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Oxidative Copper(I)-Mediated Cycloamination. Preparation and Reactions of Heteroaromatic Benzylic Zinc Compounds. Novel Preparation of Tertiary Benzylic and Phenethylic Amines

von

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aus

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Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 (in der Fassung der sechsten Änderungssatzung vom 16. August 2010) von Professor Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe bearbeitet.

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Andreas J. Wagner

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Meinen Freunden

A mes amis

To my friends

Моим друзьям

Ὁ βίος βραχύς,
ἡ δὲ τέχνη μακρή,
ὁ δὲ καιρὸς ὀξύς,
ἡ δὲ πεῖρα σφαλερή,
ἡ δὲ κρίσις χαλεπή.

- Ἱπποκράτης ὁ Κῷος -

Life is short,
art long,
opportunity fleeting,
experiment fallible,
judgment difficult.

- Hippocrates of Cos -

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A. INTRODUCTION

1. Overview

Ever since *Wöhler*'s syntheses of oxalic acid from cyanogen in 1824 and urea from ammonium cyanate in 1828 – the very experiments which established organic chemistry as a scientific discipline of its own – many important advancements have been made over the past two centuries. Not only have the modern organic chemist's analytical tools developed significantly as with the discovery of nuclear magnetic resonance (NMR) spectroscopy[1], also the synthetic methods at his disposal have enormously improved. Today, one of the most important fields of organic synthesis is that of organometallic chemistry. The utility of using polarized carbon-metal bonds as nucleophiles for the synthesis of complex organic molecules has been proven over and over ever since the first discovery of a carbon-metal bond with *Frankland*'s synthesis of diethylzinc in the 19th century.[2] *Grignard*'s method of preparing the first isolable organo-magnesium compounds at the beginning of the 20th century set another milestone in the history of organometallic chemistry.[3] Besides organozinc and organomagnesium compounds, a wide range of other metals has been thoroughly investigated in the past, and many useful applications in organic synthesis have emerged for organometallics – both in the role of catalysts and reagents.[4] When bound to carbon, the various metals of the periodic table span large areas of individual reactivities, as a function of their nature as either main-group or transition metals, and because of their difference in electronegativity. Highly polarized carbon-metal bonds (such as carbon-lithium, carbon-sodium or carbon-magnesium bonds) lead to high reactivity and low chemical selectivity when taking part in organic transformations[5], while rather covalent bonds like in organozinc or organoboron compounds excel in high stability, coupled with lower reactivity towards other organic molecules.[6]

Even though the ability to construct organic frameworks was the first and most important application of organometallic compounds, today also numerous protocols exist for the formation of carbon-heteroatom bonds *via* the use of organometallic intermediates.

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[1] Hore, P. J. *Nuclear Magnetic Resonance*, Oxford University Press, Oxford, **1995**.
[2] (a) Frankland, E. *Liebigs Ann. Chem.* **1848**, *71*, 171; (b) Frankland, E. *J. Chem. Soc.* **1848**, *2*, 263.
[3] (a) Grignard, V. *Ann. Chim.* **1901**, *24*, 433; (b) Grignard, V. *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322.
[4] Knochel, P. (Ed.) *Handbook of Functionalized Organometallics, Vol. 1 and 2*, Wiley-VCH, Weinheim, Germany, **2005.**
[5] Wu, G.; Huang, M. *Chem. Rev*. **2006**, *106*, 2596.
[6] Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.

2. Amination Reactions

Aromatic and heteroaromatic aryl amines represent important target molecules in organic synthesis, due to their versatile utility as photographic materials[7], electrically conducting polymers[8] and – most of all – pharmaceuticals[9]. For example, the fluoroquinolone Ciprofloxacin (**1**) is a very potent antibiotic with a wide range of therapeutic use[10] and the piperidone derivative Aripiprazol (**2**) has been successfully used in the treatment of schizophrenia[11]. Alprazolam (**3**), an antidepressant[12], and Capecitabin (**4**), a cytostatic for the treatment of metastasized colon cancer[13], are further examples illustrating the interest for effective synthetic methods for the preparation of functionalized aromatic amines (Figure 1).

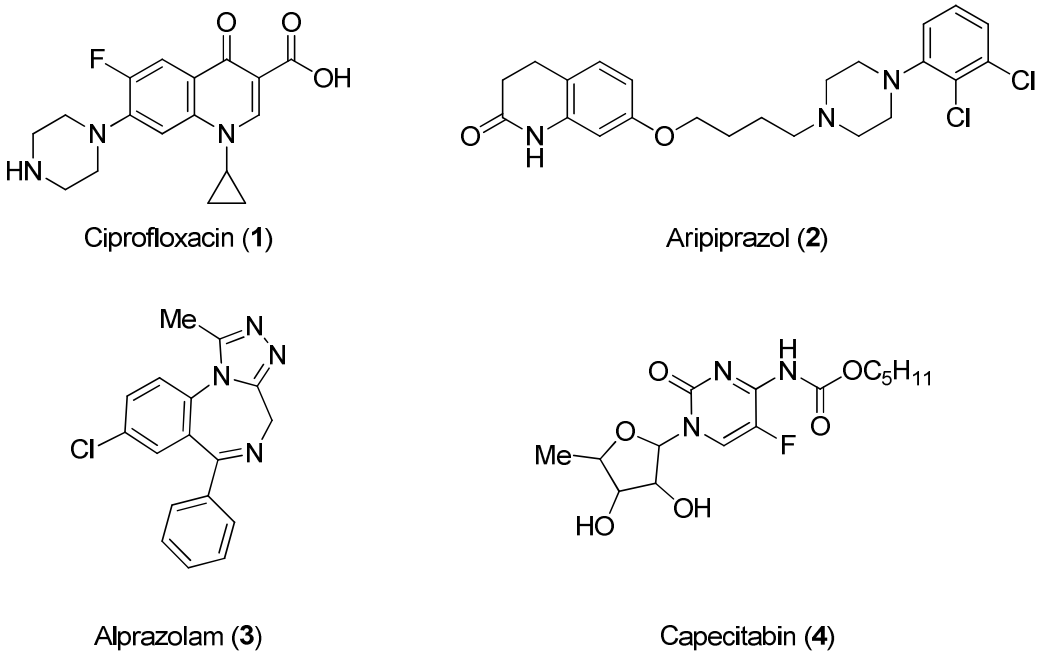


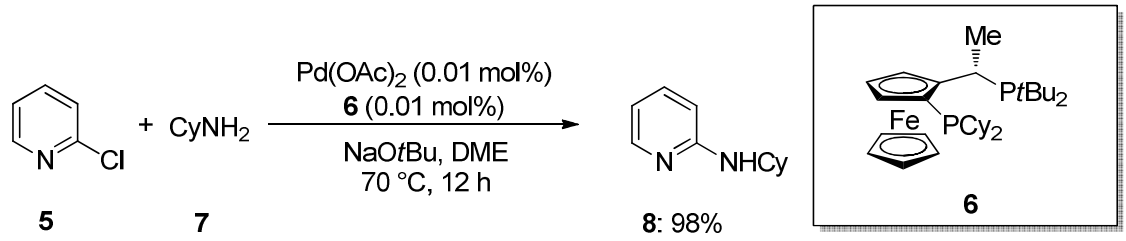
Figure 1: Selected heterocyclic amine pharmaceuticals.

[7] Law, K. Y. *Chem. Rev.* **1993**, *93*, 449.
[8] (a) Gospodinova, N.; Terlemezyan, L. *Prog. Polym. Sci.* **1998**, *23*, 1443; (b) MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27.
[9] Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112.
[10] Bamberger, D. M.; Peterson, L. R.; Gerding, D. N.; Moody, J. A.; Fasching, C. E. *J. Antimicrob. Chemotherapy* **1986**, *18*, 51.
[11] Fernald, D. S.; van Dellen, R. T.; Hovens, J. E.; Loonen, A. J. M. *Acta Psych. Scand.* **2006**, *114*, 294.
[12] Marks, I. M.; Swinson, R. P.; Basoglu, M.; Kuch, K.; Noshirvani, H.; O'Sullivan, G.; Lelliott, P. T.; Kirby, M.; McNamee, G.; Sengun, S. *Br. J. Psychiatry* **1993**, *162*, 776.
[13] Peinert, S.; Arnold, D.; Grothe, W.; Lesske, J.; Schädlich, B.; Kegel, T.; Schmoll, H.-J. *Onkologie* **2005**, *28*, 241.

In the past, especially transition-metal catalyzed amination reactions, electrophilic amination reactions and oxidative couplings of amidocuprates have proven to be useful for the preparation of functionalized amines.

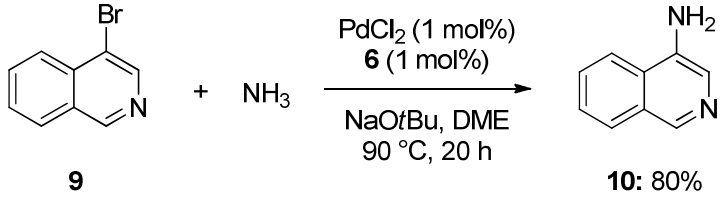
2.1. Transition-Metal Catalyzed Amination

Today, a widely spread synthetic method for preparing functionalized aryl amines is the Pd-catalyzed amination of aryl halides and related electrophiles described by *Buchwald* and *Hartwig*[14]. The choice of an appropriate ligand plays a crucial role, and today basically two classes of ligands are used: chelating bis(phosphane) ligands and biarylmonophosphane ligands. As an example, 2-chloropyridine **5** readily reacts with cyclohexylamine **7** in the presence of the JOSIPHOS-type chelating ligand **6** to give the secondary amine **8** in excellent yield (Scheme 1).[15]



Scheme 1: Pd-catalyzed amination of an aryl halide affording a secondary arylamine.

This procedure even allows the use of ammonia in order to prepare primary aromatic amines, as demonstrated on 4-bromoisoquinoline **9** to afford isoquinoline-4-amine **10** in 80% yield (Scheme 2).[16]

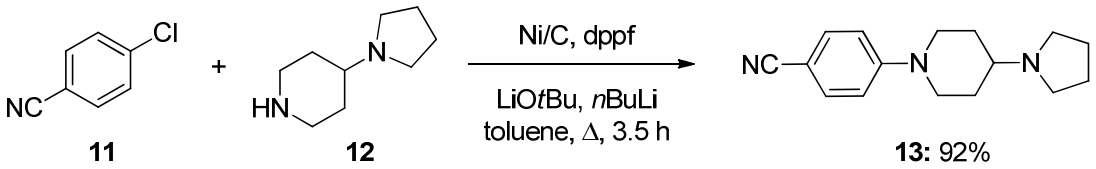


Scheme 2: Pd-catalyzed carbon-nitrogen coupling using gaseous NH_3.

[14] (a) Guram, A.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348; (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
[15] Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2005**, *44*, 1371.
[16] Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028.

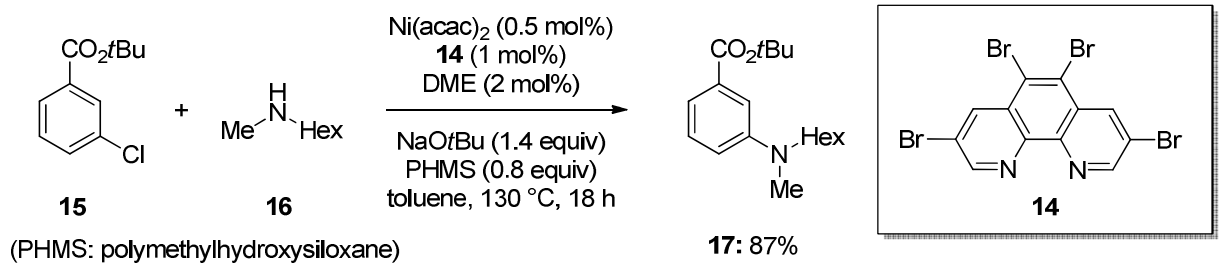
Despite the utility of this reaction, the Pd-catalyzed amination suffers from several drawbacks, which include often drastic reaction conditions, the lack of possibility to prepare triarylamines, and the long reaction times needed when dealing with sterically demanding substrates. Most importantly, bromo- or iodo-substituents are not compatible with this procedure, making it impossible to selectively monoaminate a polyhalogenated substrate.

Although palladium complexes certainly constitute the most widely used class of catalysts for aminations, Nickel catalysts have also found application recently. As *Lipshutz* reported, a Nickel/charcoal catalyst, which is activated by *n*BuLi the presence of dppf, enables the efficient C-N cross-coupling on a wide range of aryl chlorides. Thus, 4-chlorobenzonitrile **11** couples to 4-(1-pyrrolidino)piperidine **12** affording the tricyclic diamine **13** in 92% yield (Scheme 3).[17]



Scheme 3: Ni-catalyzed amination of an aryl chloride.

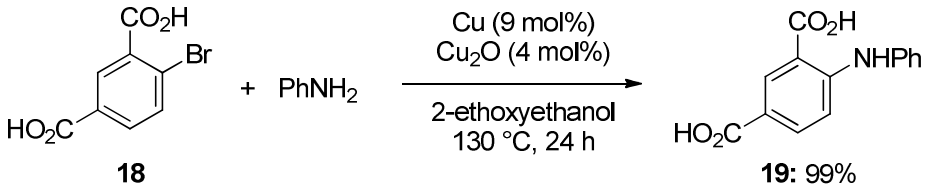
As shown by *Knochel*, 3,5,6,8-tetrabromo-1,10-phenanthroline **14** as a ligand promotes the Ni-catalyzed amination of aryl and heteroaryl chlorides, shown exemplarily with the aryl chloride **15** and the secondary alkylamine **16**. The resulting tertiary amine **17** is obtained in 87% yield (Scheme 4).[18]



Scheme 4: Ni-catalyzed amination reaction using tetrabromophenanthroline as ligand.

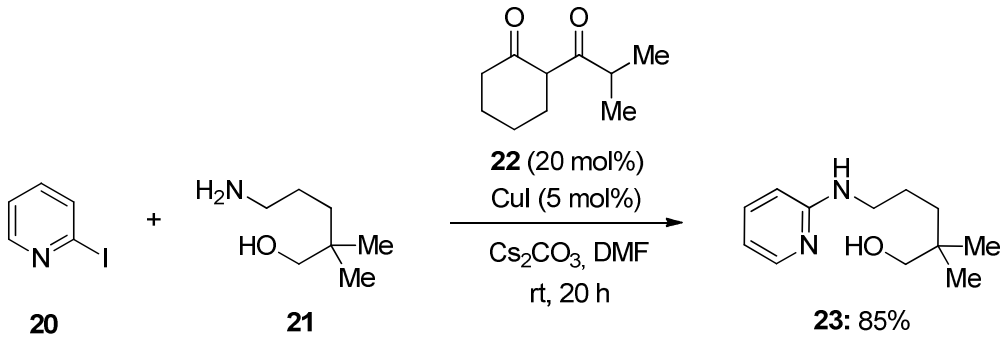
[17] Friedman, B. A.; Taft, B. R.; Lee, C.-T.; Butler, T.; Lipshutz, B. H. *Synthesis* **2005**, 2989.
[18] Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem*. **2008**, *73*, 1429.

Besides palladium and nickel, copper-catalyzed amination reactions have also continuously been improved and refined over the past decades. *Casimir* and coworkers reported in 2006 the Cu-catalyzed reaction of unprotected 4-bromoisophthalic acid **18** with aniline to give the amine **19** in excellent yield (Scheme 5).[19]



Scheme 5: Cu-catalyzed amination of a free bromocarboxylic acid.

The harsh reaction conditions needed for the original *Ullmann* coupling[20] such as long reaction times, elevated temperatures, the use of strong bases and, additionally, the need for stoichiometric amounts of copper, have been optimized significantly by the use of bidentate ligands such as 1,2-diols[21], phenanthroline derivatives[22], or amino acids.[23] Also, the use of β-diketones as ligands inhibits catalyst deactivation and reduces the required reaction times. For instance, 2-iodopyridine **20** is coupled with the aminoalcohol **21** in the presence of 2-isobutyrylcyclo-hexanone **22** within 20 h at 25 °C to afford the secondary amine **23** (Scheme 6).[24]

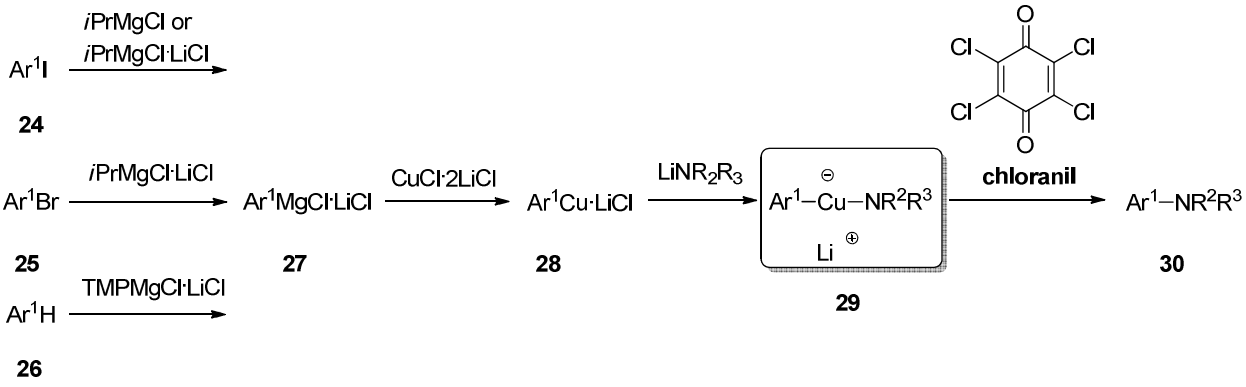


Scheme 6: Cu-catalyzed amination using a β-diketone additive.

[19] Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.*, **2006**, *71*, 3270.
[20] Ullmann, F. *Ber. Dt. Chem. Ges.* **1903**, *36*, 2382.
[21] Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.
[22] (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D.; *Org. Lett.* **2001**, *3*, 4315 ; (b) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779; (c) van Allen, D.; Venkataraman, D. *J. Org. Chem.* **2003**, *5*, 2453.
[23] Ma, D. W.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.
[24] Lu, Z. K.; Twieg, R. J.; Huang, S. P. D. *Tetrahedron Lett.* **2003**, *44*, 6289.

2.2. Oxidative Amination Reaction

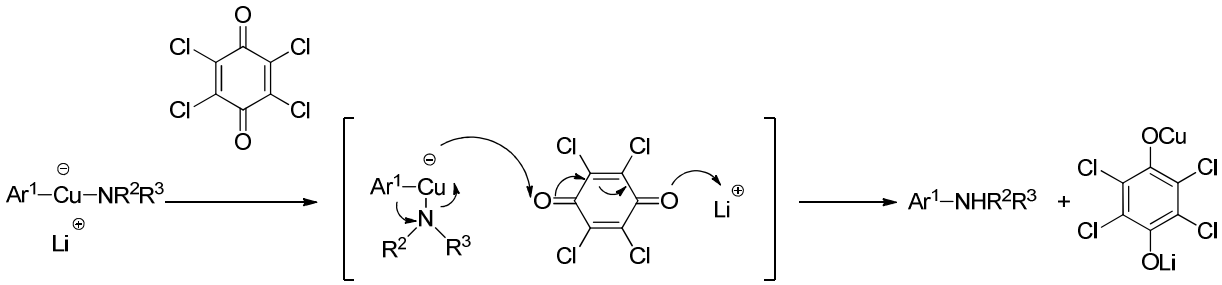
The first reports of an oxidative coupling reaction of amidocuprates were given by *Yamamoto* and *Ricci*, using oxygen or 1,3-dinitrobenzene as oxidants.[25,26] *Knochel* recently reported an alternative synthesis of primary, secondary and tertiary aryl amines *via* the oxidative coupling of polyfunctional aryl and heteroaryl amidocuprates.[27,28] Thereby, aryl iodides **24** or bromides **25** are converted to the corresponding organomagnesium compounds by iodine-magnesium or bromine-magnesium exchange using *i*PrMgCl[29] or the more reactive *i*PrMgCl·LiCl[30]. Alternatively, C-H acidic arenes **26** are directly magnesiated using TMPMgCl·LiCl.[31] The so obtained organomagnesium species **27** are subsequently transmetalated using the THF-soluble salt complex CuCl·2LiCl[32] to the organocopper compounds **28** which in turn react with lithium amides **29** to the corresponding lithium amidocuprates **30**. In the final step, oxidation using chloranil (2,3,5,6-tetrachlorobenzo-*p*-quinone) leads to the amines **31** (Scheme 7).



Scheme 7: Oxidative amination of lithium amidocuprates.

[25] Maruoka, K.; Yamamoto, H. *J. Org. Chem.* **1980**, *45*, 2739.
[26] Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620.
[27] del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.
[28] Kienle, M.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, 1272.
[29] Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.
[30] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[31] Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5683.
[32] Knochel, P.; Yeh, M. C. P.; Berk, C. S.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

In a plausible mechanistic proposal, chloranil first coordinates to the copper atom. Then, both the copper and lithium atoms are transferred to the chloranil molecule.[33] For the formation of the C-N bond, one electron pair of the amidocuprate is transferred to chloranil, which in turn undergoes aromatization. This constitutes the main driving force of the coupling reaction (Scheme 8).



Scheme 8: Mechanistic proposal for the oxidative amination reaction.

Recently, *Knochel* also reported the extension of this methodology to the amination of zinc organometallics, tolerating a wider range of functional groups.[34]

3. Organozinc Compounds

3.1. Overview

In the first years after the discovery of the carbon-zinc bond by *Frankland*[2], organozinc reagents found only little interest due to the easy accessibility of organolithium compounds and the well-established procedures for the preparation of organomagnesium reagents established by *Grignard*.[3] Organozinc compounds possess an intrinsically lower reactivity compared to the aforementioned analogs and therefore found only few applications in organic synthesis, such as the *Simmons-Smith* cyclopropanation reaction[35] or the *Reformatsky* reaction of zinc enolates.[36] However, one of the main advantages of organozinc chemistry is the significantly higher tolerance of functional groups present in both the organometallic substrate and the electrophile. This is due to the fact that the carbon-zinc bond has a higher covalent character than carbon-

[33] Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem*. **2007**, 4166.
[34] Kienle, M.; Wagner, A. J.; Dunst, C.; Knochel, P. *Chem. Asian J.* **2011**, *6*, 512.
[35] Simmons, H.E.; Cairns, T. L.; Vladiuchick, A.; Hoiness, C. M. *Org. React.* **1972**, *20*, 1.
[36] (a) Reformatsky, S. *Chem. Ber*. **1887**, *20*, 1210, Fürstner, A. *Angew. Chem. Int. Ed.* **1993**, *32*, 164.

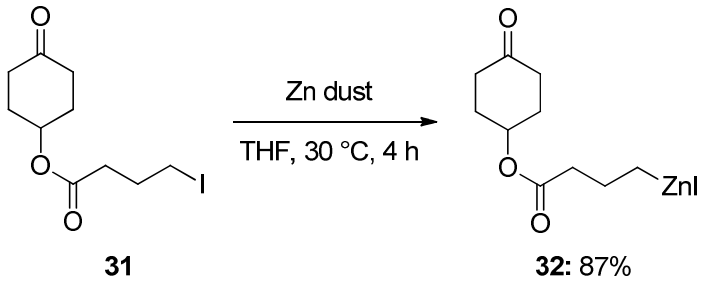
magnesium or carbon-lithium bonds. Thus, organozinc species can be handled at temperatures which are not tolerated by Grignard compounds or organolithiums.

Today, organozinc reagents, which are commonly divided in the three classes of organozinc halides (RZnX), diorganozincs (R^1R^2Zn) and triorganozincates ($R^1R^2R^3ZnMet$), constitute important fields of research and applications.[37]

3.2. Preparations of Organozinc Compounds

3.2.1. Oxidative Insertion of Metallic Zinc into Organic Halides

A general method for preparing organozinc halides is the insertion of elementary zinc into organic halides in coordinating solvents such as THF. Zinc dust or foil are equally well suited for this reaction, and many functional groups can be tolerated using this method. However, easily reduced functions such as nitro groups will cause undesired side reactions. For example, treatment of the ester **31** with Zn dust in THF leads to the alkylzinc iodide **32** in 87% yield (Scheme 9).[38]



31 **32:** 87%

Scheme 9: Direct insertion of zinc dust into an alkyl iodide.

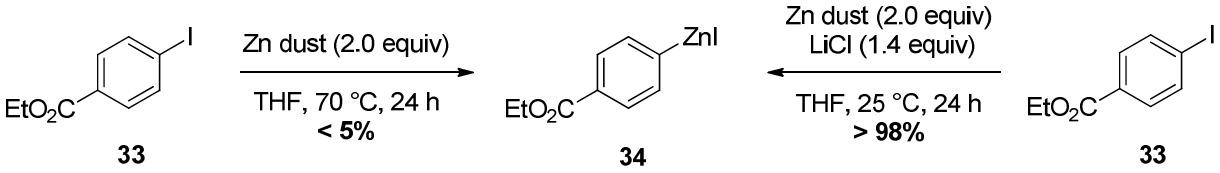
[37] (a) Knochel, P.; Langer, F.; Rottländer, M.; Stüdemann, T. *Chem. Ber*. **1997**, *130*, 387; (b) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275; (c) Knochel, P.; Jones, P. (Eds.) *Organozinc Reagents*, Oxford University Press; New York **1999**; (d) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React*. **2001**, *58*, 417; (e) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. *Handbook of Functionalized Organometallics* (P. Knochel, Ed.), Wiley-VCH, Weinheim, **2005**.

[38] Knochel, P.; Rozema, M. J.; Tucker, C. E.; Retherford, C.; Furlong, M.; Achyutha Rao, S. *Pure Appl. Chem*. **1992**, *64*, 361.

Previous activation of the zinc surface is generally necessary, since zinc metal is usually passivated by a layer of zinc oxide. A typical way of removing the passivation is the treatment of zinc metal with 1,2-dibromoethane and chlorotrimethylsilane.[39] The former generates upon heating elementary bromine which etches the oxide layer, the latter is used to remove zinc-bound oxygen from the metal surface due to the high oxophilicity of silicon.

As an alternative to the activation of zinc metal mentioned above, the reduction of zinc chloride using Li-naphthalenide in THF generates highly active elementary zinc which inserts easily into a variety of carbon-halogen bonds, leading to the corresponding organozinc halides.[40]

Knochel reported in 2006 the LiCl-facilitated insertion of zinc metal into organic halides. The addition of stoichiometric amounds of LiCl considerably enhances the reactivity of zinc and enables insertions into substrates which normally would react only very slowly, or not at all. For instance, ethyl 4-iodobenzoate **33** reacts with Zn dust to the 4-(ethoxycarbonyl)phenylzinc iodide **34** in only less than 5% after 24 h at 70 °C. The addition of 1.4 equivalents of LiCl leads instead to full conversion at 25 °C in the same reaction time (Scheme 10).[41]



33 **34** **33**

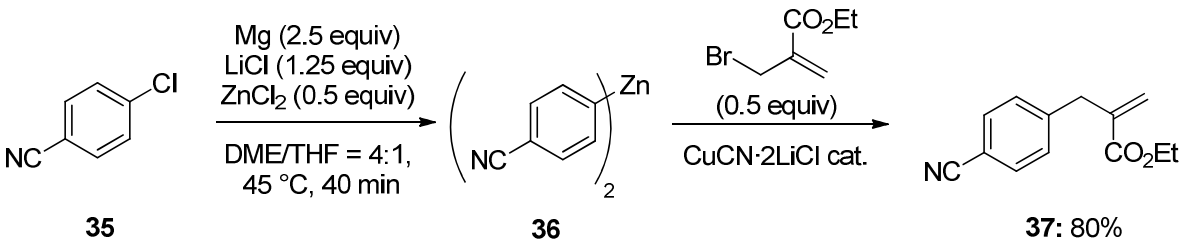
Scheme 10: Effect of LiCl as additive on the Zn insertion into ethyl 4-iodobenzoate. (LiCl in the product **34** is omitted for clarity.)

Presumably, the solubility of the generated organozinc compound is highly increased due to the formation of adducts of the type RZnI·LiCl. This leads to a faster diffusion away from the metal surface, allowing higher turnover rates since other substrate molecules can interact with the metal faster. An additional side-effect of the increased rate of diffusion is the reduced possibility for the zinc surface to be deactivated.

[39] Gaudemar, M. *Bull. Soc. Chim. Fr*. **1962**, *5*, 974.
[40] Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 9713.
[41] Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed*. **2006**, *45*, 6040.

3.2.2. Transmetalation

Although the insertion of Zn in the presence of LiCl leads to a smooth reaction with various organic halides, the use of a more strongly reducing metal such as magnesium with subsequent transmetalation to Zn allows faster insertion times. The treatment of organomagnesium or organolithium compounds with $ZnCl_2$ solution in THF allows the preparation of functionalized organozincs, with the driving force being the formation of the more covalent C-Zn bond. The resulting organozinc compounds can be trapped with a variety of electrophiles. For instance, the magnesium insertion into 4-chlorobenzonitrile **35** with *in situ* transmetalation using 0.5 equiv of $ZnCl_2$ affords the biarylzinc species **36** which undergoes Cu-catalyzed allylation to give the allylated benzonitrile **37** (Scheme 11).[42]

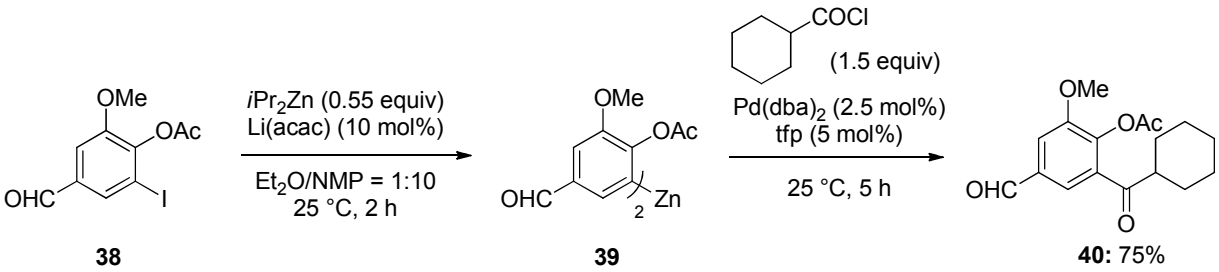


Scheme 11: *In situ* transmetalation of an arylmagnesium compound to Zn and subsequent allylation.

3.2.3. Iodine-Zinc Exchange

Yet another way for the preparation of diorganozincs is the iodine-zinc exchange reaction using dialkylzinc species such as diethylzinc or diisopropylzinc. A major advantage over transmetalation reactions is the excellent functional group tolerance. Thus, using Li(acac) as additive, the highly functionalized aldehyde **38** is smoothly converted by treatment with diisopropylzinc in an Et_2O/NMP mixture to the biarylzinc species **39**, which is exemplarily trapped with an acid chloride to afford the ketone **40** in 75% yield (Scheme 12).[43]

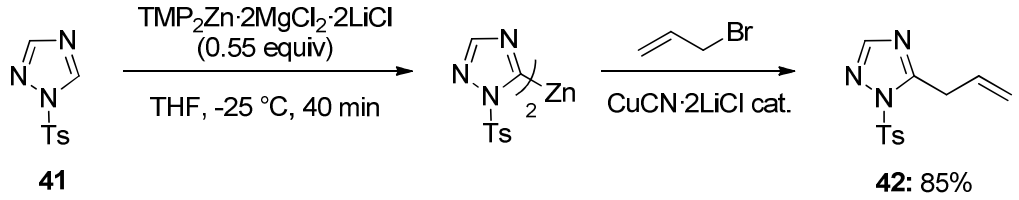
[42] Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 7192.
[43] Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 1017.



Scheme 12: Iodine-zinc exchange reaction on a highly functionalized aldehyde followed by acylation.

3.2.4. Direct Zincation Using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$

A very convenient method for the access to functionalized arylzinc compounds is the direct metalation of aromatic C-H bonds using the non-nucleophilic and mild amide base $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (TMP = 2,2,6,6-tetramethylpiperidyl). In this complex, LiCl enhances solubility of both the base and the metalated products, while $MgCl_2$ increases the base's reactivity. With this base, the zincation of sensitive heterocycles has been achieved. For example, *N*-tosyl-1,2,4-triazole **41** was selectively metalated at C-5 and the resulting bis(triazolyl)zinc species was allylated to give **42** in 85% (Scheme 13).[44]



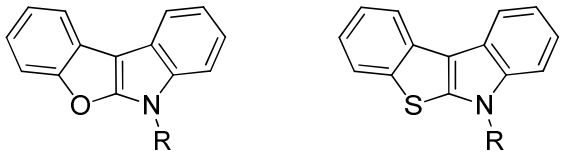
Scheme 13: Direct zincation of an aromatic C-H bond using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$.

[44] Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int Ed.*, **2007**, *46*, 7685.

4. Objectives

4.1. Oxidative Cu(I)-Mediated Cycloamination

One goal of this work is the preparation of benzofuro[2,3-*b*]indoles **43** and benzothieno[2,3-*b*]-indoles **44** via the oxidative coupling of lithium amidocuprates developed in our group (Figure 2).

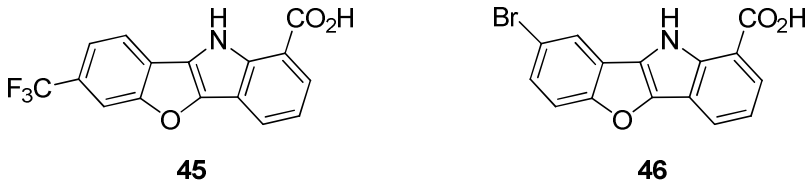


43 **44**

Figure 2: Benzofuro[2,3-*b*]- and benzothieno[2,3-*b*]indoles.

While furo[2,3-*b*]indoles are known as key components of various natural products,[45] and thieno[2,3-*b*]indole derivatives are used to treat diseases of the central nervous system,[46] molecules with benzofuro[2,3-*b*]indole frameworks are unknown to date, and only unsubstituted benzothieno[2,3-*b*]indole has been reported, although in a harsh, low-yielding synthesis involving elementary sulfur and elevated temperatures.[47] These molecules are therefore interesting synthetic targets, considering the physiologic or technical significance of the isomeric [3,2-*b*] fused analogs. For instance, the benzofuro[3,2-*b*]indole derivatives **45** and **46** are known to open calcium(II)-controlled ion channels, which possess important functions in eukaryotic cells (Figure 3).[48]

[45] (a) Morales-Rios, M. S.; Suarez-Castillo, O. R.; Joseph-Nathan, P. *Trends in Heterocyclic Chemistry* **1999**, *6*, 111; (b) Heisaburo, K.; Nozoye, T.; Minoru, T. *Ann. Rept. ITSUU Lab.* **1952**, *3*, 70; (c) Heisaburo, K.; Nozoye, T. *Ann. Rept. ITSUU Lab.* **1950**, *1*, 30.
[46] (a) Jakobsen, P.; Kanstrup, A.; Faarup, P.; Olesen, P. H. *U. S. Pat. Appl. US 5536721*, **1996**; (b) Kanbe, K. *et al*. *Biosci*. *Biotech. Biochem.* **1993**, *57*, 632.
[47] Levy, J.; Royer, D.; Guilhem, J.; Cesario, M.; Pascard, C. *Bull. Soc. Chim. France* **1987**, *1*, 193.
[48] Ha, T. S.; Lim, H. H.; Lee, G. E.; Kim, Y. C.; Park, C. S. *Mol. Pharmacol.* **2006**, *69*, 1007.

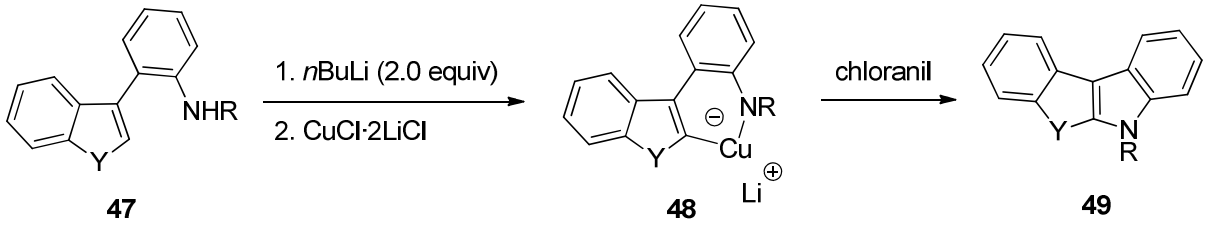


45 **46**

Figure 3: Physiologically active benzofuroindoles.

The groups of *Giro* and *Scrosati* could show that the electrochemical polymerization of benzothienoindoles affords protonated polymers, which are proton conductors at a water content of 10%.[49]

To achieve the synthesis of the [2,3-*b*]-fused backbone, 3-arylated benzofuryl or benzothienyl anilines **47** should be converted to the cyclic lithium amidocuprates **48** and, upon oxidation, cyclize under formation of a C-N bond to afford the target structures **49** (Scheme 14).



47 **48** **49**

Y = O, S

Scheme 14: Oxidative Cu(I)-mediated cycloamination.

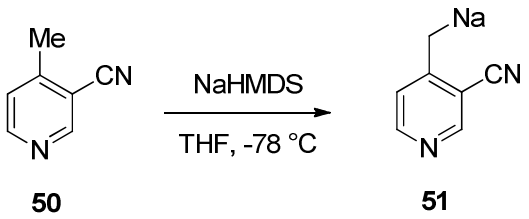
4.2. Preparation and Reactions of Non-Conjugated Heteroaromatic Benzylic Zinc Compounds

Another goal of this work is to find a general way for the preparation of non-conjugated heteroaromatic benzylic zinc reagents. While the synthesis of carbocyclic benzylic zinc reagents and their use in organic synthesis is well documented in the literature,[50] the preparation of

[49] (a) Casalbore-Miceli, G.; Beggiato, G.; Daolio, S.; Emmi, S. S.; Giro, G. *J. Appl. Electrochem.* **1987**, *17*, 1111; (b) Capuano, F.; Casalbore-Miceli, G.; Giro, G.; Scrosati, B. *J. Appl. Electrochem.* **1994**, *24*, 114.

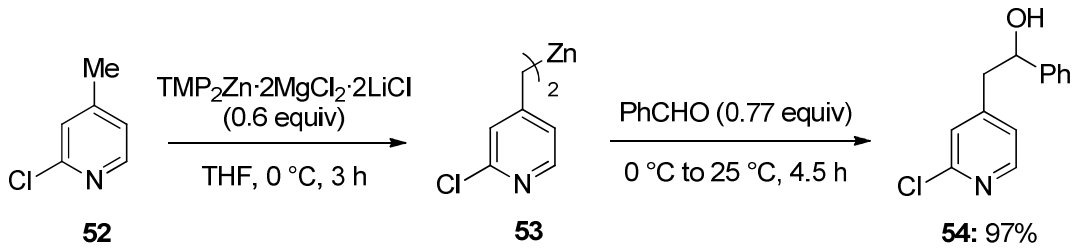
[50] (a) Klein, S.; Marek, I.; Normant, J.-F. *J. Org. Chem.* **1994**, *59*, 2925; (b) Rottländer, M.; Knochel, P. *Tetrahedron Lett.* **1997**, *38*, 1749; (c) Egorov, A. M. *J. Phys. Org. Chem.* **2006**, *19*, 664; (d) Huang, D.; Wang, J.-X. *Synlett* **2007**, 2272; (e) Krapcho, A. P.; Waterhouse, D. J.; Hammach, A.; Di Domenico, R.; Menta, E.; Oliva, A.; Spinelli, S.

heteroaromatic benzylic organometallics is to date limited to compounds with acidic methyl groups, such as 2- or 4-picolines which can be deprotonated in benzylic position. Thus, *Sharik* reported the metalation of 4-methyl-3-cyanopyridine **50** to the heterobenzylic organometallic **51** using sodium hexamethyldisilazide (Scheme 15).[51]



Scheme 15: Benzylic deprotonative metalation on a pyridine.

Also, the direct zincation of 4-picoline derivatives is possible using amide bases. Thus, 2-chloro-4-methylpyridine **52** is fully metalated in benzylic position upon treatment with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ at 0 °C after 3 h. The resulting bisbenzylic zinc reagent **53** underwent smooth addition to benzaldehyde, furnishing the heterophenethylic alcohol **54** in nearly quantitative yield (Scheme 16).[52]



Scheme 16: Direct zincation of 2-chloro-4-methylpyridine in benzylic position followed by reaction with an aldehyde.

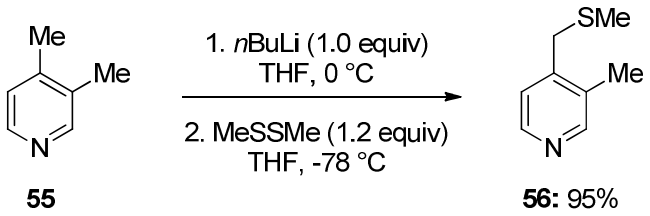
If, however, the benzylic position is not in conjugation with a heteroatom, deprotonation becomes significantly more difficult, and the direct zincation of 3-picoline with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ as described in Scheme 16 fails completely. Similarly, when treating 3,4-lutidine **55** with *n*BuLi in THF or hexane and subsequent trapping with dimethyl disulfide, *Fort* and coworkers observed the exclusive reaction of the 4-methyl group to the sulfide **56** (Scheme 17).[53]

Synth. Commun. **1997**, *27*, 781; (f) Anderson, T. J.; Vicic, D. A. *Organometallics* **2004**, *23*, 623; (g) Wu, G.; Cai, Z.-W.; Bednarz, M. S.; Kocy, O. R.; Gavai, A. V.; Godfrey, J. D. Jr.; Washburn, W. N.; Poss, M. A.; Sher, P. M. *J. Comb. Chem.* **2005**, *7*, 99; (h) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 185.

[51] Davis, F. A.; Melamed, J. Y.; Sharik, S. S. *J. Org. Chem* . **2006**, *71*, 8761.

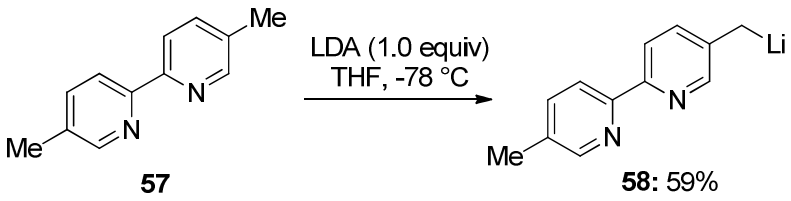
[52] Metzger, A. PhD thesis, Ludwig-Maximilians-Universität München, **2010**.

[53] Kaminski, T.; Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2003**, 3855.



Scheme 17: Benzylic deprotonation of 3,4-lutidine **55**.

The first attempts for the metalation of 3-picoline required the treatment with KNH_2 in liquid ammonia.[54] However, 5,5'-dimethyl-2,2'-bipyridine **57** could be lithiated to give compound **58** using LDA at –78 °C, as reported by *Riether* in 1995 (Scheme 18).[55]

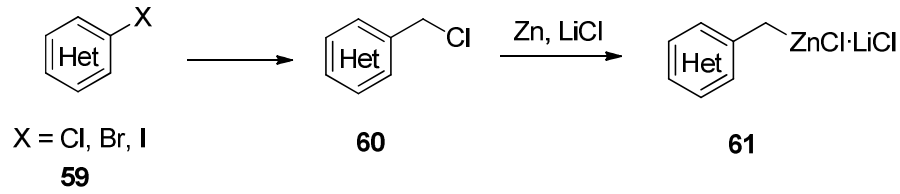


Scheme 18: Lithiation of bipicolyl **57** in benzylic position.

In summary, while the preparation of non-conjugated heterobenzyl organometallics compounds has been performed in the past, the yields of obtained products are generally poor.[56] Thus, the principal aim of this thesis was not the deprotonative metalation of heteroaromatic methyl groups, but instead the Zn insertion into heteroaromatic benzylic chlorides.

[54] Miller, A. D.; Levine, R. *J. Org. Chem.* **1959**, *24*, 1364.
[55] Albrecht, M.; Riether, C. *Synlett* **1995**, 309.
[56] For additional examples of deprotonative metalation on 3-picoline, see: Kaiser, E. D.; Petty, J. D. *Synthesis* **1975**, 705 and references cited therein.

A general method should be found to prepare those chloromethyl compounds **60** starting from readily available heteroaromatic halides **59**, and then convert them to the corresponding heterobenzylic zinc species **61** by LiCl-promoted oxidative insertion of metallic Zn (Scheme 19).



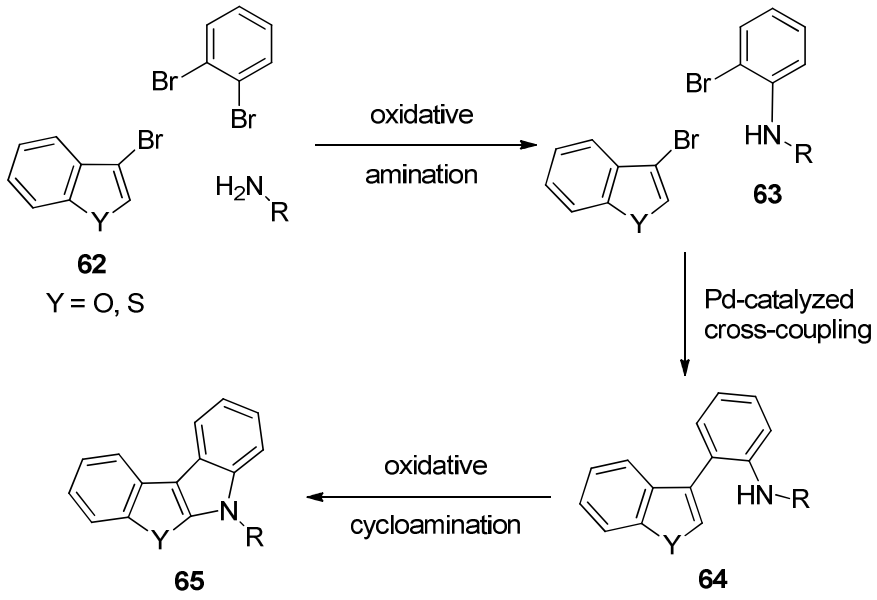
Scheme 19: Synthetic strategy for the preparation of non-conjugated heterobenzylic zinc compounds.

B. RESULTS AND DISCUSSION

1. Oxidative Cu(I)-Mediated Cycloamination

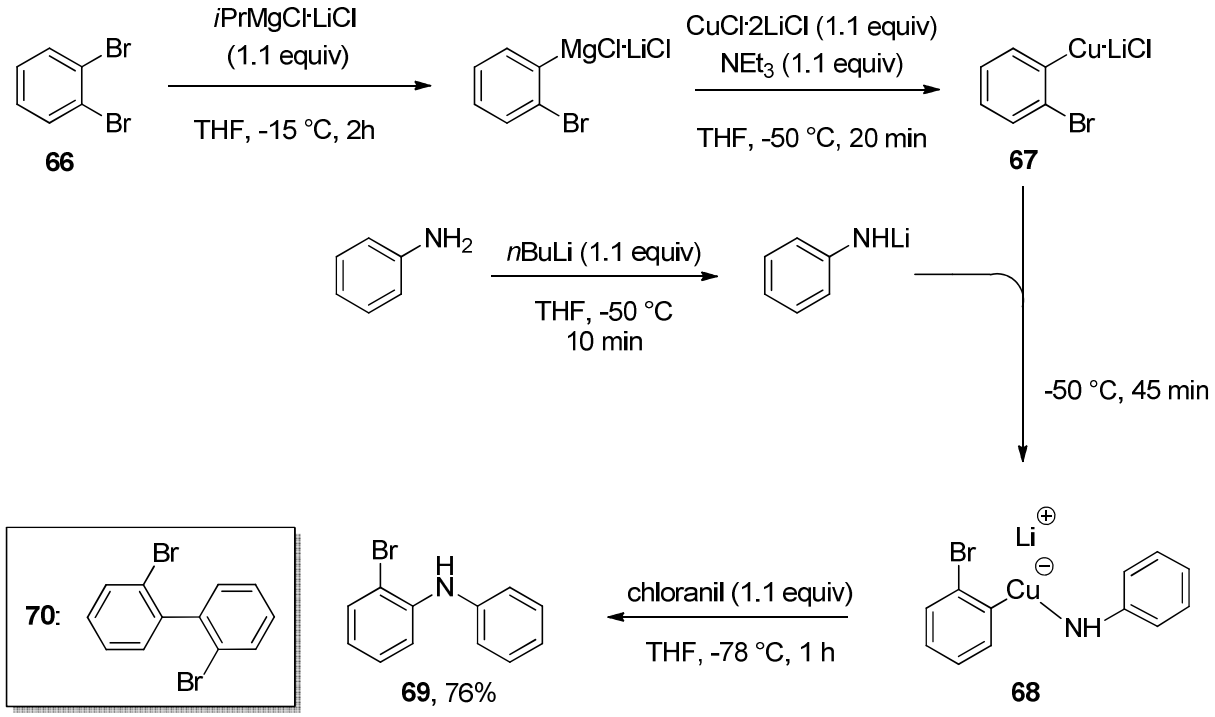
1.1. Preparation of Precursors

For the planned synthesis of [2,3-*b*] fused benzofuro- and benzothienoindoles, a three-step procedure was developed. It envolves the Pd-catalyzed cross-coupling of 3-bromobenzo[b]furan or 3-bromobenzo[b]thiophene **62** with various *N*-substituted 2-bromoanilines **63** which can themselves be prepared by the oxidative amination of 1,2-dibromobenzene. Subjecting the so obtained benzofuryl- and benzothienylanilines **64** to oxidative amination conditions should give rise to the expected tetracycles **65** (Scheme 20).



Scheme 20: Planned synthesis of [2,3-*b*]-fused benzofuro- and benzothienoindoles.

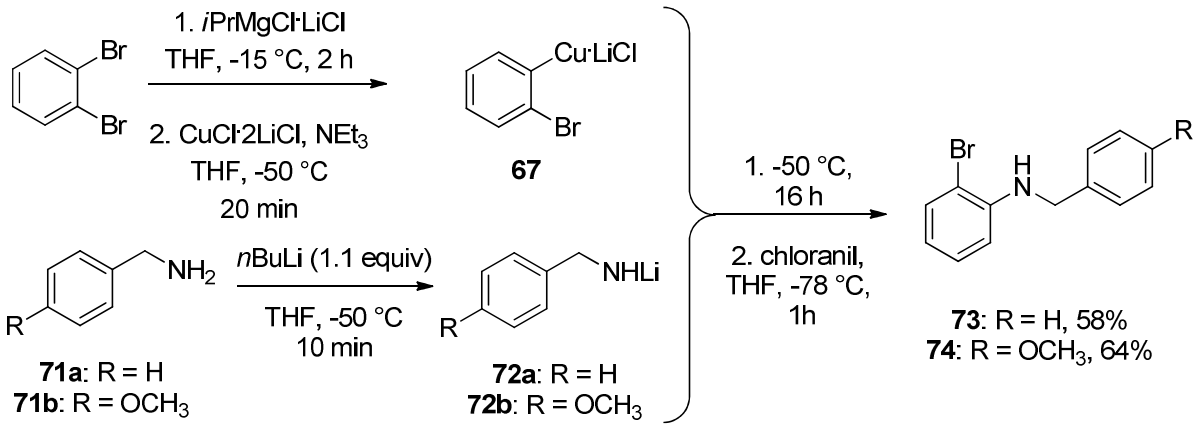
The general procedure for the amination of 1,2-dibromobenzene is shown in Scheme 21. A bromine-magnesium exchange on dibromobenzene **66** using *i*PrMgCl·LiCl was complete by iodometric titration after 2 h at –15 °C. The magnesiated species was transmetalated to the copper derivative **67** using CuCl·2LiCl and reacted with freshly prepared lithium anilide to the amidocuprate **68**.



Scheme 21: Preparation of 2-bromo-*N*-phenylaniline by oxidative amination of amidocuprates.

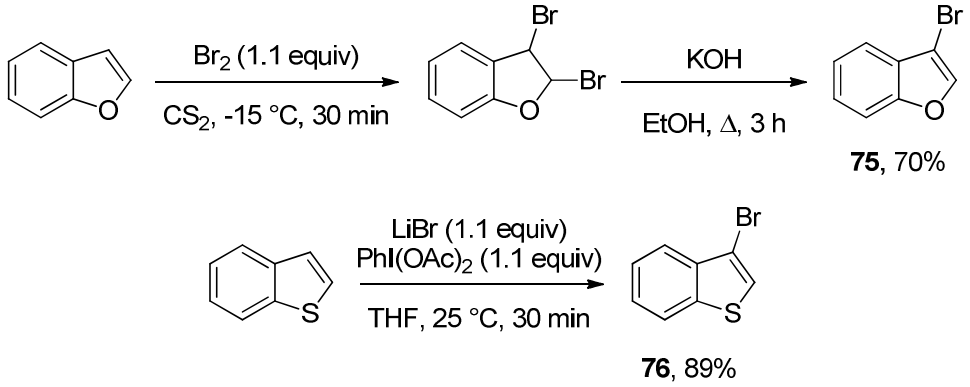
After the final oxidation step using chloranil which affords the target amine **69** in 76% yield, the only side product was the homodimer of the organocopper compound **70**. Its amount depended on the presence of an additional amine ligand. The use of NEt_3 gave the best results, and the amount of homocoupling product could be lowered to traces. Using other ligands, such as *N*-ethyldimethylamine or bis(dimethylaminoethyl)ether gave less satisfying results, and in the absence of ligand, the ratio of desired product to homocoupling product could even reach 1:1.

Similarly to the preparation of **69**, the *N*-benzyl and *N*-(4-methoxybenzyl) derivatives **73** and **74** were prepared by oxidative amination. It was found that the lithium benzylamides **72** generated from the benzylamines **71** reacted significantly slower with **67** than lithium anilide, and the formation of amidocuprates was not complete unless stirred at –50 °C for 16 h. If oxidative work-up was conducted sooner, the major product was dibromobiphenyl **70** (Scheme 22).



Scheme 22: Preparations of benzylbromoanilines by oxidative coupling of amidocuprates.

The preparation of 3-bromobenzo[b]furan **75** and 3-bromobenzo[b]thiophene **76** was carried out using literature procedures (Scheme 23).[57,58]

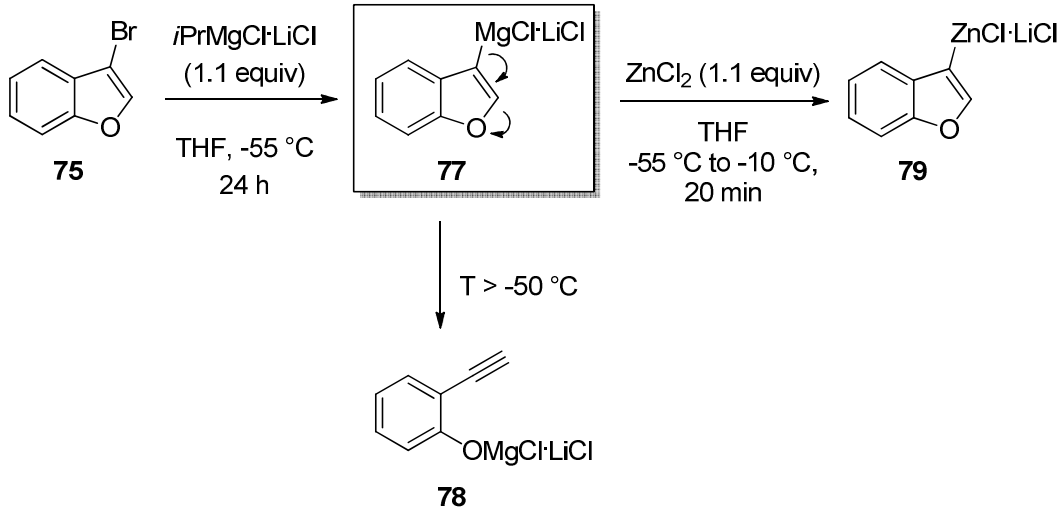


Scheme 23: Preparation of 3-bromobenzo[b]furan and 3-bromobenzo[b]thiophene.

Next, the conditions for a Br/Mg exchange on **75** and **76** were investigated.

[57] Baciocchi, E.; Ruzziconi, R.; Sebastiani, G. V. *J. Am. Chem. Soc.* **1983**, *105*, 6114.
[58] Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461.

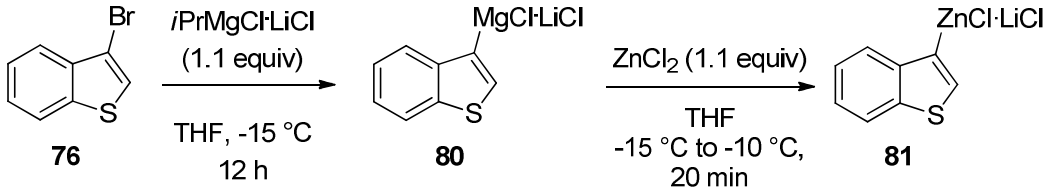
The treatment of 3-bromobenzo[b]furan **75** with 1.1 equivalents of *i*PrMgCl·LiCl at –55 °C for 24 h in THF led to the quantitative formation of the magnesium species **77**, which however underwent decomposition to the ethinyl phenoxide **78** if allowed to warm up beyond –50 °C. Transmetalation using a solution of $ZnCl_2$ in THF afforded the room-temperature stable benzofuran-3-ylzinc chloride **79** (Scheme 24).



75 **77** **79** **78**

Scheme 24: Preparation of benzofuran-3-ylzinc chloride.

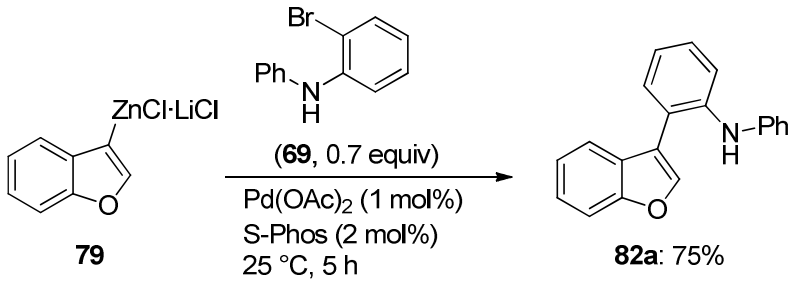
The Br/Mg exchange on 3-bromobenzo[b]thiophene **76** was achieved by treatment with *i*PrMgCl·LiCl at –15 °C for 12 h. The magnesiated species **80** was stable even at 25 °C and transmetalation using $ZnCl_2$ afforded benzothien-3-ylzinc chloride **81** (Scheme 25).



76 **80** **81**

Scheme 25: Preparation of benzothien-3-ylzinc chloride.

For the Pd-catalyzed cross-coupling of the heteroarylzinc compounds **79** and **81** with the bromoanilines prepared earlier, the system $Pd(OAc)_2$ / S-Phos proved extraordinarily efficient. Thus, benzofuran-3-ylzinc chloride **79** was coupled with 2-bromo-*N*-phenylaniline **69** in 75% yield to obtain the substituted aniline **82a** (Scheme 26).

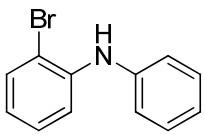
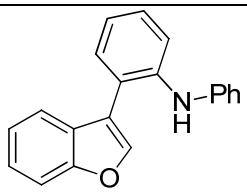
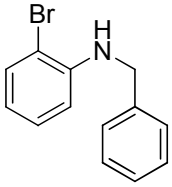
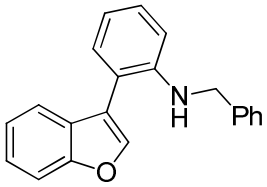


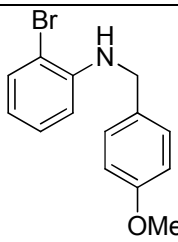
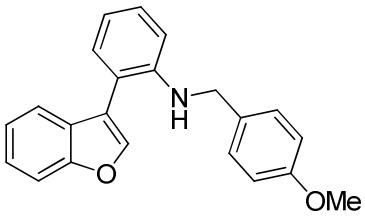
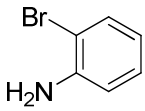
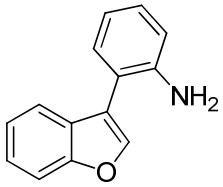
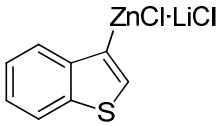
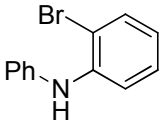
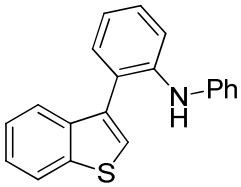
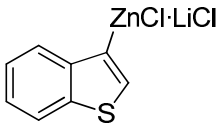
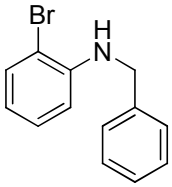
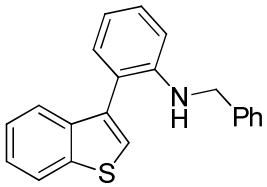
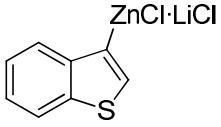
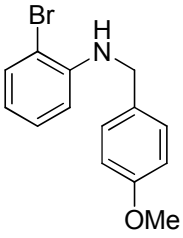
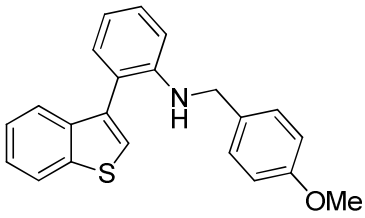
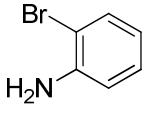
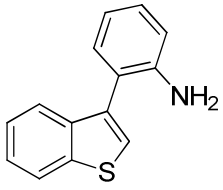
79 **82a**: 75%

Scheme 26: Negishi cross-coupling of the zinc reagent **79** with the bromoaniline **69**.

Using this procedure, the substituted anilines **82a-h** were obtained in overall good yields, and even the cross-coupling with unprotected 2-bromoaniline **83** was possible, as the catalyst's turnover rates are high enough to avoid protonolysis of the organozinc species by the aniline protons (Table 1).

Table 1: Negishi cross-coupling of zinc reagents with various bromoanilines.

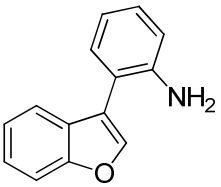
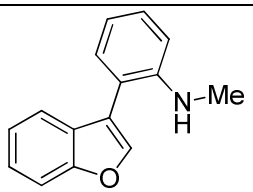
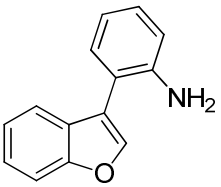
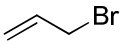
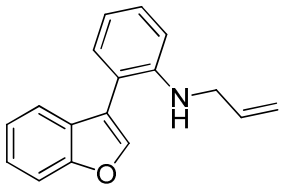
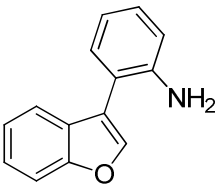
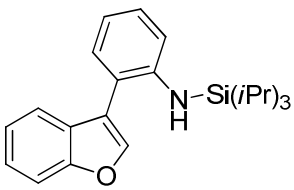
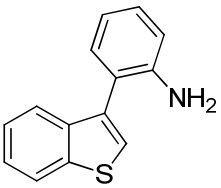
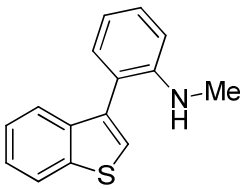
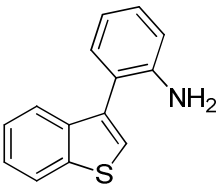
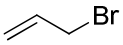
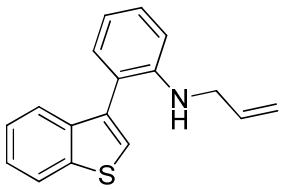
Entry	Substrate [a]	Bromoaniline	Product, Yield[b]
1	 **79**	 **69**	 **82a:** 75%
2	 **79**	 **73**	 **82b:** 86%

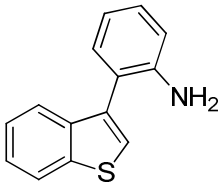
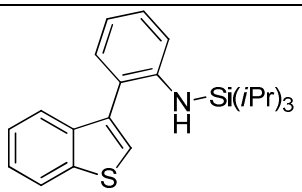
3	 **79**	 **74**	 **82c:** 91%
4	 **79**	 **83**	 **82d:** 89%
5	 **81**	 **69**	 **82e:** 43%
6	 **81**	 **73**	 **82f:** 62%
7	 **81**	 **74**	 **82g:** 68%
8	 **81**	 **83**	 **82h:** 81%

[a] Reaction conditions for the cross-coupling reaction: 25 °C, 5 h; [b] Yield of analytically pure product.

The free anilines **82d** and **82h** were then monosubstituted by deprotonation using *n*BuLi (1.0 equiv) followed by trapping with different electrophiles, leading to the resulting additional substrates **82i-n** (Table 2).

Table 2: Monosubstitution of the primary amines **82d** and **82h**.

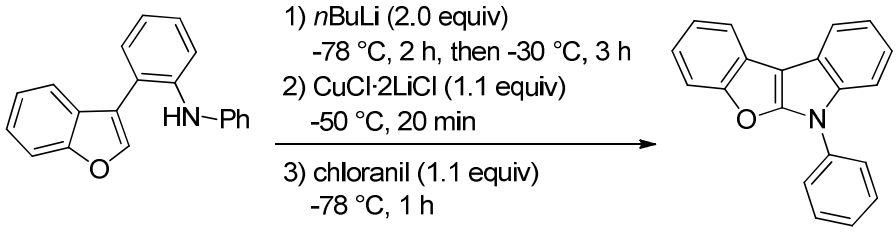
Entry	Substrate [a]	Electrophile	Product, Yield[b]
1	 **82d**	CH_3I	 **82i:** 62%
2	 **82d**		 **82j:** 94%
3	 **82d**	iPr_3SiCl	 **82k:** 48%
4	 **82h**	CH_3I	 **82l:** 96%
5	 **82h**		 **82m:** 91%

6		iPr$_3$SiCl	
	82h		**82n:** 30%

[a] Reaction conditions for the protection step; i) *n*BuLi (1.1 equiv, –30 °C, 30 min); ii) electrophile (1.1 equiv, –30 °C to 25 °C, 30 min). [b] Yield of analytically pure product.

1.2. Oxidative Cycloamination

After the successful syntheses of the secondary amines **82a-n**, they were subjected to the oxidative amination conditions for the formation of annulated indole derivatives. Thus, the benzofuran derivative **82a** was deprotonated using 2.0 equivalents of *n*BuLi, giving rise to the corresponding bis-metalated species. After transmetalation using CuCl·2LiCl (1.1 equiv, –50 °C, 20 min), the resulting cyclic amidocuprate underwent a chloranil-mediated ring closure (1.1 equiv, –78 °C, 1 h) and furnished the desired tetracyclic indole derivative **84a** in 80% yield (Scheme 27).[59] The tetracyclic scaffold is completely planar, with the *N*-phenyl substituent slightly twisted out of plane (see Experimental Part, Table 11).



82a **84a**: 80%

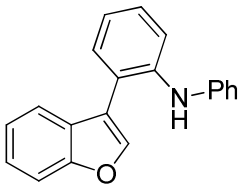
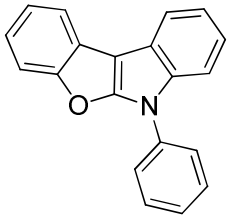
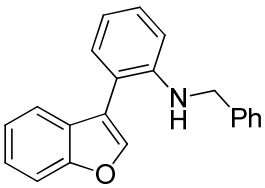
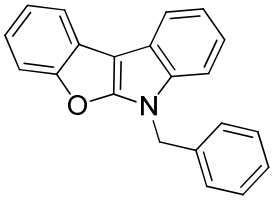
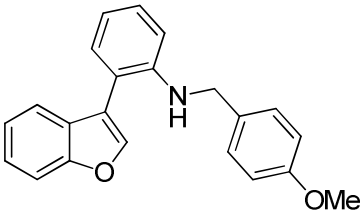
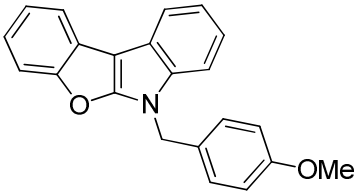
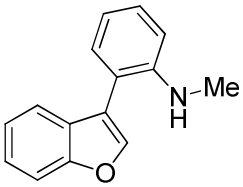
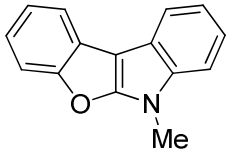
Scheme 27: Oxidative Cu(I)-mediated cycloamination of the aniline **82a** to a tetracyclic fused indole derivative **84a**.

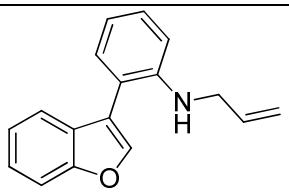
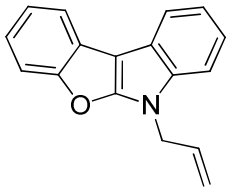
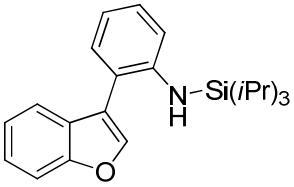
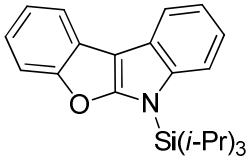
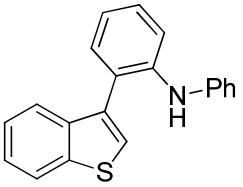
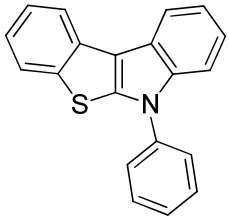
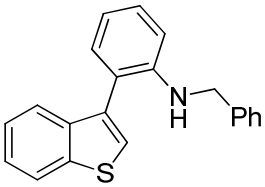
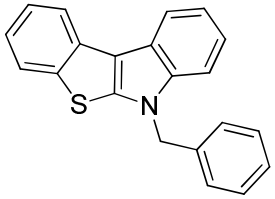
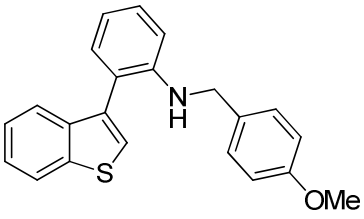
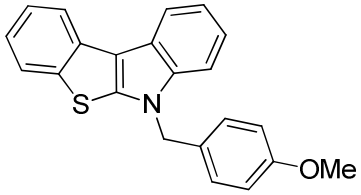
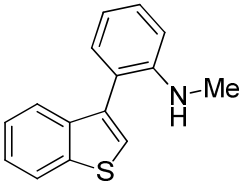
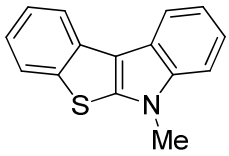
When performing this reaction in rather concentrated solution (1 M in THF), large amounts of an undesired side-product were observed, most likely an intermolecular amination. By using concentrations of 0.1 M, these side-reactions could be completely suppressed.

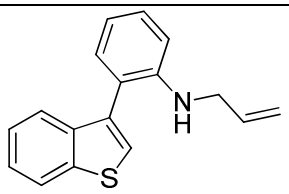
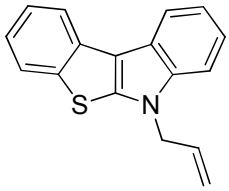
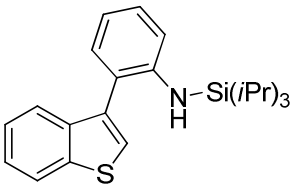
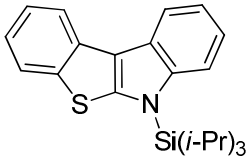
[59] Kienle, M.; Wagner, A. J.; Dunst, C.; Knochel. P. *Chem. Asian J.* **2011**, *6*, 512-523.

The reaction conditions established above proved to be quite general for such cycloamination reactions, both for non-donating and donating substituents on the aniline nitrogen. Also, sterical factors seem to play a negligible role, even when bulky substituents such as (triisopropyl)silyl were present in the substrate. Thus, the benzofuran derivatives **82a-c** and **82i-k** and the benzothiophene derivatives **82e-g** and **82l-n** could also be successfully cyclized to the expected benzofuro- and benzothieno[2,3-*b*]indoles **84a-l** in 51-89% yield (Table 3).

Table 3: Cu(I)-mediated oxidative cycloamination.

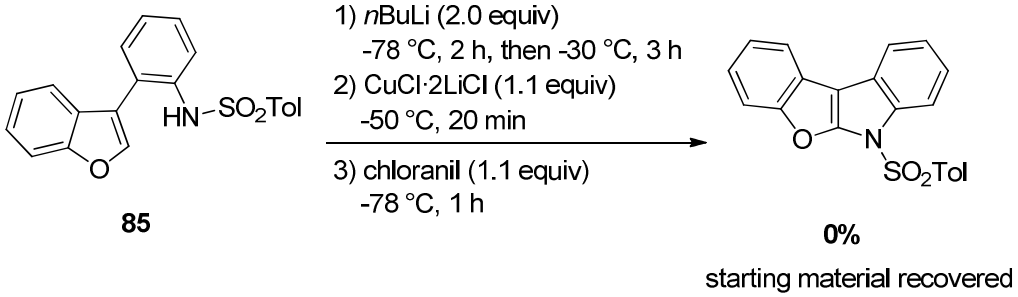
Entry	Substrate	Product, Yield[a]
1	 **82a**	 **84a:** 80%
2	 **82b**	 **84b:** 84%
3	 **82c**	 **84c:** 50%
4	 **82i**	 **84d:** 50%

5	 **82j**	 **84e:** 70%
6	 **82k**	 **84f:** 81%
7	 **82e**	 **84g:** 81%
8	 **82f**	 **84h:** 58%
9	 **82g**	 **84i:** 70%
10	 **82l**	 **84j:** 89%

11	 **82m**	 **84k:** 62%
12	 **82n**	 **84l:** 71%

[a] Yield of analytically pure product.

While the cyclization reaction worked well for non-donating and donating substituents on the aniline nitrogens, the Cu(I)-mediated oxidative cyclization is not suited for the ring closure on primary amines. Subjecting the free anilines **82d** and **82h** to the conditions described above led to the consumption of the starting material, but only trace amounts of the expected free indoles could be observed. Similarly, electron-withdrawing substituents seem to reduce the nucleophilicity of the generated lithium amide to a point where the cyclization no longer takes place. For instance, the *N*-(*p*-toluenesulfonyl)-substituted benzofurylaniline **85** was recovered quantitatively from the reaction mixture after the cyclization attempt (Scheme 28).



85 **0%** starting material recovered

Scheme 28: Attempted cycloamination on the EWG-substituted benzofurylaniline **85**.

2. Preparation and Reactions of Non-Conjugated Heteroaromatic Benzylic Zinc Reagents

2.1. Introduction

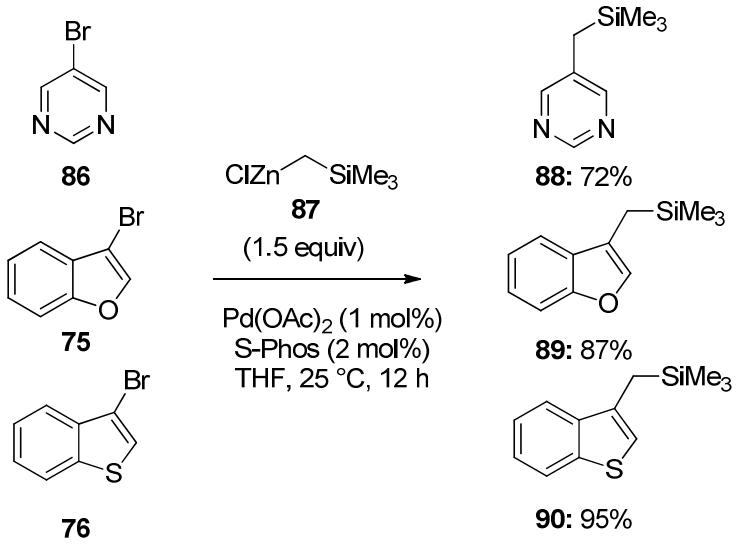
2.1.1. General Considerations

Finding a general method to prepare heteroaromatic benzylic zinc reagents relies first of all on a general procedure for the preparation of the corresponding benzylic halides. While the most obvious of reactions would be the treatment of a benzylic alcohol with thionyl chloride, phosphorus pentachloride or phosphoryl chloride, all these transformations intrinsically lead to the formation of stoichiometric amounts of HCl.[60] This is undesirable when dealing with nitrogen-containing heterocycles, as they can not only be protonated under these conditions, but also undergo unwanted side reactions or even decomposition. It was therefore our goal to find a pH-neutral way for the homologation of heteroaryl organometallics with subsequent introduction of the chloride substituent.

2.1.2. First Attempt Using Heterobenzylic Silanes

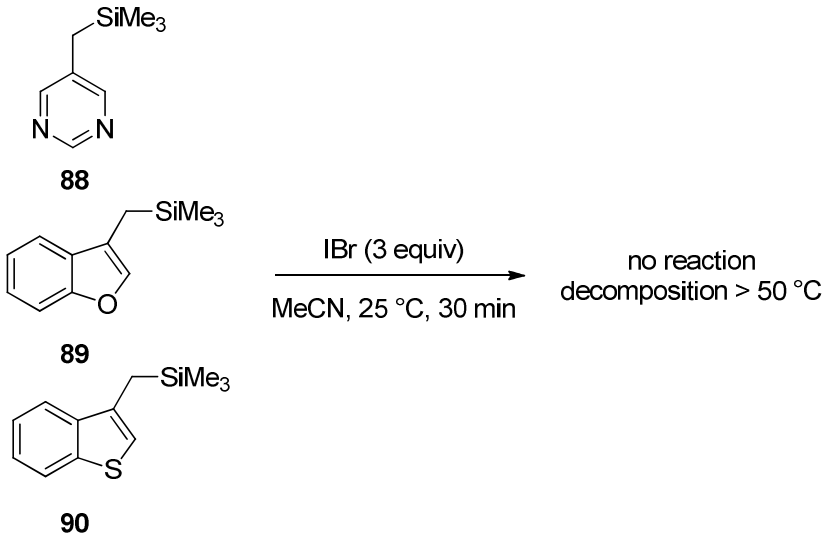
Our first approach was the cross-coupling of heteroaryl halides with (trimethylsilyl)methylzinc chloride followed by conversion of the trimethylsilyl group into a bromide substituent. Thus, the reaction of 5-methylpyrimidine **86**, 3-bromobenzo[b]furan **75** and 3-bromobenzo[b]thiophene **76** with (trimethylsilyl)methylzinc chloride **87** afforded the corresponding benzylic silanes **88-90** in high yields (Scheme 29).

[60] (a) Yoshihara, M. *et al*. *Synthesis* **1980**, *9*, 746; (b) Carman, R. M.; Shaw, I. M. *Aust. J. Chem.* **1976**, *29*, 133; (c) Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen, D. *J. Org. Chem*. **2008**, *73*, 312.



Scheme 29: Negishi cross-coupling of heteroaryl bromides with (trimethylsilyl)methylzinc chloride **87**.

However, any attempt at converting the so obtained heterobenzylic silanes into the corresponding bromides using IBr, as particularly described in the literature for benzylsilanes,[61] failed, with no reaction occurring at lower temperatures and decomposition if the mixture was heated (Scheme 30).

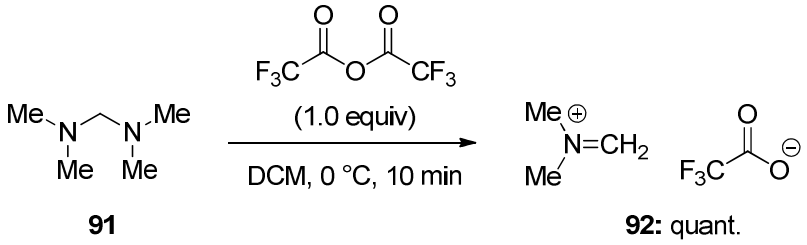


Scheme 30: Failed attempt at converting the heterobenzyl silanes **88-90** to benzyl bromides.

[61] Bordeau, M.; Villeneuve, P.; Benneteau, B.; Dunoguès, J. *J. Organomet.. Chem.* **1987**, *331(2)*, 169.

2.2. Preparation of Heterobenzylic Amines

A more rewarding route towards heterobenzyl chlorides was the chlorination of benzylic amines obtained by a literature-known procedure which involves homologating various heteroaryl organometallics using the methylene(dimethyl)iminium ion (*Mannich*'s ion). It is typically generated in aqueous solution from the reaction of formaldehyde with dimethylamine,[62] and therefore not suitable for the reaction with organometallics. However, there are various procedures for its synthesis in anhydrous reaction media with a range of counter ions.[63]
For instance, treatment of the commercially available *N*,*N*,*N'*,*N'*-tetramethylmethanediamine **91** with trifluoroacetic anhydride in anhydrous CH_2Cl_2 at 0 °C led to the formation of methylene(dimethyl)iminium trifluoroacetate **92** within 10 min (Scheme 31).[64]

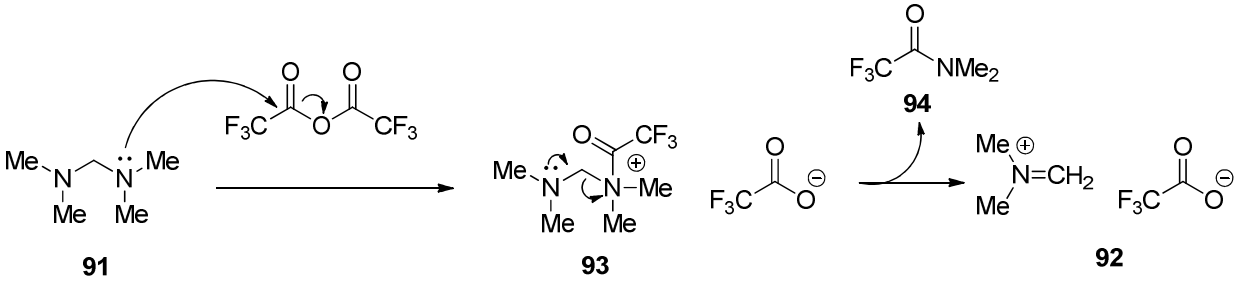


91 **92:** quant.

Scheme 31: Anhydrous preparation of the *Mannich*-type salt **92**.

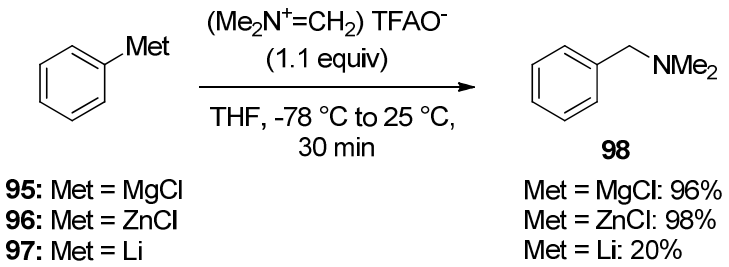
The mechanism of this transformation is shown in Scheme 32. It proceeds *via* the trifluoroacetylation of one of the nitrogen atoms present in **91**, giving rise to the acetylated salt **93**. The following step is the elimination of the highly stable *N*,*N*-dimethyltrifluoroacetamide **94**, whose stability constitutes the driving force of the reaction.

[62] For a recent review on the Mannich reaction, see: Li, J. L. *Name Reactions for Homologations*, **2009**, *2*, 653.
[63] (a) Ahond, A., Cavé, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J. ; Potier, P. *J. Am. Chem. Soc.* **1968**, *90*, 5622; (b) Grierson, D. *Org. React.* **1990**, *39*; (c) Gaudry, M.; Jasor, Y.; Khac, T. B. *Org. Synth.* **1988**, *6*, 474.
[64] Gommermann, N.; Koradin, C.; Knochel, P. *Synthesis* **2002**, *14*, 2143 and references cited therein.



Scheme 32: Mechanism of the formation of dimethyl(methylene)iminium trifluoroacetate **92**.

The product appears as a clear solution and could be stored for several days without any significant loss of activity. As a comparison experiment showed, the best yields of addition to organometallics were achieved with arylmagnesium and arylzinc compounds. Thus, phenylmagnesium chloride **95** and phenylzinc chloride **96** reacted significantly better with **92** to phenethylamine **98** than phenyllithium **97**, which gave only 20% of isolated yield (Scheme 33).

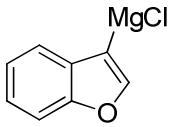
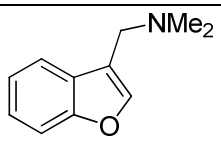
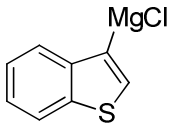
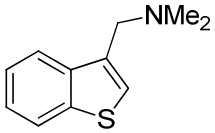
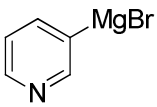
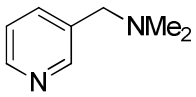
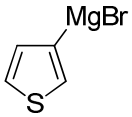
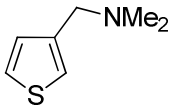
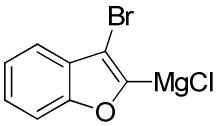
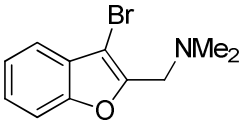
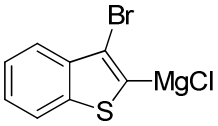
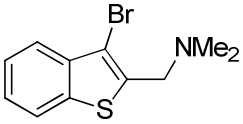
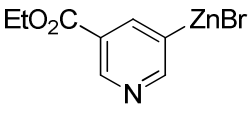
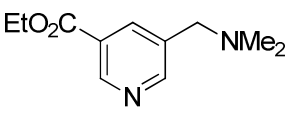


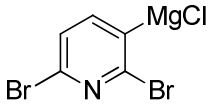
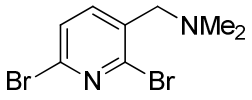
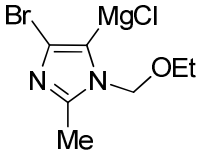
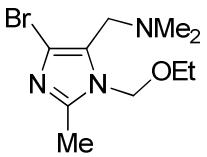
Scheme 33: Comparison of reactivity between different phenyl organometallics towards dimethyl(methylene)iminium trifluoroacetate.

Taking these results into consideration, a variety of heteroaromatic organometallic reagents was subjected to the conditions shown in Scheme 33, and the desired heterobenzylic amines could be obtained in high yields. Thus, adding a solution of the iminium salt **92** in CH_2Cl_2 to a solution of the heteroaromatic organometallics **77**, **80** and **99-105**[65] smoothly gave rise to the amines **106-114** (Table 4).

[65] For their preparation, please refer to the product syntheses in the experimental section.

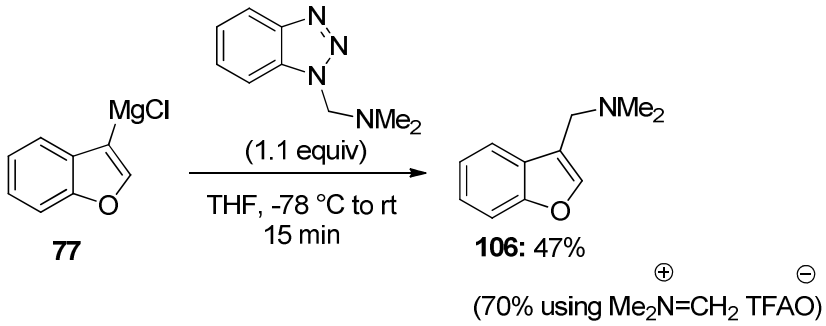
Table 4: Preparation of heterobenzyl(dimethyl)amines using *Mannich*'s ion under anhydrous conditions.

Entry	Heteroaryl organometallic	Product, Yield[a]
1	 **77**	 **106:** 70%
2	 **80**	 **107:** 78%
3	 **99**	 **108:** 68%
4	 **100**	 **109:** 60%
5	 **101**	 **110:** 70%
6	 **102**	 **111:** 70%
7	 **103**	 **112:** 63%

8	 **104**	 **113:** 66%
9	 **105**	 **114:** 93%

[a] Yield of analytically pure product.

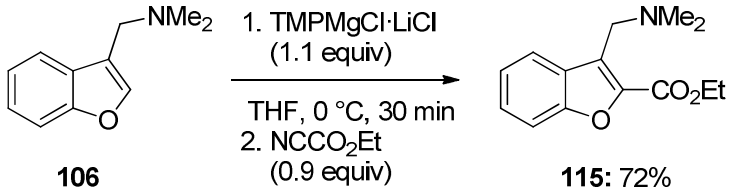
The use of 1-((dimethylamino)methyl)benzotriazole as electrophile, as reported in the literature,[66] gave, in each case, lower yields of isolated product, mostly due to the significantly more difficult separation from free benzotriazole generated during the reaction (Scheme 34).



Scheme 34: Reaction of benzofuran-3-ylmagnesium chloride **77** with 1-((dimethylamino)-methyl)benzotriazole.

By metalation of the so obtained amines and reaction with electrophiles, additionally functionalized substrates could be obtained. Thus, (benzo[b]furan-3-ylmethyl)dimethylamine **106** reacted with TMPMgCl·LiCl (1.1 equiv) in THF at 0 °C within 30 min to the corresponding magnesiated species which gave upon treatment with ethyl cyanocarbonate the functionalized ester **115** in 72% yield (Scheme 35).

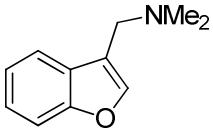
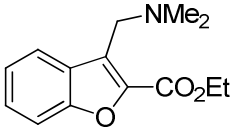
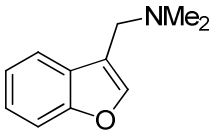
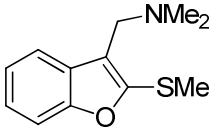
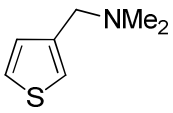
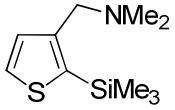
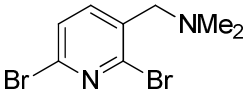
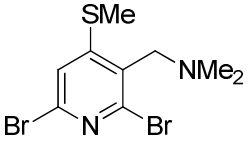
[66] Love, B. E.; Nguyen, Binh T. *Synlett* **1998**, *10*, 1123.



Scheme 35: Metalation and functionalization of the heterobenzylamine **105**.

In that manner, the functionalized amines **115-118** were obtained by deprotonative metalation using TMPMgCl·LiCl and quenching with different electrophiles (Table 5).

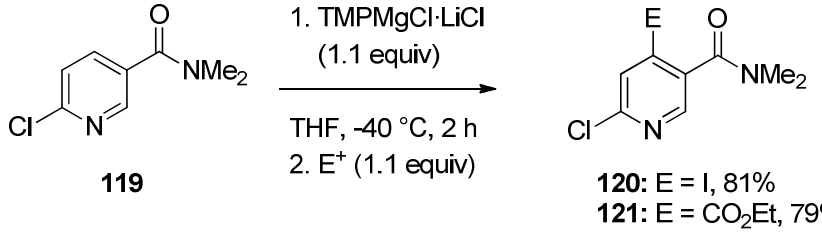
Table 5: Functionalization of heterobenzylamines by metalation using TMPMgCl·LiCl.

Entry	Substrate	Electrophile	Product, Yield[a]
1	 **106**	$NCCO_2Et$	 **115:** 72%
2	 **106**	$MeSO_2SMe$	 **116:** 83%
3	 **109**	Me_3SiCl	 **117:** 71%
4	 **113**	$MeSO_2SMe$	 **118:** 78%

[a] Yield of analytically pure product.

A second attempt at obtaining functionalized (dimethylamino)methyl-substituted heterocycles was the directed *ortho*-metalation of *N*,*N*-dimethylcarboxamides, followed by reaction with an electrophile and reduction of the carboxamide to the dimethylamine. Thus, 6-chloro-*N*,*N*-dimethylnicotinamide **119** underwent full metalation using TMPMgCl·LiCl (1.1 equiv) at –40 °C

within 2 h. Quenching the intermediate organomagnesium species with either I_2 or ethyl chloroformate gave the functionalized nicotinamides **120** and **121** in good yields (Scheme 36).

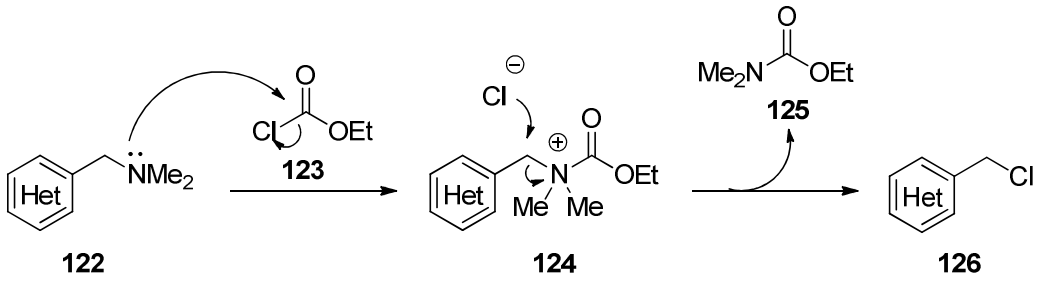


Scheme 36: Directed *ortho*-metalation of nicotinamide **119** and reaction with electrophiles.

Unfortunately however, any attempt at the reduction of **120** and **121** using literature procedures[67] led to complete decomposition of the starting materials.

2.3. Preparation of Heterobenzylic Chlorides

Having a range of (dimethylamino)methyl heteroarenes in hand, the next step was to find a way of converting them into the corresponding chloromethyl arenes. A convenient method is known in the literature, describing the treatment of a dimethylamine with ethyl chloroformate to obtain the corresponding chloride.[68] The mechanism of this transformation is illustrated in Scheme 37.



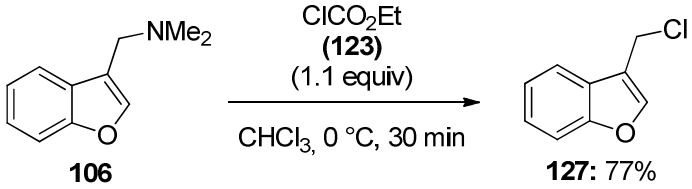
Scheme 37: Transformation of a dimethylamine **122** into the benzylic chloride **126** using ethyl chloroformate **123**.

Attack of the amine **122** onto the carbonyl group of ethyl chloroformate **123** gives an acylammonium ion **124**, which is in turn substituted by the chloride ion liberated in the first step. The resulting products are the desired chloride **126** and ethyl *N*,*N*-dimethylcarbamate **125**.

[67] Yamakawa, T.; Masaki, M.; Nohira, H. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2730 and references cited therein.
[68] Kashdan, D. S.; Schwartz, J. A.; Rapoport, H. *J. Org. Chem*. **1982**, *47*, 2638 and references cited therein.

The latter is the only byproduct of the reaction and can sometimes be conveniently removed in high vacuum, eliminating the need for column chromatographical purification of the chloride.

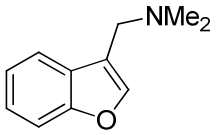
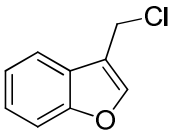
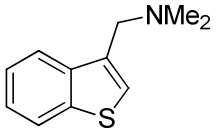
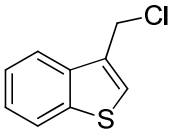
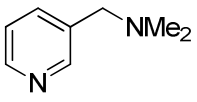
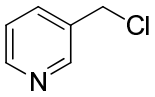
In that fashion, adding ethyl chloroformate **123** (1.1 equiv) to a solution of the amine **106** in chloroform and stirring at 0 °C for 30 min afforded the heterobenzylic chloride **127** in 77% yield (Scheme 38).

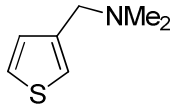
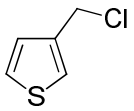
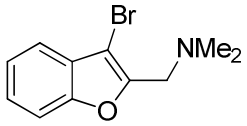
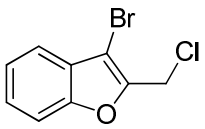
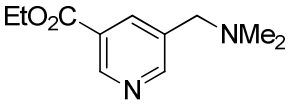
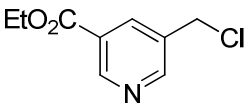
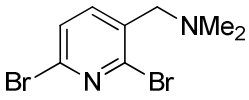
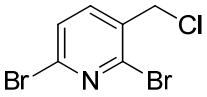
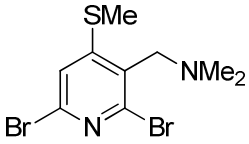
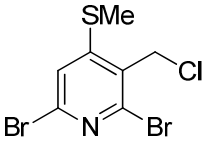
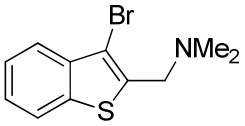
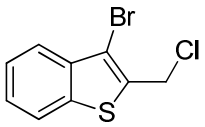
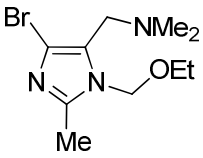
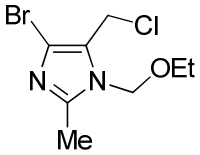
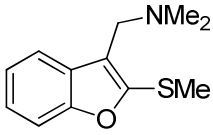
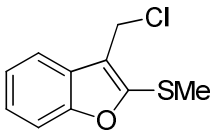


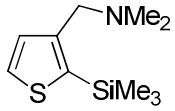
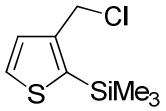
Scheme 38: Reaction of the heterobenzylic amine **106** to the heterobenzyl chloride **127**.

Subjecting the (dimethylamino)methyl heteroarenes **106-118** to the conditions outlined before produced mixed results. While some substrates reacted well to the desired chlorides **127-133** (Table 6, entries 1-8), in other cases, complete decomposition of the starting materials was observed and the target compounds **135-138** could not be observed (Table 6, entries 9-12).

Table 6: Preparation of heterobenzylic chlorides.

Entry	Substrate	Product, Yield[a]
1	 **106**	 **127:** 77%
2	 **107**	 **128:** 72%
3	 **108**	 **129:** 80%

4		
	109	**130:** 71%
5		
	110	**131:** 81%
6		
	112	**132:** 68%
7		
	113	**133:** 70%
8		
	118	**134:** 70%
9		
	111	**135:** decomp.
10		
	116	**136:** decomp.
11		
	114	**137:** decomp.

12		
	117	**138:** decomp.

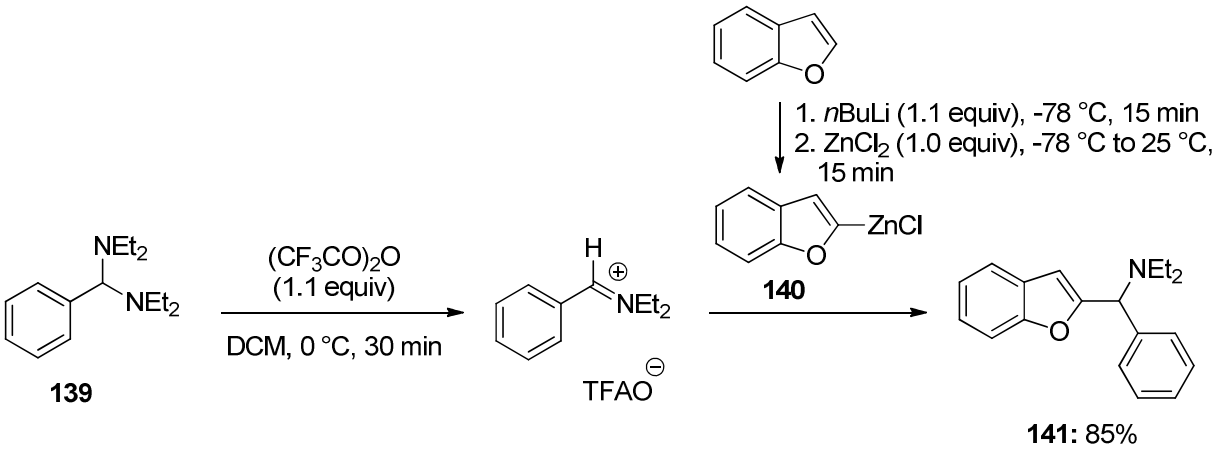
[a] Yield of analytically pure product.

Viewing these results, it appears that the presence of nucleophilic functionalities in the amine substrate favors the decomposition upon treatment with ethyl chloroformate; and strikingly, despite their high structural similarity, the benzofuran **110** reacted smoothly to the desired chloride, while the benzothiophene **111** underwent decomposition. Also, performing the reaction at significantly lower temperatures (down to –78 °C) did not prevent the decomposition but just slowed down the reaction, with unreacted starting material constantly diminishing in quantity, but never affording the desired chloride as indicated by GC/MS experiments.

By following a published procedure using 0.33 equiv of cyanuric chloride as chlorinating agent,[69] no improvements could be made, and the same decomposition was observed. This excludes the specific reaction conditions of the ethyl chloroformate variant as the critical factor, and instead suggests an intrinsic instability of the postulated chlorides **135-138**, none of which have been reported in the literature. Regardless, the method using ethyl chloroformate is more practical since the target chlorides can be isolated significantly more easily from the crude reaction mixture than when using cyanuric chloride.

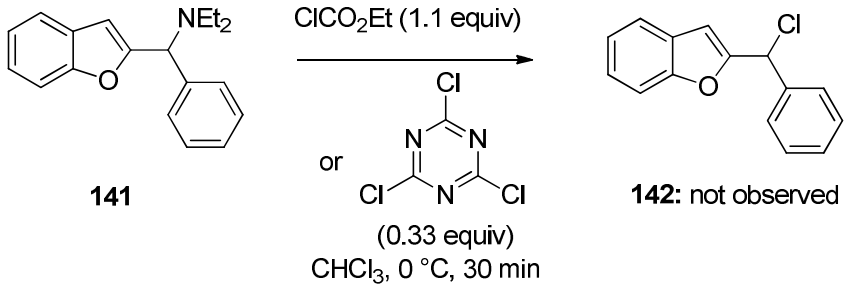
To investigate the nitrogen-chlorine exchange on a bis(benzyl)amine, the diarylmethane **141** was prepared by the reaction of benzaldehyde tetraethylaminal **139** with trifluoroacetic anhydride, followed by the addition of benzofuran-2-ylzinc chloride **140** (Scheme 39).

[69] Afonso, C. A. M.; Lourenco, N. M. T.; Rosatella, A. A. *Molecules* **2006**, *11*, 81.



Scheme 39: Preparation of the bis(benzyl)amine substrate **141**.

The so obtained diarylmethane **141** was then treated with ethyl chloroformate or cyanuric chloride as described above, which led to the formation of several undefined side-products, and no trace of the desired chloride **142** could be observed (Scheme 40).

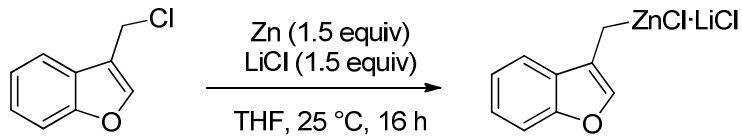


Scheme 40: Attempted chlorination of the amine **141**.

2.4. Preparation and Reactions of Heterobenzylic Zinc Reagents

2.4.1. LiCl-Mediated Zinc Insertion into Heterobenzylic Chlorides

Following the procedure previously laid out by *Metzger* and *Knochel* for the oxidative insertion of metallic Zn into benzylic chlorides mediated by LiCl,[70] we treated the heterobenzyl chloride **127** at 25 °C with commercially available Zn dust, previously activated using 1,2-dibromoethane and chlorotrimethylsilane. Following the insertion reaction by thin layer chromatography, full consumption of the starting material was detected after 16 h and iodometric titration of the solution indicated 81% active yield of the heterobenzylic zinc reagent **143** (Scheme 41).

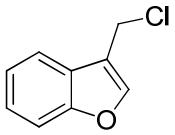
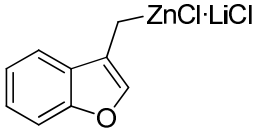


127 **143:** 81%

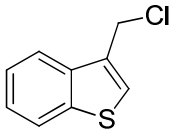
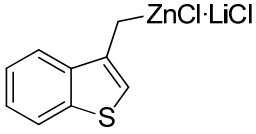
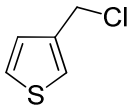
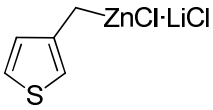
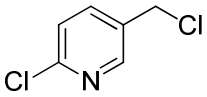
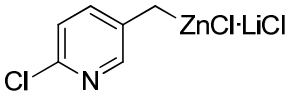
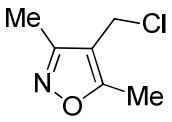
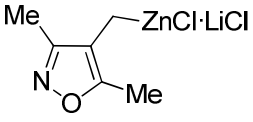
Scheme 41: Preparation of the non-conjugated heterobenzylic zinc reagent **143** *via* oxidative insertion of Zn dust.

Similarly, the chlorides **128** and **130** (prepared via the amination-chlorination procedure) as well as the commercially available substrates **144** and **145** afforded stable solutions of the corresponding zinc reagents **146-149** at 25 °C and within 2.5-16 h reaction time (Table 7).

Table 7: Preparation of heterobenzylic zinc reagents.

Entry	Substrate	reaction time (h)	Product, Yield[a]
1	 **127**	16	 **143:** 81%

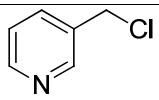
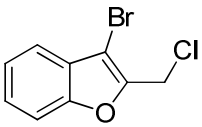
[70] Metzger, A.; Schade, A. M.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107.

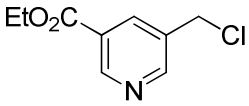
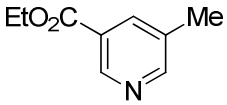
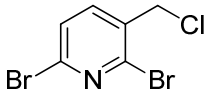
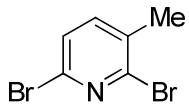
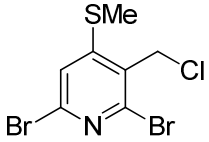
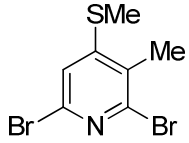
2	 **128**	16	 **146:** 77%
3	 **130**	12	 **147:** 78%
4	 **144**	2.5	 **148:** 80%
5	 **145**	4	 **149:** 83%

[a] Active yield determined by iodometric titration.

Unfortunately, however, many of the higher functionalized chlorides given in Table 6 did not react to an active organometallic compound, with the two major problems being either complete decomposition upon Zn insertion or immediate reduction of the chloromethyl moiety to a methyl group, regardless if lower temperatures were applied (Table 8).

Table 8: Decomposition or reduction reactions upon oxidative Zn insertion.

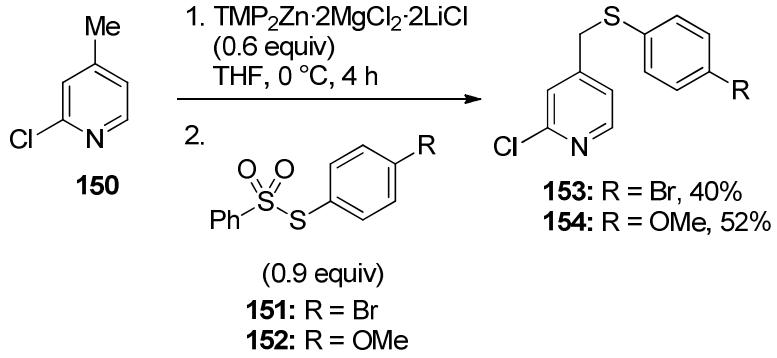
Entry	Substrate	Product
1	 **129**	decomp.
2	 **131**	decomp.

3		
	132	reduction observed
4		
	133	reduction observed
5		
	134	reduction observed

It is noteworthy that the absence of a substituent in position 2 of the pyridine **129** is the cause for decomposition upon Zn insertion, as the 2-chloro-substituted derivative **144** readily gave a stable, active benzylic zinc species (Table 7, entry 3). The unsubstituted pyridinemethylzinc chloride most likely undergoes nucleophilic addition onto itself after the insertion step, leading to the formation of a black, unsoluble polymer.

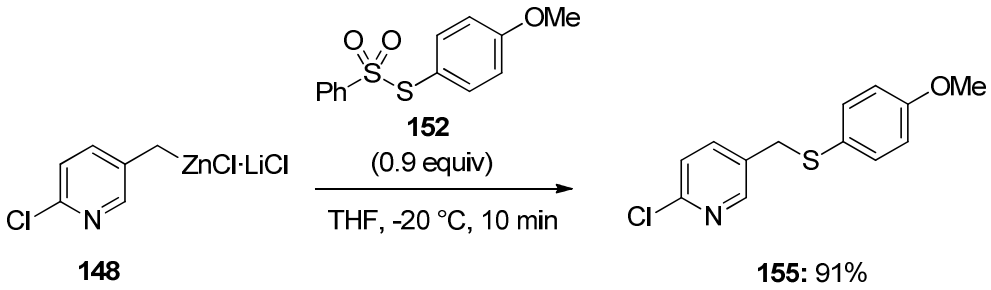
2.4.2. Reactions of Heterobenzylic Zinc Reagents with Electrophiles

The so obtained zinc reagents could be reacted with a broad range of electrophiles. For comparison, the deprotonative metalation of 2-chloro-4-picoline **150** using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ and trapping with the sulfonothioates **151** and **152** gave rise to the heterobenzyl disulfides **153** and **154** in only moderate yields (Scheme 42).



Scheme 42: Deprotonative zincation of 2-chloro-4-picoline **150** and reaction with sulfonothioates.

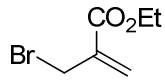
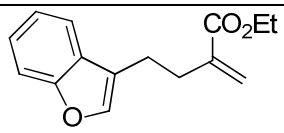
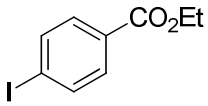
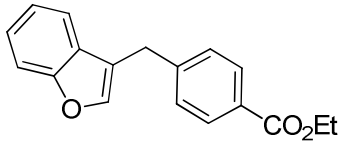
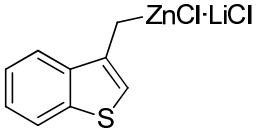
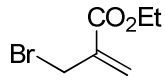
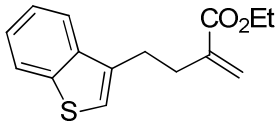
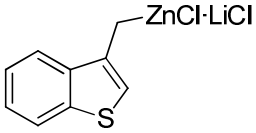
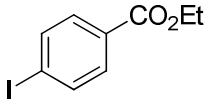
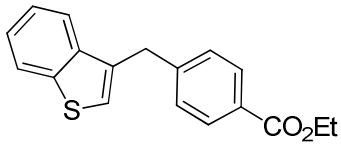
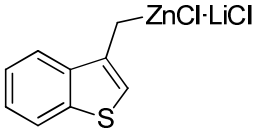
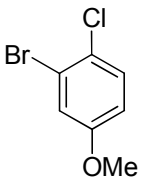
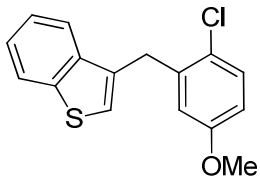
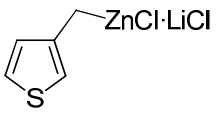
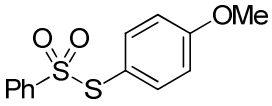
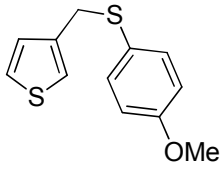
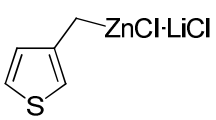
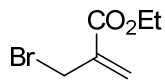
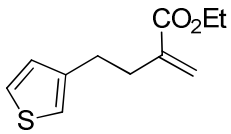
In contrast, the reaction of the non-conjugated pyridinemethylzinc species **148** (obtained by Zn insertion) with *S*-(4-methoxyphenyl)benzenesulfonothioate **152** afforded the desired sulfide **155** in 91% yield (Scheme 43).

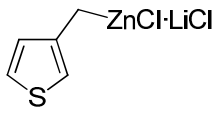
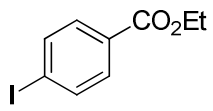
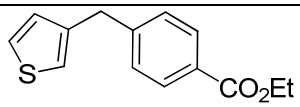
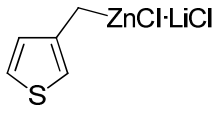
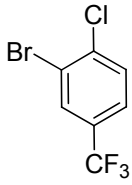
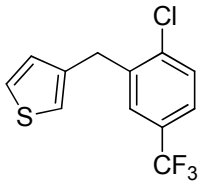
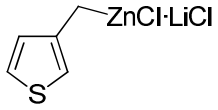
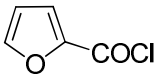
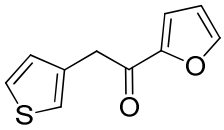
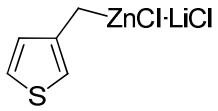
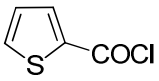
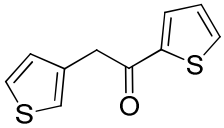
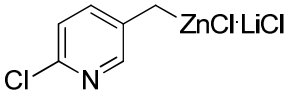
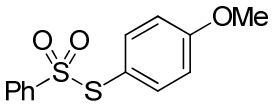
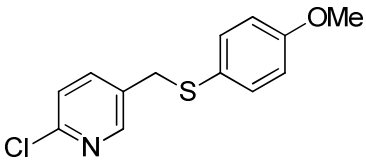
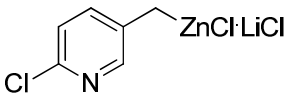
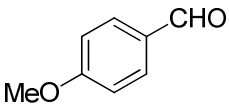
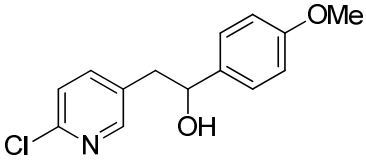
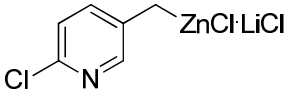
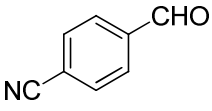
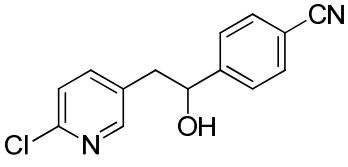


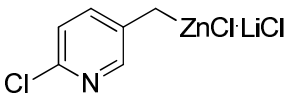
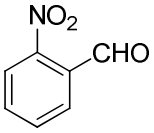
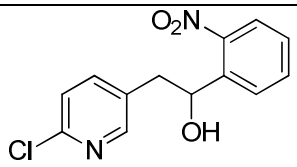
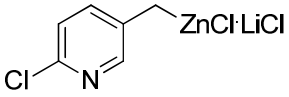
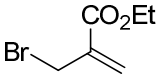
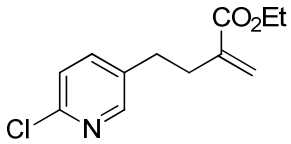
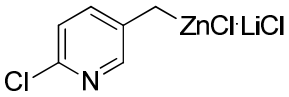
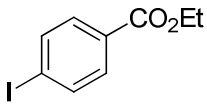
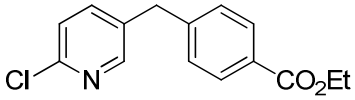
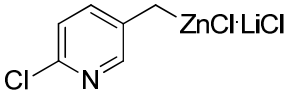
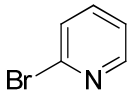
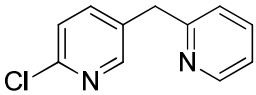
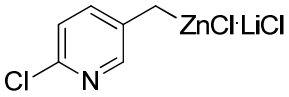
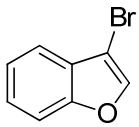
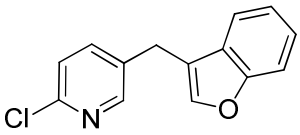
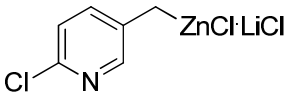
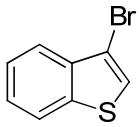
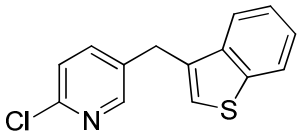
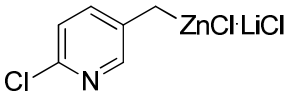
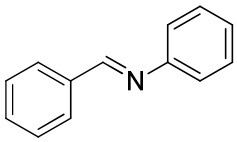
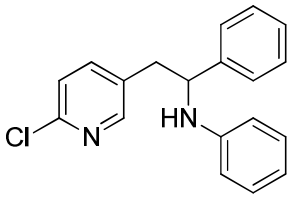
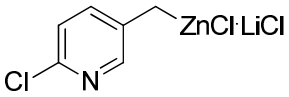
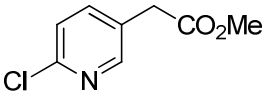
Scheme 43: Preparation of the heterobenzyl sulfide **155**.

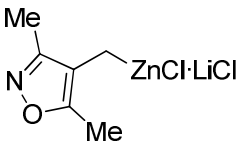
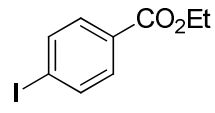
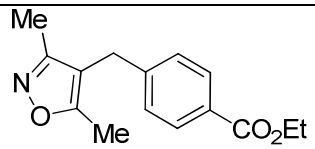
Besides trapping the heterobenzylic zinc reagents with sulfonothioates, other viable reactions include carboxylation using CO_2, addition to aldehydes, Pd-catalyzed cross-coupling or Cu-catalyzed allylation or acylation reactions. A summary of the so obtained compounds **156-178** is shown in Table 9.

Table 9: Reactions of heterobenzylic zinc reagents with electrophiles.

Entry	Substrate	Electrophile, catalyst	Temperature (°C), time (h)	Product, Yield[a]
1	 **143**	 CuCN·2LiCl (10 mol%)	0, 1	 **156:** 80%
2	 **143**	 Pd-PEPPSI-IPr (1%)	0, 3	 **157:** 77%
3	 **146**	 CuCN·2LiCl (10 mol%)	0, 1	 **158:** 78%
4	 **146**	 Pd-PEPPSI-IPr (1%)	0, 3	 **159:** 85%
5	 **146**	 Pd-PEPPSI-IPr (1%)	25, 2	 **160:** 85%
6	 **147**		–20, 12	 **161:** 80%
7	 **147**	 CuCN·2LiCl (10 mol%)	0, 1	 **162:** 93%

8	 **147**	 Pd-PEPPSI-IPr (1%)	25, 5	 **163:** 83%
9	 **147**	 Pd-PEPPSI-IPr (1%)	25, 2	 **164:** 72%
10	 **147**	 CuCN·2LiCl (1.0 equiv)	–20, 2	 **165:** 65%
11	 **147**	 CuCN·2LiCl (1.0 equiv)	–20, 2	 **166:** 70%
12	 **148**		–20, 12	 **167:** 91%
13	 **148**		–20, 16	 **168:** 76%
14	 **148**		–20, 16	 **169:** 89%

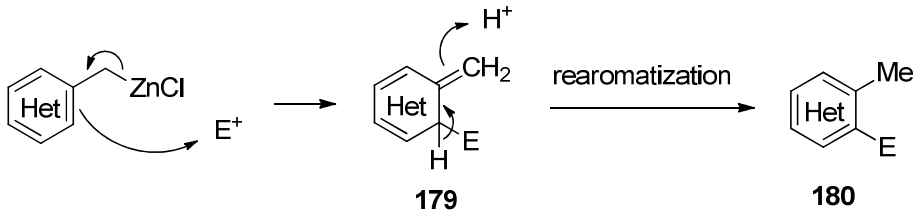
15	 **148**		–20, 16	 **170:** 91%
16	 **148**	 CuCN·2LiCl (10 mol%)	0, 1	 **171:** 96%
17	 **148**	 Pd-PEPPSI-IPr (1%)	25, 5	 **172:** 73%
18	 **148**	 Pd-PEPPSI-IPr (1%)	25, 5	 **173:** 78%
19	 **148**	 Pd-PEPPSI-IPr (1%)	0, 10	 **174:** 62%
20	 **148**	 Pd-PEPPSI-IPr (1%)	0, 10	 **175:** 93%
21	 **148**		0, 4	 **176:** 80%
22	 **148**	1. CO_2 2. $(COCl)_2$, MeOH	1.) 50, 4 2.) 0, 0.5	 **177:** 70%

23	 **149**	 Pd-PEPPSI-IPr (1%)	25, 12	 **178:** 87%

[a] Yield of analytically pure product.

2.4.3. Special Case: Allylic Reactivity

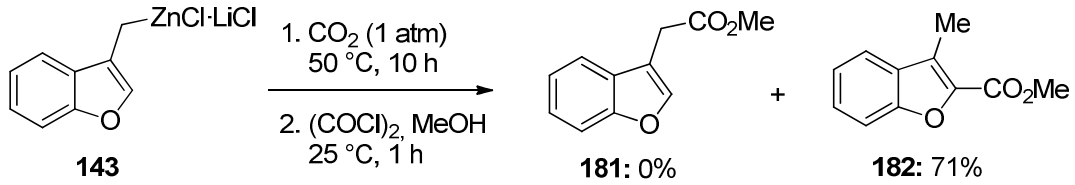
While the majority of the trapping reactions given in Table 9 provided heterobenzylic compounds as expected, there were some cases in which the organozinc species displayed allylic instead of benzylic reactivity. The attack of an aromatic π bond of the heterobenzylic zinc chloride onto the electrophile results in a dearomatized exo-methylene intermediate **179** which undergoes prototropic rearomatization, furnishing the unexpected product of type **180** (Scheme 44).



179 **180**

Scheme 44: Allylic reactivity of heterobenzylic zinc chlorides.

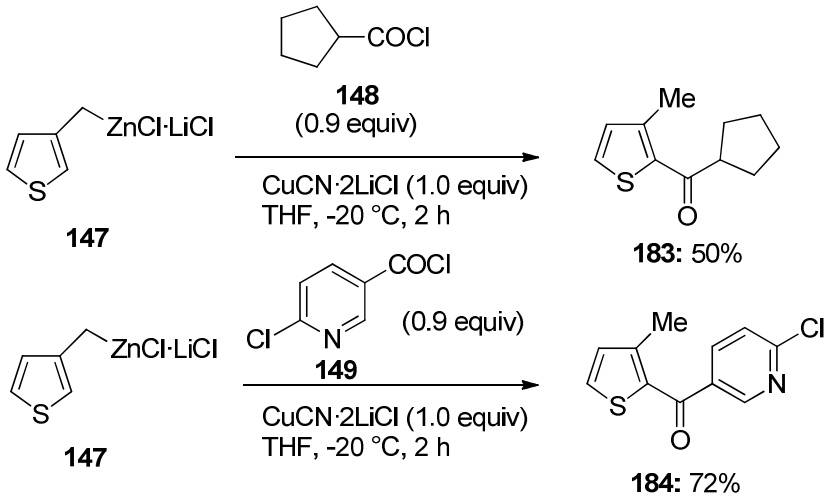
The first example of such reactivity was observed after the reaction of benzo[b]furan-3-ylmethylzinc chloride **143** with carbon dioxide, followed by esterification with methanol. Instead of the desired (benzofuryl)acetic acid methyl ester **181**, exclusively the 2-carboxylated product **182** was obtained in 71% yield (Scheme 45).



143 **181:** 0% **182:** 71%

Scheme 45: Allylic reactivity observed in the carboxylation of **143**.

The same phenomenon was observed during the reaction of 3-thienylmethylzinc chloride **147** with cyclopentanecarbonyl chloride **148** and 2-chloronicotinoyl chloride **149**. The acylation reaction took place exclusively in position 2, with no isomers being detected (Scheme 46). This is especially striking since acylation of **147** with thiophene-2-carbonyl chloride or furan-2-carbonyl chloride gave the expected benzylic carboxylates **165** and **166** (Table 9, entries 10-11).



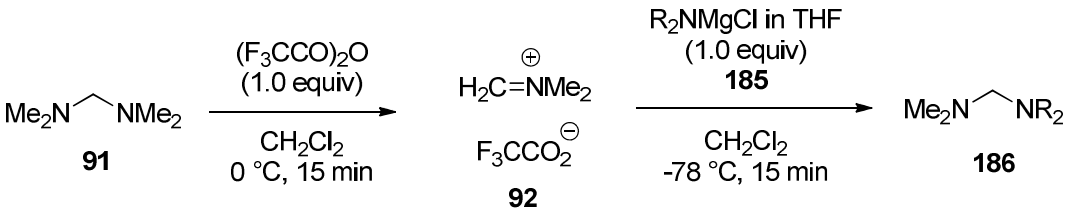
Scheme 46: Allylic reactivity observed in the acylation of **147**.

3. One-Pot Preparation of Tertiary Benzylic and Phenethylic Amines

3.1. Overview

Benzylamines and phenethylamines are highly interesting compounds which find application as reliable precursors of fine chemical derivatives[71] and as pharmacologically active compounds.[72] Synthetic multi-component reactions related to the *Mannich* reaction have almost not been reported with respect to the preparation of functionalized tertiary benzyl- or phenethylamines, despite their synthetic interest.[73] We were therefore interested in modifying the conditions employed in our syntheses of heterobenzylic amines to a one-pot procedure for the preparation of tertiary benzylamines.

Intrigued by the very smooth conversions of organometallics with methylene(dimethyl)iminium trifluoroacetate during the synthesis of heterobenzylic amines, the reaction of metal amides under the same conditions was investigated, with the goal of obtaining mixed aminals of formaldehyde, bearing one dimethyl- and one dialkylamino moiety. Supposedly, the reaction of a magnesiated amine **185** with *Mannich*'s ion should lead to the formation of the expected unsymmetrical aminal **186** (Scheme 47).



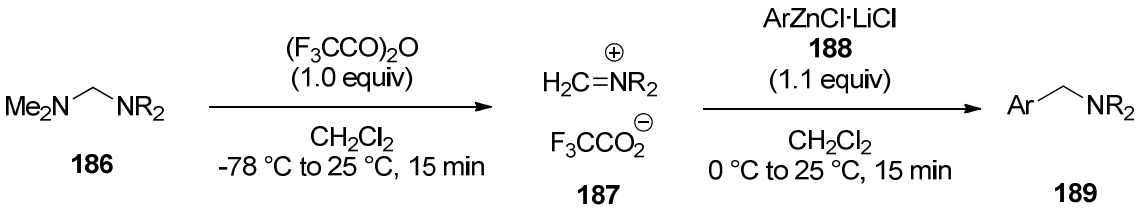
Scheme 47: Preparation of mixed aminals via *Mannich*'s cation under anhydrous conditions.

[71] (a) Kise, N.; Ozaki, H.; Terui, H.; Ohya, K.; Ueda, N. *Tetrahedron Lett.* **2001**, *42*, 7637; (b) Cecchetto, A.; Minisci, F.; Recupero, F.; Fontanab, F.; Pedullic, G. F.; *Tetrahedron Lett.* **2002**, *43*, 3605.

[72] (a) Nussbaumer, P.; Dorfstaetter, G.; Grassberger, M. A.; Leitner, I.; Meingassner, J. G.; Thirring, K.; Stuetz, A. *J. Med. Chem.* **1993**, *36*, 2115; (b) Altomare, C.; Summo, L.; Cellamare, S.; Varlamov, A. V.; Voskressensky, L. G.; Borisova, T. N.; Carotti, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 581.

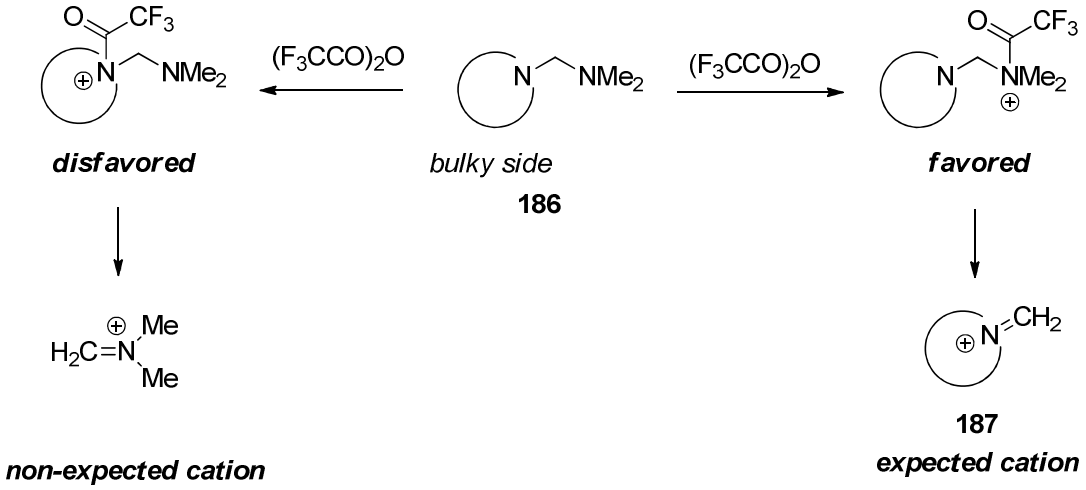
[73] Le Gall, E.; Decompte, A.; Martens, T.; Troupel, M. *Synthesis* **2010**, *2*, 249 and references cited therein.

Following this step, the resulting aminal **186** should be converted to the methylene(dialkyl)-iminium salt **187** if treated with trifluoroacetic anhydride, and the subsequent addition of an organometallic reagent **188** should give the addition product **189** (Scheme 48).



Scheme 48: Reaction of a mixed aminal to an iminium ion and trapping with an organometallic reagent.

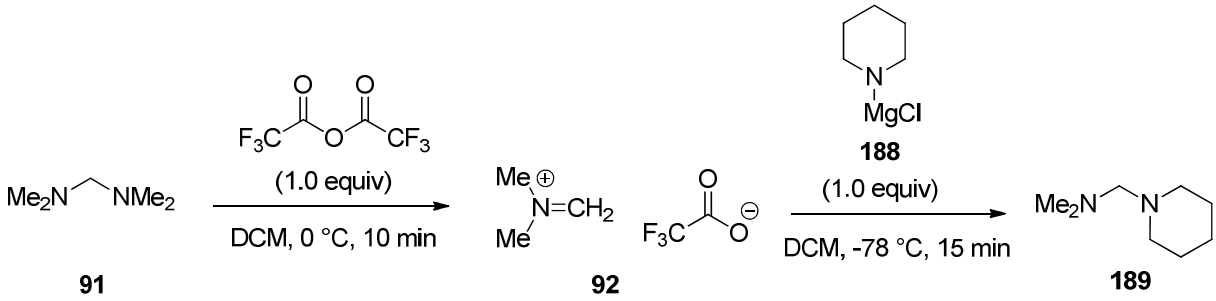
In theory, an unsymmetrical aminal of type **186** should selectively be acylated by trifluoroacetic anhydride at the sterically less hindered nitrogen, which would be at the dimethylamino group. Hence, we expected a high selectivity in the resulting iminium ions of type **187** (Scheme 49).



Scheme 49: Expected regioselectivity in acylation and iminium ion formation of mixed aminals of type **186**.

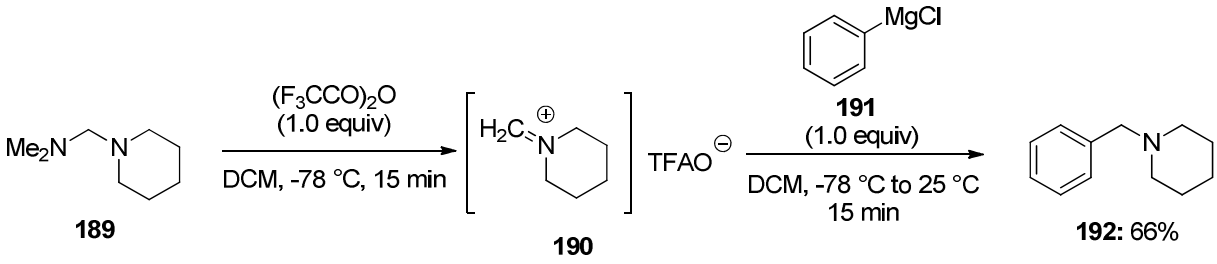
3.2. Preparation of Tertiary Benzylic and Phenethylic Amines

As expected, converting *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane **91** to the *Mannich*-type salt **92** using trifluoroacetic anhydride and adding piperidyl-*N*-magnesium chloride **188** led to the mixed aminal **189** (Scheme 50).



Scheme 50: Generation of the mixed aminal **189**.

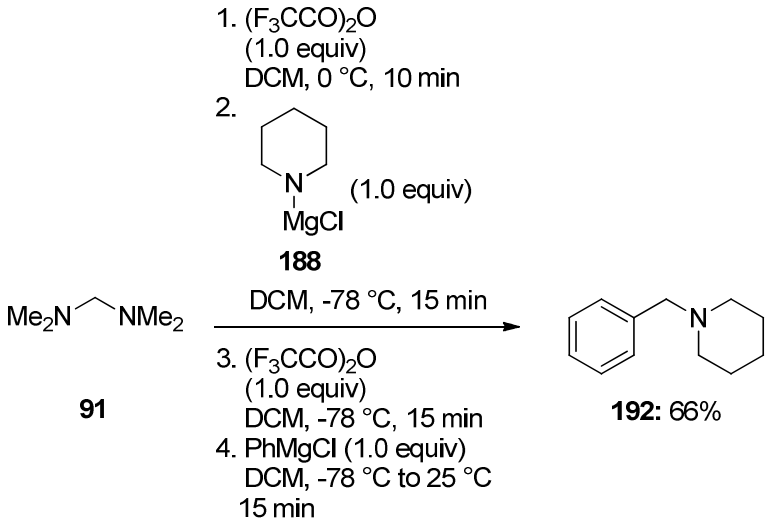
Due to its nature as full aminal, **189** could not efficiently be isolated from the reaction mixture as it immediately decomposes to formaldehyde, dimethylamine and piperidine upon contact with moisture. However, its presence became evident from the following reaction: Adding, for a second time, trifluoroacetic anhydride to the solution of **189**, obtained as depicted in Scheme 50, led to the formation of the *N*-methylenepiperidinium cation **190**, which was trapped using phenylmagnesium chloride **191**. The resulting *N*-benzylpiperidine **192** was obtained in 66% yield (Scheme 51).



Scheme 51: Synthesis of *N*-benzylpiperidine **192** from the mixed aminal **189**.

It turned out that the mixed aminals needed to be kept at –78 °C until their conversion to the (methylene)iminium salts. Allowing them to warm up resulted in partial decomposition to the corresponding symmetrical aminals.

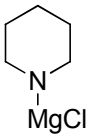
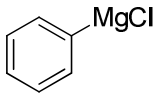
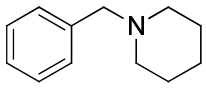
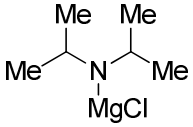
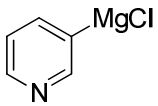
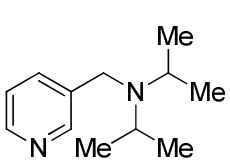
The complete reaction procedure for the preparation of **192** is summarized in Scheme 52.

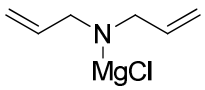
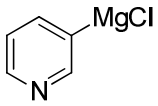
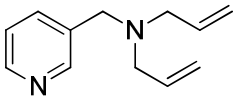
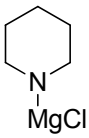
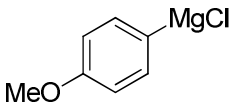
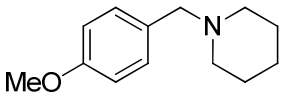
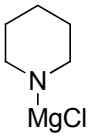
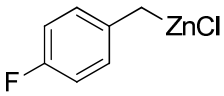
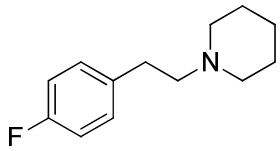
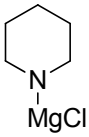
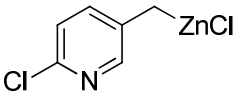
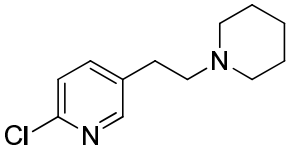
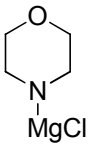
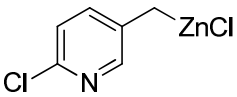
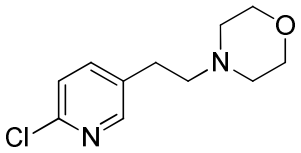


Scheme 52: Summarized synthesis of **192** from the aminal **91**.

Thus, subjecting different secondary amines to the procedure outlined above and using various aryl or benzylic organometallics as nucleophiles, the tertiary amines **192-198** were obtained. Both carbocyclic and heterocyclic organometallics could be used, and sterically demanding substituents on the aminal nitrogen were tolerated (Table 10).

Table 10: Tertiary aromatic and heteroaromatic benzylic and phenethylic amines obtained by the one-pot reaction starting from tetramethyldiaminomethane.

Entry	metal amide	organometallic substrate	Product, Yield[a]
1			 **192:** 66%
2			 **193:** 71%

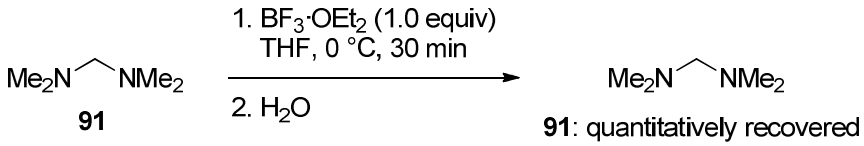
3			 **194:** 70%
4			 **195:** 76%
5			 **196:** 82%
6			 **197:** 80%
7			 **198:** 79%

[a] Yield of analytically pure product.

3.3. Reactivity of Organozincs in the Presence of $BF_3 \cdot OEt_2$

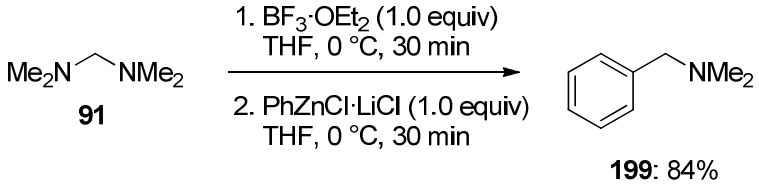
3.3.1. Substitution on Aminals Mediated by $BF_3 \cdot OEt_2$

An intriguing reactivity of the mixed aminals was observed when treated with $BF_3 \cdot OEt_2$. While the reaction with trifluoroacetic anhydride immediately led to decomposition of the aminals to the desired iminium ions, mixing them with $BF_3 \cdot OEt_2$ did not cause the ionization reaction on its own. This was proven by treating the aminal **91** with $BF_3 \cdot OEt_2$ (1.0 equiv) at 0 °C for 30 min in THF, followed by aqueous work-up, upon which **91** was fully recovered (Scheme 53).



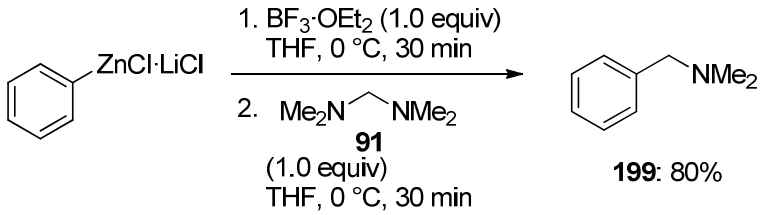
Scheme 53: Absence of decomposition of **91** when treated with boron trifluoride etherate.

However, adding phenylzinc chloride lithium chloride complex (obtained from the transmetalation of phenyllithium using anhydrous $ZnCl_2$) to the mixture of **91** and $BF_3 \cdot OEt_2$ led to the formation of *N*,*N*-dimethylbenzylamine **199** (Scheme 54).



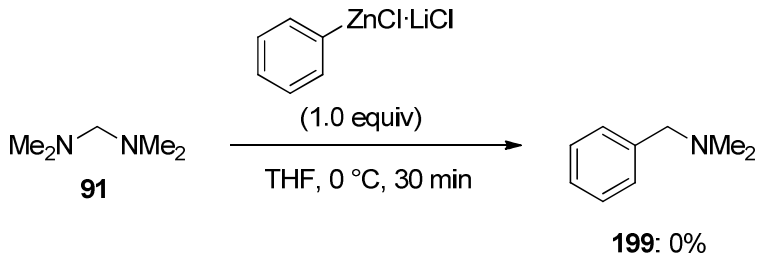
Scheme 54: Aminomethylation of phenylzinc chloride mediated by boron trifluoride etherate.

Moreover, premixing phenylzinc chloride with $BF_3 \cdot OEt_2$ (1.0 equiv) at 0 °C for 30 min in THF, followed by the addition of the neat aminal **91** afforded **199** in 80% yield (Scheme 55).



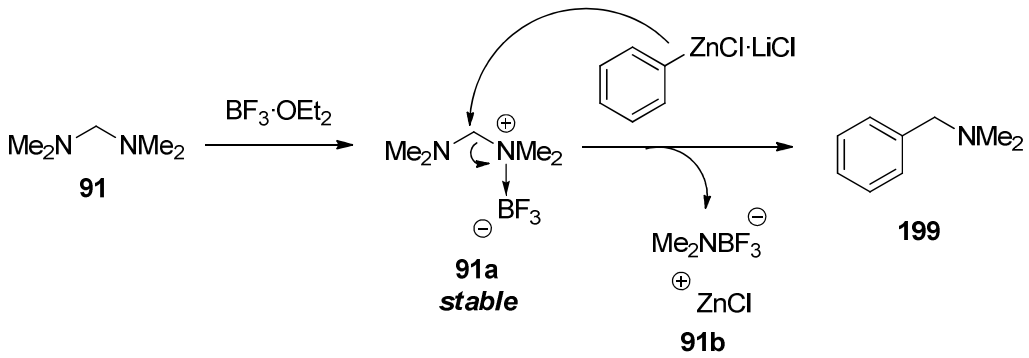
Scheme 55: Premixing phenylzinc chloride with $BF_3 \cdot OEt_2$ followed by aminomethylation using the aminal **91**.

A control experiment omitting $BF_3 \cdot OEt_2$ from the reaction mixture resulted – as expected – in no conversion to the desired amine **199** (Scheme 56).



Scheme 56: Failure to aminomethylate in the absence of $BF_3 \cdot OEt_2$.

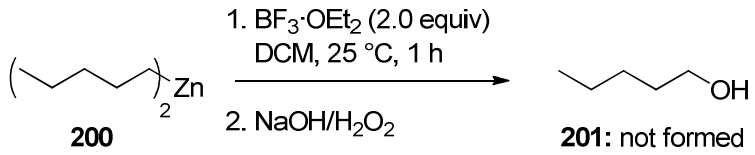
Taking into account all these observations, especially the fact that the iminium ion is not formed by the reaction of **91** with $BF_3 \cdot OEt_2$ alone, a modified reaction mechanism was proposed. Presumably, the addition of $BF_3 \cdot OEt_2$ to the aminal leads to the formation of a Lewis acid-base adduct of type **91a**. While this adduct does not decompose to the iminium ion, the nucleophilic attack of phenylzinc chloride onto the aminal's central carbon atom causes the elimination of the adduct $[Me_2N{\leftarrow}BF_3]ZnCl$ **91b** (Scheme 57).



Scheme 57: Proposed mechanism for the BF_3-mediated aminomethylation reaction.

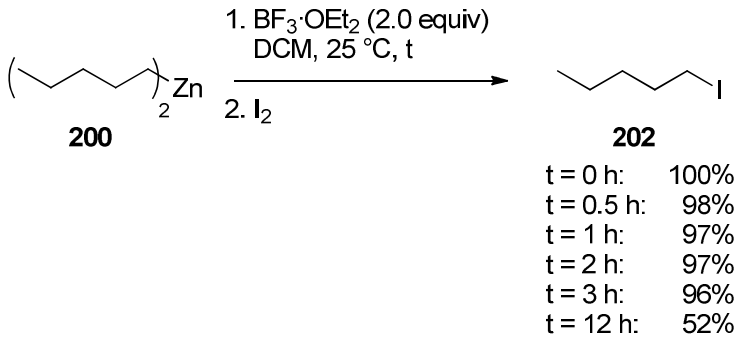
3.3.2. 1,4-Addition of Dipentylzinc to Cyclohexenone Mediated by $BF_3 \cdot OEt_2$

The fact that phenylzinc chloride was stable and did not seem to undergo transmetalation to boron when mixed with $BF_3 \cdot OEt_2$ led us to investigate the behaviour of dipentylzinc with this *Lewis* acid. To check for transmetalation, $BF_3 \cdot OEt_2$ (2.0 equiv) was added to a solution of dipentylzinc **200** (1.0 equiv) in dichloromethane at 25 °C. After stirring for 1 h, an attempted oxidative work-up of the possibly formed organoboron species using NaOH / H_2O_2 provided no traces of pentanol **201**, confirming the compatibility of dipentylzinc with boron trifluoride (Scheme 58).



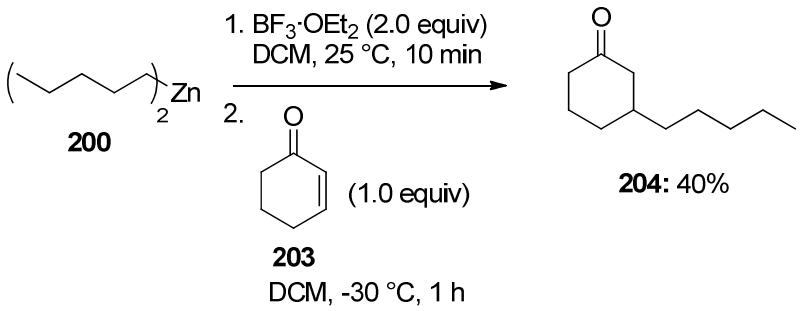
Scheme 58: Compatibility of dipentylzinc **200** with boron trifluoride.

Not only does no transmetalation occur, but also did the activity of a dipentylzinc/$BF_3 \cdot OEt_2$ mixture not diminish significantly over time. Iodometric titration of a 1:2 stoichiometric mixture of **200** with boron trifluoride which had been stirred at 25 °C over several hours showed an only minimal decrease in active organometallic species. Even after 3 h, GC experiments showed a 96% conversion to iodopentane **202** (Scheme 59).



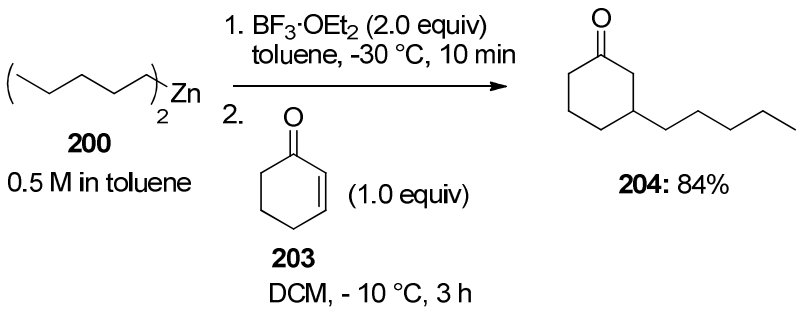
Scheme 59: Activity of dipentylzinc **200** in the presence of boron trifluoride.

It was therefore interesting to see if a new reactivity of the complex $Pent_2Zn \cdot BF_3$ could be achieved in organic transformations. The reaction of a 1:2 stoichiometric mixture of dipentylzinc and $BF_3 \cdot OEt_2$ with cyclohex-2-enone **203** in dichloromethane gave an addition product, which was identified after isolation as the 1,4-addition product **204** (Scheme 60).



Scheme 60: Conjugate addition of dipentylzinc$\cdot BF_3$ to cyclohex-2-enone.

Since these results constituted to our knowledge the first example of a Cu-free conjugate addition of a diorganozinc compound to an enone, solvents and reaction conditions were screened with the aim of improving the yield of **204**. Allowing the reaction to warm up beyond –10 °C led to the formation of a multitude of unidentifiable byproducts and decomposition of the starting material. The use of THF as solvent for this reaction proved impractical, as the addition of BF_3 to the otherwise stable solution of dipentylzinc in THF led to polymerization of the solvent. Et_2O and DCM also did not give satisfactory results; however, performing the reaction diluted in anhydrous toluene with a molecular ratio of dipentylzinc/BF_3 = 1:2 allowed the isolation of 3-pentylcyclohexanone **204** in 84% yield (Scheme 61).



Scheme 61: Improved reaction conditions for the conjugate addition of **200** to **203**.

4. Summary and Outlook

This work was focused on the oxidative Cu(I)-mediated cycloamination of benzofuran and benzothiophene derivatives; furthermore, a general pathway for the preparation of non-conjugated heteroaromatic benzylic zinc reagents has been investigated. In the last part of this thesis, the preparation of benzyl- and phenethylamines from organometallics and metal amides *via* a one-pot anhydrous aminomethylation reaction has been established.

4.1. Cu(I)-Mediated Oxidative Cycloamination

It was demonstrated that the two-fold deprotonation of benzofuran-3-yl- and benzothiophen-3-ylanilines using *n*BuLi, followed by transmetalation using CuCl·2LiCl afforded cyclic amidocuprates which were readily oxidized using 2,3,5,6-tetrachlorobenzo-*p*-quinone ("chloranil") to furnish new tetracyclic benzofuro- and benzothieno[2,3-*b*]indoles (Figure 4).

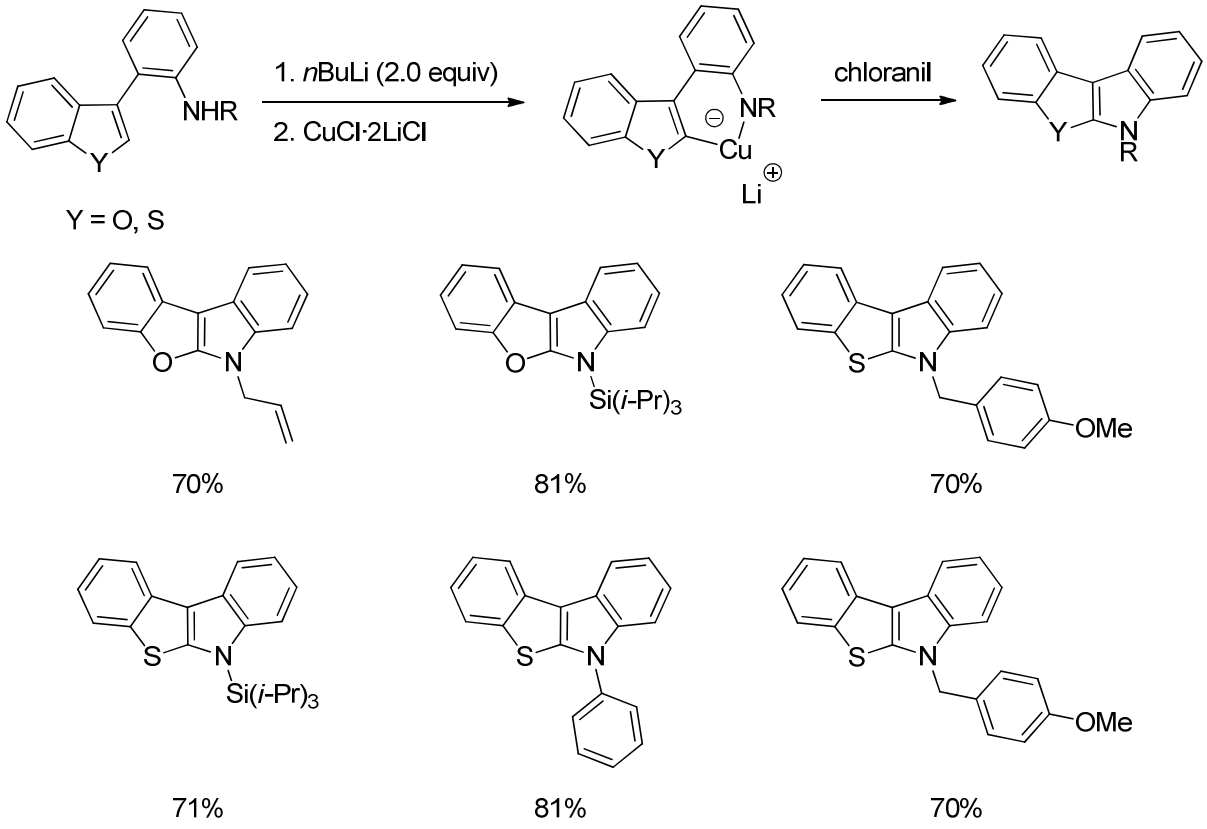


Figure 4: Examples of oxidative Cu(I)-mediated cycloamination.

These cyclization reactions enabled the first reported access to these backbones, which might in the future find applications in the synthesis of materials or pharmaceuticals. The cycloamination could be further investigated with the aim of using milder bases and thus enabling the tolerance of base-sensitive functional groups.

4.2. Preparation and Reactions of Non-Conjugated Heteroaromatic Benzylic Zinc Reagents

A method was developed for the synthesis of non-conjugated heteroaromatic benzylic zinc compounds starting from heteroaryl organometallics by converting them into the corresponding (dimethylamino)methyl compounds and transforming the amino moiety into a chloride substituent. Oxidative LiCl-promoted insertion of metallic Zn into these chlorides gave rise to various heteroaromatic benzylic zinc reagents which could be reacted with a range of electrophiles (Figure 5).

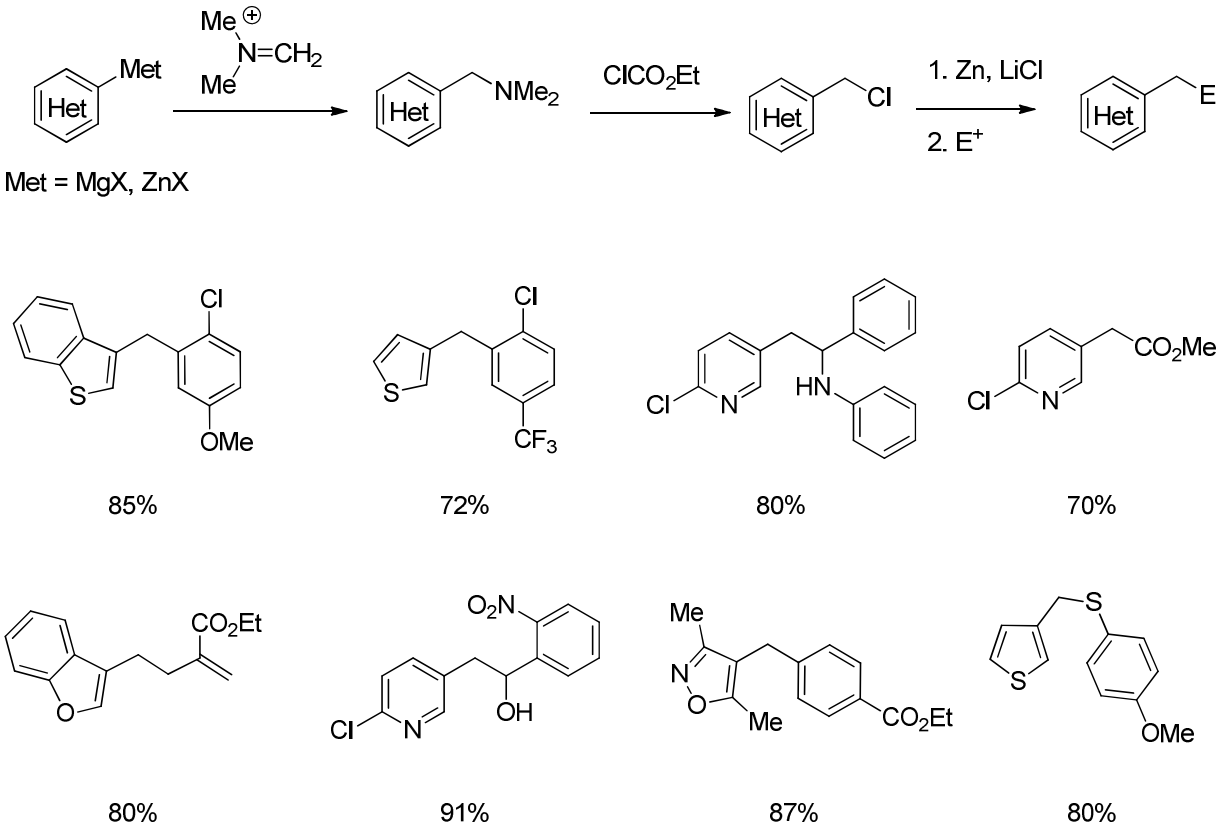


Figure 5: Examples for the reactions of non-conjugated heteroaromatic benzylic zinc reagents.

This methodology for the preparation of otherwise elusive heterobenzyl organometallics carries the potential to find application in the preparation of pharmaceutically useful substances due to its compatibility with many functional groups.

4.3. One-Pot Preparation of Tertiary Aromatic and Heteroaromatic Benzylic and Phenethylic Amines

The preparation of mixed aminals from *Mannich*'s cation and a range of metal amides was performed and their subsequent ionization to (methylene)iminium ions using trifluoroacetic anhydride was achieved. Trapping of these iminium ions with a range of organometallic substrates in a one-pot fashion led to the efficient formation of tertiary benzylic and phenethylic amines (Figure 6), which constitute important synthetic targets due to their known physiological properties, for example the psychoactivity of phenethylamine derivatives.

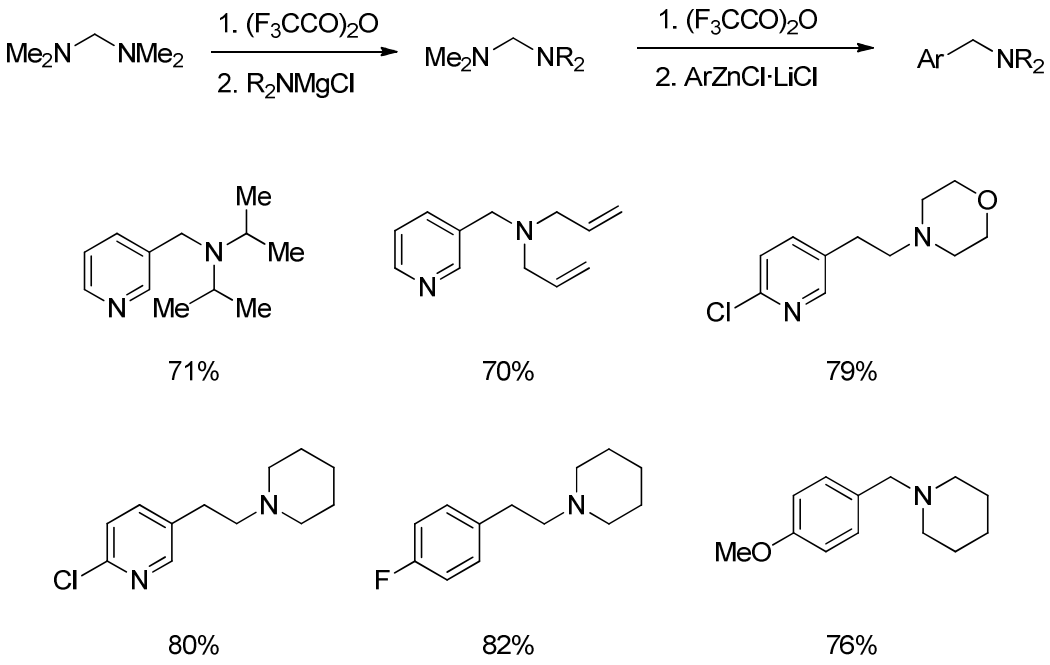


Figure 6: Examples for the one-pot aminomethylation of aromatic and heteroaromatic organometallics.

C. EXPERIMENTAL SECTION

1. General Considerations

All reactions were carried out under argon or nitrogen atmosphere in glassware dried with a heat gun. Syringes which were used to transfer anhydrous solvents or reagents were purged thrice with argon or nitrogen prior to use. THF was freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Indicated yields are isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. Unless otherwise indicated, all reagents were obtained from commercial sources. Liquid starting materials were distilled prior to use. Magnesium turnings (> 99.5%), magnesium powder (> 99%) and zinc dust (> 90%) were obtained from Riedel-de Haën. CuCl, CuCN, $ZnCl_2$ and LiCl were obtained from Fluka.

1.1. Solvents

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

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

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

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

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

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

Pyridine was dried over KOH and distilled.

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

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

NEt_3 was dried over KOH and distilled.

Solvents for column chromatography were distilled on a rotary evaporator prior to use.

1.2. Reagents

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

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

MeMgCl solution in THF was purchased from Chemetall.

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

TMPMgCl·LiCl was prepared according to a literature procedure.[74]

TMPZnCl·LiCl was prepared according to a literature procedure.[75]

$TMP_2Zn·2MgCl_2·2LiCl$ was prepared according to a literature procedure.[44]

$CuCl_2·2LiCl$ solution (1.00 M) was prepared by drying LiCl (1.7 g, 40 mmol) in a Schlenk tube under vacuum at 130 °C for 2 h. After cooling, CuCl (1.98 g, 20 mmol, 99.5% Cu) was added under inert atmosphere inside a glove box. Drying continued at 130 °C for 5 h under high vacuum. After cooling, the flask was charged with anhydrous THF (20 mL) and wrapped in aluminum foil to protect it from light. The mixture was stirred until all salts were dissolved (approx. 6 h).

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a Schlenk tube under vacuum at 140 °C for 5 h. After cooling, 80 mL dry THF were added and stirring was continued until the salts were dissolved.

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

1.3. Content determination of organometallic reagents

Organozinc and organomagnesium reagents were titrated with I_2 in a 0.5 M LiCl solution in THF.

Organolithium reagents were titrated with dry 2-propanol against 1,10-phenanthroline in THF.

TMPMgCl·LiCl, **TMPZnCl·LiCl**, and **$TMP_2Zn·2MgCl_2·2LiCl$** were titrated with benzoic acid against 4-(phenylazo)diphenylamine in THF.

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

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

1.4. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) and aluminum oxide 90 (0.063-0.200 mm) from MERCK.

Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under 254 nm UV irradiation, by incubating the plates in an iodine chamber and/or by staining of the TLC plate with one of the reagents given below followed by heating with a heat gun:

$KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).

Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).

1.5. Analytical data

^{1}H-NMR and **^{13}C-NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to tetramethylsilane. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), 5 (quintet), 7 (septet), m (multiplet) as well as br (broadened).

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

For coupled gas chromatography / mass spectrometry, a HEWLETT-PACKARD HP 6890 / MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. Wavenumbers are reported in cm^{-1} starting at an absorption of 10%.

Melting points (mp) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. Compounds decomposing upon melting are indicated by (decomp.).

2. Typical Procedures

2.1. Typical procedure for the preparation of 3-arylated benzo[b]furans and benzo[b]thiophenes by Pd-catalyzed Negishi cross-coupling (TP1)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with 3-bromobenzo[b]furan or 3-bromobenzo[b]thiophene (1.0 equiv) and THF was added to obtain a 2 M solution. The solution was cooled to –55 °C for 3-bromobenzofuran, to –15 °C for 3-bromobenzothiophene. *i*PrMgCl·LiCl (1.1 equiv) was added and the resulting mixture was stirred at –55 °C for 24 h (3-bromobenzofuran), at –15 °C for 12 h (3-bromobenzothiophene). Then, $ZnCl_2$ (1 equiv, 1.0 M in THF) was added and the solution was warmed up to –10 °C within 20 min. In the meantime, another dry and argon-flushed Schlenkflask, equipped with a magnetic stirring bar and a septum, was charged with the 2-bromoaniline derivative (0.66 equiv), $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%) and THF to obtain a 1 M solution. To this mixture, the freshly prepared zinc reagent was canulated over 10 min at 25 °C. The resulting solution was stirred at 25 °C for additional 5 h to obtain full conversion. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl (5 mL) and the product was extracted with EtOAc (3 x 25 mL). The combined organic phases were successively washed with sat. aq. thiourea (2 x 10mL) and sat. aq. NaCl (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

2.2. Typical procedure for the copper(I)-mediated oxidative cycloamination (TP2)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the benzofuranyl- / benzothienylaniline precursor (1.0 equiv) and THF was added to obtain a 1 M solution. The solution was cooled to –78 °C and freshly titrated *n*BuLi (2.0 equiv) was added dropwise. The mixture was stirred for 1 h at –78 °C and for 3 h at –30 °C. Then, the mixture was cooled to –50 °C and CuCl·2LiCl (1.1 equiv, 1.0 M in THF) was added and the reaction mixture was stirred for 20 min. After cooling to –78 °C, the solution was diluted with THF to ten-fold volume, followed by the dropwise addition of chloranil (1.1 equiv, 0.1 M in THF). Et_2O was added to the crude reaction mixture and it was filtered through Celite, washed

thoroughly with Et_2O, and the filtrate was washed with two 10 mL portions of aqueous NH_4OH (2.0 M). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure.

2.3. Typical procedure for the preparation of (dimethylamino)methyl heteroarenes using *N,N,N',N'*-tetramethylmethanediamine (TP3)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *N,N,N',N'*-tetramethylmethanediamine (1.1 equiv) and anhydrous CH_2Cl_2 to obtain a 1 M solution. After cooling to 0 °C, neat trifluoroacetic anhydride (1.1 equiv) was added dropwise. A thick white smoke formed inside the reaction vessel. After the highly exothermic reaction subsided and the smoke dissipated, the cooling was removed and the solution allowed to warm up to 25 °C and stirring was continued for 5 min. The so prepared solution of methylene(dimethyl)iminium trifluoroacetate was then canulated dropwise to a solution of the nucleophile (organometallic reagent or metal amide, 1.0 equiv) at 0 °C. In all cases, the reaction was found to be complete immediately after all of the solution had been transferred. The crude mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.4. Typical procedure for the preparation of heteroaromatic benzylic chlorides from (dimethylamino)methyl heteroarenes (TP4)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the (dimethylamino)methyl compound (1.0 equiv) and anhydrous $CHCl_3$ to obtain a 1 M solution. After cooling to 0 °C, neat ethyl chloroformate (1.1 equiv) was added dropwise. The resulting solution was stirred at 0 °C for 30 min. The crude mixture was quenched with H_2O, extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.5. Typical procedure for the preparation of heteroaromatic benzylic zinc chlorides by LiCl-promoted direct zinc insertion (TP5)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (1.5 equiv). The flask was heated to 650 °C for 5 minutes under high vacuum using a heat gun. After cooling to 25 °C, the flask was flushed with argon and charged with Zn dust (1.5 equiv), followed by THF. Neat 1,2-dibromoethane (5 mol%) was added and the resulting suspension was brought to ebullition using a heat gun. After cooling to 25 °C, neat chlorotrimethylsilane (1 mol%) was added and the mixture was heated again to ebullition using a heat gun. The suspension of now activated Zn dust was allowed to cool to 25 °C after which the heterobenzyl chloride (1.0 equiv) was added as a 1 M solution in THF. After the insertion reaction was terminated as checked by TLC or GC of hydrolyzed reaction aliquots, the Schlenk flask was centrifuged for 30 min at 2000 rpm. The supernatant solution was carefully canulated into another dry and argon-flushed Schlenk flask. The yield of resulting heterobenzylic zinc chloride was determined by iodometric titration.

2.6. Typical procedure for the preparation of diarylmethanes by the Pd-catalyzed cross-coupling of heterobenzylic zinc chlorides (TP6)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the aryl or heteroaryl halide (0.9 equiv) and THF to obtain a 1 M solution. The appropriate Pd catalyst was added (Pd-PEPPSI-IPr: 1 mol%; $Pd(OAc)_2$/S-Phos : 1 mol% / 2 mol%) and the resulting suspension was stirred for 5 min at 25 °C. After cooling to 0 °C, the heterobenzylic zinc chloride (1.0 equiv) was added dropwise. Cooling was removed and the reaction mixture was allowed to warm up to 25 °C. Stirring was continued until complete consumption of the heteroaryl halide as indicated by TLC and GC. Then, sat. aq. NH_4Cl was added and the crude mixture extracted with EtOAc (3 x 25 mL). The combined organic extracs were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.7. Typical procedure for the preparation of heterophenethylic alcohols by the reaction of heterobenzylic zinc chlorides with aldehydes (TP7)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the aldehyde compound (0.9 equiv) and THF to obtain a 1 M solution. The heterobenzylic zinc chloride (1.0 equiv) was added dropwise at 0 °C. The resulting solution was allowed to warm up to room remperature and stirring was continued until complete consumption of the aldehyde as indicated by TLC and GC. Then, sat. aq. NH_4Cl was added and the crude mixture extracted with EtOAc (3 x 25 mL). The combined organic extracs were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.8. Typical procedure for the preparation of heterobenzyl ketones by the reaction of heterobenzylic zinc chlorides with carboxylic acid chlorides (TP8)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with CuCN·2LiCl (1.1 equiv, 1 M solution in THF) followed by the dropwise addition of the desired heterobenzylic zinc chloride (1.0 equiv) at –20 °C. The solution was stirred at –20 °C for 10 min, after which the neat acid chloride (0.9 equiv) was added portionwise. The reaction mixture was allowed to warm up to 25 °C and stirring was continued until complete consumption of the acid chloride as indicated by TLC and GC. Then, a mixture of sat. aq. NH_4Cl and aq. NH_4OH (2:1) was added and the crude mixture extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.9. Typical procedure for the preparation of heterobenzyl aryl sulfides by the reaction of heterobenzylic zinc compounds with sulfonothioates (TP9)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the sulfonothioate (0.9 equiv) and anhydrous THF to obtain a 1 M solution. The desired heterobenzylic zinc chloride (1.0 equiv) was added dropwise at –20 °C. The solution was stirred at –20 °C for 10 min, after which cooling was removed and the reaction mixture allowed to warm up to 25 °C. Stirring was continued for 3 h after which TLC and GC showed complete consumption of the sulfonothioate. Then, sat. aq. NH_4Cl was added and the crude mixture

extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.10. Typical procedure for the Cu-catalyzed allylation of heterobenzylic zinc compounds (TP10)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with CuCN·2LiCl (0.1 equiv, 1 M solution in THF) followed by the dropwise addition of the desired heterobenzylic zinc chloride (1.1 equiv) at –20 °C. The solution was stirred at –20 °C for 10 min, after which the neat allyl bromide (1.0 equiv) was added portionwise. The reaction mixture was allowed to warm up to 25 °C and stirring was continued until complete consumption of the allyl bromide as indicated by TLC and GC. Then, a mixture of sat. aq. NH_4Cl and aq. NH_4OH (2:1) was added and the crude mixture extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaCl and dried over $MgSO_4$.

2.11. Typical procedure for the preparation of tertiary benzylic and phenethylic amines (TP11)

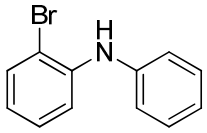
A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *N*,*N*,*N'*,*N'*-tetramethylmethanediamine (1.0 equiv) and anhydrous CH_2Cl_2 to obtain a 1 M solution. After cooling to 0 °C, neat trifluoroacetic anhydride (1.0 equiv) was added dropwise. The solution allowed to warm up to 25 °C and stirring was continued for 5 min. Next, the solution was cooled to –78 °C upon which a white slurry began to form. To this suspension, a solution of the desired magnesium amide (1.0 equiv) in THF was added over 15 min (prepared from the reaction of the corresponding secondary amine and MeMgCl at 0 °C). Stirring was continued at –78 °C for another 15 min, after which neat trifluoroacetic anhydride (1.0 equiv) was added dropwise, resulting in the formation of a white precipitate. Finally, the desired organomagnesium / organozinc substrate was added as a solution in THF at –78 °C over 15 min. After the precipitate had dissolved completely, the cooling was removed and the crude mixture allowed to warm up to 25 °C after which it was quenched using sat. aq. $NaHCO_3$, extracted with EtOAc (3 x 25 mL), the combined organic layers washed with sat. aq. NaCl and dried over $MgSO_4$.

3. Product Syntheses and Analytical Data

3.1. Oxidative Copper(I)-Mediated Cycloamination

3.1.1. Preparation of precursors

Synthesis of 2-bromo-*N*-phenylaniline (69)



To a solution of 1,2-dibromobenzene (236 mg, 1.0 mmol, 1.0 equiv) in THF (2 mL) at –15 °C was added *i*PrMgCl (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –15 °C for 2 h. Next, the so obtained solution of 2-bromophenylmagnesium bromide was added to a 1 M solution of CuCl·2LiCl (1.1 mmol, 1.1 equiv) and triethylamine (111 mg, 1.1 mmol, 1.1 equiv) in THF at –50 °C and stirring was continued for 20 min. In a second flask, a solution of aniline (186 mg, 2.0 mmol, 2.0 equiv) in THF (2 mL) was cooled to –50 °C and MeLi (2.00 mmol, 2.0 equiv) was added dropwise. The resulting mixture was stirred at –50 °C for 10 min and then canulated to the solution of 2-bromophenylcopper. Stirring was continued at –50 °C for 45 min. A solution of chloranil (270 mg, 1.1 mmol, 1.1 equiv) in THF (8 mL) was added dropwise at –78 °C. After the addition was complete, the solution was allowed to warm up to 25 °C and stirred for 1 h. Et_2O was added (10 mL) and the resulting suspension was filtrated through a pad of celite. The residue was washed with Et_2O until the filtrate was colorless. The phases were separated and the organic layer was washed with 2 M NH_4OH until the aqueous phase showed no blue color anymore. The extracts were dried over $MgSO_4$. Purification of the crude product by flash chromatography (*n*-pentane) afforded **69** as a yellow oil (188 mg, 76%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3392, 3038, 1586, 1500, 1470, 1450, 1414, 1308, 1216, 1176, 1156, 1120, 1076, 1044, 1023, 932, 884, 848, 740.

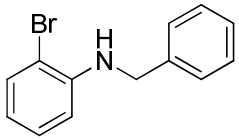
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 1H, Ar*H*), 7.39-7.33 (m, 2H, Ar*H*), 7.30-7.27 (m, 1H, Ar*H*), 7.22-7.18 (m, 3H, Ar*H*), 7.10-7.06 (m, 1H, Ar*H*), 6.80-6.75 (m, 1H, Ar*H*), 6.12 (br. s, 1H, N*H*).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.9, 141.7, 133.2, 129.7, 128.4, 123.0, 121.2, 120.6, 116.1, 112.5.

MS (70 eV, EI): *m/z* (%) = 250 (10), 249 (74), 248 (11), 247 (76), 243 (20), 241 (14), 167 (100).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}{}^{79}BrN$] 246.9997, found: 246.9983.

Synthesis of *N*-benzyl-2-bromoaniline (73)



To a solution of 1,2-dibromobenzene (236 mg, 1.0 mmol, 1.0 equiv) in THF (2 mL) at –15 °C was added *i*PrMgCl (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –15 °C for 2 h. Next, the so obtained solution of 2-bromophenylmagnesium bromide was added to a 1 M solution of CuCl·2LiCl (1.1 mmol, 1.1 equiv) and triethylamine (111 mg, 1.1 mmol, 1.1 equiv) in THF at –50 °C and stirring was continued for 20 min. In a second flask, a solution of benzylamine (214 mg, 2.0 mmol, 2.0 equiv) in THF (2 mL) was cooled to –50 °C and MeLi (2.00 mmol, 2.0 equiv) was added dropwise. The resulting mixture was stirred at –50 °C for 10 min and then canulated to the solution of 2-bromophenylcopper. Stirring was continued at –50 °C for 45 min. A solution of chloranil (270 mg, 1.1 mmol, 1.1 equiv) in THF (8 mL) was added dropwise at –78 °C. After the addition was complete, the solution was allowed to warm up to 25 °C and stirred for 1 h. Et_2O was added (10 mL) and the resulting suspension was filtrated through a pad of celite. The residue was washed with Et_2O until the filtrate was colorless. The phases were separated and the organic layer was washed with 2 M NH_4OH until the aqueous phase showed no blue color anymore. The extracts were dried over $MgSO_4$. Purification of the crude product by flash chromatography (*n*-pentane) afforded **73** as a colorless oil (152 mg, 58%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3416, 2064, 3028, 2924, 2852, 1596, 1496, 1452, 1428, 1360, 1320, 1292, 1236, 1160, 1128, 1068, 1016, 988, 924, 728.

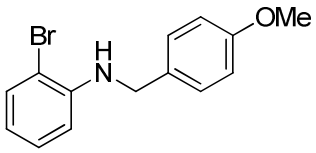
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.39-7.25 (m, 5H, ArH), 7.18-7.15 (m, 1H, Ar*H*), 6.61-6.55 (m, 2H, Ar*H*), 4.81 (br. s, 1H, N*H*), 4.40 (s, 2H, CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 144.7, 138.6, 132.3, 128.7, 128.5, 127.3, 127.2, 118.0, 111.7, 109.7, 48.0.

MS (70 eV, EI): *m/z* (%) = 264 (12), 163 (80), 262 (36), 261 (84), 260 (25), 184 (11), 182 (10), 180 (21), 91 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}{}^{79}BrN$] 261.0153, found: 261.0163.

Synthesis of 2-bromo-*N*-(4-methoxybenzyl)aniline (74)



To a solution of 1,2-dibromobenzene (236 mg, 1.0 mmol, 1.0 equiv) in THF (2 mL) at –15 °C was added *i*PrMgCl (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –15 °C for 2 h. Next, the so obtained solution of 2-bromophenylmagnesium bromide was added to a 1 M solution of CuCl·2LiCl (1.1 mmol, 1.1 equiv) and triethylamine (111 mg, 1.1 mmol, 1.1 equiv) in THF at –50 °C and stirring was continued for 20 min. In a second flask, a solution of 4-(methoxybenzyl)amine (274 mg, 2.0 mmol, 2.0 equiv) in THF (2 mL) was cooled to –50 °C and MeLi (2.00 mmol, 2.0 equiv) was added dropwise. The resulting mixture was stirred at –50 °C for 10 min and then canulated to the solution of 2-bromophenylcopper. Stirring was continued at –50 °C for 45 min. A solution of chloranil (270 mg, 1.1 mmol, 1.1 equiv) in THF (8 mL) was added dropwise at –78 °C. After the addition was complete, the solution was allowed to warm up to 25 °C and stirred for 1 h. Et_2O was added (10 mL) and the resulting suspension was filtrated through a pad of celite. The residue was washed with Et_2O until the filtrate was colorless. The phases were separated and the organic layer was washed with 2 M NH_4OH until the aqueous phase showed no blue color anymore. The extracts were dried over $MgSO_4$. Purification of the crude product by flash chromatography (*n*-pentane) afforded **74** as a white solid (187 mg, 64%).

mp: 71.9-72.4 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3408, 3064, 3000, 2952, 2932, 2904, 2836, 1596, 1508, 1456, 1428, 1360, 1320, 1288, 1244, 1172, 1128, 1108, 1076, 1032, 1016, 924, 876, 820, 740.

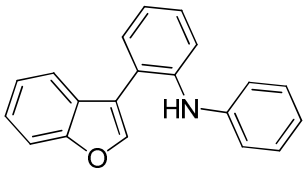
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.44 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.3 Hz, 1H, Ar*H*), 7.30-7.26 (m, 2H, Ar*H*), 7.16-7.13 (m, 1H, Ar*H*), 6.90 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar*H*), 6.63 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.3 Hz, 1H, Ar*H*), 6.58 (td, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.5 Hz, 1H, ArH), 4.69 (br. s, 1H, N*H*), 4.33 (s, 2H, CH_2), 3.81 (s, 3H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.2, 145.1, 132.6, 130.8, 128.8, 128.7, 118.1, 114.4, 111.9, 109.9, 55.5, 47.8.

MS (70 eV, EI): *m/z* (%) = 293 (19), 291 (21), 122 (10), 121 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}{}^{79}BrNO$] 291.0259, found: 291.0273.

Synthesis of 2-(benzo[b]furan-3-yl)-*N*-phenylaniline (82a)



Prepared according to **TP1** from 3-bromobenzo[b]furan (295 mh, 1.5 mmol, 1.5 equiv) and 2-bromo-*N*-phenylaniline (248 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82a** as a white solid (213 mg, 75 %).

mp: 103.0 – 103.7 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3392, 3036, 1588, 1500, 1452, 1420, 1336, 1304, 1220, 1200, 1164, 1100, 1080, 964, 856, 800, 740, 700.

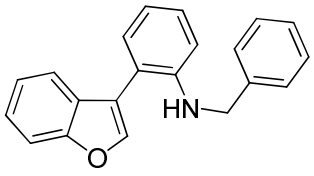
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H, Ar*H*), 7.56 (t, ^3J(H,H) = 9.3 Hz, 2H, Ar*H*), 7.42 (ddd, ^3J(H,H) = 15.7 Hz, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1,32 Hz, 2H, Ar*H*), 7.36-7.33 (m, 1H, Ar*H*), 7.31-7.29 (m, 1H, Ar*H*), 7.27-7.22 (m, 3H, Ar*H*), 7.06-7.04 (m, 2H, Ar*H*), 7.00 (td, ^3J(H,H) = 7.75 Hz, ^4J(H,H) = 1,3 Hz, 1H, Ar*H*), 6.94 (tt, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.3 Hz, 1H, Ar*H*), 5.69 (s, 1H, N*H*).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.6, 143.1, 142.9, 141.8, 131.5, 129.6, 129.0, 127.2, 125.0, 123.3, 121.7, 121.0, 120.8, 120.5, 119.0, 116.7, 112.0, 105.0.

MS (70 eV, EI): *m/z* (%) = 286 (21), 285 (100), 284 (14), 256 (12), 254 (11).

HRMS (EI): *m/z* calc. for [$C_{20}H_{15}NO$] 285.1154, found: 285.1145.

Synthesis of 2-(benzo[b]furan-3-yl)-*N*-benzylaniline (82b)



Prepared according to **TP1** from 3-bromobenzo[b]furan (295 mg, 1.5 mmol, 1.5 equiv) and *N*-benzyl-2-bromoaniline (262 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82b** as a yellow oil (257 mg, 86 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060, 3028, 1604, 1580, 1504, 1452, 1360, 1320, 1292, 1256, 1208, 1164, 1148, 1104, 1088, 1028, 1008, 960, 932, 856, 804, 740, 696.

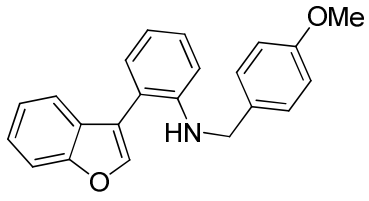
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.75 (s, 1H, Ar*H*), 7.58 (d, ^3J(H,H) = 7.8 Hz, 1H, Ar*H*), 7.54 (d, ^3J(H,H) = 8.3 Hz, 1H, Ar*H*), 7.34 (t, ^3J(H,H) = 7.2 Hz, 1H, Ar*H*), 7.30-7.21 (m, 8H, Ar*H*), 6.79 (td, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1,2 Hz, 1H, Ar*H*), 6.72 (d, ^3J(H,H) = 9.1 Hz, 1H, Ar*H*), 4.43 (s, 1H, N*H*), 4.34 (s, 2H, CH_2).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 155.7, 146.3, 142.9, 139.5, 131.0, 129.5, 128.9, 128.8, 127.4, 127.3, 125.0, 123.1, 121.3, 119.3, 117.3, 116.7, 112.0, 111.1, 48.4.

MS (70 eV, EI): *m/z* (%) = 300 (15), 299 (60), 212 (50), 208 (77), 206 (29), 180 (25), 153 (14), 152 (25), 151 (11), 91 (100), 77 (14), 65 (24).

HRMS (EI): *m/z* calc. for [$C_{21}H_{17}NO$] 299.1310, found: 299.1300.

Synthesis of 2-(benzo[b]furan-3-yl)-*N*-(4-methoxybenzyl)aniline (82c)



Prepared according to **TP1** from 3-bromobenzo[b]furan (295 mg, 1.5 mmol, 1.5 equiv) and 2-bromo-*N*-(4-methoxybenzyl)aniline (292 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82c** as a yellow oil (299 mg, 91 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3420, 2952, 2932, 2836, 2476, 1608, 1584, 1508, 1452, 1384, 1320, 1300, 1244, 1208, 1172, 1104, 1088, 1032, 960, 856, 820, 744.

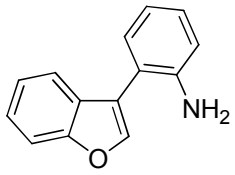
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H, Ar*H*), 7.62-7.56 (m, 2H, Ar*H*), 7.40-7.22 (m, 6H, Ar*H*), 6.87-6.78 (m, 4H, Ar*H*), 4.50 (s, 1H, N*H*), 4.30 (s, 2H, CH_2), 3.80 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.0, 155.7, 146.2, 142.9, 131.3, 131.0, 129.5, 128.7, 127.3, 125.0, 123.1, 121.2, 119.2, 117.4, 116.8, 114.2, 112.0, 111.2, 55.5, 48.0.

MS (70 eV, EI): *m/z* (%) = 329 (8), 208 (8), 122 (58), 121 (100).

HRMS (EI): *m/z* calc. for [$C_{22}H_{19}NO_2$] 329.1416, found: 329.1412.

Synthesis of 2-(benzo[b]furan-3-yl)aniline (82d)



Prepared according to **TP1** from 3-bromobenzo[b]furan (295 mg, 1.5 mmol, 1.5 equiv) and 2-bromoaniline (172 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (pentane/ether) yielded **82d** (SiO_2, *n*-pentane/Et_2O = 9:1) as a yellow oil (171 mg, 82%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3461, 3372, 3050, 1899, 1781, 1612, 1573, 1486, 1447, 1333, 1302, 1254, 1212, 1149, 1104, 1083, 1010, 960, 933, 854, 808, 740.

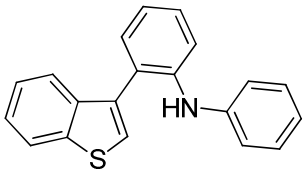
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1H, Ar*H*), 7.62 (d, ^{3}J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.57 (d, ^{3}J(H,H) = 8.4 Hz, 1H, Ar*H*), 7.37 (t, ^{3}J(H,H) = 8.4 Hz, 1H, Ar*H*), 7.32-7.22 (m, 3H, Ar*H*), 6.88-6.83 (m, 2H, Ar*H*), 3.87 (s, 2H, NH_2) .

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.6, 144.9, 142.7, 131.1, 129.2, 127.2, 124.9, 123.1, 121.2, 119.3, 118.7, 116.9, 115.8, 111.9.

MS (70 eV, EI): *m/z* (%) = 210 (13), 209 (100), 208 (16), 181 (14), 180 (40), 152 (10).

HRMS (EI): *m/z* calc. for [$C_{14}H_{11}NO$] 209.0841, found: 209.0844.

Synthesis of 2-(benzo[b]thiophen-3-yl)-*N*-phenylaniline (82e)



Prepared according to **TP1** from 3-bromobenzo[b]thiophene (319 mg, 1.5 mmol, 1.5 equiv) and 2-bromo-*N*-phenyl-aniline (248 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82e** as a yellow oil (129 mg, 43 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3403, 3055, 1944, 1586, 1573, 1499, 1452, 1415, 1341, 1302, 1257, 1244, 1175, 1157, 1057, 1020, 939, 875, 825, 732, 692.

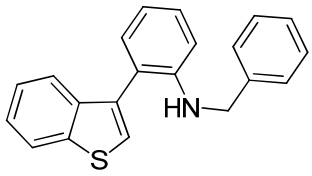
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.94 (d, ^3J(H,H) = 7.8 Hz, 1H, Ar*H*), 7.65 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.48-7.45 (m, 2H, Ar*H*), 7.40 (t, ^3J(H,H) = 7.3 Hz, 1H, Ar*H*), 7.36-7.32 (m, 3H, Ar*H*), 7.26-7.24 (m, 2H, Ar*H*), 7.05-7.01 (m, 3H, Ar*H*), 6.96-6.94 (m, 1H, Ar*H*), 5.58 (s, 1H, N*H*).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 142.9, 141.9, 140.6, 138.5, 134.7, 131.8, 129.5, 129.0, 125.5, 124.9, 124.7, 124.4, 123.4, 123.1, 121.8, 120.5, 119.3, 116.3.

MS (70 eV, EI): *m/z* (%) = 302 (12), 301 (53), 300 (23), 267 (10), 69 (12), 58 (37), 57 (12), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{20}H_{15}N^{32}S$] 301.0925, found: 301.0921.

Synthesis of 2-(benzo[b]thiophen-3-yl)-*N*-benzylaniline (82f)



Prepared according to **TP1** from 3-bromobenzo[b]thiophene (319 mg, 1.5 mmol, 1.5 equiv) and *N*-benzyl-2-bromoaniline (262 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82f** as a yellow oil (195 mg, 62 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3430, 3065, 3034, 2923, 2849, 1602, 1578, 1523, 1494, 1452, 1423, 1360, 1320, 1286, 1260, 1162, 1120, 1060, 1025, 933, 828, 788, 728, 696.

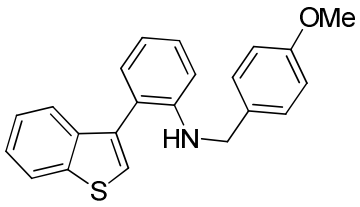
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.98-7.95 (m, 1H, Ar*H*), 7.71-7.68 (m, 1H, Ar*H*), 7.50 (s, 1H, Ar*H*), 7.44-7.41 (m, 2H, Ar*H*), 7.33-7.24 (m, 7H, Ar*H*), 6.84 (t, ^{3}J(H,H) = 7.5 Hz, 1H, Ar*H*), 6.77 (d, ^{3}J(H,H) = 8.2 Hz, 1H, Ar*H*), 4.36 (s, 2H, CH_2), 4.27 (s, 1H, N*H*).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 146.3, 140.7, 139.7, 138.6, 135.1, 131.2, 129.9, 129.5, 128.8, 127.3, 125.2, 124.9, 124.5, 123.7, 123.0, 121.1, 117.2, 111.1, 48.2.

MS (70 eV, EI): *m/z* (%) = 316 (23), 315 (100), 314 (19), 236 (15), 225 (12), 224 (62), 223 (42), 222 (11), 210 (12), 193 (12), 91 (27).

HRMS (EI): *m/z* calc. for [$C_{21}H_{17}N^{32}S$] 315.1082, found: 315.1076.

Synthesis of 2-(benzo[b]thiophen-3-yl)-*N*-(4-methoxybenzyl)aniline (82g)



Prepared according to **TP1** from 3-bromobenzo[b]thiophene (319 mg, 1.5 mmol, 1.5 equiv) and 2-bromo-*N*-(4-methoxybenzyl)aniline (292 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82g** as a yellow solid (235 mg, 68 %).

.**mp:** 103.0 – 103.7 °C.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3414, 3060, 2833, 1605, 1576, 1502, 1455, 1436, 1423, 1362, 1315, 1283, 1244, 1170, 1110, 1033, 933, 820, 732, 632.

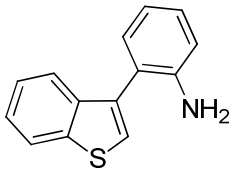
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, ^{3}J(H,H) = 7,2 Hz, 1H, Ar*H*), 7.63 (d, ^{3}J(H,H) = 7.4 Hz, 1H, Ar*H*), 7.45 (s, 1H, Ar*H*), 7.38 (5d, ^{3}J(H,H) = 7.4 Hz, ^{4}J(H,H) = 1.9 Hz, 2H, Ar*H*), 7.27 (t, ^{3}J(H,H) = 7.4 Hz, 1H, Ar*H*), 7.20 (dd, ^{3}J(H,H) = 7.4 Hz, ^{4}J(H,H) = 1.4 Hz, 1H, Ar*H*), 7.16 (d, ^{3}J(H,H) = 8.5 Hz, 2H, Ar*H*), 6.82-6.79 (m, 3H, Ar*H*), 6.75 (d, ^{3}J(H,H) = 8.1 Hz, 1H, Ar*H*), 4.25 (s, 2H, CH_2), 4.18 (s, 1H, N*H*), 3.78 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.9, 146.3, 140.6, 138.5, 135.1, 131.5, 131.2, 129.5, 128.5, 125.1, 124.8, 124.4, 123.7, 123.0, 121.1, 117.1, 114.1, 111.1, 55.5, 47.7.

MS (70 eV, EI): *m/z* (%) = 346 (21), 345 (100), 236 (12), 224 (54), 223 (29), 122 (26), 121 (18), 77 (13).

HRMS (EI): *m/z* calc. for [$C_{22}H_{19}NO^{32}S$] 345.1187, found: 345.1175.

Synthesis of 2-(benzo[b]thiophen-3-yl)aniline (82h)



Prepared according to **TP1** from 3-bromobenzo[b]thiophene (319 mg, 1.5 mmol, 1.5 equiv) and 2-bromoaniline (172 mg, 1.0 mmol, 1.0 equiv). Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) yielded **82h** as a yellow oil (182 mg, 81 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3458, 3366, 3055, 1612, 1521, 1482, 1448, 1424, 1341, 1297, 1256, 1205, 1144, 1059, 1019, 935, 839, 760.

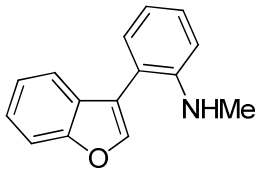
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.97-7.94 (m, 1H, Ar*H*), 7.68-7.65 (m, 1H, Ar*H*), 7.47 (s, 1H, Ar*H*), 7.45-7.36 (m, 2H, Ar*H*), 7.30-7.24 (m, 2H, Ar*H*), 6.91-6.84 (m, 2H, Ar*H*), 3.67 (s, 2H, NH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 144.6, 140.4, 138.2, 134.9, 131.1, 129.1, 124.7, 124.5, 124.2, 123.4, 122.8, 121.0, 118.4, 115.6.

MS (70 eV, EI): *m/z* (%) = 226 (18), 225 (100), 224 (82), 223 (40), 222 (11), 111 (16), 44 (22), 43 (17).

HRMS (EI): *m/z* calc. for [$C_{14}H_{11}N^{32}S$] 225.0612, found: 225.0608.

Synthesis of 2-(benzo[b]furan-3-yl)-*N*-methylaniline (82i)



Prepared by the addition of *n*BuLi (1.1 mmol, 1.1 equiv) to a solution of 2-(benzo[b]furan-3-yl)aniline **82d** (209 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL) at –30 °C and stirring for 30 min. Subsequent addition of iodomethane (155 mg, 1.1 mmol, 1.1 equiv), warming to 25 °C and stirring for 30 min gave the crude product which was extracted using Et_2O, dried over Na_2SO_4 and purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) affording **82i** as a colorless oil (138 mg, 62 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3424, 2866, 2812, 1604, 1580, 1450, 1424, 1312, 1294, 1208, 1167, 1103, 1094, 1084, 1007, 960, 856, 743.

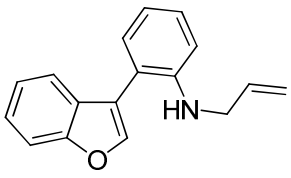
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.83 (s, 1H, Ar*H*), 7.66 (t, ^3J(H,H) = 7.8 Hz, 2H, Ar*H*), 7.48-7.33 (m, 4H, Ar*H*), 6.93-6.85 (m, 2H, Ar*H*), 4.15 (s, 1H, N*H*), 2.91 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.5, 147.4, 142.7, 130.7, 129.5, 127.3, 124.8, 122.9, 121.1, 119.2, 116.8, 116.4, 111.8, 110.0, 30.8.

MS (70 eV, EI): *m/z* (%) = 224 (17), 223 (100), 222 (55), 208 (20), 194 (15), 152 (11), 149 (11), 130 (15), 117 (10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{13}NO$] 223.0997, found: 223.0990.

Synthesis of *N*-allyl-2-(benzo[b]furan-3-yl)aniline (82j)



Prepared by the addition of *n*BuLi (1.1 mmol) to a solution of 2-(benzo[b]furan-3-yl)aniline **82d** (209 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL) at –30 °C and stirring for 30 min. Subsequent addition of allyl bromide (132 mg, 1.1 mmol, 1.1 equiv), warming to 25 °C and stirring for 30

min gave the crude product which was extracted using Et_2O, dried over Na_2SO_4 and purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) affording **82j** as a colorless oil (234 mg, 94 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3421, 3073, 2839, 1604, 1579, 1504, 1451, 1313, 1286, 1256, 1206, 1105, 961, 916, 856, 740.

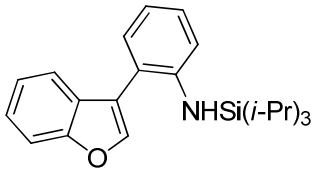
^{1}H-NMR (400 MHz, C_6D_6): δ = 7.45 (d, ^3J(H,H) = 7.0 Hz, 1H, Ar*H*), 7.34-7.32 (m, 2H, Ar*H*), 7.20-7.15 (m, 2H, Ar*H*), 7.04-6.96 (m, 2H, Ar*H*), 6.72 (t, ^3J(H,H) = 7.0 Hz, 1H, Ar*H*), 6.59 (d, ^3J(H,H) = 7.8 Hz, 1H, Ar*H*), 5.52-5.43 (m, 1H, C*H*=CH_2), 4.94 (d, ^3J(H,H) = 15.5 Hz, CH=CH_2), 4.82 (d, ^3J(H,H) = 7.0 Hz, 1H, CH=CH_2), 3,87 (s, 1H, N*H*), 3.25 (s, 2H, NH-CH_2).

^{13}C-NMR (100 MHz, C_6D_6): δ = 155.6, 146.0, 142.5, 135.2, 130.8, 129.3, 127.2, 124.7, 122.8, 121.0, 119.4, 116.9, 116.4, 115.2, 111.6, 110.8, 45.9.

MS (70 eV, EI): *m/z* (%) = 249 (25), 121 (13), 58 (42), 44 (33), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{17}H_{15}NO$] 249.1154, found: 249.1145.

Synthesis of *N*-(2-benzo[b]furan-3-yl)phenyl-1,1,1-triisopropylsilanamine (82k)



Prepared by the addition of *n*BuLi (1.1 mmol, 1.1 equiv) to a solution of 2-(benzo[b]furan-3-yl)aniline **82d** (209 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL) at –30 °C and stirring for 30 min. Subsequent addition of chlorotriisopropylsilane (211 mg, 1.1 mmol, 1.1 equiv), warming to 25 °C and stirring for 30 min gave the crude product which was extracted using Et_2O, dried over Na_2SO_4 and purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) affording **82k** as a colorless oil (175 mg, 48 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3386, 2940, 2863, 1606, 1575, 1488, 1473, 1451, 1383, 1299, 1234, 1200, 1158, 1100, 1083, 1045, 964, 880, 857, 765, 690.

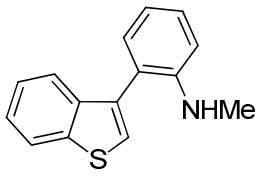
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.74 (s, 1H, Ar*H*), 7.58 (t, ^3J(H,H) = 7.6 Hz, 2H, Ar*H*), 7.38 (td, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 1.2 Hz, 1H, Ar*H*), 7.31-7.20 (m, 3H, Ar*H*), 6.92-6.78 (m, 2H, Ar*H*), 3.75 (s, 1H, N*H*), 1.32-1.16 (m, 3H, C*H*Me_2), 1.02 (d, ^3J(H,H) = 7.3 Hz, 18H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.4, 146.5, 142.5, 131.0, 129.1, 119.7, 118.4, 117.1, 115.5, 111.7, 18.4, 12.4.

MS (70 eV, EI): *m/z* (%) = 365 (27), 323 (25), 322 (100), 281 (14), 280 (63), 279 (12), 250 (11), 237 (12), 236 (40), 235 (13), 165 (12), 149 (11), 125 (12).

HRMS (EI): *m/z* calc. for [$C_{23}H_{32}NO^{28}Si$] 365.2175, found: 365.2171.

Synthesis of 2-(benzo[b]thiophen-3-yl)-*N*-methylaniline (82l)



Prepared by the addition of *n*BuLi (1.1 mmol, 1.1 equiv) to a solution of 2-(benzo[b]thiophen-3-yl)aniline **82h** (225 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL) at –30 °C and stirring for 30 min. Subsequent addition of iodomethane (155 mg, 1.1 mmol, 1.1 equiv), warming to 25 °C and stirring for 30 min gave the crude product which was extracted using Et_2O, dried over Na_2SO_4 and purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) affording **82l** as a yellow oil (229 mg, 96 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3421, 3063, 2811, 1601, 1578, 1498, 1453, 1420, 1339, 1311, 1287, 1252, 1167, 1055, 1038, 930, 829, 745.

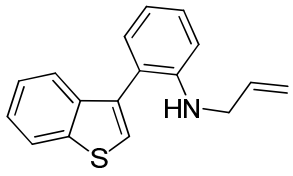
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.96 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 7.63 (d, ^3J(H,H) = 7.6 Hz, 1H, Ar*H*), 7.46 (s, 1H, Ar*H*), 7.42-7.37 (m, 3H, Ar*H*), 7.24 (d, ^3J(H,H) = 7.2 Hz, 1H, Ar*H*), 6.85 (t, ^3J(H,H) = 7.2 Hz, 1H, Ar*H*), 6.80 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 3.83 (s, 1H, N*H*), 2.81 (s, 3H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 147.3, 140.4, 138.4, 134.9, 130.8, 129.4, 124.9, 124.6, 124.3, 123.5, 122.8, 120.7, 116.5, 109.9, 30.7.

MS (70 eV, EI): *m/z* (%) = 371 (16), 324 (22), 240 (18), 239 (100), 238 (37), 236 (12), 224 (54), 223 (36), 222 (20), 206 (10), 204 (10), 165 (15), 152 (10), 130 (20), 43 (15).

HRMS (EI): *m/z* calc. for [$C_{15}H_{13}N^{32}S$] 239.0769, found: 239.0756.

Synthesis of *N*-allyl-2-(benzo[b]thiophen-3-yl)aniline (82m)



Prepared by the addition of *n*BuLi (1.1 mmol, 1.1 equiv) to a solution of 2-(benzo[b]thiophen-3-yl)aniline **82h** (225 mg, 1.0 mmol, 1.0 equiv) in THF (1 mL) at –30 °C and stirring for 30 min. Subsequent addition of allyl bromide (132 mg, 1.1 mmol, 1.1 equiv), warming to 25 °C and stirring for 30 min gave the crude product which was extracted using Et_2O, dried over Na_2SO_4 and purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) affording **82m** as a yellow oil (241 mg, 96 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3417, 3068, 2843, 1602, 1579, 1523, 1497, 1452, 1422, 1339, 1313, 1286, 1258, 1144, 1047, 1018, 992, 915, 827, 761.

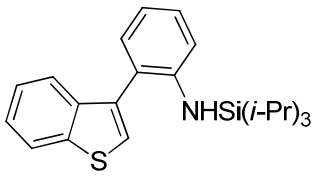
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.94 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.61 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.46 (s, 1H, Ar*H*), 7.40-7.21 (m, 4H, Ar*H*), 6.83-6.78 (m, 2H, Ar*H*), 5.87-5.82 (m, 1H, C*H*=CH_2), 5.18-5.08 (m, 2H, CH=CH_2), 4.06 (s, 1H, N*H*), 3.75 (s, 2H, NH-CH_2).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 145.7, 140.4, 138.3, 135.1, 134.5, 130.1, 129.2, 124.9, 124.6, 124.3, 123.4, 122.8, 121.0, 116.9, 116.0, 110.9, 46.3.

MS (70 eV, EI): *m/z* (%) = 266 (21), 265 (100), 264 (27), 249 (13), 238 (20), 237 (17), 236 (72), 232 (16), 224 (36), 223 (51), 222 (24), 218 (10), 217 (14), 205 (14), 165 (14), 130 (11).

HRMS (EI): *m/z* calc. for [$C_{17}H_{15}N^{32}S$] 265.0925, found: 265.0921.

Synthesis of *N*-(2-(benzo[b]thiophen-3-yl)phenyl)-1,1,1-triisopropylsilanamine (82n)



Prepared by the addition of *n*BuLi (1.1 mmol, 1.1 equiv) to a solution of 2-(benzo[b]thiophen-3-yl)aniline **82h** (225 mg, 1.0 mmol, 1.1 equiv) in THF (1 mL) at –30 °C and stirring for 30 min.

Subsequent addition of chlorotriisopropylsilane (211 mg, 1.1 mmol, 1.1 equiv), warming to 25 °C and stirring for 30 min gave the crude product which was extracted using Et_2O, dried over Na_2SO_4 and purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) affording **82n** as a yellow oil (365 mg, 96 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3383, 2941, 2864, 1604, 1574, 1523, 1484, 1451, 1427, 1385, 1339, 1298, 1237, 1058, 1014, 944, 881, 824, 788, 746.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, ^3J(H,H) = 7.6 Hz, 1H, Ar*H*), 7.58 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 7.44-7.32 (m, 3H, Ar*H*), 7.26 (s, 1H, Ar*H*), 7.22-7.18 (m, 2H, Ar*H*), 6.87-6.77 (m, 2H, Ar*H*), 3.49 (s, 1H, N*H*), 1.11-1.06 (m, 3H, C*H*Me$_2$), 0.92 (d, ^3J(H,H) = 7.1 Hz, 18H, CH_3).

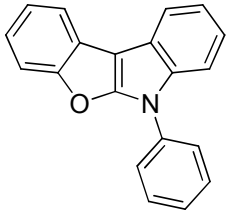
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 146.4, 140.2, 138.3, 135.5, 130.9, 128.9, 124.7, 124.5, 124.1, 123.5, 122.9, 122.7, 117.0, 115.5, 18.3, 12.2.

MS (70 eV, EI): *m/z* (%) = 381 (11), 340 (12), 339 (27), 338 (100), 265 (13), 44 (14).

HRMS (EI): *m/z* calc. for [$C_{23}H_{31}N^{32}S^{28}Si$] 381.1946, found: 381.1934.

3.1.2. Preparation of tetracyclic amination products

Synthesis of 6-phenyl-6*H*-benzo[4,5]furo[2,3-*b*]indole (84a)



Prepared according to **TP2** from 2-(benzo[b]furan-3-yl)-*N*-phenylaniline **82a** (285 mg, 1 mmol). Purification by flash chromatography (SiO_2, pentane) afforded **84a** as a white solid (192 mg, 68%).

mp: 112.0-112.4 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3184, 3052, 2920, 2852, 1912, 1872, 1624, 1592, 1560, 1500, 1448, 1400, 1328, 1300, 1204, 1176, 1148, 1108, 1076, 1012, 960, 916, 852, 784, 748, 724, 696, 676.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.90 (d, ^3J(H,H) = 7.8 Hz, 1H, Ar*H*), 7.82 (d, ^3J(H,H) = 7.8 Hz, 1H, Ar*H*), 7.72 (d, ^3J(H,H) = 7.8 Hz, 2H, Ar*H*), 7.64-7.60 (m, 3H, Ar*H*), 7.53 (d, ^3J(H,H) =

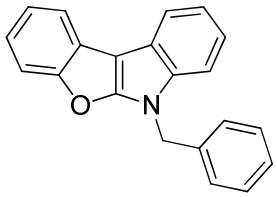
7.8 Hz, 1H, Ar*H*), 7.45 (t, ^{3}J(H,H) = 7.5 Hz, 1H, Ar*H*), 7.38-7.32 (m, 2H, Ar*H*), 7.28-7.26 (m, 1H, Ar*H*), 7.22 (t, ^{3}J(H,H) = 8.1 Hz, 1H, Ar*H*).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 157.0, 156.0, 137.5, 136.0, 130.1, 127.4, 125.0, 124.7, 124.0, 121.9, 121.8, 121.7, 121.2, 119.6, 119.0, 1112.1, 111.6, 99.5.

MS (70 eV, EI): *m/z* (%) = 284 (21), 283 (100), 254 (32), 179 (8).

HRMS (EI): *m/z* calc. for [$C_{20}H_{13}NO$] 283.0997, found: 283.0987.

Synthesis of 6-benzyl-6*H*-benzo[4,5]furo[2,3-*b*]indole (84b)



Prepared according to **TP2** from 2-(benzo[b]furan-3-yl)-*N*-benzylaniline **82b** (299 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84b** as a white solid (249 mg, 84%).

mp: 178.2-178.7 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3048, 1624, 1584, 1556, 1508, 1492, 1468, 1448, 1400, 1340, 1320, 1300, 1172, 1140, 1076, 1004, 960, 924, 780, 736, 708, 696, 648, 608.

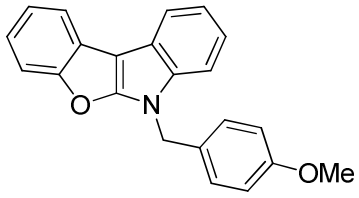
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.86 (d, ^{3}J(H,H) = 7.6 Hz, 1H, Ar*H*), 7.78 (d, ^{3}J(H,H) = 7.6 Hz, 1H, Ar*H*), 7.52 (d, ^{3}J(H,H) = 7.6 Hz, 1H, Ar*H*), 7.35-7.17 (m, 10H, Ar*H*), 5.50 (s, 2H, CH_2).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 157.2, 157.0, 137.5, 136.5, 129.1, 128.0, 127.1, 125.4, 123.9, 121.3, 121.1, 121.0, 120.9, 119.5, 118.8, 111.9, 110.7, 98.1, 47.1.

MS (70 eV, EI): *m/z* (%) = 297 (30), 206 (28), 141 (41), 91 (38), 69 (16), 58 (34), 57 (14), 55 (10), 44 (40), 43 (100), 41 (14).

HRMS (EI): *m/z* calc. for [$C_{21}H_{15}NO$] 297.1154, found: 297.1153.

Synthesis of 6-(4-methoxybenzyl)-6*H*-benzo[4,5]furo[2,3-*b*]indole (84c)



Prepared according to **TP2** from 2-(benzo[b]furan-3-yl)-*N*-(4-methoxybenzyl)aniline **82c** (329 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84c** as a white solid (163 mg, 50%).

mp: 103.7-104.1 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2948, 2928, 1624, 1584, 1556, 1508, 1464, 1444, 1336, 1304, 1124, 1172, 1108, 1032, 1008, 964, 924, 840, 808, 776, 736, 712, 684, 644, 600.

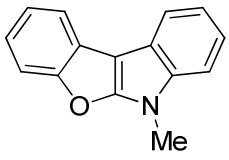
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.77 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.51 (d, ^3J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.36-7.30 (m, 2H, Ar*H*), 7.26-7.24 (m, 1H, Ar*H*), 7.21-7.16 (m, 4H, Ar*H*), 6.82-6.80 (m, 2H, Ar*H*), 5.43 (s, 2H, CH_2), 3.74 (s, 3H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 157.2, 157.0, 137.5, 136.5, 129.1, 128.0, 127.1, 125.4, 123.9, 121.3, 121.1, 121.0, 120.9, 119.5, 118.8, 111.9, 110.7, 98.1, 47.1.

MS (70 eV, EI): *m/z* (%) = 328 (8), 327 (32), 122 (10), 121 (100).

HRMS (EI): *m/z* calc. for [$C_{22}H_{17}NO_2$] 327.1259, found: 327.1259.

Synthesis of 6-methyl-6*H*-benzo[4,5]furo[2,3-*b*]indole (84d)



Prepared according to **TP2** from 2-(benzo[b]furan-3-yl)-*N*-methylaniline **82i** (223 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84d** as a white solid (110 mg, 50%).

mp: 102.2-102.7 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3046, 2922, 1880, 1622, 1561, 1509, 1453, 1443, 1399, 1319, 1279, 1177, 1147, 1097, 1006, 962, 922, 915 734.

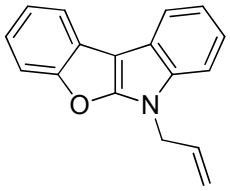
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.89-7.79 (m, 2H, Ar*H*), 7.56 (d, ^{3}J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.44-7.19 (m, 5H, Ar*H*), 3.94 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.1, 137.9, 125.3, 123.6, 120.9, 120.6, 119.1, 118.6, 29.1.

MS (70 eV, EI): *m/z* (%) = 221 (95), 220 (16), 207 (12), 206 (75), 192 (13), 178 (11), 177 (22), 166 (15), 165 (100), 151 (25), 149 (23), 110 (50), 95 (10), 57 (12).

HRMS (EI): *m/z* calc. for [$C_{15}H_{11}NO$] 221.0841, found: 221.0830.

Synthesis of 6-allyl-6*H*-benzo[4,5]furo[2,3-*b*]indole (84e)



Prepared according to **TP2** from *N*-allyl-2-(benzo[b]furan-3-yl)aniline **82j** (249 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84e** as a white solid (172 mg, 70%).

mp: 102.7-103.0 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2918, 1621, 1555, 1505, 1445, 1398, 1356, 1247, 1159, 1143, 986, 926, 771, 731.

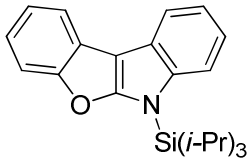
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.94-7.83 (m, 2H, Ar*H*), 7.60 (d, ^{3}J(H,H) = 7.9 Hz, 1H, Ar*H*), 7.44-7.23 (m, 5H, Ar*H*), 6.17-6.04 (m, 1H, C*H*=CH_2), 5.32-5.20 (m, 2H, CH=CH_2), 4.95-4.90 (m, 2H, N-CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.0, 156.7, 137.3, 132.1, 125.2, 123.7, 121.1, 120.9, 120.8, 120.7, 119.3, 118.6, 117.7, 111.7, 110.5, 97.9, 45.6.

MS (70 eV, EI): *m/z* (%) = 247 (54), 207 (12), 206 (100).

HRMS (EI): *m/z* calc. for [$C_{17}H_{13}NO$] 247.0997, found: 247.0984.

Synthesis of 6-(triisopropylsilyl)-6*H*-benzo[4,5]furo[2,3-*b*]indole (84f)



Prepared according to **TP2** from *N*-(2-benzo[b]furan-3-yl)phenyl-1,1,1-triisopropylsilanamine **82k** (365 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84f** as a white solid (294 mg, 81%).

mp: 109.2-109.8 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 2949, 2864, 1622, 1547, 1507, 1447, 1424, 1392, 1207, 1188, 1166, 1151, 1009, 881, 761.

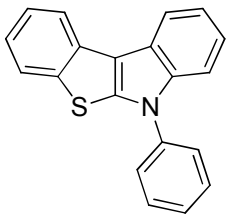
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, ^3J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.86 (d, ^3J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.68 (d, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 7.60 (d, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 7.43-7.24 (m, 4H, Ar*H*), 2.09 (7, ^3J(H,H) = 7.5 Hz, 3H, C*H*Me$_2$), 1.28 (d, ^3J(H,H) = 7.5 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.7, 156.7, 141.9, 123.5, 123.8, 123.5, 121.2, 121.0, 120.7, 118.8, 118.4, 114.8, 111.5, 100.8, 18.2, 12.9.

MS (70 eV, EI): *m/z* (%) = 364 (35), 363 (100), 207 (50), 115 (20), 73 (20), 59 (30), 57 (30), 44 (42).

HRMS (EI): *m/z* calc. for [$C_{23}H_{29}NO^{28}Si$] 363.2018, found: 363.2012.

Synthesis of 6-phenyl-6*H*-benzo[4,5]thieno[2,3-*b*]indole (84g)



Prepared according to **TP2** from 2-(benzo[b]thiophen-3-yl)-*N*-phenylaniline **82e** (301 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84g** as a white solid (242 mg, 81%).

mp: 137.1-137.5 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050, 2923, 2849, 1921, 1884, 1847, 1591, 1499, 1436, 1399, 1376, 1323, 1299, 1283, 1257, 1202, 1162, 1075, 1020, 946, 915, 849, 741, 720, 690, 630.

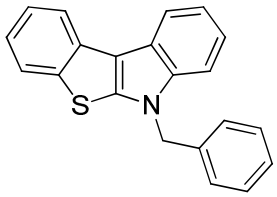
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.17-8.10 (m, 2H, Ar*H*), 7.83 (d, ^{3}J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.76-7.73 (m, 2H, Ar*H*), 7.66-7.61 (m, 3H, Ar*H*), 7.56-7.45 (m, 2H, Ar*H*), 7.40-7.29 (m, 3H, Ar*H*).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 142.8, 141.4, 138.8, 137.9, 133.1, 130.3, 127.6, 125.5, 124.3, 123.8, 123.6, 122.8, 122.5, 121.3, 120.9, 119.2, 118.9, 110.9.

MS (70 eV, EI): *m/z* (%) = 300 (18), 299 (100), 196 (7), 149 (6).

HRMS (EI): *m/z* calc. for [$C_{20}H_{13}N^{32}S$] 299.0769, found: 299.0772.

Synthesis of 6-benzyl-6*H*-benzo[4,5]thieno[2,3-*b*]indole (84h)



Prepared according to **TP2** from 2-(benzo[b]thiophen-3-yl)-*N*-benzylaniline **82f** (315 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84h** as a white solid (181 mg, 58%).

mp: 120.3-120.6 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 334, 2923, 1605, 1586, 1494, 1460, 1447, 1428, 1402, 1389, 1354, 1333, 1223, 1178, 1139, 1086, 1015, 994, 946, 928, 846, 784, 744, 720, 688, 656.

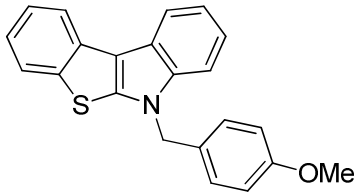
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.10 (d, ^{3}J(H,H) = 7.4 Hz, 1H, Ar*H*), 8.06 (d, ^{3}J(H,H) = 7.5 Hz, 1H, Ar*H*), 7.77 (d, ^{3}J(H,H) = 7.4 Hz, 1H, Ar*H*), 7.49-7.44 (m, 2H, Ar*H*), 7.34-7.23 (m, 8H, Ar*H*), 5.44 (s, 2H, CH_2).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 143.1, 141.7, 138.6, 135.8, 133.2, 129.1, 128.3, 127.7, 125.3, 123.8, 123.1, 122.3, 121.9, 120.8, 120.5, 119.2, 117.6, 109.9, 50.1.

MS (70 eV, EI): *m/z* (%) = 314 (27), 313 (100), 223 (13), 222 (80), 91 (64).

HRMS (EI): *m/z* calc. for [$C_{21}H_{15}N^{32}S$] 313.0925, found: 313.0931.

Synthesis of 6-(4-methoxybenzyl)-6*H*-benzo[4,5]thieno[2,3-*b*]indole (84i)



Prepared according to **TP2** from 2-(benzo[b]thiophen-3-yl)-*N*-(4-methoxybenzyl)aniline **82g** (345 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84i** as a red solid (240 mg, 70%).

mp: 116.2-116.6 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052, 2952, 2928, 2832, 1612, 1588, 1512, 1504, 1496, 1456, 1436, 1404, 1388, 1332, 1304, 1244, 1176, 1152, 1112, 1084, 1032, 1020, 948, 928, 812, 760, 740, 724, 656.

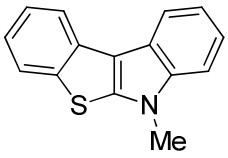
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.12 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 8.09-8.07 (m, 1H, Ar*H*), 7.77 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.51-7.56 (m, 2H, Ar*H*), 7.35-7.33 (m, 2H, Ar*H*), 7.28-7.25 (m, 1H, Ar*H*), 7.22 (d, ^3J(H,H) = 8.7 Hz, 2H, Ar*H*), 6.87 (d, ^3J(H,H) = 8.5 Hz, 2H, Ar*H*), 5.33 (s, 2H, CH_2), 3.78 (s, 3H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 159.5, 142.7, 141.5, 138.5, 133.0, 129.1, 127.5, 125.1, 123.6, 122.8, 122.0, 121.6, 120.5, 120.2, 118.9, 117.4, 114.3, 109.7, 55.3, 49.4.

MS (70 eV, EI): *m/z* (%) = 343 (27), 223 (10), 121 (100), 43 (12).

HRMS (EI): *m/z* calc. for [$C_{22}H_{17}NO^{32}S$] 343.1031, found: 343.1014.

Synthesis of 6-methyl-6*H*-benzo[4,5]thieno[2,3-*b*]indole (84j)



Prepared according to **TP2** from 2-(benzo[b]thiophen-3-yl)-*N*-methylaniline **82l** (239 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84j** as a white solid (211 mg, 89%).

mp: 131.9-132.2 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050, 1588, 1491, 1468, 1418, 1403, 1318, 1326, 1305, 1275, 1254, 1184, 1132, 1119, 1085, 1014, 946, 739.

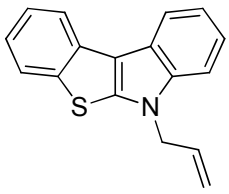
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.09 (d, ^{3}J(H,H) = 7.3 Hz, 1H, Ar*H*), 8.02 (d, ^{3}J(H,H) = 7.3 Hz, 1H, Ar*H*), 7.83 (d, ^{3}J(H,H) = 7.2 Hz, 1H, Ar*H*), 7.49 (t, ^{3}J(H,H) = 7.6 Hz, 1H, Ar*H*), 7.42 (d, ^{3}J(H,H) = 7.4 Hz, 1H, Ar*H*), 7.35-7.25 (m, 3H, Ar*H*), 3.90 (s, 3H, CH_3) .

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 143.5, 141.8, 138.0, 133.3, 125.1, 123.7, 122.6, 121.8, 121.4, 120.5, 120.0, 118.8, 116.6, 109.2, 32.3.

MS (70 eV, EI): *m/z* (%) = 238 (15), 237 (100), 222 (34), 149 (18), 118 (18), 69 (12), 57 (14), 55 (10), 44 (30), 43 (21).

HRMS (EI): *m/z* calc. for [$C_{15}H_{11}N^{32}S$] 237.0612, found: 237.0603.

Synthesis of 6-allyl-6*H*-benzo[4,5]thieno[2,3-*b*]indole (84k)



Prepared according to **TP2** from *N*-allyl-2-(benzo[b]thiophen-3-yl)aniline **82m** (265 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84k** as a white solid (163 mg, 62%).

mp: 63.4-64.0 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050, 2918, 1760, 1588, 1493, 1433, 1383, 1325, 1219, 1148, 1082, 1016, 992, 929, 842, 739.

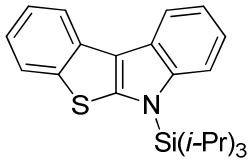
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.14-8.05 (m, 2H, Ar*H*), 7.83 (d, ^{3}J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.53-7.26 (m, 5H, Ar*H*), 6.12-6.03 (m, 1H, C*H*=CH_2), 5.35-5.23 (m, 2H, CH=CH_2), 4.89-4.86 (m, 2H, N-CH_2).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 142.6, 141.3, 138.3, 133.0, 131.5, 125.1, 123.6, 122.8, 122.0, 121.5, 120.6, 120.1, 118.9, 118.6, 117.3, 109.6, 48.6.

MS (70 eV, EI): *m/z* (%) = 264 (12), 263 (68), 222 (90), 58 (35), 44 (72), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{17}H_{13}N^{32}S$] 263.0769, found: 263.0768.

Synthesis of 6-(triisopropylsilyl)-6*H*-benzo[4,5]thieno[2,3-*b*]indole (84l)



Prepared according to **TP2** from *N*-(2-(benzo[b]thiophen-3-yl)phenyl)-1,1,1-triisopropylsilanamine **82n** (381 mg, 1.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **84l** as a colorless oil (269 mg, 71%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050, 2927, 1607, 1588, 1491, 1468, 1440, 1418, 1403, 1326, 1275, 1254, 1184, 1145, 1049, 1014, 849, 786, 739.

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 8.07 (d, ^3J(H,H) = 8.6 Hz, 1H, Ar*H*), 7.80 (d, ^3J(H,H) = 8.1 Hz, 1H, Ar*H*), 7.68 (d, ^3J(H,H) = 8.6 Hz, 1H, Ar*H*), 7.48 (t, ^3J(H,H) = 7.15 Hz, 1H, Ar*H*), 7.32-7.23 (m, 3H, Ar*H*), 2.00 (7, ^3J(H,H) = 7.6 Hz, 3H, C*H*Me$_2$), 1.23 (d, ^3J(H,H) = 7.6 Hz, 18H, CH_3).

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 146.5, 146.4, 138.5, 131.8, 125.6, 124.8, 122.8, 122.3, 121.4, 121.0, 120.5, 120.3, 118.5, 114.3, 18.4, 13.6.

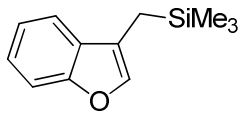
MS (70 eV, EI): *m/z* (%) = 381 (11), 380 (31), 379 (100), 227 (12), 336 (52), 208 (11), 294 (15), 266 (11), 149 (11), 140 (12), 115 (19), 87 (15), 73 (16), 59 (30), 58 (17), 44 (21), 43 (44).

HRMS (EI): *m/z* calc. for [$C_{23}H_{29}N^{32}S^{28}Si$] 379.1790, found: 379.1774.

3.2. Preparation and Reactions of Heteroaromatic Benzylic Zinc Compounds

3.2.1. Preparation of starting materials

Synthesis of (benzo[b]furan-3-ylmethyl)(trimethyl)silane (89)



To a flask containing 3-bromobenzo[b]furan (1.97 g, 10 mmol, 1.0 equiv), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 1 mol%), S-Phos (82 mg, 0.2 mmol, 2 mol%) and anhydrous THF (10 mL), a solution of (trimethylsilyl)methylzinc chloride (20 mmol, 2.0 equiv) was added dropwise at 25 °C. The resulting mixture was stirred for 10 h, quenched with H_2O and extracted with Et_2O (3 x 25 mL), the organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane) afforded **89** as a colorless oil (1.77 g, 87%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 1452, 1408, 1281, 1247, 1185, 1110, 1084, 855, 839, 741.

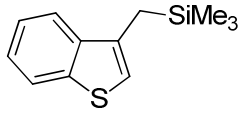
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.52-7.46 (m, 2H, Ar*H*), 7.34-7.22 (m, 3H, Ar*H*), 2.05 (s, 2H, C*H*$_2$), 0.08 (s, 9H, Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.1, 139.8, 129.0, 123.8, 121.9, 119.8, 117.6, 111.2, 12.1, -1.5.

MS (70 eV, EI): *m/z* (%) = 204 (34), 115 (10), 97 (11), 85 (19), 83 (12), 73 (100), 71 (27), 69 (12), 57 (38), 55 (16), 44 (19), 43 (21), 41 (12).

HRMS (EI): *m/z* calc. for [$C_{12}H_{16}O^{28}Si$] 204.0970, found: 204.0966.

Synthesis of (benzo[b]thiophen-3-ylmethyl)(trimethyl)silane (90)



To a flask containing 3-bromobenzo[b]thiophene (2.13 g, 10 mmol, 1.0 equiv), $Pd(OAc)_2$ (22 mg, 0.1 mmol, 1 mol%), S-Phos (82 mg, 0.2 mmol, 2 mol%) and anhydrous THF (10 mL), a solution of (trimethylsilyl)methylzinc chloride (20 mmol, 2.0 equiv) was added dropwise at 25 °C. The resulting mixture was stirred for 10 h, quenched with H_2O and extracted with Et_2O (3 x 25 mL), the organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane) afforded **90** as a colorless oil (2.09 g, 95%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068, 2953, 2892, 1427, 1353, 1248, 1161, 1075, 857, 839, 759.

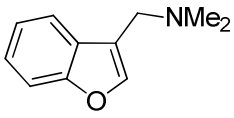
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, ^3J(H,H) = 7.0 Hz, 1H, Ar*H*), 7.70 (d, ^3J(H,H) = 7.2 Hz, 1H, Ar*H*), 7.37 (5, ^3J(H,H) = 7.0 Hz, 2H, Ar*H*), 6.89 (s, 1H, Ar*H*), 2.36 (s, 2H, CH_2), 0.06 (s, 9H, Si(CH_3)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.2, 139.3, 134.3, 123.8, 123.4, 122.7, 122.1, 118.3, 18.7, -1.3.

MS (70 eV, EI): *m/z* (%) = 220 (33), 83 (10), 73 (100), 69 (11), 57 (17), 55 (15), 44 (61), 43 (10), 40 (10).

HRMS (EI): *m/z* calc. for [$C_{12}H_{16}{}^{32}S^{28}Si$] 220.0742, found: 220.0738.

Synthesis of (benzo[b]furan-3-ylmethyl)dimethylamine (106)



To a solution of 3-bromobenzo[b]furan (1.97 g, 10.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) at –55 °C was added *i*PrMgCl·LiCl (11.0 mmol, 1.1 equiv) and the resulting mixture was stirred at –55 °C for 24 h. The resulting solution of benzo[b]furan-3-ylmagnesium chloride was then

reacted according to **TP3**. Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **106** as a colorless oil (1.22 g, 70%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2973, 2858, 2815, 2767, 1583, 1451, 1185, 1151, 1095, 1020, 850, 801, 742.

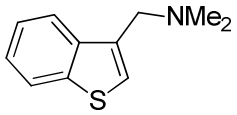
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, ^3J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.60 (s, 1H, Ar*H*), 7.50 (d, ^3J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.34-7.25 (m, 2H, Ar*H*), 3.63 (s, 2H, CH_2), 2.35 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.4, 143.3, 127.9, 124.3, 122.6, 120.2, 117.1, 111.4, 52.9, 45.2.

MS (70 eV, EI): *m/z* (%) = 175 (19), 174 (14), 167 (36), 149 (80), 132 (32), 131 (69), 119 (10), 113 (10), 83 (13), 77 (15), 71 (16), 70 (19), 69 (20), 57 (29), 55 (20), 44 (100), 43 (21), 41 (23).

HRMS (EI): *m/z* calc. for [$C_{11}H_{13}NO$] 175.0997, found: 175.1000.

Synthesis of (benzo[b]thiophen-3-ylmethyl)dimethylamine (107)



To a solution of 3-bromobenzo[b]thiophene (2.13 g, 10.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) at –15 °C was added *i*PrMgCl·LiCl (11.0 mmol, 1.1 equiv) and the resulting mixture was stirred at –55 °C for 12 h. The resulting solution of benzo[b]thiophen-3-ylmagnesium chloride was then reacted according to **TP3**. Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **107** as a yellow oil (1.49 g, 78%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2973, 2942, 2814, 2768, 1680, 1454, 1426, 1354, 1255, 1173, 1092, 1041, 1017, 942, 755, 731.

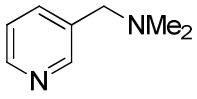
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, ^3J(H,H) = 7.0 Hz, 1H, Ar*H*), 7.88 (d, ^3J(H,H) = 7.0 Hz, 1H, Ar*H*), 7.44-7.31 (m, 3H, Ar*H*), 3.72 (s, 2H, CH_2), 2.34 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.5, 138.9, 133.5, 124.5, 124.3, 124.0, 122.7, 122.4, 57.6, 45.4.

MS (70 eV, EI): *m/z* (%) = 191 (31), 190 (13), 148 (35), 147 (100).

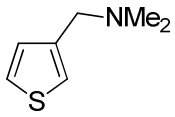
HRMS (EI): *m/z* calc. for [$C_{11}H_{13}N^{32}S$] 191.0769, found: 191.0758.

Synthesis of *N*,*N*-dimethyl-1-pyridin-3-ylmethanamine (108)



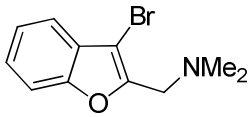
Prepared according to **TP3** from 3-pyridylmagnesium bromide obtained *via* Mg insertion into 3-bromopyridine (8.6 g, 50.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane/Et_2O = 1:1, detection using I_2 chamber) afforded **108** as a colorless oil (4.7 g, 68%). Spectral data were in full accordance with those reported in the literature: Fischer, A.; Murray, J. K.; Robinson, F. P. *Can. J. Chem.* **1978**, *56*, 3068-3071.

Synthesis of dimethyl(3-thienylmethyl)amine (109)



Prepared according to **TP3** from 3-thienylmagnesium bromide obtained *via* Mg insertion into 3-bromothiophene (8.15 g, 50.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane/Et_2O = 1:1, detection using I_2 chamber) afforded **109** as a colorless oil (4.23 g, 60%). Spectral data were in full accordance with those reported in the literature: Cooper, M. S.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1989,** *45*, 1155-66.

Synthesis of [(3-bromobenzo[b]furan-2-yl)methyl]dimethylamine (110)



To a solution of 3-bromobenzo[b]furan (1.38 g, 7.0 mmol, 1.0 equiv) in anhydrous THF (7 mL) at –78 °C was added TMPMgCl·LiCl (7.7 mmol, 1.1 equiv) and the resulting mixture was stirred at –78 °C for 1 h. The so obtained solution of 3-bromobenzo[b]furan-2-ylmagnesium chloride

was then reacted according to **TP3**. Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **110** as a yellow oil (1.24 g, 70%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972, 2858, 2772, 1675, 1614, 1449, 1366, 1245, 1184, 1143, 1106, 1033, 1015, 1004, 965, 841, 743.

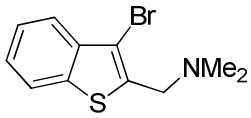
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.54-7.48 (m, 2H, Ar*H*), 7.36-7.32 (m, 2H, Ar*H*), 3.74 (s, 2H, CH_2), 2.39 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 153.9, 151.2, 127.8, 125.4, 123.3, 119.7, 111.6, 97.8, 53.8, 45.1.

MS (70 eV, EI): *m/z* (%) = 255 (18), 253 (28), 211 (100), 209 (85), 174 (30), 131 (11), 102 (19).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}NO_3$] 253.0102, found: 253.0097.

Synthesis of 1-(3-bromobenzo[b]thiophen-2-yl)-*N*,*N*,-dimethylmethanamine (111)



To a solution of 3-bromobenzo[b]thiophene (1.06 g, 5.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) at –78 °C was added TMPMgCl·LiCl (5.5 mmol, 1.1 equiv) and the resulting mixture was stirred at –78 °C for 1 h. The so obtained solution of 3-bromobenzo[b]furan-2-ylmagnesium chloride was then reacted according to **TP3**. Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **111** as a yellow oil (1.05 g, 78%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 2819, 2772, 1670, 1453, 1434, 1350, 1248, 1169, 1141, 1126, 1096, 1028, 1020, 917, 749, 725.

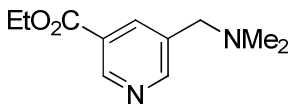
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, ^3J(H,H) = 8.5 Hz, 2H, Ar*H*), 7.44-7.34 (m, 2H, Ar*H*), 3.82 (s, 2H, CH_2), 2.37 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 138.5, 136.1, 137.9, 125.2, 124.8, 122.8, 122.5, 106.6, 57.9, 45.5.

MS (70 eV, EI): *m/z* (%) = 271 (46), 270 (18), 269 (43), 268 (13), 241 (11), 239 (11), 228 (10), 227 (100), 225 (98), 190 (75), 147 (35), 146 (22), 145 (22), 102 (20), 58 (35).

HRMS (EI): *m/z* calc. for [$C_{11}H_{12}{}^{79}BrN^{32}S$] 268.9874, found: 268.9863.

Synthesis of ethyl 5-[(dimethylamino)methyl]nicotinate (112)



A solution of ethyl 5-bromonicotinate (2.30 g, 10.0 mmol, 1.0 equiv) in THF (5 mL) was added to a flask containing THF (5 mL), LiCl (634 mg, 15.0 mmol, 1.5 equiv) and Zn dust (979 mg, 15.0 mmol, 1.5 equiv) which had previously been activated using 1,2-dibromoethane and chlorotrimethylsilane as described in **TP5**. The resulting suspension was stirred at 25 °C for 12 h after which TLC of the crude mixture showed complete consumption of the starting material. The so obtained solution of 5-ethoxycarbonylpyridin-3-ylzinc chloride was reacted according to **TP3**. Purification of the crude product by flash chromatography (SiO_2, MeOH) afforded **112** as a yellow viscous oil (1.31 g, 63%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979, 2820, 2774, 1722, 1599, 1456, 1367, 1291, 1205, 1105, 1027, 765.

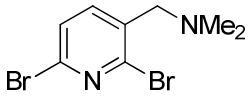
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.10 (s, 1H, Ar*H*), 8.69 (s, 1H, Ar*H*), 8.25 (m, 1H, Ar*H*), 4.40 (q, ^{3}J(H,H) = 7.0 Hz, 2H, ethyl CH_2), 3.51 (s, 2H, CH_2), 2.27 (s, 6H, N(CH_3)$_2$), 1.40 (t, ^{3}J(H,H) = 7.1 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 165.3, 153.9, 149.8, 137.5, 133.8, 126.1, 61.4, 60.9, 45.1, 12.3.

MS (70 eV, EI): *m/z* (%) = 208 (53), 207 (19), 179 (16), 164 (10), 163 (10), 120 (20), 58 (100).

HRMS (EI): *m/z* calc. for [$C_{11}H_{16}N_2O_2$] 208.1212, found: 208.1187.

Synthesis of 1-(2,6-dibromopyridin-3-yl)-*N*,*N*-dimethylmethanamine (113)



To a solution of 2,3,6-tribromopyridine (4.74 g, 15.0 mmol, 1.0 equiv) in anhydrous THF (15 mL) at 25 °C was added *i*PrMgCl·LiCl (16.5 mmol, 1.1 equiv) and the resulting mixture was stirred for 2 h. The so obtained solution of 2,6-dibromopyridin-3-ylmagnesium chloride was then

reacted according to **TP3**. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 1:1) afforded **113** as a yellow oil (2.90 g, 66%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3391, 2932, 1660, 1598, 1568, 1539, 1504, 1419, 1382, 1351, 1255, 1219, 1110, 1058, 1042, 964, 851, 808.

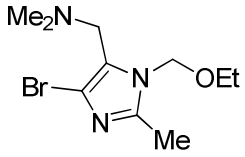
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.45 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 3.47 (s, 2H, CH_2), 2.30 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 142.2, 140.7, 138.5, 135.1, 127.2, 61.5, 45.5.

MS (70 eV, EI): *m/z* (%) = 294 (13), 250 (11), 58 (100).

HRMS (EI): *m/z* calc. for [$C_8H_{10}{}^{79}Br_2N_2$] 291.9211, found: 291.9200.

Synthesis of 1-[4-bromo-1-(ethoxymethyl)-2-methyl-1*H*-imidazol-5-yl]-*N*,*N*-dimethyl-methanamine (114)



To a solution of 4,5-dibromo-1-(ethoxymethyl)-2-methyl-1*H*-imidazole (5.34 g, 18.0 mmol, 1.0 equiv) in anhydrous THF (18 mL) at 25 °C was added *i*PrMgCl·LiCl (19.8 mmol, 1.1 equiv) and the resulting mixture was stirred for 1 h. The so obtained solution of 5-dibromo-1-(ethoxymethyl)-2-methyl-1*H*-imidazol-4-ylmagnesium chloride was then reacted according to **TP3**. Purification of the crude product by filtrating through a pad of silica afforded **114** as a yellow viscous oil (4.62 g, 93%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2942, 2898, 2862, 2818, 2770, 1509, 1455, 1413, 1385, 1358, 1215, 1177, 1103, 1087, 1013, 842, 768, 748.

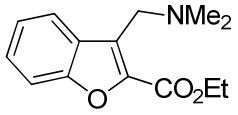
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.36 (s, 2H, NC*H*2OEt), 3.50 (q, ^3J(H,H) = 7.1 Hz, 2H, ethyl CH_2), 3.41 (s, 2H, C*H*2NMe$_2$), 2.45 (s, 3H, aryl CH_3), 2.23 (s, 6H, N(CH_3)$_2$), 1.20 (t, ^3J(H,H) = 7.1 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 146.2, 125.6, 115.4, 73.4, 63.9, 52.1, 44.9, 14.9, 13.4.

MS (70 eV, EI): *m/z* (%) = 251 (26), 233 (26), 232 (11), 93 (15), 59 (100), 58 (34), 42 (14).

HRMS (EI): *m/z* calc. for [$C_{10}H_{18}{}^{79}BrN_3O$] 275.0633, found: 275.0619.

Synthesis of ethyl 3-[(dimethylamino)methyl]benzo[b]furan-2-carboxylate (115)



To a solution of (benzo[b]furan-3-ylmethyl)dimethylamine **106** (437 mg, 2.5 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) at 0 °C was added TMPMgCl·LiCl (2.75 mmol, 1.1 equiv) and the resulting mixture was stirred at 0 °C for 30 min. Then, neat ethyl cyanocarbonate (222 mg, 2.25 mmol, 0.9 equiv) was added portionwise and stirring was continued at 0 °C for 1 h. The reaction mixture was quenched with H_2O, extracted with EtOAc (3 x 25 mL), the combined organic layers washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **115** as a colorless oil (400 mg, 72%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2977, 2819, 1710, 1678, 1594, 1448, 1394, 1376, 1351, 1293, 1261, 1223, 1173, 1142, 1091, 1020, 855, 745.

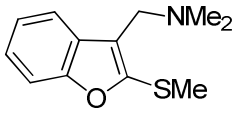
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, ^3J(H,H) = 7.3 Hz, 1H, Ar*H*), 7.57 (d, ^3J(H,H) = 8.5 Hz, 1H, Ar*H*), 7.46 (t, ^3J(H,H) = 7.3 Hz, 1H, Ar*H*), 7.32 (t, ^3J(H,H) = 7.8 Hz, 1H, Ar*H*), 4.47 (q, ^3J(H,H) = 7.3 Hz, 2H, ethyl CH_2), 4.03 (s, 2H, CH_2), 2.37 (s, 6H, N(CH_3)$_2$), 1.48 (t, ^3J(H,H) = 7.3 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.2, 154.5, 142.0, 128.4, 127.7, 126.1, 123.8, 122.7, 112.1, 61.4, 52.6, 45.6, 14.3.

MS (70 eV, EI): *m/z* (%) = 247 (29), 233 (10), 232 (63), 219 (14), 218 (100), 204 (11), 186 (17), 175 (50), 131 (10), 44 (16).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}NO_3$] 247.1208, found: 247.1205.

Synthesis of *N*,*N*-dimethyl-1-[2-(methylsulfanyl)benzo[b]furan-3-yl]methanamine (116)



(Note: The preparation of this compound must be carried out in a well-ventilated fume hood, as it possesses an extraordinarily repulsive smell.) To a solution of (benzo[b]furan-3-ylmethyl)dimethylamine **106** (437 mg, 2.5 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) at 0 °C was added TMPMgCl·LiCl (2.75 mmol, 1.1 equiv) and the resulting mixture was stirred at 0 °C for 30 min. Then, neat *S*-methyl methanesulfonothioate (284 mg, 2.25 mmol, 0.9 equiv) was added portionwise and stirring was continued at 0 °C for 1 h. The reaction mixture was quenched with H_2O, extracted with EtOAc (3 x 25 mL), the combined organic layers washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 8:1) afforded **116** as a yellow oil (458 mg, 83%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2940, 2856, 2813, 2764, 1677, 1446, 1351, 1332, 1313, 1266, 1228, 1177, 1150, 1131, 1086, 1016, 843, 740.

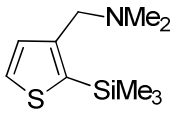
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.44 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.29-7.24 (m, 2H, Ar*H*), 3.64 (s, 2H, CH_2), 2.52 (s, 3H, SCH_3), 2.30 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.5, 149.2, 129.1, 124.4, 122.7, 120.2, 119.7, 110.7, 53.5, 45.5, 17.4.

MS (70 eV, EI): *m/z* (%) = 221 (31), 178 (12), 177 (100), 144 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{15}NO^{32}S$] 221.0874, found: 221.0865.

Synthesis of *N*,*N*-dimethyl-1-[2-(trimethylsilyl)thiophen-3-yl]methanamine (117)



To a solution of dimethyl(3-thienylmethyl)amine **109** (423 mg, 3.0 mmol, 1.0 equiv) in anhydrous THF (3 mL) at –78 °C was added *n*BuLi (3.3 mmol, 1.1 equiv) and the resulting

mixture was stirred at –78 °C for 1 h. Then, neat chlorotrimethylsilane (291 mg, 2.7 mmol, 0.9 equiv) was added and the cooling was removed. Stirring continued for 30 min, after which the reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 1:1) afforded **117** as a yellow oil (576 mg, 71%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 1667, 1469, 1455, 1404, 1249, 1165, 1095, 1013, 835, 755.

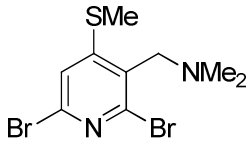
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, ^3J(H,H) = 4.6 Hz, 1H, Ar*H*), 7.23 (d, ^3J(H,H) = 4.6 Hz, 1H, Ar*H*), 3.49 (s, 2H, CH_2), 2.24 (s, 6H, N(CH_3)$_2$), 0.37 (s, 9H, Si(CH_3)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.6, 135.2, 130.8, 129.3, 59.4, 45.4, 0.4.

MS (70 eV, EI): *m/z* (%) = 213 (11), 212 (16), 170 (13), 169 (24), 168 (10), 155 (11), 73 (34), 58 (32), 57 (11), 44 (35), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{10}H_{19}N^{32}S^{28}Si$] 231.1007, found: 231.0995.

Synthesis of 1-[2,6-dibromo-4-(methylsulfanyl)pyridin-3-yl]-*N*,*N*-dimethylmethanamine (118)



To a solution of 1-(2,6-dibromopyridin-3-yl)-*N*,*N*-dimethylmethanamine **113** (2.20 g, 7.5 mmol, 1.0 equiv) in anhydrous THF (7.5 mL) at 25 °C was added TMPMgCl·LiCl (8.25 mmol, 1.1 equiv) and the resulting mixture was stirred at 25 °C for 1 h. Then, neat *S*-methyl methanesulfonothioate (850 mg, 6.75 mmol, 0.9 equiv) was added portionwise and stirring was continued for 1 h. The reaction mixture was quenched with H_2O, extracted with EtOAc (3 x 25 mL), the combined organic layers washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 1:1) afforded **118** as a brown solid (1.99 g, 78%).

mp: 125.3-127.3 °C (decomp.).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2851, 2811, 2754, 1541, 1502, 1448, 1398, 1331, 1320, 1267, 1251, 1235, 1170, 1087, 1023, 964, 841, 766, 747.

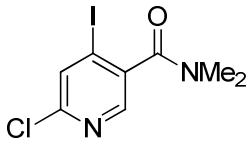
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.20 (s, 1H, Ar*H*), 3.64 (s, 2H, CH_2), 2.49 (s, 3H, SCH_3), 2.33 (s, 6H, N(CH_3)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.3, 142.8, 138.9, 130.4, 121.7, 59.6, 45.0, 15.4.

MS (70 eV, EI): *m/z* (%) = 341 (15), 340 (27), 339 (11), 338 (15), 327 (38), 325 (78), 323 (39), 296 (11), 217 (13), 215 (14), 136 (12), 58 (100), 46 (12), 44 (12), 43 (17), 42 (18).

HRMS (EI): *m/z* calc. for [$C_9H_{12}{}^{79}Br_2N_2{}^{32}S$] 337.9088, found: 337.9044.

Synthesis of 4-chloro-2-iodo-*N*,*N*-dimethylnicotinamide (120)



To a solution of 6-chloro-*N*,*N*-dimethylnicotinamide (184 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) at –40 °C was added TMPMgCl·LiCl (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –40 °C for 2 h. Then, neat iodine (380 mg, 1.5 mmol, 1.5 equiv) was added at once, cooling was removed and the resulting solution was allowed to warm up to 25 °C. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, EtOAc) afforded **120** as a white solid (251 mg, 81%).

mp: 131.0-132.7 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3066, 2923, 1620, 1553, 1537, 1526, 1504, 1440, 1399, 1301, 1257, 1114, 1099, 929, 903, 788, 747.

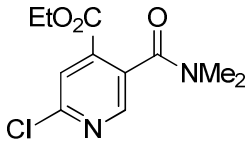
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.18 (s, 1H, Ar*H*), 7.87 (s, 1H, Ar*H*), 3.17 (s, 3H, CH_3), 2.90 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.4, 151.3, 146.3, 137.9, 133.9, 105.6, 38.4, 34.9.

MS (70 eV, EI): *m/z* (%) = 311 (19), 309 (45), 274 (62), 267 (34), 265 (100), 238 (31), 177 (14), 77 (11), 76 (11), 72 (11), 58 (34), 50 (19), 43 (93), 42 (20).

HRMS (EI): *m/z* calc. for [$C_8H_8{}^{35}ClIN_2O$] 309.9370, found: 309.9333.

Synthesis of ethyl 2-chloro-5-(dimethylcarbamoyl)isonicotinate (121)



To a solution of 6-chloro-*N*,*N*-dimethylnicotinamide (184 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) at –40 °C was added TMPMgCl·LiCl (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –40 °C for 2 h. Then, neat ethyl chloroformate (118 mg, 1.1 mmol, 1.1 equiv) was added dropwise, cooling was removed and the resulting solution was allowed to warm up to 25 °C. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **121** as a colorless oil (203 mg, 79%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3081, 2908, 1724, 1633, 1580, 1548, 1404, 1368, 1335, 1267, 1254, 1135, 1106, 1058, 1013, 927, 897, 801, 776.

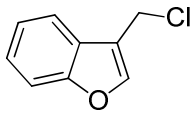
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 1H, Ar*H*), 7.87 (s, 1H, Ar*H*), 4.40 (q, ^3J(H,H) = 7.2 Hz, 2H, ethyl CH_2), 3.16 (s, 3H, NCH_3), 2.85 (s, 3H, NCH_3), 1.39 (t, ^3J(H,H) = 7.2 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.3, 163.2, 152.3, 148.2, 137.8, 131.7, 124.4, 62.6, 38.5, 34.9, 14.0.

MS (70 eV, EI): *m/z* (%) = 255 (29), 221 (12), 213 (11), 186 (30), 184 (88), 58 (24), 44 (17), 43 (100).

HRMS (EI): *m/z* calc. for [$C_{11}H_{13}{}^{35}ClN_2O_3$] 256.0615, found: 256.0646.

Synthesis of 3-(chloromethyl)benzo[b]furan (127)



Prepared according to **TP4** from (benzo[b]furan-3-ylmethyl)dimethylamine **106** (1.75 g, 10.0 mmol, 1.0 equiv) and ethyl chloroformate (1.19 g, 11.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **127** as a colorless oil (1.28 g, 77%)

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3116, 3063, 2958, 1583, 1452, 1285, 1260, 1189, 1105, 855, 744.

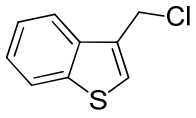
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.75-7.69 (m, 2H, Ar*H*), 7.54 (d, ^3J(H,H) = 7.0 Hz, 1*H*, Ar*H*), 7.37 (5, ^3J(H,H) = 7.0 Hz, 2H, Ar*H*), 4.79 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.6, 143.1, 126.3, 125.0, 119.9, 119.9, 117.7, 111.8, 36.2.

MS (70 eV, EI): *m/z* (%) = 166 (30), 131 (100), 103 (12).

HRMS (EI): *m/z* calc. for [$C_9H_7{}^{35}ClO$] 166.0185, found: 166.0171.

Synthesis of 3-(chloromethyl)benzo[b]thiophene (128)



Prepared according to **TP4** from (benzo[b]thiophen-3-ylmethyl)dimethylamine **107** (1.91 g, 10.0 mmol, 1.0 equiv) and ethyl chloroformate (1.19 g, 11.0 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, Et_2O) afforded **128** as a colorless oil (1.31 g, 72%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3109, 2950, 1582, 1410, 1375, 1301, 1300, 1350, 1153, 1078, 850, 720.

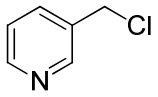
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.95-7.90 (m, 2H, Ar*H*), 7.51-7.41 (m, 3H, Ar*H*), 4.89 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.6, 137.3, 131.9, 126.3, 124.8, 124.5, 123.0, 121.9, 39.6.

MS (70 eV, EI): *m/z* (%) = 182 (23), 148 (12), 147 (100).

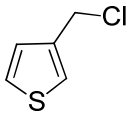
HRMS (EI): *m/z* calc. for [$C_9H_7{}^{35}Cl{}^{32}S$] 181.9957, found: 181.9945.

Synthesis of 3-(chloromethyl)pyridine (129)



Prepared according to **TP4** from *N*,*N*-dimethyl-1-pyridin-3-ylmethanamine **108** (1.36 g, 10.0 mmol) and ethyl chloroformate (1.19 g, 11.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **129** as a colorless oil (1.02 g, 80%). Spectral data were in full accordance with those reported in the literature: Ding, R.; He, Y.; Wang, X.; Xu, J.; Chen, Y.; Feng, M.; Qi, C. *Molecules* **2011**, *16*, 5665.

Synthesis of 3-(chloromethyl)thiophene (130)



Prepared according to **TP4** from dimethyl(3-thienylmethyl)amine **109** (1.41 g, 10.0 mmol) and ethyl chloroformate (1.19 g, 11.0 mmol). Purification of the crude product by flash chromatography (SiO_2, pentane) afforded **130** as a colorless oil (941 mg, 71%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101, 1416, 1264, 1240, 1162, 1137, 1081, 829, 787, 696, 671.

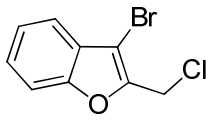
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.36-7.31 (m, 2H, Ar*H*), 7.15 (dd, ^3J(H,H) = 4.9 Hz, ^4J(H,H) = 1.2 Hz, 1H, Ar*H*), 4.65 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 138.1, 127.6, 126.7, 124.0, 40.7.

MS (70 eV, EI): *m/z* (%) = 134 (27), 132 (50), 128 (32), 98 (16), 97 (100), 83 (13), 74 (78), 59 (59), 45 (71), 44 (60), 43 (54), 41 (34).

HRMS (EI): *m/z* calc. for [$C_5H_5{}^{35}Cl{}^{32}S$] 131.9800, found: 131.9788.

Synthesis of 3-bromo-2-(chloromethyl)benzo[b]furan (131)



Prepared according to **TP4** from [(3-bromobenzo[b]furan-2-yl)methyl]dimethylamine **110** (762 mg, 3.0 mmol, 1.0 equiv) and ethyl chloroformate (358 mg, 3.3 mmol, 1.1 equiv). The only contaminant in the crude product was ethyl (*N*,*N*-dimethyl)carbamate which was removed in high vacuum over 5 hours. **131** was obtained as a yellow solid (597 mg, 81%).

mp: 73.2-74.7 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3209, 3056, 1720, 1612, 1462, 1445, 1421, 1318, 1283, 1256, 1192, 1144, 1107, 1019, 1003, 867, 843, 747, 710.

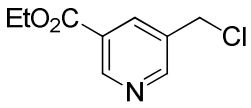
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.56-7.33 (m, 4H, Ar*H*), 4.80 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.1, 149.1, 127.6, 126.4, 123.8, 120.2, 111.8, 98.3, 35.6.

MS (70 eV, EI): *m/z* (%) = 246 (24), 244 (20), 232 (33), 211 (93), 209 (100), 149 (11), 102 (16).

HRMS (EI): *m/z* calc. for [$C_9H_6{}^{79}Br^{35}ClO$] 243.9291, found: 243.9292.

Synthesis of ethyl 5-(chloromethyl)nicotinate (132)



Prepared according to **TP4** from ethyl 5-[(dimethylamino)methyl]nicotinate **112** (1.04 g, 5.0 mmol, 1.0 equiv) and ethyl chloroformate (596 mg, 5.5 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, Et_2O:*n*-pentane = 4:1) afforded **132** as a yellow oil (676 mg, 68%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3373, 2989, 2938, 2361, 1723, 1637, 1495, 1465, 1444, 1370, 1311, 1223, 1140, 1113, 1017, 858, 760, 713.

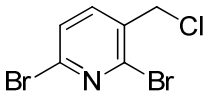
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.18 (s, 1H, Ar*H*), 8.79 (s, 1H, Ar*H*), 8.35 (s, 1H, Ar*H*), 4.66 (s, 2H, CH_2), 4.46 (q, ^{3}J(H,H) = 7.2 Hz, 2H, ethyl CH_2), 1.43 (t, ^{3}J(H,H) = 7.2 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 164.7, 152.9, 150.6, 137.1, 133.2, 126.4, 61.7, 42.5, 14.3.

MS (70 eV, EI): *m/z* (%) = 201 (11), 199 (33), 173 (19), 171 (63), 164 (20), 154 (100), 137 (10), 136 (33), 127 (11), 126 (34), 120 (14), 91 (16), 90 (12), 64 (13), 63 (20).

HRMS (EI): *m/z* calc. for [$C_9H_{10}{}^{35}ClNO_2$] 199.0400, found: 199.0304.

Synthesis of 2,6-dibromo-3-(chloromethyl)pyridine (133)



Prepared according to **TP4** from 1-(2,6-dibromopyridin-3-yl)-*N*,*N*-dimethylmethanamine **113** (1.46 g, 5.0 mmol, 1.0 equiv) and ethyl chloroformate (596 mg, 5.5 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (Al_2O_3, isohexane/Et_2O = 9:1) afforded **133** as white crystals (997 mg, 70%).

mp: 85.6-87.6 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3020, 1567, 1553, 1541, 1445, 1418, 1348, 1269, 1132, 1108, 1058, 904, 845, 829, 749.

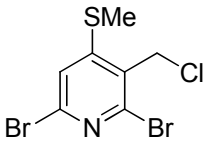
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.49 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 4.62 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 141.7, 140.3, 140.1, 133.4, 127.6, 43.8.

MS (70 eV, EI): *m/z* (%) = 250 (14), 58 (33), 43 (100).

HRMS (EI): *m/z* calc. for [$C_6H_4{}^{79}Br_2{}^{35}ClN$] 282.8399, found: 282.8393.

Synthesis of 2,6-dibromo-3-(chloromethyl)-4-(methylsulfanyl)pyridine (134)



Prepared according to **TP4** from 1-[2,6-dibromo-4-(methylsulfanyl)pyridin-3-yl]-*N*,*N*-dimethylmethanamine **118** (1.70 g, 5.0 mmol, 1.0 equiv) and ethyl chloroformate (596 mg, 5.5

mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, isohexane/Et_2O = 9:1) afforded **134** as colorless crystals (1.15 g, 70%).

mp: 108.9-110.8 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 1537, 1498, 1441, 1425, 1393, 1329, 1303, 1263, 1241, 1200, 1142, 1127, 1088, 911, 906, 833, 759.

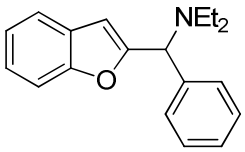
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.20 (s, 1H, Ar*H*), 4.77 (s, 2H, CH_2), 2.57 (s, 3H, SCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.6, 143.1, 140.4, 128.9, 121.6, 42.0, 15.0.

MS (70 eV, EI): *m/z* (%) = 333 (18), 331 (27), 329 (11), 298 (49), 297 (15), 296 (100).

HRMS (EI): *m/z* calc. for [$C_7H_6{}^{79}Br_2{}^{35}ClN^{32}S$] 328.8276, found: 328.8289.

Synthesis of *N*-[benzo[b]furan-2-yl(phenyl)methyl]-*N*-ethylethanamine (141)



To a solution of benzaldehyde *N,N,N',N'*-tetraethylaminal (234 mg, 1.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1 mL) at 0 °C was added neat trifluoroacetic anhydride (231 mg, 1.1 mmol, 1.1 equiv) and the resulting mixture was stirred for 30 min. Initially colorless, the solution turned over yellow to red during that time. The so generated solution of benzylidene(diethyl)iminium trifluoroacetate was then canulated to another flask containing a solution of benzofuran-2-ylzinc chloride (prepared by treating a 1 M solution of benzo[b]furan (118 mg, 1.0 mmol, 1.0 equiv) in THF (0.5 mL) with *n*BuLi (1.1 mmol, 1.1 equiv) for 15 min at –78 °C and transmetalating using anhydrous $ZnCl_2$ solution in THF (1.0 mmol, 1.0 equiv)). Cooling was removed and the resulting solution was stirred for 1 h. The reaction mixture was quenched using sat. aq. $NaHCO_3$, extracted with EtOAc (3 x 25 mL), and the combined organic extracts were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **141** as a colorless oil (237 mg, 85%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2969, 2819, 1651, 1545, 1452, 1297, 1277, 1252, 1161, 1114, 971, 801, 741, 722, 697.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.58-7.51 (m, 4H, Ar*H*), 7.41-7.24 (m, 5H, Ar*H*), 6.67 (s, 1H, Ar*H*), 5.13 (s, 1H, C*H*NEt_2), 2.78-2.60 (m, 4H, ethyl CH_2), 1.11 (t, ^3J(H,H) = 7.1 Hz, 6H, ethyl CH_3).

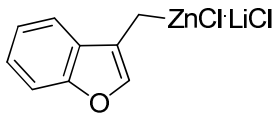
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 157.9, 154.9, 140.2, 128.5, 128.3, 128.2, 127.3, 123.7, 122.6, 120.7, 111.4, 105.3, 63.9, 43.8, 12.2.

MS (70 eV, EI): *m/z* (%) = 208 (15), 207 (100).

HRMS (EI): *m/z* calc. for [$C_{19}H_{21}NO$] 279.1623, found: 279.1623.

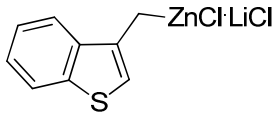
3.2.2. Preparation of heterobenzylic zinc chlorides by LiCl-promoted Zn insertion

Synthesis of benzo[b]furan-3-ylmethylzinc chloride (143)



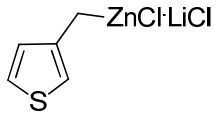
Prepared according to **TP5** from 3-(chloromethyl)benzo[b]furan **127** (830 mg, 5 mmol), Zn dust (450 mg, 7.5 mmol) and LiCl (318 mg, 7.5 mmol). Reaction time: 16 h. Iodometric titration of the centrifugated solution indicated a yield of 81%.

Synthesis of benzo[b]thiophen-3-ylmethylzinc chloride (146)



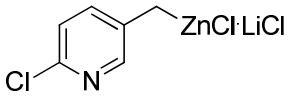
Prepared according to **TP5** from 3-(chloromethyl)benzo[b]thiophene **128** (913 mg, 5 mmol), Zn dust (450 mg, 7.5 mmol) and LiCl (318 mg, 7.5 mmol). Reaction time: 16 h. Iodometric titration of the centrifugated solution indicated a yield of 77%.

Synthesis of 3-thienylmethylzinc chloride (147)



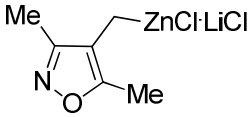
Prepared according to **TP5** from 3-(chloromethyl)thiophene **130** (663 mg, 5 mmol), Zn dust (450 mg, 7.5 mmol) and LiCl (318 mg, 7.5 mmol). Reaction time: 12 h. Iodometric titration of the centrifugated solution indicated a yield of 78%.

Synthesis of 2-chloropyridin-5-ylmethylzinc chloride (148)



Prepared according to **TP5** from commercially available 2-chloro-5-(chloromethyl)pyridine (804 mg, 5 mmol), Zn dust (450 mg, 7.5 mmol) and LiCl (318 mg, 7.5 mmol). Reaction time: 2.5 h. Iodometric titration of the centrifugated solution indicated a yield of 80%.

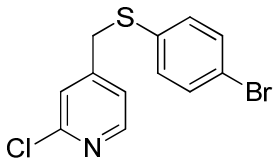
Synthesis of 3,5-dimethylisoxazol-4-ylmethylzinc chloride (149)



Prepared according to **TP5** from 4-(chloromethyl)-3,5-dimethylisoxazole (728 mg, 5 mmol), Zn dust (450 mg, 7.5 mmol) and LiCl (318 mg, 7.5 mmol). Reaction time: 4 h. Iodometric titration of the centrifugated solution indicated a yield of 83%.

3.2.3. Reactions of heterobenzylic zinc chlorides

Synthesis of 4-{[(4-bromophenyl)thio]methyl}-2-chloropyridine (153)



To a solution of 2-chloro-4-methylpyridine (127 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1 mL) at 0 °C was added $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (0.6 mmol, 1.2 equiv TMP) and the resulting mixure was stirred at 0 °C for 4 h. The so generated solution of 2-chloropyridin-4-ylmethylzinc chloride was then reacted according to **TP9** with *S*-(4-bromophenyl)benzenesulfonothioate (296 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 8:2) afforded **153** as a yellow oil (125 mg, 40%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054, 2972, 1589, 1547, 1472, 1379, 1230, 1116, 1086, 1006, 989, 884, 805, 716.

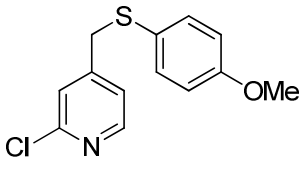
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, ^3J(H,H) = 5.1 Hz, 1H, Ar*H*), 7.38 (d, ^3J(H,H) = 8.7 Hz, 2H, Ar*H*), 7.21-7.08 (m, 4H, Ar*H*), 3.98 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 151.7, 150.0, 149.6, 133.3, 132.4, 132.3, 124.1, 122.4, 121.6, 37.9.

MS (70 eV, EI): *m/z* (%) = 317 (26), 316 (15), 315 (100), 314 (15), 313 (64), 234 (15), 189 (47), 149 (16), 128 (21), 126 (65), 109 (12), 108 (56), 99 (10), 90 (10), 63 (13), 57 (10), 55 (11), 44 (14), 43 (10), 41 (10).

HRMS (EI): *m/z* calc. for [$C_{12}H_9{}^{79}Br^{35}ClN^{32}S$] 312.9328, found: 312.9318.

Synthesis of 2-chloro-4-{[(4-methoxyphenyl)thio]methyl}pyridine (154)



To a solution of 2-chloro-4-methylpyridine (127 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1 mL) at 0 °C was added $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (0.6 mmol, 1.2 equiv TMP) and the resulting mixure was stirred at 0 °C for 4 h. The so generated solution of 2-chloropyridin-4-ylmethylzinc chloride was then reacted according to **TP9** with *S*-(4-methoxyphenyl)benzenesulfonothioate (252 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 8:2) afforded **154** as a yellow oil (137 mg, 52%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3055, 2960, 1588, 1546, 1492, 1461, 1380, 1285, 1243, 1172, 1118, 1083, 1027, 890, 824, 716.

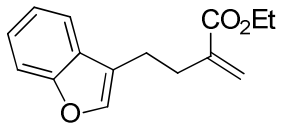
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, ^3J(H,H) = 5.1 Hz, 1H, Ar*H*), 7.28-7.22 (m, 3H, Ar*H*), 7.10 (s, 1H, Ar*H*), 7.00 (d, ^3J(H,H) = 5.1 Hz, 1H, Ar*H*), 6.83-6.80 (m, 2H, Ar*H*), 3.87 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.9, 151.3, 151.1, 149.3, 135.0, 124.3, 122.6, 114.7, 55.3, 39.9.

MS (70 eV, EI): *m/z* (%) = 267 (12), 265 (38), 139 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}{}^{35}ClNO^{32}S$] 265.0328, found: 265.0323.

Synthesis of ethyl 2-[2-(benzo[b]furan-3-yl)ethyl]acrylate (156)



Prepared according to **TP10** from benzo[b]furan-3-ylmethylzinc chloride **143** (1.0 mmol, 1.0 equiv) and ethyl (2-bromomethyl)acrylate (173 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 30:1) afforded **156** as a colorless oil (175 mg, 80%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 2932, 1713, 1631, 1453, 1306, 1279, 1241, 1185, 1136, 1092, 1029, 946, 857, 746.

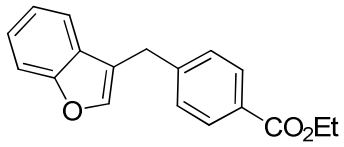
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, ^{3}J(H,H) = 7.5 Hz, 1H, Ar*H*), 7.49 (d, ^{3}J(H,H) = 7.2 Hz, 1H, Ar*H*), 7.44 (s, 1H, Ar*H*), 7.29 (5, ^{3}J(H,H) = 7.4 Hz, 2H, Ar*H*), 6.22 (s, 1H, methylene C*H*), 5.57 (s, 1H, methylene C*H*), 4.26 (q, ^{3}J(H,H) = 7.3 Hz, 2H, ethyl C*H*2), 2.93-2.87 (m, 2H, CH_2), 2.77-2.72 (m, 2H, CH_2), 1.34 (t, ^{3}J(H,H) = 7.3 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.0, 155.3, 141.2, 140.0, 128.1, 125.4, 124.2, 122.3, 119.6, 119.5, 111.4, 60.7, 31.7, 22.9, 14.2.

MS (70 eV, EI): *m/z* (%) = 245 (19), 244 (99), 215 (21), 199 (23), 171 (19), 170 (52), 169 (14), 132 (10), 131 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}O_3$] 244.1099, found: 244.1097.

Synthesis of ethyl 4-(benzo[b]furan-3-ylmethyl)benzoate (157)



Prepared according to **TP6** from benzo[b]furan-3-ylmethylzinc chloride **143** (1.0 mmol, 1.0 equiv) and ethyl 4-iodobenzoate (248 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 20:1) afforded **157** as a yellow oil (194 mg, 77%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 1803, 1711, 1642, 1610, 1463, 1452, 1416, 1366, 1272, 1177, 1099, 1063, 1019, 870, 855, 746, 726.

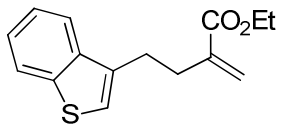
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, ^{3}J(H,H) = 8.4 Hz, 2H, Ar<u>H</u>), 7.52-7.18 (m, 7H, Ar<u>H</u>), 4.40 (q, ^{3}J(H,H) = 7.3 Hz, 2H, ethyl CH_2), 4.1 (s, 2H, CH_2), 1.41 (t, ^{3}J(H,H) = 7.3 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.5, 155.6, 144.5, 142.3, 129.9, 128.8, 128.6, 127.7, 124.4, 122.5, 119.7, 118.8, 111.5, 60.9, 30.0, 14.4.

MS (70 eV, EI): *m/z* (%) = 280 (100), 279 (21), 251 (16), 235 (33), 207 (45), 179 (16), 178 (30), 131 (18).

HRMS (EI): *m/z* calc. for [$C_{18}H_{16}O_3$] 280.1099, found: 280.1092.

Synthesis of ethyl 2-[2-(benzo[b]thien-3-yl)ethyl]acrylate (158)



Prepared according to **TP10** from benzo[b]thiophen-3-ylmethylzinc chloride **146** (1.0 mmol, 1.0 equiv) and ethyl (2-bromomethyl)acrylate (173 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 30:1) afforded **158** as a colorless oil (182 mg, 78%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060, 2980, 1712, 1630, 1428, 1368, 1305, 1193, 1140, 1028, 945, 761, 734.

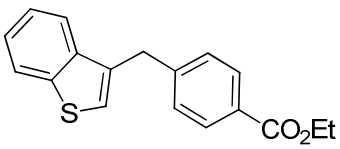
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.90-7.83 (m, 2H, Ar*H*), 7.44-7.35 (m, 2H, Ar*H*), 7.13 (s, 1H, ArH), 6.23 (s, 1H, methylene C*H*), 5.59 (s, 1H, methylene C*H*), 4.28 (q, ^3J(H,H) = 7.3 Hz, 2H, ethyl CH_2), 3.09-3.04 (m, 2H, CH_2), 2.80-2.75 (m, 2H, CH_2), 1.34 (t, ^3J(H,H) = 7.3 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.0, 140.4, 140.1, 138.9, 135.8, 125.4, 124.2, 123.9, 122.8, 121.7, 121.5, 60.7, 31.9, 27.9, 14.2.

MS (70 eV, EI): *m/z* (%) = 260 (16), 147 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}O_2{}^{32}S$] 260.0871, found: 260.0862.

Synthesis of ethyl 4-(benzo[b]thiophen-3-ylmethyl)benzoate (159)



Prepared according to **TP6** from benzo[b]thiophen-3-ylmethylzinc chloride **146** (1.0 mmol, 1.0 equiv) and ethyl 4-iodobenzoate (248 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 20:1) afforded **159** as a colorless oil (223 mg, 85%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980, 2903, 1709, 1609, 1575, 1459, 1426, 1390, 1365, 1271, 1176, 1099, 1019, 928, 875, 853, 750, 728, 715, 701.

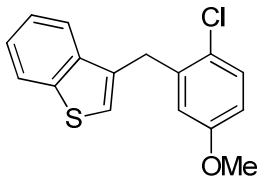
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, ^{3}J(H,H) = 8.4 Hz, 2H, Ar*H*), 7.91-7.88 (m, 1H, Ar*H*), 7.69-7.66 (m, 1H, Ar*H*), 7.38-7.33 (m, 4H, Ar*H*), 7.06 (s, 1H, Ar*H*), 4.40 (q, ^{3}J(H,H) = 7.1 Hz, 2H, ethyl CH_2), 4.27 (s, 2H, CH_2), 1.41 (t, ^{3}J(H,H) = 7.2 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.5, 144.7, 140.6, 138.6, 134.6, 129.8, 128.8, 124.4, 124.0, 123.5, 122.9, 121.8, 60.8, 35.0, 14.3. (One signal not observed; possible coincidental isochronicity.)

MS (70 eV, EI): *m/z* (%) = 297 (19), 296 (100), 295 (16), 267 (13), 251 (22), 223 (40), 222 (12), 221 (21), 147 (34).

HRMS (EI): *m/z* calc. for [$C_{18}H_{16}O_2{}^{32}S$] 296.0871, found: 296.0863.

Synthesis of 3-(2-chloro-5-methoxybenzyl)benzo[b]thiophene (160)



Prepared according to **TP6** from benzo[b]thiophen-3-ylmethylzinc chloride **146** (1.0 mmol, 1.0 equiv) and 2-bromo-1-chloro-4-methoxybenzene (199 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane:Et_2O = 9:1) afforded **160** as a yellow oil (220 mg, 85%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059, 3027, 2834, 1715, 1595, 1574, 1477, 1460, 1427, 1289, 1276, 1238, 1159, 1137, 1124, 1061, 1025, 935, 867, 803, 763, 725.

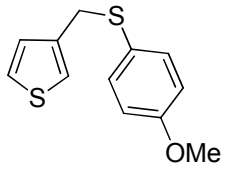
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.90-7.89 (m, 1H, Ar*H*), 7.77-7.76 (m, 1H, Ar*H*), 7.41-7.33 (m, 3H, Ar*H*), 7.02 (s, 1H, Ar*H*), 6.78-6.72 (m, 2H, Ar*H*), 4.28 (s, 2H, CH_2), 3.71 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.4, 140.5, 138.7, 138.1, 133.8, 120.1, 125.5, 124.3, 124.0, 123.4, 122.9, 121.8, 116.5, 113.1, 55.4, 32.6.

MS (70 eV, EI): *m/z* (%) = 290 (27), 289 (15), 288 (74), 254 (18), 253 (100), 237 (11), 222 (18), 221 (13), 147 (22).

HRMS (EI): *m/z* calc. for [$C_{16}H_{13}{}^{35}ClO^{32}S$] 288.0376, found: 288.0367.

Synthesis of 3-{[(4-methoxyphenyl)thio]methyl}thiophene (161)



Prepared according to **TP9** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and *S*-(4-methoxyphenyl)benzenesulfonothioate (252 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 100:1) afforded **161** as a yellow oil (169 mg, 80%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3099, 2937, 1591, 1493, 1462, 1285, 1245, 1173, 1030, 825.

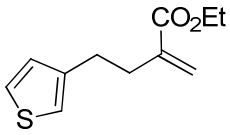
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.30-7.25 (m, 3H, Ar*H*), 7.03 (dd, ^3J(H,H) = 4.9 Hz, ^4J(H,H) = 1.2 Hz, 1H, Ar*H*), 6.95-6.93 (m, 1H, Ar*H*), 6.85-6.81 (m, 2H, Ar*H*), 4.03 (s, 2H, CH_2), 3.81 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.3, 138.5, 134.2, 128.2, 126.0, 125.7, 122.5, 114.5, 55.3, 35.7.

MS (70 eV, EI): *m/z* (%) = 236 (30), 97 (100), 53 (11), 45 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}O^{32}S_2$] 236.0330, found: 236.0309.

Synthesis of ethyl 2-[2-(3-thienyl)ethyl]acrylate (162)



Prepared according to **TP10** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and ethyl (2-bromomethyl)acrylate (173 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 100:1) afforded **162** as a colorless oil (175 mg, 93%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 2930, 1713, 1630, 1183, 1135, 1028, 942, 778.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.25 (m, 1H, Ar*H*), 6.97 (d, ^3J(H,H) = 4.1 Hz, 2H, Ar*H*), 6.19 (s, 1H, methylene C*H*), 5.53 (s, 1H, methylene C*H*), 4.24 (q, ^3J(H,H) = 7.0 Hz, 2H, ethyl

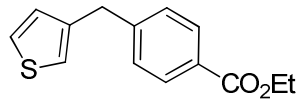
CH_2), 2.88-2.83 (m, 2H, CH_2), 2.68-2.63 (m, 2H, CH_2), 1.33 (t, ^3J(H,H) = 7.0 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.1, 141.7, 140.1, 128.2, 125.3, 123.1, 120.4, 60.6, 32.9, 29.3, 14.2.

MS (70 eV, EI): *m/z* (%) = 210 (69), 181 (15), 165 (23), 164 (14), 137 (15), 136 (21), 135 (17), 97 (100).

HRMS (EI): *m/z* calc. for [$C_{11}H_{14}O_2{}^{32}S$] 210.0715, found: 210.0714.

Synthesis of ethyl 4-(3-thienylmethyl)benzoate (163)



Prepared according to **TP6** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and ethyl 4-iodobenzoate (248 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 20:1) afforded **163** as a colorless oil (183 mg, 83%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980, 1710, 1609, 1415, 1366, 1270, 1175, 1100, 1020, 941, 858, 831, 762, 712.

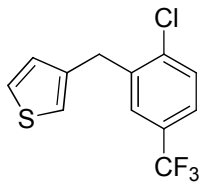
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, ^3J(H,H) = 8.0 Hz, 2H, Ar*H*), 7.30 (br. s, 3H, Ar*H*), 6.94 (d, ^3J(H,H) = 11.8 Hz, 2H, Ar*H*), 4.40 (q, ^3J(H,H) = 7.0 Hz, 2H, ethyl CH_2), 4.06 (s, 2H, CH_2), 1.42 (t, ^3J(H,H) = 8.4 Hz, 7.0 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.5, 145.8, 140.4, 129.8, 128.7, 128.6, 128.3, 125.9, 121.6, 60.8, 36.5, 14.4.

MS (70 eV, EI): *m/z* (%) = 247 (15), 217 (12), 201 (57), 173 (63), 171 (13), 129 (12), 97 (13).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}O_2{}^{32}S$] 246.0715, found: 246.0703.

Synthesis of 3-[2-chloro-5-(trifluoromethyl)benzyl]thiophene (164)



Prepared according to **TP6** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and 2-bromo-1-chloro-4-(trifluoromethyl)benzene (233 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane) afforded **164** as a colorless oil (178 mg, 72%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1610, 1482, 1438, 1412, 1329, 1303, 1256, 1166, 1120, 1079, 1045, 927, 891, 825, 788, 766, 751, 735.

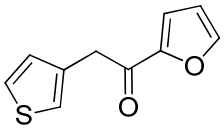
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.54-7.45 (m, 3H, Ar*H*), 7.33-7.28 (m, 1H, Ar*H*), 7.00-6.96 (m, 2H, Ar*H*), 4.17 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 139.4, 138.4, 137.8, 130.1, 129.6, 128.1, 127.5 (q, ^3J(C,F) = 3.9 Hz, *C ortho to CF_3*), 126.1, 125.5 (q, ^1J(C,F) = 274.3 Hz, *C*F_3), 124.5 (q, ^3J(C,F) = 3.9 Hz, *C ortho' to CF_3)*, 122.1, 34.0.

MS (70 eV, EI): *m/z* (%) = 279 (12), 276 (21), 241 (34), 167 (44), 149 (100), 113 (12), 97 (11), 83 (12), 71 (27), 20 (26), 69 (12), 57 (35), 55 (15), 43 (16), 42 (15), 40 (13).

HRMS (EI): *m/z* calc. for [$C_{12}H_8{}^{35}ClF_3{}^{32}S$] 275.9987, found: 275.9975.

Synthesis of 1-(2-furyl)-2-(3-thienyl)ethanone (165)



Prepared according to **TP8** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and 2-furoyl chloride (117 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et2O = 8:2) afforded **165** as a yellow oil (112 mg, 65%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3105, 2923, 1672, 1568, 1466, 1392, 1304, 1244, 1159, 1083, 1039, 1020, 759.

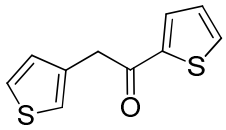
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.62-7.60 (m, 1H, Ar*H*), 7.31-7.28 (m, 1H, Ar*H*), 7.24 (d, ^{3}J(H,H) = 4.3 Hz, 1H, Ar*H*), 7.19-7.17 (m, 1H, Ar*H*), 7.05 (d, ^{3}J(H,H) = 4.5 Hz, 1H, Ar*H*), 6.56-6.54 (m, 1H, Ar*H*), 4.17 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 186.0, 152.3, 146.5, 133.6, 128.6, 125.7, 123.0, 117.8, 112.5, 39.8.

MS (70 eV, EI): *m/z* (%) = 167 (35), 150 (11), 111 (37), 97 (35), 95 (100).

HRMS (EI): *m/z* calc. for [$C_{10}H_8O_2{}^{32}S$] 192.0245, found: 192.0234.

Synthesis of 1-(2-thienyl)-2-(3-thienyl)ethanone (166)



Prepared according to **TP8** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and thiophene-2-carboxylic acid chloride (132 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et2O = 8:2) afforded **166** as a yellow oil (131 mg, 70%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3099, 1707, 1650, 1515, 1409, 1353, 1271, 1231, 1218, 1080, 1058, 858, 753, 720.

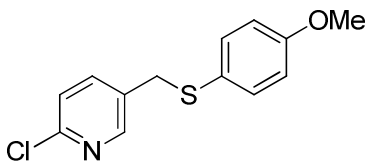
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.79 (s, 1H, Ar*H*), 7.67 (s, 1H, Ar*H*), 7.32-7.06 (m, 4H, Ar*H*), 4.24 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 189.9, 143.7, 134.1, 133.9, 132.6, 128.5, 128.2, 125.9, 122.9, 41.0.

MS (70 eV, EI): *m/z* (%) = 111 (100), 97 (11).

HRMS (EI): *m/z* calc. for [$C_{10}H_8O^{32}S_2$] 208.0017, found: 208.0009.

Synthesis of 2-chloro-5-{[(4-methoxyphenyl)thio]methyl}pyridine (167)



Prepared according to **TP9** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and *S*-(4-methoxyphenyl)benzenesulfonothioate (252 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 8.5:1.5) afforded **167** as a colorless oil (241 mg, 91%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3045, 2938, 1588, 1565, 1492, 1458, 1379, 1285, 1242, 1172, 1132, 1103, 1023, 929, 877, 822, 741.

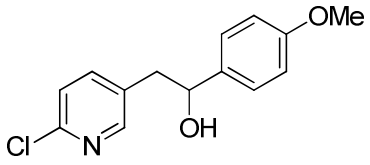
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, ^4J(H,H) = 2.4 Hz, 1H, Ar*H*), 7.48 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 2.6 Hz, 1H, Ar*H*), 7.28-7.22 (m, 3H, Ar*H*), 6.84-6.80 (m, 2H, Ar*H*), 3.91 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.8, 149.7, 149.2, 139.4, 135.0, 133.3, 124.0, 114.7, 55.3, 37.7.

MS (70 eV, EI): *m/z* (%) = 267 (16), 265 (47), 139 (100), 128 (11), 126 (37).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}{}^{35}ClNO^{32}S$] 265.0328, found: 265.0322.

Synthesis of 2-(6-chloropyridin-3-yl)-1-(4-methoxyphenyl)ethanol (168)



Prepared according to **TP7** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (122 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (Al_2O_3, *n*-pentane/Et_2O = 1:1) afforded **168** as an off-white solid (179 mg, 76%).

mp: 117.0-118.3 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3316, 2911, 1612, 1585, 1567, 1510, 1460, 1387, 1304, 1238, 1170, 1102, 1060, 1029, 835, 813, 767, 733.

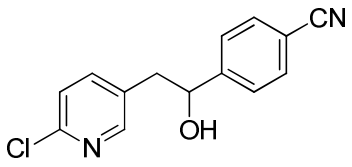
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 8.11 (d, ^{4}J(H,H) = 2.4 Hz, 1H, Ar*H*), 7.60 (dd, ^{3}J(H,H) = 8.2 Hz, ^{4}J(H,H) = 2.5 Hz, 1H, Ar*H*), 7.34 (d, ^{3}J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.20 (d, ^{3}J(H,H) = 8.0 Hz, 2H, Ar*H*), 6.83 (d, ^{3}J(H,H) = 8.0 Hz, 2H, Ar*H*), 5.28 (d, ^{3}J(H,H) = 4.5 Hz, 1H, O*H*), 4.71-4.67 (m, 1H, C*H*OH), 3.70 (s, 3H, CH_3), 2.90-2.80 (m, 2H, CH_2).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 158.6, 150.9, 148.2, 141.1, 137.4, 134.5, 127.5, 123.8, 113.8, 72.7, 55.5, 41.9.

MS (70 eV, EI): *m/z* (%) = 245 ([M-H_2O]$^+$, 10), 137 (100), 127 (60), 109 (26), 77 (13).

HRMS (ESI): *m/z* calc. for [$C_{14}H_{14}{}^{35}ClNO_2$] 263.0713, found: 264.0786 ([M+H]$^+$).

Synthesis of 4-[2-(6-chloropyridin-3-yl)-1-hydroxyethyl]benzonitrile (169)



Prepared according to **TP7** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and 4-cyanobenzaldehyde (117 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (Al_2O_3, *n*-pentane/Et_2O = 8:2) afforded **169** as a white solid (206 mg, 89%).

mp: 116.4-117.7 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3447, 3047, 2230, 1608, 1584, 1566, 1455, 1408, 1382, 1326, 1280, 1240, 1206, 1134, 1100, 1060, 1023, 827, 733.

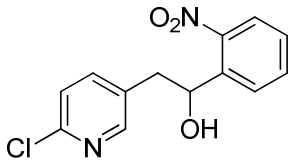
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 8.12 (d, ^{4}J(H,H) = 2.3 Hz, 1H, Ar*H*), 7.75 (d, ^{3}J(H,H) = 8.2 Hz, 2H, Ar*H*), 7.62 (dd, ^{3}J(H,H) = 8.6 Hz, ^{4}J(H,H) = 2.5 Hz, 1H, Ar*H*), 7.49 (d, ^{3}J(H,H) = 8.2 Hz, 2H, Ar*H*), 7.36 (d, ^{3}J(H,H) = 8.2 Hz, 1H, Ar*H*), 5.63 (br. s, 1H, O*H*), 4.89-4.85 (m, 1H, C*H*OH), 2.94 (dd, ^{3}J(H,H) = 13.7 Hz, ^{4}J(H,H) = 4.5 Hz, 1H, CH_2), 2.83 (dd, ^{3}J(H,H) = 13.7 Hz, ^{4}J(H,H) = 7.8 Hz, 1H, CH_2).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 151.1, 151.0, 148.5, 141.2, 133.9, 132.4, 127.3, 123.9, 119.4, 110.1, 72.3, 41.3.

MS (70 eV, EI): *m/z* (%) = 127 (100), 104 (25), 90 (18), 77 (12).

HRMS (ESI): *m/z* calc. for [$C_{14}H_{11}{}^{35}ClN_2O$] 258.0560, found: 259.0633 ([M+H]$^+$).

Synthesis of 2-(6-chloropyridin-3-yl)-1-(2-nitrophenyl)ethanol (170)



Prepared according to **TP7** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and 2-nitrobenzaldehyde (135 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (Al_2O_3, *n*-pentane/Et_2O = 1:1) afforded **170** as a yellow solid (227 mg, 91%).

mp: 146.2-147.9 °C (decomposition)

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3345, 2923, 1568, 1520, 1460, 1387, 1341, 1319, 1103, 1055, 820, 750, 708.

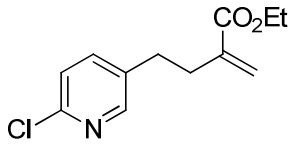
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 8.17 (d, ^4J(H,H) = 2.6 Hz, 1H, Ar*H*), 7.92 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.77-7.64 (m, 3H, Ar*H*), 7.52-7.48 (m, 1H, Ar*H*), 7.42 (d, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 5.73 (d, ^3J(H,H) = 4.7 Hz, 1H, O*H*), 5.17 (5, ^3J(H,H) = 4.7 Hz, 1H, C*H*OH), 3.00 (dd, ^3J(H,H) = 13.9 Hz, ^4J(H,H) = 3.5 Hz, 1H, CH_2), 2.86-2.80 (m, 1H, CH_2).

^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 150.8, 148.6, 147.7, 141.0, 140.3, 134.1, 133.8, 128.8, 128.7, 124.4, 124.1, 68.8, 41.0.

MS (70 eV, EI): *m/z* (%) = 152 (30), 127 (100), 104 (29), 77 (12).

HRMS (ESI): *m/z* calc. for [$C_{13}H_{11}{}^{35}ClN_2O_3$] 278.0458, found: 279.0532 ([M+H]$^+$).

Synthesis of ethyl 2-[2-(6-chloropyridin-3-yl)ethyl]acrylate (171)



Prepared according to **TP10** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and ethyl (2-bromomethyl)acrylate (173 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 8:2) afforded **171** as a yellow oil (206 mg, 96%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2870, 1710, 1630, 1586, 1565, 1459, 1384, 1313, 1242, 1184, 1136, 1103, 1026, 948, 819.

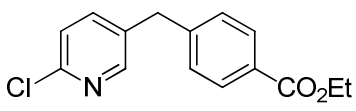
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, ^4J(H,H) = 2.4 Hz, 1H, Ar*H*), 7.50 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 2.6 Hz, 1H, Ar*H*), 7.28 (s, 1H, Ar*H*), 6.19 (s, 1H, methylene CH_2), 5.50 (s, 1H, methylene CH_2), 4.23 (q, ^3J(H,H) = 7.0 Hz, 2H, ethyl CH_2), 2.81 (t, ^3J(H,H) = 8.3 Hz, 2H, CH_2), 2.61 (t, ^3J(H,H) = 8.3 Hz, 2H, CH_2), 1.32 (t, ^3J(H,H) = 7.0 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.7, 149.5, 149.4, 139.1, 139.0, 135.5, 126.0, 123.9, 60.8, 33.5, 31.2, 14.2.

MS (70 eV, EI): *m/z* (%) = 279 (12), 243 (14), 239 (23), 238 (15), 210 (11), 194 (10), 193 (10), 175 (17), 167 (45), 166 (15), 164 (12), 150 (11), 149 (100), 128 (19), 126 (68), 71 (16), 70 (14), 43 (11), 41 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}{}^{35}ClNO_2$] 239.0713, found: 239.0705.

Synthesis of ethyl 4-[(6-chloropyridin-3-yl)methyl]benzoate (172)



Prepared according to **TP6** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and ethyl 4-iodobenzoate (248 mg, 0.9 mmol, 0.9 equiv). Catalyst system: $Pd(OAc)_2$/S-Phos. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 7:3) afforded **172** as a yellow solid (180 mg, 73%).

mp: 94.2-96.1 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3041, 2989, 1703, 1606, 1458, 1367, 1278, 1181, 1108, 1019, 767, 740, 707.

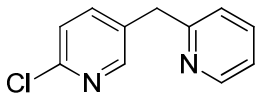
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, ^{4}J(H,H) = 2.7 Hz, 1H, Ar*H*), 8.00 (d, ^{3}J(H,H) = 8.2 Hz, 2H, Ar*H*), 7.43 (dd, ^{4}J(H,H) = 2.5 Hz, ^{3}J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.25 (t, ^{3}J(H,H) = 8.5 Hz, 3H, Ar*H*), 4.38 (q, ^{3}J(H,H) = 7.0 Hz, 2H, ethyl CH_2), 4.02 (s, 2H, CH_2), 1.40 (t, ^{3}J(H,H) = 7.0 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.3, 149.4, 144.2, 139.3, 134.7, 130.1, 129.1, 128.7, 124.2, 60.9, 38.1, 14.3. (One signal not observed; possible coincidental isochronicity.)

MS (70 eV, EI): *m/z* (%) = 277 (15), 275 (36), 249 (13), 247 (37), 232 (32), 231 (15), 230 (100), 204 (16), 203 (12), 202 (40), 201 (13), 167 (22), 166 (25), 139 (15).

HRMS (EI): *m/z* calc. for [$C_{15}H_{14}{}^{35}ClNO_2$] 275.0713, found: 275.0711.

Synthesis of 2-chloro-5-(pyridin-2-ylmethyl)pyridine (173)



Prepared according to **TP6** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and 2-bromopyridine (141 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, isohexane:Et_2O = 8:2) afforded **173** as a yellow oil (143 mg, 78%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3401, 3051, 1668, 1586, 1567, 1457, 1434, 1383, 1361, 1309, 1284, 1242, 1207, 1134, 1103, 1049, 1024, 995, 930, 842, 812, 768, 748.

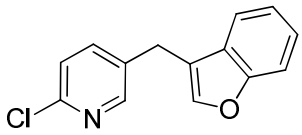
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, ^{3}J(H,H) = 4.9 Hz, 1H, Ar*H*), 8.32 (s, 1H, Ar*H*), 7.66-7.57 (m, 2H, Ar*H*), 7.28-7.13 (m, 3H, Ar*H*), 4.13 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.0, 149.9, 149.6, 149.5, 139.4, 136.9, 133.9, 124.0, 123.1, 121.8, 40.8.

MS (70 eV, EI): *m/z* (%) = 205 (30), 204 (20), 203 (100), 169 (28), 168 (20).

HRMS (EI): *m/z* calc. for [$C_{11}H_9{}^{35}ClN_2$] 204.0454, found: 204.0424.

Synthesis of 5-(benzo[b]furan-3-ylmethyl)-2-chloropyridine (174)



Prepared according to **TP6** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and 3-bromobenzo[b]furan (178 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, isohexane:Et_2O = 8:2) afforded **174** as a yellow oil (135 mg, 62%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1802, 1584, 1565, 1452, 1384, 1275, 1183, 1135, 1092, 1023, 855, 816, 741.

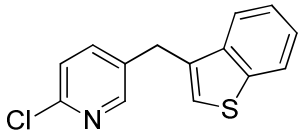
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, 1H, Ar*H*), 7.55-7.22 (m, 7H, Ar*H*), 4.03 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.6, 149.7, 149.6, 142.3, 138.9, 133.7, 127.3, 124.7, 124.2, 122.7, 119.5, 118.1, 111.7, 26.6.

MS (70 eV, EI): *m/z* (%) = 245 (37), 244 (34), 243 (100), 242 (54), 214 (11), 208 (13), 131 (42), 77 (11), 76 (10).

HRMS (EI): *m/z* calc. for [$C_{14}H_{10}{}^{35}ClNO$] 243.0451, found: 243.0441.

Synthesis of 5-(benzo[b]thiophen-3-ylmethyl)-2-chloropyridine (175)



Prepared according to **TP6** from 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and 3-bromobenzo[b]thiophene (191 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, isohexane:Et_2O = 9:1) afforded **175** as colorless crystals (216 mg, 93%).

mp: 75.5-77.1 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086, 3056, 1584, 1562, 1455, 1431, 1381, 1366, 1289, 1256, 1212, 1133, 1109, 1093, 1022, 863, 817, 778, 757, 739, 728.

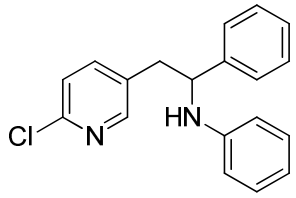
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.38 (s, 1H, Ar*H*), 7.91-7.89 (m, 1H, Ar*H*), 7.66-7.63 (m, 1H, Ar*H*), 7.50-7.48 (m, 1H, Ar*H*), 7.40-7.37 (m, 2H, Ar*H*), 7.28-7.24 (m, 1H, Ar*H*), 7.07 (s, 1H, Ar*H*), 4.19 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.7, 149.3, 139.1, 138.9, 138.2, 133.8, 133.6, 124.6, 124.3, 124.2, 123.8, 123.1, 121.6, 31.4.

MS (70 eV, EI): *m/z* (%) = 261 (32), 260 (24), 259 (100), 258 (48), 224 (12), 223 (11), 222 (12), 147 (47).

HRMS (EI): *m/z* calc. for [$C_{14}H_{10}{}^{35}ClN^{32}S$] 259.0222, found: 259.0212.

Synthesis of *N*-[2-(6-chloropyridin-3-yl)-1-phenylethyl]aniline (176)



To a solution of *N*-benzylideneaniline (163 mg, 0.9 mmol, 0.9 equiv, freshly prepared from the condensation of benzaldehyde and aniline) in anhydrous THF (1 mL) at 25 °C was added 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) and the resulting mixture was stirred overnight. The reaction was quenched with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 4:1) afforded **176** as yellow crystals (221 mg, 80%).

mp: 129.7-130.5 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3309, 3029, 2918, 2362, 2339, 1739, 1601, 1585, 1564, 1517, 1497, 1459, 1428, 1387, 1311, 1266, 1137, 1105, 827, 820, 748, 702, 690.

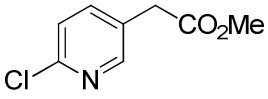
^{1}H-NMR (300 MHz, C_6D_6): δ = 7.81 (d, ^{4}J(H,H) = 2.6 Hz, 1H, Ar*H*), 7.09-6.88 (m, 7H, Ar*H*), 6.67-6.64 (m, 2H, Ar*H*), 6.49 (dd, ^{3}J(H,H) = 8.0 Hz, ^{4}J(H,H) = 2.5 Hz, 1H, Ar*H*), 6.36 (d, ^{3}J(H,H) = 7.5 Hz, 2H, Ar*H*), 4.19 (t, ^{3}J(H,H) = 6.8 Hz, 1H, NHC*H*), 3.54 (br s, 1H, N*H*), 2.38 (d, ^{3}J(H,H) = 7.1 Hz, 2H, CH_2).

^{13}C-NMR (75 MHz, C_6D_6): δ = 150.3, 149.9, 146.7, 142.1, 138.7, 131.8, 129.1, 128.5, 127.2, 126.3, 123.4, 118.0, 113.7, 58.4, 40.3.

MS (70 eV, EI): *m/z* (%) = 183 (13), 182 (100).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}{}^{35}ClN_2$] 308.1080, found: 308.1073.

Synthesis of methyl 2-(6-chloropyridin-3-yl)acetate (177)



A Schlenk flask, equipped with a magnetic stirring bar and a septum, was dried for 10 min at 650 °C with a heat gun. After cooling to 25 °C, the flask was filled with CO_2 from evaporating dry ice and passing the gas through a column of $CaCl_2$. Next, a solution of 2-chloropyridin-5-ylmethylzinc chloride **148** (1.0 mmol, 1.0 equiv) in THF was added. A flux of dry CO_2 was passed through the stirred reaction mixture for around 5 min, until a rubber balloon attached to the reaction vessel was completely inflated. The reaction mixture was then heated to 50 °C and stirred under static CO_2 atmosphere for 10 h, upon which it solidified. After cooling to 25 °C, neat oxalyl chloride (139 mg, 1.1 mmol, 1.1 equiv). After the vigorous gas evolution had subsided, the obtained solution was treated with anhydrous MeOH (1 mL) and anhydrous NEt_3 (1 mL) and stirring was continued at 25 °C for 1 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et2O = 1:1) afforded **177** as a colorless oil (130 mg, 70%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 1732, 1588, 1567, 1460, 1436, 1386, 1339, 1265, 1231, 1196, 1140, 1101, 1026, 1006, 820, 746.

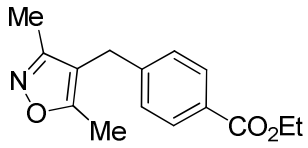
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1H, Ar*H*), 7.60 (d, ^3J(H,H) = 8.3 Hz, 1H, Ar*H*), 7.28 (d, ^3J(H,H) = 8.3 Hz, 1H, Ar*H*), 3.70 (s, 3H, CH_3), 3.61 (s, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 170.6, 150.3, 150.0, 139.7, 128.6, 124.1, 52.3, 37.3.

MS (70 eV, EI): *m/z* (%) = 185 (13), 173 (10), 171 (18), 149 (17), 129 (20), 128 (31), 127 (66), 126 (100), 125 (10), 91 (31), 55 (92).

HRMS (EI): *m/z* calc. for [$C_8H_8{}^{35}ClNO_2$] 185.0244, found: 185.0238.

Synthesis of ethyl 4-[(3,5-dimethylisoxazol-4-yl)methyl]benzoate (178)



Prepared according to **TP6** from 3,5-dimethylisoxazol-4-ylmethylzinc chloride **149** (1.0 mmol, 1.0 equiv) and ethyl 4-iodobenzoate (248 mg, 0.9 mmol, 0.9 equiv). Catalyst system: Pd-PEPPSI-IPr. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 1:1) afforded **178** as a yellow oil (203 mg, 87%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2987, 1705, 1610, 1478, 1449, 1416, 1365, 1278, 1179, 1124, 1107, 1020, 880, 743, 730.

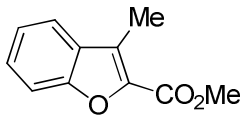
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, ^3J(H,H) = 8.2 Hz, 2H, Ar*H*), 7.19 (d, ^3J(H,H) = 8.2 Hz, 2H, Ar*H*), 4.37 (q, ^3J(H,H) = 7.1 Hz, 2H, ethyl CH_2), 3.74 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 1.39 (t, ^3J(H,H) = 7.1 Hz, 3H, ethyl CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.3, 165.6, 159.8, 143.9, 129.9, 128.9, 128.0, 111.6, 60.9, 28.2, 14.3, 11.0, 10.3.

MS (70 eV, EI): *m/z* (%) = 260 (18), 259 (100), 258 (36), 231 (30), 230 (69), 216 (20), 215 (14), 214 (87), 189 (20), 188 (29), 187 (10), 186 (56), 149 (18), 145 (21), 144 (28), 143 (10), 131 (13), 115 (15), 103 (12), 102 (12), 77 (11), 43 (41).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO_3$] 259.1208, found: 259.1207.

Synthesis of methyl 3-methylbenzo[b]furan-2-carboxylate (182)



A Schlenk flask, equipped with a magnetic stirring bar and a septum, was dried for 10 min at 650 °C with a heat gun. After cooling to 25 °C, the flask was filled with CO_2 from evaporating dry ice and passing the gas through a column of $CaCl_2$. Next, a solution of benzo[b]furan-3-ylmethylzinc chloride **143** (1.0 mmol, 1.0 equiv) in THF was added. A flux of dry CO_2 was passed through the

stirred reaction mixture for around 5 min, until a rubber balloon attached to the reaction vessel was completely inflated. The reaction mixture was then heated to 50 °C and stirred under static CO_2 atmosphere for 10 h, upon which it solidified. After cooling to 25 °C, neat oxalyl chloride (139 mg, 1.1 mmol, 1.1 equiv). After the vigorous gas evolution had subsided, the obtained solution was treated with anhydrous MeOH (1 mL) and anhydrous NEt_3 (1 mL) and stirring was continued at 25 °C for 1 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **182** as a colorless oil (135 mg, 71%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 1711, 1579, 1440, 1384, 1366, 1341, 1294, 1269, 1215, 1194, 1162, 1143, 1094, 837, 761, 750, 715.

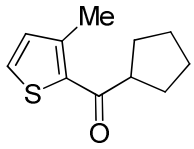
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, ^3J(H,H) = 8.7 Hz, 1H, Ar*H*), 7.54 (d, ^3J(H,H) = 8.6 Hz, 1H, Ar*H*), 7.45 (t, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 7.29 (t, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 3.99 (s, 3H, CO_2CH_3), 2.59 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 160.8, 154.4, 140.7, 128.9, 127.8, 125.9, 123.2, 121.0, 112.1, 51.9, 9.3.

MS (70 eV, EI): *m/z* (%) = 191 (11), 190 (100), 175 (22), 167 (26), 160 (11), 159 (67), 149 (54), 130 (18), 103 (10), 77 (12), 71 (11), 70 (11), 57 (15).

HRMS (EI): *m/z* calc. for [$C_{11}H_{10}O_3$] 190.0630, found: 190.0634.

Synthesis of cyclopentyl(3-methyl-2-thienyl)methanone (183)



Prepared according to **TP8** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and cyclopentanecarboxylic acid chloride (119 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **183** as a colorless oil (87 mg, 50%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2867, 1746, 1656, 1520, 1448, 1402, 1380, 1352, 1203, 1128, 1030, 991, 941, 835, 784, 726.

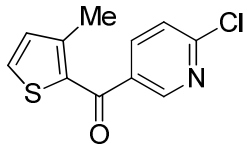
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, ^{3}J(H,H) = 4.9 Hz, 1H, Ar*H*), 6-96 (d, ^{3}J(H,H) = 4.9 Hz, 1H, Ar*H*), 3.48 (5, ^{3}J(H,H) = 7.7 Hz, 1H, cyclopentyl C*H*), 2.59 (s, 3H, CH_3), 1.97-1.59 (m, 8H, cyclopentyl CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.9, 145.4, 135.4, 132.7, 129.1, 50.0, 30.5, 26.4, 16.8.

MS (70 eV, EI): *m/z* (%) = 194 (20), 125 (100).

HRMS (EI): *m/z* calc. for [$C_{11}H_{14}O^{32}S$] 194.0765, found: 194.0764.

Synthesis of (6-chloropyridin-3-yl)(3-methyl-2-thienyl)methanone (184)



Prepared according to **TP8** from 3-thienylmethylzinc chloride **147** (1.0 mmol, 1.0 equiv) and 6-chloronicotinoyl chloride (159 mg, 0.9 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 8:2) afforded **184** as yellow crystals (153 mg, 72%).

mp: 96.8-98.4 °C.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3117, 3031, 2360, 2340, 1718, 1633, 1577, 1555, 1523, 1449, 1401, 1383, 1372, 1271, 1152, 1107, 1014, 904, 834, 763, 743.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.85 (s, 1H, Ar*H*), 8.10 (d, ^{3}J(H,H) = 8.1 Hz, 1H, Ar*H*), 7.59 (d, ^{3}J(H,H) = 4.7 Hz, 1H, Ar*H*), 7.49 (d, ^{3}J(H,H) = 8.2 Hz, 1H, Ar*H*), 7.08 (d, ^{3}J(H,H) = 4.7 Hz, 1H, Ar*H*), 2.56 (s, 3H, CH_3).

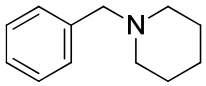
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 186.0, 154.6, 150.1, 147.4, 138.9, 134.4, 133.8, 132.7, 132.0, 124.1, 16.9.

MS (70 eV, EI): *m/z* (%) = 239 (23), 238 (51), 237 (57), 236 (100), 203 (12), 202 (83), 201 (11), 140 (10), 125 (78), 112 (17), 97 (10), 53 (15).

HRMS (EI): *m/z* calc. for [$C_{11}H_8{}^{35}ClNO^{32}S$] 237.0015, found: 237.0022.

3.3. Preparation of Tertiary Aromatic and Heteroaromatic Benzylic and Phenethylic Amines

Synthesis of *N*-benzylpiperidine (192)



Prepared according to **TP11** from phenylmagnesium chloride (1.0 mmol, 1.0 equiv) and piperidylmagnesium chloride (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, isohexane/Et_2O = 9:1) afforded **192** as a yellow oil (115 mg, 66 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 2853, 2793, 2755, 1493, 1453, 1442, 1346, 1298, 1153, 1120, 1113, 1038, 994, 860, 787, 734, 697.

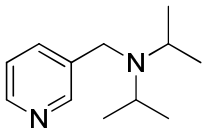
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34-7.28 (m, 5H, Ar*H*), 3.51 (s, 2H, CH_2), 1.65-1.43 (m, 10H, alkyl).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 138.4, 129.3, 128.1, 126.9, 63.8, 54.4, 25.9, 24.3.

MS (70 eV, EI): *m/z* (%) = 175 (54), 174 (71), 98 (53), 92 (15), 91 (100), 84 (46), 65 (16), 43 (11).

HRMS (EI): *m/z* calc. for [$C_{12}H_{17}N$] 175.1361, found: 175.1346.

Synthesis of *N*-(1-methylethyl)-*N*-(pyridin-3-ylmethyl)propan-2-amine (193)



Prepared according to **TP11** from pyridin-3-ylmagnesium bromide (1.0 mmol, 1.0 equiv) and magnesium chloride *N*,*N*-diisopropylamide (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, Et_2O = 9:1) afforded **193** as a yellow oil (136 mg, 71 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2964, 2933, 1634, 1590, 1576, 1465, 1423, 1381, 1363, 1320, 1271, 1205, 1174, 1117, 1101, 1022, 961, 827, 793, 755, 710.

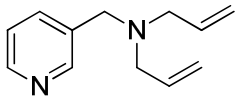
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.55 (s, 1H, Ar*H*), 8.41 (d, ^3J(H,H) = 4.7 Hz, 1H, Ar*H*), 7.70 (d, ^3J(H,H) = 8.0 Hz, 1H, Ar*H*), 7.18 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 4.7 Hz, 1H, Ar*H*), 3.62 (s, 2H, CH_2), 2.98 (5, ^3J(H,H) = 6.6 Hz, 2H, CH(CH_3)$_2$), 1.00 (d, ^3J(H,H) = 6.6 Hz, 12H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.6, 147.6, 138.4, 135.6, 123.1, 47.9, 46.4, 20.7.

MS (70 eV, EI): *m/z* (%) = 178 (12), 177 (100), 135 (51), 93 (13), 92 (87), 65 (12).

HRMS (EI): *m/z* calc. for [$C_{12}H_{20}N_2$] 192.1626, found: 192.1620.

Synthesis of *N*-prop-2-en-1-yl-*N*-(pyridin-3-ylmethyl)prop-2-en-1-amine (194)



Prepared according to **TP11** from pyridin-3-ylmagnesium bromide (1.0 mmol, 1.0 equiv) and magnesium chloride *N*,*N*-diallylamide (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 1) afforded **194** as a yellow oil (132 mg, 70 %).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2807, 1642, 1576, 1478, 1423, 1368, 1261, 1148, 1115, 1098, 1027, 993, 917, 787, 712.

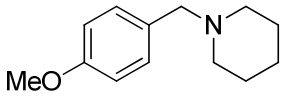
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.53 (s, 1H, Ar*H*), 8.46 (d, ^3J(H,H) = 4.9 Hz, 1H, Ar*H*), 7.64 (d, ^3J(H,H) = 7.7 Hz, 1H, Ar*H*), 7.20 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 4.9 Hz, 1H, Ar*H*), 5.89-5.76 (m, 2H, C*H*=CH_2), 5.20-5.10 (m, 4H, CH=CH_2), 3.55 (s, 2H, CH_2), 3.05 (d, ^3J(H,H) = 6.3 Hz, 4H, CH_2CH=CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 150.3, 148.4, 136.4, 135.5, 134.8, 123.2, 117.6, 56.4, 54.7.

MS (70 eV, EI): *m/z* (%) = 188 (21), 187 (14), 161 (53), 147 (27), 133 (12), 131 (13), 119 (11), 110 (29), 96 (12), 93 (16), 92 (100), 65 (31), 43 (17), 40 (42).

HRMS (EI): *m/z* calc. for [$C_{12}H_{16}N_2$] 188.1313, found: 188.1310.

Synthesis of 1-(4-methoxybenzyl)piperidine (195)



Prepared according to **TP11** from 4-methoxyphenylzinc chloride (1.0 mmol, 1.0 equiv) and piperidylmagnesium chloride (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (Al_2O_3, isohexane/Et_2O = 9:1) afforded **195** as a yellow oil (156 mg, 76%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 2793, 2754, 1612, 1511, 1299, 1242, 1178, 1114, 1100, 1038, 994, 830, 820.

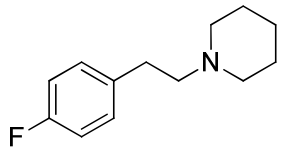
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar*H*), 6.84 (d, ^3J(H,H) = 8.6 Hz, 2H, Ar*H*), 3.8 (s, 3H, OCH_3), 3.41 (s, 2H, CH_2), 2.40-2.30 (m, 4H, alkyl), 1.57-1.39 (m, 6H, alkyl).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 158.5, 130.5, 130.4, 113.4, 63.2, 55.2, 54.3, 25.6, 24.4.

MS (70 eV, EI): *m/z* (%) = 205 (25), 204 (21), 122 (13), 121 (100), 98 (12), 84 (18).

HRMS (EI): *m/z* calc. for [$C_{13}H_{19}NO$] 205.1467, found: 205.1463.

Synthesis of 1-(4-fluorophenethyl)piperidine (196)



Prepared according to **TP11** from 4-fluorobenzylzinc chloride (1.0 mmol, 1.0 equiv) and piperidylmagnesium chloride (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (Al_2O_3, isohexane/Et_2O = 9:1) afforded **196** as a yellow oil (170 mg, 82%).

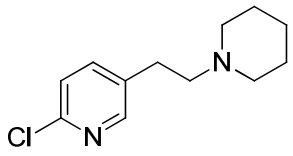
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2934, 2856, 1664, 1601, 1509, 1444, 1221, 1157, 1112, 828.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.16-7.12 (m, 2H, Ar*H*), 6.97-6.92 (m, 2H, Ar*H*), 2.85-2.75 (m, 2H, alkyl), 2.53-2.45 (m, 6H, alkyl), 1.64-1.58 (m, 4H, alkyl), 1.46-1.43 (m, 2H, alkyl).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 161.0 (d, ^1J(C,F) = 243.4 Hz), 163.2, 129.9 (d, ^3J(C,F) = 8.1 Hz), 115.1 (d, ^2J(C,F) = 21.1 Hz), 61.4, 54.5, 32.8, 25.9, 24.3.

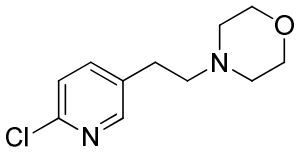
MS (70 eV, EI): *m/z* (%) = 123 (17), 122 (11), 109 (87), 103 (15), 99 (30), 98 (100), 96 (11), 83 (13), 70 (14), 55 (22), 44 (12), 42 (25), 41 (22).
HRMS (EI): *m/z* calc. for [$C_{13}H_{18}FN$] 207.1423, found: 207.1415.

Synthesis of 2-chloro-5-(2-piperidin-1-ylethyl)pyridine (197)



Prepared according to **TP11** from 2-chloropyridin-5-ylmethylzinc chloride (1.0 mmol, 1.0 equiv) and piperidylmagnesium chloride (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (Al_2O_3, isohexane/Et_2O = 9:1) afforded **197** as a yellow oil (179 mg, 80%).
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2854, 2810, 1583, 1563, 1460, 1441, 1400, 1382, 1256, 1140, 1113, 1103, 1080, 1034, 1007, 914, 869, 850, 834.
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1H, Ar*H*), 7.48 (d, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 7.20 (d, ^3J(H,H) = 8.2 Hz, 1H, Ar*H*), 2.76-2.72 (m, 2H, alkyl), 2.51-2.41 (m, 6H, alkyl), 1.58-1.54 (m, 4H, alkyl), 1.45-1.40 (m, 2H, alkyl).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.8, 149.1, 139.1, 135.0, 123.8, 60.3, 54.5, 29.9, 25.9, 24.3.
MS (70 eV, EI): *m/z* (%) = 98 (100).
HRMS (EI): *m/z* calc. for [$C_{12}H_{17}{}^{35}ClN_2$] 224.1080, found: 224.0931.

Synthesis of 4-[2-(6-chloropyridin-3-yl)ethyl]morpholine (198)



Prepared according to **TP11** from 2-chloropyridin-5-ylmethylzinc chloride (1.0 mmol, 1.0 equiv) and morpholinylmagnesium chloride (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (Al_2O_3, isohexane/Et_2O = 9:1) afforded **198** as a yellow oil (178 mg, 79%).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 2850, 1585, 1563, 1458, 1385, 1350, 1264, 1137, 1124, 1099, 1070, 867, 838, 825.

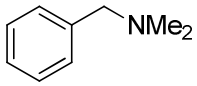
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1H, Ar*H*), 7.50 (d, ^{3}J(H,H) = 8.2 Hz, 1H, Ar*H*), 7.23 (d, ^{3}J(H,H) = 8.2 Hz, 1H, Ar*H*), 3.70 (t, ^{3}J(H,H) = 4.5 Hz, 4H, alkyl), 2.75 (t, ^{3}J(H,H) = 8.2 Hz, 2H, alkyl), 2.57-2.47 (m, 6H, alkyl).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 149.8, 149.2, 139.0, 134.5, 123.8, 66.9, 59.7, 53.5, 29.5.

MS (70 eV, EI): *m/z* (%) = 104 (10), 100 (100), 70 (13), 56 (34), 42 (25).

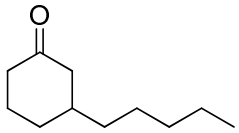
HRMS (EI): *m/z* calc. for [$C_{11}H_{15}{}^{35}ClN_2O$] 226.0873, found: 226.0727.

Synthesis of *N*,*N*-dimethylbenzylamine (199)



To a solution of *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (102 mg, 1.0 mmol) in anhydrous THF (1 mL) at 0 °C was added freshly distilled boron trifluoride diethyl etherate (142 mg, 1.0 mmol) and the resulting mixture was stirred for 30 min. Next, a solution of phenylzinc chloride lithium chloride complex (1.0 mmol, prepared from the transmetalation of phenyllithium with anhydrous $ZnCl_2$ solution at 0 °C for 15 min) was added and stirring was continued at 0 °C for 30 min. Sat. aq. $NaHCO_3$ was added and the crude mixture was extracted using EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **199** as a colorless oil (113 mg, 84%). Spectral data were in full accordance with those reported in the literature: Hamid, M. H. S. A.; Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 8263.

Synthesis of 3-pentylcyclohexanone (204)



A dry and argon-flushed Schlenk flask was charged with anhydrous toluene (4 mL) and freshly distilled dipentylzinc (414 mg, 2.0 mmol). The solution was cooled to –30 °C and freshly distilled $BF_3 \cdot Et_2O$ (284 mg, 2.0 mmol) was added dropwise. Stirring was continued at –30 °C for 10 min. Next, a solution of cyclohex-2-enone (96 mg, 1.0 mmol) in anhydrous toluene (2 mL) was added at –30 °C over 5 min. The resulting clear solution was allowed to warm up to –10 °C and stirring was continued at that temperature for 3 h. The reaction was terminated by adding a solution of aq. NH_4OH/NH_4Cl (1:9) and the reaction mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over $MgSO_4$. Purification of the crude product by flash chromatography afforded **204** as a colorless oil with a characteristic banana-like smell (141 mg, 83%). Spectral data were in full accordance with those reported in the literature: Reddy, C. K.; Devasagarayaj, A.; Knochel, P. *Tetrahedron Lett*. **1996**, *37*, 4459.

3.4. Crystallographical Data

3.4.1. Crystallographical Data of 6-phenyl-6*H*-benzo[4,5]furo[2,3-*b*]indole (84a)

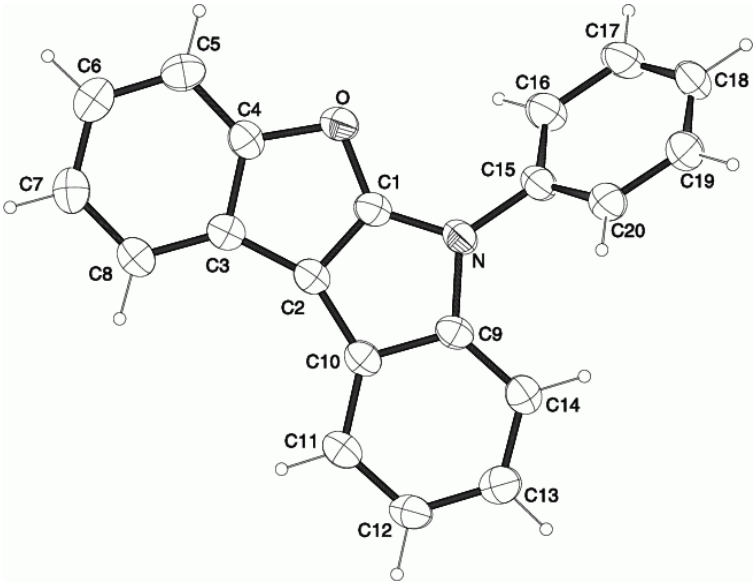


Table 11: Cell parameters obtained for **84a**.

Parameter	**Value**
net formula	$C_{20}H_{13}NO$
M_r/g mol^{-1}	283.323
crystal size/mm	0.50 × 0.14 × 0.11
T/K	200(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	4.0598(3)
b/Å	12.2904(8)
c/Å	14.1137(9)

α/°	98.623(5)
β/°	93.880(6)
γ/°	96.006(6)
V/Å^3	689.95(8)
Z	2
calc. density/g cm^{-3}	1.36380(16)
μ/mm^{-1}	0.084
absorption correction	'multi-scan'
transmission factor range	0.77277–1.00000
refls. measured	5548
R_{int}	0.0276
mean σ(I)/I	0.0508
θ range	3.89–26.34
observed refls.	1743
x, y (weighting scheme)	0.0537, 0
hydrogen refinement	constr
refls in refinement	2766
parameters	199
restraints	0
$R(F_{obs})$	0.0410
$R_w(F^2)$	0.0980
S	0.910
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.157
min electron density/e Å^{-3}	−0.237

D. APPENDIX

List of Abbreviations

Ac	acetyl
acac	pentane-1,3-dionato (acetylacetonato)
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
br	broad (NMR)
Bu	butyl
conc.	concentrated
d	doublet (NMR)
dba	*trans,trans*-dibenzylideneacetone
dist.	distilled
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
equiv	equivalent
E	electrophile
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
LDA	lithium *N,N*-diisopropylamide
M	mol/L

m	*meta*
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidin-2-one
o	*ortho*
p	*para*
PEPPSI-IPr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	phenyl
ppm	parts per million
R	organic substituent
rpm	revolutions per minute
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
t	reaction time
$TFAO^-$	trifluoroacetate
TLC	thin layer chromatography
THF	tetrahydrofuran
tfp	tris(2-furyl)phosphine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl
TP	typical procedure

Curriculum Vitae

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Personal Information

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Educational Background

2001	Allgemeine Hochschulreife (A-levels)
2001 – 2002	military service (Grundwehrdienst) at I./Luftwaffenausbildungsregiment 3 Oberschwaben-Kaserne, Mengen/Hohentengen
2002 – 2007	studies of chemistry (diploma) at Ludwig-Maximilians-Universität, Munich
02/2007 – 07/2007	Diploma thesis under the supervision of Prof. Dr. Paul Knochel “Kupfer(I)-vermittelte Oxidative Cycloaminierung an Benzofuran- und Benzothiophenderivaten” („Copper(I)-Mediated Oxidative Cycloamination on Derivatives of Benzofuran and Benzothiophene“)
12/2007	Graduation as Diplom-Chemiker (Univ.)
02/2008 – 08/2011	PhD studies in the research group of Prof. Dr. Paul Knochel

Language Proficiency

German	mother tongue
French	fluent
English	fluent
Russian	basic proficiency

Memberships

GDCh e.V. (German Chemical Society)

DARC e.V. (German Amateur Radio Association)

FDP (Free Democratic Party)

Publications

1. Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. **"Functionalized Magnesium Organometallics as Versatile Intermediates for the Synthesis of Polyfunctional Heterocycles"**, *Chem. Commun*. **2006**, 583-589.

2. Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. **"Preparation and Reactions of Heteroaryl Organomagnesium Compounds"**, *Chem. Lett.* **2006**, *35*, 2-7.

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

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5. Kienle, M.; Wagner, A. J.; Dunst, C.; Knochel, P. **„Preparation of Heterocyclic Amines via an Oxidative Amination of Zinc Organometallics Mediated by Cu(I). A New Oxidative Cycloamination for the Preparation of Annulated Indole Derivatives"**, *Chem. Asian J.* **2011**, *6*, 512-523.

6. Wagner, A. J.; Monzón, G.; Metzger, A.; Knochel, P. **„Preparation and Reactions of Heteroaromatic Benzylic Zinc Reagents"**, *manuscript in preparation.*

7. Wagner, A. J.; Monzón, G.; Knochel, P. **„Novel Mannich-Type Cations for the One-Pot Preparation of Heteroaromatic Benzylic and Phenethylic Amines",** *manuscript in preparation*.

Posters and Oral Presentations

Wagner, A. J.; Knochel, P**. „Access to Benzofuro- and Benzothieno[2,3-*b*]indoles via Oxidative Coupling of Amidocuprates“**, June 11th 2008, sanofi-aventis AG, Frankfurt, Germany.

Wagner, A. J.; Kienle, M.; Knochel, P. **„Oxidative Copper(I)-Mediated Cycloamination: An Application in the Synthesis of Benzofuro- and Benzothieno[2,3-*b*]indoles“**, June 28th – July 3rd 2008, Bayer PhD student course, Cologne, Germany.

Kienle, M.; Wagner, A. J.; Knochel, P. **„Copper(I)-Mediated Oxidative Cross-Coupling Reactions: Synthesis of Functionalized Amines and Acetylenes“**, March 18th 2009, Synthesefest 2009, LMU München, Munich, Germany.

Wagner, A. J.; Knochel, P. „**Preparation and Reactivity of Heteroaromatic Benzylic Zinc Reagents“**, July 20th – July 24th 2010, International Symposium on Carbanion Chemistry, Florence, Italy.

Wagner, A. J.; Monzón, G.; Knochel, P. **„Novel Mannich-Type Cations for the One-Pot Preparation of Heteroaromatic Benzylic and Phenethylic Amines“**, September 20th – September 21st 2010, Eli Lilly Drug Discovery Workshop, Erl Wood, England, United Kingdom.