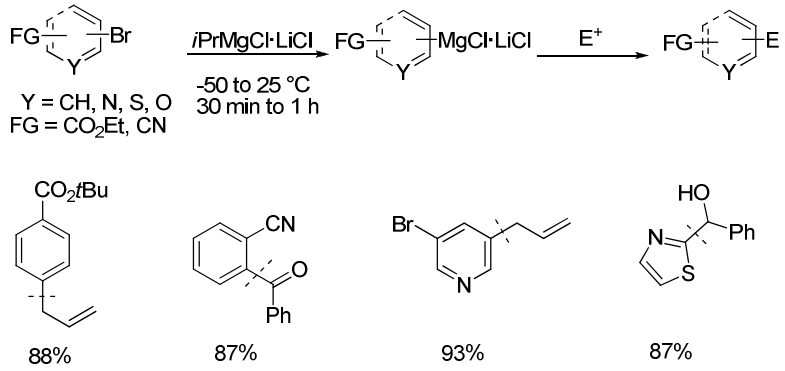
A wide range of polyfunctionalized organomagnesium reagents were prepared using this protocol. This method was further improved by the addition of one equivalent of LiCl to the exchange reagent *i*PrMgCl giving the formal composition *i*PrMgCl·LiCl. Interestingly this reagent displays a far higher reactivity, making the Br/Mg-exchange generally possible (Scheme 8).[19]

[16] C. Prévost, *Bull. Soc. Chem. Fr.* **1931**, *49*, 1372.
[17] a) J. Villéras, *Bull. Chem. Soc. Fr.* **1967**, *5*, 1520; b) J. Villéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Chem. Soc. Fr.* **1986**, *24*, 470.
[18] 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.
[19] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.



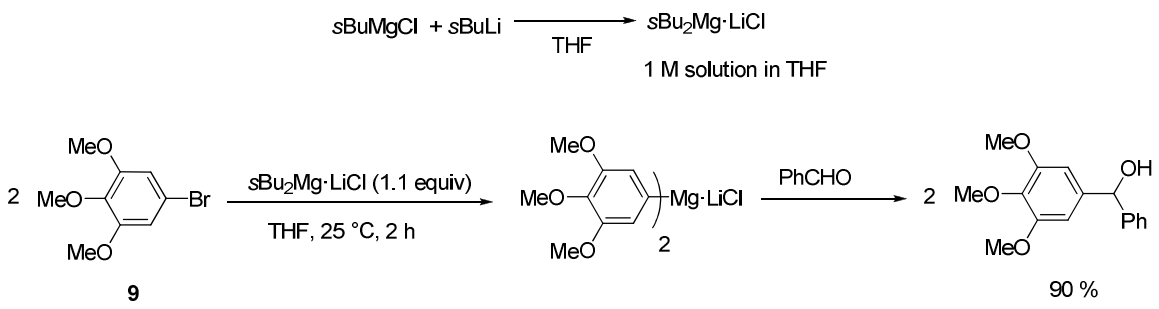
Scheme 8: Deaggregation of *i*PrMgCl achieved by LiCl.

The assumed ate like intermediate of this composition is proposed to be responsible for both, higher solubility and reactivity of the *Grignard* reagent. Thus, a broad range of aromatic and heteroaromatic bromides were converted into the corresponding Mg-reagents (Scheme 9)[20]



Scheme 9: Br/Mg-exchange using *i*PrMg·LiCl.

Surprisingly, the increased reactivity does not limit the functional group tolerance. However, some electron rich arenes still resisted to undergo the Br/Mg-exchange. This gap was briged by the development of exchange reagents of the type RMg_2·LiCl.[21]



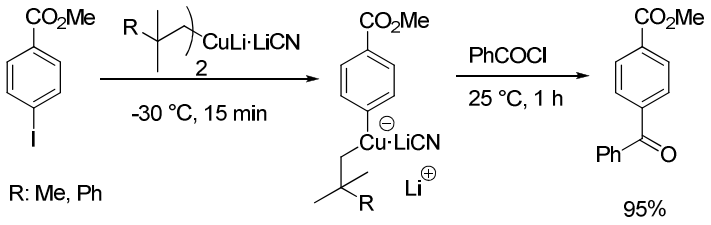
Scheme 10: Br/Mg-exchange on electron rich substrates using *s*BuMg_2·LiCl.

Quantum chemical model calculations of halogen/magnesium-exchange reactions showed that

[20] For selected examples of Br/Mg-exchange, see: H. Ren, P. Knochel, *Chem. Comm.* **2006**, 726; b) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; c) N. Boudet, P. Knochel, *Org. Lett.* **2006**, *8*, 3737; d) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.
[21] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

the exchange becomes more likely if the the exchange reagent's ate character is increased. Thus, *bis*-Mg reagents of type RMg_2·LiCl could complete the exchange on substrates like **9** where *i*PrMgCl·LiCl failed.[21]

Corey demonstrated that Li-dialkylcuprates can be used to achieve an iodine copper exchange of aryl iodides.[22] The limitation of this method was that one alkyl rest was also transferred onto the substrate. *Knochel* improved this method in 2002 by utilizing sterically hindered non transferable lithiumdialkyl cuprates. These reagents rapidly react with various functionalized aryl halides generating the corresponding copper reagents (Scheme 11).[23]



Scheme 11: I/Cu-exchange using sterically hindered Li-dialkylcuprates.

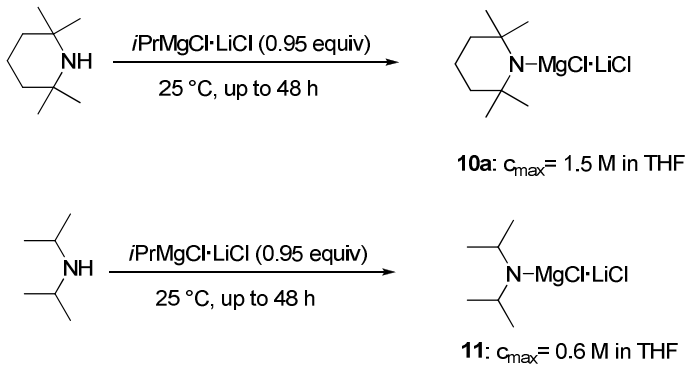
A drawback in all halogen/metal-exchange reactions, despite excellent functional group tolerance, is the necessity of a reactive C-X bond (X: Cl, Br, I) in the molecule. Many organic bromides and iodides suffer from dehalogenation reactions due to their thermal- or photoinstability. The generation of organometallics by C-H activation will be described in the following chapter.

1.4.2. Hydrogen Metal Exchange

Besides metal insertion and halogen/metal-exchange, the directed metalation using metal (R-Met) and metal amide (R^1R^2N-Met) bases is the third major pathway for the synthesis of organometallics.[24, 25] In contrast to the previously presented methods (insertion and exchange reaction), there is no need for a halogen-carbon bond. Thus, a more or less activated

[22] a) E. J. Corey, G. H. Posner, *J. Am. Chem. Soc.* **1967**, *89*, 3911; b) E. J. Corey, G. H. Posner, *J. Am. Chem. Soc.* **1968**, *90*, 5615.
[23] a) C. Piazza, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 3263; b) X. Yang, T. Rotter, C. Piazza, P. Knochel, *Org. Lett.* **2003**, *5*, 1229; c) M. I. Calaza, X. Yang, D. Soorukram, P. Knochel, *Org. Lett.* **2004**, *6*, 529; d) X. Yang, A. Althammer, P. Knochel, *Org. Lett.* **2004**, *6*, 1665; e) X. Yang, P. Knochel, *Org. Lett.* **2006**, *8*, 1941.
[24] For an early overview about metalation using organolithium compounds, see: J. M. Mallan, R. L. Bebb, *Chem. Rev.* **1969**, *69*, 693 and references therein.
[25] For reviews, see: a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 380; b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.

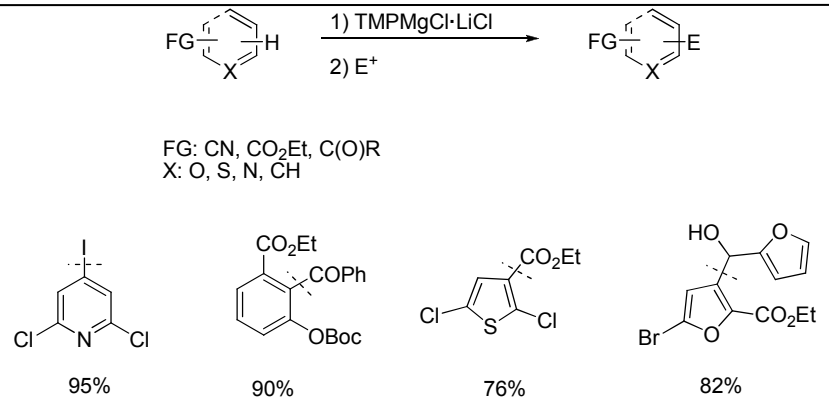
hydrogen-carbon bond is directly transformed into the corresponding metal species. In pioneering studies, *Meunier*,[26] *Hauser*,[27] *Eaton*[28] and *Mulzer*[29] demonstrated the feasibility of these metalations mediated by Mg-amide bases ("Hauser-Bases"). However, their reagents suffered from low reactivity due to the formation of aggregates. Therefore, a large excess of the metalating agent as well as the electrophile had to be used to overcome these problems. The observation, that the addition of 1 equiv of LiCl resulted in the formation of highly reactive, deaggregated exchange reagents ("Turbo-*Grignard*" (e.g. *i*PrMgCl·LiCl, (*s*Bu)$_2$Mg·LiCl)) paved the way for the development of highly reactive Mg-amide bases of the type $R^1R^2NMgX{\cdot}LiCl$ ("Turbo-Hauser-Bases"; Scheme 12). The recent determination of the metalated amide's crystal structure showed that LiCl achieves deaggregation to form a monomeric species.[30]



Scheme 12: Preparation of Turbo-Hauser-Bases.

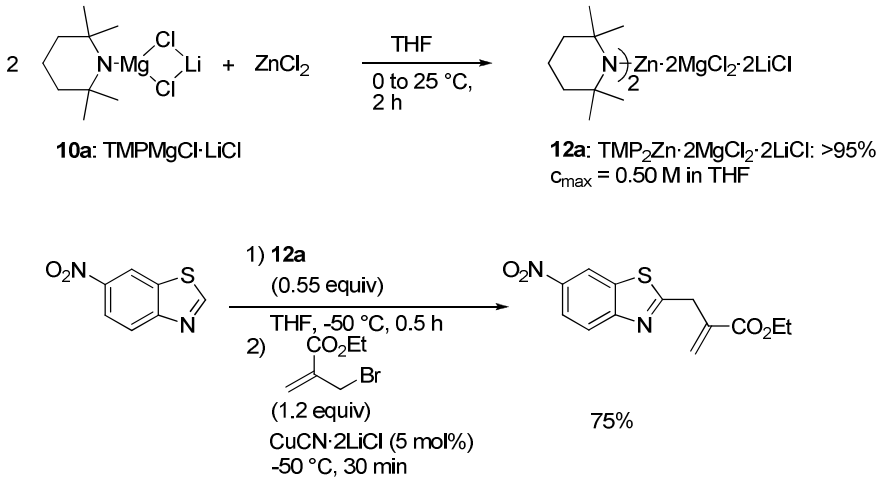
These bases are able to deprotonate many aromatics and heteroaromatics using approx. 1.1 equiv of the base and the generated organomagnesium reagents react with a wide range of electrophiles (Scheme 13).[31]

[26] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[27] 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.
[28] a) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016; b) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370.
[29] A. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[30] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; for a crystal structure of **10a**, see: P. García-Alvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, S.; *Angew. Chem. Int. Ed.* **2008**, *47*, 8079
[31] Selected examples, see: a) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; b) N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715; c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; d) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; e) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113.



Scheme 13: Magnesiation of arenes and heteroarenes using the Base **10a**.

However, substrates bearing extremely sensitive groups (e. g. aldehyde, nitro group) as well as some heterocycles are precluded from a metalation with **10a**. These substrates are best metalated with a more sensitive base. Thus, the transmetalation of **10a** with $ZnCl_2$ furnishes a highly reactive and chemoselective base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**12a**) which is able to achieve the zincation of arenes and heteroarenes (Scheme 14).[32]

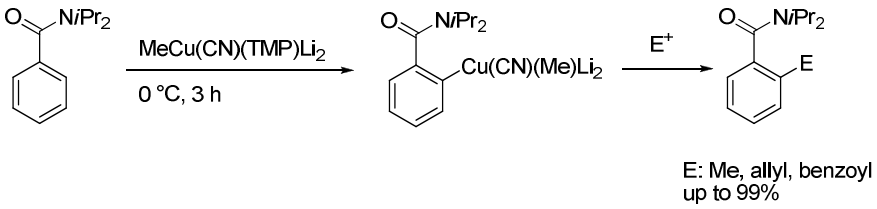


Scheme 14: Direct zincation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**12a**).

A direct cupration was developed by *Uchiyama* in 2007. Thus, the TMP derived base $MeCu(CN)(TMP)Li_2$ allowed the metalation of various aromatics and heteroaromatics. The generated cuprates may be intercepted with a broad range of electrophiles (Scheme 15).[33] Other metal amide bases have been developed to adress the different demands of metalation

[32] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel; *Org. Lett.* **2008**, *10*, 4705; c) S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008,** *47*, 6387.
[33] S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley, M. Uchiyama, *J. Am. Chem. Soc.* **2007**, *129*, 15102; b) J. Haywood, J. V. Morey, A. E. H. Wheatley, C.-Y. Liu, S. Yasuike, J. Kurita, P. R. Raithby, M. Uchiyama, O*rganometallics* **2009**, *28*, 38.

and quenching reactions.[34]



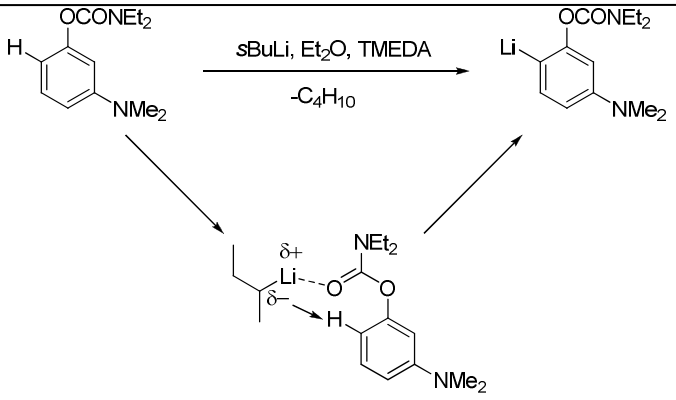
Scheme 15: Direct cupration of arenes.

1.4.3. Directed *ortho* Metalation

Beak and *Snieckus* investigated intensively the directed *ortho* metalation (D*o*M) using lithium bases and the complex-induced proximity effect.[35] The D*o*M concept describes the regioselective functionalization of aromatics if a directing metalation group (DMG) is present in the molecule. For example, amides, carbamides, sulfonamides, esters, cyanides or phosphorous-containing substituents are considered to be efficient directing groups in contrast to ethers or amines. In the presence of such a group, the metalating agent is complexed and therefore the corresponding base is conducted to the next activated proton, in general in *ortho*-position to the directing group (Scheme 16). In some cases, the directing effect of one group can overrule the effect of the other one or the presence of two groups with equal properties lead to a decreased regioselectivity of the metalation process.

[34] For the preparation of Al-, Mn-, Fe- and La-amide bases see: a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 1501; b) S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256; c) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717-9720; d) S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *in press.*

[35] For an overview, see: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; c) P. Beak, A. I. Meyers, *Acc. Chem. Res*. **1986**, *19*, 356; d) E. Anctil, V. Snieckus, *The Directed ortho Metalation-Cross-Coupling Nexus. Synthetic Methodology for Aryl-Aryl and Aryl-Heteroatom-Aryl Bonds*, in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: F. Diederich, A. de Meijere) Wiley-VCH, Weinheim, **2004**, pp 761-813; e) C. G. Hartung, V. Snieckus, *The Directed ortho Metalation Reacton. A Point of Departure for new Synthetic Aromatic Chemistry*, in *Modern Arene Chemistry*, (Ed.: D. Astruc), Wiley-VCH, New York, **2002**, pp 330-367.



Scheme 16: Directed *ortho*-metalation using a DMG.

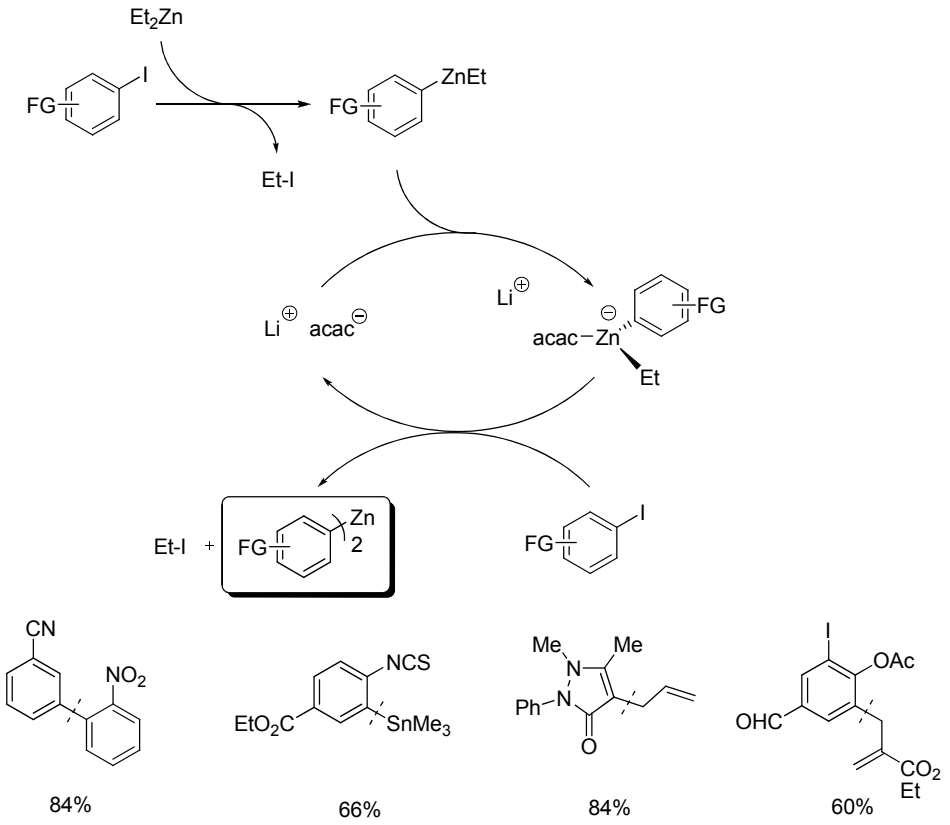
The used DMG must possess special properties. On the one hand, it has to offer a good coordinating site for the used base but on the other hand it should not contain a good electrophilic site for the attack by the metal base or the formed organometallic intermediates. Therefore, heteroatoms are a nearly obligatory component in a DMG. Additionally, existing steric hinderance (R-CONEt$_2$ or R^1-P(O)NR^{2}R^3), charge deactivation (R-CON$^-$ or R-CSN$^-$) or the combination of both effects may be found in DMGs. Substituent effects on the substrate also influence the rate of deprotonation, especially electron withdrawing groups may control the compound's behavior during metalation reactions.[35]

1.5. Catalytic Bond Activations for the Synthesis of Organometallics

Catalyzed reactions are useful processes in organic chemistry. Numerous helpful and effective protocols have been developed until now. Most reactions deal with the formation of new carbon-carbon bonds or tandem reactions using organometallic intermediates and/or catalysts.[36] The synthesis of organometallics using catalytic conditions is less prominent due to limited long term stability of the formed products. An exception are organoboron-[37] and organotin [38] reagents. Their Pd-catalyzed synthesis from aryl iodides were reported by *Miyaura*, *Migita* and *Beletskaya*. Moreover, the synthesis of organozinc reagents *via* a catalytic process was reported by *Knochel*. A Li(acac)-catalyzed preparation of zincorganyls

[36] a) *Metal-catalyzed Cross-coupling Reactions* (Eds.: A. de Meijere, F. Diederich), 2nd Ed., Wiley-VCH, Weinheim, **2004**; b) *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), 2nd Ed., Wiley-VCH, **2004**; c) *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; d) *Modern Arylation Methods* (Ed. L. Ackermann), Wiley-VCH, Weinheim, **2009**.
[37] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508.
[38] M, Kosugi, K. Shiminu, A, Ohtani, T. Migita, *Chem. Lett.* **1981**, 829; b) A. N. Kashin, I. G. Bumagina, N. A. Bumagin, V. N. Bakunin, I. P. Beletskaya, *Zh. Org. Khim.* **1981**, *17*, 905; c) M. Kosugi, T. Ohaya, T. Migita, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3855.

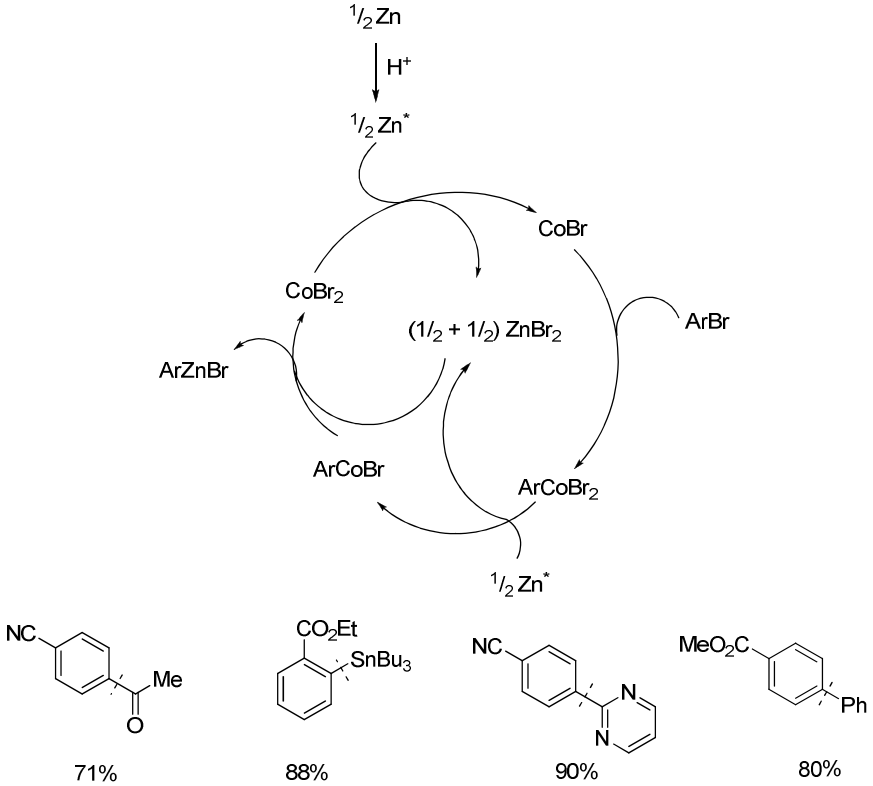
from aryl halides was developed in 2004 (Scheme 17).[39] The reaction mechanism is assumed to be the following: in the first step, a mixed arylalkyl zinc reagent is formed which is converted into the diaryl zinc species after activation of the complex with the catalyst. The formed compounds can be further used in cross-coupling-, acylation- or allylation reactions.



Scheme 17: Li-catalyzed I/Zn-exchange.

Gosmini reported the synthesis of arylzincbromides *via* cobalt catalysis in the presence of zinc dust. After activation of the zinc with traces of acid, the catalyst is reduced and performs oxidative addition into the C-Br bond. Subsequent reduction and transmetalation of the arylcobalt species leads then to the desired zinc compounds in good yields (Scheme 18).[40]

[39] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[40] a) C. Gosmini, Y. Rollin, J.-Y. Nédélec, J. Périchon, *J. Org. Chem.* **2000**, *65*, 6024; b) H. Fillion, E. Le Gall, C. Gosmini, J. Périchon, *Tetrahedron Lett.* **2002**, 43, 5941; c) H. Fillion, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867; d) I. Kazmierski, M. Bastienne, C. Gosmini, J.-M. Paris, J. Périchon, *J. Org. Chem.* **2004**, *69*, 936; e) J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221.



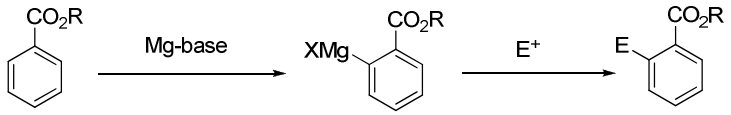
Scheme 18: Mechanism of the Co-catalyzed preparation of arylzinc reagents.

Both reactions have excellent functional group tolerance (aldehydes, esters, nitriles or isothiocyanates) but they require the use of expensive aryl bromides or iodides. In a multi-step sequence, the conversion of a phenol to a reactive organometallic may be achieved, however with moderate atom economy.[41]

[41] a) OH→OTf→SnR_3: R. C. Winstead, T. H . Simpson, G. A. Lock, M. D. Schiavelli, D. W. Thompson, *J. Org. Chem.* **1986**, *51*, 277; b) ArOH→ArOTf/ArOMs→ArZnX: I. Kazmiersi, C. Gosmini, J.-M. Paris, J. Perichon, *Synlett* **2006**, 881; c) for a review see: J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

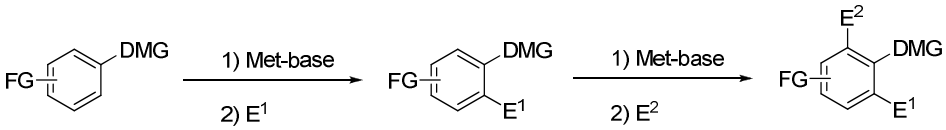
1.6. Objectives

The first topic includes the development of a highly active magnesium amide base which is able to deprotonate unreactive substrates such as benzoates or benzonitriles. Despite the higher reactivity, the new tool should have the same functional group compatibility as TMPMgCl·LiCl. The metalation reactions should be easy to handle and the formed Mg-intermediates should show a certain stability to undergo typical interception reactions (Scheme 19).



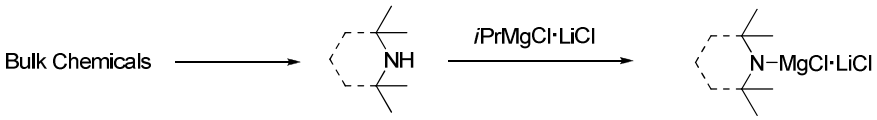
Scheme 19: General pathway for the magnesiation of a poorly activated benzoate.

In addition thereto, a directed metalation group (DMG) should be combined with the new base. This group should allow multiple selective metalations without stability problems in these reactions. In the end, easy removal and/or further conversion of this group is desirable (Scheme 20).



Scheme 20: Directed metalation using a new Mg-amide base in combination with a new DMG.

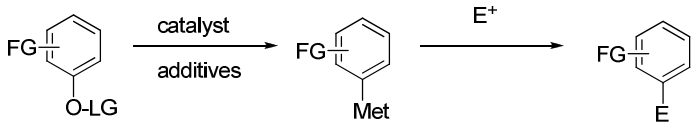
Additionally, different sterically demanding amines should be tested if they are able to replace TMP-H as this is the most expensive component in the base. These amines should be easy to prepare from inexpensive bulk chemicals (Scheme 21).



Scheme 21: General reaction pathway for the synthesis of alternative sterically hindered amines.

The second part includes the development of a new a catalyzed activation of the carbon-

oxygen bond in phenol derivatives. This pathway should give an access to organometallic reagents without the necessity of halogens in the molecule (Scheme 22).



Scheme 22: Transition metal-catalyzed bond activation.

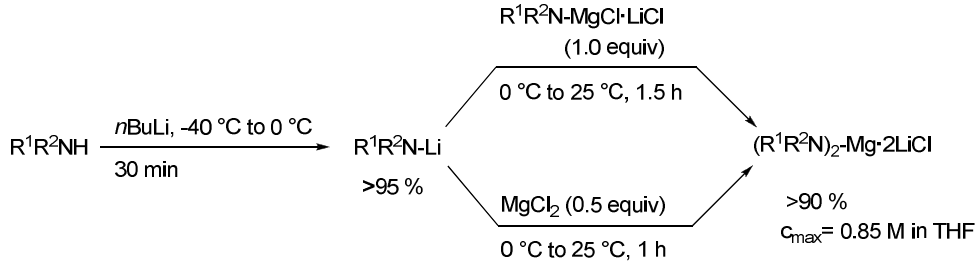
2. RESULTS AND DISCUSSION

3. Magnesiations on Weakly Activated Substrates via Stoichiometric C-H Bond Activation

3.1. Preparation and use of Magnesium *bis*-amide Bases

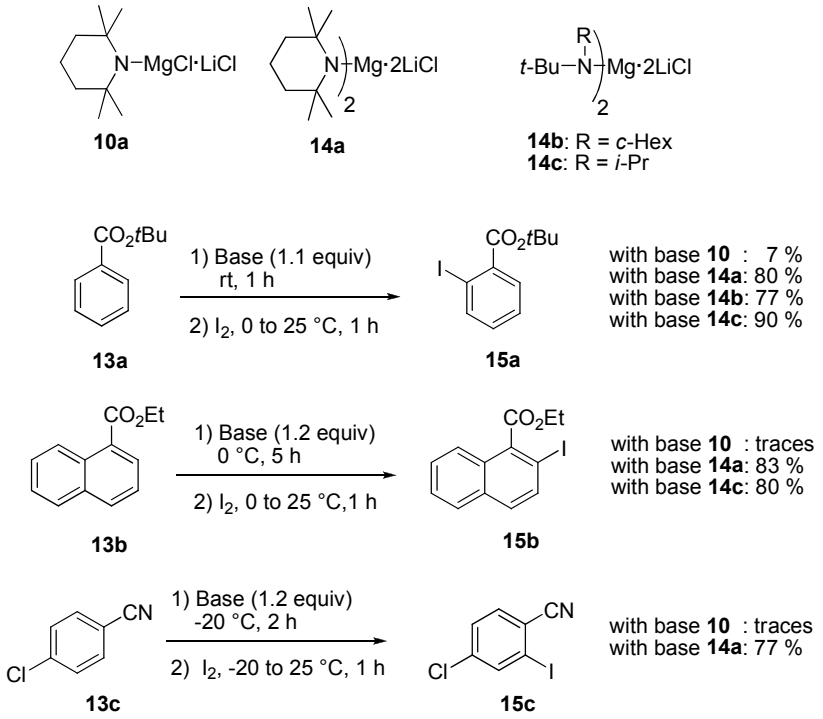
As mentioned in above, the directed metalation of aromatics and heteroaromatics is a very important tool for the functionalization of these scaffolds. Directed lithiations are affected (as mentioned above) by serveral problems (high reactivity, low functional group tolerance, required cryogenic conditions). Directed magnesiations using mixed Li/Mg-amide bases of the type $R^1R^2NMgX{\cdot}LiCl$ were used to adress these problems.[30] However, some weakly activated substrates, such as benzoates, benzonitriles or pyridines only undergo magnesiations sluggishly or not at all. By developing TMP_2Mg and using it for the deprotonation of methyl benzoate, *Eaton* pointed in the right direction. Though, his reagent suffered from low solubility and a large excess of the base was needed to accomplish full magnesiation. Additionally, a large excess of electrophile had to be used in the quenching reaction (up to 12 equiv). [28] Again, deaggregation of the base is achived by the formal addition of two molecules of LiCl. Therefore, this new class of mixed Mg/Li bases was able to brigde this gap: $(R^1R^2N)_2Mg{\cdot}2LiCl$. The reagents **14a-c** were readily prepared by reacting R^1R^2NLi with $MgCl_2$ in THF at 0 °C for 0.5 h Alternatively, it was found that these bases can also be conveniently prepared by reacting $R^1R^2NMgCl{\cdot}LiCl$ with R^1R^2NLi[42] for 30 min at 0 °C. Since $R^1R^2NMgCl{\cdot}LiCl$ bases can be stored in THF at 25 °C for several months, this method appears to be the best for routine experiments. (Scheme 23).

[42] For a review of the chemistry of LiTMP, see: M. Campbell, V. Snieckus in *Encyclopedia of Reagents for Organic Synthesis*; (ed.: L. A. Paquette), John Wiley & Sons: Chichester, U.K. and New York, **1995**; Vol. 5. About stability of lithium amide bases in ether solvents see: I. E. Kopka, Z. A. Fataftah, M. W. Rathke, *J. Org. Chem.* **1987**, 52, 448.



Scheme 23: General reaction pathway for the preparation of bases of type $((R^1R^2N)_2Mg{\cdot}2LiCl$.

Whereas with TMPMgCl·LiCl (**10a**) no significant deprotonation of **13a-c** was observed, the use of magnesium bisamides complexed with 2 equivalents of LiCl such as **14a-c** led to excellent results (Scheme 24). $TMP_2Mg{\cdot}2LiCl$ (**14a**) proved to be the most powerful base.[43]



Scheme 24. Comparison between the different Mg-amide bases.[44]

The best results were obtained when base **14a** was freshly prepared as its activity decreased significantly after 24 h. Surprisingly, $[t\text{Bu}(i\text{Pr})]_2Mg{\cdot}2LiCl$ (**14c**) can be stored in THF at 4 °C for 3 weeks with no significant reduction of activity (see chapter 3.4. for further results).

[43] For the use of *ate* Bases see: a) H. Naka, M. U. Uchiyama, Y. Matsumoto, A. E. H, Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921; b) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; c) M. Uchiyama, T. Miyoshi, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514; d) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526.

[44] Experments were done by G. C. Clososki and are given here for the sake of completeness.

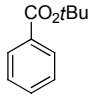
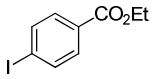
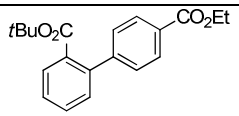
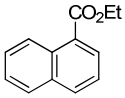
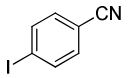
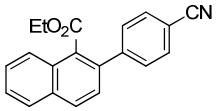
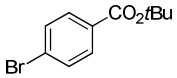
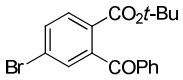
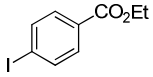
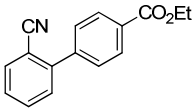
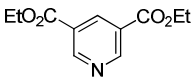
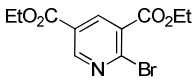
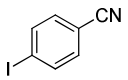
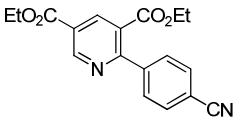
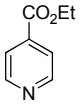
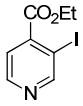
Therefore, a number of aromatic and heterocyclic substrates were cleanly metalated with TMP_2Mg·2LiCl (**14a**; Table 1). Thus, *tert*-butyl benzoate (**13a**) was converted into the *ortho*-magnesiated intermediate by the reaction with TMP_2Mg·2LiCl (**14a**) within 1 h at 25 °C. The magnesiated intermediate was smoothly transmetalated with $ZnCl_2$ (1.2 equiv) and underwent a *Negishi* cross-coupling[1,45] with ethyl 4-iodobenzoate (1.5 equiv), in the presence of P(2-furyl)$_3$ (4 mol%) and Pd(dba)$_2$ (2 mol%)[46] at 25 °C for 12 h, leading to the biphenyl derivative **15d** in 82% yield (Table 1, entry 1). Additionally, reaction of TMP_2Mg·2LiCl (1.2 equiv) with ethyl 1-naphthoate (**13b**) led to the corresponding Mg-reagent within 5 h at 0 °C a subsequent *Negishi*-type[44, 45] cross-coupling with 4-iodo benzonitrile afforded the corresponding functionalized derivative **15e** in 81% yield (entry 2). The presence of an electron-withdrawing group such as a bromine substituent in the case of *tert*-butyl 4-bromobenzoate (**13d**) accelerated the metalation, furnishing the magnesiated product within 1 h at –20 °C. A copper(I)-mediated benzoylation [47] gave the corresponding *tert*-butyl 2-benzoyl-4-bromobenzoate (**15f**) in 77% yield (entry 3). Whereas benzonitriles are sluggishly metalated with TMPMgCl·LiCl (**10a**), the use of **14a** (1.2 equiv) led to a smooth magnesiation of benzonitrile (**13e**) within 3 h at –30 °C. Transmetalation ($ZnCl_2$) followed by a cross-coupling with ethyl 4-iodobenzoate afforded the corresponding functionalized biphenyl derivative **15g** in 70% yield (entry 4). Ester-substituted pyridines are also excellent substrates and the diester **13f** was converted to the corresponding 2-magnesiated pyridine (–40 °C, 5 h), which provided after bromolysis with $(BrCl_2C)_2$ or *Negishi* cross-coupling with 4-iodobenzonitrile the expected polyfunctional pyridines **15h-i** in 70-77% yield (entries 5, 6). Similarly ethyl isonicotinate (**13g**) reacted smoothly with **14a** (–40 °C, 12 h) leading after iodolysis to the 3-iodopyridine **15j** in 66% yield (entry 7).

[45] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *J. Org. Chem.* **1980**, *45*, 5223; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; for Pd-catalyzed Kumada-Corriu cross-coupling reactions see: d) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3844.

[46] a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585; b) V. Farina, S. Kapadina, B. Krishnan, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905; c) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, *Tetrahedron* **1996**, *52*, 7201.

[47] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

Table 1: Products of type **15** obtained after magnesiation with $TMP_2Mg{\cdot}2LiCl$ (**14a**) and subsequent reaction with an electrophile.

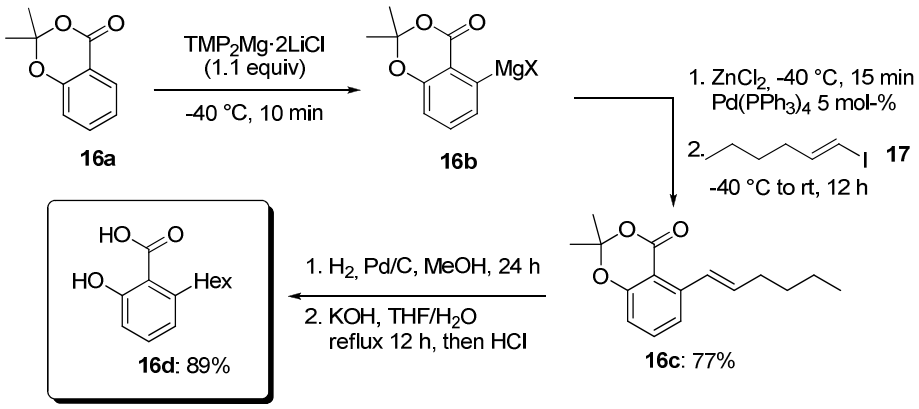
Entry	Substrate	*T* [°C], *t* [h]	Electrophile	Product/Yield [%][a]
				
1	**13a**	25, 1		**15d**: 82[c]
				
2	**13b**	0, 5		**15e**: 81[c]
			PhCOCl	
3	**13d**	–20, 1		**15f**: 77[b]
				
4	**13e**	–30, 3		**15g**: 70[c]
			$(BrCl_2C)_2$	
5	**13f**	–40, 3		**15h**: 70
				
6	**13f**	–40, 3		**15i**: 73[c]
			I_2	
7	**13g**	–40,12		**15j**: 66

[a]Isolated yield of analytically pure product; [b] A transmetalation with CuCN·2LiCl (20 mol%) was performed; [c]Obtained by palladium-catalyzed cross-coupling after transmetalation with $ZnCl_2$ (1.2 to 1.3 equiv).

The metalating power of **14a** was used in the short synthesis of 6-hexylsalicylic acid (**16d**), a natural product, found in the extract of *Pelargonium sidoides DC*.[48] In the first step, the acetonide **16a** was magnesiated with **14a** at –40 °C within 10 min. The arylmagnesium compound **16b** was then transmetalated with $ZnCl_2$ and subsequently used in a cross-coupling reaction[45, 46] with the iodo alkene **17** leading to the functionalized arene **16c** in 77% yield. The final product **16d** was obtained after hydrogenation of the double bond in the presence of catalytic amounts of Pd/C followed by the cleavage of the acetonide, furnishing 6-

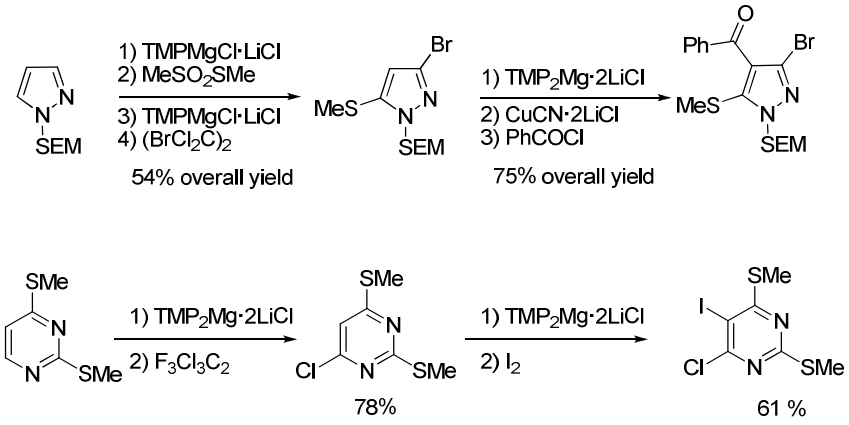
[48] a) O. Kayser, K. Lattè, H. Kolodziej, F.-J. Hammerschmidt, *Flavour Fragrance J.* **1998**, *13*, 209.

hexylsalicylic acid in 89% yield (Scheme 25).[49]



Scheme 25: Synthesis of 6-hexylsalicylic acid (**16d**).

The base **14a** was also used, to bypass problems in the synthesis of fully functionalized pyrrazoles.[50] The metalations on position C3 and C5 were readily performed using TMPMgCl·LiCl (**10a**) whereas the remaining C4 position proved to be inert to this base, TMP_2Mg·2LiCl had to be used to achieve the functionalization of this site. Similarly, the full functionalization of 2,4-bis(methyl)thio pyrimidine was only possible when using the highly active base TMP_2Mg·2LiCl (**14a**) (Scheme 26).[51]



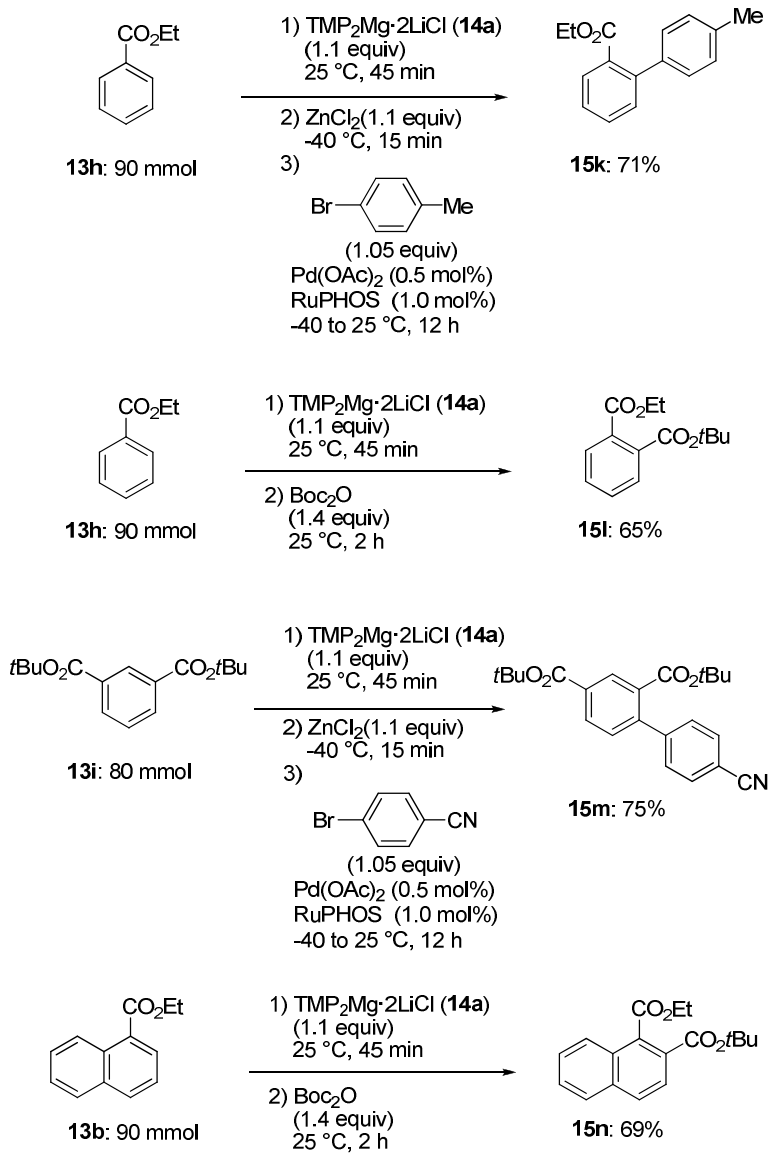
Scheme 26: Functionalizations of *N*-heterocycles using TMP_2Mg·2LiCl.

[49] Experments were done by G. C. Clososki and are given here for the sake of completeness.
[50] C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.
[51] M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237.

3.2. Scale-up Experiments

The above described experiments were mainly conducted on small scale (up to 2 mmol). To demonstrate that the reagent **14a** is able to provide the magnesiated arenes even on larger scale in a satisfying yield some scale-up experiments were conducted. The base **14a** was prepared as usual and the substrate was added direcly into the solution omitting additional solvent for economic and kinetic reasons. Thus, ethyl benzoate **13h** was reacted with **14a** at 25 °C giving the magnesiated species after 45 min. After a transmetalation using $ZnCl_2$ in THF, a *Negishi* cross-coupling reaction with 4-bromotoluene in the presence of $Pd(OAc)_2$ (0.5 mol%) and RuPHOS (1.0 mol%)[52] was performed and gave the biphenyl **15k** in 71% yield. The introduction of an additional ester was achieved by reacting the magnesiated ethyl benzoate with Boc_2O, yielding the diester **15l** in 65% (Scheme 27).

[52] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028.



Scheme 27: Scale-up Experiments using $TMP_2Mg·2LiCl$.

Furthermore, the magnesiation of di-*tert*-butyl isophthalate (**13i**) using $TMP_2Mg·2LiCl$ (**14a**; 1.1 equiv) was complete within 45 min at 25 °C (compared to 1 h for 2 mmol scale). Subsequently, after transmetalation with $ZnCl_2$ (90 mL, 1.1 equiv) a Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (1.0 equiv) using $Pd(OAc)_2$ (0.5 mol%) and RuPHOS (1.0 mol%)[52] as catalytic system provided the functionalized biaryl **15m** in 75% yield. Additionally, the complete metalation of ethyl 1-naphthoate (**13b**; 18.0 g) was obtained within 45 min at 25 °C using $TMP_2Mg·2LiCl$ (**14a** compared to 1 h for 2 mmol scale reactions) by applying this large scale protocol. After quenching with Boc_2O (1.4 equiv), the desired mixed diester **15h** was isolated in 69% yield (Scheme 27). For economic reasons the recycling of TMPH was examined as it is used in large quantities in these reactions. A slightly

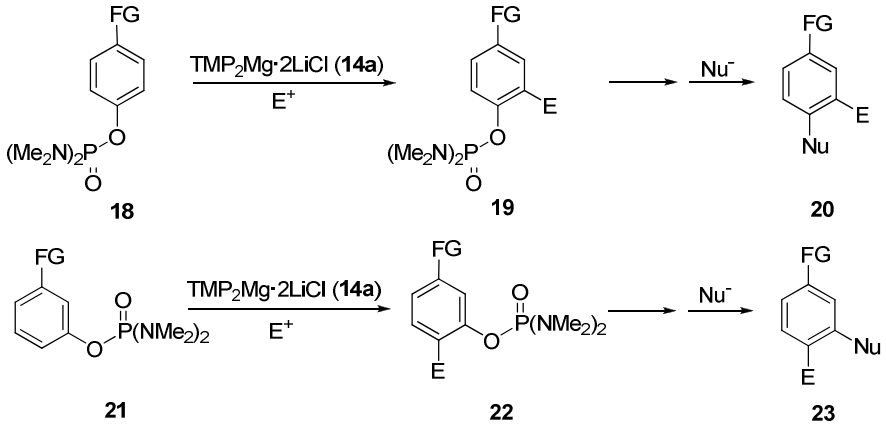
modfied workup allows the recovery of up to 75% of the TMP-H used.

3.3. Formal *meta*- and *para*-Functionalizations

As shown above, the directed *ortho* metalation is an important method for the functionalization of various arenes and heterocycles. Various directed-metalation groups (DMGs) have been used for achieving efficient lithiations. DMGs mediate fast and *ortho* selective metalation mainly by chelation (entropic effect). Polar DMGs may furthermore transfer electron density to the metal base and increase their metalating power.[35] During the studies on TMP_2Mg·2LiCl (**14a**) (see preceeding chapter) the demand for a new, stable protecting group for phenols, which is at the same time a DMG, arose. In the course of these studies, it was observed that the DMG *N*,*N*,*N'*,*N'*-tetramethylphosphorodiamidate ($OP(O)(NMe_2)_2$)[53] is a very strong directing group for magnesiation and that it may overrule the effects of other directing substituents present on the aromatic substrate. In contrast to directed lithiations which are usually performed at –105 °C to avoid Fries-type rearrangements,[53] the magnesiation with TMP_2Mg·2LiCl (**14a**) occurs (even at 0 °C) without anionic migration of the tetramethylphosphorodiamidate group. This would allow new types of functionalization such as formal *meta*-[54] or *para*-functionalization (Scheme 28).

[53] a) M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki, S. Furukawa, *Chem. Pharm. Bull.* **1989**, *37*, 2564; b) R. E. Ireland, D. C. Muchmore, U. Hengartner, *J. Am. Chem. Soc.* **1972**, *94*, 5098; c) D. Seebach, J.-J. Lohmann, M. A. Syfrig, M. Yoshifuji, *Tetrahedron* **1983**, *39*, 1963; d) J. H. Näsman, N. Kopola, G. Pensar, *Tetrahedron Lett.* **1986**, *27*, 1391; e) M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki, S. Furukawa, *Chem. Pharm. Bull.* **1990**, *37*, 2637; e) M. P. Sibi, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1935; f) O. Middel, Z. Greff, N. J. Taylor, W. Verboom, D. N. Reinhoudt, V. Snieckus, *J. Org. Chem.* **2000**, *65*, 667.

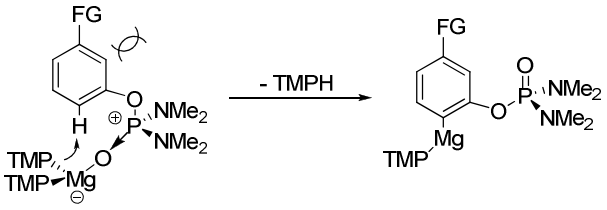
[54] a) P. C. Andrikopoulos, D. R. Armstrong, D. V. Graham, E. Hevia, A. R. Kennedy, R. E. Mulvey, C. T. O' Hara, C. Talmard, *Angew. Chem. Int. Ed.* **2005**, *44*, 3459; b) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G.W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 3775.



Scheme 28: Formal *meta*- and *para*-functionylization of arenes.

It was found that a range of aromatic phosphorodiamidates bearing a functional group (FG) either in the *para* position (type **18**) or in the *meta* position (type **21**) underwent efficient magnesiation with $TMP_2Mg{\cdot}2LiCl$ (**14a**) leading to products of type **19** and **22**, respectively, after the addition of an electrophile. Substitution of the $OP(O)(NMe_2)_2$ group with a nucleophile (Nu) should then yield *meta*, *para*- and *para*, *meta*-difunctionalized molecules of the type **20** and **23** as described below (Scheme 28 and Table 2). The magnesiation of substrates of type **18** and **21** using $TMP_2Mg{\cdot}2LiCl$ (**14a**) proceeds smoothly within a few hours at 0 °C for cyano- and ester-substituted phosphorodiamidates **18a** and **21a** (entries 1-3, 10-13). For halogen-substituted starting materials (**18b**, **3c** and **18d**; entries 4-9) as well as for the trifluoromethyl-substituted phosphorodiamidate **21b** (entry 13), lower temperatures (–40 to –50 °C) led to optimum results. In general, the regioselectivity of the metalation of aromatics is governed by a combination of electronic and/or sterical effects.[25, 35] However, the tetramethylphosphorodiamidate group is one of the strongest donor in organic synthesis[55] and kinetically activates the Mg-N bond giving to the base an additional ate character (Scheme 29).[25, 56]

[55] a) C. A. Hunter, *Angew. Chem. Int. Ed.* **2004**, *43*, 5310; b) C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, **2002**.
[56] a) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333; b) J. Kondo, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem. Int. Ed.* **2001**, *40*, 2085.



Scheme 29: Sugested mechanism of the *meta*- and *para*-metalation.

This electronic effect increases the metalation power of the base and no additional chelation or inductive effects are necessary for achieving the magnesiation. Normally, this phosphorodiamidate-triggered magnesiation preferentially occur at the sterically less hindered position of the aromatic ring promoting formal *meta*-metalation. However, in the case of *meta*-substituted substrates bearing bromo, chloro and fluoro atoms as one of the functional groups, it was observed that the regioselectivity of the metalation is affected[57] by the competitive directing effects of these halogens. Various electrophiles such as acid chlorides, TsCN, allylic halides, aldehydes or aromatic iodides reacted with the magnesium organometallic intermediates providing the desired products of type **19** or **22** in 72 to 90% yields (Table 2). In the case of allylation and acylation reactions, the best results were obtained when the arylmagnesium species were transmetalated with $ZnCl_2$ (1.2 equiv) and CuCN·2LiCl[47] (0.5 – 1.3 equiv) prior to the addition of the acid chloride, TsCN or the allylic halide (entries 2-4, 7, 8 and 12). Similarly, *Negishi* cross-couplings[45] with aryl iodides in the presence of $Pd(dba)_2$ (2 mol%) and P(2-furyl)$_3$ (4 mol%)[46] were successfully performed after transmetalation of the *Grignard*-reagents with $ZnCl_2$ (entries 1, 5, 6 and 13). The phosphorodiamidate **21c** derived from 3-iodophenol was smoothly magnesiated within 0.5 h at 0 °C without the occurence of halogen dance reactions. Bromolysis of the Mg-reagent gave the double halogenated arene **22e** in 76% yield (entry 14).

[57] Magnesiation of the phosphorodiamidate prepared from 3-bromophenol gave after iodolysis a mixture of 5-bromo-2-iodophenyl- (44% yield) and 3-bromo-2-iodophenyl-*N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (43% yield). For the 3-chlorophenolderivative, a mixture of 5-chloro-2-iodophenyl- (29% yield) and 3-chloro-2-iodophenyl-*N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (57% yield) was obtained. Moreover, metalation of the 3-fluorophenol derivative gave exclusively after iodolysis the 3-fluoro-2-iodophenyl-*N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate in 73% yield.

Table 2: Products of Type **19** or **22** obtained after Magnesiation with $TMP_2Mg{\cdot}2LiCl$ (**14a**) and Subsequent Reaction with an Electrophile.

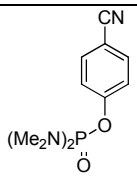
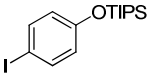
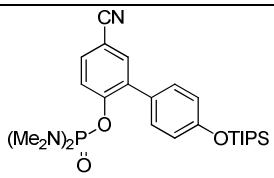
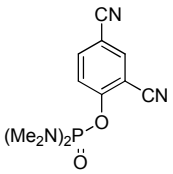
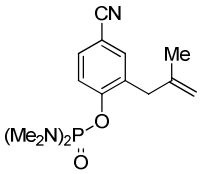
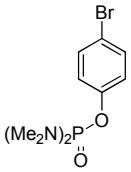
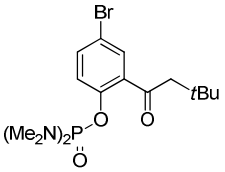
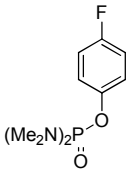
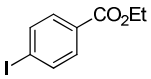
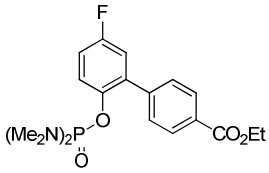
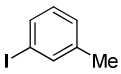
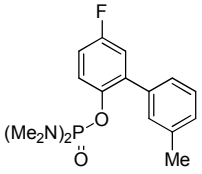
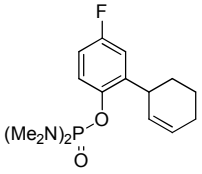
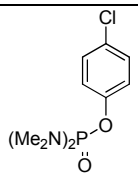
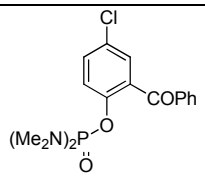
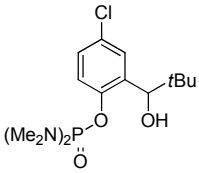
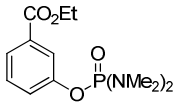
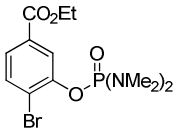
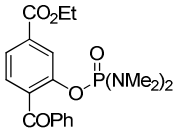
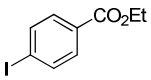
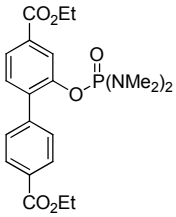
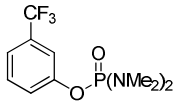
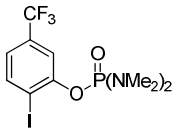
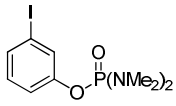
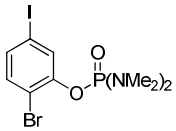
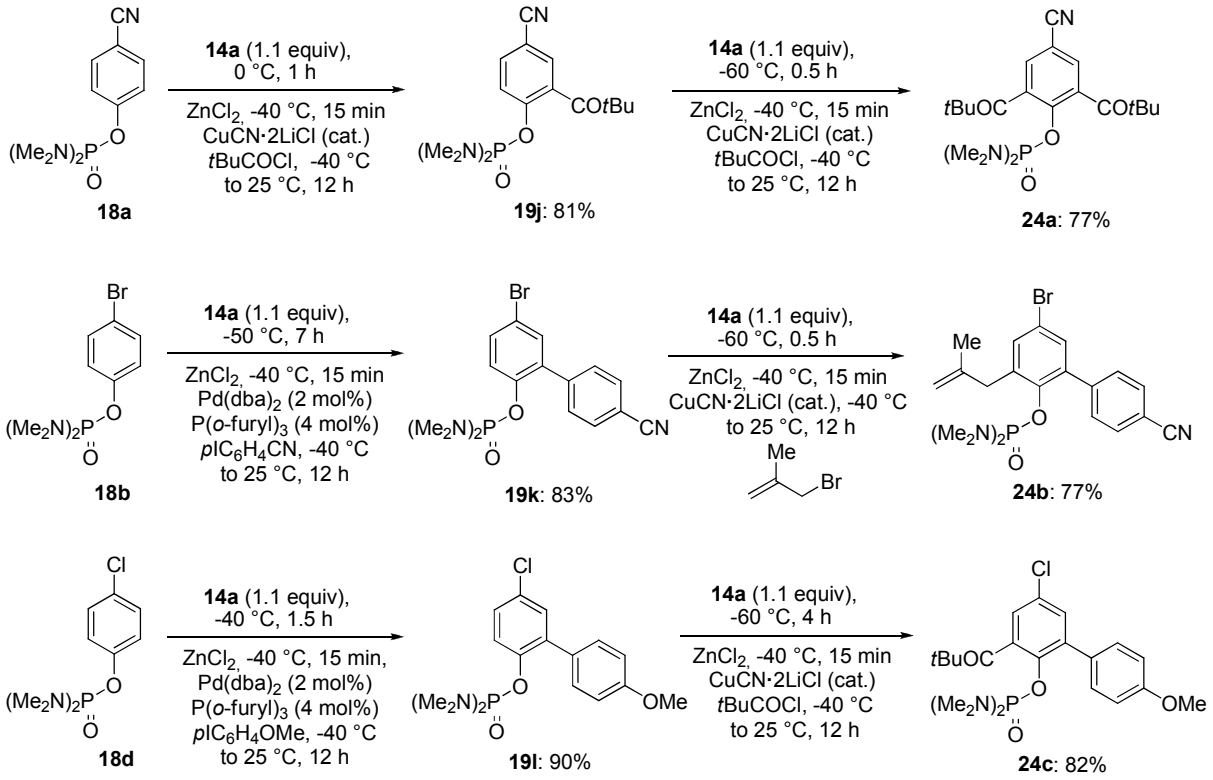
Entry	Substrate	*T* [℃], *t* [h]	Electrophile	Product/Yield [%][a]
				
1	**18a**	0, 1		**19a:** 83[c]
			TsCN	
2	**18a**	0, 1		**19b:** 77
				
3	**18a**	0, 1		**19c**: 84[b]
			$tBuCH_2COCl$	
4	**18b**	–50, 7		**19d**: 72[b]
				
5	**18c**	–40, 4		**19e**: 78[c]
				
6	**18c**	–40, 4		**19f:** 75[c]
				
7	**18c**	–40, 4		**19g**: 85[b]

Table 2 (continued)

Entry	Substrate	*T* [°C], *t* [h]	Electrophile	Product/Yield [%][a]
			PhCOCl	
8	**18d**	–40, 1.5		**19h:** 85[b]
			*t*BuCHO	
9	**18d**	–40, 1.5		**19i**: 79
			$(BrCl_2C)_2$	
10	**21a**	0, 1		**22a**: 80
			PhCOCl	
11	**21a**	0, 1		**22b**: 73[b]
				
12	**21a**	0, 1		**22c**: 78[c]
			I_2	
13	**21b**	–40, 2		**22d**: 88
			$(BrCl_2C)_2$	
14	**21c**	0, 0.5		**22e**: 76

[a] Isolated yield of analytically pure product; [b] A transmetalation with $ZnCl_2$ (1.1 equiv) and CuCN·2LiCl (0.5 - 1.3 equiv) was performed; [c] Obtained by a palladium-catalyzed cross-coupling after transmetalation with $ZnCl_2$ (1.1 equiv).

A double functionalization in *meta*, *meta'*-positions has also been achieved. Thus, the treatment of the nitrile **18a** with TMP_2Mg·2LiCl (**14a**; 1.1 equiv, 0 °C, 4 h) followed by a copper(I)-catalyzed reaction[47] with *t*BuCOCl provided the ketone **19j** in 81% yield. By applying the same reaction sequence (metalation at –60 °C for 0.5 h), the ketone **19j** was converted to the diketone **24a** in 77% yield.

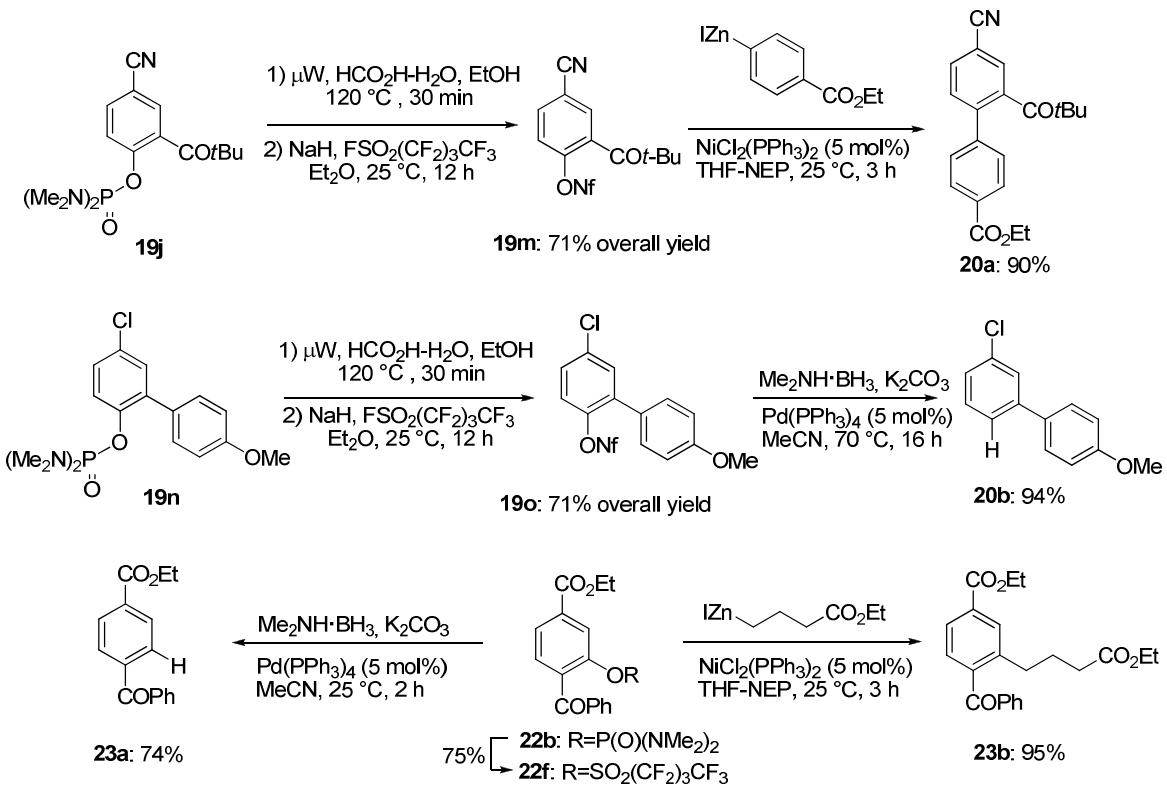


Scheme 30: *meta, meta'*-functionalization.

Furthermore, the double functionalization of the bromo- and chloro-substituted phosphorodiamidates **18b** and **18d** led to the preparation of the highly functionalized phosphorodiamidates **24b** and **24c** in good overall yields showing the high directing power of the $OP(O)(NMe_2)_2$ group (Scheme 30).

The further manipulation of the functionalized aryl phosphorodiamidates of type **19** and **22** was best achieved by converting these intermediates into nonaflates.[58]

[58] a) M. Piber, A. E. Jensen, M. Rottländer, P. Knochel, *Org. Lett.* **1999**, *1*, 1323; b) M. Rottländer, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203; c) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Tetrahedron* **2006**, *62*, 7521; for a recent application of aryl nonaflates in palladium-catalyzed amination reactions see: d) R. E. Tundel, K.W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2006**, *71*, 430; e) K.W. Anderson, M. Mendez-Perez, J. Priego, S. L. Buchwald, *J. Org. Chem.* **2003**, *68*, 9563.



Scheme 31: Replacement of the DMG and further functionalization.

Thus, a microwave assisted deprotection of the aryl phosphorodiamidates **19j** and **19n** with formic acid in aqueous ethanol (120 °C, 30 min) provided polyfunctional phenols, which after the reaction with $C_4F_9SO_2F$ (NaH, Et_2O, 25 °C, 12 h) allowed the isolation of the corresponding nonaflates **19m** and **19o** in 71% yield (Scheme 31). A nickel-catalyzed cross-coupling of nonaflate **19m** with an arylzinc reagent afforded the biphenyl **20a** in 90% yield. On the other hand, reaction of **19o** with dimethylamine-borane complex in the presence of catalytic amount of $Pd(PPh_3)_4$[59] gave the reduced derivative **20b** in 94% yield. Similarly, the aryl phosphorodiamidate **22b** was successfully converted to the diester **23a** and to the ketoester **23b** in 74% and 95% yield respectively, showing that this reaction sequence allows either efficient functionalization or removal of the directing metalation group (Scheme 31).[49]

[59] a) B. H. Lipshutz, D. J. Buzard, R.W. Vivian, *Tetrahedron Lett.* **1999**, *40*, 6871; for a recent protocol for the reduction of aryl sulfonates see: b) B. H. Lipshutz, B. A. Frieman, T. Butler, V. Kogan, *Angew. Chem. Int. Ed.* **2006**, *45*, 800.

3.4. Regioselective Metalations on *N*-Heterocycles

3.4.1. Metalations on Pyridines, Quinolines and Quinoxalines

Heteroaromatics are important scaffolds in medicinal chemistry.[60] Especially skeletons of quinolines, pyridines and quinoxalines are often found in modern pharmaceuticals such as the quinoline based NK_3 receptor antagonist Talnetant[61] (**25**; GSK), the pyridine based COX-2 inhibitor Etoricoxib[62] (**26**; Arcoxia®, Merck) or the quinoxaline based tachykinin receptor antagonist[63] (**27**; Mitsubishi Tanabe Pharma) (Figure 1).

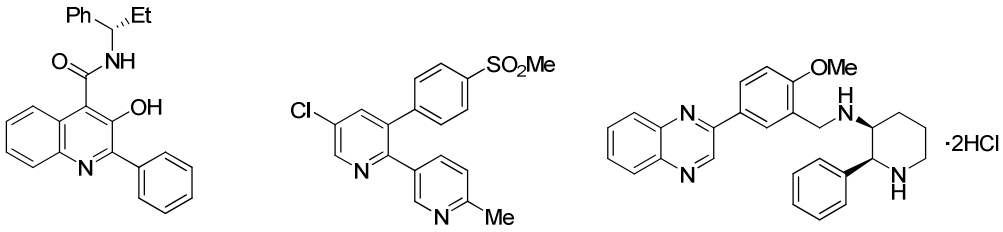


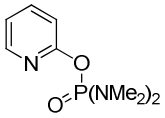
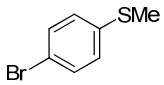
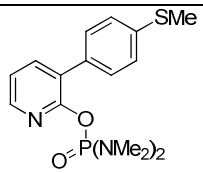
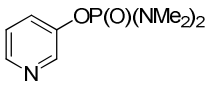
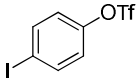
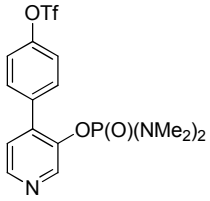
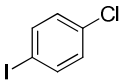
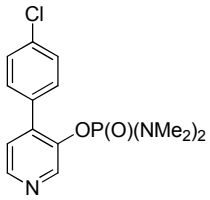
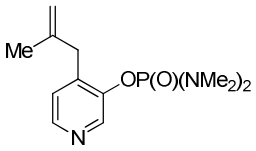
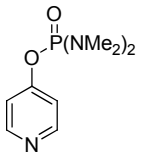
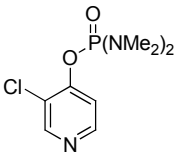
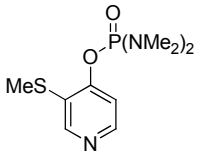
Figure 1: Pharmaceuticals containing a quinoline, pyridine or quinoxaline skeleton.

Lithiations and magnesiations of these scaffolds using either halogen/metal exchange[64] or directed metalation[65] have been reported. Lithiations suffer from a lack of regioselectivity even when carried out at low temperatures (see chapter 3). The formed organometallic reagents are also prone to undergo electrophilic subtitution reactions at the C2 position. Recently, it was reported that the use of TMP derived bases allow the efficient magnesiation or zincation (see chapter 1.4.2. & 3.1) of functionalized aromatics and heteroaromatics. It has

[59] a) A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, *Heterocycles in Life and Society*; John Wiley & Sons: Weinheim, 1997; b) P. Wipf, Z. Wang, *Org. Lett.* **2007**, *9*, 1605.
[61] a) G. A. M. Giardina, L. F. Raveglia, M. Grugni, H. M. Sarau, C. Farina, A. D. Mendhurst, D. Graziani, D. B. Schmidt, R. Rigolio, M. Luttmann, S. Cavagnera, J. J. Foley, V. Vecchietti, D. W. P. Hay, *J. Med. Chem.* **1999**, *42*, 1053; b) J. M. Elliot, R. W. Carling, M. Chambers, G. C. Chicchi, P. H. Hutson, B. A. Jones, A. MacLeod, R. Marwood, G. Meneses-Lorente, E. Mezzogori, F. Murray, M. Rigby, I. Royo, M. G. N. Russel, B. Sohal, K. L. Tsao, B. Williams, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5748.
[61] a) L. A. Sorbera, R. M. Castaner, J. Silvestre, J. Castaner, *Drugs Fut.* **2001**, *26*, 346; b) R. W. Firesen, C. Brideau, C. C. Chan, S. Charleson, D. Deschênes D. Dubé, D. Eithier, R. Fortin, J. Y. Gauthier, Y. Girard, R. Gordon, G. M. Greig, D. Riendeau, C. Savoie, Z. Wang, E. Wong, D. Visco, L. J. Xu, R. N. Young, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2777; c) D. Dubé, C. Brideau, D. Deschênes, R. Fortin, R. W. Friesen, R. Gordon, Y. Girard, D. Riendeau, C. Savoie, C.-C. Chan, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1715.
[63] M. Takahashi, M. Sugahara, H. Mizuuchi, A. Saito, T. Ishii, PCT Int. Appl. 2002028853 A1, 2002.
[64] a) D. L. Comins, J. M. I. Nolan, D. Bori, *Tetrahedron Lett.* **2005**, *46*, 6697; b) S. Dumouchel, F. Mongin, F. Trécourt, G. Quéguiner, *Tetrahedron Lett.* **2003**, *44*, 2033; c) H. Ren, P. Knochel, *Chem. Comm.* **2006**, 726 and references therein.
[65] For reviews, see: a) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; b) F. Chevallier, F. Mongin, *Chem Soc. Rev.* **2008**, *37*, 595.

also been investigated that the use of the *N,N,N',N'*-tetramethylphosphorodiamidate group is a strong DMG and allows fast and selective magnesiations of aromatics with unusual regioselectivity (see preceeding chapter). The metalations of pyridines, quinolines and quinoxalines using TMPMgCl·LiCl (**10a**), TMP_2Mg·2LiCl (**14a**) and TMP_2Zn·$2MgCl_2$·2LiCl (**12a**) combined with the -$P(O)(NMe_2)_2$ DMG has also been studied. Thus, the phosphorodiamidate **28a** (derived from 2-pyridinol) reacted with TMPMgCl·LiCl (**10a**) at 0 °C within 1 h and gave exclusively the 3-magnesiated heterocycle which reacted after transmetalation to zinc in a *Negishi* cross-coupling reaction in the presence of $Pd_2(dba)_3$ (1 mol%) and RuPHOS (2 mol%)[52] with 4-bromo thiomethylbenzene giving the biaryl **29a** in 74% yield (Table 3, entry 1). The phosphorodiamidate **28b** synthesized from 3-hydroxy pyridine was best metalated at 25 °C using **12a**. Deprotonations with TMPMgCl·LiCl (**10a**) or TMP_2Mg·2LiCl (**14a**) resulted in lower yields, even when carried out at low temperatures (–20 to –50 °C). Thus, the pyridine **28b** was zincated selectively in position 4 at 25 °C within 1 h using TMP_2Zn·$2MgCl_2$·2LiCl (**12a**). The formed zinc reagent was quenched in a cross-coupling reaction using either 4-iodophenyl triflate or 4-chloro iodobenzene with a Pd-catalyst yielding the 4-arylated pyridines **29b** and **29c** in 79-88% yield (entries 2, 3; see appendix for a x-ray structure of **29b**). An allylation of the zinc reagent was achieved with 3-bromo-2-methylpropene in in the presence of CuCN·2LiCl (10 mol%)[47] furnishing the allylated pyridine **29d** in 74% yield (entry 4). Moreover, a chlorination in position 3 was obtained by metalating the pyridine **28c** using **10a** (0 °C, 1 h). After addtition of 1,1,2-trichlorotrifluoro ethane, the desired 3-chloro pyridine **29e** was isolated in 83% yield (entry 5). The magnesium reagent also reacted with *S*-methyl methanesulfothionate and gave the thioether **29f** in 88% yield (entry 6).

Table 3: Pyridines of type **29** obtained after metalation with TMPMgCl·LiCl (**10a**) or $TMP_2Zn·2MgCl_2·2LiCl$ (**12a**) and subsequent reaction with an electrophile.

Entry	Substrate	*T* [℃] , *t* [h]	E^+	Product/Yield [%][a]
				
1	**28a**	0, 1		**29a**: 74[b, d]
				
2	**28b**	25, 1		**29b**: 88[c, e]
				
3	**28b**	25, 1		**29c**: 79[c, e]
				
4	**28b**	25, 1		**29d**: 74[c, f]
			$C_2Cl_3F_3$	
5	**28c**	0, 1		**29e**: 83[b]
			$MeSSO_2Me$	
6	**28c**	0, 1		**29f**: 88[b]

[a]Yield of isolated, analytically pure product; [b]TMPMgCl·LiCl (1.5 equiv) was used; [c]$TMP_2Zn·2MgCl·2LiCl$ (0.75 equiv) was used; [d]Obtained by Pd-catalyzed cross-coupling reaction after transmetalation with $ZnCl_2$ (1.6 equiv) using $Pd_2(dba)_3$ (1 mol%) and RuPHOS (2 mol%) as catalyst; [e]Obtained by Pd-catalyzed cross-coupling reaction using $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%) as catalyst; [f]A transmetalation with CuCN·2LiCl (10 mol%) was performed.

Furthermore, the phosphorodiamidate **30a** derived from 2-hydroxyquinoline was magnesiated regioselectively in position 3 and then thioethylated with $EtSSO_2Ph$[66] yielding the thioether

[66] A. H. Stoll, A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 606.

31a in 85% (Table 4, entry 1). Remarkably, magnesiations at the 3 position of the quinoline *without* abstracting the kinetically more active proton at the C2 position were also possible. Thus, the quinoline **30b** was smoothly deprotonated with TMPMgCl·LiCl (**10a**) at 0 °C within 1 h. The generated magnesium reagent was then transmetalated with $ZnCl_2$ and subsequently used in an acylation reaction with pivaloyl chloride in the presence of CuCN·2LiCl (10 mol%)[47] giving the heteroaromatic ketone **31b** in 62 % yield (entry 2). A cross-coupling reaction with the Zn-reagent derived from **30b** with ethyl 4-iodobenzoate in the presence of a Pd-catalyst furnished the 3-arylated quinoline **31c** in 83% yield (entry 3). Moreover, the regioselective functionalization of the C7 was possible using this protocol. Thus, the 2-chloroquinoline derivative **30c** was readily magnesiated with TMPMgCl·LiCl (**10a**) at 0 °C in 1 h. A transmetalation with $ZnCl_2$ in THF followed by the addition of methallyl bromide in the presence of CuCN·2LiCl (10 mol%)[47] led to the allylated product **31d** in 87% yield (entry 4). The addition of 4-chloro benzoyl chloride under the same conditions furnished the ketone **31e** in 74% yield (entry 5). The 2-bromoquinoline **30d** also underwent a smooth magnesiation at 0 °C with the base **10a**. After transmetalation to zinc, a cross-coupling reaction with the (4-iodophenoxy)(triisopropyl)silane in the presence of $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%)[45, 46] led to the phenylated bromoquinoline **31f** in 81% yield (entry 6). The introduction of an ethyl ester in position 7 was achieved by reacting the magnesiated quinoline derivative **30d** with NC-CO_2Et leading to the ester **31g** in 77% yield (entry 7). Magnesiations or lithiations on quinoxalines are often difficult to achieve due to the electrophilic character of this substrate, leading to competetive dimerizations.[65] However, the quinoxaline **30e** bearing a phosphorodiamidate group as DMG, was smoothly magnesiated with TMP_2Mg·2LiCl (**14a**) at –30 °C in 1.5 h without any dimerization side reaction. After a transmetalation with $ZnCl_2$ it reacted in a *Negishi* reaction in the presence of a Pd-catalyst with either 4-chloro iodobenzene or ethyl 4-iodobenzoate leading to the 2-arylated quinoxalines **31h** and **31i** in up to 79% yield (Table 2, entries 8, 9). Treatment of the zinc compound with methallyl bromide in the presence of CuCN·2LiCl (10 mol%) furnished the allylated quinoxaline **31j** in 71% yield (entry 10).

Table 4: Quinolines and quinoxalines of type **31** obtained after magnesiation with TMPMgCl·LiCl (**10a**) or TMP_2Mg·2LiCl (**14a**) and subsequent reaction with an electrophile.

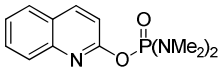
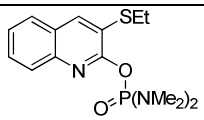
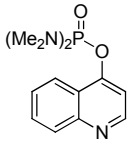
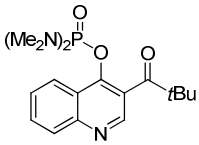
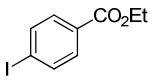
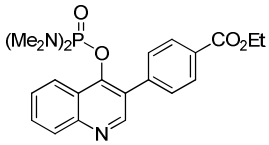
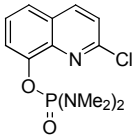
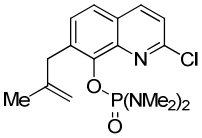
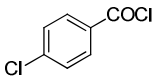
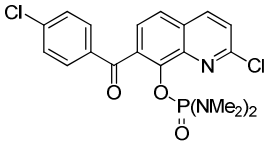
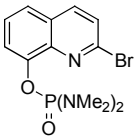
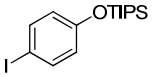
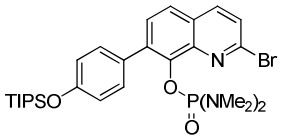
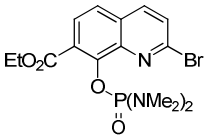
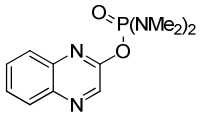
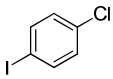
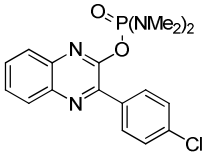
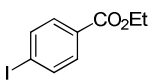
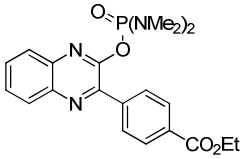
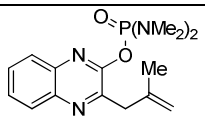
Entry	Substrate	*T* [°C] , *t* [h]	E^+	Product/Yield [%][a]
			$EtSSO_2Ph$	
1	**30a**	0, 1		**31a**: 85[b]
			*t*BuCOCl	
2	**30b**	0, 1		**31b**: 62[b, d]
				
3	**30b**	0, 1		**31c**: 83[b, e]
				
4	**30c**	0, 1		**31d**: 87[b, d]
				
5	**30c**	0, 1		**31e**: 74[b, d]
				
6	**30d**	0, 1		**31f**: 81[b, e]
			$NC\text{-}CO_2Et$	
7	**30d**	0, 1		**31g**: 77[b]
				
8	**30e**	–30, 1.5		**31h**: 78[d, e]
				
9	**30e**	–30, 1.5		**31i**: 79[d, e]

Table 4 (continued)

Entry	Substrate	*T* [°C] , *t* [h]	E^+	Product/Yield [%][a]
10	**30e**	–30, 1.5		 **31j**: 71[c, d]

[a]Yield of isolated, analytically pure product; [b]TMPMgCl·LiCl (1.5 equiv) was used; [c]TMP_2Mg·2LiCl (1.5 equiv) was used; [d] A transmetalation with CuCN·2LiCl (10 mol%) was performed after transmetalation with $ZnCl_2$ (1.6 equiv.); [e]Obtained by Pd-catalyzed cross-coupling reaction after transmetalation with $ZnCl_2$ (1.6 equiv) using $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%) as catalyst.

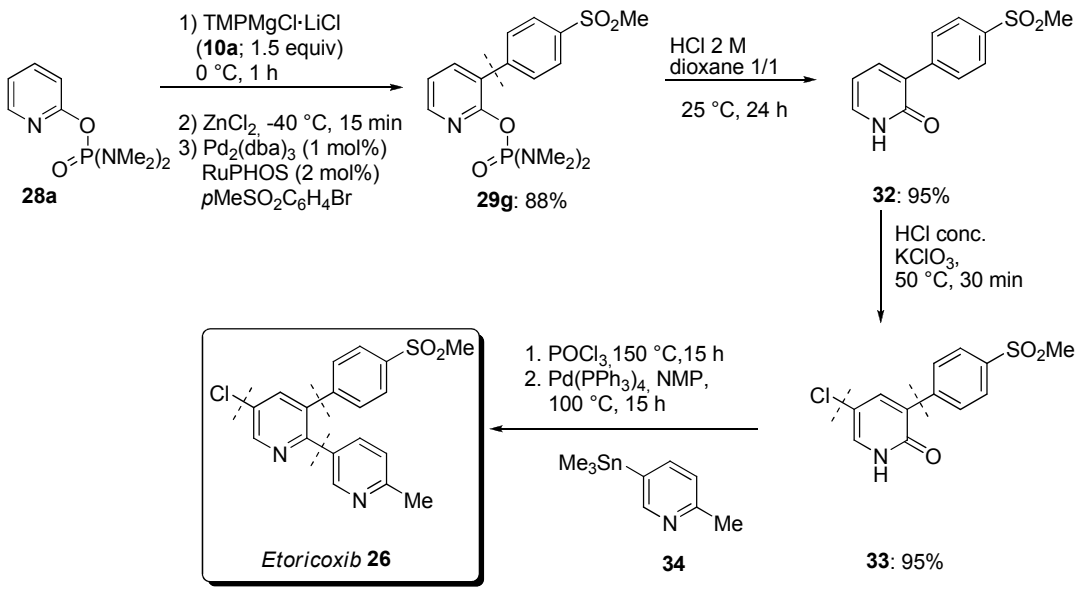
3.4.2. Synthesis of Talnetant, Etoricoxib and a P-Selectin Antagonist

Using this method, the pharmaceutically relevant compounds Etoricoxib, Talnetant and a P-Selectin[67] antagonist were prepared. In this synthesis, the phosphorodiamidate DMG was first attached at commercially available 2-pyridinol giving **28a**. In a second step, **28a** was selectively metalated in the 3-position using **10a** (1.5 equiv, 0 °C, 1 h). After a transmetalation with $ZnCl_2$ a cross-coupling reaction with 4-bromophenyl methylsulfone in the presence of $Pd_2(dba)_3$ (1 mol%) and RuPHOS (2 mol%)[52] gave the arylated pyridine **29g** in 88% yield. Cleavage of the directing group with a HCl/dioxane mixture[68] (25 °C, 24 h) gave back the pyridone backbone **32** in 95% yield. Chlorination at C5 position was accomplished by reacting **32** with $KClO_3$ in the presence of HCl (conc.)[69] furnishing the 5-chloropyridine **33** quantitatively. The final product was assembled applying a literature procedure. Thus, the reaction of the pyridone with $POCl_3$ gave the 2,5-dichloro pyridine which was subsequently used in a Stille cross-coupling with the tin reagent **34** derived from 5-bromo 2-picoline furnishing *Etoricoxib* **26** (Scheme 32).

[67] a) N. Kaila, K. Janz, S. DeBernardo, P. W Bedard, R. Camphausen, S. Tam, D. H. H. Tsao, J. C. Keith, C. Nickerson-Nutter, A. Shilling, R. Young-Sicame, Q. Wang, *J. Med. Chem.* **2007**, *50*, 21; b) N. Kaila, K. Janz, A. Huang, A. Moretto, S. DeBernardo, P. W. Bedard, S. Tam, V. Clerin, J. C. Keith, D. H. H. Tsao, N. Shushkova, G. D. Shaw, R. Camphausen, R. G. Schaub, Q. Wang, *J. Med. Chem.* **2007**, *50*, 40.

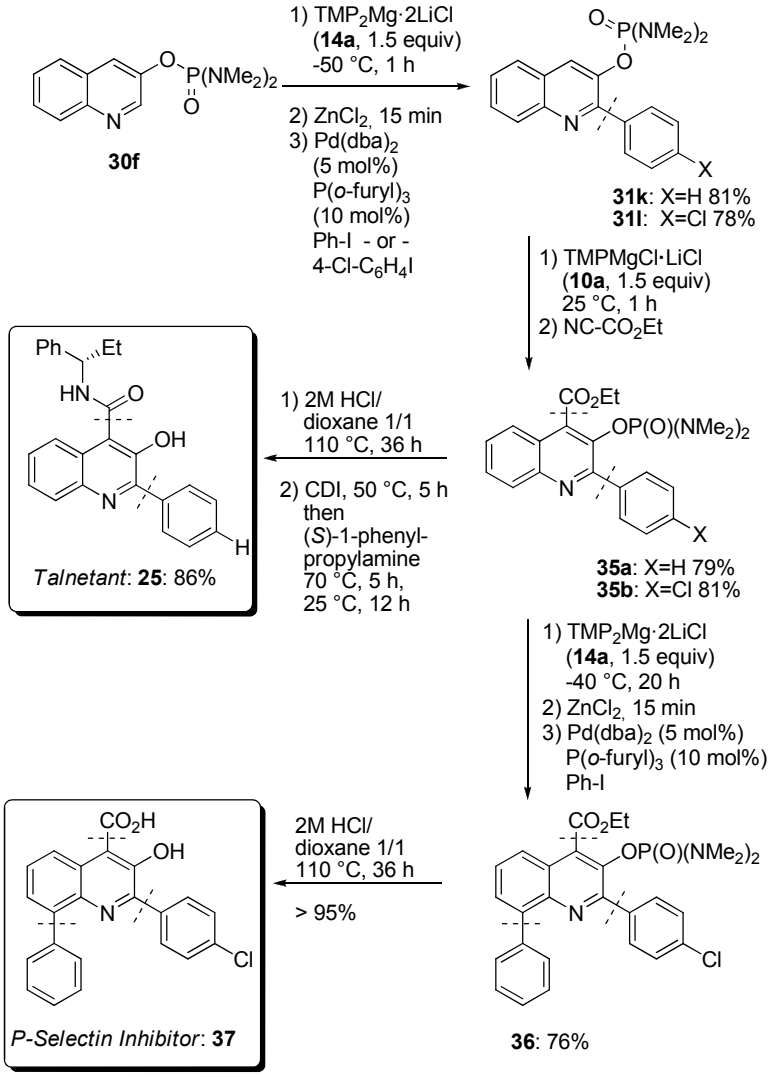
[68] H.-G. Chao, B. Leitning, P. D. Reiss, A. L. Burkhardt, C. E. Klimas, J. B. Bolen, G. R. Matsueda, *J. Org. Chem.* **1995**, *60*, 7710.

[69] V. Koch, S. Schnatterer, *Synthesis*, **1990**, 499.



Scheme 32: Synthesis of Etoricoxib (**26**).

The combined use of the phosphorodiamidate and the bases TMPMgCl·LiCl (**10a**), TMP_2Mg·2LiCl (**14a**) was also applied to build up two pharmaceuticals with a quinoline salicylic acid spine. Accordingly, the lynchpin for both syntheses is 3-hydroxy quinoline which was first converted into the corresponding phosphorodiamidate **30f**. The metalation with TMP_2Mg·2LiCl (**14a**) occured at the C2 position (–50 °C, 1 h). Transmetalation with $ZnCl_2$, followed by a cross-coupling[45] with either iodobenzene or 4-chloro iodobenzene in the presence of a Pd-catalyst[46] furnished the quinolines **31k**,**l** in up to 81% yield. A subsequent metalation at the C4 position was obtained using TMPMgCl·LiCl (**10a**, 25 °C, 1 h). The Mg-reagent was quenched with NC-CO_2Et and gave the desired esters **35a**,**b** in 79 and 81% yield, respectively (see appendix for a x-ray structure of **35a**). Cleavage of both, the DMG and the ester was achieved by refluxing **35a** in a HCl/dioxane mixture[68] (110 °C, 36 h). The acid was then reacted with (*S*)-phenylpropylamine and CDI providing *Talnetant* (**25**) in 86% yield (Scheme 33, see appendix for a x-ray structure). For the synthesis of the P-Selectin antagonist **38** a third metalation for the arylation of the C8 position of **35b** is performed using **14a** (–40 °C, 20 h).[31] After a transmetalation with $ZnCl_2$ a cross coupling[45] reaction with iodobenzene in the presence of $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%)[46] was performed, yielding the highly functionalized quinoline **36** in 76%. Combined deprotection/saponification was again achieved by refluxing **36** in a HCl dioxane mixture (110 °C, 36 h)[68] leading to the P-Selectin Inhibitor **37** quantitatively (Scheme 33).



Scheme 33: Synthesis of Talnetant and a P-selectin inhibitor.

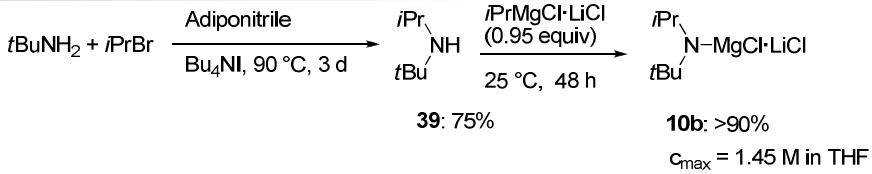
3.5. Alternative Amines for the Preparation of Mixed Li/Mg and Li/Mg/Zn-amide Bases

3.5.1. Preparation and use of the Reagent [*t*Bu(*i*Pr)N]MgCl·LiCl (10b)

During the development of $TMP_2Mg{\cdot}2LiCl$ (**14a**) the reaction behavior of several sterically demanding amines was studied (Scheme 34). It turned out that $[t\text{Bu}(i\text{Pr})\text{N}]_2\text{Mg}{\cdot}2\text{LiCl}$ (**14c**) leads to comparable results concerning activity and isolated yields (see chapter 3.). The used sterically hindered acyclic *tert*-butyl(*iso*-propyl)amine is therefore a more economical alternative to TMP-H, despite its constantly decreasing price. *tert*-Butyl(*iso*-propyl)amine can be readily prepared starting form cheap bulk chemicals such as *iso*-propyl bromide, *tert*-butylamine and adiponitrile according to a literature procedure of *Brown*.[70] Thus, refluxing the 3 components (1:1.5:1 ratio) in the presence of catalytical amounts of Bu_4NI (10 mol%) at 90 °C for 3 d produced after a basic workup the amine **39** in 75% yield (Scheme 34). This synthesis was performed at a 3 mol scale. After treatment of the amine **39** with *i*PrMgCl·LiCl[30], the corresponding base **10b** was obtained as a 1.45 M solution in THF. This concentration is comparable to TMPMgCl·LiCl (**10a**) letting us suspect a similar aggregation of these two bases (monomeric or dimeric in solution). Interestingly, the hindered base **10b** is twice as soluble in THF as $i\text{Pr}_2\text{NMgCl}{\cdot}\text{LiCl}$ (**11**; max. 0.6 M in THF) which is much more aggregated and does not react in a stoichiometric way with aromatic or heteroaromatic substrates.[30, 71]

[70] H. C. Brown, J. V. B. Kanth, P. V. Dalvi, M. Zaidlewicz, *J. Org. Chem.* **1999**, *64*, 6263.

[71] R. E. Mulvey (University of Strathclyde, Glasgow), personal communication on 02.12.08 in Munich. Crystalline $i\text{Pr}_2\text{MgCl}{\cdot}\text{LiCl}$ consists of numerous dimeric species. The LiCl does not achieve full deaggregation in this composition. See also upcomming publication by R. E: Mulvey for details.



Scheme 34: Preparation of the base **10b**.

Accordingly, the scope of this Li/Mg-amide base was investigated in more detail. The magnesiation of the substituted ethyl benzoate derivative **40a** with the hindered base **10b** gave the corresponding magnesium reagent within 1 h which, after a transmetalation with CuCN·2LiCl (10 mol%)[47], was allylated with 3-bromo-2-methylpropene affording the tetra-substituted benzoate **41a** in 85% yield (Table 5, entry 1). Iodolysis of this magnesium reagent led to the iodoester **41b** in 81% (entry 2). The magnesiation of the Boc-protected isophtalate **40b** was complete within 1 h at 0 °C. Copper(I)-mediated allylation[47] with 3-bromocyclohexene furnished the allylated product **41c** in 93% yield (entry 3). The magnesiation of diethyl 2-bromo-terephthalate (**40c**) and diethyl 4-bromo-isophthalate (**40d**) occured at –30 °C within 30 min. After the addition of anisaldehyde, the newly formed lactones **41d** and **41e** were isolated in 86-96% yield (entries 4 and 5). The metalation of heterocycles was performed using similar conditions to those used with the base **10a**. Thus, 3-bromoquinoline (**40e**) reacted with the magnesium base **10b** at –25 °C within 20 min. Quenching with *N,N*-dimethylformamide introduced a formyl function at position 2 and produced the aldehyde **41f** in 81% yield (entry 6). 2,6-Dichloropyridine (**40f**) reacted with the magnesium amide **10b** at 25 °C within 10 min. Transmetalation using $ZnCl_2$ in THF at –40 °C gave the corresponding organozinc reagent which underwent a Pd-catalyzed *Negishi* cross-coupling[45, 46] reaction with 4-iodoanisole affording the 4-substituted pyridine **41g** in 85% yield (entry 7). A Pd-catalyzed acylation[72] of this zinc reagent using $Pd(PPh_3)_4$ as catalyst (2 mol%) and pivaloyl chloride (3.0 equiv, –40 to 25 °C, 2 h) furnished to the ketone **41h** in 86% yield (entry 8). The dibromopyridine **40h** required lower temperatures to prevent halogen dance reactions.[73] The deprotonation at position 4 was complete within 30 min at –50 °C. After the addition of pivaldehyde, the alcohol **41i** was obtained in 86% yield (entry 9). The reaction of benzothiazole (**40i**) with the magnesium base **10b** proceeded at 25 °C within 15 min. After the addition of pivaldehyde, the secondary alcohol **41j** was isolated in 86% yield (entry 10). A Pd-catalyzed acylation[72] with $Pd(PPh_3)_4$ (2 mol%) and 2-chloronicotinyl chloride led to the ketone **41k** in 83% yield (entry 11). Benzothiophene (**40h**) reacted within

[72] a) E. Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, *Tetrahedron Lett.* **1983**, *24*, 5181; b) R. A. Grey, *J. Org. Chem.* **1984**, *49*, 2288.
[73] E. Arzel, P. Rocca, F. Marsais, A. Goddard, G. Quéguiner, *Tetrahedron Lett.* **1998**, *39*, 6465.

12 h at 0 °C with the base **10b**. The benzylic alcohol **41l** was obtained in 71% yield after quenching with PhCHO (entry 12).

Table 5: Products of Type **41** obtained after magnesiation with [*t*Bu(*i*Pr)N]MgCl·LiCl (**10b**) and subsequent reaction with an electrophile.

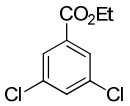
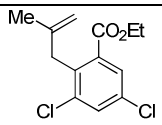
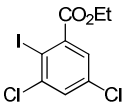
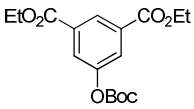
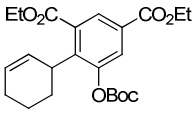
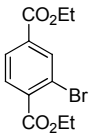
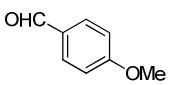
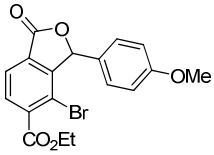
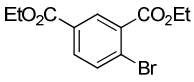
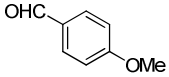
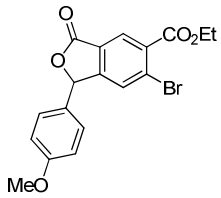
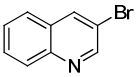
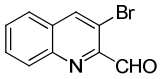
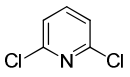
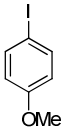
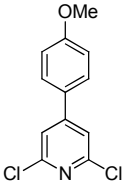
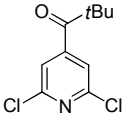
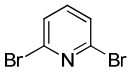
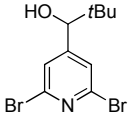
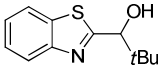
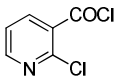
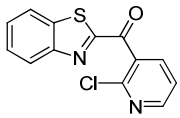
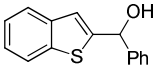
Entry	Substrate	*T* [°C] , *t* [h]	Electrophile	Product/Yield [%][a]
				
1	**40a**	0, 1		**41a**: 85[b]
			I_2	
2	**40a**	0, 1		**41b**: 81
				
3	**40b**	0, 1		**41c**: 93[b] (92)
				
4	**40c**	–30, 0.5		**41d**: 96
				
5	**40d**	–30, 0.5		**41e**: 86 (88)
			DMF	
6	**40e**	–25, 0.3		**41f**: 81 (91)
				
7	**40f**	25, 0.2		**41g**: 85[c] (93)
			*t*BuCOCl	
8	**40f**	25, 0.2		**41h**: 86[d]
			*t*BuCHO	
9	**40h**	–50, 0.5		**41i**: 84

Table 5 (continued)

Entry	Substrate	*T* [°C] , *t* [h]	E^+	Product/Yield [%][a]
			*t*BuCHO	
10	**40i**	25, 0.2		**41j**: 86 (98)
				
11	**40i**	25, 0.2		**41k**: 83[d]
			PhCHO	
12	**40h**	0, 12		**41l**: 71 (93)

[a] Isolated yield of analytically pure product, yields in parentheses are obtained by the use of TMPMgCl·LiCl (**1**); [b] Obtained after transmetalation with CuCN·2LiCl (10 mol%); [c]Obtained after transmetalation with $ZnCl_2$ (1.2 -1.6 equiv) and $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%); [d] Obtained after transmetalation with $ZnCl_2$ (1.2 -1.6 equiv) and $Pd(PPh_3)_4$ (2 mol%).

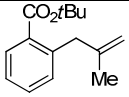
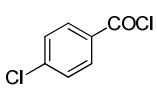
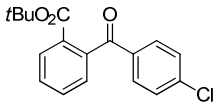
3.5.2. Preparation and use of the Reagent [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl (14c)

As mentioned above, the Mg-*bis*-amide [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl (**14c**) displays comparable properties to those of TMP_2Mg·2LiCl (**14a**). Its synthesis is similar to that of TMP_2Mg·2LiCl (**14a**) as shown in Scheme 23. Hence, further studies on **14c** were conducted to examine its scope. Thus, *tert-b*utyl benzoate (**13a**) was magnesiated with [*t*Bu(*i*Pr)N]Mg·2LiCl (**14c**; 1.1 equiv) at 25 °C within 1 h. After transmetalation to the corresponding arylzinc species, a copper(I)-mediated allylation[47] was performed, to give the allylated benzoate **42a** in 91% yield (Table 6, entry 1). This arylzinc species was also used for a Pd-catalyzed acylation reaction[72] ($Pd(PPh_3)_4$, 2 mol%) leading to the benzophenone **42b** in 77% yield (entry 2). Pd-catalyzed *Negishi* cross-coupling[45] reactions were also performed using $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%)[46] and 4-iodotoluene or (4-iodophenoxy)(triisopropyl)silane as electrophiles providing the desired products **42c** and **42d** in 82-89% yield (entries 3 and 4). The reaction of *tert*-butyl 1-naphthoate (**43a**) with the magnesium *bis*-amides **14c** proceeded smoothly at 25 °C within 3 h. The resulting organomagnesium reagent was transmetalated with $ZnCl_2$ (1.1 equiv, 1 M in THF) and used in a *Negishi* cross-coupling reaction with 4-iodo-1-chlorobenzene affording the naphthyl derivative **42e** in 97% yield (entry 5). This organozinc species also underwent a copper(I)-mediated[47] allylation, yielding **42f** in 88% yield. After transmetalation with $ZnCl_2$, the addition of $Pd(PPh_3)_4$ (2 mol%)[72] and pivaloyl chloride led to the ketone **42g** in 83% yield (entry 6). Palladium-catalyzed acylation was also used for the introduction of a new ethyl ester. After the addition of the Pd-catalyst $Pd(PPh_3)_4$ (2 mol%) and ethyl chloroformate, the diester **42h** was isolated in 83% yield (entry 7). The formation of tri-*tert*-butyl benzene-1,2,4-tricarboxylate (**42i**) was accomplished by the

reaction of di-*tert*-butyl benzene-1,3-dicarboxylate (**43b**) with [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl (**14c**) at 25 °C within 6 h. The resulting magnesium reagent was quenched with Boc_2O providing the desired tri *tert*-butyl ester **42i** in 90 % (entry 9). This compound is usually prepared by a ruthenium catalyzed [2+2+2] alkyne trimerisation reaction and produces mixtures of isomers.[74] Further treatment of **43b** with [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl at 25 °C (6 h) followed by the addition of $ZnCl_2$, methallyl bromide and catalytic amounts of CuCN·2LiCl (1 M in THF, 10 mol%) gave the allylated benzoate **42j** in 77% yield (entry 10). Moreover, *tert*-butyl isonicotinate (**43c**) was fully magnesiated within 12 h at –40 °C. After transmetalation with $ZnCl_2$, a Pd-catalyzed *Negishi* reaction[45] with iodobenzene was carried out, providing the arylated pyridine **42k** in 68% yield (entry 11). 2-(Methylthio)pyrimidine (**43d**) was smoothly metalated within 1 h at –30 °C. After transmetalation with $ZnCl_2$, a *Negishi* cross-coupling reaction with 3-iodotoluene was performed yielding the pyrimidine **42l** in 76% (entry 12). Benzonitrile (**13e**) was magnesiated within 3 h at –30 °C. After transmetalation with $ZnCl_2$, *Negishi* cross-coupling ($Pd(dba)_2$, 5 mol%; P(2-furyl)$_3$, 10 mol%)[46] was conducted leading to the biphenyl derivative **42m** in 66% yield (entry 13).

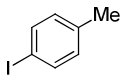
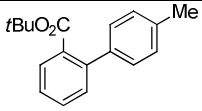
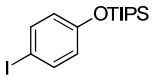
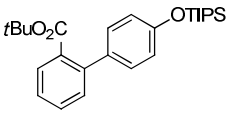
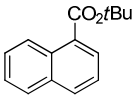
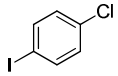
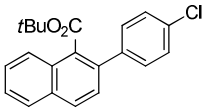
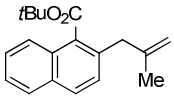
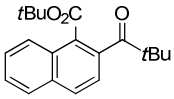
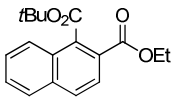
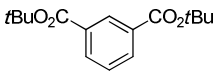
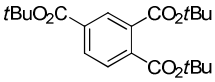
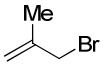
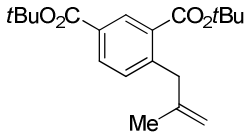
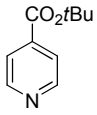
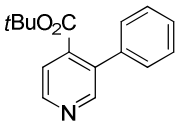
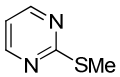
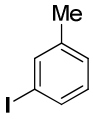
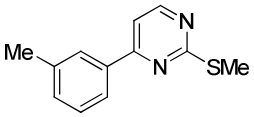
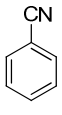
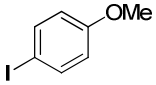
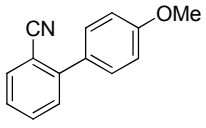
These results show that [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl (**14c**) is a viable alternative to TMP_2Mg·2LiCl (**14a**) although some difficulties were observed. For example, ethyl esters are not tolerated and the extensive formation of the corresponding amide is observed. Only *tert*-butyl esters[75] can be used as substrates for metalation reactions with the *bis*-amide base **14c**. Surprisingly, in the case of di-*tert*-butyl pyridine-3,5-dicarboxylate the amide formation is still observed and TMP_2Mg·2LiCl (**14a**) has to be used for metalating this heterocycle.

Table 6: Products of Type **42** obtained after Magnesiation with [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl (**14c**) and Subsequent Reaction with an Electrophile.

Entry	Substrate	*T* [°C], *t* [h]	Electrophile	Product/Yield [%][a]
				
1	**13a**	25, 1		**42a**: 91[b] (93)
				
2	**13a**	25, 1		**42b**: 77[d]

[74] V. Cadierno, S. E. García-Garrado, J. Gimeno, *J. Am. Chem. Soc.* **2006**, *128*, 15094.
[75] For preparation of *t*Bu-esters see: D. Lagnoux, E. Delort, C. Douat-Cassassus, A. Esposito, J.-L. Reymond *Chem. Eur. J.* **2004**, *10*, 1215.

Table 6 (continued)

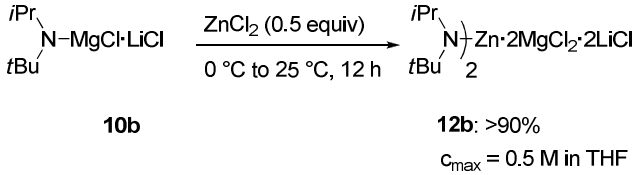
Entry	Substrate	*T* [℃] , *t* [h]	Electrophile	Product/Yield [%][a]
				
3	**13a**	25, 1		**42c**: 82[c]
				
4	**13a**	25, 1		**42d**: 89[c]
				
5	**43a**	25, 3		**42e**: 97[c] (83)
				
6	**43a**	25, 3		**42f**: 88[b]
			*t*BuCOCl	
7	**43a**	25, 3		**42g**: 83[d]
			EtOCOCl	
8	**43a**	25, 3		**42h**: 83[d]
			Boc_2O	
9	**43b**	25, 6		**42i**: 90 (94)
				
10	**43b**	25, 6		**42j**: 77[b]
			Ph-I	
11	**43c**	–40, 12		**42k**: 68[c]
				
12	**43d**	–30, 1		**42l**: 76[c] (93)
				
13	**13e**	–30, 3		**42m**: 66[c] (70)

[a] Isolated yield of analyticaly pure product, yields in parentheses obtained by the use of $TMP_2MgCl{\cdot}2LiCl$; [b] Obtained after

transmetalation with CuCN·2LiCl (10 mol%); [c] Obtained after transmetalation with $ZnCl_2$ (1.2 -1.6 equiv.) and $Pd(dba)_2$ (5 mol%) and P(2-furyl)$_3$ (10 mol%); [d] Obtained after transmetalation with $ZnCl_2$ (1.2 -1.6 equiv.) and $Pd(PPh_3)_4$ (2 mol%).

3.5.3. Preparation and use of the Reagent [*t*Bu(*i*Pr)N]$_2$Zn·2MgCl$_2$·2LiCl (12b)

To complete the studies on the non-cyclic sterically demanding amides the investigations were extended to mixed Li/Mg/Zn-amides. Thus, the transmetalation of [*t*Bu(*i*Pr)N]MgCl·LiCl (**10b**) with $ZnCl_2$ (0.5 equiv) furnished the corresponding zinc-base [*t*Bu(*i*Pr)N]$_2$Zn·2MgCl$_2$·2LiCl **12b**. A concentration of 0.5 M in THF was obtained (**Scheme 35**). The related base TMP$_2$Zn·2MgCl$_2$·2LiCl (**12a**) has been found to be a mild zincation reagent for highly functionalized substrates (aldehydes, nitro groups).

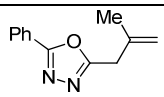
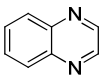
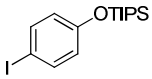
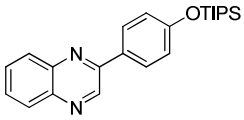
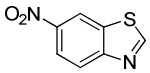
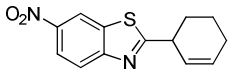
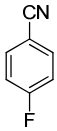
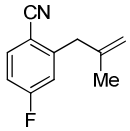
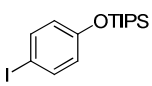
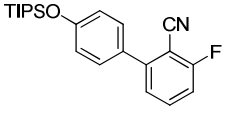
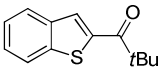


Scheme 35: Synthesis of the zinc *bis*-amide **12b**.

Thus, 2-phenyl-1,3,4-oxadiazole (**44a**) was metalated within 45 min at 25 °C using zinc base **12b** (0.55 equiv). The resulting diorganozinc reagent underwent a copper-catalyzed allylation reaction furnishing the allylated product **45a** in 88% yield (Table 7, entry 1). The magnesiation or lithiation of this substrate is complicated by a competitive ring opening reaction leading to benzonitrile (**13e**). This can be completely avoided by using the zinc *bis*-amides **12a**,**b** as base.[32] Quinoxaline (**44b**) was readily zincated within 9 h at 25 °C. After a Pd-catalyzed[45, 46] cross-coupling reaction, the quinoxaline derivative **45b** was isolated in 81% yield (entry 2). During this reaction, no dimerization of quinoxaline (**44b**) was noted. Such dimerization reactions are typically observed during magnesiation or lithiation reactions of this substrate (see chapter 3.3.). Nitro groups were also tolerated as shown for the zincation of 5-nitro-1,3-benzothiazole (**44c**). This metalation occured at –50 °C within 1 h selectively at position 2. After a copper(I)-mediated[47] allylation reaction with 3-bromocyclohexene, the 2-allylated benzothiazole **45c** was obtained in 79% yield (entry 3). For poorly activated substrates, the zincation can be accelerated by microwave irradiation.[32] Thus, 4-fluoro benzonitrile (**44d**) was mixed with 0.55 equiv of the zinc *bis*-amide **12b**. This mixture was subjected to microwave irradiation on a Initiator Sixty EXP Microwave System from Biotage.

After 2 h at 100 °C, a full conversion to the corresponding Zn-reagent was observed which underwent a copper(I)-catalyzed allylation reaction yielding the allylated benzonitrile **45d** in 81% yield (entry 4). The 2-fluoro isomer **44e** required higher temperatures (140 °C) and 2 h of reaction time for a complete formation of the zinc reagent. A Pd-catalyzed cross-coupling reaction with (4-iodophenoxy)(triisopropyl)silane provided the biphenyl **45e** in 83% yield (entry 5). Benzothiophene (**40h**) was zincated at 140 °C within 1 h and underwent a Pd-catalyzed acylation with pivaloyl chloride affording the polyfunctionalized ketone **45f** in 83% yield (entry 6). The new zinc *bis*-amide base **12b** displays a similar reactivity than $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**12a**). However, this last base seems to have a broader scope than **12b** as ethyl esters are converted to the corresponding amides under these harsh metalation conditions.

Table 7: Products of Type **45** obtained after zincation with [*t*Bu(*i*Pr)N]$_2$Zn·2MgCl$_2$·2LiCl (**12b**) and Subsequent Reaction with an Electrophile.

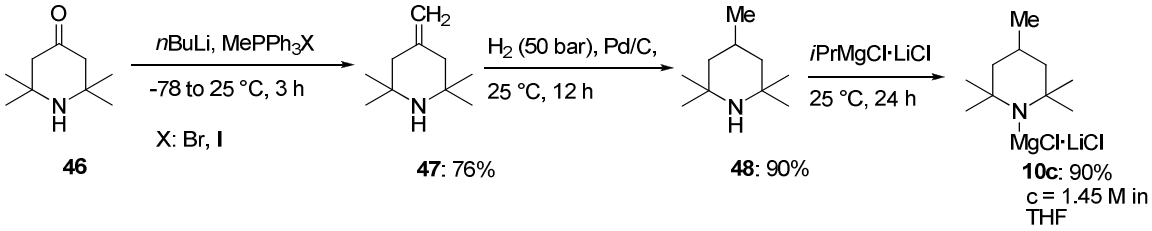
Entry	Substrate	*T* [°C] , *t* [h]	E^+	Product/Yield [%][a]
				
1	**44a**	25, 0.75		**45a**: 88[b, 76]
				
2	**44b**	25, 9		**45b**: 81[c, 76]
				
3	**44c**	–50, 1		**45c**: 79[b, 76]
				
4	**44d**	100, 2		**45d**: 81[b]
				
5	**44e**	140, 2		**45e**: 83[c]
			*t*BuCOCl	
6	**40h**	140, 1		**45f**: 83[b]

[a] Isolated yield of analytically pure product, yields in parentheses obtained by the use of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$; [b] Obtained after transmetalation with CuCN·2LiCl (10 mol%); [c] Obtained via Pd-catalyzed cross-coupling with $Pd(dba)_2$ (5 mol%) and $P(2\text{-furyl})_3$ (10 mol%).

[76] These experiments were done by S. H. Wunderlich and are shown here for the sake of completeness.

3.5.4. Preparation and use of the Reagent PMPMgCl·LiCl (10c)

Another approch towards alternative amines was to start from the TMP-H precursor 2,2,6,6-tetramethyl-4-piperidone (**46**) which is comparatively cheap.[77] Thus, the conversion of the amino ketone **46** into the corresponding *exo*-methylene derivative **47** by a Wittig reaction was envisioned. The treatment of $MePPh_3I$ or $MePPh_3Br$ with *n*BuLi at –78 °C and subsequent addition of **46** led to the unsaturated amine **47** in 76% yield.[78] Catalytic reduction with H_2 in the presence of Pd/C[79] provided 2,2,4,6,6-pentamethylpiperidine (PMPH; **48**) in 90% yield (Scheme 36).



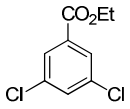
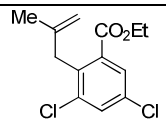
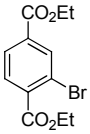
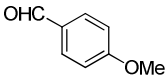
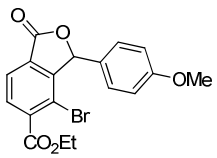
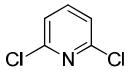
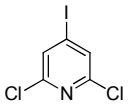
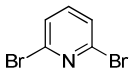
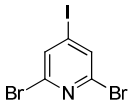
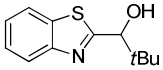
Scheme 36: Preparation of the mixed Li/Mg-amide **10c**.

Thus, the treatment of the new piperidine **48** with *i*PrMgCl·LiCl (0.95 equiv, 25 °C, 24 h)[30] led to the corresponding PMPMgCl·LiCl (**10c**) as a 1.45 M solution in THF. The additional methyl group in **48** compared to TMP-H does not increase the base solubility in THF. Its concentration is comparable to those of TMPMgCl·LiCl (**10a**) and [(*t*Bu)(*i*Pr)]NMgCl·LiCl (**10b**). Magnesiations of various aromatics with the magnesium base **10c** are summarized in Table 8. As expected, sensitive functional groups such as esters or a Boc-group are well tolerated and the metalation of heterocycles was also possible. The quenching of these magnesium reagents with various electrophiles led to products of type **41-47** in 87-95% yield. Thus, the metalation of the dichlorobenzoate **40a** proceeded smoothly at 0 °C within 1 h. A copper(I)-mediated[47] allylation reaction gave the allylated product **41a** in 93% yield (Table 8, entry 1). Also the trapping of the intermediate organomagnesium reagent derived from the diester **40d** generated within 30 min at –30 °C with an aldehyde was readily achieved. After

[77] D. Kampmann, G. Stuhlmüller, R. Simon, F. Cotett, F. Leroux, M. Schlosser, *Synthesis* **2005**, 1028. Estimated retail prices: TMPH: ca. 350 €/mol; 2,2,6,6-tetramethyl-4-piperidone (**46**): ca. 20 €/mol; VWR International, retail prices 2009: TMPH ca. 270 €/mol; **46**: ca. 50 €/mol.
[78] a) P. L. Hall, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, D. B. Collum, *J. Am. Chem. Soc.* **1991**, *113*, 9575; b) compound **5** was synthesized according to: P. Karrer, J.-M. Mas, G. Mignani, Rhone-Poulenc Chimie, Int. Pat. Appl. WO 96/16124, **1996**.
[79] P. N. Rylander, *Hydrogenation Methods*, Academic Press, London, **1985**.

the addition of anisaldehyde, the newly formed lactone **41d** was obtained in 90% yield (entry 2). 2,6-Dichloropyridine (**40g**) reacted with **10c** (1.5 equiv) within 10 min at 25 °C while the dibromo derivative **40h** again required lower temperatures (–30 °C, 0.5 h) to suppress possible halogen dance reactions.[73] After iodolysis, the iodopyridines **46** and **47** were isolated in 91 and 87% yield (entries 3 and 4). Benzothiazole (**40i**) reacted at 25 °C with the base **10c** providing the corresponding *Grignard* reagent within 10 min. The addition of pivaldehyde led to the secondary alcohol **41l** in 91% yield (entry 5).

Table 8: Products of type **41**-**47** obtained after magnesiation with PMPMgCl·LiCl (**10c**) and subsequent reaction with an electrophile.

Entry	Substrate	*T* [°C] , *t* [h]	Electrophile	Product/Yield [%][a]
				
1	**40a**	0, 1		**41a**: 93[b]
				
2	**40d**	–30, 0.5		**41d**: 90 (88)
			I_2	
3	**40g**	25, 0.2		**46**: 91 (93)
			I_2	
4	**40h**	–30, 0.5		**47**: 87
			*t*BuCHO	
5	**40i**	25, 0.2		**41l**: 91 (98)

[a] Isolated yield of analytically pure product, yields in parentheses obtained by the use of TMPMgCl·LiCl; [b] Obtained after transmetalation with CuCN·2LiCl (10 mol%).

These results show that the magnesium bases **10a-c** display a similar behaviour concerning solubility, metalation rates and yields of the resulting products. However, PMPH is gained from a two step synthesis, which includes a Wittig-reaction. Although this reaction is used in industry for the synthesis of Vitamine A,[80] the use of the amine **39** for the preparation of the corresponding base **10b** is favored because of its easy one step synthesis.

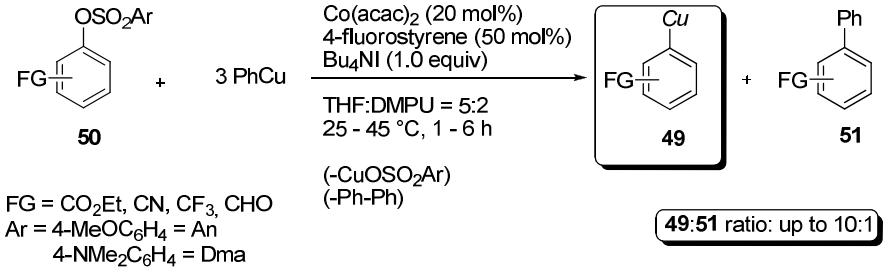
[80] a) H. Pommer, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 423; b) W. Reif, H. Grassner, *Chem. Ing.-Techn.*, **1973**, *43*, 646; c) R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2001**, *40*, 1411.

3.6. Preparation of Aryl Copper Reagents via a Cobalt-Catalyzed C-O Bond Activation

As described in chapter 1.2., organocopper reagents display a special role within organometallic reagents. The high reactivity combined with high functional group tolerance as well as their high thermal stability makes them to preferred reagents in chemical transformations. Alternatively, phenol derivatives such as sulfonates have been seldomly used for the preparation of aryl organometallics due to the strength of the carbon oxygen bond.[81, 82] Transformations starting from aryl triflates are also known. These intermediates are converted into the corresponding tin species which can subsequently be transmetalated to organocopper reagents. However, this method suffers from low atom economy and the toxicity of the used tin reagents (see chapter 1.5.). Therefore, a *transition metal-catalyzed activation* of the aryl-oxygen bond has been envisioned to achieve this goal. Due to its high reactivity and moderate price, cobalt has been the metal of choice for elaborating new organometallic reactions.[83, 84] A preparation of polyfunctional arylcopper reagents of type **49** bearing a range of sensitive functional groups (ester, nitrile or aldehyde) starting from aryl sulfonates of type **50** using a cobalt-catalyzed sulfonate/copper-exchange reaction mediated by phenylcopper (PhCu) was found to be possible (Scheme 37). During studies on Co-catalyzed cross-couplings[85] it has been observed that the reaction of electron-deficient aryl *p*-tolylsulfonates (ArOTs) with PhCu produced together with the cross-coupling product (Ar-Ph) of type **51,** an arylcopper ArCu (**49**) which is the result of a OTs/Cu-exchange. Although this was a minor product under

[81] a) R. J. K. Taylor, *Organocopper Reagents*, Oxford University Press, Oxford, **1994**; b) *Modern Organocopper Chemistry* (Ed. N. Krause), Wiley-VCH, Weinheim, **2002**; c) A. Hoffmann-Röder, N. Krause, *Synthesis* **2001**, 171.
[82] a) M. Yus, *Recent Res. Devel. Org. Chem.* **1997**, *1*, 397; b) Guijarro, M. Yus, *Recent Res. Devel .Org. Chem.* **1998**, 2, 713; c) D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, 225; d) C. G. Screttas, M. Micha-Screttas, *J. Org. Chem.* **1978**, *43*, 1064.
[83] a) H. Avedissian, L. Bérillon, G. Cahiez, P. Knochel, *Tetrahedron Lett.* **1998**, *39*, 6163; b) C. Gosmini, Y. Rollin, J.-Y. Nédélec, J. Périchon, *J. Org. Chem.* **2000**, *65*, 6024; c) H. Fillion, E. Le Gall, C. Gosmini, J. Périchon, *Tetrahedron Lett.* **2002**, 43, 5941, d) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2002**, *41*, 4137; e) H. Fillion, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867; f) H. Ohmiya, H. Yorimitsu, K. Oshima, *Chem. Lett.* **2004**, *33*, 1240; g) I. Kazmierski, M. Bastienne, C. Gosmini, J.-M. Paris, J. Périchon, *J. Org. Chem.* **2004**, *69*, 936; h) T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 2947; i) J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221.
[84] H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2081.
[85] a) T. J. Korn, M. A. Schade, S. Wirth, P. Knochel, *Org. Lett.* **2006**, *8*, 725.; b) T. J. Korn, M. A. Schade, M. N. Cheemala, S. Wirth, S. A. Guevara, G. Cahiez, P. Knochel, *Synthesis* **2006**, 3547.

standard cross-coupling conditions, it was possible to optimize its formation. By replacing the Ts-group by an aryl sulfonate bearing a donor substituent in *para*-position (e.g.: –OMe; –NMe_2), by using a higher catalyst loading (from 7.5 mol% to 20 mol%) and by performing the reaction in a 5:2 THF:DMPU mixture, the sulfonate/copper-exchange became the major reaction pathway (ratio of ArCu (**1**):Ar-Ph (**3**) up to 10:1) (Scheme 37).



Scheme 37: Co^{II}-catalyzed aryl sulfonate/copper-exchange reaction.

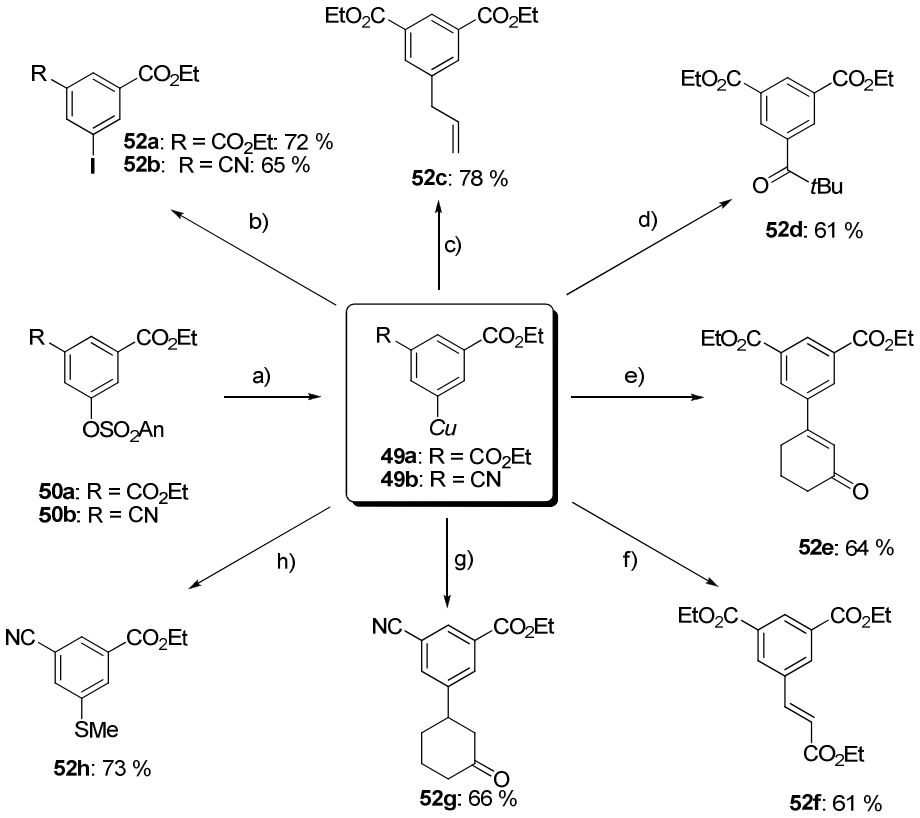
Thus, the reaction of 1,3-dicarbethoxy benzenesulfonate (**50a**; 1 equiv) with PhCu (3 equiv) in the presence of $Co(acac)_2$ (20 mol%), 4-fluorostyrene (50 mol%)[86], Bu_4NI (1.0 equiv)[87] in a 5:2 THF:DMPU mixture furnished the arylcopper reagent **49a** within 2 h at 25 °C and provided after iodolysis the aryl iodide (**52a**) in 72% yield. Similarly, trapping the arylcopper species **49b** obtained by the reaction with PhCu (3.0 equiv after 3 h at 25 °C) with iodine furnished ethyl 3-cyano-5-iodobenzoate (**52b**) in 65% yield. The copper reagent **49a** could also be trapped by various other electrophiles. Thus, its allylation with 3-bromopropene afforded the allylated product **52c** in 78% yield. An acylation using pivaloyl chloride gave the ketone **52d** in 61% yield. The organocopper reagent derived from **50a** underwent a smooth substitution reaction with 3-iodocyclohexen-1-one yielding the cyclohexenone **52e** in 64% yield. A carbocupration[88] of ethyl propiolate with the copper reagent **49a** furnished the alkene **52f** in 61% yield. The related copper reagent **49b** underwent a 1,4-addition with cyclohexenone in the presence of TMSCl affording the corresponding Michael-adduct **52g** in

[86] 4-Fluorostyrene facilitates the reductive elimination step during the catalytic cycle. Its presence is essential for performing the sulfonate/copper-exchange reaction. Apparently, 4-fluorostyrene is not consumed during the reaction as shown by GC-analysis using an internal standard; see: a) M. Piber, A. E. Jensen, M. Rottländer, P. Knochel, *Org. Lett.* **1999**, *1*, 1323; b) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79.

[87] The role of the Bu_4NI may be to deaggregate organometallic reagents. See: a) S. W. Wright, D. L. Hageman, L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095; b) M. T. Reetz, R. Breinbauer, K. Wanninger, *Tetrahedron Lett.* **1996**, *37*, 4499; c) N. A. Powell, S. D. Rychnowski, *Tetrahedron Lett.* **1996**, *37*, 7901; d) K. Nakamura, H. Okubo, M. Yamaguchi, *Synlett*, **1999**, 549; e) T. Jeffrey, J.-C. Galland, *Tetrahedron Lett.* **1994**, *35*, 4103; f) V. Penalva, L. Lavenot, C. Gozzi, M. Lemaire, *App. Cat. A* **1999**, *182*, 399; g) W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033; h) C. Amatore, A. Jutland, A. Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531; i) A. Jutland, A. Mosleh, *Organometallics* **1995**, *14*, 1810; i) C. Amatore, M. Azzabi, A. Jutland, *J. Am. Chem. Soc.* **1991**, *113*, 1670; j) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 8704.

[88] J.-F. Normant, A. Alexakis, *Synthesis* **1981**, 841.

66% yield. The reaction of the arylcopper **49b** with *S*-methyl thiomethylsulfonate furnished the thioether **52h** in 73% yield (Scheme 38). Further trapping reactions of arylcopper reagents prepared from the aryl sulfonates **50c**-**h** are summarized in Table 9. Aromatic compounds with a 1,3,5-trisubstitution pattern which are usually difficult to prepare, can also be easily accessed via this methodology.[89] Thus, 3,5-dicyanophenyl 4-methoxybenzenesulfonate **50c** reacted under standard conditions within 6 h at 45 °C leading to the corresponding copper reagent which was quenched with iodine yielding 5-iodo isophthalonitrile **52i** in 63 % yield (Table 9, entry 1).



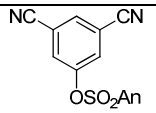
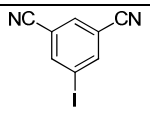
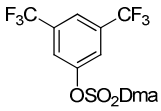
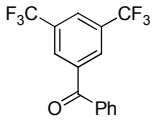
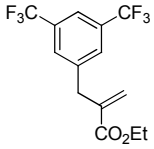
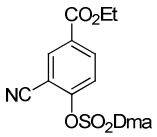
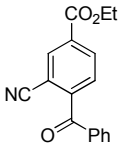
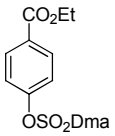
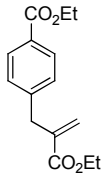
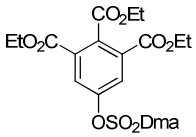
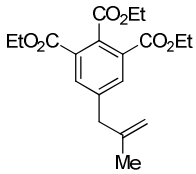
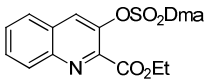
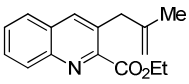
Scheme 38: Aryl sulfonate/copper-exchange of the sulfonates **50a**,**b** and trapping with various electrophiles. Reagents and conditions: a) PhCu (3.0 equiv) $Co(acac)_2$ (20 mol%), 4-fluorostyrene (50 mol%), Bu_4NI (1.0 equiv), THF:DMPU = 5:2, 25 °C, 2-3 h; b) I_2 (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h; c) 3-bromopropene (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h; d) *t*BuCOCl (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h, e) 3-iodocyclohexene-1-one (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h; f) ethyl propiolate (2.0 equiv), –40 °C, 30 min, 25 °C, 2 h; g) cyclohexenone (2.0 equiv), TMSCl (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h; h) $MeSSO_2Me$ (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h.

Other aryl sulfonates bearing electron-withdrawing groups were readily converted to the corresponding copper species. Thus, 3,5-bis(trifluoromethyl)phenyl 4-(dimethylamino)benzenesulfonate **50d** gave the arylcopper **49d** within 4 h at 25 °C. Its benzoylation yielded the benzophenone **52j** in 61% yield (entry 2). Alternatively, its allylation

[89] J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc* **2007**, *129*, 15434.

with ethyl 2-(bromomethyl)acrylate[90] gave the 1,3,5-trisubstituted arene **52k** in 71% yield (entry 3).

Table 9: Products obtained via Co-catalyzed arylsulfonate/copper-exchange and reaction with an electrophile.

Entry	Substrate	*T [°C] , t [h]*	E^+	Yield/Product [%][b]
				
1	**50c**	45, 6		**52i**: 63
			PhCOCl	
2	**50d**	25, 4		**52j**: 61
				
3	**50d**	25, 4		**52k**: 71
			PhCOCl	
4	**50e**	25, 5		**52l**: 70[91]
				
5	**50f**	50, 5		**52m**:62[91]
				
6	**50g**	25, 1		**52n**: 70[91]
				
7	**50h**	25, 3		**52o**:53[91]

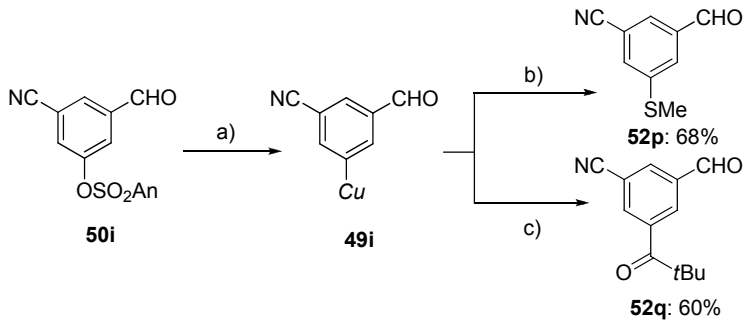
[a] An= 4-$MeOC_6H_4$, Dma= 4-$Me_2NC_6H_4$; [b] Isolated yield of analytically pure product.

Remarkably, an aldehyde function was also tolerated during the exchange reaction. Thus, 3-cyano-5-formylphenyl 4-methoxybenzenesulfonate (**50i**) afforded under standard conditions the arylcopper reagent **49i** which was then trapped with *S*-methyl thiomethylsulfonate

[90] J. Villiéras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.

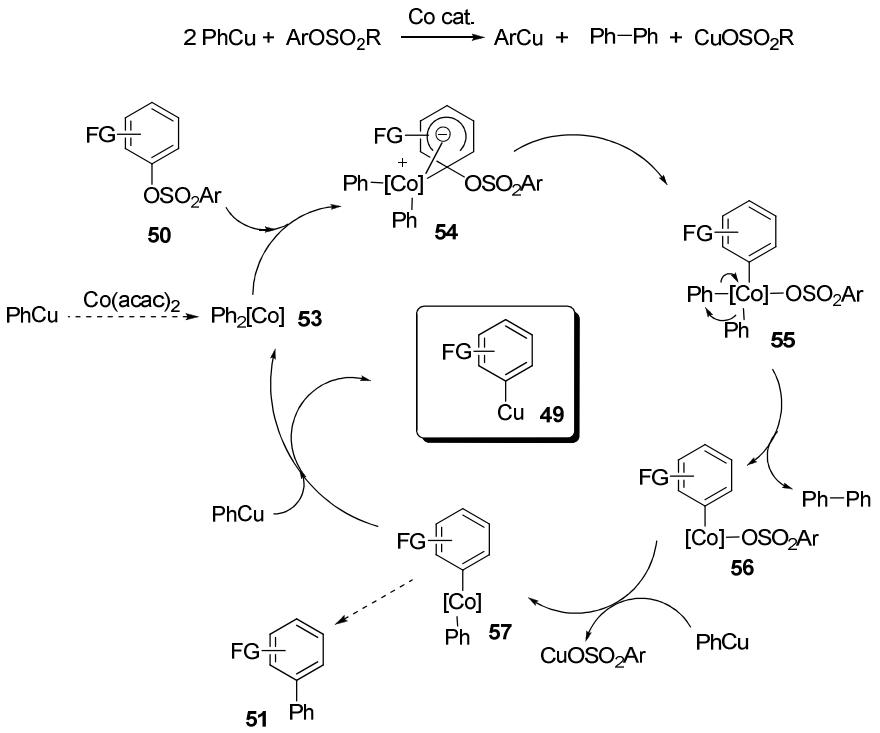
[91] Experiments were done by C. R. Diène and are shown here for the sake of completeness.

yielding the thioether **52p** in 68% yield. Acylation of **49i** furnished the ketone **52q** in 60% yield (Scheme 39).



Scheme 39: Aryl sulfonate/copper-exchange on substituted benzaldehydes. Reagents and conditions: a) PhCu (3.0 equiv) $Co(acac)_2$ (20 mol%), 4-fluorostyrene (50 mol%), Bu_4NI (1.0 equiv), THF:DMPU = 5:2, 25 °C, 1 h; b) $MeSSO_2Me$ (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h, c) *t*BuCOCl (2.0 equiv), –20 °C, 30 min, 25 °C, 2 h.

This new sulfonate/copper-exchange reaction allows the elaboration of various substitution patterns of aromatics, otherwise difficult to access. Under the current reaction conditions, the presence of electron-withdrawing groups is necessary for obtaining the exchange reaction in satisfactory yields.



Scheme 40. Tentative reaction mechanism.

As a tentative reaction mechanism, the following catalytic cycle is proposed. In a first step,

PhCu undergoes a transmetalation to the corresponding cobalt derivative Ph_2Co (**53**). Its addition to an electron-deficient aryl sulfonate of type **50** would lead via nucleophilic attack to a Co^{IV}-intermediate of type **54** stabilized by a η^5-complexation which may explain why electron-poor aromatic systems react faster. After rearomatization, this cobalt complex produces a cobalt(IV)-intermediate[92] of type **55**. Reductive elimination of the cobalt reagent **55** will afford biphenyl[93] and the arylcobalt(II) reagent **56**. The reaction of this intermediate with PhCu results in the formation of compound **57** which only slowly undergoes a reductive elimination to Ar-Ph (**51**). A subsequent transmetalation with PhCu leads to the arylcopper reagent **49** and regenerates Ph_2Co (**53**) (Scheme 40). This pathway is preferred over the formation of **51** as ratios of 10:1 are obtained (Scheme 37).

[92] We have tested that Co(0)-species (generated by a prereduction of $Co(acac)_2$ with PhCu) is not a catalytically active species. The use of $Co(acac)_3$ as a catalyst did not lead to any conversion. For a report of a Co^{IV} species see: Z. Nagy-Magos, L. Markó, G. Bor, *J. Organomet. Chem.* **1968**, *14*, 205.

[93] $Co(acac)_2$ promotes the decomposition of PhCu to biphenyl. The additional presence of 4-fluorostyrene and Bu_4NI even accelerates this homo-coupling process explaining the need of an excess of PhCu.

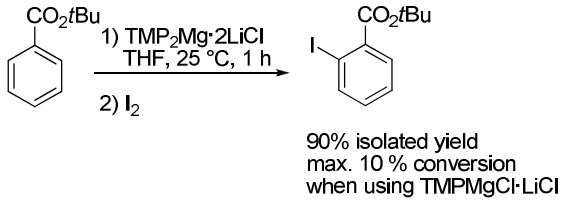
3.7. Summary and Outlook

In this work, two different pathways for the synthesis of organometallic reagents were presented, the stoichiometric activation of carbon-hydrogen bonds as well as the catalytic activation of a carbon-oxygen bond in phenol derivatives (aryl sulfonates).

3.8. Stoichiometric Bond Activation Using Mixed Li/Mg- and Li/Mg/Zn-Amide Bases

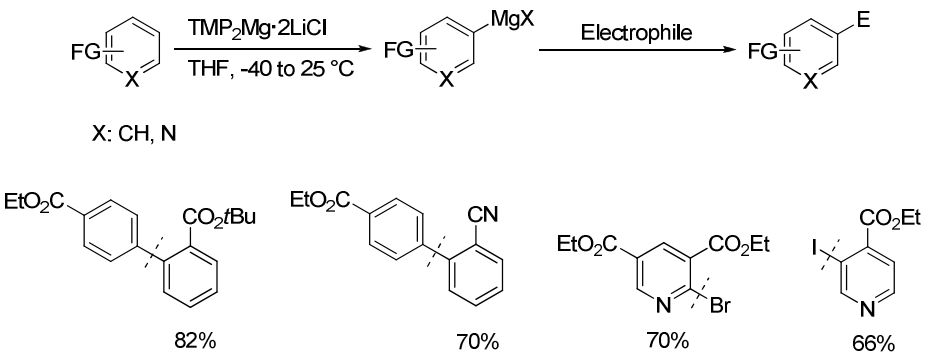
3.8.1. Preparation and use of the Highly Active Base $TMP_2Mg·2LiCl$

The new reagent $TMP_2Mg·2LiCl$ allowed a smooth C-H activation on poorly activated arenes and heteroarenes. These substrates were only sluggishly metalated with the mixed Li/Mg-base TMPMg·LiCl (Scheme 41).



Scheme 41: Efficient magnesiation using $TMP_2Mg·2LiCl$ (**14a**).

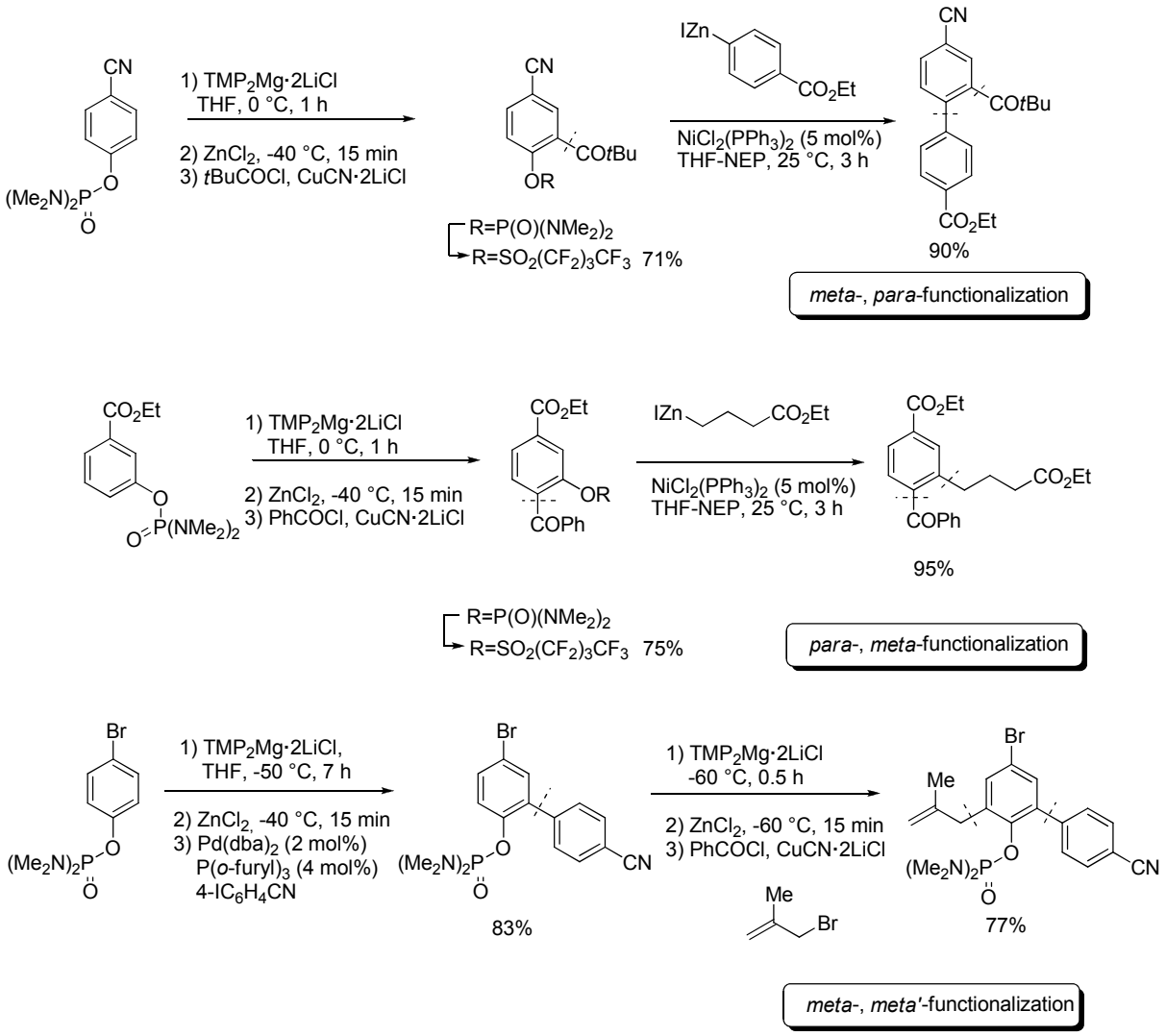
Remarkably, the functional group compatibility was not affected by the high reactivity of the new base. Functionalities like esters, nitriles or ketones were well tolerated during the magnesiation. A scale-up of these metalations was also possible (Scheme 42).



Scheme 42: Various polyfunctionalized arenes and heterocycles obtained using $TMP_2Mg·2LiCl$.

3.8.2. Formal *meta*- and *para*-Functionalization of Arenes using $TMP_2Mg·2LiCl$

Furthermore, the use of the *N*,*N*,*N'*,*N'*-tetramethylphosphorodiamidate as DMG permitted formal *meta*- and *para*-functionalizations by overruling the directing effects of other groups present in the molecule. This high directing power was used to generate unusual substitution patterns, which are normally diffucult to achieve (Scheme 43).



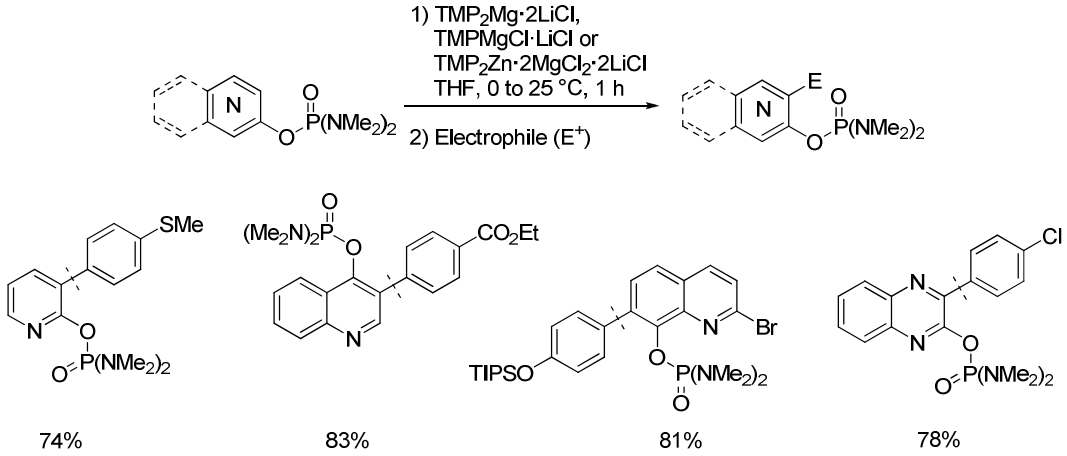
Scheme 43: Formal *meta*-, *para*-, *para*-, *meta*- or *meta*-, *meta'*-functionalizations on arenes.

Using this method, a *meta*-, *para*-functionalization, a *para*-, *meta*-functionalization or a *meta*-, *meta'*-functionalization pattern was readily installed on aromatics. Further studies on the selectivities of phosphorodiamdates derived from anilines and aromatic thiols might be of interest. Investigations concering the use of the DMG as aleaving group in cross-coupling reactions would also be challenging.

3.8.3. Improved Selectivity for the Metalation of *N*-Heterocycles

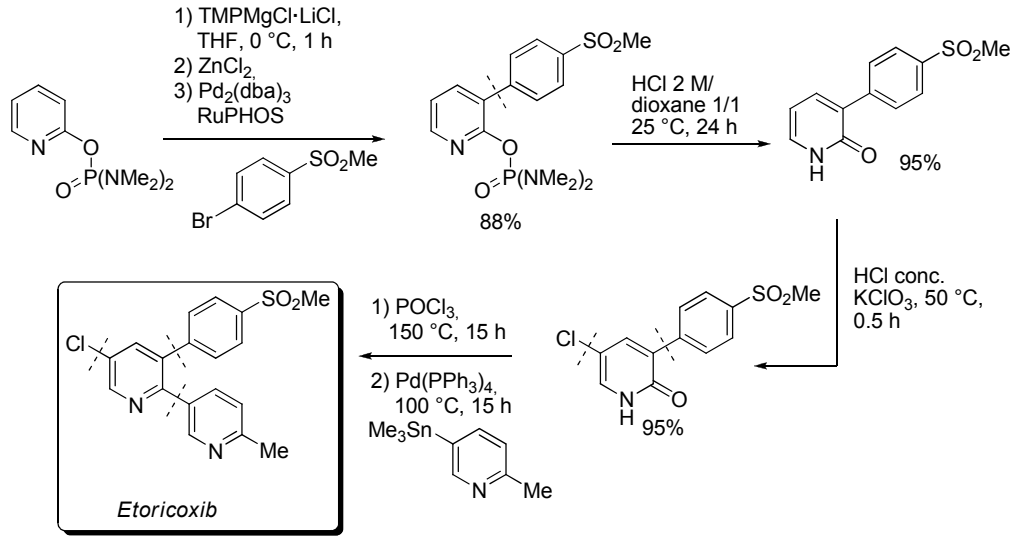
The *N,N,N',N'*-tetramethylphosphorodiamidate attached to *N*-heterocycles and the TMP-derived bases developed by *Knochel* led to smooth and regioselective functionalizations of

these scaffolds (Scheme 44). Other DMGs (e. g. Boc) failed to succeed in these reactions due to stability and selectivity problems.



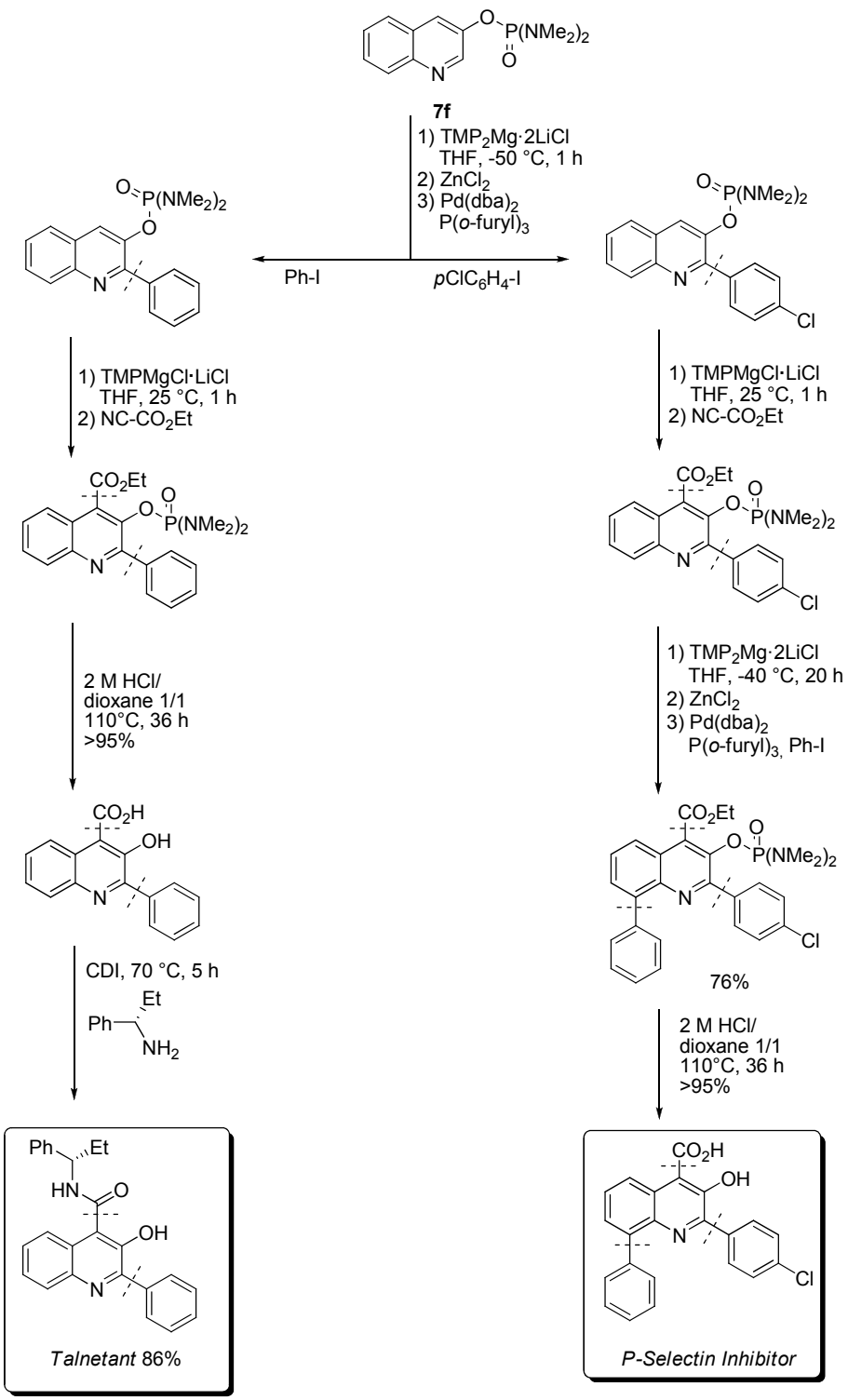
Scheme 44: Efficient and regioselctive functionalizations on *N*-heteroarenes.

This new protocol was used for the preparation of the pyridine based COX-2 inhibitor Etoricoxib (Arcoxia, Merck). The straightforward synthesis only required five steps starting from comercially available 2-hydroxy pyridine (Scheme 45).



Scheme 45: Synthesis of Etoricoxib.

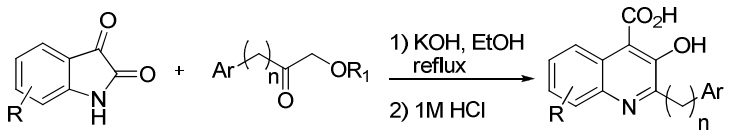
The synthesis of two active compounds with a quinoline salicylic acid backbone was also accomplished applying this new method (Scheme 46).



Scheme 46: Synthesis of Talnetant and a P-Selectin Inhibitor.

Both compounds were obtained starting from commercially available 3-hydroxy quinoline after only five steps. This developed method is also an alternative for the Pfitzinger reaction which is commonly used to build up quinoline salicyclic acids starting from substituted

isatines (Scheme 47).

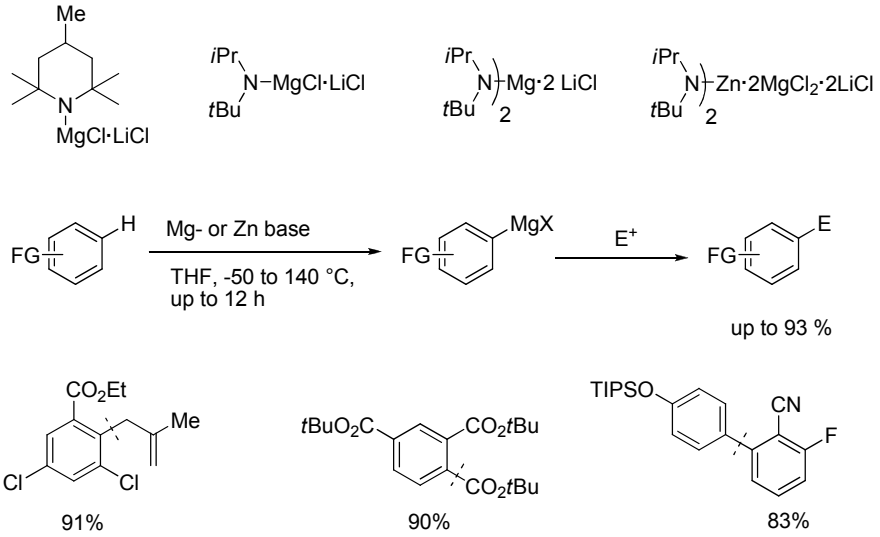


Scheme 47: Pfitzinger synthesis leading to quinoline salicylic acids.

Further work could be the functionalization of indoles using this method.

3.8.4. Alternative Sterically Demanding Amines to TMP-H

As TMP-H is the most expensive compound for metalation reactions two readily prepared, less expensive amines were tested for their performance in magnesiations and zincations. It turned out, that their efficiency is comparable to TMP-H in terms of concentration and reaction behavior (Scheme 48).

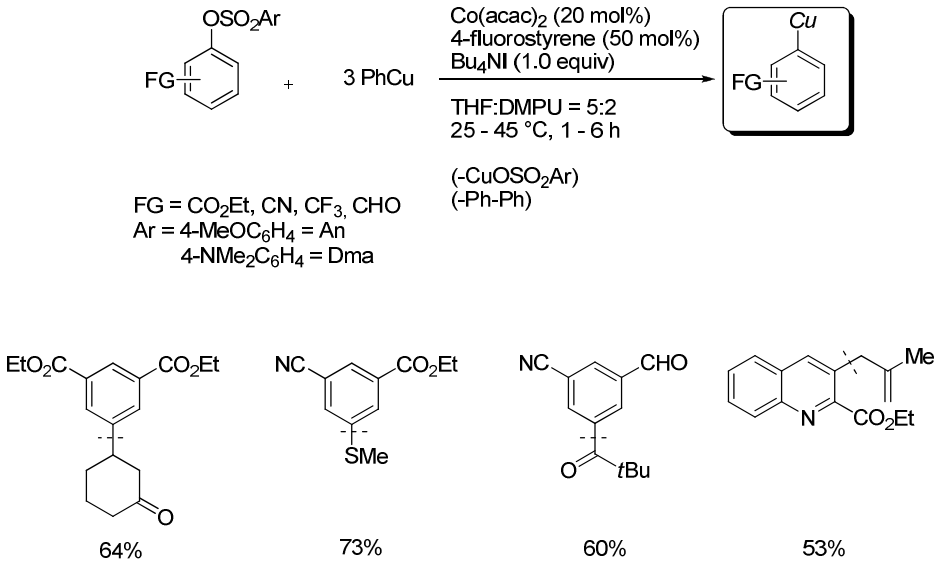


Scheme 48: Economically interesting amines as an alternative to TMP-H.

The use of these amines in the preparation of manganese-, iron- and lanthanum bases would be of great interest.

3.9. Cobalt-Catalyzed Aryl Sulfonate/Copper Exchange

A new cobalt-catalyzed aryl sulfonate/copper exchange reaction was developed. This method allowed the synthesis of highly functionalized aryl copper reagents from sulfonates bearing electron-deficient substituents under mild conditions (25-45 °C, 1-6 h). Sensitive functional groups, such as aldehydes, esters, and nitriles, were well-tolerated (Scheme 49).



Scheme 49: Co-catalyzed arylsulfonate/copper exchange.

Further studies involving other leaving groups as well as different transitionmetal-catalysts for the preparation of various organometallic species would be challenging.

4. EXPERIMENTAL SECTION

4.1. General Considerations

All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame dried glassware under argon. For this case, all glassware was oven dried (80 °C) overnight (min. 12 h), evacuated in high vacuum ($1 \cdot 10^{-3}$mbar) and backfilled with argon (this procedure was repeated three times). Syringes were used to transfer solvents and reagents, and were purged with argon prior to use.

Solvents

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

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

DMPU was stirred over CaH_2 for 12 h, distilled and stored under argon and over molecular sieves.

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

Triethylamine was dried over KOH and distilled.

Chromatography

Thin layer chromatography (TLC) was performed using aluminium 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:

- Phosphomolybdic 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.

Analytical data

NMR spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak.

NMR spectra were recorded on solutions in $CDCl_3$ (residual chloroform: δ 7.25 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR), d_6-DMSO (residual DMSO: δ 2.49 ppm for ^1H NMR and δ 39.5 ppm for ^{13}C NMR. For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), q (quartet), qn (quintet), m (multiplet), as well as br (broad).

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

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

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 air; alkanes like decane or tetradecane were used as internal standards.

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.

Reagents

As not otherwise stated, all reagents were obtained from commercial sources. Reagents of >97% purity were used without purification, except technical grade tosyl cyanide (purity 95%). Liquid acid chlorides and aldehydes were distilled prior to use. TMPH was distilled from CaH_2 and stored under argon.

The following substances were prepared according to literature procedures:
2,2,4,6,6-pentamethylpiperidine (**48**),[94] *tert*-butyl(*iso*propyl)amine (**39**), *tert*-butyl benzoate

[94] P. L. Hall, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, D. B. Collum, *J. Am Chem. Soc.* **1991**, *113*, 9575.

(**13a**), [95] *tert*-butyl naphthoate[95] (**43b**), *tert*-butyl isonicotinate[95] (**43c**), di-*tert*-butyl isophtalate[95] (**43b**), diethyl 5-[(*tert*-butoxycarbonyl)oxy]isophthalate[95] (**40b**), ethyl 3,5-dichlorobenzoate[95] (**40a**), diethyl 4-bromoisophthalate[95] (**40d**), diethyl 2-bromoterephthalate[95] (**40c**).

$Co(acac)_2$ was dried in high vacuum ($1 \cdot 10^{-3}$mbar) with stirring for 5 h at 140 °C and stored under argon.

***n*BuLi** was obtained from Chemetall GmbH (Frankfurt, Germany) and titratred[96] prior to use (approx. 2.5 M in hexane).

PhMgCl was obtained from Chemetall GmbH (Frankfurt, Germany) and titratred[97] prior to use (1.72 M in THF).

***i*PrMgCl·LiCl** was obtained from Chemetall GmbH (Frankfurt, Germany) and titratred[97] prior to use (1.33 M in THF).

$ZnCl_2$ (1.0 M in THF) was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) under high vacuum ($1 \cdot 10^{-3}$mbar) for 6 h at 150 °C. After cooling to 25 °C, dry THF (500 mL) was added and stirring was continued until the salt was completely dissolved.

CuCN·2LiCl (1.0 M in THF) was prepared by drying LiCl (6.8 g, 160 mmol) and CuCN (7.2 g, 80 mmol, 99% pure) at 150 °C for 5 h under high vacuum ($1 \cdot 10^{-3}$mbar), cooled to 25 °C and charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The mixture was stirred for at least 24 h at 25 °C. CuCN·2LiCl (1.0 M in THF) appears as a pale yellow solution.

Preparation of the reagent TMPMgCl·LiCl (10a):

A dried and argon-flushed 1-L *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, is charged with *i*PrMgCl·LiCl (792 mL, 1.2 m in THF, 950 mmol) then

[95] For preparation of *tert*-butyl esters see: D. Lagnoux, E. Delort, C. Douat-Cassassus, A. Esposito, J.-L. Reymond *Chem. Eur. J.* **2004**, *10*, 1215.
[96] H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[97] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

2,2,6,6-tetramethylpiperidine (141.3 g, 1.00 mol) is added dropwise within 5 min via syringe. The mixture is stirred until gas evolution ceases (24–48 h). Complete formation of the base was checked by GC/MS analysis of aliquots quenched with benzaldehyde. The absence of 2-methyl-1-phenylpropan-1-ol (M^+=150) indicates a full conversion. Titration[30] prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator shows a concentration of 1.45 M.

Preparation of the reagent [(*t*Bu)(*i*Pr)]NMgCl·LiCl (10b):

A dry and argon flushed *Schlenk*-flask was charged with *i*PrMgCl·LiCl (1.2 M in THF, 208 mL, 250 mmol). *tert*-Butyl(*iso*-propyl)amine (**39**; 30.3 g, 263 mmol) was added dropwise within 5 min. The mixture was stirred at 25 °C, until gas evolution ceased (48 h). Complete formation of the base was checked by GC/MS analysis of aliquots quenched with benzaldehyde. The absence of 2-methyl-1-phenylpropan-1-ol (M^+=150) indicates a full conversion. The freshly prepared [(*t*Bu(*i*Pr))NMgCl·LiCl solution was titrated[30, 98] prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 1.45 M in THF was obtained.

Preparation of the reagent PMPMgCl·LiCl (10c):

A dry and argon flushed *Schlenk*-flask was charged with *i*PrMgCl·LiCl (1.2 M in THF, 208 mL, 250 mmol). 2,2,4,6,6-Pentamethylpiperidine (**48**, 40.8 g, 263 mmol) was added dropwise within 5 min. The mixture was stirred at 25 °C, until gas evolution ceased (24-48 h). Complete formation of the base was checked by GC/MS analysis of aliquots quenched with benzaldehyde. The absence of 2-methyl-1-phenylpropan-1-ol (M^+=150) indicates a full conversion. The freshly prepared PMPMgCl·LiCl solution was titrated[30, 98] prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 1.45 M in THF was obtained.

Preparation of the reagent TMP_2Mg·2LiCl (14a) from TMPMgCl·LiCl (10a) and TMPLi:

In an argon flushed *Schlenk*-flask, 2,2,6,6-tetramethylpiperidine (TMPH, 5.07 mL, 30.0 mmol)

[98] L. P. Hammett, G. H. Walden, S. M. Edmonds, *J. Am. Chem. Soc.* **1934**, 56, 1092.

was dissolved in THF (30 mL). This solution was cooled to –40 °C and *n*-BuLi (2.4 M in hexane, 12.5 mL, 30.0 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated TMPMgCl·LiCl (**10a**) (1.45 M in THF, 20.7 mL, 30.0 mmol) was then added dropwise to the LiTMP solution, the reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C and stirred for 1 h. The solvents were then removed *in vacuo* without heating, affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until a complete dissolution of the salts was observed. The fresh TMP_2Mg·2LiCl (**14a**) solution was titrated[30] prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 0.7 M in THF was obtained.

Preparation of the reagent [(*t*Bu)(*i*Pr)]N_2Mg·2LiCl (14c) from [(*t*Bu)(*i*Pr)]NMgCl·LiCl (10b) and [(*t*Bu)(*i*Pr)]N-Li:

In an argon flushed *Schlenk*-flask, *tert*-Butyl(*iso*-propyl)amine (**39**, 2.30, 30.0 mmol) was dissolved in THF (30 mL). This solution was cooled to –40 °C and *n*-BuLi (2.4 M in hexane, 12.5 mL, 30.0 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated [(*t*Bu)(*i*Pr)]NMgCl·LiCl (**10b**) (1.45 M in THF, 20.7 mL, 30.0 mmol) was then added dropwise to the LiTMP solution, the reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C and stirred for 1 h. The solvents were then removed *in vacuo* without heating, affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until a complete dissolution of the salts was observed. The fresh [(*t*Bu)(*i*Pr)]N_2Mg·2LiCl (**14c**) solution was titrated[30] prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 0.85 M in THF was obtained.

Preparation of the reagent TMP_2Zn·2$MgCl_2$·2LiCl (12a):

A dried, argon flushed 250 mL *Schlenk*-flask equipped with magnetic stirring bar and rubber septum was charged with $ZnCl_2$ (4.09 g, 30 mmol). The flask was heated to 150 °C under high vacuum ($1 \cdot 10^{-3}$ mbar) for at least 6 h under vigorous stirring. After cooling to 25 °C, dry THF (10 mL) was added and the resulting slurry was cooled to 0 °C with an ice bath. Then TMPMgCl·LiCl (**10**; 42.9 mL, 1.4 M in THF, 60 mmol) was added via syringe. The mixture

was stirred for 12 h until complete dissolution of the salts. Precipitates of the base can easily be redissolved by adding a few mL of dry THF. The freshly prepared $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**12a**) solution was titrated[30] prior to use at 0 °C against benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 0.6 M in THF was obtained.

Preparation of $[(t\text{Bu})N(i\text{Pr})]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (12b):

A dried, argon flushed 250 mL Schlenk-flask equipped with magnetic stirring bar and rubber septum was charged with $ZnCl_2$ (4.09 g, 30 mmol). The flask was heated to 150 °C under high vacuum for at least 6 h under vigorous stirring. After cooling to 25 °C, dry THF (10 mL) was added and the resulting slurry was cooled to 0 °C with an ice bath. Then [(*t*Bu)(*i*Pr)]NMgCl·LiCl (**10b**; 41.4 mL, 1.45 M in THF, 60 mmol) was added via syringe. The mixture was stirred for 12 h until complete dissolution of the salts. Precipitates of the base can easily be redissolved by adding a few mL of dry THF. The freshly prepared $[(t\text{Bu})(i\text{Pr})N]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$) (**12b**) solution was titrated[30] prior to use at 0 °C against benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.5 M in THF was obtained.

4.2. Typical Procedures

Typical Procedure 1 (TP1): Synthesis of the phosphorodiamidates from phenols:

In a 100 mL round-bottom flask the phenol (20.0 mmol) and 4-DMAP (244 mg, 2.0 mmol) were dissolved in THF (20 mL), then $Cl\text{-}P(O)(NMe_2)_2$ (4.50 g, 3.9 mL, 24.0 mmol) was carefully added, followed by the addition of triethylamine (2.43 g, 3.33 mL, 24.0 mmol). The resulting suspension was stirred at 25 °C for 12 h. The reaction mixture was quenched by the addition of a half concentrated aq. NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Typical Procedure 2 (TP2): Synthesis of the phosphorodiamidates from the corresponding hydroxy pyridines, hydroxy quinolines and hydroxy quinoxalines:

In a 100 mL round-bottom flask the hydroxy compound (20.0 mmol) and 4-DMAP (244 mg, 2.0 mmol) were dissolved or slurried up in THF (20 mL), then Cl-P(O)(NMe_2)$_2$ (4.50 g, 3.9 mL, 24.0 mmol) was added, followed by the addition of triethylamine (2.43 g, 3.33 mL, 24.0 mmol). The resulting suspension was stirred at 25 °C for 12 h. The reaction mixture was quenched by the addition of brine (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Typical Procedure 3 (TP3): Preparation of aryl sulfonates from phenols:

In a 100 mL round bottom flask equipped with a magnetic stirring bar the phenol (20 mmol) was dissolved in 40 mL of dry THF. Then, NEt_3 (2.43 g, 24 mmol) was added and the mixture was cooled with an ice bath (approx. 0 °C). The sulfonyl chloride (24 mmol) was added portionwise and the resulting mixture was stirred and allowed to reach 25 °C within 12 h. Then 50 mL of a saturated aqueous NH_4Cl solution were added and the resulting mixture was extracted into EtOAc (50 mL). The organic layer was washed twice with 50 mL of a saturated aqueous NH_4Cl solution. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solids were recrystallized from *n*-heptane/EtOAc.

Typical procedure 4 (TP4): Br/Mg-Exchange or I/Mg-Exchange on aryl sulfonates:

In a dry and argon flushed Schlenk-tube, the arylsulfonate (20 mmol) was dissolved in dry THF and cooled to –40°C. Then, *i*PrMgCl·LiCl (16.5 mL, 1.33 M in THF, 22 mmol) was dropwise added. The resulting mixture was stirred until GC showed full conversion to the organomagnesium reagent (aliquots were quenched with I_2 in THF and extracted with Et_2O). Then, the electrophile (20 mmol) was added. The reaction mixture was stirred for 30 min at –40°C and 1 h at 25 °C. The reaction was quenched with 50 mL of a saturated aqueous NH_4Cl solution and extracted into 50 ml EtOAc. The organic layer was washed twice with 50 mL of a saturated aqueous NH_4Cl solution. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solids recrystallized from *n*-heptane/EtOAc.

Typical Procedure 5 (TP5): Metalation using metal amide bases:

In a flame dried and argon flushed Schlenk-tube equipped with a rubber septum and a magnetic stirring bar the substrate (1 equiv) was dissolved in dry THF (1 M solution). The mixture was cooled to the indicated temperature. Then the Mg- or Zn-base (0.6-2.0 equiv) was added dropwise via syringe. The mixture was stirred at the given temperature. Complete metalation was detected by GC-analysis of reaction aliquots, quenched with allyl bromide (approx. 5 drops) in the presence of CuCN·2LiCl (approx. 0.5 mL). The reaction mixture was then quenched with an electrophile according to **TP7-9**. The reaction mixture was quenched by the addition of 15-30 mL of brine (*N*-heterocycles) or a sat. aq. NH_4Cl solution. Formed precipitate was filtered off with a fritted funnel (P3, 300 mbar). The filter cake was washed with EtOAc (3 x 25 ml) and the filtrate was brought into a separatory funnel with Et_2O (10-20 mL) and EtOAc (10-20 mL). The organic layer was extracted with brine (3 x 15 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL). The organic layers were washed with brine (20 mL) dried over anhydrous $MgSO_4$ filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatographical purification on silica.

Typical Procedure 6 (TP6): Microwave assisted zincation reaction:

In a flame dried and argon flushed 10 mL µW sealed tube equipped a magnetic stirring bar the corresponding substrate (1 equiv.) was dissolved in the indicated amount of **54** (0.6 equiv.). The mixture was heated to the indicated temperature with an Initiator Sixty EXP Microwave System (Biotage) and stirred at this temperature for the given period. Complete metalation was detected by GC-Analysis of reaction aliquots, quenched with I_2 in dry THF. Then the reaction mixture was then quenched with an electrophile and worked up as described below (according to **TP7-9**).

Typical Procedure 7 (TP7): Quenching by performing a *Negishi* Cross-Coupling Reaction:

After complete metalation was achieved according to **TP5** $ZnCl_2$ (1 M in THF, 1.6 – 2.2 equiv) was added at –40 °C (if required, see specific procedures). The resulting mixture was stirred for 15 min. Then $Pd(dba)_2$ (5 mol%) and $P(2\text{-furyl})_3$ (10 mol%) (for aryl iodides) or $Pd_2(dba)_3$ (1 mol%) and RuPHOS (2 mol%) (for aryl bromides) was added together with the corresponding aryl iodide or bromide and the mixture was allowed to warm to 25 °C. Complete consumption of the organozinc reagent was monitored via GC-analysis (approx. 1 -

3 h). The reaction mixture was quenched by the addition of 15-30 mL of brine (*N*-heterocycles) or a sat. aq. NH_4Cl solution. Formed precipitate was filtered off with a fritted funnel (P3, 300 mbar). The filter cake was washed with EtOAc (3 x 25 ml) and the filtrate was brought into a separatory funnel with Et_2O (10-20 mL) and EtOAc (10-20 mL). The organic layer was extracted with brine (3 x 15 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL). The organic layers were washed with brine (20 mL) dried over anhydrous $MgSO_4$ filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatographical purification on silica.

Typical Procedure 8 (TP8): Quenching by performing an Acylation Reaction:

After complete metalation was achieved according to **TP5** $ZnCl_2$ (1 M in THF, 1.6 equiv) was added at –40 °C (if required, see specific procedures). The mixture was the stirred for 15 min. Then CuCN·2LiCl (1 M in THF, 0.1 equiv) or $Pd(PPh_3)_4$ (2 mol%) was added (see specific procedures). After the addition of the corresponding acid chloride, the mixture was briefly warmed with to 25 °C. Complete consumption of the organozinc reagent was monitored via GC-analysis (approx. 1 - 3 h). The reaction mixture was quenched by the addition of 15-30 mL of brine (*N*-heterocycles) or a sat. aq. NH_4Cl solution. Formed precipitate was filtered off with a fritted funnel (P3, 300 mbar). The filter cake was washed with EtOAc (3 x 25 ml) and the filtrate was brought into a separatory funnel with Et_2O (10-20 mL) and EtOAc (10-20 mL). The organic layer was extracted with brine (3 x 15 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL). The organic layers were washed with brine (20 mL) dried over anhydrous $MgSO_4$ filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatographical purification on silica.

Typical Procedure 9 (TP9): Quenching by performing an Allylation Reaction **:**

After complete metalation was achieved according to **TP5** $ZnCl_2$ (1 M in THF, 1.6 equiv) (if required, see specific procedures) was added at –40 °C. The resulting mixture was stirred for 15 min. CuCN·2LiCl (1 M in THF, 0.1 equiv) was added together with the corresponding allylbromide and the mixture was allowed to warm to room temperature. Complete consumption of the organozinc reagent was monitored via GC-analysis (approx. 1 - 3 h). The reaction mixture was quenched by the addition of 15-30 mL of brine (*N*-heterocycles) or a sat. aq. NH_4Cl solution. Formed precipitate was filtered off with a fritted funnel (P3, 300 mbar).

The filter cake was washed with EtOAc (3 x 25 ml) and the filtrate was brought into a separatory funnel with Et_2O (10-20 mL) and EtOAc (10-20 mL). The organic layer was extracted with brine (3 x 15 mL). The combined aqueous layers were extracted with EtOAc (2 x 20 mL). The organic layers were washed with brine (20 mL) dried over anhydrous $MgSO_4$ filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatographical purification on silica.

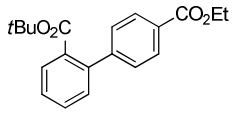
Typical Procedure 10 (TP10): Co-catalyzed aryl sulfonate/copper-exchange:

A dry and argon flushed 25 mL Schlenk-tube was charged with PhMgCl (1.74 mL, 1.72 M in THF, 3.00 mmol) and cooled to –20 °C. Then, CuCN·2LiCl (3.6 mL, 1.0 M in THF, 3.6 mmol) was dropwise added. The resulting yellow solution was stirred for 20 min at –20 °C. Then, Bu_4NI (369 mg, 1.00 mmol), the arylsulfonate (1.00 mmol), $Co(acac)_2$ (51 mg, 20 mol%), 4-fluorostyrene (65 mg, 50 mol%) and dry DMPU (2.2 mL) were added. The resulting suspension was warmed to 25 °C (or 45 °C see specific procedure) and stirred until GC-analysis showed full consumption of the starting material. The formation of the copper reagent was monitored by performed iodolysis of reaction aliquots (GC-analysis). The reaction mixture was cooled to –20 °C and the electrophile (2.00 mmol) was added. The reaction mixture was stirred 30 min at –20 °C and for 2 h at 25 °C. The mixture was quenched by the addition of NH_4Cl/NH_3 (9:1) (15 mL) and extracted with Et_2O (3 x 25 mL). The aqueous phase was extracted with EtOAc (25 mL) twice. The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica furnished the desired product.

4.3. Magnesiation on Weakly Activated Substrates Using a Highly Reactive Mg-Base.

4.3.1. Directed Metalation and Reaction with Electrophiles

Synthesis of 2-*t*-butyl 4'-ethyl biphenyl-2,4'-dicarboxylate (15d):



The title compound was prepared from *tert*-butyl benzoate (**13a**; 178 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), 4-iodobenzoate (414 mg, 1.5 mmol), $ZnCl_2$ (1.6 ml, 1 M in THF, 1.6 mmol), $Pd(dba)_2$ (11 mg, 2 mol%) and P(*2-furyl*)$_3$ (9 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: 25 °C, 60 min. Flash chromatography on silica (*n*-pentane/Et_2O, 9:1) gave a colorless oil (267 mg, 82%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, J = 8.2 Hz, 2 H), 7.86 (dd, J = 7.7 Hz, J = 1.5 Hz, 1 H), 7.54 (dd, J = 7.4 Hz, J = 1.4 Hz, 1 H), 7.46 (dd, J = 7.5 Hz, J = 1.4 Hz, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.33 (dd, J = 7.5 Hz, J = 1.3 Hz, 1 H), 4.43 (q, J = 7.1 Hz, 2 H), 1.45 (t, J = 7.1 Hz, 3 H), 1.29 (s, 9 H).

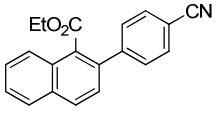
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.8, 166.8, 146.9, 141.4, 138.8, 132.9, 131.1, 130.6, 130.2, 129.4, 128.9, 127.9, 81.8, 61.2, 27.9, 14.6.

MS (70 eV, EI) *m/z* (%): 326 (5) [M^+], 281 (5), 270 (100), 253 (7), 242 (32), 225 (71), 181 (10), 152 (15), 151 (6), 57 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2933, 1707, 1610, 1367, 1268, 1125, 1098, 847, 752, 703.

HRMS (EI): 326.1500 (calcd.: 326.1518).

Synthesis of ethyl 2-(4-cyanophenyl)-1-naphthoate (15e):



The title compound was prepared from ethyl 1-naphtoate (**13b**; 200 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), 4-iodobenzonitrile (342 mg, 1.5 mmol), $ZnCl_2$ (1.6 ml, 1 M in THF, 1.6 mmol), $Pd(dba)_2$ (11 mg, 2 mol%) and P(2-furyl)$_3$ (9 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: 0 °C, 3 h. Flash chromatography on silica (*n*-pentane/Et_2O 4:1) furnished a pale yellow solid (244 mg, 81%).

m.p.: 105.6 - 107.9 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 8.00 (m, 2 H), 7.90 (m, 1 H), 7.72 (ddd, *J* = 8.4 Hz, *J* = 1.9 Hz, *J* = 1.7 Hz, 2 H), 7.58 (m, 4 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 1.03 (t, *J* = 7.1 Hz, 3 H).

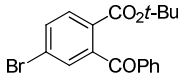
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.0, 146.1, 136.3, 133.0, 132.3, 132.0, 130.7, 130.5, 130.1, 129.7, 128.4, 127.2, 126.7, 125.4, 118.9, 111.7, 61.7, 14.0.

MS (70 eV, EI) *m/z* (%): 302 (17), 301 (77) [M^+], 273 (9),257 (27), 256 (100), 228 (36), 227 (71), 226 (13), 201 (18), 200 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 2899, 2223, 1711, 1604, 1593, 1502, 1470, 1429, 1377, 1281, 1233, 1149, 1137, 1033, 1022, 1002, 959, 862, 822, 801, 757, 663.

HRMS (EI): 301.1084 (calcd.: 301.1103).

Synthesis of *t*-butyl 2-benzoyl-4-bromobenzoate (15f):



The title compound was prepared from *tert*-butyl 4-bromobenzoate (**13d**; 257 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), benzoyl chloride (265 ml, 2.2 mmol), $CuCN{\cdot}2LiCl$ (0.1 mL, 1 M in THF, 10 mol%) applying **TP5** and **TP8**. Metalation conditions: –20 °C, 1 h. Flash chromatography on silica (*n*-pentane/Et_2O 5:1) furnished a pale yellow solid (278 mg, 77%).

m.p.: 71.1 - 73.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ : 7.90 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.78 (m, 2 H), 7.70 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1 H), 7.62 – 7.57 (m, 1 H), 7.53 – 7.44 (m, 3 H), 1.24 (s, 9 H).

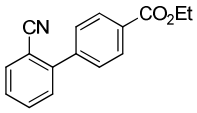
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.2, 164.7, 142.8, 136.9, 133.7, 132.9, 131.8, 130.8, 130.2, 129.9, 128.8, 127.1, 83.4, 27.7.

MS (70 eV, EI) *m/z* (%): 360 (7) [M^+-H], 307 (89), 305 (39), 287 (65), 227 (11), 181 (100), 152 (39), 105 (80), 77 (35), 57 (43).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 2933, 1713, 1674, 1538, 1449, 1392, 1368, 1299, 1289, 1128, 1093, 946, 848, 696.

HRMS (EI): 360.0343 (calcd.: 360.0361).

Synthesis of ethyl 2'-cyanobiphenyl-4-carboxylate (15g):



The title compound was prepared from benzonitrile (**13e**; 103 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), ethyl 4-iodobenzoate (414 mg, 1.5 mmol), $ZnCl_2$ (1.6 ml, 1 M in THF, 1.6 mmol), $Pd(dba)_2$ (11 mg, 2 mol%) and $P(2\text{-furyl})_3$ (9 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –30 °C, 3 h. Flash chromatography on silica (*n*-pentane/Et_2O 4:1) furnished a colorless solid (176 mg, 70%).

m.p.: 115.0 - 117.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ : 8.1 (d, J = 8.2 Hz, 2 H), 7.8 (d, J = 8.2 Hz, 1 H), 7.6 (m, 3 H), 7.5 (m, 2 H), 4.4 (q, J = 7.3 Hz, 2 H), 1.4 (t, J = 7.1 Hz, 3 H).

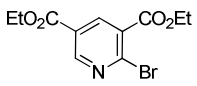
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.4, 144.7, 142.6, 134.1, 133.2, 131.1, 130.3, 130.2, 129.1, 128.4, 118.6, 11.6, 61.4, 14.6.

MS (70 eV, EI) *m/z* (%): 251 (30) [M^+], 223 (33), 207 (17), 206 (100), 179 (26), 178 (32), 177 (30), 152 (11), 151 (39), 150 (15), 75 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2908, 2224, 1708, 1607, 1594, 1559, 1478, 1406, 1366, 1315, 1272, 1184, 1110, 1097, 1030, 860, 763, 740, 721, 704.

HRMS (EI): 251.0960 (calcd.: 251.0946).

Synthesis of diethyl 2-bromopyridine-3,5-dicarboxylate (15h):



The title compound was prepared from diethyl pyridine-3,5-dicarboxylate (**13f**; 223 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), $BrCl_2CCCl_2Br$ (779 mg, 2.4 mmol) applying **TP5**. Metalation conditions: –40 °C, 3 h. Flash chromatography on silica (*n*-pentane/Et_2O 9:1) furnished a pale yellow solid (211 mg, 70%).

m.p.: 40.2 - 41.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.9 (d, J = 2.3 Hz, 1 H), 8.5 (d, J = 2.3 Hz, 1 H), 4.3 (q, J = 7.1 Hz, 2 H), 4.3 (q, J = 7.1 Hz, 2 H), 1.3 (t, J = 7.1 Hz, 3 H), 1.3 (t, J = 7.1 Hz, 3 H).

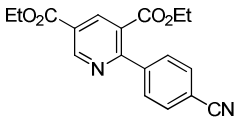
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.6, 164.0, 152.7, 140.3, 139.0, 130.2, 125.6, 63.3, 62.8, 14.4, 14.3.

MS (70 eV, EI) *m/z* (%): 301 (40) [M^+], 275 (28), 273 (30), 258 (100), 255 (94), 230 (37), 228 (39), 202 (11), 194 (27), 166 (15), 76 (15), 45 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2996, 1733, 1717, 1588, 1551, 1380, 1243, 1229, 1109, 1049, 1017, 762.

HRMS (EI): 300.9952 (calcd.: 300.9949).

Synthesis of diethyl 2-(4-cyanophenyl)pyridine-3,5-dicarboxylate (15i):



The title compound was prepared from diethyl pyridine-3,5-dicarboxylate (**13f**; 223 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), ethyl 4-iodobenzonitrile (342 mg, 1.5 mmol), $ZnCl_2$ (1.6 ml, 1 M in THF, 1.6 mmol), $Pd(dba)_2$ (11 mg, 2 mol%) and P(2-furyl)$_3$ (9 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –40 °C, 3 h. Flash chromatography on silica (*n*-pentane/Et_2O 3:1) furnished a colorless solid (237 mg, 73%).

m.p.: 119.0 - 113.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 9.3 (d, J = 2.0 Hz, 1 H), 8.7 (d, J = 2.2 Hz, 1 H), 7.7 (d, J = 8.6 Hz, 2 H), 7.6 (d, J = 8.6 Hz, 2 H), 4.5 (d, J = 7.1 Hz, 2 H), 4.2 (d, J = 7.1 Hz, 2 H), 1.4 (t, J = 7.1 Hz, 3 H), 1.1 (t, J = 7.1 Hz, 3 H).

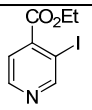
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.5, 164.4, 160.5, 152.4, 144.0, 139.6, 132.1, 129.7, 127.2, 125.5, 118.8, 113.2, 62.3, 62.2, 14.5, 14.0.

MS (70 eV, EI) *m/z* (%): 324 (9) [M^+], 296 (17), 295 (100), 179 (24), 267 (59), 251 (11), 223 (10), 152 (10),140 (7), 102 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 2911, 2224, 1721, 1596, 1448, 1398, 1319, 1244, 1227, 1148, 1091, 1018, 149, 852, 798, 775, 743, 646.

HRMS (EI): 324.1111 (calcd.: 324.1110).

Synthesis of ethyl 3-iodopyridine-4-carboxylate (15j):



The title compound was prepared from ethyl isonicotinate (**13g**; 151 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), I_2 (609 mg, 2.4 mmol) applying **TP5**. Metalation conditions: –40 °C, 12 h. Flash chromatography on silica (*n*-pentane/Et_2O 7:3) furnished a pale brown oil (152 mg, 66 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.1 (s, 1 H), 8.6 (d, *J* = 4.9 Hz, 1 H), 7.6 (d, *J* = 4.9 Hz, 1 H), 4.4 (q, *J* = 7.1 Hz, 2 H), 1.4 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.2, 159.8, 149.3, 142.7, 124.6, 92.6, 62.7, 14.4.

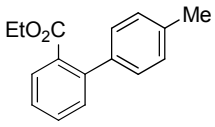
MS (70 eV, EI) *m/z* (%): 277 (100) [M^+], 248 (47), 232 (57), 204 (24), 177 (23), 127 (5), 122 (10), 94 (7), 78 (4), 50 (1).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 1727, 1464, 1260, 1078, 1010, 776, 700, 662.

HRMS (EI): 276.9590 (calcd.: 276.9599).

4.3.2. Scale up Experiments

Synthesis of ethyl 4'-methylbiphenyl-2-carboxylate (15k):



In a flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (110 mL, 100 mmol) was provided, ethyl benzoate (**13h**; 13.5 g, 90 mmol) was added and the reaction mixture was stirred for 45 min at 25 °C. The resulting solution was cooled to –40 °C and $ZnCl_2$ (100 mL, 100 mmol, 1.1 equiv) was added and the resulting mixture is stirred for 15 min. Then, $Pd(OAc)_2$ (0.5 mol%), RuPHOS (1 mol%) and 4-bromotoluene (16.2 g, 95 mmol, 1.05 equiv) were added. After warming to 25 °C and stirring for 12 h at 25 °C, the reaction was quenched with a sat. aqueous NH_4Cl solution (250 mL) and extracted with Et_2O (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (*n*-pentane/Et_2O 9:1) and gave a pale yellow oil (15.4 g,

71%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 (m, 1 H), 7.5 (m, 1 H), 7.4 (m, 2 H), 7.2 (m, 4 H), 4.2 (q, J = 7.0 Hz, 2 H), 2.4 (s, 3 H), 1.1 (t, J = 7.2 Hz, 3 H).

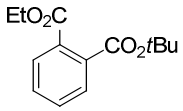
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.9, 142.5, 138.6, 136.8, 131. 5, 131.1, 130.7, 129.7, 128.8, 128.37, 127.0, 60.9, 21.2, 13.8.

MS (70 eV, EI) *m/z*: 240 (51) [M^+], 213 (10), 212 (10), 196 (18), 195 (100),167 (23), 166 (18), 165 (51), 153 (10), 152 (48), 82 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3024, 2981, 2924, 2870, 1713, 1600, 1518, 1445, 1365, 1286, 1276, 1241, 1172, 1125, 1112, 1085, 1047, 1016, 1006, 854, 819, 758, 730, 709, 656.

HRMS (EI): 240.1142 (calcd.: 240.1150).

Synthesis of 2-*tert*-butyl ethyl phthalate (15l)



In a flame-dried and nitrogen-flushed 500-mL Schlenk flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (110 mL, 100 mmol) was added followed by ethyl benzoate (**13h**; 13.5 g, 90 mmol) and the reaction mixture was stirred for 45 min at 25 °C. Boc_2O (28.0 g, 130 mmol, 1.44 equiv) was added in one portion at 25 °C and the reaction mixture was stirred for 2 h. A sat. aqueous NH_4Cl solution (250 mL) was added and the mixture was extracted with Et_2O (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (*n*-pentane/Et_2O 4:1) and gave a yellow oil (15.1 g, 67%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.6 (m, 2 H), 7.4 (m, 2 H), 4.3 (q, J = 7.2 Hz, 2 H), 1.5 (s, 9 H), 1.3 (t, J = 7.0 Hz, 3 H).

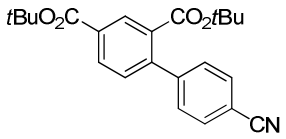
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.8, 166.3, 133.2, 132.3, 130.5, 130.45, 128.8, 128.4, 81.8, 61.3, 27.8, 13.9.

MS (70 eV, EI) *m/z*: 251 (29), 246 (21), 195 (100), 177 (23) [M+-CO2Et], 150 (4), 149 (35).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 1715, 1599, 1579, 1477, 1447, 1392, 1367, 1286, 1255, 1172, 1123, 1072, 1038, 1017, 845, 784, 737, 705.

HRMS (EI): 251.1280 (calcd.: 251.1278).

Preparation of di-*tert*-butyl 4'-cyanobiphenyl-2,4-dicarboxylate (15m)



In a flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (100 mL, 90 mmol) was provided, di-*tert*-butylisophthalate (**13i**; 22.2 g, 80 mmol) was added and the reaction mixture was stirred for 45 min at 25 °C. The resulting solution was cooled to –40 °C and $ZnCl_2$ (90 mL, 90 mmol, 1.1 equiv) was added and the resulting mixture was stirred for 15 min. Then, $Pd(OAc)_2$ (0.5 mol%), RuPHOS (1 mol%) and 4-bromobenzonitrile (15.3 g, 84 mmol, 1.05 equiv) were added. After warming to 25 °C and stirring for 12 h at 25°C, the reaction mixture was quenched with a sat. aqueous NH_4Cl solution (250 mL) and extracted with Et_2O (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The crude product was purified by recrystallization (*n*-heptane/EtOAc) and gave a yellow solid (22.8 g, 75%).

m.p.: 158.5 - 158.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.4 (d, *J*=1.5 Hz, 1 H), 8.1 (dd, *J* = 8.0, 1.9 Hz, 1 H), 7.7 (d, *J* = 8.5 Hz, 2 H), 7.4 (d, *J* = 8.5 Hz, 2 H), 7.3 (d, *J* = 8.0 Hz, 1 H), 1.6 (s, 9 H), 1.3 (s, 9 H).

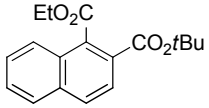
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.3, 164.5, 146.0, 143.9, 132.6, 132.0, 131.8, 131.7, 131.13, 130.3, 129.2, 118.6, 111.4, 82.2, 81.8, 28.2, 27.6.

MS (70 eV, EI) *m/z*: 323 (19) [M^+ - *t*Bu], 306 (17), 268 (53), 267 (100), 266 (11), 250 (50), 177 (22), 166 (10), 57 (76), 56 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2933, 2228, 1722, 1711, 1604, 1477, 1368, 1324, 1302, 1276, 1254, 1250, 1158, 1146, 1121, 1089, 838, 775, 754, 740.

HRMS (EI): 379.1785 (calcd.: 379.1784).

Preparation of 2-*tert*-butyl 1-ethyl naphthalene-1,2-dicarboxylate (15n)



In a flame-dried and nitrogen-flushed 500-mL Schlenk flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (110 mL, 100 mmol) was added followed by ethyl 1-naphthoate (**13b**; 18.0 g, 90 mmol) and the reaction mixture was stirred for 45 min at 25 °C. Boc_2O (28.0 g, 130 mmol, 1.44 equiv) was added in one portion at 25 °C and the reaction mixture was stirred for 2 h. A sat. aqueous NH_4Cl solution (250 mL) was added and the mixture was extracted with Et_2O (3 x 250 mL). The combined organic layers were washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The crude product was purified by recrystallization (*n*-heptane/EtOAc) and gave a colorless solid (12.4 g, 69%).

m.p.: 70.5 - 70.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.9 (m, 4 H), 7.5 (m, 2 H), 4.5 (q, J = 7.3 Hz, 2 H), 1.64 (s, 9 H), 1.4 (t, J = 7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.0, 165.0, 134.8, 134.3, 129.3, 129.2, 128.0, 127.5, 127.0, 125.9, 125.2, 82.2, 61.7, 28.1, 14.1.

MS (70 eV, EI) *m/z*: 300 (16) [M^+], 244 (41), 227 (10), 216 (11), 200 (20), 199 (100), 198 (10), 172 (21), 155 (29), 154 (14), 127 (25), 126 (30), 57 (15).

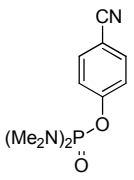
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2982, 2939, 1720, 1708, 1365, 1294, 1269, 1238, 1168, 1139, 1116, 1036, 1014, 860, 848, 833, 798, 790, 764, 733.

HRMS (EI): 300.1358 (calcd.: 300.1362).

4.4. Formal *meta*- and *para*-functionalizations

4.4.1. Starting Material Synthesis

Synthesis of 4-cyanophenyl-*N,N,N',N'*-tetramethyldiamido-phosphate (18a):



Prepared according to **TP1** from 4-cyanophenol (2.38 g, 20.0 mmol). The colorless oil was

used without further purification (4.72 g, 93%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.6 (d, J = 9.0 Hz, 2 H), 7.3 (dd, J = 8.9 Hz, J = 1.0 Hz, 2 H), 2.7 (m, 12 H).

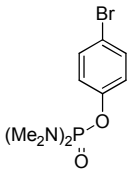
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.4, 134.2, 121.2, 118.8, 108.7, 36.8.

MS (70 eV, EI) *m/z* (%): 253 (27) [M^+], 209 (12), 155 (11), 145 (22), 136 (11), 135 (100), 102 (15), 92 (27), 90 (16), 76 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3456, 2932, 2900, 2856, 2816, 2228, 1604, 1500, 1456, 1416, 1308, 1216, 1164, 1108, 1068, 988, 896, 848, 792, 760, 684, 664.

HRMS (ESI): 253.1050 (calcd.: 253.0980).

Synthesis of 4-bromophenyl-*N,N,N',N'*-tetramethyldiamido-phosphate (18b):



Prepared according to **TP1** from 4-bromophenol (3.46 g, 20.0 mmol). The colorless oil was used without further purification (5.28 g, 86%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.4 (d, J = 9.0 Hz, 2 H), 7.1 (m, 2 H), 2.7 (m, 12 H).

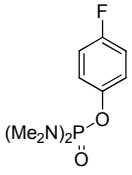
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.8, 132.9, 132.7, 122.2, 122.1, 117.1 , 36.9.

MS (70 eV, EI) *m/z* (%): 309 (20), 308 (100), 307 (27), 306 (100) [M^+], 293 (12), 291 (12), 264 (32), 262 (33), 220 (15), 218 (16), 201 (53), 200 (82), 199 (55), 198 (80), 174 (40), 173 (31), 172 (41), 171 (29), 157 (17), 155 (18), 145 (30), 143 (31), 136 (40), 135 (100), 92 (66), 91 (16), 64 (10), 63 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3452, 2928, 2896, 2852, 2812, 1580, 1484, 1456, 1400, 1304, 1272, 1208, 1164, 1096, 1068, 984, 900, 832, 768, 748, 700, 668.

HRMS (EI): 306.0124 (calcd.: 306.0133).

Synthesis of 4-fluorophenyl-*N,N,N',N'*-tetramethyldiamido-phosphate (18c):



Prepared according to **TP1** from 4-fluorophenol (2.24 g, 20.0 mmol). The colorless oil was used without further purification (2.23 g, 92%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.1 (ddd, J = 9.0 Hz, J = 4.5 Hz, J = 1.2 Hz, 2 H), 7.0 (m, 2 H), 2.7 (m, 12 H).

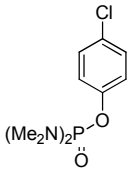
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 160.3, 158.7, 147.5, 121.7, 116.4, 115.8, 36.9. Observed complexity due to C-F splitting, definitive assignments have not been made.

MS (70 eV, EI) *m/z* (%): 246 (43) [M^+], 202 (19), 158 (10), 139 (19), 138 (44), 136 (20), 135 (100), 112 (21), 111 (31), 95 (20), 92 (66), 90 (12), 83 (33), 76 (12), 75 (16), 57 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3456, 3000, 2932, 2896, 2856, 2812, 1644, 1500, 1456, 1364, 1304, 1224, 1180, 1092, 1068, 984, 904, 840, 820, 760, 704, 664.

HRMS (EI): 246.0925 (calcd.: 246.0933).

Synthesis of 4-chlorophenyl-*N,N,N',N'*-tetramethyldiamido-phosphate (18d):



Prepared according to **TP1** from 4-chlorophenol (2.57 g, 20.0 mmol). The colorless oil was used without further purification (4.73 g, 90%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.3 (m, 2 H), 7.1 (d, J = 8.6 Hz, 2 H), 2.7 (m, 12 H).

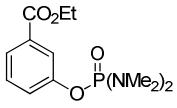
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 150.3, 129.7, 129.5, 121.7, 36.9.

MS (70 eV, EI) *m/z* (%): 262 (18) [M^+], 218 (6), 155 (11), 154 (18), 136 (10), 135 (100), 127 (11), 99 (12), 92 (25), 75 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2892, 2852, 2812, 1592, 1484, 1456, 1404, 1304, 1232, 1212, 1184, 1164, 1088, 1068, 984, 900, 832, 772, 752, 704, 672.

HRMS (EI): 262.0637 (calcd.: 262.0638).

Synthesis of ethyl 3-{[bis(dimethylamino)phosphoryl]oxy} benzoate (21a):



Prepared according to **TP1** from ethyl 3-hydroxybenzoate (3.32 g, 20.0 mmol). The colorless oil was used without further purification (5.57 g, 93%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 – 7.7 (m, 2 H), 7.5 – 7.4 (m, 2 H), 4.4 (q, J = 7.1 Hz, 2 H), 2.8 (m, 12 H) 1.4 (t, J = 7.1 Hz, 3 H).

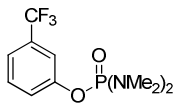
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.1, 151.7, 132.4, 129.8, 125.5, 124.9, 121.5, 61.4, 36.9, 14.5.

MS (70 eV, EI) *m/z* (%): 301 (11), 300 (65) [M^+], 255 (20), 226 (13), 192 (36), 135 (100), 92 (16), 44 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3435, 2997, 1715, 1584, 1483, 1440, 1366, 1268, 1229, 1203, 1097, 1072, 986, 947, 849, 752, 673.

HRMS (EI): 300.1247 (calcd.: 300.1239).

Synthesis of 3-(trifluoromethyl)phenyl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (21b):



Prepared according to **TP1** from 3-(trifluoromethyl)phenol (3.24 g, 20.0 mmol). The colorless oil was used without further purification (5.33 g, 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.4 (m, 4 H), 2.7 (m, 12 H).

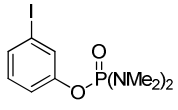
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 151.9, 132.3 (q, J(C-F) = 32.6 Hz), 130.4, 123.9, 123.8 (q, J(C-F) = 272.2 Hz), 121.1, 117.6, 36.9.

MS (70 eV, EI) *m/z* (%): 296 (15) [M^+], 188 (13), 135 (100), 92 (18), 44 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 2900, 1596, 1492, 1448, 1324, 1308, 1280, 1228, 1208, 1164, 1120, 1092, 1064, 988, 928, 884, 796, 760, 732, 696, 676.

HRMS (ESI): 296.0896 (calcd.: 296.0901).

Synthesis of 3-iodophenyl *N*,*N*,*N'*,*N'*-tetramethyldiamido-phosphate (21c):



Prepared according to **TP1** from 3-iodophenol (4.4 g, 20.0 mmol). Flash chromatography on

silica (Et_2O) furnished **4c** as a colorless solid (6.5 g, 92%).

m.p.: 75.0 - 77.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.5 (m, 1 H), 7.4 (m, 2 H), 7.0 (t, J = 7.9 Hz, 1 H), 2.7 (m, 12 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 151.7, 133.3, 130.8, 129.3, 119.6, 93.8, 36.6.

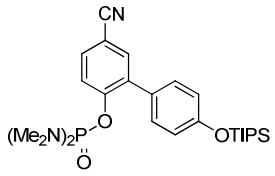
MS (70 eV, EI) *m/z* (%): 355 (2) [M^++H], 354 (12) [M^+], 246 (12), 135 (100), 92 (8), 44 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2922, 2176, 1572, 1463, 1299, 1228, 1199, 1067, 991, 915, 794, 758, 687, 670, 584.

HRMS (ESI): 355.007 (calcd.: 355.007).

4.4.2. Directed Magnesiation Using $TMP_2Mg{\cdot}2LiCl$ and Reaction with Electrophiles

Synthesis of 5-cyano-4'-[(triisopropylsilyl)oxy]biphenyl-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (19a):



The title compound was prepared from **18a** (506 mg, 2.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (3.14 mL, 0.7 M in THF, 2.2 mmol), (4-iodophenoxy)-(triisopropyl)silane (828 mg, 2.2 mmol), $ZnCl_2$ (2.2 ml, 1 M in THF, 2.2 mmol), $Pd(dba)_2$ (22 mg, 2 mol%), P(2-furyl)$_3$ (18 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: 0 °C, 1 h. Flash chromatography on silica (EtOAc) furnished a yellow oil (833 mg, 83%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.6 (m, 3 H), 7.3 (d, *J* = 8.1 Hz, 2 H), 6.9 (d, *J* = 8.4 Hz, 2 H), 2.5 (m, 12 H), 1.3 (m, 3 H), 1.1 (m, 18 H).

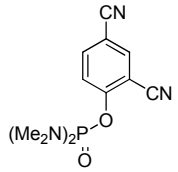
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.4, 152.3, 135.0, 134.6, 132.4, 130.8, 128.7, 121.5, 120.0, 118.8, 108.1, 36.7, 18.1, 12.9.

MS (70 eV, EI) *m/z* (%): 501 (16) [M^+], 459 (30), 458 (100), 415 (10), 135 (40).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944, 2892, 2868, 2228, 1604, 1512, 1484, 1464, 1420, 1392, 1260, 1216, 1172, 1132, 1104, 1068, 1040, 988, 900, 856, 836, 764, 740, 684, 660.

HRMS (ESI): 502.2653 (calcd.: 502.2655).

Synthesis of 2,4-dicyanophenyl *N*,*N*,*N*',*N*'-tetramethyldi-amidophosphate (19b):



The title compound was prepared from **18a** (254 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), TsCN (199 mg, 1.10 mmol), $ZnCl_2$ (1.2 ml, 1 M in THF, 1.2 mmol), CuCN·2LiCl (1 m in THF, 1.3 mL, 1.30 mmol) applying **TP5** and **TP8**. Metalation conditions: 0 °C, 1 h. Flash chromatography on silica (EtOAc) furnished a colorless solid (209 mg, 77%).

m.p.: 143.0 - 144.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.9 (d, J = 1.1 Hz, 1 H), 7.8 (m, 2 H), 2.8 (m, 12 H).

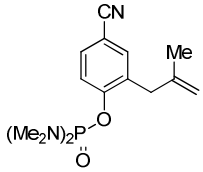
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 156.9, 138.0, 137.4, 122.0, 116.7, 114.0, 108.7, 106.9, 36.8.

MS (70 eV, EI) *m/z* (%): 278 (66) [M^+], 207 (100), 206 (23), 135 (50), 97 (16), 95 (14), 83 (32), 73 (54), 57 (18), 55 (27), 43 (13), 41 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2936, 2892, 2236, 1604, 1488, 1456, 1312, 1296, 1252, 1224, 1192, 1164, 1108, 1068, 1000, 984, 924, 912, 864, 844, 764, 744, 716, 684, 660.

HRMS (EI): 278.0920 (calcd.: 278.0933).

Synthesis of 4-cyano-2-(2-methylprop-2-en-1-yl)phenyl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (19c):



The title compound was prepared from **18a** (254 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol), 3-bromo-2-methylpropene (156 mg, 1.2 mmol), CuCN·2LiCl (0.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP9**. Metalation conditions: 0 °C, 1 h. Flash chromatography on silica (EtOAc) furnished a colorless oil (258 mg, 84%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.5 (m, 2 H), 7.5 (s, 1 H), 4.9 (d, J = 1.8 Hz, 1 H), 4.6 (d, J = 0.9 Hz, 1 H), 3.4 (s, 2 H), 2.7 (m, 12 H) 1.7 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.7, 142.8, 135.0, 132.2, 131.8, 120.1, 119.0, 113.3, 107.6,

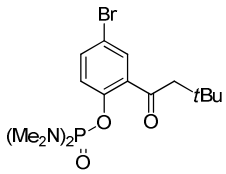
38.0, 36.9, 22.7.

MS (70 eV, EI) *m/z* (%): 307 (29) [M^+], 306 (23), 263 (22), 200 (15), 199 (13), 173 (15), 156 (11), 154 (14), 136 (15), 135 (100), 92 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3460, 2932, 2904, 2856, 2812, 2228, 1652, 1600, 1580, 1492, 1456, 1412, 1376, 1304, 1248, 1212, 1180, 1112, 1068, 988, 940, 924, 876, 832, 756, 724, 704, 684, 664.

HRMS (EI): 307.1410 (calcd.: 307.1450).

Synthesis of 4-bromo-2-(3,3-dimethyl-2-oxobutyl)phenyl *N,N,N',N'*-tetramethyldiamidophosphate (19d)



The title compound was prepared from **18b** (614 mg, 2.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (3.14 mL, 0.7 M in THF, 2.2 mmol), $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol), 3,3-dimethylbutanoyl chloride (323 mg, 2.4 mmol), $CuCN{\cdot}2LiCl$ (0.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP8**. Metalation conditions: –50 °C, 7 h. Flash chromatography on silica (EtOAc) furnished a colorless oil (293 mg, 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.5 (m, 1 H), 7.5 (m, 2 H), 2.9 (s, 2 H), 2.7 (m, 12 H), 1.1 (s, 9 H).

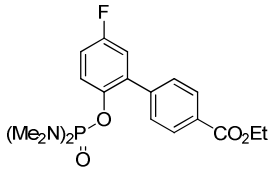
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 201.3, 153.4, 148.2, 135.0, 131.8, 122.4, 116.8, 55.4, 36.9, 31.8, 30.0.

MS (70 eV, EI) *m/z* (%): 404 (5) [M^+], 363 (10), 362 (62), 361 (17), 360 (62), 346 (20), 344 (20), 335 (34), 333 (35), 307 (45), 306 (100), 305 (52), 304 (100), 303 (19), 299 (11), 297 (11), 262 (12), 260 (11), 225 (21), 224 (11), 201 (10), 199 (11), 198 (12), 135 (100), 92 (19), 57 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3460, 2952, 2904, 2868, 2812, 1688, 1588, 1568, 1472, 1388, 1364, 1304, 1264, 1212, 1176, 1116, 1068, 988, 896, 820, 760, 744, 724, 676.

HRMS (EI): 404.0811 (calcd.: 404.0863).

Synthesis of ethyl 2'-{[bis(dimethylamino)phosphoryl]oxy}-5'-fluorobiphenyl-4-carboxylate (19e):



The title compound was prepared from **18c** (246 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), ethyl-4-iodobenzoate (414 mg, 1.5 mmol), $ZnCl_2$ (1.2 ml, 1 M in THF, 1.2 mmol), $Pd(dba)_2$ (11 mg, 2 mol%), $P(2\text{-furyl})_3$ (9 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –40 °C, 4 h. Flash chromatography on silica (EtOAc) furnished a pale yellow solid (307 mg, 78%).

m.p.: 77.0 - 78.6 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.1 (d, J = 8.4 Hz, 2 H), 7.6 (d, J = 8.6 Hz, 2 H), 7.5 (dd, J = 9.8 Hz, J = 5.4 Hz, 1 H), 7.0 (m, 2 H), 4.4 (q, J = 7.1 Hz, 2 H), 2.7 (m, 2 H), 2.5 (m, 10 H), 1.4 (t, J = 7.2 Hz, 3 H).

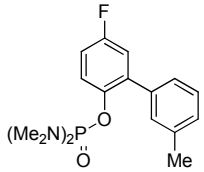
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.6, 159.9, 158.3, 144.6, 141.9, 133.9, 129.9, 129.7, 129.6, 122.3, 117.5, 116.0, 115.8, 61.3, 36.9, 36.7, 14.5. Observed complexity due to C-F splitting, definitive assignments have not been made.

MS (70 eV, EI) *m/z* (%): 394 (3) [M^+], 286 (13), 260 (10), 186 (10), 157 (10), 135 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3040, 3004, 2928, 2908, 2856, 2816, 1708, 1668, 1608, 1592, 1568, 1512, 1488, 1452, 1424, 1400, 1372, 1304, 1280, 1252, 1224, 1172, 1128, 1100, 1068, 1016, 992, 940, 912, 884, 860, 828, 772, 756, 732, 712, 700, 672.

HRMS (ESI): 395.1529 (calcd.: 395.1536).

Synthesis of 5-fluoro-3'-methylbiphenyl-2-yl *N*,*N*,*N*',*N*'-tetra-methyldiamidophosphate (19f):



The title compound was prepared from **18c** (1.23 g, 5.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (7.85 mL, 0.7 M in THF, 5.5 mmol), 3-iodotoluene (1.2 g, 5.5 mmol)., $ZnCl_2$ (6.0 ml, 1 M in THF, 6.0 mmol), $Pd(dba)_2$ (55 mg, 2 mol%), $P(2\text{-furyl})_3$ (45 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –40 °C, 4 h. Flash chromatography on silica (EtOAc) furnished a pale

yellow oil (1.26 g, 75%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.4 (ddd, J = 9.0 Hz, J = 4.9 Hz, J = 1.2 Hz, 1 H), 7.3 (ddd, J = 15.2 Hz, J = 7.8 Hz, J = 7.7 Hz, 3 H), 7.1 (d, J = 7.6 Hz, 1 H), 7.0 (ddd, J = 9.0 Hz, J = 3.2 Hz, J = 1.0 Hz, 1 H), 7.0 (ddd, J = 9.0 Hz, J = 7.7 Hz, J = 3.2 Hz, 1 H), 2.7 (m, 1 H), 2.5 (m, 11 H), 2.4 (s, 3 H).

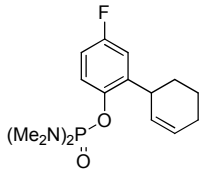
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 159.9, 158.4, 144.6, 137.8, 137.2, 130.4, 128.6, 128.3, 126.7, 122.1, 117.5, 115.1, 36.9, 21.6. Observed complexity due to C-F splitting, definitive assignments have not been made.

MS (70 eV, EI) *m/z* (%): 337 (15), 336 (100) [M^+], 248 (12), 247 (14), 228 (83), 185 (13), 183 (12), 169 (10), 136 (12), 135 (42), 92 (11), 44 (71).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3464, 2992, 2924, 2896, 2852, 2812, 1608, 1584, 1496, 1476, 1412, 1396, 1304, 1220, 1164, 1116, 1096, 1068, 1044, 984, 936, 892, 816, 788, 760, 720, 700, 664.

HRMS (EI): 336.1377 (336.1403).

Synthesis of 2-cyclohex-2-en-1-yl-4-fluorophenyl *N,N,N',N'*-tetramethyldiamidophosphate (19g):



The title compound was prepared from **18c** (246 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol), 3-bromocyclohexene (354 mg, 1.2 mmol), CuCN·2LiCl (0.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP9**. Metalation conditions: –40 °C, 4 h. Flash chromatography on silica (EtOAc) furnished a colorless oil (277 mg, 85%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.2 (ddd, J = 8.9 Hz, J = 4.9 Hz, J = 1.2 Hz, 1 H), 6.9 (ddd, J = 9.6 Hz, J = 3.2 Hz, J = 1.0 Hz, 1 H), 6.8 (ddd, J = 8.9 Hz, J = 7.7 Hz, J = 3.2 Hz, 1 H), 6.0 (m, 1 H), 5.6 (m, 1 H), 3.8 (s, 1 H), 2.7 (m, 12 H), 2.1 (m, 2 H), 2.0 (m, 1 H), 1.7 (m, 1 H), 1.6 (m, 2 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 160.1, 145.2, 138.8, 129.8, 129.0, 120.3, 115.9, 113.6, 36.9, 35.1, 30.4, 25.1, 20.8. Observed complexity due to C-F splitting, definitive assignments have not been made.

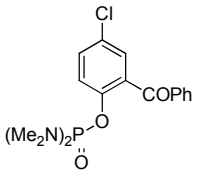
MS (70 eV, EI) *m/z* (%): 327 (20), 326 (100) [M^+], 192 (12), 190 (12), 153 (23), 135 (95), 92

(15), 44 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3456, 3220, 3020, 2928, 2856, 2812, 1652, 1616, 1592, 1484, 1456, 1420, 1392, 1308, 1240, 1220, 1168, 1096, 1068, 984, 956, 900, 864, 816, 756, 736, 708, 664.

HRMS (EI): 326.1574 (326.1559).

Synthesis of 2-benzoyl-4-chlorophenyl *N*,*N*,*N*',*N*'-tetramethyl-diamidophosphate (19h):



The title compound was prepared from **18d** (1.31 g, 5.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (7.85 mL, 0.7 M in THF, 5.5 mmol), $ZnCl_2$ (1 M in THF, 6.0 mL, 6.0 mmol), benzoyl chloride (773 mg, 5.5 mmol), CuCN·2LiCl (2.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP8**. Metalation conditions: –40 °C, 4 h. Flash chromatography on silica (EtOAc) furnished a pale red oil (1.57 g, 85%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.8 (m, 2 H), 7.6 (m, 1 H), 7.5 (dd, J = 8.8 Hz, J = 0.9 Hz, 1 H), 7.5 (t, J = 7.8 Hz, 2 H), 7.4 (m, 1 H), 7.4 (dd, J = 2.7 Hz, J = 1.0 Hz, 1 H), 2.4 (m, 12 H).

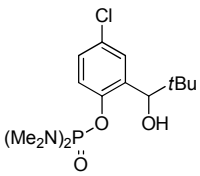
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 194.2, 147.8, 137.2, 133.8, 132.6, 131.8, 130.1, 129.4, 128.8, 121.8, 36.5.

MS (70 eV, EI) *m/z* (%): 366 (3) [M^+], 324 (35), 323 (24), 322 (100), 321 (11), 280 (12), 278 (34), 258 (13), 228 (12), 135 (100), 105 (10), 77 (16), 44 (36).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3460, 3064, 2928, 2896, 2852, 2812, 1668, 1596, 1472, 1448, 1400, 1312, 1288, 1264, 1216, 1180, 1156, 1116, 1068, 988, 956, 900, 832, 808, 788, 760, 740, 712, 700, 668.

HRMS (EI): 366.0900 (calcd.: 366.0900).

Synthesis of 4-chloro-2-(1-hydroxy-2,2-dimethylpropyl)phenyl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (19i):



4-Chlorophenyl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (**18d**) (525 mg, 2.0 mmol) was reacted with $TMP_2Mg{\cdot}2LiCl$ (3.14 mL, 0.7 M in THF, 2.2 mmol) in THF (2 mL) at –40 °C for 1.5 h. Complete metalation was detected by GC-analysis of reaction aliquots, quenched with I_2 in THF. Then the mixture was cooled to –80 °C and pivaline aldehyde (215 mg, 2.5 mmol) was slowly added. The reaction mixture was slowly warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 × 15 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (EtOAc) furnished a colorless solid (550 mg, 79%).

m.p.: 158.3 - 160.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.5 (d, J = 2.0 Hz, 1 H), 7.2 (m, 2 H), 4.8 (s, 1 H), 3.1 (br, 1 O*H*), 2.7 (m, 12 H), 1.0 (s, 9 H).

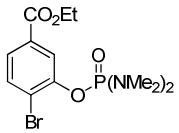
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 147.5, 136.3, 129.5, 129.4, 128.2, 120.6, 74.3, 36.9, 36.5, 26.1.

MS (70 eV, EI) *m/z* (%): 348 (2) [M^+], 290 (16), 189 (12), 288 (44), 247 (31), 246 (10), 245 (100), 153 (21), 135 (67), 91 (10), 44 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3336, 2944, 2928, 2904, 2876, 1472, 1384, 1348, 1312, 1292, 1256, 1232, 1208, 1168, 1116, 1092, 1060, 1000, 984, 928, 908, 896, 868, 808, 752, 724, 672.

HRMS (EI): 348.1354 (calcd.: 348.1370).

Synthesis of ethyl 3-{[bis(dimethylamino)phosphoryl]oxy} 4-bromobenzoate (22a):



Ethyl 3-{[bis(dimethylamino)phosphoryl]oxy}benzoate (**21a**) (300 mg, 1.0 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. Then $TMP_2Mg{\cdot}2LiCl$ (0.6 M in THF, 1.83 mL, 1.1 mmol) was added dropwise. The mixture was stirred for 1 h, and after that $BrCl_2CCCl_2Br$ (779 mg, 2.4 mmol), dissolved in dry THF (2 mL), was added dropwise at –40 °C and the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 × 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (EtOAc) furnished a pale yellow oil (302 mg, 80%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.0 (m, 1 H), 7.7 (m, 1 H), 7.6 (d, J = 7.9 Hz, 1 H), 4.4 (q, J

= 7.1 Hz, 2 H), 2.8 (m, 12 H), 1.4 (m, 3 H).

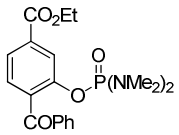
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 165.6, 150.0, 133.6, 131.4, 126.1, 121.8, 120.1, 61.6, 37.0, 14.5.

MS (70 eV, EI) *m/z* (%): 378 (1) [M^+-H], 299 (39), 135 (100), 92 (17), 63 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929, 2811, 1717, 1589, 1573, 1475, 1405, 1366, 1279, 1212, 1101, 1068, 988, 954, 850, 754, 680, 663.

HRMS (EI): 378.0377 (calcd.: 378.0344).

Synthesis of ethyl 4-benzoyl-3-{[bis(dimethylamino)-phosphoryl]oxy}benzoate (22b):



The title compound was prepared from **21a** (300 mg, 1.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol), benzoyl chloride (155 mg, 1.1 mmol), $CuCN{\cdot}2LiCl$ (0.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP8**. Metalation conditions: 0 °C, 1 h. Flash chromatography on silica (EtOAc) furnished a greenish yellow oil (296 mg, 73%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.1 (m, 1 H), 7.9 (dd, J = 7.9 Hz, 1.3 Hz, 1 H), 7.8 (m, 2 H), 7.6 (m, 1 H), 7.4 (m, 3 H), 4.4 (q, J = 7.1 Hz, 2 H), 2.5 (m, 12 H), 1.4 (t, J = 7.2 Hz, 3 H).

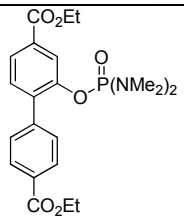
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 195.0, 165.5, 149.1, 137.1, 135.5, 134.0, 133.8, 130.2, 129.5, 128.9, 127.6, 125.1, 121.5, 61.7, 36.5, 14.5.

MS (70 eV, EI) *m/z* (%): 404 (1) [M^+], 361 (23), 360 (100), 359 (15), 317 (35), 289 (15), 269 (10), 266 (14), 168 (13), 152 (11), 135 (45), 105 (26), 92 (16), 77 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929, 1718, 1668, 1596, 1405, 1281, 1205, 1089, 990, 964, 920, 851, 756, 703, 652.

HRMS (EI): 404.1493 (calcd.: 404.1501).

Synthesis of diethyl 2-{[bis(dimethylamino)phosphoryl]oxy}-biphenyl-4,4'-dicarboxylate (22c):



The title compound was prepared from **21a** (300 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), ethyl-4-iodobenzoate (414 mg, 1.5 mmol), $ZnCl_2$ (1.2 ml, 1 M in THF, 1.2 mmol), $Pd(dba)_2$ (11 mg, 2 mol%), P(2-furyl)$_3$ (9 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –40 °C, 4 h. Flash chromatography on silica (EtOAc) a yellowish solid (351 mg, 78%).

m.p.: 53.0 - 55.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.1 (m, 2 H), 8.0 (m, 1 H), 7.9 (m, 1 H), 7.6 (m, 2 H), 7.4 (dd, J = 8.1 Hz, J = 1.0 Hz, 1 H), 4.4 (m, 4 H), 2.5 (m, 12 H), 1.4 (m, 6 H).

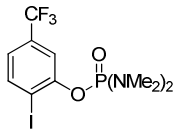
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 166.6, 165.9, 148.6, 148.5, 142.1, 137.2, 131.8, 131.1, 130.0, 129.8, 129.6, 125.6, 121.9, 61.5, 61.3, 36.7, 14.5.

MS (70 eV, EI) *m/z* (%): 448 (4) [M^+], 403 (3), 374 (10), 340 (24), 314 (31), 195 (11), 169 (7), 139 (15), 135 (100), 92 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2987, 2901, 1707, 1605, 1556, 1518, 1474, 1392, 1366, 1272, 1235, 1181, 1197, 1124, 1099, 1070, 1026, 999, 958, 958, 906, 854, 845, 781, 757, 728, 675.

HRMS (EI): 448.1777 (calcd.: 448.1763).

Synthesis of 2-iodo-5-(trifluoromethyl)phenyl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (22d):



A solution of **21b** (592 mg, 2.0 mmol) in THF (2 mL) was cooled to -40 °C. Then $TMP_2Mg{\cdot}2LiCl$ (0.6 M in THF, 3.67 mL, 2.2 mmol) was added dropwise and the resulting mixture was stirred for 2 h at –40 °C. Complete metalation was detected by GC-analysis of reaction aliquots, quenched with I_2 in THF. I_2 (558 mg, 2.2 mmol) in THF (2 mL) was added and the mixture was warmed to 25 °C within 12 h. The reaction mixture was quenched by the addition of sat. aq. $Na_2S_2O_3$ (10 mL) and sat. aq. NH_4Cl solution (10 mL). The mixture was extracted with Et_2O (3 x 20 mL) and with EtOAc (3 x 20 mL). The combined organic layers

were washed with brine, dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica (Et_2O/*n*-pentane 3:1) furnishing a colorless solid (749 mg, 88%).

m.p.: 85.3 - 86.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.9 (d, J = 8.4 Hz, 1 H), 7.7 (s, 1 H), 7.1 (dd, J = 8.3 Hz, J = 2.1 Hz, 1 H), 2.8 (m, 12 H).

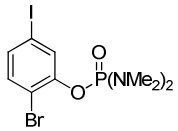
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.1, 140.3, 132.4 (q, J(C-F) = 33.3 Hz), 123.8, 123.7 (q, J(C-F) = 272.2 Hz), 122.0, 116.6, 37.1.

MS (70 eV, EI) *m/z* (%): 423 (16), 422 (93), 378 (39), 314 (41), 296 (57), 295 (100), 287 (10), 276 (47), 252 (15), 250 (14), 232 (10), 207 (23), 188 (19), 160 (37), 145 (11), 144 (34), 141 (11), 136 (25), 135 (100), 132 (29), 92 (46), 91 (12), 90 (20), 76 (14), 63 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 2908, 2856, 1596, 1576, 1480, 1460, 1404, 1324, 1292, 1260, 1232, 1204, 1168, 1120, 1080, 1028, 1000, 980, 940, 892, 824, 764, 732, 716, 676.

HRMS (EI): 421.9870 (calcd.: 421.9868).

Synthesis of 2-bromo-5-iodophenyl *N,N,N′,N′*-tetramethyldiamidophosphate (22e):



3-Iodophenyl *N,N,N′,N′*-tetramethyldiamidophosphate (**21c**) (400 mg, 1.0 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. Then $TMP_2Mg{\cdot}2LiCl$ (0.6 M in THF, 1.83 mL, 1.1 mmol) was added dropwise. The mixture was stirred for 1 h, and after that $BrCl_2CCCl_2Br$ (488 mg, 1.5 mmol), dissolved in dry THF (1 mL), was added dropwise at 0 °C and the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 × 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (EtOAc) furnished a yellowish solid (329 mg, 76%).

m.p.: 64.9 - 66.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.7 (m, 1 H), 7.3 (dd, J = 1.2 Hz, J = 8.4 Hz, 1 H), 7.2 (dd, J = 0.9 Hz, J = 8.2 Hz, 1 H), 2.7 (, 12 H).

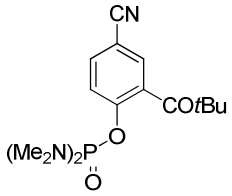
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 149.6, 134.9, 134.6, 130.2, 114.7, 92.5, 37.2.

MS (70 eV, EI) *m/z* (%): 432 (1) [M^++H], 353 (100), 135 (90), 92 (5), 63 (2), 44(11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2931, 2884, 2845, 2811, 1566, 1467, 1383, 1310, 1290, 1215, 1172, 1068, 999, 983, 920, 799, 755, 675.

HRMS (EI): 432.9178 (calcd.: 432.9178).

Synthesis of 4-cyano-2-(2,2-dimethylpropanoyl)phenyl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (19j):



The title compound was prepared from **5a** (1.27 g, 5.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (7.85 mL, 0.7 M in THF, 5.5 mmol), $ZnCl_2$ (1 M in THF, 6.0 mL, 6.0 mmol), pivaloyl chloride (664 mg, 5.5 mmol), CuCN·2LiCl (2.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP8**. Metalation conditions: 0 °C, 1 h. Flash chromatography on silica (EtOAc) furnished a colorless solid (1.32 g, 78%).

m.p.: 65.4 - 67.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 (m, 1 H), 7.6 (dd, J = 8.7 Hz, J = 2.1 Hz, 1 H), 7.4 (m, 1 H), 2.7 (m, 12 H), 1.2 (s, 9 H).

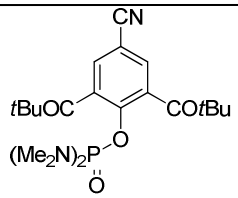
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 209.4, 151.5, 134.3, 133.7, 130.3, 120.8, 118.2, 107.2, 45.5, 36.9, 26.8.

MS (70 eV, EI) *m/z* (%): 338 (1) [M^+], 337 (1), 295 (47), 294 (100), 293 (10), 281 (85), 280 (100), 278 (13), 237 (18), 230 (19), 186 (59), 184 (10), 173 (12), 146 (10), 145 (23), 136 (12), 135 (100), 92 (34), 90 (10), 57 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3392, 3196, 3076, 2228, 1696, 1600, 1484, 1408, 1364, 1300, 1224, 1132, 988, 892, 852, 764, 748, 692, 660.

HRMS (EI): 337.1566 (calcd.: 337.1555).

Synthesis of 4-cyano-2,6-bis(2,2-dimethylpropanoyl)phenyl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (24a):



The title compound was prepared from **19j** (1.67 g, 5.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (7.85 mL, 0.7 M in THF, 5.5 mmol), $ZnCl_2$ (1 M in THF, 6.0 mL, 6.0 mmol), pivaloyl chloride (660 mg, 5.5 mmol), $CuCN{\cdot}2LiCl$ (2.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP8**. Metalation conditions: –60 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/Et_2O 1:1) furnished a colorless solid (648 mg, 77%).

m.p.: 167.3 - 168.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.6 (s, 2 H), 2.6 (m, 12 H), 1.3 (s, 18 H).

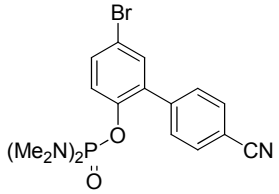
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 208.1, 148.2, 136.9, 131.2, 117.7, 107.0, 45.1, 36.8, 27.8.

MS (70 eV, EI) *m/z* (%): 421 (1) [M^+], 378 (15), 377 (78), 365 (58), 364 (31), 319 (68), 135 (54), 46 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2932, 2912, 2872, 2808, 2236, 1752, 1692, 1676, 1592, 1576, 1476, 1436, 1408, 1392, 1364, 1304, 1284, 1240, 1220, 1192, 1148, 1080, 1044, 1020, 996, 944, 904, 888, 872, 836, 800, 780, 752, 712, 696, 668.

HRMS (EI): 421.2127 (calcd.: 421.2130).

Synthesis of 5-bromo-4'-cyanobiphenyl-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (19k):



The title compound was prepared from **18b** (1.54 g, 5.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (7.85 mL, 0.7 M in THF, 5.5 mmol), 4-iodobenzonitrile (1.26 g, 5.50 mmol), $ZnCl_2$ (6.0 ml, 1 M in THF, 6.0 mmol), $Pd(dba)_2$ (55 mg, 2 mol%), P(2-furyl)$_3$ (45 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –50 °C, 7 h. Flash chromatography on silica (EtOAc) furnished a pale yellow solid (1.63 g, 80%).

m.p.: 128.8 - 129.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.7 (d, J = 8.6 Hz, 2 H), 7.6 (d, J = 8.6 Hz, 2 H), 7.5 (m, 1

H), 7.4 (m, 2 H), 2.5 (m, 12 H).

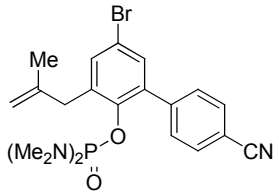
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 147.7, 141.7, 135.4, 133.5, 132.9, 132.2, 130.5, 122.6, 118.8, 117.3, 111.8, 36.7.

MS (70 eV, EI) *m/z* (%): 407 (4) [M^+], 193 (13), 164 (6), 135 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2928, 2904, 2856, 2808, 2224, 1608, 1508, 1468, 1452, 1408, 1384, 1300, 1260, 1228, 1212, 1184, 1124, 1108, 1068, 1028, 1016, 984, 904, 852, 816, 804, 768, 756, 728, 684.

HRMS (EI): 407.0386 (calcd.: 407.0398).

Synthesis of 5-bromo-4'-cyano-3-(2-methylprop-2-en-1-yl)bi-phenyl-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (24b):



The title compound was prepared from **19k** (408 mg, 1.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (1.57 mL, 0.7 M in THF, 1.1 mmol), $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol), 3-bromo-2-methylpropene (150 mg, 1.1 mmol), $CuCN{\cdot}2LiCl$ (0.5 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP9**. Metalation conditions: –60 °C, 0.5 h. Flash chromatography on silica (EtOAc) furnished a colorless solid (356 mg, 77%).

m.p.: 124.0 - 125.2 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.7 (d, J = 7.9 Hz, 2 H), 7.6 (d, J = 8.2 Hz, 2 H), 7.4 (d, J = 2.4 Hz, 1 H), 7.3 (d, J = 2.4 Hz, 1 H), 4.9 (s, 1 H), 4.6 (s, 1 H), 3.6 (s, 2 H), 2.3 (m, 12 H), 1.8 (s, 3 H).

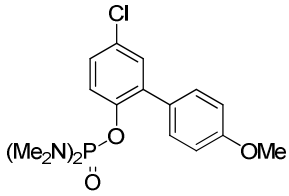
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 145.7, 143.7, 136.5, 135.3, 134.3, 132.3, 132.1, 130.6, 118.8, 118.3, 113.3, 111.5, 39.1, 36.4, 22.8.

MS (70 eV, EI) *m/z* (%): 452 (1) [M^+], 410 (15), 409 (10), 408 (41), 397 (30), 396 (19), 395 (100), 135 (100), 44 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3068, 2932, 2904, 2848, 2804, 2228, 1648, 1608, 1572, 1552, 1504, 1484, 1448, 1412, 1396, 1376, 1300, 1256, 1224, 1196, 1176, 1112, 1096, 1072, 1004, 988, 940, 912, 880, 844, 808, 776, 748, 688, 664.

HRMS (EI): 461.0865 (calcd.: 461.0868).

Synthesis of 5-chloro-4'-methoxybiphenyl-2-yl *N*,*N*,*N*',*N*'-tetra-methyldiamidophosphate (19l):



The title compound was prepared from **18d** (2.62 g, 8.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (12.6 mL, 0.7 M in THF, 8.8 mmol), $ZnCl_2$ (1 M in THF, 9.6 mL, 9.6 mmol), 3-bromo-2-methylpropene (150 mg, 1.1 mmol), $Pd(dba)_2$ (88 mg, 2 mol%), $P(2\text{-furyl})_3$ (72 mg, 4 mol%) applying **TP5** and **TP7**. Metalation conditions: –40 °C, 1.5 h. Flash chromatography on silica (EtOAc) furnished an orange oil (2.78 g, 90%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.5 (dd, J = 8.7 Hz, J = 1.2 Hz, 1 H), 7.4 (d, J = 8.8 Hz, 2 H), 7.3 (dd, J = 2.6 Hz, J = 1.1 Hz, 1 H), 7.2 (dd, J = 8.6 Hz, J = 2.6 Hz, 1 H), 6.9 (d, J = 8.8 Hz, 2 H), 3.8 (s, 3 H), 2.5 (m, 12 H).

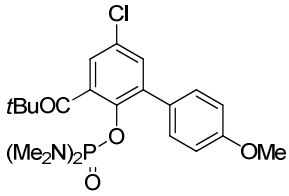
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 159.4, 147.3, 134.8, 134.7, 130.8, 129.5, 129.4, 128.2, 122.1, 113.7, 55.5, 36.7.

MS (70 eV, EI) *m/z* (%): 370 (29), 369 (17), 368 (100) [M^+], 279 (27), 260 (21), 236 (18), 234 (61), 198 (14), 139 (17), 136 (13), 135 (64), 91 (10), 44 (47).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3464, 3000, 2932, 2900, 2852, 2812, 1608, 1580, 1564, 1516, 1480, 1464, 1420, 1388, 1296, 1244, 1204, 1176, 1128, 1112, 1096, 1068, 1040, 1024, 984, 904, 816, 780, 756, 724, 696, 668.

HRMS (EI): 326.1574 (calcd.: 326.1559).

Synthesis of 5-chloro-3-(2,2-dimethylpropanoyl)-4'-methoxybi-phenyl-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (24c):



The title compound was prepared from **19l** (738 g, 2.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (3.14 mL, 0.7

M in THF, 2.2 mmol), $ZnCl_2$ (1 M in THF, 2.2 mL, 2.2 mmol), pivaloyl chloride (265 mg, 2.2 mmol), CuCN·2LiCl (1.0 mL, 1 M in THF, 50 mol%) applying **TP5** and **TP8**. Metalation conditions: –60 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/Et_2O 1:2) furnished a colorless solid (744 mg, 82%).

m.p.: 155.2 - 156.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.4 (d, J = 8.8 Hz, 2 H), 7.3 (m, 1H), 7.2 (d, J = 2.6 Hz, 1 H), 7.0 (d, J = 8.8 Hz, 2 H), 3.9 (s, 3 H), 2.3 (m, 12 H), 1.4 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 209.1, 159.6, 143.7, 137.9, 137.0, 132.2, 131.0, 130.2, 128.9, 125.9, 114.0, 55.6, 44.8, 36.4, 28.6.

MS (70 eV, EI) *m/z* (%): 463 (10), 461 (10) [M^+], 135 (100), 44 (16).

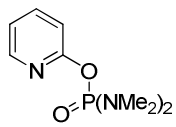
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2956, 2928, 2904, 2852, 2816, 1752, 1728, 1692, 1608, 1576, 1508, 1480, 1456, 1428, 1412, 1388, 1364, 1296, 1268, 1248, 1236, 1204, 1188, 1172, 1120, 1108, 1072, 1028, 988, 932, 900, 872, 832, 816, 796, 784, 756, 724, 692, 664.

HRMS (EI): 452.1650 (calcd.: 452.1632).

4.5. Regioselective Metalation on *N*-Heterocycles

4.5.1. Starting Material Synthesis:

Synthesis of pyridin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (28a):



The title compound was prepared from 2-hydroxypyridine (1.90 g, 20 mmol) applying **TP2**. The dark red oil (4.12 g, 90%) was used without further purification.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.2 (m, 1 H), 7.7 (t, J = 7.9 Hz, 1 H), 7.1 (d, J = 8.1 Hz, 1 H), 7.0 (t, J = 6.0 Hz, 1 H), 2.7 (m, 12 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 158.3, 148.1, 139.6, 120.1, 113.9, 106.5, 36.7. Observed complexity due to C-P splitting, definitive assignments have not been made.

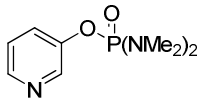
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3466, 2930, 2894, 1590, 1468, 1430, 1302, 1246, 1214, 1180, 986, 908,

794, 770, 750, 670.

MS (70 eV, EI) *m/z* (%): 186 (42), 185 (63), 141 (100), 139 (35), 122 (13), 96 (42), 78 (69), 51 (11), 44 (70).

HRMS (EI): 229.0966 (calcd.: 229.0980).

Synthesis of pyridin-3-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (28b):



The title compound was prepared from 3-hydroxypyridine (1.90 g, 20 mmol) applying **TP2**. The dark red oil (4.03 g, 88%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.5 (m, 1 H), 8.4 (d, *J* = 4.2 Hz, 1 H), 7.7 (m, 1 H), 7.3 (dd, *J* = 8.4, 4.7 Hz, 1 H), 2.7 (m, 12 H).

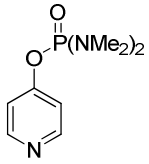
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 148.48, 145.05, 142.07, 127.84, 124.18, 36.66.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3446, 2930, 2896, 2814, 1476, 1424, 1306, 1230, 1210, 1188, 986, 896, 814, 770, 752, 706, 670.

MS (70 eV, EI) *m/z* (%): 229 (54) [M^+], 186 (52), 135 (90), 121 (23), 92 (32), 78 (20), 44 (23).

HRMS (EI): 229.0955 (calcd.: 229.0980).

Synthesis of pyridin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (28c):



The title compound was prepared from 4-hydroxypyridine (1.90 g, 20 mmol) applying **TP2**. The yellow oil (3.71 g, 81%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.4 (m, 2 H), 7.1 (m, 2 H), 2.6 (m, 12 H).

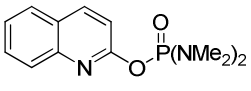
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.4 (dd, *J*(C-P) = 5.7, 1.7 Hz, 1 C), 151.3, 110.3, (d, *J*(C-P) = 5.7, 2 C), 36.5 (dd, *J*(C-P) = 4.0, 1.0 Hz, 4 C).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3443, 2922, 2886, 2814, 1472, 1420, 1312, 1229, 1215, 1192, 987, 898, 815, 777, 742, 701, 680.

MS (70 eV, EI) *m/z* (%): 229 (18) [M^+], 186 (16), 122 (54), 95 (15), 78 (30), 44 (61).

HRMS (EI): 229.0971 (calcd.: 229.0980).

Synthesis of quinolin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (30a):



The title compound was prepared from 2-hydroxyquinoline (2.90 g, 20 mmol) applying **TP2**. The yellow solid (5.08 g, 91%) was used without further purification.

m.p.: 65.3 - 65.6 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (d, *J* = 8.7 Hz, 1 H), 7.9 (d, *J* = 8.4 Hz, 1 H), 7.8 (m, 1 H), 7.6 (m, 1 H), 7.5 (m, 1 H), 7.2 (d, *J* = 8.7 Hz, 1 H), 2.8 (m, 12 H).

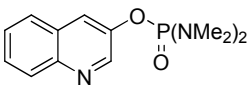
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.0, 156.6, 156.5, 146.5, 140.8, 140.0, 138.6, 130.5, 129.8, 128.2, 127.6, 127.4, 126.2, 125.5, 122.5, 121.4, 119.8, 116.2, 114.0, 113.9, 36.8. Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3440, 2924, 2806, 2454, 1646, 1598, 1468, 1428, 1312, 1260, 1242, 1222, 1214, 1176, 974, 946, 924, 834, 818, 776, 756, 730, 690, 680, 670, 662.

MS (70 eV, EI) *m/z* (%): 280 (12) [M^+]235 (51), 192 (75), 172 (10), 145 (100), 143 885), 128 (45), 117 (15)44, 44 (14).

HRMS (EI): 279.1130 (calcd.: 279.1137).

Synthesis of quinolin-3-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (30f):



The title compound was prepared from 3-hydroxyquinoline (2.90 g, 20 mmol) applying **TP2**. The colorless solid (5.30 g, 95%) was used without further purification.

m.p.: 66.6 - 66.9 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.7 (d, *J* = 2.8 Hz, 1 H), 8.0 (m, 2 H), 7.7 (m, 1 H), 7.6 (m, 1 H), 7.5 (m, 1 H), 2.7 (d, 12 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 145.3, 145.2, 145.1, 145.0, 144.9, 129.1, 128.4, 128.3, 127.5, 127.2, 123.4, 36.7, 36.6.

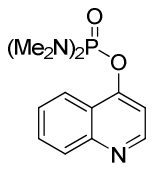
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3432, 2928, 2890, 1646, 1600, 1458, 1422, 1340, 1300, 1220, 1212, 1188, 1178, 1154, 1140, 980, 914, 902, 850, 784, 762, 754, 738, 722, 690, 672, 656.

MS (70 eV, EI) *m/z* (%): 280 (12) [M^+], 235 (51), 192 (75), 172 (10), 145 (100), 143 (85), 128 (45), 117 (15), 44 (14).

HRMS (EI): 279.1130 (calcd.: 279.1137).

Synthesis of quinolin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (30b):



The title compound was prepared from 4-hydroxyquinoline (2.90 g, 20 mmol) applying **TP2**. The colorless oil (4.63 g, 83%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.8 (d, J = 5.1 Hz, 2 H), 8.6 (d, J = 5.6 Hz, 1 H), 8.1 (m, 1 H), 7.7 (m, 1 H), 7.6 (m, 1 H) 2.8 (m, 12 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 154.9, 154.8, 151.3, 149.9, 129.9, 129.4, 126.3, 122.1, 121.2, 109.1, 109.0, 44.0, 36.8, 36.7.

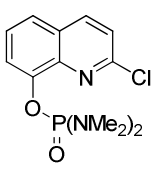
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3416, 2946, 2860, 2844, 2792, 1574, 1510, 1454, 1422, 1392, 1334, 1296, 1230, 1188, 1134, 1098, 1046, 990, 934, 906, 830, 810, 764, 692, 664.

MS (70 eV, EI) *m/z* (%): 236 (22), 193 (16), 146 (58), 135 (41), 129 (45), 118 816), 92 (35), 44 (100).

HRMS (EI): 279.1134 (calcd.: 279.2748).

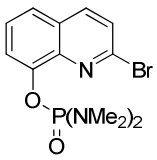
Synthesis of 2-chloroquinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (30c):



The title compound was prepared from 2-chloroquinolin-8-ol[99] (3.59 g, 20 mmol) applying **TP2**. The brown oil (5.08 g, 81%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.8 (m, 2 H), 7.5 – 7.3 (m, 3 H), 2.6 (m, 12 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 150.3, 150.2, 146.5, 146.4, 146.4, 140.8, 140.7, 138.7, 128.0, 127.9, 126.8, 123.4, 122.6, 122.6, 120.9, 36.7, 36.6.
Observed complexity due to C-P splitting, definitive assignments have not been made.
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2894, 2810, 1588, 1566, 1492, 1460, 1420, 1300, 1252, 1224, 1170, 1118, 1080, 1054, 984, 912, 850, 836, 814, 800, 754, 704, 686, 658.
MS (70 eV, ESI) *m/z* (%): 314 (100) [M^+], 280 (12), 162 (3).
HRMS (ESI): 314.0820 (calcd.: 314.0825).

Synthesis of 2-bromoquinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (30d):

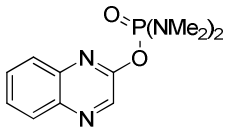


The title compound was prepared from 2-bromoquinolin-8-ol[99] (3.59 g, 20 mmol) applying **TP2**. The brown oil (5.08 g, 81%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.8 (m, 2 H), 7.5 – 7.3 (m, 3 H), 2.8 (m, 12 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 146.6, 141.6, 138.2, 128.3, 127.3, 127.2, 126.2, 123.8, 123.7, 121.2, 121.1, 36.9, 36.8.
Observed complexity due to C-P splitting, definitive assignments have not been made.
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3466, 2926, 2894, 2810, 1582, 1564, 1488, 1460, 1420, 1296, 1252, 1222, 1168, 1104, 1078, 984, 908, 834, 812, 754, 702, 682, 672, 656.
MS (70 eV, EI) *m/z* (%): 357 (8) [M^+], 324 (40), 322 (35), 294 (54), 251 (100), 248 (15), 142 (28), 135 (24), 114 (11), 44 (33).
HRMS (EI): 357.9771 (calcd.: 358.1701).

[99] a) O. Sigouin, A. L Beauchamp, *Can. J. Chem.* **2005**, *83*, 460; b) H. Gernshorn, D. D. Clarke, *Monatsh. Chem.* **1991**, *122*, 935.

Synthesis of quinoxalin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (30e):



The title compound was prepared from 2-hydroxyquinoxaline (2.92 g, 20 mmol) applying **TP2**. The brown oil (5.08 g, 81%) was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.6 (s, 1 H), 7.9 (d, J = 8.3 Hz, 1 H), 7.8 (d, J = 8.3 Hz, 1 H), 7.6 (m, 1 H), 7.5 (m, 1 H), 2.7 (m, 12 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 170.9, 170.8, 152.1, 152.0, 140.2, 140.1, 139.4, 139.4, 130.4, 128.8, 128.2, 128.1, 36.6. Observed complexity due to C-P splitting, definitive assignments have not been made.

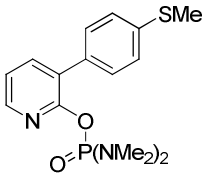
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3476, 2930, 2894, 2812, 1570, 1494, 1458, 1404, 1296, 1268, 1232, 1212, 1202, 1178, 1134, 1124, 982, 924, 830, 758, 688.

MS (70 eV, EI) *m/z* (%): 280 (1) [M^+], 236 (22), 193 (17), 146 (45), 135 (41), 129 (45), 92 (25).

HRMS (EI): 280.1099 (calcd.: 280.2629).

4.5.2. Directed Magnesiation or Zincation and Reaction with Electrophiles

Synthesis of 3-[4-(methylthio)phenyl]pyridin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (29a):



The title compound was prepared from **28a** (229 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), 4-bromo methylthiobenzene (223 mg, 1.00 mmol), $ZnCl_2$ (1.6 ml, 1

M in THF, 1.6 mmol), $Pd_2(dba)_3$ (9 mg, 1 mol%), RuPHOS (9 mg, 2 mol%) applying **TP5** and **7**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a pale yellow solid (260 mg, 74%).

m.p.: 88.3 - 88.7 °C

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.2 (m, 1 H), 7.6 (d, J = 8.1 Hz, 1 H), 7.5 (s, 1 H), 7.4 (d, J = 1.9 Hz, 1 H), 7.3 (d, J = 6.7 Hz, 2 H), 7.1 (dd, J = 7.4, 5.0 Hz, 1 H), 2.6 (m, 12 H), 2.5 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 155.5, 155.4, 146.8, 139.7, 138.4, 132.9, 129.7, 126.3, 126.2, 126.1, 120.1, 36.7, 15.7.

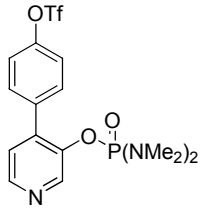
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2884, 2850, 2812, 1586, 1572, 1422, 1398, 1308, 1286, 1260, 1242, 1214, 1202, 1168, 1152, 1110, 1092, 1072, 1064, 1000, 980, 892, 840, 800, 780, 760, 736, 716, 670.

MS (70 eV, EI) *m/z* (%): 351 (1) [M^+], 307 (27), 217 (100), 215 (38), 153 (6), 44 (6).

HRMS (EI): 351.1169 (calcd.: 351.1170).

Synthesis of 4-(3-{[bis(dimethylamino)phosphoryl]oxy}pyridin-4-yl)phenyl trifluoromethanesulfonate (29b):



The title compound was prepared from **28b** (229 mg, 1.00 mmol), $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.5 mL, 0.5 M in THF, 0.75 mmol), 4-iodophenyl trifluoromethanesulfonate[100] (223 mg, 1.00 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), P(2-furyl)$_3$ (23 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions 25 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a colorless oil (398 mg, 88%).

m.p.: 78.3 - 78.5 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.6 (s, 1 H), 8.4 (d, J = 4.9 Hz, 1 H) 7.6 (m, 2 H), 7.4 (m, 2 H), 7.2 (s, 1 H), 2.5 (m, 12 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.1, 149.5, 145.6, 145.3, 145.2, 144.4, 143.1, 139.2,

[100] I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 1654.

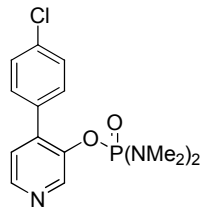
139.1, 135.8, 131.2, 130.6, 125.1, 124.6, 123.5, 121.4, 120.3, 117.1, 115.5, 113.9, 36.4, 36.3.
Observed complexity due to C-P & C-F splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1478, 1420, 1406, 1312, 1296, 1272, 1246, 1202, 1170, 1134, 1056, 1002, 984, 914, 886, 862, 842, 832, 792, 778, 764, 748, 708, 688, 672.

MS (70 eV, EI) *m/z* (%): 453 (8) [M^+], 365 (9), 314 (6), 134 (100), 91 (6), 44 (8).

HRMS (EI): 453.0729 (calcd.: 453.0735).

Synthesis of 4-(4-chlorophenyl)pyridin-3-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (29c):



The title compound was prepared from **28b** (229 mg, 1.00 mmol), $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.5 mL, 0.5 M in THF, 0.75 mmol), 1-chloro-4-iodobenzene (238 mg, 1.00 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), P(2-furyl)$_3$ (23 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions 25 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a colorless oil (268 mg, 79%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.7 (s, 1 H), 8.5 (d, *J* = 5.0 Hz, 1 H), 7.5 (m, 4 H), 7.3 (d, *J* = 4.7 Hz, 1 H), 2.6 (m, 12 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 145.6, 145.5, 144.6, 142.1, 140.6, 140.5, 135.0, 133.5, 130.6, 128.7, 125.0, 36.5, 36.4.

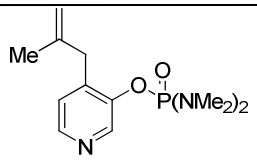
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3470, 2914, 2896, 1600, 1476, 1412, 1396, 1306, 1282, 1226, 1208, 1172, 1090, 1064, 986, 894, 822, 780, 764, 756, 740, 716, 670.

MS (70 eV, EI) *m/z* (%): 339 (20) [M^+], 251 (22), 231 (20), 201 (14), 135 (100), 44 (22).

HRMS (EI): 339.0894 (calcd.: 338.0903).

Synthesis of 4-(2-methylprop-2-en-1-yl)pyridin-3-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (29d):



The title compound was prepared from **28b** (229 mg, 1.00 mmol), $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.5 mL, 0.5 M in THF, 0.75 mmol), 3-bromo-2-methylpropene (135 mg, 1.00 mmol), CuCN·2LiCl (0.1 mL, 1 M in THF, 10 mol%) applying **TP5** and **TP9**. Metalation conditions 25 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a colorless oil (268 mg, 79%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.5 (s, 1 H), 8.3 (m, 1 H), 7.2 (m, 1 H), 4.9 (s, 1 H), 4.7 (s, 1 H), 3.4 (s, 2 H), 2.8 (m, 12 H) 1.8 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 147.4, 144.6, 142.0, 141.0, 125.4, 113.4, 37.6, 36.7, 36.6, 22.6.

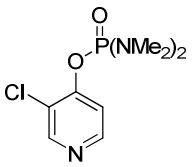
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3492, 2928, 2898, 1652, 1594, 1492, 1456, 1408, 1306, 1246, 1224, 1196, 1148, 1140, 1064, 984, 924, 900, 836, 816, 770, 750, 730, 670.

MS (70 eV, EI) *m/z* (%): 283 (13) [M^+], 135 (57), 70 (20), 61 (25), 45 (31), 42 (100).

HRMS (EI): 283.1444 (calcd.: 283.1450).

Synthesis of 3-chloropyridin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (29e):



The title compound was prepared from **28c** (229 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), 1,1,2-trichlorotrifluoroethane (188 mg, 1.00 mmol) applying **TP5**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc) gave a colorless oil (268 mg, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.6 (s, 1 H), 8.4 (d, J = 5.4 Hz, 1 H), 7.5 (d, J = 5.7 Hz, 1 H), 2.8 (m, 12 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 154.4, 154.3, 150.7, 149.3, 115.7, 36.7, 36.6.

Observed complexity due to C-P splitting, definitive assignments have not been made.

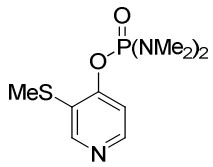
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3480, 2930, 2900, 1570, 1480, 1400, 1290, 1266, 1230, 1176, 1100,

1036, 988, 904, 838, 756, 702, 668.

MS (70 eV, EI) *m/z* (%): 263 (16) [M^+], 228 (80), 175 (17), 135 (100), 90 820), 44 (46).

HRMS (EI): 263.0583 (calcd.: 263.0590).

Synthesis of 3-(methylthio)pyridin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (29f):



The title compound was prepared from **28c** (229 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), *S*-methyl methanethiolsulfonate (127 mg, 1.00 mmol) applying **TP5**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc) gave a colorless solid (217 mg, 88%).

m.p.: 76.9 - 77.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.4 (s, 1 H), 8.3 (d, J = 5.6 Hz, 1 H), 7.4 (d, J = 5.4 Hz, 1 H), 2.8 (m, 12 H), 2.5 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 155.7, 155.6, 147.7, 147.5, 126.6, 126.5, 113.7, 36.7, 36.6, 14.6.

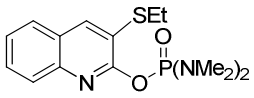
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924, 1562, 1486, 1470, 1408, 1298, 1266, 1216, 1172, 1110, 1072, 1040, 1004, 988, 906, 824, 774, 756, 724, 698, 672.

MS (70 eV, EI) *m/z* (%): 275 (52) [M^+], 231 (64), 228 (63), 141 (31), 135 (100), 44 (33).

HRMS (EI): 275.0856 (calcd.: 275.0857).

Synthesis of 3-(ethylthio)quinolin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31a):



The title compound was prepared from **30a** (279 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), *S*-ethyl benzenesulfonothioate (182 mg, 0.9 mmol) applying **TP5**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc) gave a colorless solid (289 mg, 85%).

m.p.: 82.5 - 82.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.9 (m, 2 H), 7.7 (d, J = 8.2 Hz, 1 H), 7.6 (m, 1 H), 7.5 (d, J = 7.9 Hz, 1 H), 3.0 (q, J = 7.4 Hz, 2 H), 2.9 (m, 12 H), 1.4 (t, J = 7.3 Hz, 3 H).

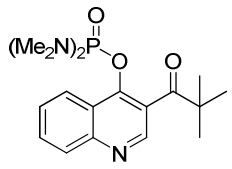
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 153.4, 153.3, 143.9, 140.8, 134.3, 130.5, 128.5, 128.1, 127.7, 126.7, 126.0, 125.6, 124.3, 124.2, 122.6, 121.6, 119.8, 115.9, 36.9, 36.8, 25.6, 13.5. Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2924, 2850, 1638, 1456, 1404, 1248, 1222, 1190, 990, 932, 860, 812, 772, 756, 700, 670.

MS (70 eV, EI) *m/z* (%): 339 (7) [M^+], 295 (27), 232 (21), 192 (74), 172 (100), 145 (10), 128 (12).

HRMS (EI): 339.1160 (calcd.: 339.1170).

Synthesis of 3-(2,2-dimethylpropanoyl)quinolin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31b):



The title compound was prepared from **30b** (279 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), CuCN·2LiCl (0.1 mL, 1 M in THF, 10 mol%), pivaloyl chloride (122 mg, 1.00 mmol) applying **TP5** and **TP8**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a brown oil (225 mg, 62%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.8 (s, 1 H), 8.3 (m, 1 H), 8.1 (d, J=8.4 Hz, 1 H), 7.7 (m, 1 H), 7.6 (m, 1 H), 2.7 (m, 12 H), 1.3 (s, 8 H).

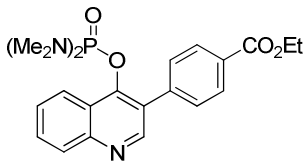
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 208.9, 151.8, 151.7, 149.8, 147.8, 130.5, 129.3, 127.0, 125.8, 123.4, 123.3, 45.4, 36.9, 36.8, 27.1. Observed complexicity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930, 1702, 1586, 1560, 1490, 1376, 1306, 1228, 1170, 1104, 990, 906, 858, 812, 792, 756, 694.

MS (70 eV, EI) *m/z* (%): 363 (1) [M^+], 319 (31), 306 (100), 212 (8), 194 (6), 135 (26).

HRMS (EI): 363.1713 (calcd.: 363.1712).

Synthesis of ethyl 4-(4-{[bis(dimethylamino)phosphoryl]oxy}quinolin-3-l)benzoate (31c):



The title compound was prepared from **30b** (279 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), ethyl 4-iodobenzoate (276 mg, 1.00 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), $P(2\text{-furyl})_3$ (23 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a colorless solid (354 mg, 83%).

m.p.: 136.8 - 137.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.8 (s, 1 H), 8.4 (d, J = 7.7 Hz, 1 H), 8.3 (d, J = 8.2 Hz, 2 H), 8.2 (d, J = 8.4 Hz, 1 H), 7.8 (m, 1 H), 7.7 (m, 3 H), 4.4 (q, J = 7.1 Hz, 2 H), 2.5 (m, 12 H), 1.4 (t, J = 7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 152.2, 152.1, 151.9, 151.8, 140.1, 130.2, 130.1, 130.0, 129.8, 129.0, 127.1, 125.5, 125.4, 123.8, 123.7, 123.7, 61.2, 36.4, 36.4, 14.3.

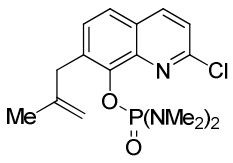
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 1702, 1306, 1290, 1276, 1226, 1170, 1116, 1100, 992, 910, 856, 812, 792, 768, 762, 700, 692.

MS (70 eV, EI) *m/z* (%): 427 (23) [M^+], 353 (12), 319 (179, 247 (10), 135 (100), 44 (15).

HRMS (EI): 427.1654 (calcd.: 427.1661).

Synthesis of 2-chloro-7-(2-methylprop-2-en-1-yl)quinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31d):



The title compound was prepared from **30c** (314 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 m in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), CuCN·2LiCl (0.1 mL, 1 M in THF, 10 mol%), 3-bromo-2-methylpropene (135 mg, 1.00 mmol) applying **TP5** and **TP9**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave

a colorless oil (320 mg, 87%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (d, *J* = 8.5 Hz, 1 H), 7.6 (d, *J* = 8.5 Hz, 1 H), 7.4 (d, *J* = 8.5 Hz, 1 H), 7.4 (d, *J* = 8.5 Hz, 1 H), 4.9 (s, 1 H), 4.6 (s, 1 H), 3.8 (s, 2 H), 2.9 (m, 12 H), 1.8 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 150.3, 144.8, 144.7, 143.8, 141.9, 141.8, 138.6, 133.8, 133.7, 129.9, 129.8, 126.9, 126.8, 123.6, 123.5, 122.2, 112.7, 39.0, 37.0, 36.9, 22.8.

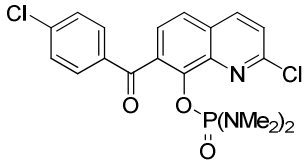
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1702, 1588, 1488, 1438, 1310, 1218, 1120, 1100, 1078, 990, 908, 896, 844, 824, 800, 754, 690.

MS (70 eV, EI) *m/z* (%): 367 (2) [M^+], 325 (27), 323 (100), 231 (22), 228 (16), 218 (29), 214 (17). 135 (159, 44 (12).

HRMS (EI): 367.1209 (calcd.: 367.1216).

Synthesis of 2-chloro-7-(4-chlorobenzoyl)quinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31e):



The title compound was prepared from **30c** (314 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), CuCN·2LiCl (0.1 mL, 1 M in THF, 10 mol%), 4-chloro benzoylchloride (175 mg, 1.00 mmol) applying **TP5** and **TP8**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a colorless solid (320 mg, 87 %).

m.p.: 178.2 - 178.9 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.2 (d, *J* = 8.7 Hz, 1 H), 7.9 (d, *J* = 8.5 Hz, 2 H), 7.7 (d, *J* = 8.5 Hz, 1 H), 7.5 (m, 4 H), 2.6 (m, 12 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 193.0, 151.4, 144.7, 142.0, 139.9, 138.7, 135.3, 133.1, 133.0, 132.0, 129.1, 129.0, 128.8, 126.5, 126.4, 124.1, 123.6, 123.5, 36.7, 36.6.

Observed complexity due to C-P splitting, definitive assignments have not been made.

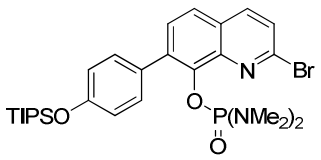
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1666, 1586, 1486, 1438, 1424, 1326, 1310, 1262, 1224, 1200, 1182, 1122, 1108, 1096, 1080, 992, 910, 880, 854, 844, 820, 798, 756, 746, 706, 688, 670.

MS (70 eV, EI) *m/z* (%): 452 (81) [M^+], 410 (51), 365 (25), 312 (100), 288 (14), 202 (12),

111 (14), 44 (39).

HRMS (EI): 452.0706 (calcd.: 452.0619).

Synthesis of 2-bromo-7-{4-[(triisopropylsilyl)oxy]phenyl}quinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31f):



The title compound was prepared from **30d** (358 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL, 1.4 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), 4-(iodophenoxy)-(triisopropyl)silane (414 mg, 1.10 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), $P(2\text{-furyl})_3$ (23 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a pale brown oil (490 mg, 81%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.0 (d, J = 8.7 Hz, 1 H), 7.6 (d, J = 8.4 Hz, 1 H), 7.5 (m, 4 H), 7.0 (d, J = 8.4 Hz, 2 H), 2.6 (m, 12 H) 1.3 (m, 3 H), 1.2 (m, 18 H).

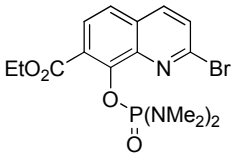
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 155.8, 144.1, 144.0, 142.9, 142.9, 141.6, 138.0, 135.8, 135.7, 131.1, 130.9, 130.6, 130.6, 127.5, 127.5, 125.9, 123.5, 123.5, 119.5, 36.7, 36.6, 18.0, 12.8. Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942, 2866, 1704, 1588, 1512, 1488, 1438, 1304, 1260, 1238, 1214, 1200, 1184, 1174, 1118, 1102, 1084, 1072, 992, 908, 884, 840, 828, 800, 754, 688, 658

MS (70 eV, EI) *m/z* (%): 605 (5) [M^+], 563 (100), 526 (40), 498 (34), 469 (19), 455 (25), 194 (18), 135 (40).

HRMS (EI): 605.1845 (calcd.: 605.1838).

Synthesis of ethyl 8-{[bis(dimethylamino)phosphoryl]oxy}-2-bromoquinoline-7-carboxylate (31g):



The title compound was prepared from **30d** (358 mg, 1.00 mmol), TMPMgCl·LiCl (1.07 mL,

1.4 M in THF, 1.5 mmol), ethyl cyanoformate (100 mg, 1.00 mmol) applying **TP5**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a pale brown solid (331 mg, 77%).

m.p.: 127.8 - 128.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.0 (d, J = 8.7 Hz, 1 H), 7.9 (d, J = 8.7 Hz, 1 H), 7.6 (m, 2 H), 4.5 (q, J = 7.2 Hz, 2 H), 2.8 (m, 12 H), 1.4 (t, J = 7.2 Hz, 3 H).

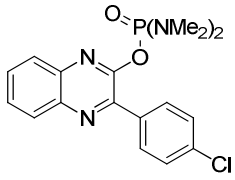
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.5, 165.4, 146.2, 146.1, 142.6, 142.6, 142.2, 137.9, 129.7, 129.7, 127.8, 127.7, 127.6, 126.6, 126.5, 123.4, 123.4, 77.2, 61.6, 37.1, 37.0, 14.3. Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2912, 1702, 1586, 1490, 1438, 1424, 1326, 1312, 1258, 1222, 1214, 1192, 1136, 1098, 1080, 994, 954, 906, 856, 822, 802, 756, 688, 666.

MS (70 eV, EI) *m/z* (%): 430 81) [M^+], 386 (24), 356 (40), 294 (54), 251 (100), 248 (15), 135 (24), 44 (44).

HRMS (EI): 430.0520 (calcd.: 430.0453).

Synthesis of 3-(4-chlorophenyl)quinoxalin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31h):



The title compound was prepared from **30e** (280 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (2.5 mL, 0.6 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), 1-chloro-4-iodobenzene (238 mg, 1.00 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), P(2-furyl)$_3$ (23 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions –30 °C, 1.5 h. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a pale brown solid (305 mg, 78%).

m.p.: 148.9 - 149.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (d, J = 9.0 Hz, 1 H), 8.0 (m, 3 H), 7.7 (m, 2 H), 7.5 (d, J = 8.5 Hz, 2 H), 2.8 (m, 12 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 150.3, 150.2, 146.1, 146.0, 140.2, 139.8, 136.0, 134.4, 131.0, 130.3, 129.0, 128.6, 128.5, 127.8, 36.8, 36.7.

Observed complexity due to C-P splitting, definitive assignments have not been made.

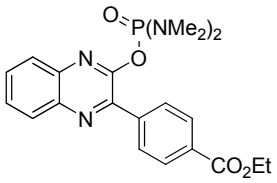
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2894, 1484, 1396, 1316, 1244, 1204, 1192, 1176, 1140, 1090, 998, 978,

926, 866, 854, 830, 796, 766, 756, 736, 686, 668.

MS (70 eV, EI) *m/z* (%): 390 (1) [M^+], 254 (100), 239 (15), 228 (20), 135 (15), 90 (10), 44 (29).

HRMS (EI): 390.1007 (calcd.: 390.1012).

Synthesis of ethyl 4-(3-{[bis(dimethylamino)phosphoryl]oxy}quinoxalin-2-yl)benzoate (31i):



The title compound was prepared from **30e** (280 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (2.5 mL, 0.6 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), ethyl 4-iodobenzoate (276 mg, 1.00 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), $P(2\text{-furyl})_3$ (23 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions –30 °C, 1.5 h. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a pale brown solid (338 mg, 78%).

m.p.: 135.7 - 136.1 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.2 (m, 2 H), 8.1 (m, 3 H), 8.0 (m, 1 H), 7.7 (m, 2 H), 4.4 (q, *J* = 7.0 Hz, 2 H), 2.8 (m, 12 H), 1.5 (t, *J* = 7.0 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 150.4, 150.3, 146.3, 146.2, 140.2, 140.1, 139.9, 131.3, 130.5, 129.7, 129.4, 129.1, 128.6, 127.9, 61.2, 36.8, 36.8, 14.3.

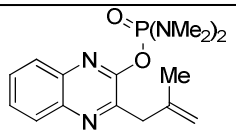
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2900, 1716, 1400, 1308, 1294, 1272, 1228, 1204, 1138, 1124, 1112, 1106, 992, 928, 858, 846, 806, 796, 778, 764, 740, 704, 690.

MS (70 eV, EI) *m/z* (%): 428 (1) [M^+], 384 (12), 292 (100), 266 (17), 249 (17), 219 (47), 135 (17), 90 (10), 44 (28).

HRMS (EI): 428.1597 (calcd.: 428.1613).

Synthesis of 3-(2-methylprop-2-en-1-yl)quinoxalin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31j):



The title compound was prepared from **30e** (280 mg, 1.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (2.5 mL, 0.6 M in THF, 1.5 mmol), $ZnCl_2$ (1.6 mL, 1 M in THF, 1.6 mmol), $CuCN{\cdot}2LiCl$ (0.1 mL, 1 M in THF, 10 mol%), 3-bromo-2-methylpropene (135 mg, 1.00 mmol) applying **TP5** and **TP9**. Metalation conditions –30 °C, 1.5 h. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a pale brown oil (237 mg, 71%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.0 (m, 1 H), 7.9 (m, 1 H), 7.6 (m, 2 H), 4.9 (s, 1 H), 4.6 (s, 1 H), 3.8 (s, 2 H), 2.8 (m, 12 H), 1.9 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 151.4, 151.3, 148.6, 148.5, 147.5, 145.9, 145.1, 143.5, 141.7, 140.0, 139.7, 138.7, 129.5, 129.0, 128.5, 128.0, 127.9, 127.8, 127.7, 118.0, 112.8, 41.8, 36.8, 36.7, 23.1.

Observed complexity due to C-P splitting, definitive assignments have not been made.

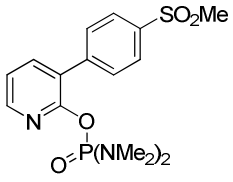
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3074, 2932, 1668, 1648, 1580, 1446, 1402, 1332, 1300, 1232, 1222, 1212, 1160, 1136, 1066, 988, 930, 872, 824, 794, 770, 758, 710, 684, 666.

MS (70 eV, EI) *m/z* (%): 334 (41) [M^+], 289 (63), 245 (66), 198 (100), 185 (42), 183 (79), 135 842), 44 (34).

HRMS (EI): 334.1563 (calcd.: 334.1559).

4.5.3. Synthesis of Etoricoxib:

Synthesis of 3-[4-(methylsulfonyl)phenyl]pyridin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (29g):



The title compound was prepared from **28a** (2.29 g, 10.0 mmol), TMPMgCl·LiCl (10.7 mL, 1.4 M in THF, 15.0 mmol), 4-bromophenyl methylsulfone (2.35 g, 10.0 mmol), $ZnCl_2$ (16 ml, 1 M in THF, 16.0 mmol), $Pd_2(dba)_3$ (90 mg, 1 mol%), RuPHOS (90 mg, 2 mol%) applying

TP5 and **TP7**. Metalation conditions 0 °C, 60 min. Flash chromatography on silica (EtOAc/EtOH, 9:1 then 4:1) gave a highly viscious yellow oil (3.37 g, 88%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.4 (m, 1 H), 8.0 (d, J = 8.5 Hz, 2 H), 7.7 (m, 3 H), 7.2 (m, 1 H), 3.1 (s, 3 H), 2.6 (m, 12 H).

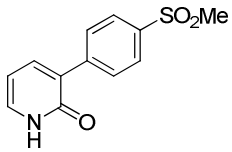
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 155.1, 155.0, 148.1, 141.5, 140.5, 140.1, 130.3, 129.4, 127.4, 127.3, 125.4, 125.3, 120.7, 44.5, 36.6, 36.5. Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2886, 2814, 1576, 1426, 1386, 1306, 1298, 1246, 1218, 1202, 1148, 1092, 1002, 982, 896, 804, 792, 782, 762, 736, 720.

MS (70 eV, EI) *m/z* (%): 383 (1) [M^+], 340 (10), 296 (15), 249 (100), 152 (12), 44 (20).

HRMS (EI): 383.1088 (calcd.: 383.1069).

Synthesis of 3-[4-(methylsulfonyl)phenyl]pyridin-2(1*H*)-one (32):



29g (1.91 g, 5.0 mmol) was dissolved in a 1:1 mixture of 2 M HCl and dioxane and stirred at 25 °C for 24 h. The formed white precipitate was collected by filtration (P4, 300 mbar) washed with water (3 x 25 ml) and oven dried overnight (1.24 g, quant.).

m.p.: 273 °C (decomp.)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 11.9 (s, 1 H), 8.0 (m, 2 H), 7.9 (d, J = 8.6 Hz, 2 H), 7.8 (dd, J = 6.9, 1.9 Hz, 1 H), 7.5 (dd, J = 6.3, 1.9 Hz, 1 H), 6.3 (t, J = 6.6 Hz, 1 H), 3.2 (s, 3 H).

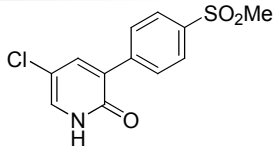
^{13}C-NMR (100 MHz, DMSO) δ (ppm): 161.4, 142.3, 140.6, 139.5, 136.6, 129.2, 128.3, 127.0, 106.0, 44.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1638, 1426, 1388, 1298, 1264, 1246, 1218, 1202, 1192, 1176, 1148, 1110, 1092, 1066, 1002, 982, 896, 806, 790, 780, 762, 736, 722.

MS (70 eV, ESI) *m/z* (%): 248 (100) [M^+].

HRMS (ESI): 267.0790 (calcd.: 267.0798 +NH_4^+).

Synthesis of 5-chloro-3-[4-(methylsulfonyl)phenyl]pyridin-2(1*H*)-one (33):



32 (996 mg, 4.00 mmol) was dissolved in 4 mL conc. HCl and warmed to 50 °C. To the clear solution was added $KClO_3$ (172 mg, 1.4 mmol) in 2.4 mL water. The mixture was stirred at 50 °C for 15 min. and then cooled to 0 °C. Formed precipitate is filtered off (P4, 300 mbar) washed with water (3 x 25 mL) and oven dried overnight. **33** remains as colorless solid (1.12 g, quant.)

m.p.: 213 °C (decomp.)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 12.3 (s, 1 H), 8.0 (m, 2 H), 7.9 (d, J = 8.6 Hz, 2 H), 7.8 (d, J = 2.9 Hz, 1 H), 7.7 (d, J = 2.7 Hz, 1 H), 3.2 (s, 3 H).

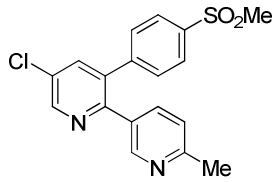
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 160.1, 140.9, 140.4, 140.2, 137.0, 129.6, 127.0, 126.6, 107.9, 43.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1640, 1426, 1388, 1304, 1246, 1218, 1150, 1108, 1092, 1002, 982, 894, 806, 790, 782, 760, 736, 722.

MS (70 eV, EI) *m/z* (%): 283 [M^+] (100), 267 (12), 248 (12), 206 (14), 204 (41), 169 (17), 141 (10).

HRMS (EI): 283.0065 (calcd.: 283.0070).

Synthesis of 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine (Etoricoxib; 26):



The title compound was prepared according to a literature[101] proceedure starting from **33**. A white solid was obtained.

^{1}H-NMR (400 MHz, d_6-DMSO) δ (ppm): 8.5 (s, 1 H), 8.0 (d, J = 8.2 Hz, 2 H), 7.9 (m, 3 H),

[101] a) D. Dube, R. Fortin, R. Friesen, Z. Wang, J. Y. Gauthier, J. Y. PCT Int. Appl. 9803484 A1 19980129, 1998;. b) R. Friesen, D. Dube, D. Deschenes, R. Fortin, R. PCT Int. Appl. 9914194 A1, 1999; c) R. Friesen, D. Dube, D. Deschenes, PCT Int. Appl. 9914195 A1, 1999.

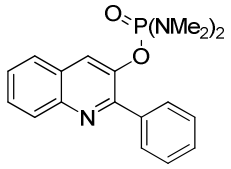
7.8 (d, *J* = 2.1 Hz, 1 H), 7.7 (s, 1 H), 7.2 (d, *J* = 8.2 Hz, 1 H), 3.2 (s, 3 H), 2.4 (s, 3 H).

^{13}C-NMR (100 MHz, d_6-DMSO) δ (ppm): 160.1, 157.3, 149.9, 140.9, 140.4, 140.1, 139.3, 135.0, 129.6, 129.2, 127.0, 125.6, 117.7, 44.0, 23.8.

NMR data matches published data[102]

4.5.4. Synthesis of Talnetant and the P-Selectin Antagonist:

Synthesis of ethyl 2-phenylquinolin-3-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31k):



The title compound was prepared from **30f** (2.79 g, 10.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (25 mL, 0.6 M in THF, 15.0 mmol), $ZnCl_2$ (16 mL, 1 M in THF, 16.0 mmol), iodobenzene (2.04 g, 10.0 mmol), $Pd(dba)_2$ (300 mg, 5 mol%), P(2-furyl)$_3$ (230 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions –50 °C, 1 h. Flash chromatography on silica (EtOAc/CH_2Cl_2, 1:1) gave a brown solid (2.87 g, 81%).

m.p.: 87.3 - 87.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.3 (s, 1 H), 8.1 (d, *J* = 8.4 Hz, 1 H), 7.9 (m, 3 H), 7.7 (m, 1 H), 7.5 (m, 4 H), 2.6 (m, 12 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 153.1, 153.0, 144.8, 143.5, 143.4, 129.7, 129.2, 128.9, 128.6, 128.2, 128.1, 127.2, 127.0, 124.5, 124.4, 77.5, 77.1, 76.6, 36.5, 36.4.

Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2894, 1596, 1488, 1418, 1306, 1300, 1226, 1156, 1140, 996, 980, 918, 908, 868, 850, 802, 788, 762, 746, 726, 714, 698, 680, 656.

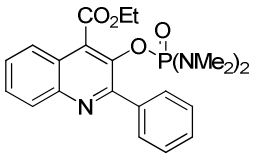
MS (70 eV, EI) *m/z* (%): 355 (100) [M$^+$], 268 (41), 247 (40), 221 (40), 165 (13), 135 (83), 92 (11), 44 (37).

HRMS (EI): 355.1451 (calcd.: 355.1450).

Synthesis of ethyl 3-{[bis(dimethylamino)phosphoryl]oxy}-2-phenylquinoline-4-

[102] J.-F. Marcoux, E. G. Corley, K. Rossen, P. Pye, J. Wu, M. A. Robbins, I. W. Davies, R. D. Larsen, P. J. Reider, *Org. Lett.* **2000**, *2*, 2339.

carboxylate (35a):



The title compound was prepared from **31k** (1.78 g, 5.0 mmol), TMPMgCl·LiCl (5.4 mL, 1.4 M in THF, 7.5 mmol), ethyl cyanoformiate (495 mg, 5.00 mmol) applying **TP5**. Metalation conditions 25 °C, 1 h. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a yellow solid (1.69 g, 79%).

m.p.: 124.1 - 124. 9 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (dd, J = 17.4, 8.4 Hz, 2 H), 7.8 (d, J = 7.4 Hz, 2 H), 7.7 (t, J = 7.5 Hz, 1 H), 7.6 (t, J = 7.7 Hz, 1 H), 7.5 (t, J = 7.7 Hz, 2 H), 7.4 (t, J = 7.4 Hz, 1 H), 4.6 (q, J = 7.1 Hz, 2 H), 2.3 (m, 12 H), 1.5 (t, J = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 165.1, 154.8, 154.8, 145.2, 145.2, 139.7, 139.6, 138.2, 131.2, 131.2, 129.8, 129.6, 128.9, 128.9, 128.3, 127.6, 125.2, 124.8, 124.8, 62.1, 36.2, 36.1, 14.2.

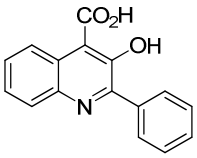
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2934, 1724, 1598, 1486, 1422, 1348, 1310, 1280, 1242, 1168, 1142, 1094, 992, 970, 920, 858, 820, 756, 688.

MS (70 eV, EI) *m/z* (%): 427 (3) [M^+], 383 (100), 355 (63), 274 (119, 248 (36), 219 (15), 135 (76), 44 (22).

HRMS (EI): 428.1647 (calcd.: 427.1661).

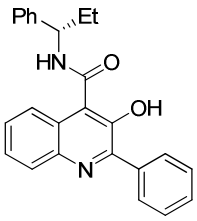
Synthesis of 3-hydroxy-2-phenylquinoline-4-carboxylic acid:



35a (854 mg, 2.00 mmol), was dissovled in 20 mL of a 1:1 mixture of 2 M HCl and dioxane then heated to reflux for 36 h. The mixture was cooled to 25 °C. The formed yellow precipitate was collected by filtration washed with water (3 x 20 ml) and oven dried overnight (530 mg, quant.).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 10.1 (br, 2 H), 8.7 (d, J = 8.0 Hz, 1 H), 8.1 (m, 1 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 7.5 (m, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 171.2, 151.9, 130.2, 129.0, 128.5, 127.2, 125.8, 125.1.
NMR data matches published data.[31]

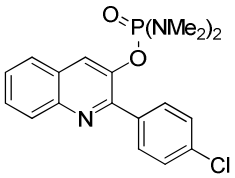
Synthesis of 3-hydroxy-2-phenyl-*N*-[(1*S*)-1-phenylpropyl]quinoline-4-carboxamide (Talnetant; 25):



This compound was prepared from 3-hydroxy-2-phenylquinoline-4-carboxylic acid (265 mg, 1.00 mmol) by applying a known procedure.[103] Crystallization from acetone gave colorless crystals (329 mg, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 11.2 (br, 2 H), 8.2 (s, 1 H), 8.1 (d, J = 6.9 Hz, 2 H), 8.0 (m, 1 H), 7.5 - 7.3 (m, 10 H), 5.2 (q, J = 7.5 Hz, 2 H), 2.0 (m, 1 H), 1.0 (t, J = 7.3 Hz, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 167.5, 151.8, 150.8, 140.8, 129.8, 129.6, 129.0, 128.5, 128.2, 127.9, 126.7, 123.8, 121.8, 56.3, 29.1, 10.9.
NMR data matches published data.[31]

Synthesis of 2-(4-chlorophenyl)quinolin-3-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate (31l):



The title compound was prepared from **30f** (2.79 g, 10.0 mmol), $TMP_2Mg{\cdot}2LiCl$ (25 mL, 0.6 M in THF, 15.0 mmol), $ZnCl_2$ (16 mL, 1 M in THF, 16.0 mmol), 4-chloro-1-iodobenzene

[103] C. S. Labaw, P. Liu, PCT Int. Appl. 2007, WO2007016609.

(2.38 g, 10.0 mmol), $Pd(dba)_2$ (300 mg, 5 mol%), $P(2\text{-furyl})_3$ (230 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions –50 °C, 1 h. Flash chromatography on silica ($EtOAc/CH_2Cl_2$, 1:1) gave a brown solid (3.04 g, 78%).

m.p.: 104.5 - 104.9 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.3 (s, 1 H), 8.1 (d, J = 8.4 Hz, 1 H), 7.8 (m, 3 H), 7.7 (m, 1 H), 7.6 (m, 2 H), 7.5 (m, 1 H), 2.6 (m, 12 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 151.6, 151.5, 144.8, 143.4, 143.3, 136.1, 135.0, 131.1, 129.2, 128.7, 128.3, 127.2, 127.1, 124.5, 124.4, 36.6, 36.5.

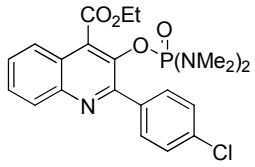
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2934, 1592, 1486, 1422, 1308, 1242, 1168, 1142, 1086, 1008, 992, 972, 918, 874, 860, 842, 830, 794, 784, 756, 740, 708, 688, 660.

MS (70 eV, EI) *m/z* (%): 389 (60) [M^+], 302 (20), 281 (25), 255 (24), 135 (100), 91 (12), 43 (41).

HRMS (EI): 389.1052 (calcd.: 389.1060).

Synthesis of ethyl 3-{[bis(dimethylamino)phosphoryl]oxy}-2-(4-chlorophenyl)quinoline-4-carboxylate (35b):



The title compound was prepared from **31l** (1.95 g, 5.0 mmol), TMPMgCl·LiCl (5.4 mL, 1.4 M in THF, 7.5 mmol), ethyl cyanoformiate (495 mg, 5.00 mmol) applying **TP5**. Metalation conditions 25 °C, 1 h. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a yellow solid (1.87 g, 81 %).

m.p.: 109.5 - 109.8 °C

^{1}H-NMR (300 MHz, DMSO) δ (ppm): 8.2 (d, J = 8.2 Hz, 1 H), 8.1 (d, J = 8.5 Hz, 1 H), 7.8 (d, J = 8.5 Hz, 2 H), 7.7 (t, J = 7.5 Hz, 1 H), 7.6 (t, J = 7.5 Hz, 1 H), 7.5 (d, J = 8.5 Hz, 2 H), 4.6 (q, J = 7.1 Hz, 2 H), 2.4 (m, 12 H), 1.5 (t, J = 7.1 Hz, 3 H)

^{13}C-NMR (75 MHz, DMSO) δ (ppm): 164.8, 153.3, 153.2, 144.7, 139.6, 139.5, 135.4, 131.3, 129.4, 129.2, 128.6, 128.0, 125.2, 124.9, 124.8, 62.2, 36.5, 36.4, 36.3, 36.2, 14.2.

Observed complexity due to C-P splitting, definitive assignments have not been made.

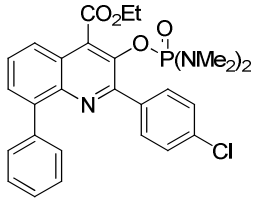
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 1728, 1592, 1488, 1456, 1422, 1348, 1308, 1294, 1288, 1230,

1218, 1206, 1170, 1140, 1090, 990, 972, 918, 872, 860, 844, 830, 818, 794, 786, 760, 740, 708, 702, 690, 658.

MS (70 eV, EI) *m/z* (%): 461 (2) [M^+], 417 (61), 389 (48), 354 (10), 282 (19), 190 (10), 135 (100), 44 (22).

HRMS (EI): 461.1261 (calcd.: 461.1271).

Synthesis of ethyl 3-{[bis(dimethylamino)phosphoryl]oxy}-2-(4-chlorophenyl)-8-phenylquinoline-4-carboxylate (36):



The title compound was prepared from **35b** (1.38 g, 3.00 mmol), $TMP_2Mg{\cdot}2LiCl$ (7.5 mL, 0.6 M in THF, 4.5 mmol), $ZnCl_2$ (4.8 mL, 1 M in THF, 4.8 mmol), iodobenzene (612 mg, 3.0 mmol), $Pd(dba)_2$ (90 mg, 5 mol%), P(2-furyl)$_3$ (69 mg, 10 mol%) applying **TP5** and **TP7**. Metalation conditions –40 °C, 20 h. Flash chromatography on silica (EtOAc/EtOH, 9:1) gave a brown oil (1.22 g, 81%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.1 (d, *J* = 8.2 Hz, 1 H), 8.1 (d, *J* = 8.5 Hz, 1 H), 7.9 (d, *J* = 2.2 Hz, 1 H), 7.8 (dd, *J* =8.2, 2.2 Hz, 1 H), 7.7 (t, *J* = 7.8 Hz, 1 H), 7.6 (d, *J* = 8.2 Hz, 1 H), 7.6 (t, *J* = 7.7 Hz, 1 H), 7.4 (m, 5 H), 4.6 (q, *J* = 7.1 Hz, 2 H), 2.4 (m, 12 H), 1.5 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 164.8, 153.2, 153.1, 145.0, 140.5, 140.1, 139.5, 139.4, 139.0, 138.9, 136.9, 136.5, 133.5, 133.1, 132.8, 131.3, 131.2, 131.0, 130.9, 130.0, 129.9, 129.8, 129.7, 129.4, 129.3, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 125.2, 124.9, 124.8, 62.2, 36.3, 36.3, 14.2.

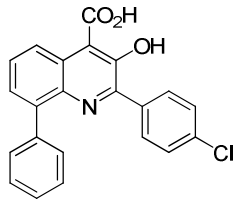
Observed complexity due to C-P splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 2854, 1726, 1376, 1352, 1300, 1286, 1222, 1176, 1138, 994, 974, 826, 760, 742, 716, 698.

MS (70 eV, EI) *m/z* (%): 537 (2) [M^+], 493 (100), 465 (62), 430 (12), 360 (13), 329 (14), 135 (86), 44 (33).

HRMS (EI): 537.1573 (calcd.: 537.1584).

Synthesis of 2-(4-chlorophenyl)-3-hydroxy-8-phenylquinoline-4-carboxylic acid (37):



36 (538 mg, 1.00 mmol), was dissovled in 10 mL of a 1:1 mixture of 2 M HCl and dioxane then heated to reflux for 36 h. The mixture was cooled to 25 °C. The formed yellow precipitate was collected by filtration washed with water (3 x 20 ml) and oven dried overnight (375 mg, quant.).

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 10.9 (br, 2 H), 8.6 (d, J = 8.2 Hz, 1 H), 8.0 (m, 4 H), 7.7 (dd, J = 9.1, 6.5 Hz, 1 H), 7.6 (m, 2 H), 7.5 (m, 4 H).

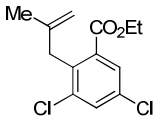
^{13}C-NMR (100 MHz, DMSO$_3$) δ (ppm): 171.5, 167.1, 150.9, 150.4, 147.6, 142.3, 139.8, 139.0, 136.7, 130.0, 129.8, 129.7, 128.8, 128.4, 127.6, 127.2, 124.0, 120.8, 116.3.

NMR data matches published data.[104]

4.6. Alternative Amines for the Preparation of Mixed Li/Mg- an Li/Mg/Zn-amide bases

Directed Metalations and Reactions with Electrophiles

Synthesis of ethyl-3,5-dichloro-2-(2-methylallyl)benzoate (41a):



The title compound was prepared according to **TP5** and **TP9** from ethyl 3,5-di-chloro benzoate (436 mg, 2.00 mmol), Mg-base **10b** or **10c** (1.51 mL, 1.45 M in THF, 2.20 mmol), 3-bromo-2-methylpropene (327 mg, 0.35 mL, 2.40 mmol) and CuCN·2LiCl (0.2 mL, 1 M in

[104] N. Kaila, K. Janz, S. DeBernardo, P. Bedard, R. T. Camphausen, S. Tam, D. H. H. Tsao, J. C. Keith Jr. C. Nickerson-Nutter, A. Shilling, R. Young-Sciame, Q. Wang, *J. Med. Chem.* **2007**, *50*, 21.

THF, 0.1 mmol). Metalation conditions 0 °C, 1 h. Flash chromatography on silica (*n*-pentane/Et_2O 20:1) gave a light yellow oil (465 mg, 85% with base **10c**; 506 mg, 93% with base **10b**).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.7 (s, 1 H), 7.6 (s, 1 H), 4.8 (s, 1 H,) 4.3 (q, J = 7.0 Hz, 2 H), 4.2 (s, 1 H), 3.8 (s, 2 H), 1.8 (s, 3 H), 1.4 (t, J = 7.2 Hz, 3 H).

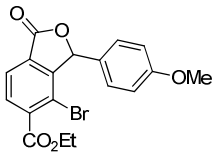
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.0, 143.1, 137.1, 136.9, 134.3, 132.3, 132.2, 128.8, 110.5, 61.6, 37.1, 23.3, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 1726, 1581, 1556, 1444, 1387, 1374, 1365, 1291, 1249, 1219, 1198, 1162, 1139, 1082, 1038, 1021, 935, 885, 873, 843, 792, 782, 769, 750, 727.

MS (70 eV, EI) *m/z* (%): 272 (88) [M^+], 257 (48), 231 (49), 229 (100), 228 (49), 227 (66), 226 (64), 191 (60), 163 (40), 128 (34).

HRMS (EI): 272.0375 (calcd. 272.0371).

Synthesis of ethyl 4-bromo-3-(4-methoxyphenyl)-1-oxo-1,3-dihydro-2-benzofuran-5-carboxylate (41d):



The title compound was prepared according to **TP5** from diethyl 2-bromoterephthalate (603 mg, 2.00 mmol), Mg-base **10b** or **10c** (2.07 mL, 1.45 M in THF, 3.00 mmol), anisaldehyde (409 mg, 0.37 mL, 3.00 mmol). Metalation conditions –30 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/Et_2O 1:1) gave a yellow oil (703 mg, 90% with base **10c**; 750 mg, 96% with base **10b**).

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.0 (d, J = 7.9 Hz, 1 H), 7.9 (d, J = 7.8 Hz, 1 H), 7.1 (d, J = 8.7 Hz, 2 H), 6.9 (d, J = 9.0 Hz, 2 H), 6.3 (s, 1 H), 4.4 (q, J = 7.2 Hz, 2 H), 3.8 (s, 3 H), 1.4 (t, J = 7.1 Hz, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 168.3, 165.4, 160.6, 149.7, 138.6, 132.2, 130.1, 129.9, 125.7, 124.2, 117.3, 114.3, 84.0, 62.4, 55.3, 14.1.

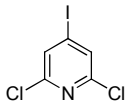
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2937, 1767, 1725, 1609, 1586, 1514, 1457, 1444, 1407, 1392, 1368, 1320, 1297, 1273, 1248, 1200, 1176, 1139, 1113, 1064, 1026, 966, 861, 852, 833, 820, 774, 746, 726, 648, 644, 632, 606, 575.

MS (70 eV, EI) *m/z* (%): 436 (1) [M^+], 393 (48), 392 (41), 391 (51), 347 (39), 345 (39), 275

(93), 273 (95), 267 (100), 239 (88), 135 (64).

HRMS (EI): 436.0536 (calcd. 436.0522).

Synthesis of 2,6-dichloro-4-iodopyridine (46):



The title compound was prepared according to **TP5** from 2,6-dichloropyridine (296 mg, 2.00 mmol), **10c** (2.07 mL, 1.45 M in THF, 3.00 mmol), iodine (558 mg, 2.20 mmol), metalation conditions 25 °C, 10 min. Flash chromatographical purification on silica (*n*-pentane/Et_2O 20:1) gave a colorless solid (465 mg, 85%).

m.p.: 157 - 158.8 °C (decomp.).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.7 (br, 2 H).

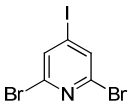
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.6, 131.5, 107.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 1738, 1536, 1521, 1360, 1217, 1159, 1146, 848, 807, 740.

MS (70 eV, EI) *m/z* (%): 272 (100) [M^+], 147 (27), 109 (18), 75 (15), 50 (12).

HRMS (EI): 272.8599 (calcd. 272.8609).

Synthesis of 2,6-dibromo-4-iodopyridine (47):



The title compound was prepared according to **TP5** from 2,6-dibromopyridine (474 mg, 2.00 mmol), **10c** (2.07 mL, 1.45 M in THF, 3.00 mmol), iodine (558 mg, 2.20 mmol), metalation conditions –30 °C, 30 min. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a colorless solid (631 mg, 87%).

m.p.: 180.7 - 181.6 °C (decomp.).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.9 (s, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 140.9, 135.4, 107.4.

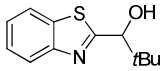
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 2970, 1739, 1531, 1510, 1365, 1342, 1228, 1221, 1156, 1086, 850, 758, 719, 701.

MS (70 eV, EI) *m/z* (%): 362 (100) [M^+], 360 (51), 283 (559, 281 (58), 156 (11), 154 (11),

126 (12), 76 (28). 50 (19).

HRMS (EI): 360.7574 (calcd. 360.7599).

Synthesis of 1-(1,3-benzothiazol-2-yl)-2,2-dimethylpropan-1-ol (41l):



The title compound was prepared according to **TP5** from benzothiazole (270 mg, 0.22 mL, 2.00 mmol), Mg-base **10b** or **10c** (2.07 mL, 1.45 M in THF, 3.00 mmol) and pivaldehyde (233 mg, 0.30 mL, 2.20 mmol). Metalation conditions 25 °C, 0.2 h. Flash chromatography on silica (*n*-pentane/Et_2O 3:1) gave yellow solid (402 mg, 91% with base **10c**; 380 mg, 86% with base **10b**).

m.p.: 107.0 - 109.3 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.0 (d, J = 8.1 Hz, 1 H), 7.9 (d, J = 7.9 Hz, 1 H), 7.5 (t, J = 7.7 Hz, 1 H), 7.4 (t, J = 7.6 Hz, 1 H), 4.7 (s, 1 H), 3.4 (s, 1 H), 1.1 (s, 9 H).

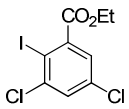
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 173.6, 152.1, 134.8, 125.9, 125.0, 122.9, 121.5, 80.0, 36.1, 25.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3422, 3060, 2972, 2961, 2951, 2929, 2867, 1510, 1500, 1475, 1464, 1453, 1436, 1390, 1368, 1360, 1329, 1313, 1284, 1236, 1218, 1187, 1168, 1153, 1125, 1086, 1075, 1060, 1015, 900, 862, 764, 757, 731, 709, 687.

MS (70 eV, EI) *m/z* (%): 221 (6) [M^+], 167 (10), 165 (100), 136 (10), 57 (10).

HRMS (EI): 221.0860 (calcd. 221.0874).

Synthesis of ethyl-3,5-dichloro-2-iodobenzoate (41b):



The title compound was prepared according to **TP5** from 3,5-di-chloro ethylbenzoate (436 mg, 2.00 mmol), Mg-base **10b** (1.51 mL, 1.45 M in THF, 2.20 mmol) and iodine (611 mg, 2.40 mmol). Metalation conditions 0 °C, 1 h. Flash chromatography on silica (*n*-pentane/Et_2O 60:1) gave a pale brown oil (556 mg, 81%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.6 (d, J = 2.4 Hz, 1 H), 7.5 (d, J = 2.4 Hz, 1 H), 4.4 (q, J =

7.2 Hz, 2 H), 1.4 (t, *J* = 7.0 Hz, 3 H).

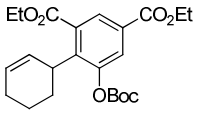
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.1, 141.6, 141.3, 135.0, 130.8, 127.7, 95.7, 62.5, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2979, 1728, 1564, 1546, 1464, 1443, 1404, 1390, 1379, 1363, 1266, 1236, 1184, 1140, 1112, 1093, 1012, 907, 897, 868, 858, 816, 797, 770, 734, 725, 701.

MS (70 eV, EI) *m/z* (%): 344 (81) [M^+], 318 (25), 315 (38), 301 (62), 271 (20), 254 (16), 144 (22), 109 (17), 44 (24).

HRMS (EI): 272.0375 (calcd. 272.0371).

Synthesis of diethyl-5-(*tert*-butoxycarbonyloxy)-4-(cyclohex-2- enyl)isophthalate (41c):



The title compound was prepared according to **TP5** and **TP9** from diethyl 5-[(*tert*-butoxycarbonyl)oxy]isophthalate (678 mg, 2.00 mmol), Mg-base **10b** (1.51 mL, 1.45 M in THF, 2.20 mmol), 3-bromocyclohexene (355 mg, 0.28 mL, 2.40 mmol) and CuCN·2LiCl (0.2 mL, 1 M in THF, 0.2 mmol). Metalation conditions 0 °C, 1 h. Flash chromatography on silica (*n*-pentane/Et_2O 1:1) gave a yellow solid (778 mg, 93%).

m.p.: 70.3 - 73.1 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.1 (d, *J* = 1.9 Hz, 1 H), 7.8 (d, *J* = 1.7 Hz, 1 H), 5.8 (m, 1 H), 5.5 (d, *J* = 9.8 Hz, 1 H), 4.3-4.5 (m, 4 H), 4.0 (m, 1 H), 2.1-2.2 (m, 1 H), 2.0-2.1 (m, 1 H), 1.9-2.0 (m, 2 H), 1.6 (m, 2 H), 1.5 (s, 9 H), 1.2-1.5 (m, 6 H).

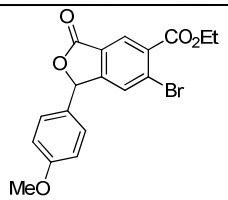
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 167.6, 164.9, 151.4, 150.3, 142.8, 134.3, 129.4, 128.2, 127.9, 127.4, 127.1, 83.6, 61.6, 61.4, 37.5, 28.5, 27.7, 27.4, 24.4, 22.7, 14.3, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2935, 1758, 1719, 1457, 1448, 1394, 1368, 1319, 1277, 1266, 1238, 1218, 1174, 1144, 1100, 1060, 1024, 984, 951, 927, 907, 898, 866, 843, 821, 787, 764, 719, 639.

MS (70 eV, EI) *m/z* (%): 418 (2) [M^+], 362 (43), 318 (26), 317 (11), 273 (31), 272 (100), 271 (15), 244 (13), 243 (11), 238 (13), 199 (14), 193 (12), 57 (66), 44 (26), 41 (18).

HRMS (EI):418.1995 (calcd. 418.1992).

Synthesis of ethyl 6-bromo-1-(4-methoxyphenyl)-3-oxo-1,3-dihydro-2-benzofuran-5-carboxylate (41e)



The title compound was prepared according to **TP5** from 4-bromo diethylisophthalate (603 mg, 2.00 mmol), Mg-base **10b** (2.07 mL, 1.45 M in THF, 3.00 mmol), anisaldehyde (409 mg, 0.37 mL 3.00 mmol). Metalation conditions–30 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/Et_2O 1:1) gave a colorless solid (671 mg, 86%).

m.p.: 130.2 - 132.3 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.3 (s, 1 H), 7.6 (s, 1 H), 7.1 (d, J = 8.8 Hz, 2 H), 6.9 (d, J = 8.8 Hz, 2 H), 6.3 (s, 1 H), 4.4 (q, J = 7.2 Hz, 2 H), 3.8 (s, 3 H), 1.4 (t, J = 7.2 Hz, 3 H).

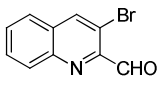
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 168.6, 164.9, 160.8, 152.7, 134.2, 129.1, 128.8, 128.4, 128.1, 126.8, 125.2, 114.6, 82.1, 62.3, 55.4, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2990, 2967, 2955, 1757, 1727, 1616, 1579, 1514, 1468, 1460, 1449, 1443, 1428, 1392, 1365, 1325, 1307, 1290, 1283, 1248, 1200, 1178, 1159, 1114, 1105, 1078, 1028, 1020, 969, 932, 924, 893, 878, 867, 843, 834, 821, 802, 781, 754, 734, 726, 681, 658.

MS (70 eV, EI) *m/z* (%): 392 (95), 391 (23) [M^+], 390 (100), 275 (20), 273 (21), 267 (20), 256 (27), 254 (24), 135 (61).

HRMS (EI): 391.0087 (calcd. 391.0181).

Synthesis of 3-Bromoquinoline-2-carbaldehyde (41f):



The title compound was prepared according to **TP5** from 3-bromoquinoline (415 mg, 2.00 mmol), Mg-base **10b** (2.0 mL, 1.45 M in THF, 3.00 mmol) and dry DMF (257 mg, 0.27 mL, 3.50 mmol). Metalation conditions –25 °C, 0.3 h. Flash chromatography on silica (*n*-pentane/Et_2O 3:1) gave a yellow solid (304 mg, 65 %).

m.p.: 104.8 - 106.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.4 (s, 1 H) 8.5 (s, 1 H) 8.3 (d, J = 8.3 Hz, 1 H) 7.8-7.9 (m, 2 H) 7.7-7.8 (m, 1 H).

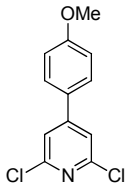
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 191.2, 147.8, 146.4, 141.5, 130.9, 130.5, 130.3, 130.1, 126.7, 114.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2857, 1713, 1677, 1661, 1632, 1611, 1582, 1566, 1544, 1485, 1444, 1403, 1392, 1361, 1315, 1298, 1254, 1227, 1192, 1145, 1133, 995, 985, 964, 912, 893, 874, 783, 757, 637, 611.

MS (70 eV, EI) *m/z* (%): 235 (57) [M^+], 209 (75), 208 (22), 207 (77), 206 (14), 128 (100), 127 (46), 101 (29), 75 (14), 44 (19).

HRMS (EI): 234.9626 (calcd. 234.9633).

Synthesis of 2,6-dichloro-4-(4-methoxyphenyl)pyridine (41g):



The title compound was prepared according to **TP5** and **TP7** from 2,6-dichloropyridine (296 mg, 2.00 mmol), Mg-base **10b** (2.07 mL, 1.45 M in THF, 3.00 mmol), $ZnCl_2$ (3.1 mL, 1 M in THF, 3.1 mmol) 4-iodoanisole (515 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), $P(2\text{-furyl})_3$ (46 mg, 10 mol%), metalation conditions 25 °C, 10 min. Flash chromatographical purification on silica (*n*-pentane/Et_2O 19:1) gave a colorless solid (437 mg, 85%).

m.p.: 68.7 - 70.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.6 (d, J = 9.0 Hz, 2 H), 7.4 (s, 2 H), 7.0 (d, J = 9.0 Hz, 2 H), 3.9 (s, 3 H).

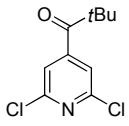
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.4, 153.4, 151.0, 120.0, 114.8, 113.9, 55.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2937, 2839, 1739, 1607, 1580, 1515, 1417, 1371, 1289, 1255, 1232, 1184, 1173, 1113, 1065, 1036, 985, 866, 821, 808, 767.

MS (70 eV, EI) *m/z* (%): 253 (100) [M^+], 239 (10), 237 (16), 209 (22), 114 (11).

HRMS (EI): 253.0070 (calcd. 253.0061).

Synthesis of 1-(2,6-dichloropyridin-4-yl)-2,2-dimethylpropan-1-one (41h):



The title compound was prepared according to **TP5** and **TP8** from 2,6-dichloropyridine (296

mg, 2.00 mmol), Mg-base **10b** (2.07 mL, 1.45 M in THF, 3.00 mmol), $ZnCl_2$ (3.1 mL, 1 M in THF, 3.1 mmol), pivaloyl chloride (724 mg, 6.00 mmol), $Pd(PPh_3)_4$ (46 mg, 2 mol%), 25 °C, 10 min. Flash chromatographical purification on silica (*n*-pentane/Et_2O 20:1) gave a colorless solid (399 mg, 86%).

m.p.: 58.6 - 60.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.3 (s, 2 H), 1.3 (s, 9 H).

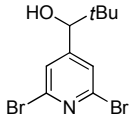
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 206.2, 151.4, 150.9, 120.4, 44.6, 27.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072, 2979, 2938, 1738, 1688, 1577, 1521, 1481, 1460, 1395, 1364, 1284, 1211, 1168, 1048, 1002, 879, 831, 818, 764, 753, 721, 632.

MS (70 eV, EI) *m/z* (%): 233 (2) [M^+], 231 (3), 177 (17), 175 (26), 149 (18), 147 (25), 57 (100), 41 (23).

HRMS (EI): 231.0221 (calcd. 231.0218).

Synthesis of 1-(2,6-dibromopyridin-4-yl)-2,2-dimethylpropan-1-ol (41i):



The title compound was prepared according to **TP5** from 2,6-dibromo pyridine (475 mg, 2.00 mmol), Mg-base **10b** (2.0 mL, 1.45 M in THF, 3.00 mmol), pivaldehyde (277 mg, 2.20 mmol). Metalation conditions –50 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/Et_2O 40:1) gave a colorless solid (544 mg, 84%).

m.p.:167.8 - 169.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.4 (s, 2 H), 4.3 (s, 1 H), 2.1 (s, 1 H), 1.0 (s, 9 H).

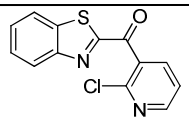
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 156.6, 140.4, 126.3, 80.3, 36.1, 25.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3432, 2968, 2962, 2931, 2866, 1575, 1528, 1480, 1402, 1373, 1364, 1325, 1295, 1236, 1217, 1201, 1175, 1158, 1087, 1072, 1015, 985, 938, 927, 897, 884, 860, 774, 752, 681, 615.

MS (70 eV, EI) *m/z* (%): 321 (1) [M^+], 269 (97), 268 (18), 267 (88), 265 (100), 186 (9), 158 (10), 156 (9), 57 (50), 41 (9).

HRMS (EI): 320.9370 **(**calcd. 320.9364).

Synthesis of 1,3-benzothiazol-2-yl(2-chloropyridin-3-yl)methanone (41k):



The title compound was prepared according to **TP5** and **TP8** from benzothiazole (270 mg, 2.00 mmol), Mg-base **10b** (2.07 mL, 1.45 M in THF, 3.00 mmol), $ZnCl_2$ (3.1 mL, 1 M in THF, 3.1 mmol), 3-chloro nicotinylchloride (1.06 g, 6.00 mmol), $Pd(PPh_3)_4$ (46 mg, 2 mol%), 25 °C, 10 min. Flash chromatographical purification on silica (*n*-pentane/Et_2O 20:1) gave a colorless solid (456 mg, 83%).

m.p.: 142.2 - 143.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.6 (m, 1 H), 8.2 (m, 1 H), 8.1 (dd, *J* = 7.6, 1.9 Hz, 1 H), 8.0 (m, 1 H), 7.6 (m, 2 H), 7.4 (dd, *J* = 7.4, 5.0 Hz, 1 H) .

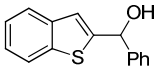
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 186.2, 165.1, 153.6, 151.5, 148.8, 139.4, 137.5, 132.6, 128.3, 127.3, 126.0, 122.4, 121.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 2989, 2970, 1739, 1674, 1575, 1554, 1486, 1456, 1424, 1397, 1324, 1291, 1278, 1230, 1137, 1126, 1080, 1052, 954, 890, 843, 809, 755, 726, 702, 652, 602.

MS (70 eV, EI) *m/z* (%): 274 (5) [M^+], 246 (11), 240 (50), 239 (62), 238 (55), 141 (28), 139 (100), 113 (16), 111 (54), 76 (16).

HRMS (EI): 273.9962 (calcd. 273.9968).

Synthesis of 1-benzothien-2-yl(phenyl)methanol (41l):



The title compound was prepared according to **TP5** from benzothiophene (266 mg, 0.23 mL, 2.00 mmol), Mg-base **10b** (2.07 mL, 1.45 M in THF, 3.00 mmol) and benzaldehyde (233 mg, 0.22 mL, 2.20 mmol). Metalation conditions 0 °C, 12 h. Flash chromatography on silica (*n*-pentane/Et_2O 4:1) gave a colorless solid (338 mg, 71%).

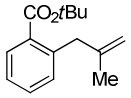
mp.: 87.4 - 88.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.8 (d, *J* = 7.2 Hz, 1 H) 7.7 (d, *J* = 8.3 Hz, 1 H) 7.5 (d, *J* = 7.6 Hz, 2 H) 7.4 (t, *J* = 7.5 Hz, 2 H) 7.3 (s, 2 H) 7.3 (s, 1 H) 7.1 (s, 1 H) 6.1 (d, *J* = 3.1 Hz, 1 H) 2.5 (d, *J* = 4.1 Hz, 1 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 148.6, 142.5, 139.9, 139.4, 128.6, 128.3, 126.4, 124.3, 124.2, 123.6, 122.4, 121.2, 73.0.

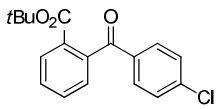
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3143, 3058, 3028, 1492, 1455, 1434, 1327, 1306, 1295, 1247, 1197, 1177, 1154, 1103, 1031, 1021, 1010, 1001, 818, 786, 769, 749, 728, 722, 699, 666, 627.
MS (70 eV, EI) *m/z* (%): 240 (79) [M^+], 223 (15), 221 (16), 161 (16), 136 (12), 135 (100), 105 (50), 91 (12), 77 (17), 44 (11).
HRMS (EI): 240.0595 (calcd. 240.0609).

Synthesis of *tert*-butyl 2-(2-methylprop-2-en-1-yl)benzoate (42a):



The title compound prepared according to **TP5** and **TP9** from *tert*-butyl benzoate (356 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), CuCN·2LiCl (0.2 ml, 1.0 M in THF, 10 mol%), 3-bromo-2-methylpropene (297 mg, 2.20 mmol), metalation conditions 25 °C, 1 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a colorless oil (422 mg, 91%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 (m, 1 H), 7.4 (m, 1 H), 7.3 (m, 2 H), 4.8 (s, 1 H), 4.5 (s, 1 H), 3.7 (s, 2 H), 1.8 (s, 3 H), 1.6 (s, 9 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.5, 145.2, 139.9, 132.8, 131.0, 131.0, 130.0, 126.0, 111.7, 81.1, 41.6, 28.2, 22.8.
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2938, 1738, 1716, 1447, 1366, 1293, 1275, 1252, 1229, 1217, 1172, 1129, 1077, 1049, 890, 849, 738, 711.
MS (70 eV, EI) *m/z* (%): 232 (0.04) [M^+], 177 (29), 176 (100), 162 (35), 161 (74), 159 (94), 158 (91), 143 (15), 134 (24).
HRMS (EI): 232.1444 (calcd. 232.1463).

Synthesis of *tert*-butyl 2-(4-chlorobenzoyl)benzoate (42b):



The title compound was prepared according to **TP5** and **TP8** from *tert*-butyl benzoate (356 mg, 2.00 mmol), Mg-base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), 4-chloro benzoylchloride (385 mg, 2.20 mmol), $Pd(PPh_3)_4$ (46 mg, 2 mol%),

metalation conditions 25 °C, 1 h. Flash chromatographical purification on silica (*n*-pentane:Et_2O = 5:1) gave a colorless solid (422 mg, 91%).

m.p.: 65.8 - 67.3 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.0 (m, 1 H), 7.7 (d, *J* = 8.7 Hz, 2 H), 7.6 (m, 2 H), 7.4 (d, *J* = 8.7 Hz, 2 H), 7.3 (m, 1 H), 1.3 (s, 9 H).

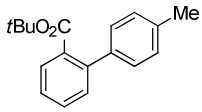
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 195.6, 165.0, 140.6, 139.5, 135.7, 132.0, 131.1, 130.9, 130.1, 129.7, 128.8, 127.4, 82.7, 27.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2933, 1737, 1706, 1666, 1583, 1571, 1485, 1455, 1441, 1396, 1366, 1301, 1286, 1267, 1173, 1138, 1082, 1011, 969, 930, 896, 866, 849, 775, 762, 748, 737, 712, 676, 645.

MS (70 eV, EI) *m/z* (%): 316 (5) [M^+], 261 (34), 260 (23), 245 (27), 243 883), 181 8100), 152 (28), 149 (17), 139 (32), 111 (11), 57 (21).

HRMS (EI): 318.0869 (calcd. 316.0866).

Synthesis of *tert*-butyl 4'-methylbiphenyl-2-carboxylate (42c):



The title compound was prepared according to **TP5** and **TP7** from *tert*-butyl benzoate (356 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol) 4-iodotoluene (480 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-furyl)$_3$ (46 mg, 10 mol%), metalation conditions 25 °C, 1 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 20:1) gave a colorless oil (440 mg, 82%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 (m, 1 H), 7.5 (m, 1 H), 7.4 (m, 1 H), 7.3 (m, 1 H), 7.2 (s, 4 H), 2.4 (s, 3 H), 1.3 (s, 9 H).

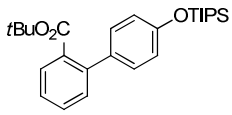
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.2, 142.0, 138.9, 136.7, 133.0, 130.6, 130.5, 129.5, 128.6, 128.5, 126.9, 81.2, 27.6, 21.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2928, 1706, 1599, 1477, 1444, 1366, 1298, 1247, 1217, 1172, 1126, 1087, 1047, 848, 819, 755, 705.

MS (70 eV, EI) *m/z* (%): 268 (6) [M^+], 213 (13), 212 (100), 195 (37), 165 (16), 152 (11).

HRMS (EI) 268.1458 (calcd. 268.1463).

Synthesis of *tert*-butyl 4'-[(triisopropylsilyl)oxy]biphenyl-2-carboxylate (42d):



The title compound was prepared according to **TP5** and **TP7** from *tert*-butyl benzoate (356 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol) (4-iodophenoxy)(triisopropyl)silane (850 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-furyl)$_3$ (46 mg, 10 mol%), metalation conditions 25 °C, 1 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 20:1) gave a colorless oil (758 mg, 89%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.7 (m, 1 H), 7.5 (m, 1 H), 7.4 (m, 2 H), 7.2 (d, J = 8.7 Hz, 2 H), 6.9 (d, J = 8.7 Hz, 2 H), 1.3 (s, 9 H), 1.1 (m, 21 H).

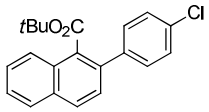
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.6, 155.4, 141.4, 134.4, 133.3, 130.5, 130.4, 129.6, 129.3, 126.7, 119.3, 81.2, 27.7, 18.0, 12.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2944, 2867, 1737, 1712, 1607, 1515, 1477, 1444, 1366, 1301, 1260, 1232, 1217, 1172, 1126, 1047, 911, 882, 837, 762, 686, 652.

MS (70 eV, EI) *m/z* (%): 427 (12), 426 (36) [M^+], 328 (25), 327 (100), 309 (22), 299 (28), 281 (22), 255 (10), 254 (11), 253 (53), 239 (279, 127 (14), 75 (11), 57 (14).

HRMS (EI): 426.2586 (calcd. 426.2590).

Synthesis of *tert*-butyl 2-(4-chlorophenyl)-1-naphthoate (42e):



The title compound was prepared according to **TP5** and **TP7** from *tert*-butyl 1-naphthoate (456 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol) 4-iodo-1-chlorobenzene (525 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-furyl)$_3$ (46 mg, 10 mol%), metalation conditions 25 °C, 3 h. Trituration with *n*-pentane gave a brown solid (657 mg, 97%).

m.p.: 95.6 - 97.1 °C (decomp.).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.0 (m, J = 8.3 Hz, 1 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 7.4 (m, 5 H), 1.4 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.3, 139.5, 136.0, 133.6, 132.5, 131.7, 130.4, 129.8, 129.4,

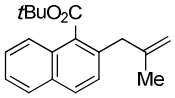
129.0, 128.2, 128.1, 127.1, 126.4, 125.0, 82.4, 27.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2971, 2930, 1737, 1711, 1597, 1491, 1364, 1286, 1274, 1243, 1175, 1162, 1135, 1109, 1091, 1014, 1009, 959, 890, 859, 849, 814, 795, 748, 723, 676, 664.

MS (70 eV, EI) *m/z* (%): 338 (10) [M^+], 284 (27), 282 (100), 265 (28), 202 (26).

HRMS (EI): 338.1075 (calcd. 338.1074).

Synthesis of *tert*-butyl 2-(2-methylprop-2-en-1-yl)-1-naphthoate (42f):



The title compound was prepared according to **TP5** and **TP9** from *tert*-butyl 1-naphthoate (456 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), CuCN·2LiCl (0.2 ml, 1.0 M in THF, 10 mol%), 3-bromo-2-methylpropene (297 mg, 2.20 mmol), metalation conditions 25 °C, 3 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 50:1) gave a colorless oil (496 mg, 88%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 (m, 3 H), 7.5 (m, 2 H), 7.4 (d, J = 8.5 Hz, 1 H), 4.9 (s, 1 H), 4.7 (s, 1 H), 3.6 (s, 2 H), 1.8 (s, 3 H), 1.7 (s, 9 H).

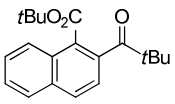
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.9, 144.1, 133.8, 132.3, 132.0, 129.9, 129.0, 128.0, 127.4, 126.8, 125.6, 124.7, 112.8, 82.4, 41.7, 28.3, 22.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2942, 1738, 1718, 1508, 1455, 1366, 1283, 1248, 1227, 1222, 1171, 1152, 1132, 1044, 1023, 891, 847, 807, 755, 735.

MS (70 eV, EI) *m/z* (%): 282 (1) [M^+], 226 (45), 211 (100), 209 (15), 181 (23), 165 (19).

HRMS (EI): 282.1606 (calcd. 282.1620).

Synthesis of *tert*-butyl 2-(2,2-dimethylpropanoyl)-1-naphthoate (42g):



The title compound was prepared according to **TP5** and **TP8** from *tert*-butyl 1-naphthoate (456 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), pivaloyl chloride (385 mg, 2.20 mmol), $Pd(PPh_3)_4$ (46 mg, 2 mol%),

metalation conditions 25 °C, 3 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a colorless solid (518 mg, 83 %).

m.p.: 76.1 - 78.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.2 (m, 1 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 7.5 (d, J = 8.7 Hz, 1 H), 1.7 (s, 9 H), 1.4 (s, 9 H).

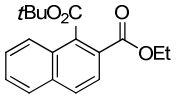
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 221.3, 167.6, 138.7, 133.4, 130.9, 130.0, 129.4, 128.2, 127.6, 127.0, 125.9, 122.0, 83.0, 44.4, 28.2, 27.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2932, 2871, 1737, 1711, 1683, 1622, 1567, 1475, 1458, 1395, 1380, 1366, 1266, 1248, 1159, 1133, 1069, 1026, 997, 882, 864, 852, 842, 822, 802, 790, 762, 741, 727, 682, 624.

MS (70 eV, EI) *m/z* (%): 312 (0.1) [M^+], 254 (5), 199 (12), 198 (100), 126 (4), 57 (11).

HRMS (EI): 312.1710 (calcd. 312.1725).

Synthesis of 1-*tert*-butyl 2-ethyl naphthalene-1,2-dicarboxylate (42h):



The title compound was prepared according to **TP5** and **TP8** from *tert*-butyl naphthoate (456 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), ethyl chloroformate (1.08 g, 10.0 mmol), $Pd(PPh_3)_4$ (46 mg, 2 mol%), metalation conditions 25 °C, 3 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a colorless solid (498 mg, 83 %).

m.p.: 103.8 -105.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.0 (m, 2 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 4.5 (q, J = 7.2 Hz, 2 H), 1.7 (s, 9 H), 1.4 (t, J = 7.2 Hz, 3 H).

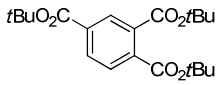
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.9, 165.8, 136.0, 135.1, 129.5, 128.9, 128.1, 128.1, 127.5, 126.0, 125.1, 124.7, 82.8, 61.4, 28.2, 14.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2970, 1738, 1722, 1712, 1467, 1438, 1364, 1289, 1265, 1241, 1217, 1173, 1158, 1133, 1116, 1042, 1018, 867, 850, 828, 796, 766, 752, 730, 669.

MS (70 eV, EI) *m/z* (%): 300 (32) [M^+], 245 (16), 244 (100), 227 (25), 200 (30), 199 (90), 172 (27), 155 (73), 127 (29), 115 (19), 57 (17).

HRMS (EI): 300.1354 (calcd. 300.1262).

Synthesis of tri-*tert*-butyl benzene-1,2,4-tricarboxylate (42i):



The title compound was prepared according to **TP5** from di-*tert*-butyl isophtalate (556 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), Boc_2O (1.08 g, 5.00 mmol), metalation conditions 25 °C, 6 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a pale green oil (685 mg, 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.2 (d, J = 1.2 Hz, 1 H), 8.1 (dd, J = 8.0, 1.7 Hz, 1 H), 7.6 (d, J = 8.0, 1 H), 1.6 (m, 23 H), 1.5 (m, 4 H).

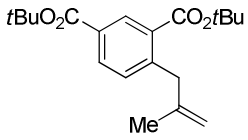
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.4, 166.0, 164.3, 137.4, 133.6, 133.6, 131.2, 129.8, 128.6, 85.2, 83.9, 82.4, 81.9, 28.0, 27.6, 27.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2941, 1736, 1718, 1455, 1393, 1367, 1293, 1273, 1245, 1217, 1157, 1113, 1066, 935, 869, 841, 763, 741.

MS (70 eV, EI) *m/z* (%): 378 (0.02) [M^+], 305 (47), 267 (36), 249 (24), 211 (51), 194 (37), 193 (23), 175 (19), 167 (80), 148 (47), 57 (38), 56 (100).

HRMS (EI): 378.2047 (calcd. 378.2842).

Synthesis of di-*tert*-butyl 4-(2-methylprop-2-en-1-yl)isophthalate (42j):



The title compound was prepared according to **TP5** and **TP9** from di-*tert*-butyl isophtalate (556 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), CuCN·2LiCl (0.2 ml, 1 M in THF, 10 mol%), 3-bromo-2-methylpropene (297 mg, 2.20 mmol), metalation conditions 25 °C, 6 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 20:1) gave a colorless oil (680 mg, 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.4 (d, J = 1.7 Hz, 1 H), 8.2 (dd, J = 7.7, 1.7 Hz, 1 H), 7.9 (dd, J = 8.0, 1.9 Hz, 1 H), 4.8 (s, 1 H), 4.5 (s, 1 H), 3.8 (s, 2 H), 1.6 (m, 21 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.8, 165.1, 144.6, 133.2, 132.9, 132.2, 131.6, 131.1, 130.4, 130.0, 128.2, 112.1, 81.6, 81.5, 81.2, 28.2, 28.1, 22.8.

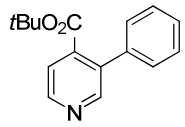
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2938, 1738, 1715, 1608, 1452, 1393, 1366, 1315, 1290, 1247,

1217, 1156, 1140, 1117, 1075, 939, 891, 849, 768, 756, 732.

MS (70 eV, EI) *m/z* (%): 332 (0.02) [M^+], 276 (52), 259 (16), 220 (59), 205 (100), 203 (28), 202 (16), 149 (7), 57 (25).

HRMS (EI): 332.1976 (calcd. 332.1988).

Synthesis of *tert*-butyl 3-phenylisonicotinate (42k):



The title compound was prepared according to **TP5** and **TP7** from *tert*-butyl isonicotinate (358 mg, 2.00 mmol), Mg-base **14c** (3.53 mL, 0.85 M in THF, 3.00 mmol), $ZnCl_2$ (3.2 mL, 1 M in THF, 3.2 mmol) iodobenzene (449 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-furyl)$_3$ (46 mg, 10 mol%), metalation conditions –40 °C, 12 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 1:1) gave a red oil (347 mg, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.7 (d, J = 5.1 Hz, 1 H), 8.6 (s, 1 H), 7.6 (d, J = 5.6 Hz, 1 H), 7.4 (m, 3 H), 7.3 (m, 2 H), 1.3 (s, 9 H).

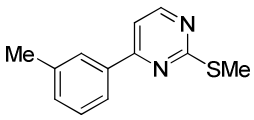
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.2, 151.0, 148.7, 140.0, 137.7, 135.9, 128.8, 127.9, 122.5, 99.4, 82.8, 27.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 1736, 1715, 1477, 1445, 1397, 1368, 1316, 1296, 1217, 1159, 1119, 1075, 1006, 856, 837, 761, 717, 699, 672.

MS (70 eV, EI) *m/z* (%): 255 (3) [M^+], 200 (16), 199 (100), 198 (19), 182 (30), 154 (9), 127 (10), 57 (11).

HRMS (EI): 255.1264 (calcd. 255.1259).

Synthesis of 4-(3-methylphenyl)-2-(methylthio)pyrimidine (42l):



The title compound was prepared according to **TP5** and **TP7** from 2(methylthio)pyrimidine (252 mg, 2.00 mmol), Mg-base **14c** (3.53 mL, 0.85 M in THF, 3.00 mmol), $ZnCl_2$ (3.2 mL, 1 M in THF, 3.2 mmol) 3-iodotoluene (480 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-

furyl)$_3$ (46 mg, 10 mol%), metalation conditions –40 °C, 12 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 1:4) gave a colorless solid (328 mg, 76%).

m.p.: 55.2 - 56.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.5 (d, J = 5.3 Hz, 1 H), 7.9 (s, 1 H), 7.8 (d, J = 8.0 Hz, 1 H), 7.4 (m, 3 H), 2.7 (s, 3 H), 2.5 (s, 3 H).

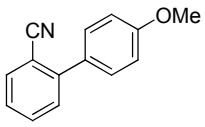
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.7, 164.1, 157.4, 138.6, 136.3, 131.9, 128.8, 127.8, 124.4, 112.0, 21.5, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2970, 2925, 1739, 1561, 1542, 1492, 1415, 1348, 1315, 1301, 1208, 1194, 1185, 1126, 1080, 969, 918, 890, 850, 796, 768, 693, 654, 628.

MS (70 eV, EI) *m/z* (%): 217 (14), 216 (100) [M^+], 215 (30, 170 (37), 169 (22), 155 (14), 115 (12).

HRMS (EI): 216.0708 (calcd. 216.0721).

Synthesis of 4'-methoxybiphenyl-2-carbonitrile (42m):



The title compound was prepared according to **TP5** and **TP9** from benzonitrile (206 mg, 2.00 mmol), Mg-base **14c** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.40 mmol) 3-iodoanisole (480 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-furyl)$_3$ (46 mg, 10 mol%), metalation conditions –30 °C, 3 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a colorless solid (328 mg, 76%).

m.p.: 77.1 - 79.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.8 (m, 1 H), 7.6 (m, 1 H), 7.5 (d, J = 9.0 Hz, 2 H), 7.4 (m, 2 H), 7.0 (d, J = 9.0 Hz, 2 H) 3.9 (s, 3 H).

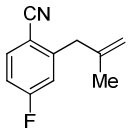
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.1, 133.7, 132.7, 130.5, 130.0, 129.9, 129.0, 128.4, 127.0, 114.2, 77.4, 76.6, 55.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2994, 2970, 2224, 1739, 1611, 1598, 1516, 1480, 1443, 1435, 1370, 1300, 1270, 1248, 1184, 1035, 833, 820, 750, 696.

MS (70 eV, EI) *m/z* (%): 209 (100) [M^+], 194 (17), 166 (30), 140 (12).

HRMS (EI): 209.0841 (calcd. 209.0841).

Synthesis of 4-fluoro-2-(2-methylprop-2-en-1-yl)benzonitrile (45d):



The title compound was prepared according to **TP6** and **TP9** from 4-fluoro benzonitrile (242 mg, 2.00 mmol), Zn-base **12b** (2.4 mL, 0.5 M in THF, 1.2 mmol), CuCN·2LiCl (0.2 ml, 1 M in THF 10 mol%), 3-bromo-2-methylpropene (297 mg, 2.20 mmol), metalation conditions 100 °C, 2 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 19:1) gave a colorless oil (283 mg, 81%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.6 (dd, J = 4.7, 2.1 Hz, 1 H), 7.5 (m, 1 H), 7.1 (t, J = 9.1 Hz, 1 H), 4.9 (s, 1 H), 4.7 (s, 1 H), 3.4 (s, 2 H), 1.7 (s, 3 H).

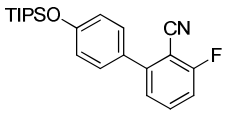
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.2, 161.9, 142.1, 135.4, 135.3, 132.5, 132.3, 128.9, 128.7, 118.2, 116.8, 116.5, 113.3, 108.4, 108.4, 36.5, 36.5, 22.1. Observed complexity due to C-F splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2942, 2920, 2231, 1739, 1653, 1590, 1493, 1443, 1376, 1247, 1230, 1217, 1103, 1066, 895, 829, 780, 728, 682.

MS (70 eV, EI) *m/z* (%): 175 (66) [M^+], 161 (10), 160 (100), 158 (10), 147 (13), 135 (12), 134 (30), 133 (11), 107 (11), 57 (13), 43 (59).

HRMS (EI): 175.0790 (calcd. 175.0797).

Synthesis of 3-fluoro-4'-[(triisopropylsilyl)oxy]biphenyl-2-carbonitrile (45e):



The title compound was prepared according to **TP6** and **TP7** from 2-fluoro benzonitrile (242 mg, 2.00 mmol), Zn-base **12b** (2.4 mL, 0.5 M in THF, 1.2 mmol), (4-iodophenoxy)(triisopropyl)silane (850 mg, 2.20 mmol), $Pd(dba)_2$ (56 mg, 5 mol%), P(2-furyl)$_3$ (46 mg, 10 mol%), metalation conditions 140 °C, 2 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 9:1) gave a colorless solid (610 mg, 83%).

m.p.: 81.7-82.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.7 (td, J = 7.7, 1.7 Hz, 1 H), 7.6 (m, 1 H), 7.4 (dd, J = 6.7, 1.8, 1.7 Hz, 2 H), 7.0 (m, 3 H), 1.3 (m, 3 H), 1.1 (d, J = 7.0 Hz, 18 H).

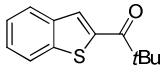
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.9, 158.4, 156.7, 135.3, 135.3, 131.6, 130.4, 130.2, 130.0, 130.0, 126.1, 126.1, 124.9, 124.8, 120.2, 114.2, 114.2, 102.4, 102.1, 17.9, 12.7 (observed complexity due to C-F splitting, definitive assignments have not been made).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2946, 2867, 2231, 1739, 1604, 1513, 1457, 1403, 1384, 1366, 1304, 1264, 1235, 1171, 1110, 1074, 1014, 993, 909, 883, 847, 822, 791, 740, 721, 688, 650, 625.

MS (70 eV, EI) *m/z* (%): 369 (57) [M^+], 326 (28), 298 (41), 271 (64), 257 (29), 196 (24), 135 (100) 128 (22), 77 (20).

HRMS (EI): 369.1916 (calcd. 369.1924).

Synthesis of 1-(1-benzothien-2-yl)-2,2-dimethylpropan-1-one (45f):



The title compound was prepared according to **TP6** and **TP8** from benzothiophene (268 mg, 2.00 mmol), Zn-base **12b** (2.4 mL, 0.5 M in THF, 1.2 mmol), pivaloyl chloride (385 mg, 2.20 mmol), CuCN·2LiCl (0.2 ml, 1 M in THF, 10 mol%), metalation conditions 140 °C, 1 h. Flash chromatographical purification on silica (*n*-pentane/Et_2O 40:1) gave a colorless oil (363 mg, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.0 (s, 1 H), 7.9 (m, 2 H), 7.4 (m, 2 H), 1.5 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 200.3, 142.1, 141.6, 139.2, 128.8, 127.1, 125.8, 124.8, 122.5, 44.2, 28.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970, 2930, 2901, 1739, 1647, 1593, 1558, 1510, 1474, 1457, 1430, 1394, 1366, 1274, 1217, 1144, 1126, 1072, 937, 898, 864, 842, 789, 758, 742, 723.

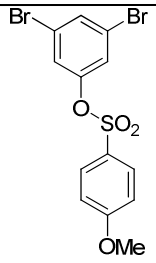
MS (70 eV, EI) *m/z* (%): 218 (15) [M^+], 161 8100), 89 (11), 43 (14).

HRMS (EI): 218.0759 (calcd. 218.0765).

4.7. Co-catalyzed aryl sulfonate/copper-exchange

4.7.1. Starting Material Synthesis

Synthesis of 3,5-dibromophenyl 4-methoxybenzenesulfonate:



The title compound was prepared following **TP3** from 3,5-dibromophenol (5.04 g, 20 mmol), 4-methoxybenzenesulfonyl chloride (4.96 g). 7.96 g (90%) of a brown solid were isolated.

m.p.: 102.4 - 103 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.8 (d, J = 9.2 Hz, 2 H), 7.6 (t, J = 1.7 Hz, 1 H), 7.1 (m, 2 H), 7.0 (m, 2 H), 3.9 (s, 3 H).

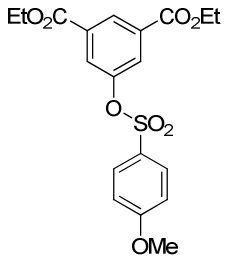
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.6, 150.1, 132.9, 130.8, 125.9, 124.8, 122.9, 114.6, 55.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1593, 1566, 1497, 1417, 1378, 1268, 1200, 1192, 1185, 1170, 1095, 1016, 912, 872, 858, 832, 805, 740, 712, 679, 667, 634.

MS (70 eV, EI) *m/z* (%): 421 (12), 419 [M^+] (6), 172, (24), 171 (100), 170 (60), 123 (31), 107 (84), 92 (31), 77 (45), 64 (16).

HRMS (EI): 419.8671 (calcd.: 419.8667).

Synthesis of diethyl 5-{[(4-methoxyphenyl)sulfonyl]oxy}isophthalate (50a):



The title compound was prepared following **TP3** from diethyl 5-hydroxyisophthalate (4.77 g, 20 mmol), 4-methoxybenzenesulfonyl chloride (4.96 g). 7.59 g (93%) of a colorless solid were isolated.

m.p.: 85.3 - 86.0 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.6 (t, J = 1.5 Hz, 1 H), 7.9 (d, J = 1.5 Hz, 2 H), 7.8 (m, 2 H), 7.0 (m, 2 H), 4.4 (q, J = 7.2 Hz, 4 H), 3.9 (s, 3 H), 1.4 (t, J = 7.2 Hz, 6 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.5, 164.4, 149.6, 132.6, 130.8, 129.0, 127.6, 126.2,

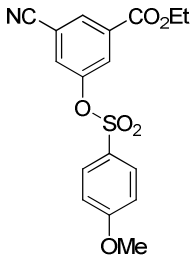
114.6, 61.7, 55.8, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1717, 1310, 1170, 1022, 953, 844, 821, 760, 748, 704.

MS (70 eV, EI) *m/z* (%): 408 (8) [M^+], 363 (15), 193 (15), 171 (100), 123 (14), 107 (27), 77 (14).

HRMS (EI): 408.0879 (calcd.: 408.0881).

Synthesis of ethyl 3-cyano-5-{[(4-methoxyphenyl)sulfonyl]oxy}benzoate (50b):



The title compound was prepared from 3,5-dibromophenyl 4-methoxybenzenesulfonate (8.44 g, 10 mmol), *i*PrMgCl·LiCl, TsCN (1.81 g, 10 mmol) following **TP 4** (Exchange time: 60 min). The second Br/Mg-exchange was performed on the crude product according to **TP 4** (Exchange time: 60 min) using ethyl cyanoformate (991 mg, 10 mmol) as an electrophile furnishing (2.0 g, 56%) a colorless solid.

m.p.: 90.1 - 90.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.2 (t, *J* = 1.4 Hz, 1 H), 7.9 (dd, *J* = 2.4, 1.5 Hz, 1 H), 7.8 (m, 2 H), 7.5 (dd, *J* = 2.3, 1.4 Hz, 1 H), 7.0 (m, 2 H), 4.4 (q, *J* = 7.1 Hz, 2 H), 3.9 (s, 3 H), 1.4 (t, *J* = 7.1 Hz, 3 H).

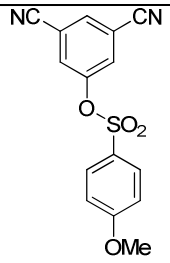
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.7, 163.3, 149.8, 133.7, 131.6, 130.8, 129.7, 128.1, 125.6, 116.6, 114.8, 114.0, 62.2, 55.9, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1717, 1592, 1378, 1316, 1303, 1265, 1224, 1195, 1183, 1172, 1116, 1093, 1011, 968, 894, 843, 807, 778, 769, 739, 678, 668, 626 .

MS (70 eV, EI) *m/z* (%): 361 (2) [M^+], 316 (5), 171 (100), 123 (10), 107 (23), 77 (12), 74 (27), 59 (37), 45 (26).

HRMS (EI): 361.0607 (calcd.: 361.0620).

Synthesis of 3,5-dicyanophenyl 4-methoxybenzenesulfonate (50c):



The title compound was prepared from 3,5-dibromophenyl 4-methoxybenzenesulfonate (8.44 g, 10 mmol), *i*PrMgCl·LiCl, TsCN (1.81 g, 10 mmol) following **TP 4** (Exchange time: 60 min). The second Br/Mg-exchange was performed on the crude product according to **TP 4** (Exchange time: 60 min) using TsCN (1.81 g, 10 mmol) as an electrophile furnishing (1.54 g, 49%) as a colorless solid.

m.p.: 98.8 - 100.2 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83 (t, *J* = 1.5 Hz, 1 H), 7.78 (m, 2 H), 7.56 (d, *J* = 1.5 Hz, 2 H), 7.04 (m, 2 H), 3.94 (s, 3 H).

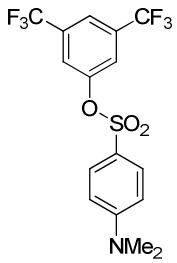
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 150.1, 133.6, 130.8, 130.4, 125.1, 115.5, 115.4, 114.9, 55.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3071, 2942, 2910, 1575, 1498, 1272, 1169, 1135, 1093, 964, 749.

MS (70 eV, EI) *m/z* (%): 314 (2) [M^+], 171 (100), 107(38), 123 (19), 92 (17), 77 (24), 64 (10), 44 (4).

HRMS (EI): 314.0358 (calcd.: 314.0361).

Synthesis of 3,5-bis(trifluoromethyl)phenyl 4-(dimethylamino)benzenesulfonate (50d):



The title compound was prepared following **TP3** from 3,5-bis(trifluoromethyl)phenol (2.30 g, 10 mmol), 4-(dimethylamino)benzenesulfonyl chloride (2.20 g, 12 mmol). 3.3g (79%) of a colorless solid were isolated.

m.p.: 151.0 - 153.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74 (bs, 1 H), 7.59 (m, 2 H), 7.44 (bs, 2 H), 6.66 (m, 2 H), 3.08 (s, 6 H).

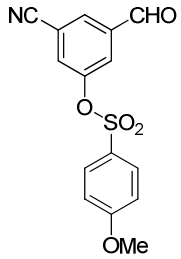
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 154.2, 150.4,133.6, 133.2, 132.7, 130.5, 127.9, 124.3, 123.6, 123.5, 120.7, 120.5, 120.5, 120.4, 120.4, 120.3, 118.2, 117.1, 110.9, 40.1. (observed complexity due to C-F splitting, definitive assignments have not been made).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3079, 2973, 1594, 1585, 1498, 1354, 1170, 1093, 965, 749, 669.

MS (70 eV, EI) *m/z* (%): 413 (30) [M^+], 394 (12), 184 (100), 136 (79), 120 (63), 105 (14), 77 (17), 41 (14).

HRMS (EI): 413.0508 (calcd.: 413.0520).

Synthesis of 3-cyano-5-formylphenyl 4-methoxybenzenesulfonate (50i):



The title compound was prepared from 3,5-dibromophenyl 4-methoxybenzenesulfonate (8.44 g, 10 mmol), *i*PrMgCl·LiCl, TsCN (1.8 g, 10 mmol) following **TP 4** (Exchange time: 60 min). The second Br/Mg-exchange was performed on the crude product according to **TP 4** (Exchange time: 60 min) using DMF (10 mmol) as an electrophile furnishing (1.68 g, 53%) of a colorless solid.

m.p.: 108.3 - 108.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 10.0 (s, 1 H), 8.1 (m, 1 H), 7.8 (m, 4 H), 7.5 (dd, J = 2.4, 1.4 Hz, 1 H), 7.0 (m, 1 H) 3.9 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 188.4, 164.9, 150.4, 138.5, 131.2, 131.0, 130.8, 127.4, 125.4, 116.3, 114.9, 55.9.

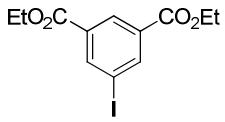
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1705, 1590, 1572, 1497, 1342, 1266, 1166, 1092, 966, 952, 839, 806, 750, 719, 704, 670.

MS (70 eV, EI) *m/z* (%): 317 (1) [M^+], 171 (52), 140 (31), 108 (25), 74 (69), 65 (14), 59 (100), 45 (75).

HRMS (EI): 317.0355 (calcd.: 317.0358).

4.7.2. Aryl Sulfonate/Copper-Exchange

Synthesis of diethyl 5-iodoisophthalate (52a):



The title compound was prepared from **50a** (408 mg, 1.0 mmol), iodine (508 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 6:1) furnished a yellow solid (251 mg, 72%).

m.p.: 75.2 - 75.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.6 (t, *J* = 1.7 Hz, 1 H), 8.5 (d, *J* = 1.5 Hz, 2 H), 4.4 (q, *J*=7.2 Hz, 4 H), 1.4 (t, *J*=7.2 Hz, 6 H).

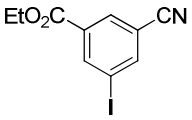
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.3, 142.3, 132.5, 129.8, 93.4, 61.7, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3083, 2984, 2903, 1710, 1290, 1231, 1142, 1103, 1021, 747, 714.

MS (70 eV, EI) *m/z* (%): 347 (64) [M^+], 319 (24), 312 (24), 302 (100), 291 (22), 274 (36), 247 (22), 246 (16), 75 (10).

HRMS (EI): 347.9853 (calcd.: 347.9858).

Synthesis of ethyl 3-cyano-5-iodobenzoate (52b):



The title compound was prepared from **50b** (361 mg, 1.0 mmol), I_2 (507 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 9:1) furnished a yellow solid (196 mg, 65%).

m.p.: 71.2 - 71.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.6 (t, *J* = 1.6 Hz, 1 H), 8.3 (t, *J* = 1.6 Hz, 1 H), 8.2 (t, *J* = 1.6 Hz, 1 H), 4.4 (q, *J* = 7.1 Hz, 2 H), 1.4 (t, *J* = 7.2 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.2, 144.0, 142.6, 132.3, 127.1, 116.3, 114.5, 93.6, 62.2, 14.2.

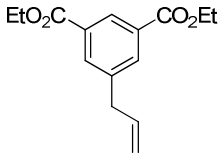
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3084, 3075, 2980, 2236, 1726, 1561, 1431, 1393, 1368, 1279, 1255,

1191, 1156, 1128, 1106, 1020, 996, 939, 926, 890, 862, 809, 762, 722, 698, 667.

MS (70 eV, EI) *m/z* (%): 301 (36) [M^+], 272 (100), 255 (81), 227 (43), 207 (45), 115 (27), 101 (51), 73 (48), 44 (47).

HRMS (EI): 300.9600 (calcd.: 300.9589).

Synthesis of diethyl 5-(prop-2-en-1-yl)isophthalate (52c):



The title compound was prepared from **50a** (408 mg, 1.0 mmol), allyl bromide (240 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 6:1) furnished a colorless oil (204 mg, 78%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.4 (t, *J* = 1.7 Hz, 1 H), 8.0 (d, *J* = 1.7 Hz, 2 H), 5.9 (m, 1 H), 5.0 (m, 2 H), 4.3 (q, *J* = 7.0 Hz, 4 H), 3.4 (d, *J* = 6.5 Hz, 2 H), 1.3 (t, *J* = 7.1 Hz, 6 H).

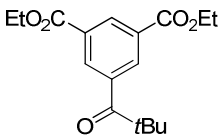
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.7, 140.7, 136.1, 133.7, 130.9, 128.4, 116.8, 61.1, 39.6, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3081, 2982, 2938, 2907, 1717, 1369, 1322, 1303, 1229, 1189, 1127, 1105, 1096, 1024, 997, 920, 753, 717, 701.

MS (70 eV, EI) *m/z* (%): 262 (49) [M^+], 234 (15), 218 (15), 217 (100), 190 (12), 189 (47), 117 (36), 115 (56), 105 (12), 77 (11).

HRMS (EI): 262.1197 (calcd.: 262.1205).

Synthesis of diethyl 5-(2,2-dimethylpropanoyl)isophthalate (52d):



The title compound was prepared from **50a** (408 mg, 1.0 mmol), pivaloyl chloride (240 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 19:1) furnished a colorless solid (187 mg, 61%).

m.p.: 72 - 72.3 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.8 (t, *J* = 1.6 Hz, 1 H), 8.5 (d, *J* = 1.7 Hz, 2 H), 4.4 (q, *J* = 7.1 Hz, 4 H), 1.4 (t, *J* = 7.1 Hz, 6 H), 1.35 (s, 9 H).

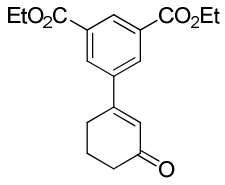
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 207.7, 165.2, 139.2, 132.6, 132.4, 131.0, 61.7, 44.3, 27.8, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 2934, 2908, 2876, 1726, 1717, 1672, 1474, 1434, 1396, 1367, 1239, 1172, 1107, 1032, 1022, 1000, 880, 857, 733, 722, 607.

MS (70 eV, EI) *m/z* (%): 306 (1) [M^+], 250 (15), 249 (100), 222 (11), 221 (8), 194 (5), 57 (8).

HRMS (EI): 306.1461 (calcd.: 306.1467).

Synthesis of diethyl 5-(3-oxocyclohex-1-en-1-yl)isophthalate (52e):



The title compound was prepared from **50a** (408 mg, 1.0 mmol), 3-iodocyclohexenone (444 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 1:1) furnished a colorless solid (202 mg, 64%).

m.p.: 108 - 108.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.7 (t, *J* = 1.6 Hz, 1 H), 8.4 (d, *J* = 1.5 Hz, 2 H), 6.5 (t, *J* = 1.5 Hz, 1 H), 4.4 (q, *J* = 7.1 Hz, 4 H), 2.8 (m, 2 H), 2.5 (m, 2 H), 2.2 (m, 2 H), 1.4 (t, *J* = 7.2 Hz, 6 H).

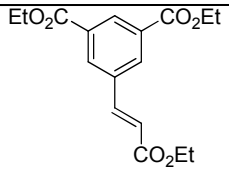
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 199.5, 165.3, 157.6, 139.6, 131.6, 131.5, 131.0, 126.7, 61.7, 37.2, 28.1, 22.7, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2922, 2877, 1713, 1672, 1646, 1613, 1450, 1434, 1369, 1332, 1319, 1290, 1257, 1239, 1222, 1193, 1174, 1133, 1108, 1032, 1021, 964, 930, 920, 891, 861, 751, 716, 690, 680.

MS (70 eV, EI) *m/z* (%): 316 (32) [M^+], 288 (25), 271 (27), 244 (10), 243 (70), 242 (100), 215 (10), 197 (10).

HRMS (EI): 316.1314 (calcd.: 316.1311).

Synthesis of diethyl 5-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]isophthalate (52f):



The title compound was prepared from **50a** (408 mg, 1.0 mmol), ethyl propiolate (196 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 9:1) furnished a yellow solid (195 mg, 61%).

m.p.: 78.9 - 79.5 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.7 (m, 1 H), 8.4 (d, *J* = 1.5 Hz, 2 H), 7.7 (d, *J* = 16.1 Hz, 1 H), 6.6 (d, *J* = 16.1 Hz, 1 H), 4.4 (q, *J* = 7.1 Hz, 4 H), 4.3 (d, *J* = 7.1 Hz, 2 H), 1.4 (t, *J* = 7.1 Hz, 6 H), 1.3 (t, *J* = 7.1 Hz, 3 H).

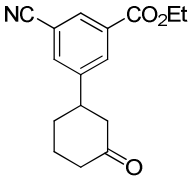
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 165.2, 142.3, 130.7, 135.2, 134.4, 132.6, 131.7, 120.7, 61.6, 60.8, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072, 2984, 2941, 2906, 1716, 1708, 1643, 1442, 1368, 1332, 1309, 1289, 1256, 1236, 1195, 1172, 1131, 1117, 1106, 1094, 1030, 998, 990, 967, 928, 917, 862, 826, 755, 730, 717, 666.

MS (70 eV, EI) *m/z* (%): 320 (47) [M+], 292 (11), 275 (100), 247 (24), 229 (52), 202 (14), 99 (10), 85 (20), 71 (24), 57 (32), 43 (19).

HRMS (EI): 320.1247 (calcd.: 320.1260).

Synthesis of ethyl 3-cyano-5-(3-oxocyclohexyl)benzoate (52g)



The title compound was prepared from **50b** (361 mg, 1.0 mmol), cyclohexenone (194 mg, 2.0 mmol), TMSCl (217 mg, 2.0 mmol) following **TP10**. Purification on silica (*n*-pentane/Et_2O 1:1) furnished a colorless oil (179 mg, 65%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.3 (t, *J* = 1.6 Hz, 1 H), 8.2 (t, *J* = 1.7 Hz, 1 H), 7.7 (t, *J* = 1.7 Hz, 1 H), 4.4 (q, *J* = 7.1 Hz, 2 H), 3.1 (s, 1 H), 2.7 – 2.4 (m, 4 H), 2.3 – 2.1 (m, 2 H), 2.0 – 1.8 (m, 2 H), 1.4 (t, *J* = 7.0 Hz, 3 H).

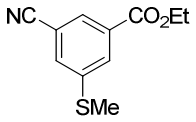
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 209.1, 164.5, 146.2, 134.0, 132.3, 132.0, 131.6, 117.9, 113.3, 61.9, 48.2, 44.1, 40.9, 32.4, 25.3, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3079, 2939, 2234, 1720, 1668, 1596, 1447, 1369, 1307, 1296, 1247, 1226, 1214, 1190, 1118, 1021, 891, 844, 767, 689.

MS (70 eV, EI) *m/z* (%): 271 (32), 242 (100), 228 (41), 195 (44), 182 (22), 140 (17).

HRMS (EI): 271.1205 (calcd.: 271.1208).

Synthesis of ethyl 3-cyano-5-(methylthio)benzoate (52h):



The title compound was prepared from ethyl **50b** (361 mg, 1.0 mmol), *S*-methyl thiomethylsulfonate (252 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 1:1) furnished a colorless solid (161 mg, 73%).

m.p.: 77.3 - 77.9 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.1 (m, 2 H), 7.6 (s, 1 H), 4.4 (q, J = 7.1 Hz, 2 H), 2.6 (s, 3 H), 1.4 (t, J = 7.2 Hz, 3 H) .

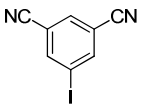
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.4, 142.0, 132.2, 132.0, 130.7, 129.0, 117.7, 113.4, 61.9, 15.3, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2984, 2232, 1720, 1572, 1434, 1370, 1282, 1188, 1158, 1133, 1111, 1025, 951, 929, 906, 888, 868, 858, 766, 751, 672.

MS (70 eV, EI) *m/z* (%): 221 (100) [M^+], 207 (23), 193 (44), 177 (20), 176 (72), 149 (26), 133 (18), 104 (12), 73 (15), 68 (10), 44 (20), 41 (12).

HRMS (EI): 221.0502 (calcd.: 221.0510)

Synthesis of ethyl 5-iodoisophthalonitrile (50i):



The title compound was prepared from **50c** (314 mg, 1.0 mmol), I_2 (507 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 9:1) furnished a colorless solid (163 mg, 63%).

m.p.: 79.5 - 81.0 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (d, J = 1.4 Hz, 1 H), 7.90 (dd, J = 1.4, 1.4 Hz, 2 H).

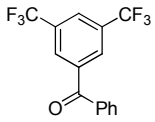
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 144.4, 134.2, 115.4, 115.1, 94.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3069, 2945, 2911, 1571, 1498, 1268, 1150, 1138, 1097, 961, 758.

MS (70 eV, EI) *m/z* (%): 254 (100) [M^+], 127 (59), 100 (12), 75 (6), 52 (2), 50 (3), 44 (3).

HRMS (EI): 253.9340 (calcd.:253.9341).

Synthesis of [3,5-bis(trifluoromethyl)phenyl](phenyl)methanone (52j):



The title compound was prepared from **50d** (413 mg, 1.0 mmol), benzoyl chloride (281 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 50:1) furnished a colorless solid (194 mg, 61%).

m.p.: 109.0 - 110.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (bs, 2 H), 8.09 (bs, 1 H), 7.78 (m, 2 H), 7.67 (dt, J = 6.6, 1.5 Hz, 1 H), 7.54 (m, 2 H).

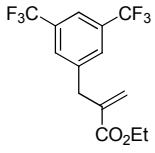
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 193.6, 139.4, 135.9, 133.6, 132.3, 132.2, 131.9, 131.70, 130.3, 130.2, 130.0, 129.9, 129.8, 129.5, 128.9, 128.8, 128.6, 125.9, 125.6, 125.6, 125.6, 123.8, 121.9, 121.7 (observed complexity due to C-F splitting, definitive assignments have not been made).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 3016, 2970, 1670, 1598, 1375, 1274, 1257, 1217, 1274, 1108, 1079, 908, 797, 680.

MS (70 eV, EI) *m/z* (%): 318 (21) [M^+], 241 (12), 213 (19), 163 (8), 105 (100), 77 (42), 51 (17).

HRMS (EI): 318.0480 (calcd.: 318.0479).

Synthesis of ethyl 2-(3,5-bis(trifluoromethyl)benzyl)acrylate (52k):



The title compound was prepared from **50d** (413 mg, 1.0 mmol), ethyl 2-(bromomethyl)acrylate (384 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 50:1) furnished a colorless oil (209 mg, 71%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.72 (bs, 1 H), 7.67 (bs, 2 H), 6.33 (bs, 1 H), 5.60 (m, 1 H), 4.17 (q, *J* = 7.3 Hz, 2 H), 3.75 (s, 2 H), 1.24 (t, *J* = 7.3 Hz, 3 H).

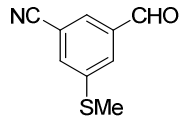
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.1, 141.5, 138.7, 132.3, 131.8, 131.4, 131.0, 129.2, 129.2, 129.1, 129.1, 129.1, 129.1, 129.1, 129.0, 129.0, 129.0, 127.4, 127.2, 125.1, 121.5, 120.6, 120.5, 120.4, 120.4, 117.9, 61.1, 38, 21.6, 14.0 (observed complexity due to C-F splitting, definitive assignments have not been made).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 2935, 2870, 1714, 1620, 1525, 1481, 1446, 1403, 1403, 1317, 1278, 1253, 1173, 1278, 1253, 1173, 1136, 1057, 1024, 755,

MS (70 eV, EI) *m/z* (%): 326 (38) [M^+], 247 (48), 226 (54), 183 (41), 164 (24), 115 (23), 57 (30), 43 (100)

HRMS (EI): 326.0732 (calcd.: 326.0742).

Synthesis of 3-formyl-5-(methylthio)benzonitrile (52p):



The title compound was prepared from **50i** (317 mg, 1.0 mmol), *S*-methyl thiomethylsulfonate (252 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 9:1) furnished a colorless solid (120 mg, 68%).

m.p.: 139.2 - 139.7 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 10.0 (s, 1 H), 7.9 (m, 2 H), 7.7 (m, 1 H), 2.6 (s, 3 H).

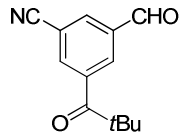
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 189.6, 143.2, 137.0, 134.9, 133.5, 129.6, 129.1, 114.2, 15.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 2925, 2856, 2234, 1699, 1576, 1438, 1429, 1403, 1385, 1300, 1267, 1243, 1195, 1146, 1136, 1127, 1057, 1012, 993, 981, 973, 954, 889, 874, 852, 830, 770, 728, 722, 695, 671, 624, 617, 602.

MS (70 eV, EI) *m/z* (%): 177 (100) [M^+], 176 (65), 133 (10), 104 (17), 69 (8), 45 (9).

HRMS (EI): 177.0239 (calcd.: 177.0248).

Synthesis of 3-(2,2-dimethylpropanoyl)-5-formylbenzonitrile (52q):



The title compound was prepared from **50i** (317 mg, 1.0 mmol), pivaloyl chloride (240 mg, 2.0 mmol) following **TP10**. Column chromatographical purification on silica (*n*-pentane/Et_2O 2:1) furnished a colorless solid (129 mg, 60%).

m.p.: 42.2 - 42.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 10.1 (s, 1 H), 8.4 (t, *J* = 1.5 Hz, 1 H), 8.3 (t, *J* = 1.5 Hz, 1 H), 8.2 (t, *J* = 1.5 Hz, 1 H), 1.4 (s, 9 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 205.8, 189.1, 140.4, 136.8, 136.2, 134.5, 132.1, 116.9, 114.0, 44.5, 27.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2935, 2853, 2236, 1729, 1701, 1676, 1585, 1476, 1462, 1446, 1401, 1380, 1372, 1291, 1266, 1240, 1150, 1132, 1052, 1031, 1012, 1002, 948, 931, 896, 848, 787, 762, 704, 688, 674, 622, 607.

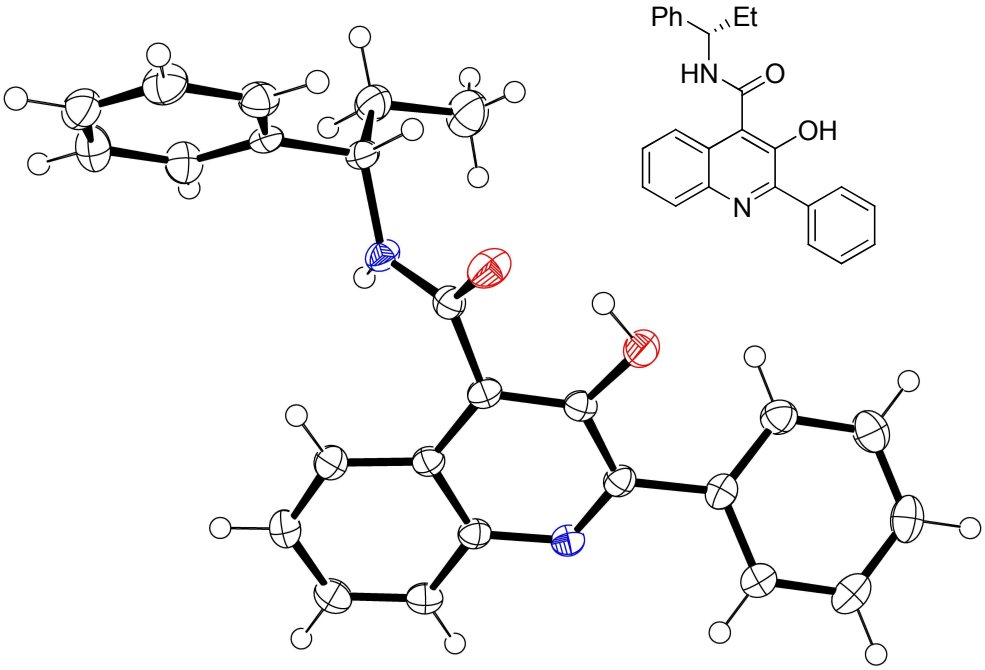
MS (70 eV, EI) *m/z* (%): 215 (1) [M^+], 187 (12), 158 (10), 131 (6), 102 (7), 57 (100), 40 (30).

HRMS (EI): 215.0939 (calcd.: 215.0946).

5. APPENDIX

5.1. Data of the X-rayAnalysis:

3-Hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]quinoline-4-carboxamide (Talnetant; 25)

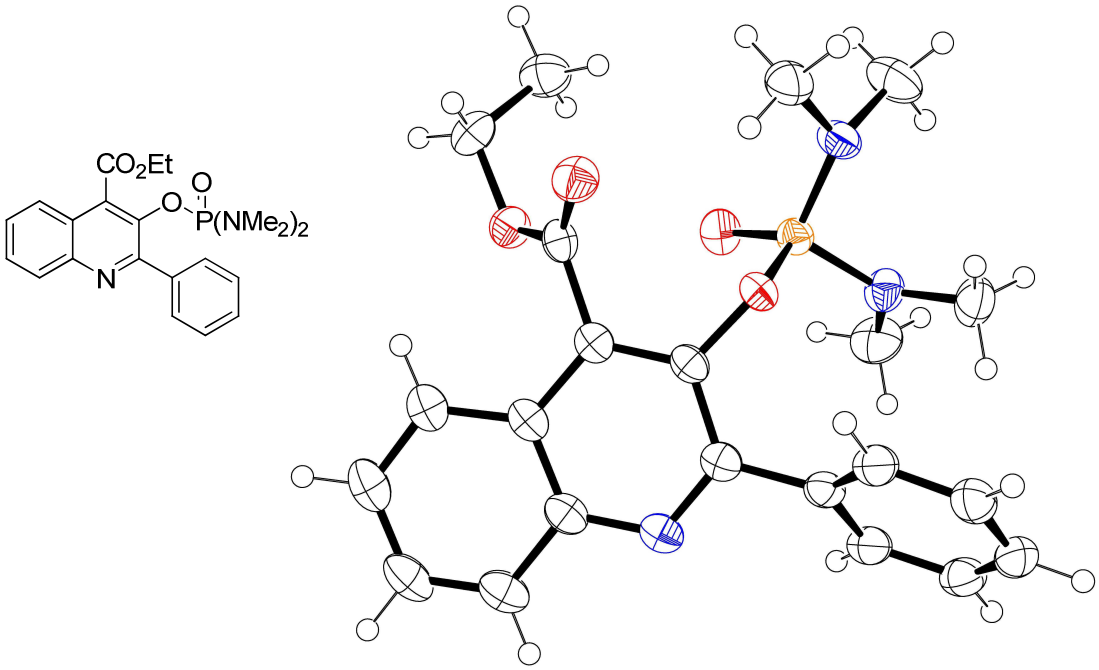


Empirical formula	C25 H22 N2 O2	
Formula weight	382.454	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 7.3472(3) Å	α= 90°.
	b = 9.8722(4) Å	β= 90°.
	c = 26.8795(10) Å	γ = 90°.
Volume	1949.65(13) $Å^3$	
Z	4	
Density (calculated)	1.30298(9) Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	808	
Crystal size	0.44 x 0.33 x 0.24 mm^3	
Theta range for data collection	4.32 to 26.35°.	

Index ranges	-9<=h<=7, -7<=k<=12, -33<=l<=32
Reflections collected	8157
Independent reflections	2285 [R(int) = 0.0283]
Completeness to theta = 26.35°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98000 and 0.95671
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2285 / 0 / 271
Goodness-of-fit on F^2	0.932
Final R indices [I>2sigma(I)]	R1 = 0.0297, wR2 = 0.0597
R indices (all data)	R1 = 0.0413, wR2 = 0.0619
Absolute structure parameter	?
Largest diff. peak and hole	0.135 and -0.156 e.$Å^{-3}$

CCDC 766951 contains the supplementary crystallographic data for this compound. This data has been deposited in the Cambridge Crystallographic Data Centre and can be obtained free of charge via the internet: www.ccdc.cam.ac.uk/data_request/cif

Ethyl 3-{[bis(dimethylamino)phosphoryl]oxy}-2-phenylquinoline-4-carboxylate (31a)

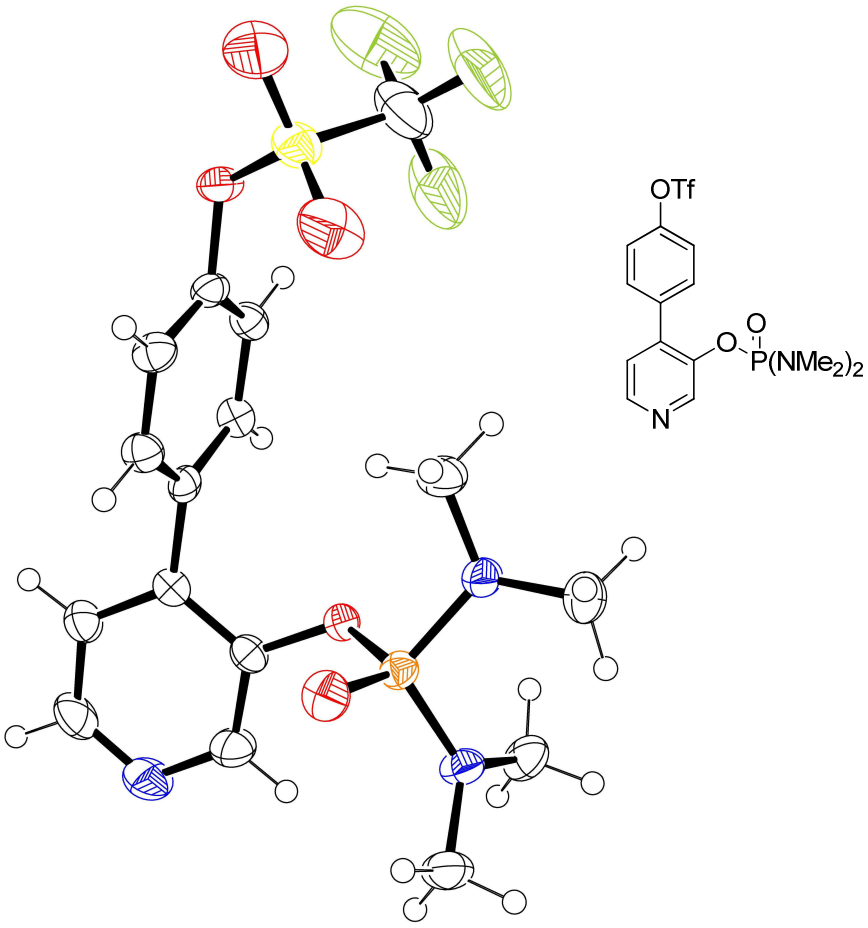


Empirical formula	C22 H26 N3 O4 P	
Formula weight	427.433	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 13.619(3) Å	α= 90°.
	b = 11.209(2) Å	β= 94.89(3)°.
	c = 14.083(3) Å	γ = 90°.
Volume	2142.0(7) $Å^3$	
Z	4	
Density (calculated)	1.3255(4) Mg/m^3	
Absorption coefficient	0.162 mm^{-1}	
F(000)	904	
Crystal size	0.19 x 0.15 x 0.06 mm^3	
Theta range for data collection	3.15 to 27.10°.	
Index ranges	-17<=h<=17, -14<=k<=13, -18<=l<=18	
Reflections collected	15784	

Independent reflections	4700 [R(int) = 0.0482]
Completeness to theta = 27.10°	99.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4700 / 0 / 276
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0438, wR2 = 0.1020
R indices (all data)	R1 = 0.0737, wR2 = 0.1153
Absolute structure parameter	?
Largest diff. peak and hole	0.202 and -0.425 e.$Å^{-3}$

CCDC 766953 contains the supplementary crystallographic data for this compound. This data has been deposited in the Cambridge Crystallographic Data Centre and can be obtained free of charge via the internet: www.ccdc.cam.ac.uk/data_request/cif

4-(3-{[bis(dimethylamino)phosphoryl]oxy}pyridin-4-yl)phenyl trifluoromethanesulfonate (29b):



Empirical formula	C16 H19 F3 N3 O5 P S	
Formula weight	453.374	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 10.2499(4) Å	α= 90°.
	b = 10.0927(4) Å	β= 98.197(4)°.
	c = 19.7258(8) Å	γ = 90°.
Volume	2019.77(14) $Å^3$	

Z	4
Density (calculated)	1.49097(10) Mg/m^3
Absorption coefficient	0.300 mm^{-1}
F(000)	936
Crystal size	0.31 x 0.29 x 0.27 mm^3
Theta range for data collection	4.26 to 26.34°.
Index ranges	-12<=h<=8, -12<=k<=11, -24<=l<=21
Reflections collected	8084
Independent reflections	4075 [R(int) = 0.0241]
Completeness to theta = 26.34°	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.92200 and 0.90136
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4075 / 0 / 266
Goodness-of-fit on F^2	0.911
Final R indices [I>2sigma(I)]	R1 = 0.0359, wR2 = 0.0830
R indices (all data)	R1 = 0.0574, wR2 = 0.0880
Absolute structure parameter	?
Largest diff. peak and hole	0.274 and -0.366 $e.Å^{-3}$

CCDC 766952 contains the supplementary crystallographic data for this compound. This data has been deposited in the Cambridge Crystallographic Data Centre and can be obtained free of charge via the internet: www.ccdc.cam.ac.uk/data_request/cif

5.2. Curriculum Vitae

Christoph Josef Rohbogner

Personal Information:

Date of Birth:	August 24th, 1980
Place of Birth:	Munich, Germany
Nationality:	German

Education

05/2006-04/2010	Ph.D. Thesis in the group of Prof. Dr. Paul Knochel
09/2005-03/2006	Diploma Thesis in the group of Prof. Dr. Paul Knochel on "Cobalt-Catalyzed Arylsulfonate Copper-Exchange"
10/2000-09/2005	Studies in Chemistry at the Department of Chemistry, Ludwig-Maximilians-University (LMU), Munich
9/1991-6/2000	High School: Gymnasium Bad Aibling High School Diploma (Main Subjects: English, Geography)
9/1987-6/1991	Primary Education: Grundschule der Gemeinde Feldkirchen Westerham

Language Skills:

German:	mother tongue
English:	fluent
French:	basic skills

Awards and Distinctions

2009 Fellowship of the Dr. Klaus Römer Stiftung

Personal Interests

Photography
Sports (Badminton, Cycling)

Voluntary Service

Member of the "Volunteer Fire Department Feldolling"

Publications:

C. J. Rohbogner, S. Wirth, P. Knochel **"Phosphorodiamidate-Directed Metalation of *N*-Heterocycles Using Mg- and Zn-TMP Bases"**, *Org. Lett.* **2010**, *ASAP*, **DOI:** 10.1021/ol100453x.

S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel **"Scaleable Preparation of Functionalized Organometallics *via* Directed *ortho*-Metalation Using Mg- and Zn-Amide Bases"**, *Org. Process. Res. Dev.* **2010**, *14*, 339-345.

C. J. Rohbogner, C. R. Diène, T. J. Korn, P. Knochel **"A Cobalt-Catalyzed Sulfonate/Copper-Exchange for the Preparation of Highly Functionalized Electron-Deficient Arylcopper Reagents"**, *Angew. Chem. Int. Ed.* **2010**, *49*. 1874-1877; *Angew. Chem.* **2010**, *122, 1918*-1921.

S. Wirth, C. J. Rohbogner, M. Cieslak, J. Kazmierczak-Baranska, S. Donevski, B. Nawrot, I.-P. Lorenz **"Rhodium(III) and Iridium(III) Complexes with 1,2-naphthoquinone-1-oximate as Bidentate Ligand : Synthesis, Structure and Biological Activity"**, *J. Biol. Inorg. Chem.* **2009**, *accepted*.

C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel **"Magnesiation of Poorly Activated Substrates Using $TMP_2Mg{\cdot}2LiCl$. Synthesis of *tert*-butyl ethyl phthalate"**, *Org. Synth.* **2009**, *86*, 374-384.

C. J. Rohbogner, S. H. Wunderlich, G. C. Clososki, P. Knochel **"New Mixed Li/Mg- and Li/Mg/Zn-Amides for the Chemoselective Metallation of Arenes and Heteroarenes"** *Eur. J. Org. Chem.* **2009**, 1781-1795. *(special issue dedicated to Prof. Alain Krief)*

C. J. Rohbogner, G. C. Clososki, P. Knochel **"A General Method for *meta*- and *para*-Functionalization of Aromatics Using $TMP_2Mg{\cdot}2LiCl$"**, *Angew. Chem. Int. Ed.* **2009**, *47*, 1503-1507, *Angew. Chem.* **2009**, *120*, 1526-1530.

G. C. Clososki, C. J. Rohbogner, P. Knochel **"Direct Magnesiation of Polyfunctionalized Arenes and Heteroarenes Using $TMP_2Mg{\cdot}2LiCl$"**, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684; *Angew. Chem.* **2007**, *119*, 7825-7828. Highlighted in *Nachr. Chem.* **2008**, *56*, 280.

C. Galvez-Ruiz, C. J. Holl, K. Karaghiosoff, T. M. Klapoetke, K. Löhnwitz, H. Nöth, P. Mayer, K. Polborn, C. J. Rohbogner, M. Suter, J. J. Weigand **"Derivatives of 1,5-diamino-1*H*-tetrazole; A new Family of Energetic Heterocyclic – Based Salts"**, *Inorg. Chem.* **2005**, *44*, 4237-4253.

Reviews and Book Chapters :

T. Thaler, H. Ren, N. Gommermann, G. C. Clososki, C. J. Rohbogner, S. H. Wunderlich, P. Knochel **"New Catalytic Cu-, Pd- and Stochiometric Mg- and Zn-Mediated Bond Activations"** in *Activating Unreactive Substrates: The Role of Secondary Interactions* (Eds. C. Bolm, F. E. Hahn), Wiley-VCH, Weinheim (Germany), **2009**, 359-375.

P. Knochel, P. Appukkuttan, A. Gavryshin, G. Manolikakes, A. Metzger, M. Mosrin, F. M. Piller, C. J. Rohbogner, M. A. Schade, S. H. Wunderlich **"Functionalization of Heterocyclic Compounds using Polyfunctional Magnesium and Zinc Reagents"**, *Pfizer In-House Journal Synthon*, **2008**.

Patent Application

P. Knochel, G. C. Clososki, A. Krasovskiy, V. Krasovskaya, C. J. Rohbogner **"Preparation and use of Magnesium Amides"**, *Eur. Pat. Appl.* **2007** Nr. 07703987.3

Oral Presentations

"C-H Activation with Mg-bases" Presentation at the LMU, 02.07.2007 in Munich

"New Mixed Li/Mg-Amides as Highly Efficient and Selective Magnesiation Reagents" Presentation at the LMU, 22.02.2008 in Munich

"New Commercializable Mixed Li/Mg Amides for the Application in Organic Synthesis" Presentation at the LMU, 18.07.2008 in Munich

Poster Presentation

C. J. Rohbogner, G. C. Clososki, P. Knochel **"A General Method for *meta*- and *para*-Functionalization of Aromatics Using $TMP_2Mg \cdot 2LiCl$"** (Poster 12) at the 5th Asian-European Symposium on Metal-Mediated Efficient Organic Synthesis, May 25th to 28th, Obernai, France.