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New Preparations and Reactions of Organometallic Reagents of Mg, Zn, Li, Al and B for the Functionalization of Aromatics and Heteroaromatics

von

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Erklärung

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Andreas Unsinn

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Parts of this PhD thesis have been published

Communications and Full Papers

1.) Stefan H. Wunderlich, Christoph J. Rohbogner, Andreas Unsinn, Paul Knochel, „Scaleable Preparation of Functionalized Organometallics *via* Directed Ortho Metalation Using Mg- and Zn-Amide Bases“, *Org. Process Res. Dev.*, **2010**, *14* (2), 339.

2.) Marcel Kienle, Andreas Unsinn, Paul Knochel, „Synthesis of Dibenzothiophenes and Related Classes of Heterocycles by Using Functionalized Dithiocarbamates”, *Angew. Chem.* **2010**, *122*, 4860; *Angew. Chem. Int. Ed.* **2010**, *49*, 4751.

3.) Milica Jaric, Benjamin A. Haag, Andreas Unsinn, Konstantin Karaghiosoff, Paul Knochel, „Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or TMP-Zinc and TMP-Magnesium Bases with $BF_3{\cdot}OEt_2$”, *Angew. Chem.* **2010**, *122*, 5582; *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

4.) Andreas Unsinn, Paul Knochel, „Regioselective Zincation of Indazoles Using TMP_2Zn and Negishi Cross-Coupling with Aryl and Heteroaryl Iodides”, *Chem. Commun.* **2012**, *48*, 2680.

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6.) Andreas Unsinn, Cora Dunst, Paul Knochel, „Stereoselective Synthesis of Tetrasubstituted Alkenes *via* a Sequential Carbocupration and a new Sulfur–Lithium Exchange“ *Beilstein J. Org. Chem.* **2012**, *8*, 2202.

7.) Andreas Unsinn, Mark J. Ford, Paul Knochel, „ New Preparation of TMPZnCl·LiCl by Zn Insertion into TMPCl. Application to the Functionalization of Dibromodiazines”, *Org. Lett.* **2013**, *15*, 1128.

8.) Andreas Unsinn, Stefan H. Wunderlich, Paul Knochel, „Accelerated Zincations for an Efficient and Mild Functionalization of Aromatics and Heterocycles“, *Adv. Synth. Catal.* **2013**, *355*, 989.

9.) Andreas Unsinn, Stefan H. Wunderlich, Anukul Jana, Konstantin Karaghiosoff, Paul Knochel, „A Convenient Alumination of Functionalized Aromatics Using the Frustrated Lewis Pair Et_3Al and TMPMgCl·LiCl“, *Chem. Eur. J.* **2013**, DOI: chem.201301869.

Patents

1.) Andreas Unsinn, Mark J. Ford, Paul Knochel, „Darstellung von Zinkamiden, insbesondere TMPZnCl·LiCl“, DE 10 2012 018 535.9

„Das Geheimnis aller Erfinder ist, nichts für unmöglich anzusehen.“

Justus Freiherr von Liebig

für meine Eltern

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A. INTRODUCTION

1 OVERVIEW

At the beginning of the 21st century mankind is facing previously unseen and unprecedented challenges. The mega trend world population growth is a key driver for the economic growth since the demand for food, goods and services has increased with the increasing poulation. According to the *United Nations* estimates the world's population will increase from 7 billion to 8.3 billion within the next 20 years and will reach 9.3 billion in 2050.[1] In the developing and emerging countries the population is expected to grow dynamically. It's been projected that more than 85% of the global population will make up these regions and in 2030 and 2050 these countries will contain as many as 7 billion and 8 billion inhabitants, respectively.

Undoubtedly, the expanding population is continuing to put an enormous amount of strain on limited resources, such as soil, water, fossil and mineral raw materials or energy. Due to the global population and economic growth, resources in the next 20 years are expected to become relatively scarce. Nevertheless, the total energy consumption in 2030 is presumed to be 50 percent higher than today's level.[2] As the growing demand meets a limited supply, it can be assumed that the prices of energy and raw materials will continue to rise in the future. The International Energy Agency expects the oil price to increase to $135 per barrel by 2030 (based on the price per barrel in 2010).[3] Adjusted for inflation based on the cost of the GDP of the USA a nominal price of $243 per barrel in 2030 is resulting. Thus, scarce resources and high energy prices provide an incentive to resource efficient production and for the production of energy-efficient products.

Furthermore, the threat of climate change is globally acknowledged[4] and it is very likely that this is predominantly caused by the increasing human interference with the atmosphere.[5] Therefore, the political and social importance of environmental and climate protection will continue to increase.

Technological and scientific progress and the knowledge gained in one hand are further important drivers of global economic growth, but on the other hand, play a major role in providing solutions to these new challenges and threats.[6]

With an annual turnover of 184 billion € and more than 428.000 employees in 2011 the German chemical and pharmaceutical industry is the largest in Europe and 4th largest worldwide.[7] It also represents one of the most important branches of the German economy. The chemical industry, in terms of production value, is the fifth largest industrial sector in Germany. Although only 6% of German manufacturing industries employees work in the chemical industry, they produced 10% of

[1] Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, *World Population Prospects. The 2010 Revision. World Population change per year (thousands) Medium variant 1950–2050*.
[2] Verband der chemischen Industrie (VCI), *Die deutsche chemische Industrie 2030*, **2012**.
[3] International Energy Agency (IEA), *World Energy Outlook 2012*. *Current Policies Scenario*.
[4] Joint Science Academies, *Science* **2010**, 392, 1261.
United Nations Environment Programme, *Unep Yearbook 2013: Emerging Issues in Our Global Environment*.
[5] Joint science academie's statement 2007: Statement on Growth and Responsibility: Sustainability, Energy Efficiency and Climate Protection
[6] S. Kuznets, *Amer. Econ. Rev.* **1973**, *63*, 247.
[7] Verband der chemischen Industrie (VCI), *Auf einen Blick: Chemische Industrie 2012*.

the production volume. The key to this is that chemical industry is one of the most highly innovative sectors of the German economy. 10 percent of all chemical employees in Germany work in research and development (R&D). The sector invested in 2011 around 8.8 billion € in R&D. With its pointing the way ahead materials, intermediate products, and ideas as well as their application know-how, the chemical industry is a stimulus for innovation also in other sectors. In a unique way, chemistry and especially organic chemistry has been and is providing practical and efficient solutions to a variety of problems.

The development of fertilizers, herbicides, fungicides and insecticides has not only led to an increase in total harvested area[8] due to multiple cropping and reduced fallows, but also to more efficient cultivation of the available acreage, therefore more crops are being harvested per acre.[9] Pharmaceutical chemistry is providing us with drugs rising life expectancy and joie de vivre (Figure 1). Other branches of chemistry are also responsible for provididing us with new, efficient and practical materials for heat insulation, photovoltaic conversion or solar thermal energy. In addition, chemistry has paved the way for the development of novel light weight yet functional composite materials for aircrafts and cars and also light emitting diodes (LED) as well as organic LEDs (OLED), which have led to a reduction in energy consumption.

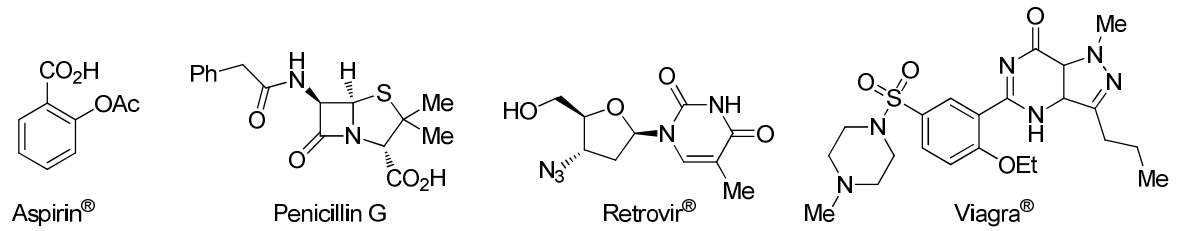


Figure 1: Selected important medicaments.

But of course the field of chemistry will continue to face new challenges as the 21st century progresses. In the words of *Royoji Noyori*, "*Indeed, our ability to devise straightforward and practical chemical syntheses is indispensable to the survival of our species … Without attention to what is now called ''green chemistry'',*[10] *chemical manufacturing will be unsustainable in this century … Green chemistry is not a mere catch-phrase but an indispensable principle that will sustain our civilized society in the 21st century*."[11] Therefore, chemical reactions should proceed with a high atom economy[12] and a low E-factor.[13] Furthermore, unnecessary interconversions of functional groups or protection/deprotection steps should be avoided.[14] Organometallic chemistry meets many of these requirements, as novel organometallic chemistry allows for transformations which were impossible

[8] Food and Agriculture Organization of the United Nations (FAO), *FAO Statistical Yearbook 2012*.
[9] Food and Agriculture Organization of the United Nations (FAO), *World Agriculture Towards 2030/2050*. The 2012 Revision.
[10] P. T. Anastas, J. C. Warner, *Green Chemistry, Theory and Practice*, Oxford University Press, Oxford, **1998**.
[11] R. Noyori, *Chem. Commun.* **2005**, 1807.
[12] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed.* **1995**, *34*, 259; c) A. Matlack, *Introduction to Green Chemistry*, CRC Press, Boca Raton, **2010**.
[13] a) R. A. Sheldon, *Chem. Ind.* (London), **1992**, 903; b) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273; c) R. A. Sheldon, I. Arends and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**.
[14] a) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404; b) R. W. Hoffmann, *Synthesis* **2006**, 3531; c) V. Sofiyev, G. Navarro, D. Trauner, *Org. Lett.* **2008**, *10*, 149.

to perform through conventional synthetic methods. In the last decades, much shorter syntheses of complex organic molecules have been successfully performed, using the powerful methodology of organometallic chemistry. Indeed, organometallic chemistry has revolutionized organic synthesis and therefore has become one of the most important areas of chemical research. According to 2010 Nobel-Price laureate *E.-I. Negishi,* "*Nowadays, it is not only unwise but rather difficult to accomplish an efficient and selective multiple synthesis without using organometallics.*"[15]

1.1 PREPARATION OF ORGANOMETALLIC REAGENTS

In 1760, *Louis Claude Cadet* synthesized a mixture of Me_4As_2 (cacodyl) and Me_4As_2O (cacodyl oxide), named "*Cadet's fuming liquid*".[16] These are considered to be the first organometallic compounds synthesized.[17] Another milestone in organometallic chemistry was the isolation of potassium trichloro(ethene)platinate(II) (*Zeise's salt*) by *William Christopher Zeise* in 1827.[18] Since the first presentation of the Nobel-Prize in 1901, 25 Nobel-Prize laureates have received the prize for contributions in the field of organic chemistry, including the nine awarded Nobel-Prizes in the field of organometallic chemistry,[19] demonstrating the impressive significance of this field. Nowadays, organometallic chemistry combines the study of chemical compounds containing bonds between carbon and a metal and their use in organic synthesis and therefore provides versatile tools for modern organic synthesis. Synthetic organic chemists can choose from an ever-growing toolbox of organometallic reagents and catalysts, each possessing a unique reactivity and selectivity depending on the nature of the metal used.

The origin of the diversity in the properties of organometallic reagents relies mainly on the differences in polarity of the carbon-metal bond.[20] Highly reactive organometallics derived from alkali metals, such as organolithium, -sodium and -potassium reagents, possess a very ionic carbon-metal bond and therefore provide very nucleophilic carbon atoms displaying an excellent reactivity towards many electrophiles, even at low temperatures. However, this drastically diminishes the tolerance towards functional groups.[21] Organoboron, -indium and -tin reagents are located at the other end of the spectrum. With a very covalent carbon-metal bond, they show a high functional group tolerance, but need either harsh conditions or an appropriate catalyst for reactions with electrophiles. Organomagnesium, -copper and -zinc reagents combine both, a high functional group tolerance and reactivity with electrophiles.[22] Perhaps the most important role in organometallic chemistry play transition metals since the presence of d-electrons in their valence shell distinguishes the organometallic chemistry of these elements from the main-group elements. The d-orbitals of

[15] E.-I. Negishi, *Organometallics in Organic Synthesis*, Wiley-VCH, Weinheim, **1980**.
[16] a) D. Seyferth, *Organometallics* **2001**, *20*, 1488; b) J. J. Berzelius, *Jahresber.* **1839** *18*, 487; c) J. H. Burns, J. Waser, *J. Am. Chem. Soc.* ***1957***, *79*, 859.
[17] C. Elschenbroich, *Organometallchemie,* Wiley-VCH, Weinheim, **2008**.
[18] a) W. C. Zeise, *Poggendorff's Ann. Phys.* **1827**, *9*, 632; b) W. C. Zeise, *Poggendorff's Ann. Phys.* **1831**, *21*, 497; c) W. C. Zeise, *Poggendorff's Ann. Phys.* **1837**, *40*, 234.
[19] **1912**: Grignard, Sabatier, **1963**: Ziegler, Natta, **1973**: Wilkinson, Fischer, **1976**: Lipscomb; **1979**: Brown, Wittig; **1981**: Fukui, Hoffmann; **2001**: Knowles, Noyori, Sharpless; **2005**: Chauvin, Grubbs, Schrock, **2010**: Heck, Negishi, Suzuki.
[20] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4585; *Angew. Chem. Int. Ed.* **2003**, *39*, 4415.
[21] J. Clayden, *Organolithiums: Selectivity for Synthesis* (Ed. J. E. Baldwin), Pergamon Press, Oxford, **2002**.
[22] *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

transition metals have an energy suitable for interaction with a variety of reagents. Therefore they can be used as catalysts for organic synthesis. Transition metal catalyzed reactions are currently one of the most important methods for catalytic C-C and C-hetero coupling, cyclization, oxidation and reduction reactions, representatively shown in the synthesis of several pharmaceutics (Figure 2).[23]

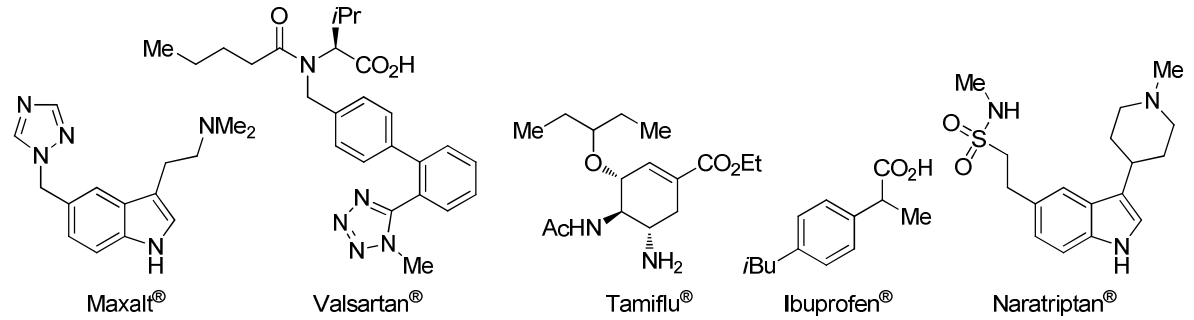


Figure 2: Selected medicaments with syntheses involving transition metals.

In the literature numerous methods for the preparation of organometallic compounds are known. They can mainly be divided in two categories, reactions using elemental metals and reactions of already formed organometallics, each categorie consisting of a variety of methods. However, due to this immense complexity only three of these methods will be pointed out and summarized: oxidative insertion, exchange reactions or direct metalation *via* C-H activation.

1.1.1 OXIDATIVE INSERTION

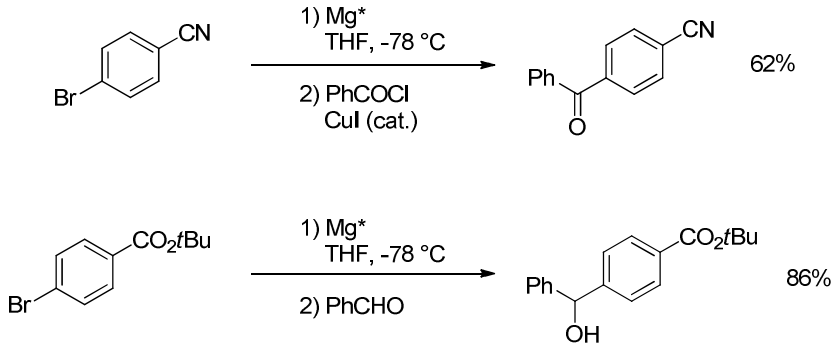
In 1849, *Edward Frankland* was the first to synthesize an organometalllic compound *via* oxidative insertion. In his ground-breaking experiments, he prepared dialkylzinc reagents by reaction of zinc metal with alkyliodides.[24] Exactly ten years later, *Hallwachs* and *Schaferik* investigated the reaction between ethyl or methyl iodide with aluminum.[25] They also experimented with magnesium, but could not isolate a magnesium compound. The first one to succeed in doing so was *Cahours* in 1860.[26] But even after *Cahours*' discovery, organometallic chemistry continued to attract very little attention for almost half a century more.

The greatest milestone in organometallic chemistry was achieved 40 years later, in 1900, by *Victor Grignard*. His supervisor, *Barbier* originally had developed a one pot synthesis of alcohols starting from alkyl halides, magnesium metal and carbonyl containing compounds.[27] But it was *Grignard*, who succeeded in the separate preparation of organomagnesium reagents in etheral solvents before

[23] a) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**; b) M. L. Crawley, B. Trost, *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective,* Wiley-VCH, Weinheim, **2012**; c) R. Bates, *Organic Synthesis Using Transition Metals*, Wiley-VCH, Weinheim, **2012**; d) J. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito, **2009**.
[24] a) E. Frankland, *Ann. Chem.* **1849**, *71*, 171; b) E. Frankland, *Ann. Chem.* **1849**, *71*, 213.
[25] W. Hallwachs, A. Schaferik, *Ann. Chem.* **1859**, *109*, 206.
[26] A. Cahours, *Ann. Chem*. **1860**, *114*, 227.
[27] P. Barbier, *C. R. Hebd. Séances Acad. Sci.* **1899**, *128*, 110.

addition of the carbonyl compound.[28] Today, more than a century after *Grignard*'s findings, *Grignard* reagents continue to play an integral role in organic synthesis.

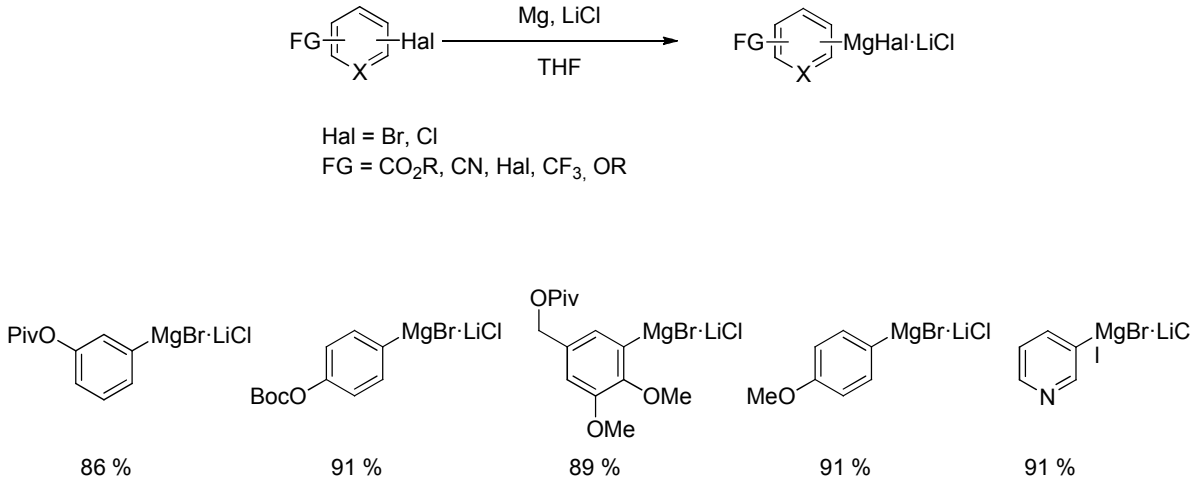
Although the precise mechanism of this reaction is still not entirely elucidated, radical pathways are generally accepted.[29] The reaction usually requires reflux conditions and therefore the functional group tolerance is limited. The induction period is another drawback of the direct magnesium insertion. It is dependent on the amount of moisture present in the reaction, and dependent on the surface of the magnesium. Generally, magnesium metal is passivized by a layer of magnesium oxide or magnesium hydroxide. Therefore, it is essential to remove these coatings by adding either 1,2-dibromoethane or diisobutylaluminum hydride. Industrial chemistry uses the latter.[30] The problems faced with magnesium metal can be avoided by using highly reactive metal powders, such as *Rieke* metals. *Rieke* metals are prepared by reduction of an anhydrous metal chloride with an alkali metal in THF. Typically used alkali metals are potassium, sodium, and lithium. The method allows for the preparation of *Grignard* reagents from relatively unreactive halides as well as tolerance of some functional groups, such as *tert*-butylester or nitriles (Scheme 1).[31]



Scheme 1: Preparation of functionalized *Grignard* reagents using *Rieke* magnesium.

Although this method allows for an atom efficient preparation of various *Grignard* reagents, it still has some drawbacks. The reagent has to be freshly prepared, the functional group tolerance is still limited and extensive cooling is necessary. Recently, *Knochel* and coworkers found that LiCl promoted magnesium insertion allows for an efficient and mild preparation of highly functionalized *Grignard* reagents starting from aromatic or heteroaromatic bromides and chlorides (Scheme 2).[32]

[28] V. Grignard, *C. R. Hebd. Seanes Acad. Sci.* **1900**, *130*, 1322.
[29] a) H. M. Walborksy, *Acc. Chem. Res.* **1990**, *23*, 286; b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95; c) J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[30] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[31] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; c) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; d) R. D. Rieke, *Aldrichchim. Acta* **2000**, *33*, 52.
[32] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem.* **2008**, *120*, 6907; *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

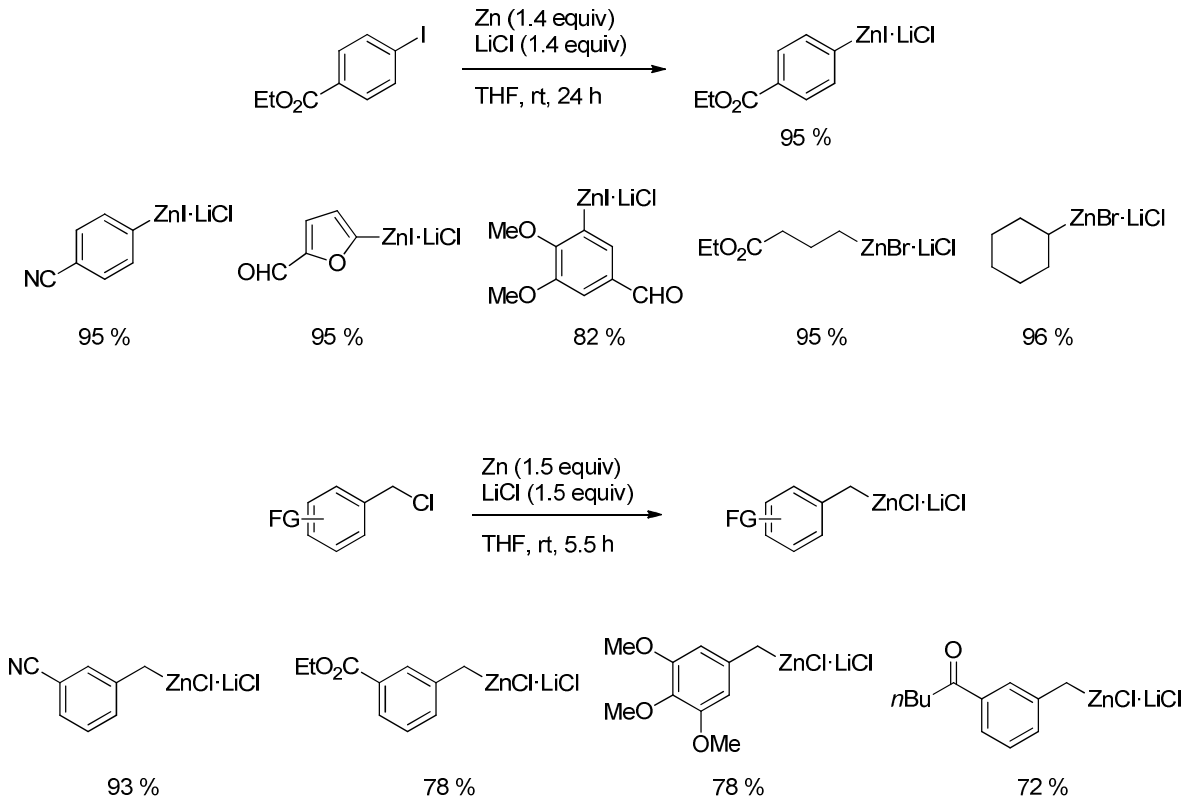


Scheme 2: Synthesis of organomagnesium reagents using Mg in the presence of LiCl.

More sensitive functionalities can be tolerated by performing the magnesium insertion in presence of trialkylborates[33] or zinc salts.[34] The usage of $Zn(OPiv)_2$ even allows for the preparation of solid organozinc compounds that show air stability for a period of time.[35]

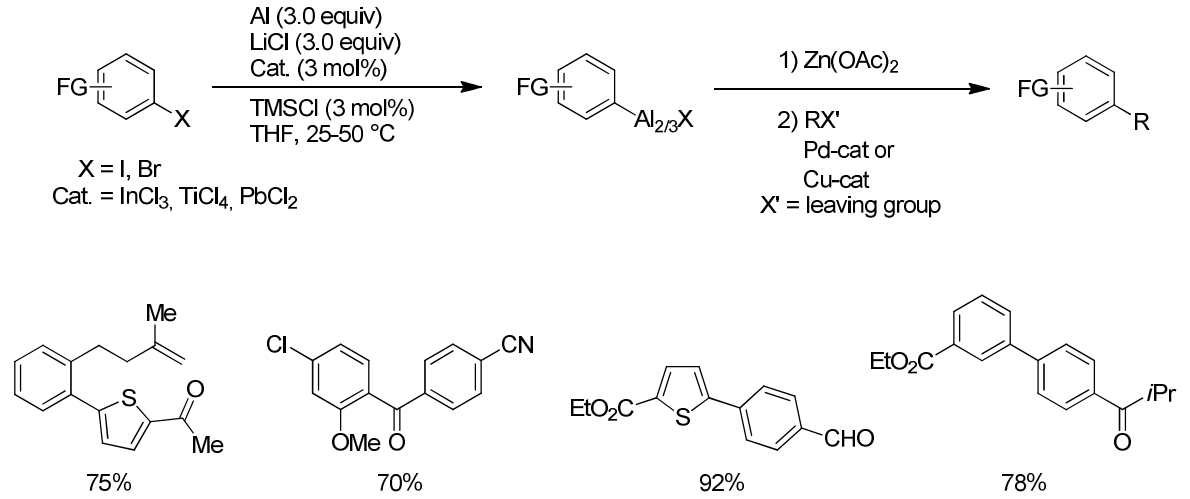
Analogously to the magnesium reagents, organozinc compounds can be prepared *via* insertion of zinc metal into halide bonds. This is possible either in the form of zinc dust[36] (typically activated with 1,2-dibromoethane, TMSCl and iodine),[37] at elevated temperature and in polar solvents, such as dimethylacetamide, HMPA, DMF, or DMSO,[38] or *via Rieke* zinc.[39] *Knochel* and coworkers showed that LiCl facilitates the zinc insertion, providing functionalized organozinc reagents from the corresponding aromatic or heteroaromatic iodides and bromides, alkyl bromides and benzyl chlorides at convenient temperatures (Scheme 3).[40]

[33] B. A. Haag, C. Sämann, A. Jana, P. Knochel, *Angew. Chem.* **2011**, *123*, 7428; *Angew. Chem. Int. Ed*. **2011**, *50*, 7290.
[34] a) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824; b) T. Blümke, F. M. Piller P. Knochel, *Chem. Commun.* **2010**, 4082.
[35] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem.* **2011**, *123*, 9372; *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem.* **2012**, *124*, 9563; *Angew. Chem. Int. Ed.* **2012**, *51*, 9428.
[36] a) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413; b) H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974; c) P. Knochel, C. Janakiram, *Tetrahedron* **1993**, *49*, 29; d) T. M. Stevenson, B. Prasad, J. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375
[37] a) M. Gaudemar, *Bull. Soc. Chim. Fr*. **1962**, *5*, 974; b) E. Erdik, *Tetrahedron* **1987**, *43*, 2203.
[38] a) H. Hunsdiecker, H. Erlbach, E. Vogt, *German Patent 722467*, **1942**; b) K. Tagaki, N. Hayama, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691; c) K. Tagaki, *Chem. Lett.* **1994**, 469; d) K. Tagaki, Y. Shimoishi, K. Sasaki, *Chem. Lett.* **1994**, 2055; e) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.
[39] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) M. V. Hanson, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; c) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; d) M. V. Hanson, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 1445; e) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.
[40] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.



Scheme 3: LiCl-mediated preparation of functionalized organozinc reagents.

Knochel and coworkers also showed that aluminum powder undergoes a LiCl-mediated oxidative insertion into aryl iodides and bromides, although the reaction requires an additional catalyst such as $TiCl_4$, $BiCl_3$, $InCl_3$ or $PbCl_2$. The resulting arylaluminum halides, possessing the sesquihalide structure ($Ar_3Al_2X_3$=$ArAl_{2/3}X$), undergo Pd-catalyzed cross-couplings and acylations or Cu-catalyzed allylations after transmetalation with $Zn(OAc)_2$ (Scheme 4).[41]



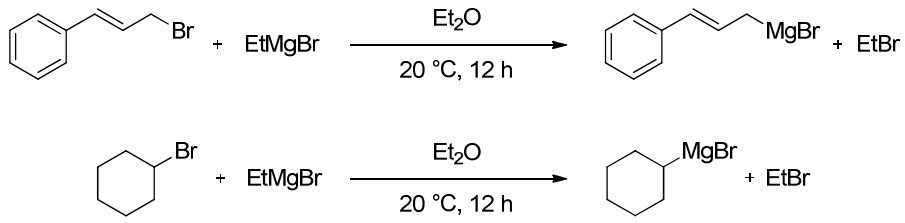
Scheme 4: Preparation and reactions of functionalized organoaluminum reagents.

[41] a) T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; b) L.-N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 9829; c) Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem.* **2010**, *122*, 8695; *Angew. Chem. Int. Ed.* **2010**, *49*, 8516; d) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440.

Furthermore, Knochel and coworkers have also reported LiCl-mediated oxidative insertions of indium[42] and manganese[43] metal into benzylic, aromatic or heteroaromatic halides, tolerating a large variety of functional groups.

1.1.2 HALOGEN-MAGNESIUM EXCHANGE

Ever since the first report of organomagnesium reagents, the direct insertion of magnesium metal into carbon-halogen bonds has been the most straightforward approach to their preparation.[44] Another important method for the preparation of organomagnesium species is the halogen-magnesium exchange. The first example of a bromine-magnesium exchange reaction was published in 1931 by *Prévost*.[45] The reaction of cinnamyl bromide with ethylmagnesium bromide gave cinnamylmagnesium bromide and the homocoupling product. Three years later *Urion* published the reaction of cyclohexyl bromide with ethylmagnesium bromide which led to cyclohexylmagnesium bromide (Scheme 5).[46]



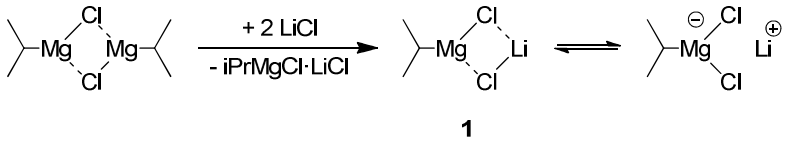
Scheme 5: First examples of a halogen-magnesium exchange.

The halogen-magnesium exchange is an equilibrium in which the formation of the most stable organomagnesium species is favoured. The exact mechanism of this exchange is still not known. However, a halogen ate complex is assumed to be an intermediate in this process.[47] Similar complexes have also been proposed for the halogen-lithium exchange.[48] Furthermore, the electronic properties of the halogen as well as of the organic substrate play an important role for the generation of the magnesiated compounds.[49]

Thus, *Knochel* and coworkers have impressively demonstrated the synthetic power of this reaction by developing a general protocol for an iodine-magnesium exchange on aromatic iodides bearing sensitive functional groups, such as an ester or a nitro-group using *i*PrMgBr or PhMgCl.[50] The halogen-magnesium exchange reaction could be further improved by the development of the

[42] a) Y.-H. Chen, P. Knochel, *Angew. Chem.* **2008**, *120*, 7760; *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem.* **2009**, *121*, 2270; *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.
[43] Z. Peng, P. Knochel, *Org. Lett*. **2011**, *13*, 3198.
[44] a) *Handbook of Grignard Reagents*, (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**; b) *Grignard Reagents, New Developments* (Ed.: H. G. Richey jr.), Wiley & Sons, New York, **2000**.
[45] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, 1372.
[46] E. Urion, *C. R. Hebd. Séances Acad. Sci.* **1934**, *198*, 1244.
[47] a) R. W. Hoffmann, M. Bönstrup, M. Müller, *Org. Lett.* **2003**, *5*, 313; b) V. P. W. Böhm, V. Schulze, M. Bönstrup, M. Müller, R. W. Hoffmann, *Organometallics* **2003**, *22*, 2925.
[48] a) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1; b) H. J. Reich, N. H. Phillips, I. L. Reich, *J. Am. Chem. Soc.* **1985**, *107*, 4101; c) W. B. Farnham, J. C. Calabrese, *J. Am. Chem. Soc.* **1986**, 108, 2449.
[49] C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153.
[50] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, P. Knochel, *Angew. Chem.* **2002**, *114*, 1680 *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; c) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565.

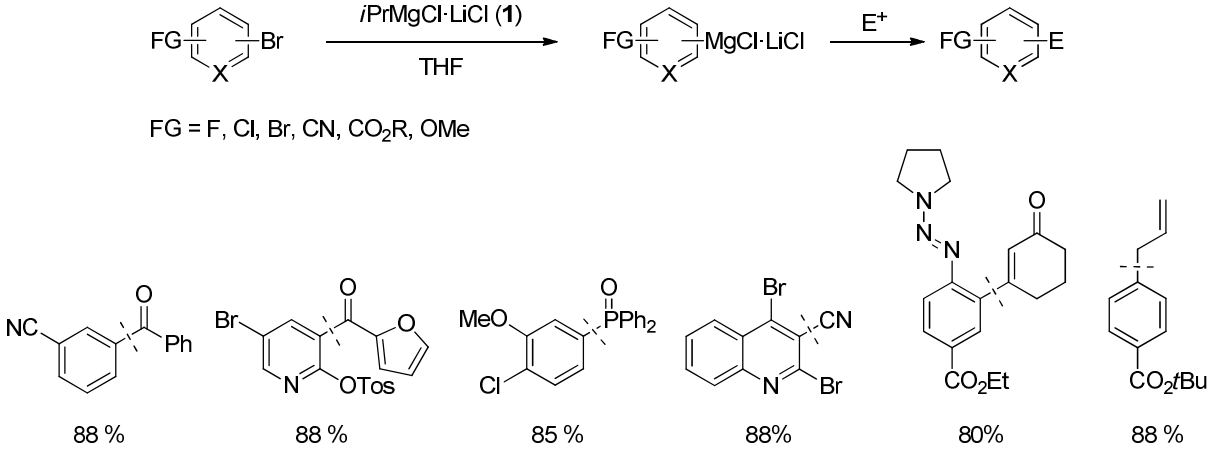
reagent *i*PrMgCl·LiCl (**1**). The exceptional reactivity boost may be best explained by the formation of magnesium-lithium ate complexes (Scheme 6).



1

Scheme 6: Effect of LiCl on *i*PrMgCl (**1**).

Using this new exchange reagent called "Turbo-*Grignard*", a broad range of aromatic and heteroaromatic bromides were converted into their corresponding organomagnesium reagents (Scheme 7).



Scheme 7: *i*PrMgCl·LiCl (**1**) as a reagent for the bromine-magnesium exchange.

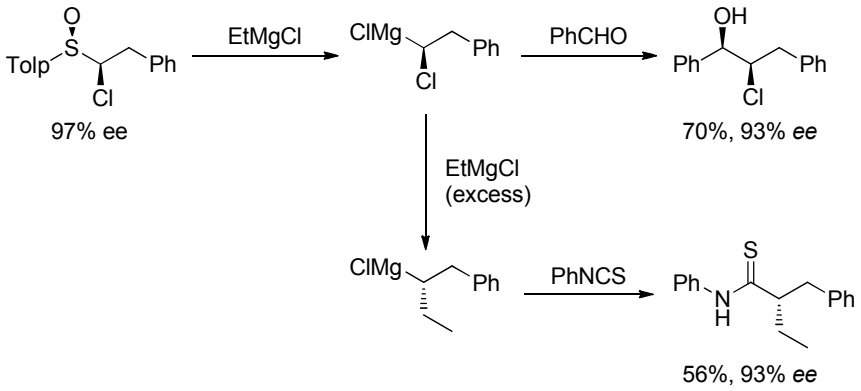
Iodine-zinc exchange reactions have also been reported. They proceed well on alkyl iodides in the presence of catalytic amounts of Cu(I)-salts,[51] whereas the same reaction on aryl iodides proceeds well with $(i\text{Pr})_2\text{Zn}$ in the presence of catalytic amounts of Li(acac).[52]

1.1.3 OTHER EXCHANGE REACTIONS

Sulfoxides are another class of substrates that undergo exchange reactions. This methodology is based on the pioneering works of *Satoh*, who reported in 1995 a series of sulfoxide-magnesium exchanges on *α*-chloro-substituted vinyl sulfoxides, yielding vinyl *Grignard* reagents.[53] Before, such exchanges had only been reported for the synthesis of chiral molecules using highly reactive lithium

[51] a) M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956; b) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115.
[52] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem.* **2004**, *116*, 1032; *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[53] a) T. Satoh, K. Takano, H. Someya, K. Matsuda. *Tetrahedron Lett.* **1995**, *36*, 7097; b) T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, K. Yamakawa, *Tetrahedron* **1998**, *54*, 5557; c) T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561.

reagents, nevertheless the functional group tolerance in these syntheses was limited.[54] *Satoh*[55] and *Hoffmann*[56] further investigated the sulfoxide magnesium exchange, and the latter used this methodology for the preparation of chiral *Grignard* reagents. These organomagnesium reagents could then be reacted with electrophiles to generate products with a second chiral center and transfer the stereochemical information (Scheme 8).



Scheme 8: Sulfoxide-magnesium exchange on chiral sulfoxides.

Recently, *Knochel* and coworkers used the sulfoxide group for the regioselective functionalization of arenes and heteroaromatics.[57] *Knochel* and coworkers also reported an S-Mg exchange for the preparation of benzyl magnesium reagents.[58]

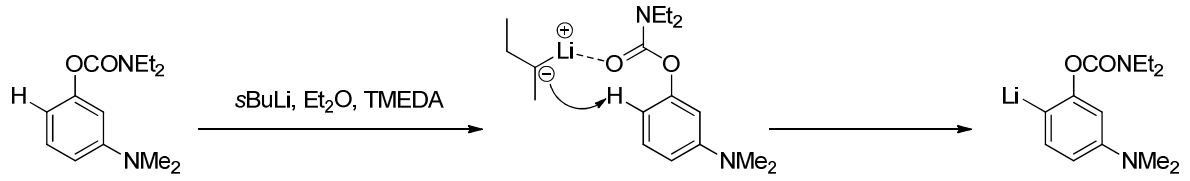
1.1.4 DIRECTED METALATION

The third major way to generate organometallics is the directed metalation using alkyl metals or metal amide bases. In contrast to insertion and exchange reactions, there is no need for an "expensive" halogen-carbon bond. Directed metalation requires only the smallest and therefore most common organic structure characteristic: a carbon-hydrogen-bond. The first organometallic deprotonation reaction studied involved the reaction between fluorene and EtLi reported by *Schlenk* in 1928.[59] This reaction thus led to extensive investigations into this methodology.[60]

In the following years, the methodology was in the focus of research and numerous new approaches and applications have been published.[61] In particular, *Beak* and *Snieckus* intensively investigated the directed *ortho*-metalation (D*o*M) using lithium bases and the complex-induced proximity effect

[54] a) D. Guillaneux, H. B. Kagan, *J. Org. Chem.* **1995**, *60*, 2502; b) H. B. Kagan, T. O. Luukas in *Transition Metals for Organic Synthesis* (Eds. M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**; c) R. J. Kloetzing, P. Knochel, *Tetrahedron: Asymm.* **2006**, *17*, 116.
[55] a) T. Satoh, D. Taguchi, C. Suzuki, S. Fujisawa, *Tetrahedron* **2001**, *57*, 493; b) T. Satoh, K. Akita, *Chem. Pharm. Bull.* **2003**, *51*, 181; c) T. Satoh, M. Miura, K. Sakai, Y. Yokoyama, *Tetrahedron* **2006**, *62*, 4253; d) S. Sugiyama, H. Shimizu, T. Satoh, *Tetrahedron Lett.* **2006**, *47*, 8771; e) T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561.
[56] a) R. W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, *Angew. Chem.* **2000**, *112*, 3206; *Angew. Chem. Int. Ed.* **2000**, *39*, 3072; b) B. Hölzer, R. W. Hoffmann, *Chem. Commun.* **2003**, 732; c) R. W. Hoffmann *Chem. Soc. Rev.* **2003**, *32*, 225.
[57] a) C. B. Rauhut, L. Melzig, P. Knochel, *Org. Lett*. **2008**, *10*, 3891; b) L. Melzig, C. B. Rauhut, P. Knochel, *Synthesis* **2009**, *6*, 1041; c) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 5362.
[58] A. H. Stoll, A. Krasovskiy, P. Knochel, *Angew. Chem.* **2006**, *118*, 621; *Angew. Chem. Int. Ed.* **2006**, *45*, 606.
[59] W. Schlenk, E. Bergmann, *Ann. Chem.* **1928**, *463*, 98.
[60] For an early overview about metalation using organolithium compounds, see: J. M. Mallan, R. L. Bebb, *Chem. Rev.* **1969**, *69*, 693 and references therein.
[61] a) H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109; b) G. Wittig, G. Fuhrmann, *Chem. Ber.* **1940**, *73*, 1197.

(CIPE).[62] The concept D*o*M describes the regioselective functionalization of aromatic systems, if a directing metalation group (DMG) is present in the molecule. The DMG is typically a lewis basic moiety that interacts with the lewis acidic alkyl cation allowing for deprotonation *ortho* to the directing group (Scheme 9). For instance, amides, carbamides, sulfonamides, esters, cyanides, phosphorous-containing substituents, sulfoxides or sulfones are considered to be efficient directing groups in contrast to ethers or amines. In contrast CIPE is especially an important factor for non-aromatic metalations. It describes the pre-lithiation complex formed between a lewis-basic heteroatom on the DMG and the alkyllithium. By the establishment of this complex the lithiating species is in close proximity to the relatively acidic proton of the substrate. Consequently it is accounting for the observed regioselectivity.



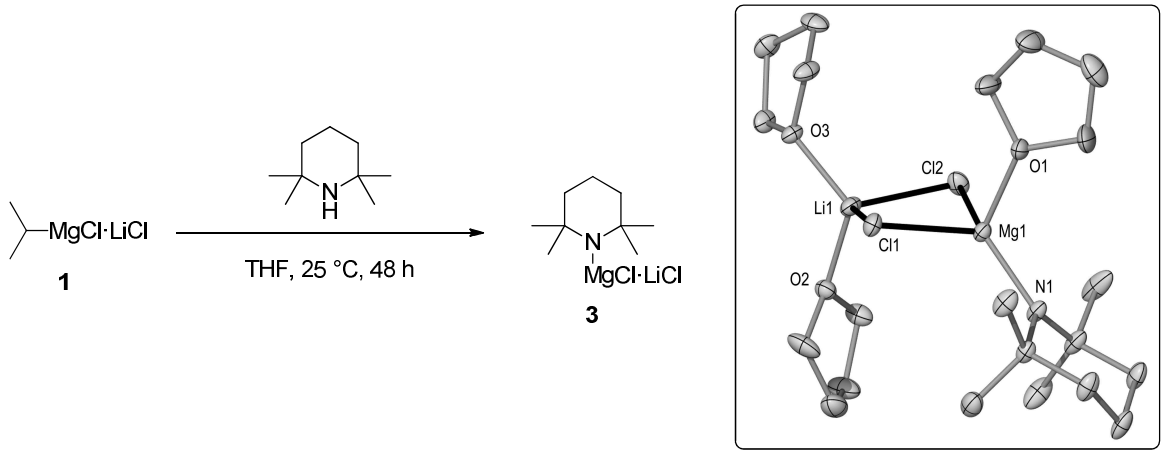
Scheme 9: Regioselective lithiation of a carbamate.

Traditionally, strong bases such as alkyllithium reagents (RLi like *s*BuLi) and lithium amides (R_2NLi like LiTMP) have been extensively used for these kinds of metalations. However, such bases create complications since they often lead to undesired side reactions due to their high reactivity, their strong nucleophilicity (e.g. *Chichibabin* addition[63]) and their low functional group tolerance. Another serious drawback is the low stability of organolithium reagents in THF solution at ambient temperature. Furthermore, such deprotonation reactions have often to be carried out at very low temperatures (-78 to -100 °C), which is not convenient for upscaling.

To overcome these problems, metalations mediated by much milder Mg-amide bases have been investigated. Based on *Meunier*'s original discoveries,[64] *Hauser*[65] reported the use of diethyl- and diisopropylaminomagnesium bromide, whereas *Eaton*[66] and later *Mulzer*[67] used the more sterically demanding 2,2,6,6-tetramethylpiperidine (**2**: TMPH) for their bases of type R_2NMgX, R_2NMgR' and $(R_2N)_2Mg$. However, similar to classic *Grignard* reagents, these magnesium amides are aggregated, leading to low kinetic basicity and low solubility. Consequently, large excesses of the magnesiumamide and electrophile had to be used to overcome these drawbacks.

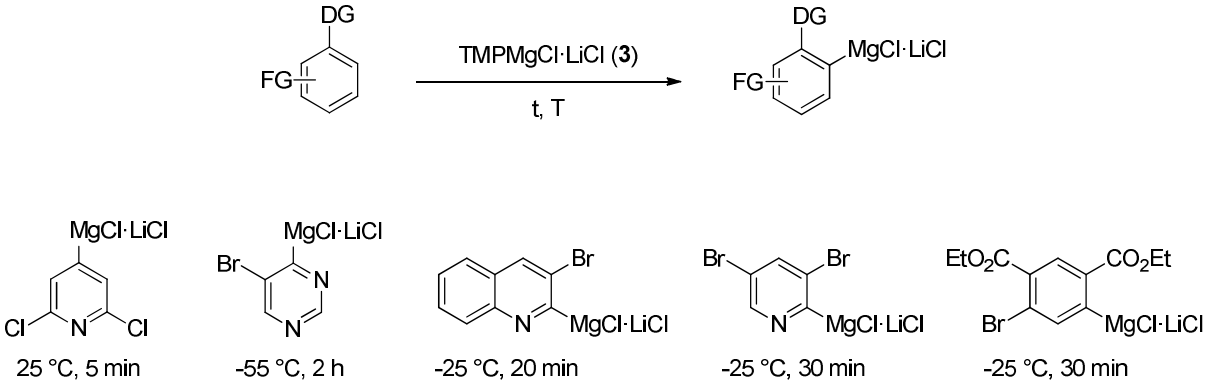
[62] For an overview, see: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667; c) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; d) P. Beak, A. I. Meyers, *Acc. Chem. Res*. **1986**, *19*, 356.
[63] A.E. Chichibabin, O.A. Zeide*, J. Russ. Phys. Chem. Soc.* **1914**, *46*,1216.
[64] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[65] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[66] a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc*. **1989**, *111*, 8016; b) M.-X. Zhang, P. E. Eaton, *Angew. Chem.* **2002**, *114*, 2273; *Angew. Chem. Int. Ed.* **2002**, *41*, 2169; c) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc*. **1993**, *115*, 11375; d) Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans 1,* **1996**, 2331.
[67] a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414; b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann.* **1995**, 1441; c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis* **1995**, 1225.

A big improvement was the development of the highly active mixed Mg/Li-bases of type $R_2NMgCl{\cdot}LiCl$.[68] Similarly to the deaggregated exchange reagents ("Turbo-Grignard" e.g. *i*PrMgCl·LiCl (**1**), *vide supra*) the addition of LiCl also provides deaggregated amide bases, therefore called "Turbo-*Hauser*-Bases". These reagents and especially TMPMgCl·LiCl (**3**) possess a high solubility in THF and increased reactivity. TMPMgCl·LiCl (**3**) has been crystallized as a monomeric species. Although it cannot be concluded unevoquelly that this is the magnesiating species, it is *bona fide* to do so.[69]



Scheme 10: Preparation and structure of TMPMgCl·LiCl (**3**).

The considerable advantages of this new base not only include the excellent kinetic basicity and the very good solubility, but also the excellent thermal stability in a solution of THF, which results in the ability for long term storage. TMPMgCl·LiCl (**3**) has proven to be suitable for the deprotonation of a wide range of activated aromatics and heterocycles with excellent regio- and chemoselectivity at convenient temperatures[70] (Scheme 11).



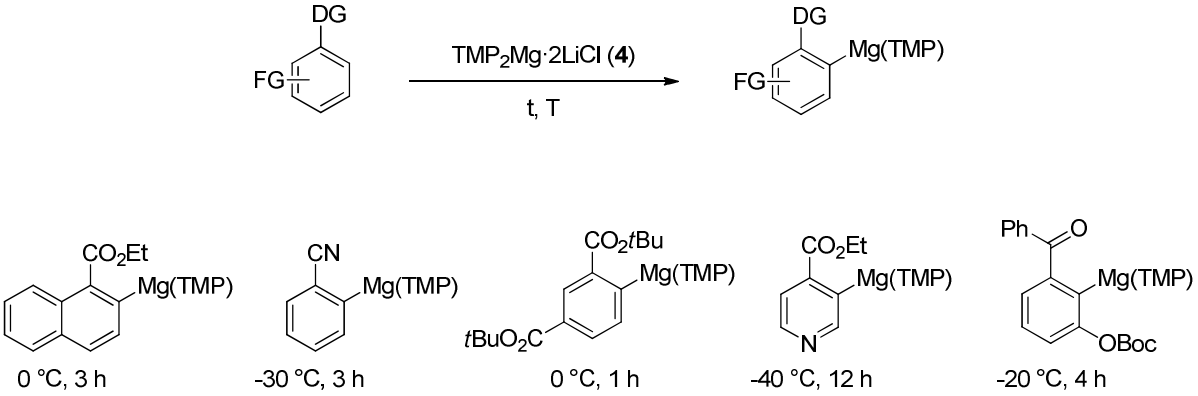
Scheme 11: TMPMgCl·LiCl (**3**) as a reagent in metalation reactions.

[68] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) T. Kunz, P. Knochel, *Angew. Chem.* **2012**, *124*, 1994; *Angew. Chem. Int. Ed.* **2012**, *51*, 1958

[69] P. García-Alvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem.* **2008**, *120*, 8199, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.

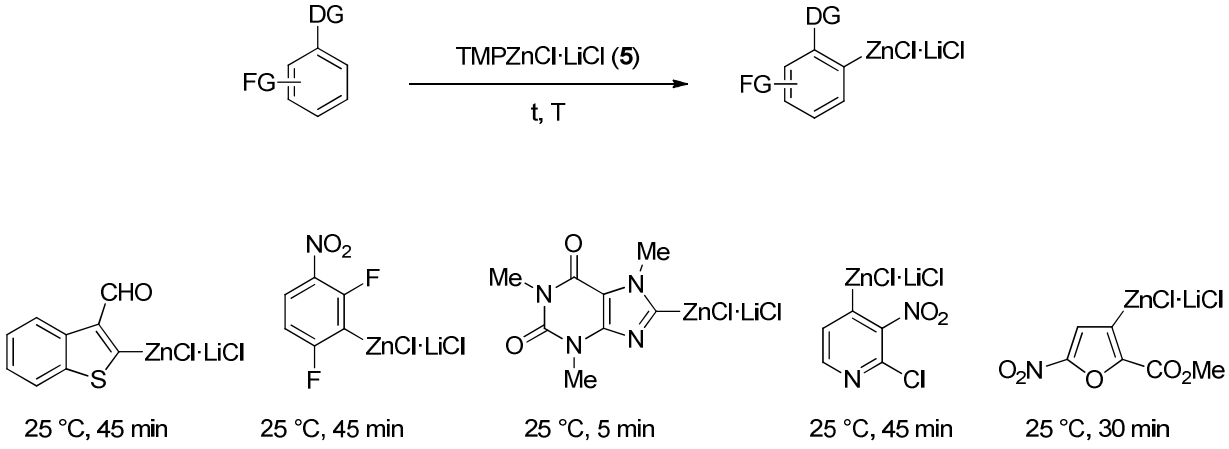
[70] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113.

The concept of these Turbo-Bases was significantly enhanced by the development of magnesium bisamide bases, such as $TMP_2Mg{\cdot}2LiCl$ (**4**).[71] Due to its enhanced kinetic basicity, this base allows for the metalation of less electron-poor and therefore less activated substrates (Scheme 12).



Scheme 12: $TMP_2Mg{\cdot}2LiCl$ (**4**) as a reagent in metalation reactions.

However, some substrates bearing extremely sensitive functionalities, such as a nitro group, an aldehyde and also some heterocycles are excluded from magnesiation with these bases due to degradation. For the metalation of these substrates, milder bases, like TMPZnCl·LiCl (**5**; Scheme 13)[72] and $TMP_2Zn{\cdot}2MgCl{\cdot}2LiCl$ (**6**; Scheme 14)[73] have been developed.

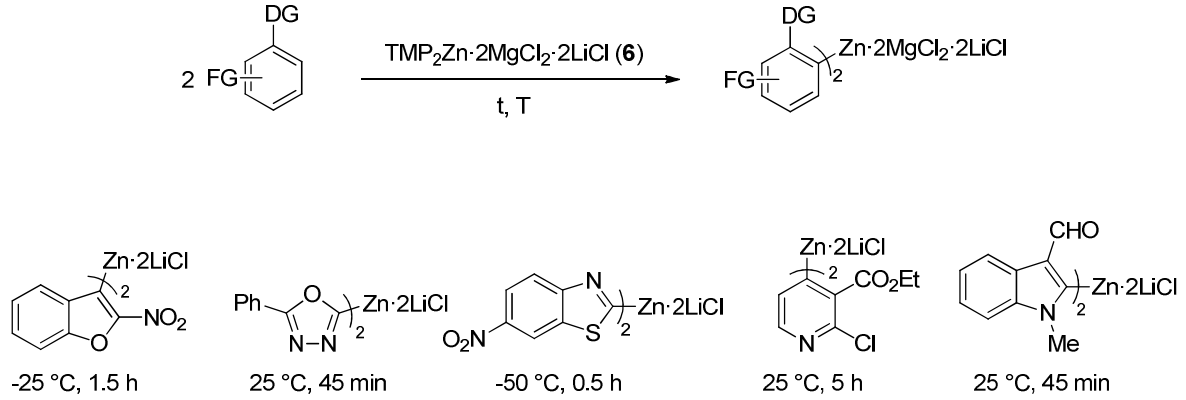


Scheme 13: TMPZnCl·LiCl (**5**) as reagent in metalation reactions

[71] a) G. C. Clososki, C. J. Rohbogner; P. Knochel, *Angew. Chem.* **2007**, *119*, 7825; *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem.* **2008**, *120*, 1526; *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; c) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374.

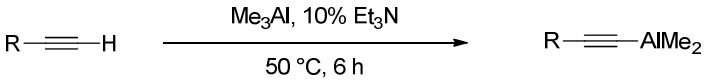
[72] a) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584; b) T. Bresser, P. Knochel, *Angew. Chem.* **2011**, *123*, 1954*; Angew. Chem. Int. Ed.* **2011**, *50*, 1914; c) M. Mosrin, P. Knochel, *Org. Lett*. **2009**, *11*, 1837.

[73] a) S. H. Wunderlich, P. Knochel, *Angew. Chem*. **2007**, *119*, 7829*; Angew. Chem. Int. Ed*. **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; c) S. H. Wunderlich, P. Knochel; *Chem. Commun.* **2008**, *47*, 6387.



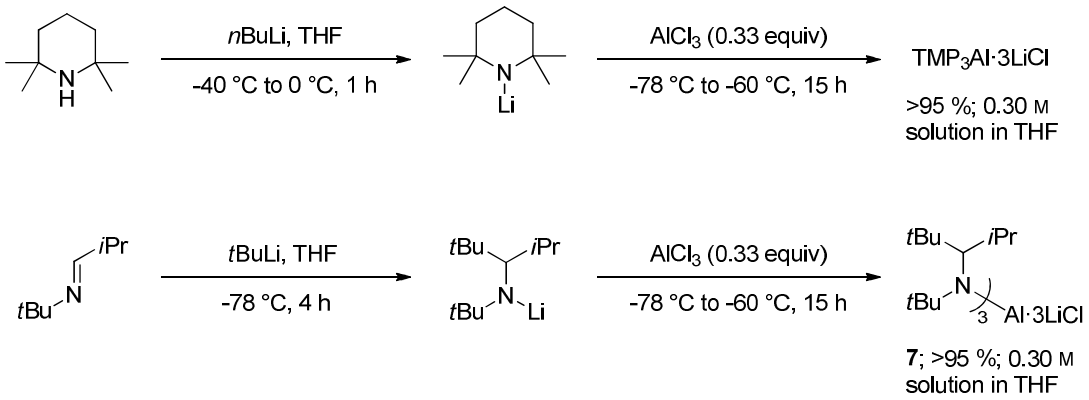
Scheme 14: $TMP_2Zn·2MgCl_2·2LiCl$ (**6**) as reagent in metalation reactions.

In recent years directed aluminations have also been achieved. Therefore, alkynes in hydrocarbon solvents are in the presence of a catalytic amount of tertiary amines deprotonated by Me_3Al, providing alkynylaluminums (Scheme 15).[74]



Scheme 15: Triethylamine-catalyzed alumination of terminal alkynes.

The alumination of aromatic systems was first reported by *Uchiyama.* The aluminate base "*i*Bu$_3$Al(TMP)Li" deprotonates a variety of aromatics and heterocycles, although the base is relatively unstable and two equivalents are needed for achieving full conversion.[75] Later on, *Knochel* and coworkers have reported LiCl-enhanced aluminium bases, such as $TMP_3Al·3LiCl$ and [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**; Scheme 16).

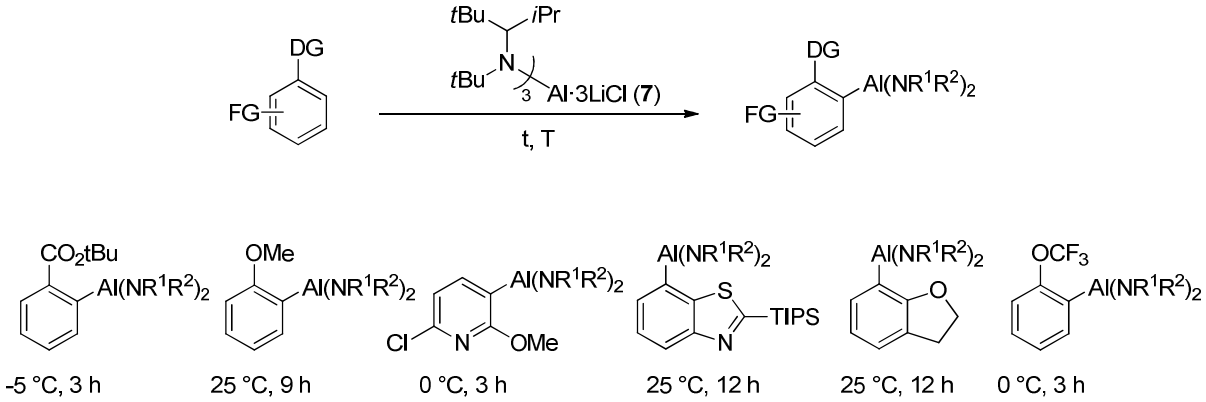


Scheme 16: Synthesis of aluminum trisamide bases.

[74] a) B. Wang,M.; Bonin, L. Micouin, *J. Org. Chem.* **2005**, *70*, 6126; b) B. Wang,M.; Bonin, L. Micouin, *Org. Lett.* **2004**, *6*, 3481; c) C. Feuvrie, J. Blanchet, M. Bonin, L. Micouin, *Org. Lett.* **2004**, *6*, 2333; d) J. Blanchet, M. Bonin, L. Micouin, H.-P. Husson, *Eur. J. Org. Chem.* **2002**, 2598; e) J. Blanchet, M. Bonin, A. Chiaroni, L. Micouin, C. Riche, H.-P. Husson, *Tetrahedron Lett.* **1999**, *40*, 2935; f) J. J. Eisch, W. C. Kaska, *J. Organomet. Chem*. **1964**, *2*, 184.

[75] a) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526; b) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc*. **2007**, *129*, 1921; c) H. Naka, J. V. Morey, J. Haywood, D. J. Eisler, M. McPartlin, F. Garcia, H. Kudo, Y. Kondo, M. Uchiyama, A. E. H. Wheatley, *J. Am. Chem. Soc*. **2008**, *130*, 16193.

These bases proved to be suitable for the preparation of a range of aryl and heteroaryl-aluminium reagents without using an excess of base at convenient temperatures (Scheme 17).[76]



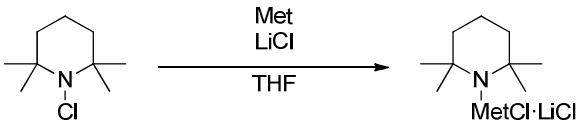
Scheme 17: [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) as reagent in metalation reactions.

Finally, Mn-,[77] Fe-,[78] La-[79] and Zr-amide[80] bases have been reported, addressing the diverse demands for metalating a wide palette of suitable compounds and quenching reactions with a large variety of electrophiles.

[76] S. H. Wunderlich, P. Knochel, *Angew. Chem.* **2009**, *121*, 1530; *Angew. Chem. Int. Ed.* **2009**, *48,* 1501
[77] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem.* **2009**, *121*, 7392; *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[78] S. H. Wunderlich, P. Knochel, *Angew. Chem.* **2009**, *121*, 9897; *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.
[79] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304.
[80] M. Jeganmohan, P. Knochel, *Angew. Chem.* **2010**, *122*, 8699; *Angew. Chem. Int. Ed.* **2010**, *49*, 8520.

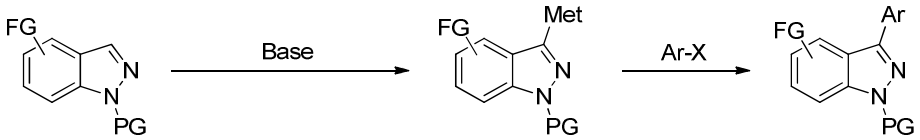
1.2 OBJECTIVES

The aim of the first project was to investigate a new preparation for the amide bases TMPMetCl·LiCl since the known prepration for lab scale has several disadvantages on industrial scale. Thus a preparation *via* oxidative insertion starting from readily available *N*-chloroamines and commercial metal powders should be investigated (Scheme 18). Though, hitherto no useful method for the oxidative insertion into N-Cl bonds is known.



Scheme 18: Intended synthesis for TMP-amide bases.

In the second project a general method for the metalation and arylation of *N*1-protected indazoles in position 3 should be studied. These heterocycles are of interest due to their potential biological activities. However, they are prone to undergo ring-opening reactions when lithium bases are employed.



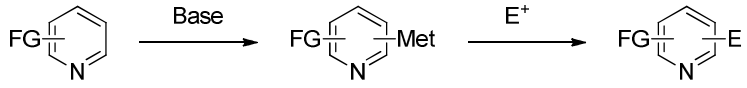
Scheme 19: Desired arylation of *N*1-protected indazoles.

The deprotonation of arenes and heteroarenes using zinc amides is an important method for the functionalization of these scaffolds. Nevertheless, for only mediocre activated compounds very long reaction times or external heating is needed. Previously known procedures lack convenience since they require the use of reagents that cannot be stored. Therefore, a practical and general procedure for an efficient zincation of these compounds would be desirable.[81] As magnesium and especially zinc amides tolerate a wide range of functional groups and sensitive heterocyclic scaffolds, the deprotonation using these reagents should be studied on larger scale for potential industrial application.[82]

Another project focused on the regioselective functionalization of pyridines[83] and condensed S-heterocycles. Attempts to magnesiate, zincate or aluminate unactivated pyridines with LiCl-complexed 2,2,6,6-tetramethylpiperidyl metal amide bases proved to be unsatisfactory. Consequently, a methodology allowing for the regioselective functionalization of these important

[81] This project was developed in cooperation with S. H. Wunderlich, see: S. H. Wunderlich, Dissertation, LMU-München **2010**.
[82] This project was developed in cooperation with S. H. Wunderlich and C. J. Rohbogner, see: S. H. Wunderlich, Dissertation, LMU-München **2010**; C. J. Rohbogner, Dissertation, LMU-München **2010**.
[83] This project was developed in cooperation with M. Jaric and B. A. Haag, see: M. Jaric, Dissertation, LMU-München **2011**; B. A. Haag, Dissertation, LMU-München **2010**.

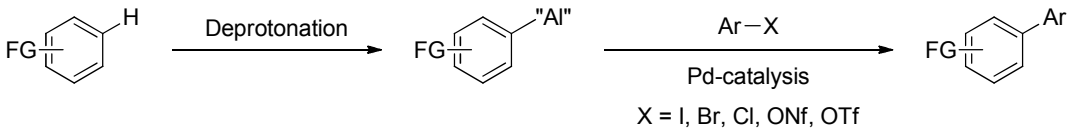
heterocycles was investigated. The method should combine good functional group compatibility with a high reactivity in typical interception reactions (Scheme 20).



Scheme 20: General pathway for the regioselective functionalization of pyridines.

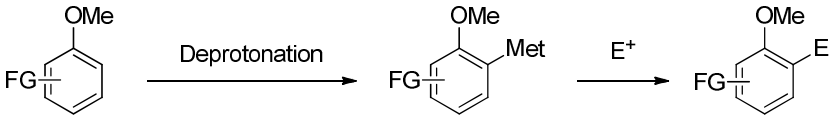
Furthermore, a general method for the functionalization of dibenzothieno[2,3-b]thiophenes and related annulated heterocycles[84] as well as a method for the steroselective synthesis of tetrasubstituted alkenes or *Z*-alkenyllithiums would be desirable.[85]

Organoaluminum compounds offer due to the Lewis-acidity of the metal a unique reactivity. However, the use of such reagents proved to be contradictory to the concept of atom economy. On one hand in aluminations 2 equivalents of amide are not used and on the other hand the obtained reagents need a prior transmetalation, mostly to zinc, to perform an efficient subsequent reaction. Thus, a direct cross-coupling of these aluminum reagents would be highly necessary (Scheme 21).[86]



Scheme 21: General pathway for the direct cross-coupling of organoaluminum reagents.

Finally, the metalation of functionalized, electron-rich aromatics was investigated. On one hand lithiation of these scaffolds does not allow the presence of functional groups in the molecule, on the other hand magnesiation or zincation of these scaffolds proceeds only sluggish and aluminum bases are difficult in their handling. Consequently, a practical and efficient procedure for the metalation of these scaffolds and subsequent reaction of the organometallics in typical interception reactions would be desirable (Scheme 22).[87]



Scheme 22: General pathway for the regioselective functionalization of electron-rich aromatics.

[84] This project was developed in cooperation with M. Kienle, see: M. Kienle, Dissertation, LMU-München **2010**.
[85] This project was developed in cooperation with C. Dunst, see: C. Dunst, Dissertation, LMU-München **2011**.
[86] This project was developed in cooperation with K. Groll, see: K. Groll, Dissertation, LMU-München **2013**.
[87] This project was developed in cooperation with S. H. Wunderlich and Dr. A. Jana, see: S. H. Wunderlich, Dissertation, LMU-München **2010**.

B. RESULTS AND DISCUSSION

1 NEW PREPARATION OF TMPZnCl·LiCl BY Zn INSERTION INTO TMPCl. APPLICATION TO THE FUNCTIONALIZATION OF DIBROMODIAZINES

1.1 INTRODUCTION

The preparation of functionalized aromatic molecules and heterocycles is of great importance due to their potential biological activity. These structures are present in many pharmaceuticals or agrochemicals.[88] Direct metalation has proven to be an excellent tool for the regioselective functionalization of these compounds.[89] Therefore, the availability of chemoselective as well as kinetically highly active bases is an important synthetic goal.[90] Besides the already mentioned methods for the generation of organozincs, *Kondo* reported the use of Li*t*Bu$_2$ZnTMP allowing an efficient zincation due to the ate-character of this reagent (the structures of the metalated intermediates were extensively studied by *Mulvey*).[91] The major drawbacks of this method are the low atom-economy, thus excess of base is necessary and consequently also a high excess of electrophile for achieving full conversion and the non-compatibility with sensitive functional groups like aldehydes or nitro groups.

Recently, *Knochel* and coworkers have shown that TMPZnCl·LiCl (**5**) is an exceptionally active and chemoselective base, allowing to perform highly selective zincations at a convenient temperature range (typically 0 °C to 80 °C).[72] The preparation of **5** has been done in two steps starting from 2,2,6,6-tetramethylpiperidine (**2**: TMPH) in >95% yield. Thus, the amine **2** is first deprotonated with *n*BuLi in hexanes (1 equiv, -10 °C, 1 h) leading to TMPLi (**8**) in quantitative yield. Transmetalation with $ZnCl_2$ (1.05 equiv, -10 °C to 25 °C, 0.5 h) furnishes after evaporation of the hexanes:THF solvent mixture and redissolving in dry THF 1.2-1.4 M solutions of TMPZnCl·LiCl (**5**). Although the overall yield of this synthesis is high (ca. 90%; Pathway A; Scheme 23), it has several drawbacks. The reaction conditions require the use of dry $ZnCl_2$. Also *n*BuLi is only available in nonpolar solvents (alkanes or toluene). Since this solvent mixture reduces significantly the solubility of TMPZnCl·LiCl (**5**) and therefore also its metalation power, a tedious solvent evaporation and redissolution is required. These impractical conditions as well as the relatively high price of *n*BuLi solution and safety considerations led to the design of a new synthesis of TMPZnCl·LiCl (**5**) which would be conducted in

[88] a) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles,* Thieme, Stuttgart, **1995**; b) A. R. Katritzky, C. W. Rees, E. F. V. Scriven, *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, **1996**.

[89] a) N. Chatani, *Topics in Organometallic Chemistry: Directed Metallation*, Springer, Berlin, **2007**; b) G. Dyker, *Handbook of C-H Transformations*, Wiley-VCH, Weinheim, **2005**; c) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; d) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

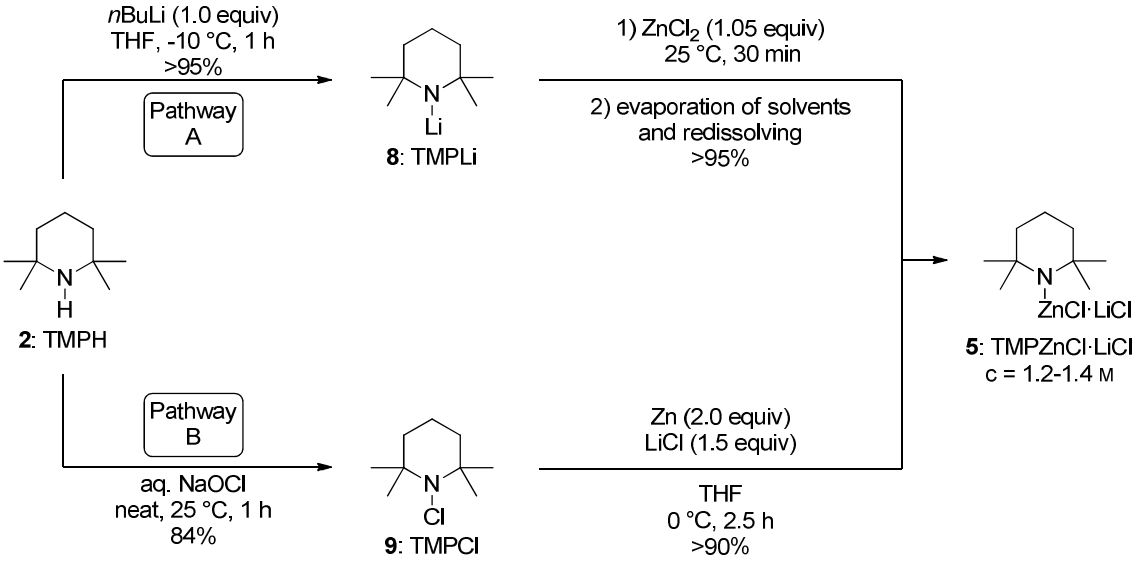
[90] a) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem.* **2007**, *119*, 3876; *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem.* **2011**, *123*, 9968; *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

[91] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) T. Imahori, M. Uchiyama, Y. Kondo, *Chem. Comm.* **2001**, 2450; c) P. F. H. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443; d) M. Uchiyama, T. Miyoshi, Y. Kajihana, T. Sakamoto, Y. Otami, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514; e) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 3859; *Angew. Chem. Int. Ed.* **2006**, *45*, 3775; f) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Z. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc*. **2008**, *130*, 472; g) R. E. Mulvey, *Acc. Chem. Res.* **2009**, *42*, 743; h) W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, C. T. O'Hara, L. Russo, *Angew. Chem.* **2008**, *120*, 743; *Angew. Chem. Int. Ed.* **2008**, *47*, 731; i) W. Clegg, B. Conway, E. Hevia, M. D. McCall, L. Russo, R. E. Mulvey, *J. Am. Chem. Soc.* **2009**, *131*, 2375.

a more favorable temperature range and involve cheap and safe reagents. TMPH (**2**) is readily converted either by chlorination with NCS or by treatment with an aq bleach solution (13% aq NaOCl) at 25 °C to the corresponding chloramine 1-chloro-2,2,6,6-tetramethylpiperidine (**9**: TMPCl) in 84% yield.[92] A direct insertion of a metal (Met) into the nitrogen-chlorine bond of TMPCl (**9**) in the presence of LiCl, which would afford the metallic amides TMPMetCl·LiCl, has been envisioned.

1.2 NEW PREPARATION OF TMPZnCl·LiCl

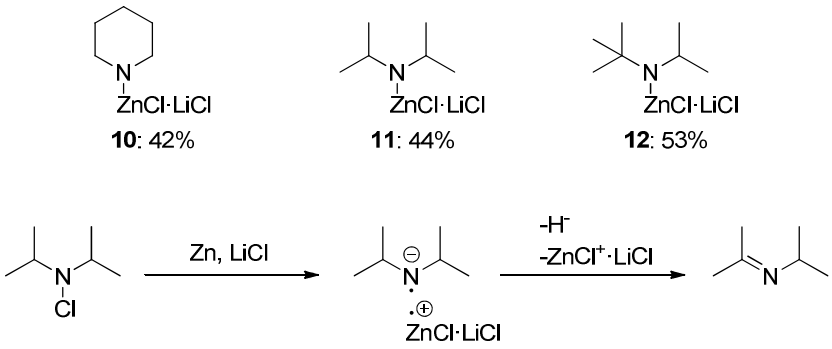
Preliminary results showed that for Met = magnesium (turnings or powder), only reduction of the chloroamine (**9**) is observed. However, switching to zinc dust and performing a slow addition of the chloroamine *via* syringe pump at 0 °C allows the preparation of TMPZnCl·LiCl (**5**) in >90% yield as indicated by titration with benzoic acid[93] (Pathway B; 50 mmol scale; Scheme 23).



Scheme 23: Preparation of TMPZnCl·LiCl (**5**).

TMPZnCl·LiCl (**5**) was directly obtained in concentrations that made evaporation of solvents obsolete. The excess of zinc powder can simply be removed by filtration. Thus, a fast preparation of this organozinc base is possible starting from cheap commercial zinc and the *N*-chloroamine TMPCl (**9**). This method could also be applied to other *N*-chloroamines, like 1-chloro-diisopropylamine, 1-chloro-*tert*-butyl-isopropylamine or 1-chloro-piperidine.[94] However, the yields of the corresponding zinc amides **10**, **11** and **12** drop significantly compared to the yield of TMPZnCl·LiCl (**5**). A possible reason for this yield decrease could be imine formation in course of the insertion (Scheme 24).

[92] a) N. Bodor, J. J. Kaminski, S. D. Worley, R. J. Colton, T. H. Lee, J. W. Rabalais, *J. Pharm. Sci.* **1974**, *63*, 1387; b) N. C. Deno, R. Fishbein, J. C. Wyckoff, *J. Am. Chem. Soc.* **1971**, *93*, 2065.
[93] T. Huguchi, J. Concha, R. Kuramota, *Anal. Chem.* **1952**, *24*, 685.
[94] Note: *N*-chloroamines which can readily eliminate HCl are energy rich compounds that are inherently much less stable than TMPCl, as such considerable care must be taken during their preparation and use.



Scheme 24: Further prepared bases and possible imine formation.

1.3 APPLICATION TO THE FUNCTIONALIZATION OF DIBROMODIAZINES

We have verified that the deprotonation power (temperature, reaction time) of TMPZnCl·LiCl (**5**) prepared by pathways A and B are identical and report some new directed zincations of bromo-substituted pyridazine **13a** and pyrazines **13b-e**. Pyrazine and pyridazine derivatives are biologically highly active and therefore their functionalization is of great interest since many examples of natural products or pharmaceutically important compounds contain these scaffolds (Figure 3).

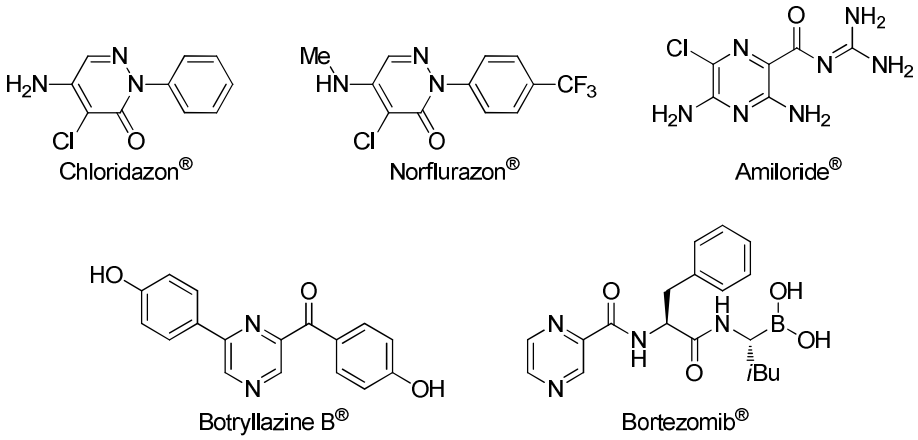
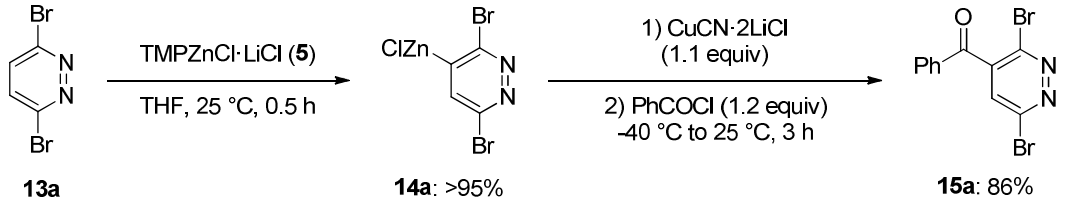


Figure 3: Biologically active compounds containing a pyrazine or pyridazine scaffold.

To this end organozincs are especially well suited. Due to the high covalent character of their carbon-zinc bond, organozinc compounds can be considered as one of the most stable group of organometallics.[95] Furthermore, the high electrophilicity of these heterocycles requires low temperatures for their metalation.[96] TMPZnCl·LiCl (**5**) proved to be especially well suited for zincation of heterocycles of type **13** and related scaffolds since more active bases, such as $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**)[73] or TMPMgCl·LiCl (**3**)[68] lead to the decomposition of these sensitive

[95] a) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**; b) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
[96] a) C. Y. Zhang, J. M. Tour, *J. Am. Chem. Soc.* **1999**, *121*, 8783; b) W. Liu, D. S. Wise, L. B. Townsend, *J. Org. Chem.* **2001**, *66*, 4783; c) F. Buron, N. Plé, A. Turck, G. Quéguiner, *J. Org. Chem.* **2004**, *70*, 2616; d) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595.

heterocyclic bromides.[97] In contrast, treatment of the dibromo-pyridazine **13a**[98] with TMPZnCl·LiCl (**5**; 1.1 equiv, 25 °C, 0.5 h) led to the quantitative formation of the zincated pyridazine **14a** which provides the ketone **15a** in 86% isolated yield after transmetalation with CuCN·2LiCl[99] (1.1 equiv) and benzoylation (PhCOCl, 1.2 equiv, -40 °C to 25 °C, 3 h) (Scheme 25).

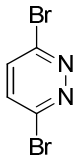
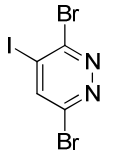
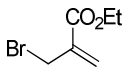
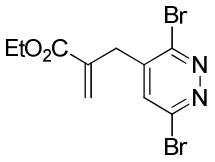
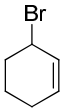
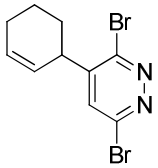


13a **14a**: >95% **15a**: 86%

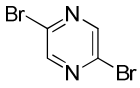
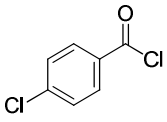
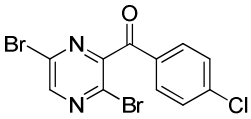
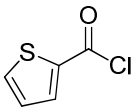
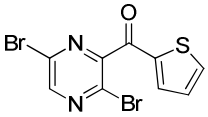
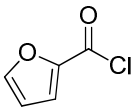
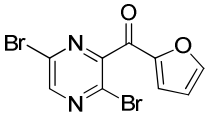
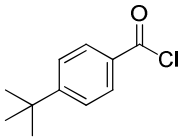
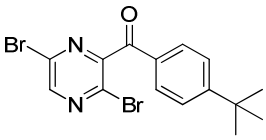
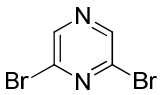
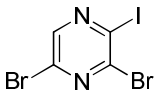
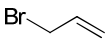
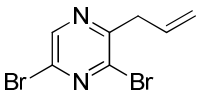
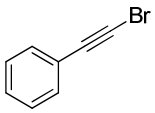
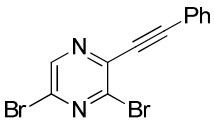
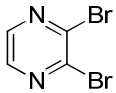
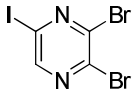
Scheme 25: Directed zincation of 3,5-dibromopyridazine (**13a**).

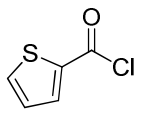
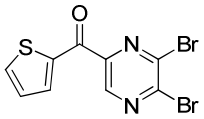
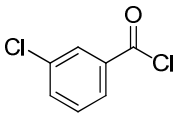
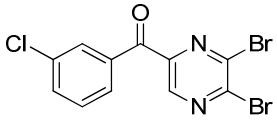
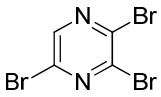
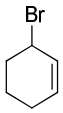
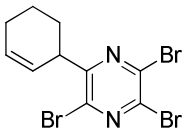
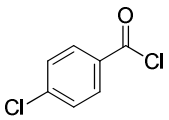
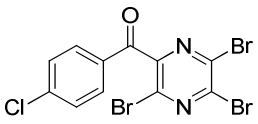
Similary, the zincated pyridazine **14a** reacted smoothly with iodine and allylic bromides, leading to the *N*-heterocycles **15b-d** in 71–76% yield (Table 1, Entries 1–3).

Table 1: Monofunctionalization of bromodiazines of type **5**

Entry	Substrate	Electrophile	Product / Yield[a]
1	 **13a**	I_2	 **15b**: 71%
2	**13a**		 **15c**: 73%[b]
3	**13a**		 **15d**: 76%[b]

[97] L. Decrane, N. Plé, A. Turck, *J. Heterocyclic Chem*. **2005**, *42*, 509.
[98] W. Dankulich, D. G. McGarry, C. Burns, T. F. Gallagher, F. A. Volz, Substituted (aminoiminomethyl or aminomethyl) benzoheteroaryl compounds. U.S. Patent 6,541,505, April, 01, 2003.
[99] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert *J. Org. Chem.* **1988**, *53*, 2390; b) P. Knochel, S. A. Rao, *J. Am. Chem. Soc.* **1990**, *112*, 6146.

Entry	Substrate	Electrophile	Product / Yield[a]
4	 **13b**		 **15e**: 79%[c]
5	**13b**		 **15f**: 65%[c]
6	**13b**		 **15g**: 53%[c]
7	**13b**		 **15h**: 71%[c]
8	 **13c**	I_2	 **15i**: 83%
9	**13c**		 **15j**: 90%[b]
10	**13c**		 **15k**: 74%[c]
11	 **13d**	I_2	 **15l**: 71%

Entry	Substrate	Electrophile	Product / Yield[a]
12	**13d**		 **15m**: 76%[c]
13	**13d**		 **15n**: 56%[c]
14	 **13e**		 **15o**: 55%[b]
15	**13e**		 **15p**: 66%[c]

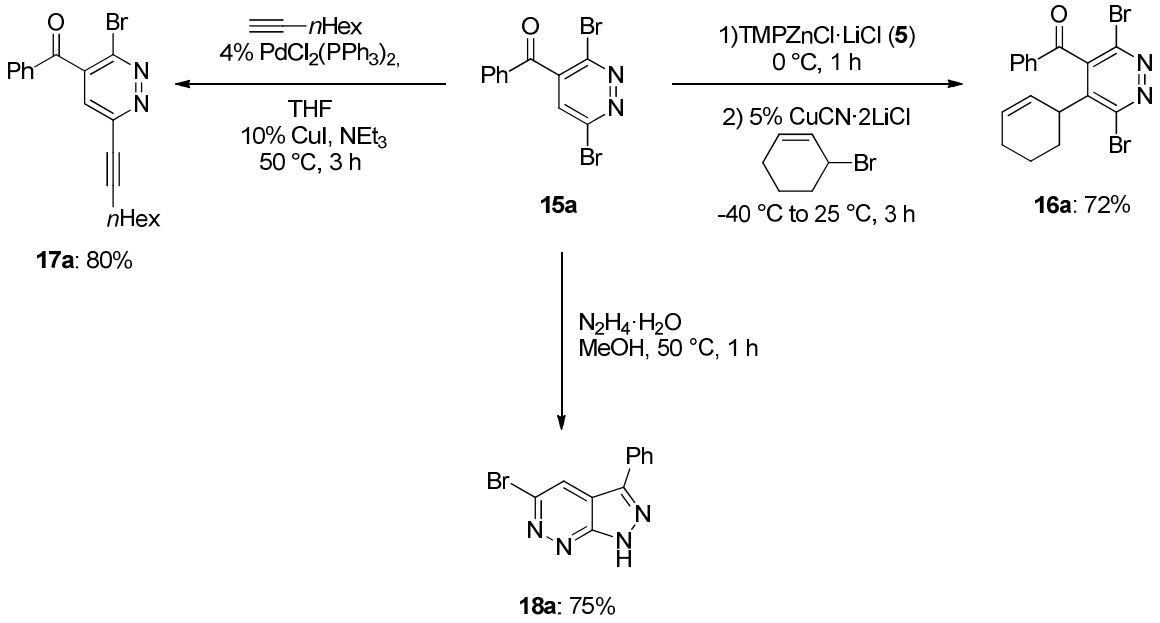
[a] Yield of analytically pure isolated product. [b] Catalyzed by 5% CuCN·2LiCl. [c] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv).

Similarly 2,5-dibromopyrazine **13b**[100] was zincated with the base **5** (1.1 equiv, 25 °C, 1 h). Copper mediated acylation with various acid chlorides furnishes the expected acylpyrazines **15e-h** in 53–79% yield (Entries 4–6). The symmetrical 2,6-dibromopyrazine **13c**[101] was readily zincated (**5**, 1.1 equiv, 25 °C, 1 h). It reacts with iodine, allyl bromide and 1-bromophenylacetylene[102] under standard conditions providing the trisubstituted pyrazines **15i-k** in 74-90% (Entries 8–10). The isomeric 2,3-dibromopyrazine **13d**[103] is only zincated at elevated temperature with TMPZnCl·LiCl, since no adjacent bromine substituent is available for further acidification of the protons, (**5**; 1.1 equiv, 50 °C, 12 h) leading to the expected zinc reagent which was iodinated to give the iodopyrazine **15l** (71%, Entry 11). Copper-mediated acylation provides the heterocyclic ketones **15m-n** in 56-76%; (Entries 12, 13). Finally, the tribromopyrazine **13e**[104] is zincated with TMPZnCl·LiCl (**5**, 1.1 equiv, 25 °C, 1 h) leading to a sensitive zinc reagent. Copper-catalyzed allylation and acylation provides the tetrasubstituted pyrazines in 55-66% yield (Entries 14, 15).

[100] R. C. Ellingson, R. L. Henry, *J. Am. Chem. Soc.* **1949**, *71*, 2798.
[101] A. E. Erickson, P. E. Spoerri, *J. Am. Chem. Soc.* **1946**, *68*, 400.
[102] M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799.
[103] G. Karmas, P. E. Spoerri, *J. Am. Chem. Soc.* **1957**, *79*, 680.
[104] H. Brachwitz, *J. Prakt. Chem.* **1969**, *311*, 40.

1.4 FURTHER FUNCTIONALIZATIONS

These diazines can be further functionalized *via* a second zincation. Thus, the treatment of **15a** with TMPZnCl·LiCl (**5**, 1.1 equiv, 0 °C, 1 h) provides an intermediate zinc reagent which was allylated with 3-bromocyclohexene in the presence of 5% CuCN·2LiCl to furnish the fully substituted pyridazine **16a** in 72% yield (Scheme 26).



Scheme 26: Further functionalizations of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**).

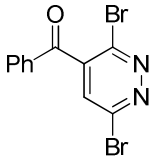
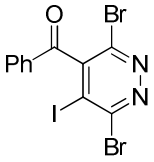
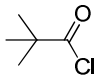
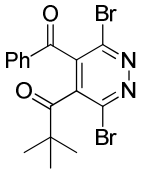
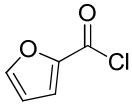
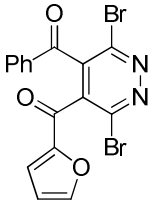
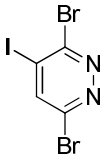
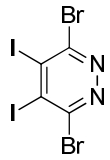
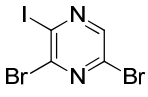
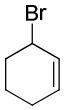
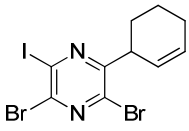
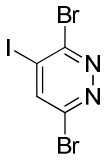
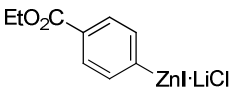
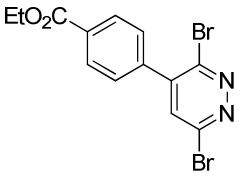
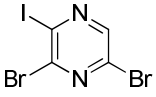
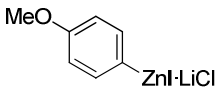
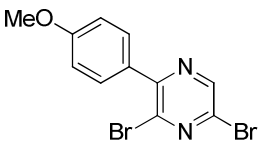
This zincated pyridazine is also iodinated and acylated providing the expected pyridazines **16b-d** in 57-67% yield (Table 2, Entries 1–3). Similarly, the iododibromopyridazine **15b** and the iododibromopyrazine **15i** are zincated with TMPZnCl·LiCl (**5**, 1.1 equiv, 0 °C, 1 h) leading after iodolysis or copper catalyzed allylation to the diiododibromopyridazine **16e** and the fully functionalized pyrazine **16f** in yields of 74 and 70%, respectively (Entries 4 and 5). Furthermore the dibromopyridazine **15a** undergoes a regioselective Pd-catalyzed *Sonogashira* reaction[105] with 1-octyne in the presence of 4% $PdCl_2(PPh_3)_2$, 10% CuI and Et_3N (50 °C, 3 h) to afford the pyridazine **17a** in 80% yield. Also, the mixed iodobromopyrazines such as **15b**, **15i** and **15l** lead, as expected, to the preferential cross-coupling of the iodide in various *Negishi* cross-couplings[106] with arylzinc iodides[107] giving the pyrazines **17b-d** in 49-79% yield (Entries 6–8).

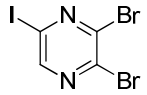
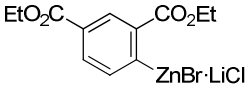
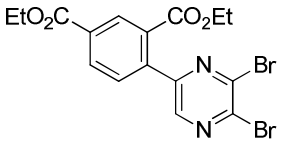
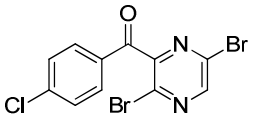
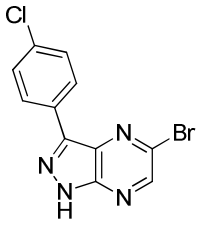
[105] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467; b) R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* **2011**, *40*, 5084; c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874; d) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850; *Angew. Chem., Int. Ed.* **2007**, *46*, 834; e) K. Sonogashira, in *Metal-catalyzed Cross-coupling Reactions* (Diederich, F.; Stang, P. J.; Eds.), Wiley-VCH, Weinheim, **1998**.

[106] a) E. Negishi, S. Baba, *J. Chem. Soc. Chem. Commun.* **1976**, 596; b) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729; c) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; d) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254; e) E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393; f) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; g) E. Negishi, *Angew. Chem.* **2011**, *123*, 6870; *Angew. Chem. Int. Ed.* **2011**, *50*, 6738.

[107] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780.

Table 2: Further functionalization of compounds of type **15**

Entry	Diazine	Electrophile / Nucleophile	Product / Yield[a]
1	 **15a**	I_2	 **16b**: 67%
2	**15a**		 **16c**: 57%[b]
3	**15a**		 **16d**: 62%[b]
4	 **15b**	I_2	 **16e**: 74%
5	 **15i**		 **16f**: 70%[c]
6	 **15b**		 **17b**: 56%[d]
7	 **15i**		 **17c:** 49%[d]

Entry	Diazine	Electrophile / Nucleophile	Product / Yield[a]
8	 **15l**		 **17d**: 79%[d]
9	 **15e**	$N_2H_4 \cdot H_2O$	 **18b**: 84%

[a] Yield of analytically pure isolated product. [b] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv). [c] Catalyzed by 5% of CuCN·2LiCl. [d] Obtained by palladium-catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp.

Finally, these dibromopyrazines are also regioselectively converted to annulated heterocycles, which are potentially biological active.[108] Thus, the treatment of **15a** with hydrazine hydrate (MeOH, 50 °C, 1 h) gives the pyrazolopyrazine **18a** in 75% yield (Scheme 26). The same reaction converts the pyrazine **15e** to the condensed heterocycle **18b** in 84% yield (Table 2, Entry 9).

[108] a) R. Brenk, L. Naerum, U. Grädler, H.-D. Gerber, G. A. Garcia, K. Reuter, M. T. Stubbs, G. Klebe, *J. Med. Chem.* **2003,** *46,* 1133; b) J. Witherington, V. Bordas, S. L. Garland, D. M. B. Hickey, R. J. Ife, J. Liddle, M. Saunders, D. G. Smith, R. W. Ward, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1577.

2 REGIOSELECTIVE ZINCATION OF INDAZOLES USING TMP_2Zn AND *NEGISHI* CROSS-COUPLING WITH ARYL AND HETEROARYL IODIDES

2.1 INTRODUCTION

Natural products bearing an indazole structure are rare,[109] at present only three examples are known: Nigeglanine (**19**) found in *Nigella glandulifera*, Nigellicine (**20**) and Nigellidine (**21**), both isolated from the widely distributed plant *Nigella sativa* (black cumin). Nevertheless, indazoles are an important class of *N*-heterocycles which have found numerous pharmaceutical applications. Indazole derivatives may act as dopamine antagonists, anti-inflammatory, analgesic or antipyretic agents, antiarthritic drugs or enzyme inhibitors. Other derivates are used in the treatment of diabetes, exhibit herbicide activity or are used as bactericides and fungicides. In addition, indazoles may show antispermatogenetic or anticancer activity,[110] finally Cortivazol (**22**) is an indazole-based drug classified as glucocorticoid (Figure 4).[111]

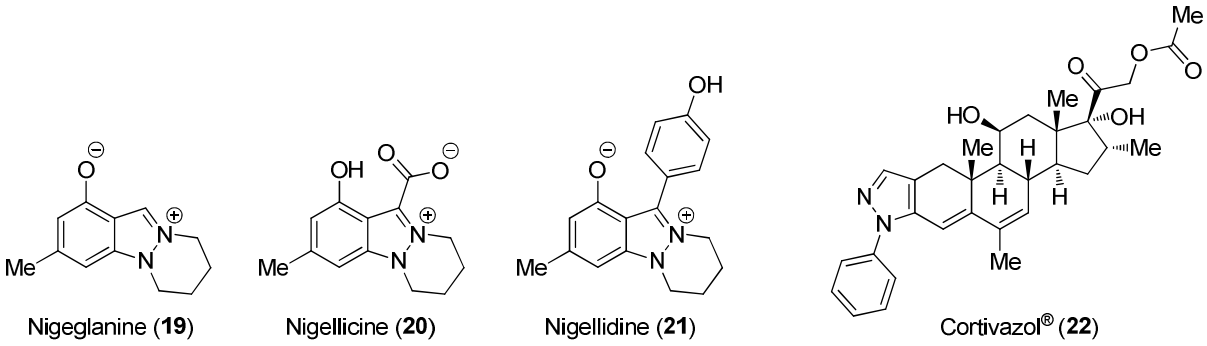
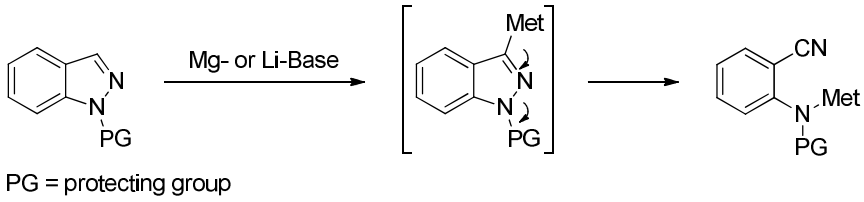


Figure 4: Natural products and a drug containing an indazole core.

The direct lithiation or magnesiation of indazoles at position 3 is difficult due to a facile fragmentation of these heterocycles leading to aminonitriles (Scheme 27).[112]



Scheme 27: Fragmentation of 3-metalated indazoles.

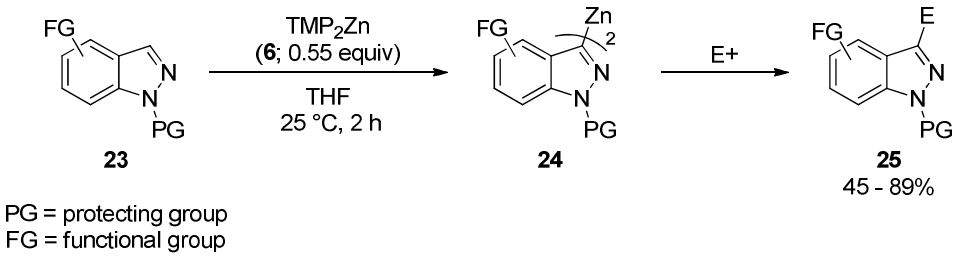
[109] A. Schmidt, *Adv. Heterocycl. Chem*. **2003**, *85*, 67.
[110] a) W. Stadlbauer, *Science of Synthesis* **2002**, Vol. 12, pp. 227; b) M. S. Malamas, J. Millen, *J. Med. Chem.* **1991**, *34*, 1492; c) S. Peruncheralathan, T. A. Khan, H. Ila, H. Junjappa, *Tetrahedron* **2004**, *60*, 3457; d) C. Pabba, H.-J. Wang, S. R. Mulligan, Z.-J. Chen, T. M. Stark, B. T. Gregg, *Tetrahedron Lett*. **2005**, *46*, 7553; e) V. Collot, P. Dallemagne, P. R. Bovy, S. Rault, *Tetrahedron* **1999**, *55*, 6917; f) J.-H. Sun, C. A. Teleha, J.-S. Yan, J. D. Rodgers, D. A. Nugiel, *J. Org. Chem.* **1997**, *62*, 5627; g) D. G. Batt, J. J. Petraitis, G. C. Houghton, D. P. Modi, G. A. Cain, M. H. Corjay, S. A. Mousa, P. J. Bouchard, M. S. Forsythe, P. P. Harlow, F. A. Barbera, S. M. Spitz, R. R. Wexler, P. K. Jadhav, *J. Med. Chem.* **2000**, *43*, 41.
[111] J. A. Schlechte, S. S. Simons, D. A. Lewis, E. B. Thompson, *Endocrinology* **1995**, *117*, 1355.
[112] a) A. Bunnell, C. O'Yang, A. Petrica, M. J. Soth, *Synth. Comm*. **2006** ,*36*, 285; b) J. D. Perez, G. I. Yranzo, M. A. Ferraris, J.Elguero, R. Ma. Claramunt, D. Sanz, *Bull. Soc. Chim. Fr*., **1991** , *4*, 592; c) W. M. Welch, C. E. Hanau, W. M. Whalen, *Synthesis* **1992**, 937.

Alternatively, 3-iodoindazoles undergo a selective I-Cu-exchange with $(PhMe_2CCH_2)_2CuLi$[113] leading to stable 3-cuprated indazoles which can be readily acylated.[114] The lithiation,[115] magnesiation[116] and zincation[117] of isoindazoles (2*H*-indazoles) have been reported. Also the direct arylation[118] of 2*H*-indazoles as well as the use of 3-iodoindazoles in *Suzuki*[119] or *Stille*[120] cross-couplings is known.

However, the direct metalation and transition metal-catalyzed arylation of 1*H*-indazoles has not been reported. This reaction is especially interesting due to the potential pharmaceutical activity of 3-arylated indazoles.[121] Recently, *Knochel* has described the synthesis of a kinetically highly active zinc base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; abbreviated TMP_2Zn)[122] which combines a high metalation activity with an excellent functional group tolerance.[123]

2.2 FUNCTIONALIZATION OF INDAZOLES *VIA* ZINCATION

Remarkably, TMP_2Zn (**6**) allows for the first time a direct metalation of a range of *N*-protected indazoles of type **23** under mild conditions (without concomitant ring opening) leading to *bis*-indazolylzincs of type **24**. Their reaction with electrophiles (E) has been successfully accomplished, leading to products of type **25** (Scheme 28).



Scheme 28: Zincation of indazoles and subsequent trapping.

Zinc reagents **24** react well with various electrophiles like allylic bromides and acid chlorides, but also reaction conditions to perform direct arylations *via Negishi* cross-couplings[106] with various aryl iodides have been found.

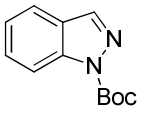
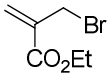
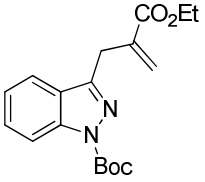
Thus, preliminary experiments performed in order to find the optimal protecting group (PG) for indazole (**23**) showed that both, a *tert*-butoxycarbonyl (Boc; **23a**) or a methoxymethyl protected indazole (MOM; **23b**) readily react with TMP_2Zn (**6**; THF, 25 °C, 30 min) to produce the expected

[113] C. Piazza, P. Knochel, *Angew. Chem.* **2002**, *114*, 3397; *Angew. Chem. Int. Ed*. **2002**, *41*, 3263.
[114] X. Yang, P. Knochel, *Synlett* **2004**, 2303.
[115] G. Luo, L. Chen, G. Dubowchik, *J. Org. Chem.* **2006**, *71*, 5392.
[116] C. Despotopoulou, C. Gignoux, D. McConnell, P. Knochel, *Synthesis* **2009**, 3661.
[117] B. Haag, Z. Peng, P. Knochel, *Org. Lett.* **2009**, *11*, 4270.
[118] S. A. Ohnmacht, A. J. Culshaw, M. F. Greaney, *Org. Lett.* **2010**, *12*, 224.
[119] A. Fraile, M. Rosario Martín, J. L. García Ruano, J. A. Díaz, E. Aranz, *Tetrahedron* **2011**, *67*, 100.
[120] F. Crestey, V. Collot, S. Stiebing, S. Rault, *Synthesis* **2006**, 3506.
[121] a) L. A. Clutterbuck, C. Garcia Posado, C. Visintin, D. R. Riddall, B. Lancaster, P. J. Gane, J. Garthwaite, D. L. Selwood, *J. Med. Chem.* **2009**, *52*, 2694; b) A. Schmidt, A. Beutler, B. Snovydoch, *Eur. J. Org. Chem.* **2008**, 4073 and references cited therein
[122] a) M. Kienle, C. Dunst, P. Knochel, *Org. Lett*. **2009**, *11*, 5158; b) C. Dunst, M. Kienle, P. Knochel, *Synthesis,* **2010**, 2313;
[123] For general reviews on the metallation of aromatics and heterocycles see: a) F. Chevallier, F. Mongin, *Chem. Soc. Rev.*, **2008**, *37*, 595; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem*. **2011**, *123*, 9968; *Angew. Chem. Int. Ed.* **2011**, *50*, 9794

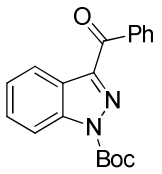
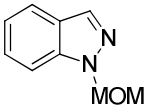
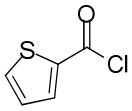
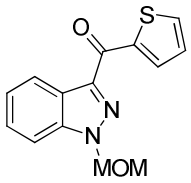
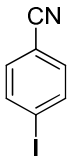
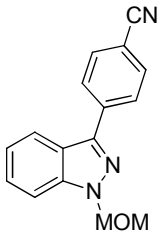
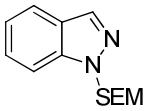
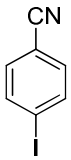
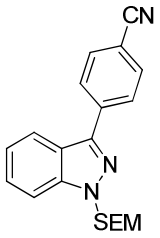
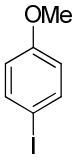
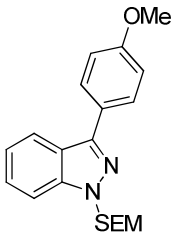
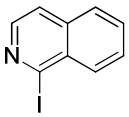
bis-(3-indazolyl)zinc reagents (**24a**-**b**). Copper-catalyzed trapping with various electrophiles such as ethyl 2-(bromomethyl)acrylate[124] or acid chlorides provides the desired 3-functionalized indazoles (**25a**-**c**) in 72-89% yield (Table 3, Entries 1-3). A 3-arylation could be realized for the first time with the MOM-protected *bis*-indazolylzinc reagent (**24b**). Its reaction with 4-iodobenzonitrile (1.2 equiv) in the presence of 2% $Pd(dba)_2$ and 4% tfp[125] at 50 °C for 8 h leads to the desired 3-arylated indazole (**25d**) in 76 % yield (Entry 4). Attemps to couple bromoarenes with other catalytic systems[17] were not successful. Furthermore these *Negishi* cross-couplings had to be performed at 50 °C. This elevated temperature proved to be a problem for the cross-coupling of further functionalized indazoles leading to partial ring opening byproducts. By switching to SEM-protected[126] indazoles the corresponding zinc reagents undergo Pd-catalyzed cross-couplings in high yields. Thus, the arylation of SEM-protected indazole (**23c**) with 4-iodobenzonitrile gives the cross-coupling product (**25e**) in 76% yield (Entry 5). Less reactive aryl iodides, such as 4-iodoanisole (50 °C, 12 h) react now very well leading to the 3-arylated indazole (**25f**) in 81% yield (Entry 6). A heterocyclic iodide, such as 2-iodoisoquinoline undergoes the cross-coupling smoothly, affording the desired product (**25g**) in 62% yield (Entry 7). This cross-coupling reaction could be extended to functionalized indazoles bearing a chlorine substituent (**23d**, Entries 8-9), a bromine substituent (**23e**, Entries 10-11), a methoxy group (**23f**, Entry 12), as well as sensitive functions like a nitrile (**23g**, Entry 13) and an ester group (**23h**, Entry 14). The desired 3-arylated indazoles (**25h**-**n**) are produced in 45-86% yield. We verified also that these SEM-protected indazoles also undergo acylation reactions. Thus, the ester substituted indazole (**23h**) after zincation with TMP_2Zn (**1**) and transmetalation with CuCN·2LiCl reacts with benzoyl chloride leading to the 3-benzoylated indazole **25o** (Entry 15).

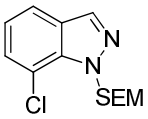
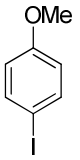
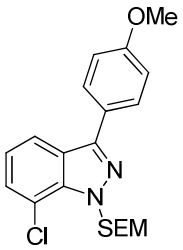
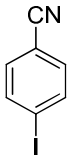
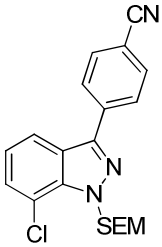
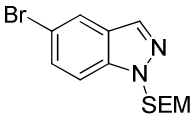
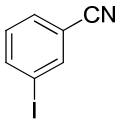
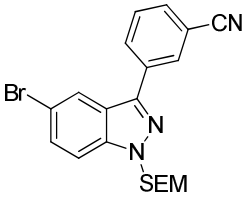
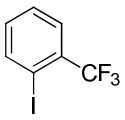
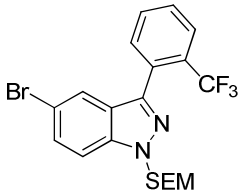
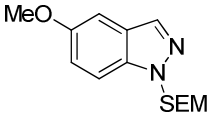
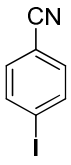
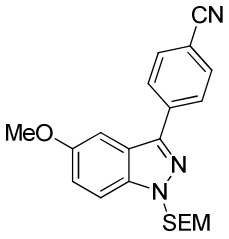
We have also found that the SEM protected 2*H*-indazole (**23i**) was metalated with TMP_2Zn (**6**) under similar conditions (25 °C, 2 h) leading after copper-catalyzed acylation with thiophene-2-carbonyl chloride to the desired ketoindazole (**25p**) in 81% yield (Entry 16).[127]

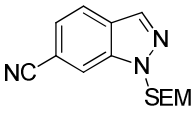
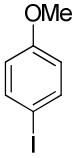
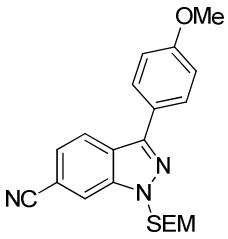
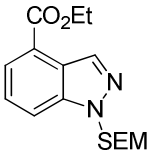
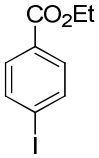
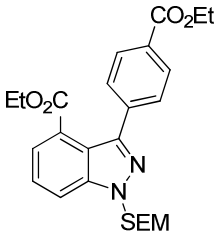
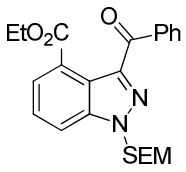
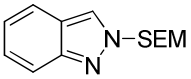
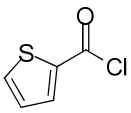
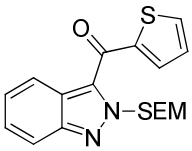
Table 3: Products obtained after zincation using TMP_2Zn.

Entry	Indazole	Electrophile / Conditions	Product / Yield (%)[a]
1	 **23a**	 -40 to 25 °C, 2 h	 **25a**: 89%

[124] J. Villieras, M. Rambaud, *Synthesis* **1982**, 924.
[125] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.
[126] The following catalytic systems have been tried without success: PEPPSI-IPr; $Pd(OAc)_2$/S-Phos; $Pd(OAc)_2$/Ru-Phos; $Pd(PPh_3)_4$; $NiCl_2$/dppe; $Ni(acac)_2$/dpe.
[127] This shows that it is in principle unnecessary to separate the isomeric 1*H*- and 2*H*-indazoles that are usually obtained as mixtures in several preparation methods.

Entry	Indazole	Electrophile / Conditions	Product / Yield (%)[a]
2	**23a**	PhCOCl -40 to 25 °C, 2 h	 **25b**: 72%
3	 **23b**	 -40 to 25 °C, 2 h	 **25c**: 74%[b]
4	**23b**	 50 °C, 8 h	 **25d**: 76%[c]
5	 **23c**	 50 °C, 8 h	 **25e**: 76%[c]
6	**23c**	 50 °C, 12 h	 **25f**: 81%[c]
7	**23c**	 50 °C, 6 h	 **25g**: 62%[c]

Entry	Indazole	Electrophile / Conditions	Product / Yield (%)[a]
8	 **23d**	 50 °C, 12 h	 **25h**: 71%[c]
9	**23d**	 50 °C, 8 h	 **25i**: 86%[c]
10	 **23e**	 50 °C, 6 h	 **25j**: 62%[c]
11	**23e**	 50 °C, 10 h	 **25k**: 63%[c]
12	 **23f**	 50 °C, 6 h	 **25l**: 81%[c]

Entry	Indazole	Electrophile / Conditions	Product / Yield (%)[a]
13	 **23g**	 50 °C, 10 h	 **25m**: 71%[c]
14	 **23h**	 50 °C, 24 h	 **25n**: 45%[c]
15	**23h**	PhCOCl -40 to 25 °C, 2 h	 **25o**: 77%[b]
16	 **23i**	 -40 to 25 °C, 2 h	 **25p**: 81%[b]

[a] Yield of isolated analytically pure product. [b] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [c] Obtained by palladium-catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp(50 °C, 6-12 h).

3 ACCELERATED ZINCATIONS FOR AN EFFICIENT AND MILD FUNCTIONALIZATION OF AROMATICS AND HETEROROMATICS

3.1 INTRODUCTION

As already mentioned, the directed *ortho*-metalation of aromatic and heterocyclic compounds is an efficient method for the functionalization of these scaffolds.[89] Besides conventional lithium bases a range of new bimetallic ate-bases have been introduced by *Kondo*, *Mulvey*, *Mongin* and *Uchiyama*.[91] These bases allow a smooth metalation of a number of unsaturated systems due to synergetic effects between the two metals. Alternatively, *Schwesinger*'s P4 *t*Bu-base[128] or *Hagadorn*'s TMP_2Zn[129] can be used for the generation of carbanions. However, these ate bases and the phosphazene lack atom-economy, whereas TMP_2Zn is only sufficient for the metalation of highly activated substrates. Thus, it allows for the generation of Zn-enolates and the metalation of very electron-poor substrates, such as pyridine *N*-oxides or DMSO. Recently, *Knochel* and coworkers have reported highly soluble metal amides complexed by LiCl such as TMPMgCl·LiCl (**3**), (TMP = 2,2,6,6-tetramethylpiperidyl), TMP_2Mg·2LiCl (**4**), TMPZnCl·LiCl (**5**), TMP_2Zn·2$MgCl_2$·2LiCl (**6**) and [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) which allowed a chemo- and regioselective metalation of a broad range of functionalized aromatics and heteroaromatics. An additional procedure involving a complexation of some organic substrates with $ZnCl_2$ prior to the addition of TMP_2Mg·2LiCl (**4**), which led to improved metalation yields has also been reported.[130] However, this last method had several drawbacks: (i) the stability of TMP_2Mg·2LiCl (**4**) is limited due to its high kinetic basicity;[131] (ii) the tolerance of functional groups and sensitive heterocycles is also moderate. In contrast, the zinc amides **5** and **6** tolerate a wide range of functional groups in the organic substrate. Nevertheless, either highly activated arenes or heteroaromatics are needed, otherwise only a sluggish metalation occurs. Since especially functionalized heterocycles are of interest for pharmaceutical industry (Figure 5), an improved zincation protocol would be desirable.

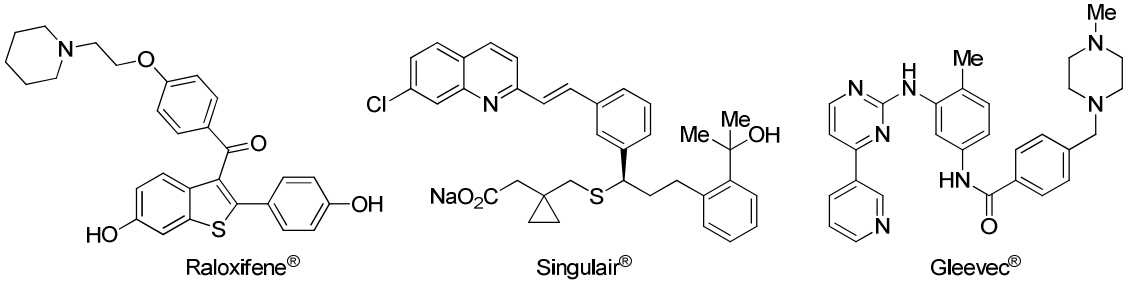


Figure 5: Heterocyclic pharmaceuticals.

[128] a) R. Schwesinger, H. Schlemper, *Angew. Chem.* **1987**, *99*, 1212; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1167; b) R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G.-Z. Ji, E.-M. Peters, K. Peters, H. G. von Schnering, L. Walz, *Liebigs Ann.* **1996**, 1055; c) T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082.

[129] a) M. L. Hlavinka, J. R. Hagadorn, *Organometallics* **2007**, *26*, 4105; b) M. L. Hlavinka, J. F. Greco J. R. Hagadorn, *Chem. Comm.* **2005**, 5304; c) M. L. Hlavinka and J. R. Hagadorn, *Tetrahedron Lett.* **2006**, *47*, 5049; d) W. Rees, O. Just. H. Schumann, R. Weimann, *Polyhedron* **1998**, *17*, 1001.

[130] Z. Dong, G. Clososki, S. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457.

[131] C. J. Rohbogner, S. H Wunderlich, G. C. Clososki, P. Knochel, *Eur. J. Org. Chem.* **2009**, 1781.

3.2 ACCELERATED ZINCATIONS

Since zincations may be performed at elevated temperatures,[132] the use of the transmetalation energy to perform fast and efficient zincations at moderately elevated temperatures (reaction temperature up to 40 °C) has been envisoined. Remarkably, we wish to report that this moderate increase of temperature leads to a dramatic decrease in the reaction time. Remarkably, this small temperature increase (10-15 °C) is sufficient to provide a rate acceleration of up to 50 times.

Thus, whereas the zincation of coumarin (**26**) with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) requires 4 h at 25 °C to reach >95% conversion, the sequential treatment of **26** with $ZnCl_2$ (0.5 equiv) followed by the addition of TMPMgCl·LiCl (**3**; 1.1 equiv) leads to the zincated species **27** within 2 h. If $ZnCl_2{\cdot}LiCl$[133] (0.5 equiv) is used followed by the addition of TMPMgCl·LiCl (**3**; 1.1 equiv) **27** is obtained in 5 min (Figure 6, Scheme 29).

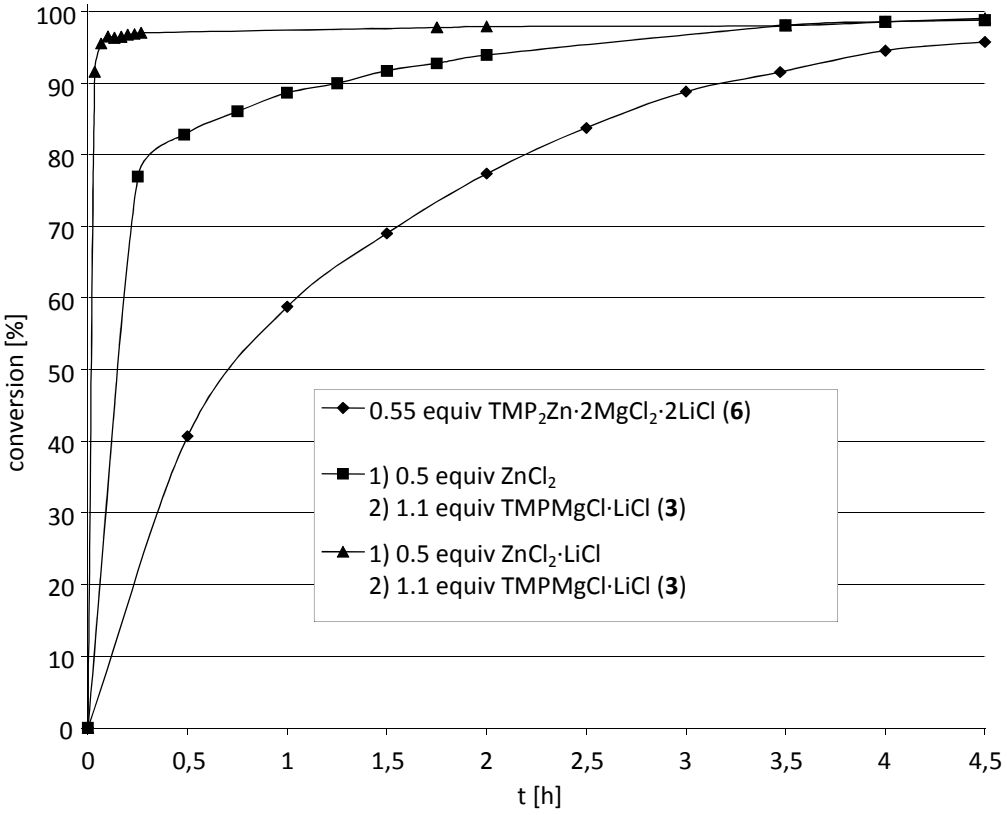


Figure 6: Progress of the metalation of coumarin (**26**) using different metalation procedures.

After a Pd-catalyzed *Negishi* cross-coupling[106] with 4-iodoanisole, the expected coumarin derivative **28** is obtained in 82% yield (Scheme 29). A similar behavior is found for quinoxaline (**29**). The addition of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 0.55 equiv) provides the diheteroaryl zinc reagent **30** after 5 h at 25 °C. Whereas the sequential treatment of the substrate with $ZnCl_2$ (0.5 equiv) followed by the addition of TMPMgCl·LiCl (**3**; 1.1 equiv) leads to the zincated species **30** in >95% within 2 h. In this case also the

[132] S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.
[133] for the effects of LiCl see: E. Hevia, R. E. Mulvey *Angew. Chem.* **2011**, *123*, 6576; *Angew. Chem. Int. Ed.* **2011**, *50*, 6448.

usage of $ZnCl_2$·LiCl (0.5 equiv) followed by TMPMgCl·LiCl (**3**; 1.1 equiv) accelerates the metalation and leads to complete conversion within 1 h. The reaction can be further accelerated by addition of one extra equivalent of LiCl. Thus, if the monomeric complex $ZnCl_2$·2LiCl[134] (0.5 equiv) is used instead, followed by the addition of TMPMgCl·LiCl (**3**; 1.1 equiv), **30** is obtained within 15 min (Figure 7).

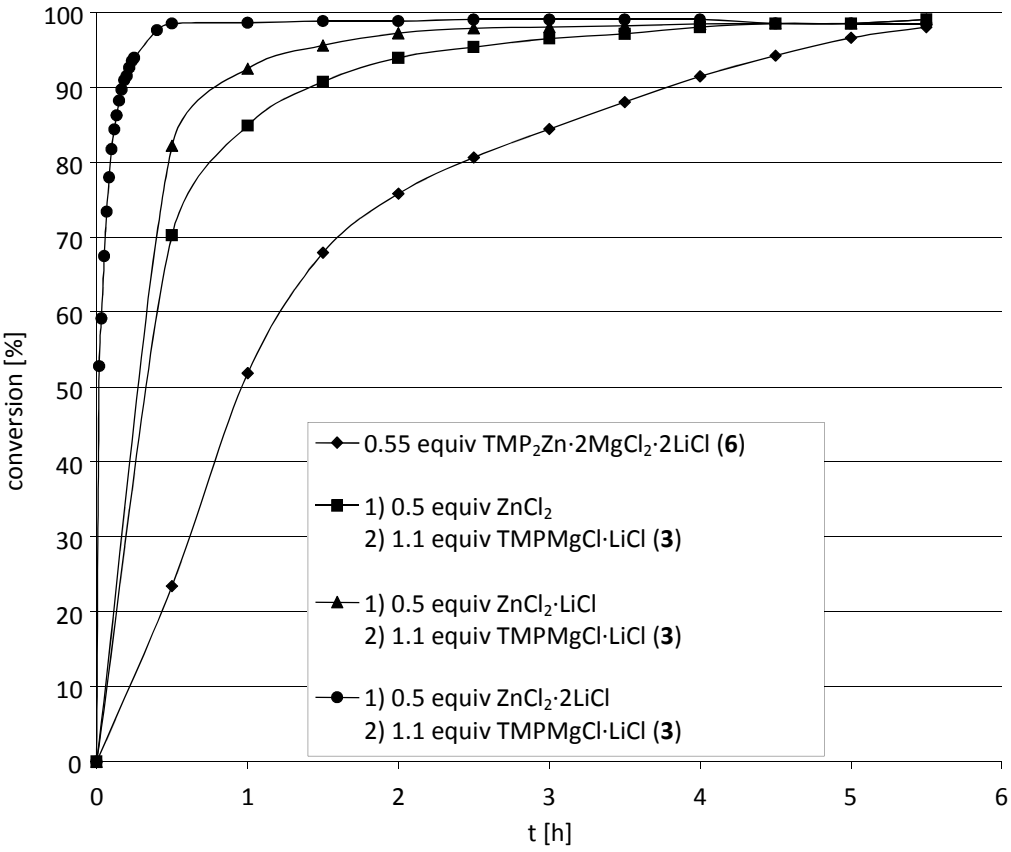
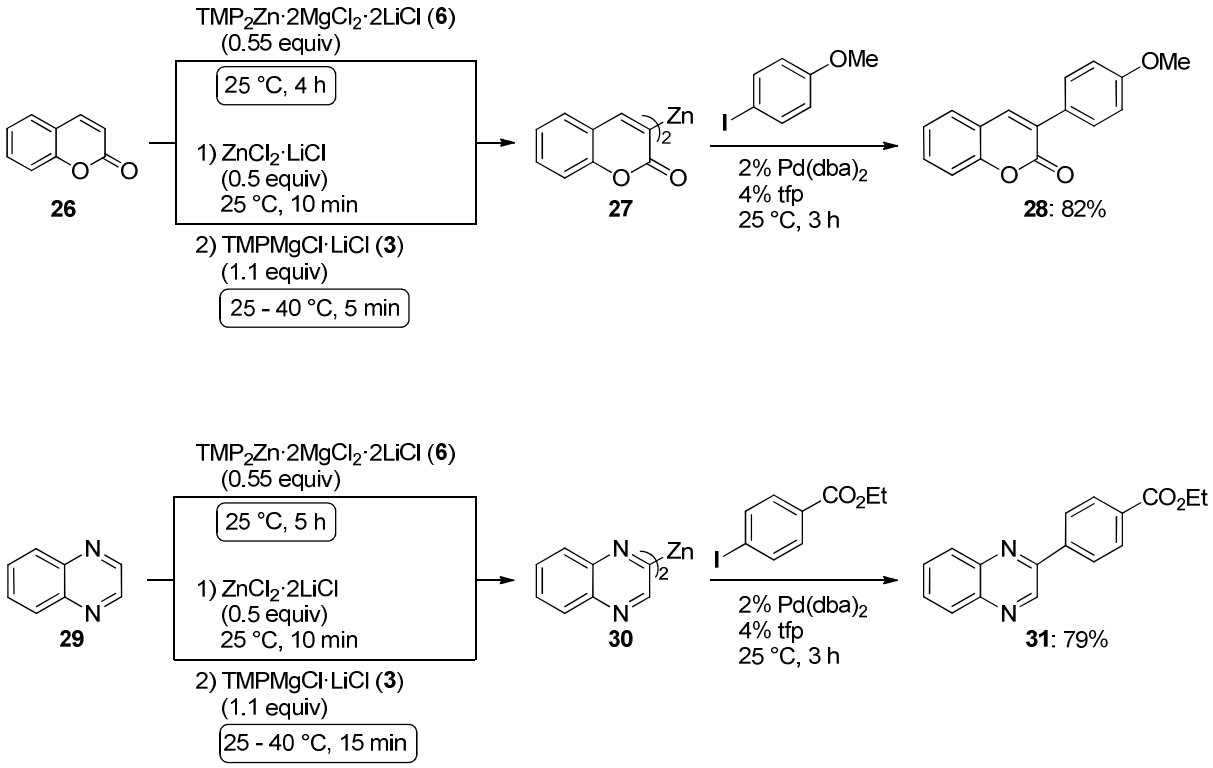


Figure 7: Progress of the metalation of quinoxaline (**29**) using different metalation procedures.

Careful monitoring of the reaction temperature (20 mmol scale experiments) indicates that the temperature increases moderately to reach 34 °C when the addition of TMPMgCl·LiCl (**3**) to the substrate/$ZnCl_2$ solution is complete. Whereas the temperature rises to 38 °C in the case of substrate/$ZnCl_2$·2LiCl solution. This high rate increase in the metalation for a comparatively small temperature increase may be rationalized by an alternative reaction pathway, where the organic substrate is activated by forming a Lewis acid adduct with $ZnCl_2$·2LiCl and then reacts with kinetically enhanced TMPMgCl·LiCl (**3**), to generate *in situ* an organomagnesium intermediate, which can then easily transmetalate with carbophilic $ZnCl_2$ already present in the solution. On the other hand, these results may be an indication for a species different from TMP_2Zn·2$MgCl_2$·2LiCl (**6**) being present in the metalation. The alternative species TMP_3Zn has been proven to be unstable.[135]

[134] a) B. Brehler, H. Jacobi, *Naturwissenschaften* **1964**, *51*, 11; b) I. Solinas, H. D. Lutz, *J. of Solid State Chem.* **1995**, *117*, 34.
[135] a) J-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama, F. Mongin, *J. Org. Chem.* **2008**, *73*, 177; b) R. E. Mulvey, *Chem. Comm.* **2001**, 1049; c) P. García-Álvarez, R. E. Mulvey, J. A. Parkinson, *Angew. Chem.* **2011**, *123*, 9842; *Angew. Chem. Int. Ed.* **2011**, *50*, 9668.

Pd-catalyzed cross-coupling of **30** with ethyl 4-iodobenzoate (25 °C, 3 h) furnishes the expected product **31** in 79% yield (Scheme 29).

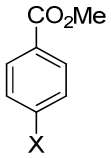
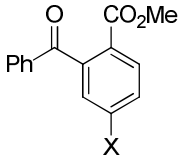
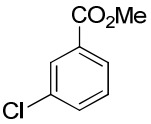
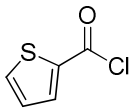
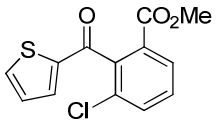
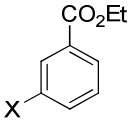
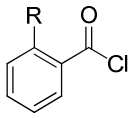
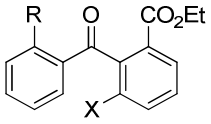


Scheme 29: Dramatic acceleration of the metalation of coumarin (**26**) and quinoxaline (**29**) with $TMP_2Zn·2MgCl_2·2LiCl$ (**6**) and the new sequential procedure.

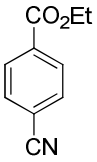
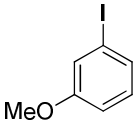
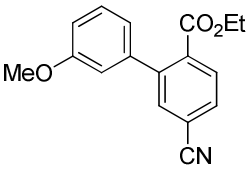
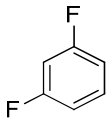
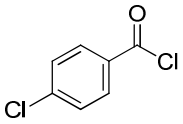
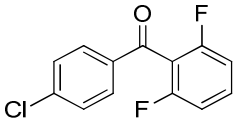
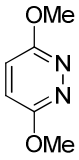
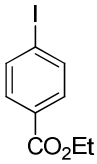
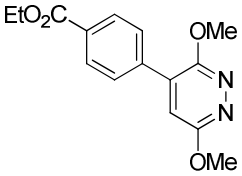
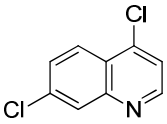
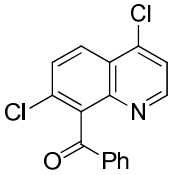
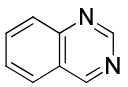
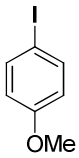
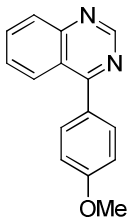
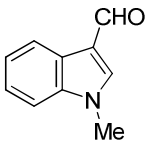
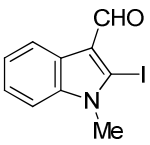
The new procedure is quite general and by treating a variety of aromatics of type **32** and heterocycles of type **33** with $ZnCl_2·2LiCl$ (0.5 equiv), $ZnCl_2·LiCl$ (0.5 equiv) or $ZnCl_2$ (0.5 equiv) followed by TMPMgCl·LiCl (**3**, 1.1 equiv, 25 °C), a range of polyfunctional diorganozincs were prepared at slightly elevated temperature, leading after quenching with electrophiles to the expected products of type **34** in 57-94% yield (Table 4). Thus, methyl esters like methyl 4-bromo- and 4-chlorobenzoate (**32a-b**) are readily zincated within 20 h providing after a copper(I)-mediated benzoylation[99] [CuCN·2LiCl (1.1 equiv), PhCOCl (1.2 equiv), -40 to 25 °C, 20 h] the corresponding keto ester **34a** and **34b** in 85-86% yield (Entries 1-2). Interestingly, the zincation of **32a-b** with $TMP_2Zn·2MgCl_2·2LiCl$ (**6**, 0.55 equiv) requires a considerably longer reaction time (110 h instead of 20 h for the new procedure). Similarly, the methyl ester **32c** is zincated within 5 h and furnishes after acylation with 2-thiophene carboxylic acid chloride the polyfunctional ketone **13c** in 82% yield (Entry 3). Substituted ethyl benzoates like **32d-f** are zincated similarly. After copper(I)-mediated acylations, the ketones **34d-e** are obtained in 91-94% yield (Entries 4-5). *Negishi* cross-coupling of metalated **32f** with 3-iodoanisole using 2% $Pd(dba)_2$ and 4% tfp gave the biphenyl **34f** in 87% yield (Entry 6). The zincation of 1,3-difluorobenzene (**32g**) is completed within 6 h using the new procedure (a reaction time of 90 h is required with $TMP_2Zn·2MgCl_2·2LiCl$ (**6**)). Copper(I)-mediated acylation with 4-chlorobenzoyl chloride furnishes the benzophenone **34g** in 80% yield (Entry 7). Furthermore, various heterocycles undergo this accelerated zincation. Thus, 3,6-dimethoxypyridazine (**33a**) is metalated within 5 h.

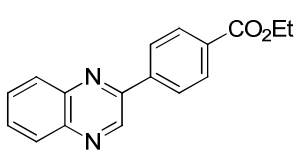
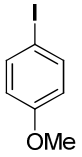
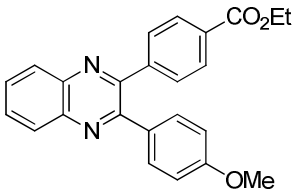
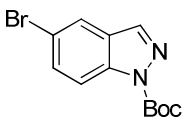
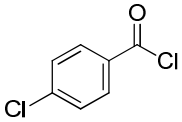
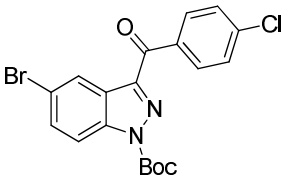
Negishi cross-coupling with ethyl 4-iodobenzoate provides the substituted pyridazine **13h** in 65% yield (Entry 8). Interestingly, the heterocycles **33b-c** are zincated regioselectively affording after reaction with typical electrophiles the products **34i-j** in 57-82% yield (Entries 9-10). The metalation of aldehyde **33d** proceeds smoothly within 2 h and iodolysis leads to the 2-iodoindole **34k** in 78% yield (Entry 11). The quinoxaline **31** (see Scheme 29) can be further zincated within 2 h and a Pd(0)-catalyzed cross-coupling with 4-iodoanisole furnishes the double functionalized quinoxaline **34l** in 57% yield (Entry 12). This method allows the zincation of *N*-Boc protected 5-bromoindazole (**33e**) in position 3. Such metalation is hard to achieve since a ring fragmentation usually occurs.[136] The mild conditions of the zincation procedure [(i) $ZnCl_2$·LiCl (0.5 equiv), 25 °C, 10 min; (ii) TMPMgCl·LiCl (**3**, 1.1 equiv), 25 °C, 0.1 h] lead to the 3-zincated indazole. Copper(I)-catalyzed acylation with 4-chlorobenzoyl chloride provides the product **34m** in 74% yield (Entry 13).

Table 4: Products obtained by using the stepwise metalation procedure with $ZnCl_2$·nLiCl (n = 0, 1, 2) and TMPMgCl·LiCl (**3**).[a]

Entry	Substrate / t[h][b]	Electrophile	Product / Yield[c]
1	 **32a**: X = Br n = 0; 20 (110)	PhCOCl	 **34a**: X = Br: 85%[d]
2	**32b**: X = Cl n = 0; 20 (110)		**34b**: X = Cl: 86%[d]
3	 **32c** n = 0; 5 (36)		 **34c**: 82%[d]
4	 **32d**: X = Br n = 0; 4 (72)		 **34d**: X = Br; R = H: 91%[d]
5	**32e**: X = F n = 0; 2 (12)		**34e**: X = F; R = Cl: 94%[d]

[136] W. M. Welch, C. E. Hanau, W. M. Whalen, *Synthesis* **1992**, 937.

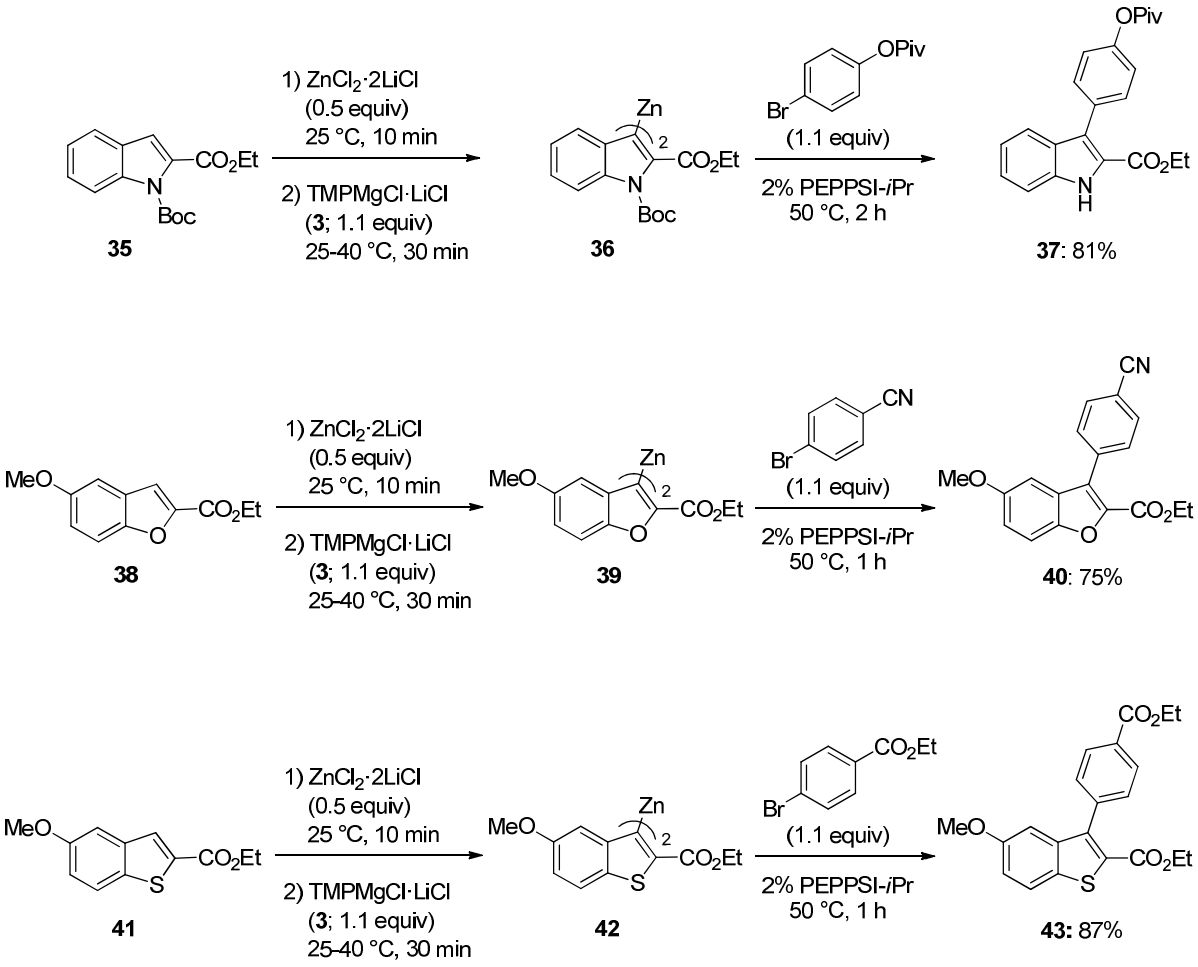
Entry	Substrate / t[h][b]	Electrophile	Product / Yield[c]
6	 **32f** n = 0; 3 (25)		 **34f**: 87%[e]
7	 **32g** n = 0; 6 (90)		 **34g**: 80%[d]
8	 **33a** n = 0; 5		 **34h**: 65%[e]
9	 **33b** n = 1; 0.1	PhCOCl	 **34i**:82%[d]
10	 **33c** n = 1; 1		 **34j**: 57%[e]
11	 **33d** n = 1; 2	I_2	 **34k**: 78%

Entry	Substrate / t[h][b]	Electrophile	Product / Yield[c]
12	 **31** n = 2; 2		 **34l**: 57%[e]
13	 **33e** n = 2; 0.1		 **34m**: 74%[d]

[a] *Reactions conditions*: 2 mmol substrate, 2 mL THF, 1 mL 1 M $ZnCl_2$·nLiCl solution, 2 mL 1.2 M TMPMgCl·LiCl solution. [b] In parentheses the metalation times using $TMP_2Zn·2MgCl_2·2LiCl$ (4) (0.55 equiv) are given. [c] Isolated yield of analytically pure product. [d] A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. [e] Obtained by palladium-catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp.

Remarkably, this method also allows a smooth zincation of *N*-Boc ethyl indole-2-carboxylate (**35**) in position 3. The fast and efficient zincation procedure [(i) $ZnCl_2·2LiCl$ (0.5 equiv), 25 °C, 10 min; (ii) TMPMgCl·LiCl (**3**, 1.1 equiv), 25 °C, 0.5 h] leads smoothly to the 3-zincated indole **36** within 30 min. Pd-catalyzed cross-coupling using 2% PEPPSI-*i*Pr[137] as catalyst and gentle heating to 50 °C for 2 h allows the coupling with an electron deficient aryl bromide (1.1 equiv), providing smoothly the 3-arylated indole **37** in 81% yield. Applying our new procedure to ethyl 5-methoxybenzofuran-2-carboxylate (**38**) gives the expected zinc reagent **39** within 30 min at only moderately elevated temperature. Using the already known conditions (PEPPSI-*i*Pr, 50 °C) the cross-coupling with 4-bromobenzonitrile is successful within 1 h providing the desired polyfunctional benzofuran **40** in 75% yield. Similarly, ethyl 5-methoxybenzothiophene-2-carboxylate **41** is metalated readily under the same conditions, providing the 3-metalated benzothiophene derivative **42** after 30 min. Once more cross-coupling is achieved within 1 h at 50 °C, yielding the desired highly functionalized benzothiophene derivative **43** in 87% yield (Scheme 30).

[137] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; c) J. Nasielski, N. Hadei, G. Achonduh, E. A. B. Kantchev, C. J. O'Brien, A. Lough, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844; d) H. N. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achonduh, S. Avola, D. K. Bohme, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 7845; e) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem.* **2011**, *123*, 9372; *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.

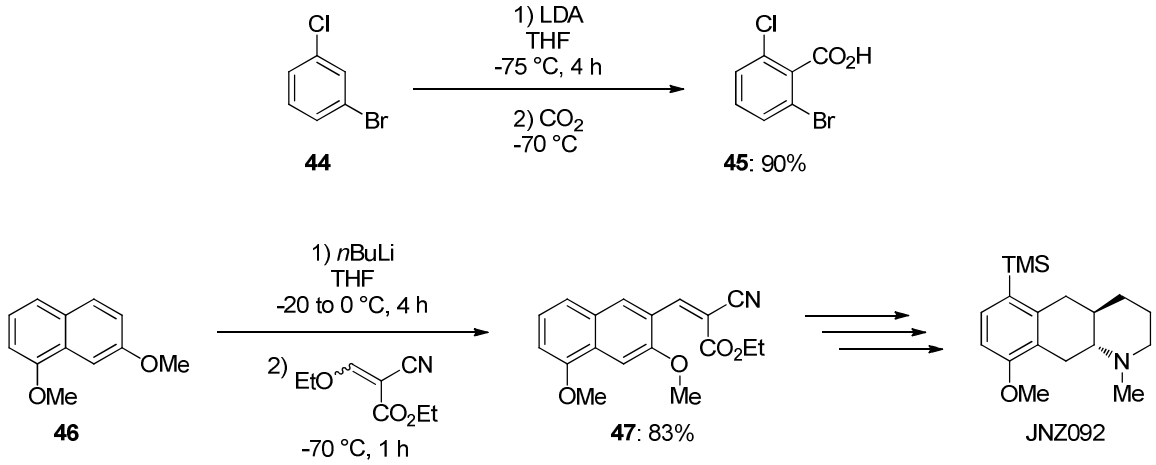


Scheme 30: Expeditive zincation at position 3 of indole, benzofuran and benzothiophene derivatives.

4 SCALEABLE PREPARATION OF FUNCTIONALIZED ORGANOMETALLICS *VIA* DIRECTED ORTHO METALATION USING Mg- AND Zn-AMIDE BASES

4.1 INTRODUCTION

Over the last few decades, the directed *ortho*-metalation for the functionalization of unsaturated substrates has become more and more important.[138] The use of lithium reagents for performing such transformations has been thoroughly investigated and is enjoying more and more application in large-scale process chemistry. To illustrate, Merck chemists optimized the metalation of 300 mol (60 kg) 1-bromo-3-chlorobenzene (**44**), which led to the synthesis of 2-bromo-6-chlorobenzoic acid (**45**) in an excellent yield of 90%.[139] Furthermore, Novartis developed a pilot plant synthesis of the lead compound JNZ092 involving the metalation of 100 mol (20 kg) of dimethoxynaphthalene **46** and electrophilic quenching to give **47** in 83% yield. (Scheme 31)[140]



Scheme 31: Industrial applications of D*o*M.

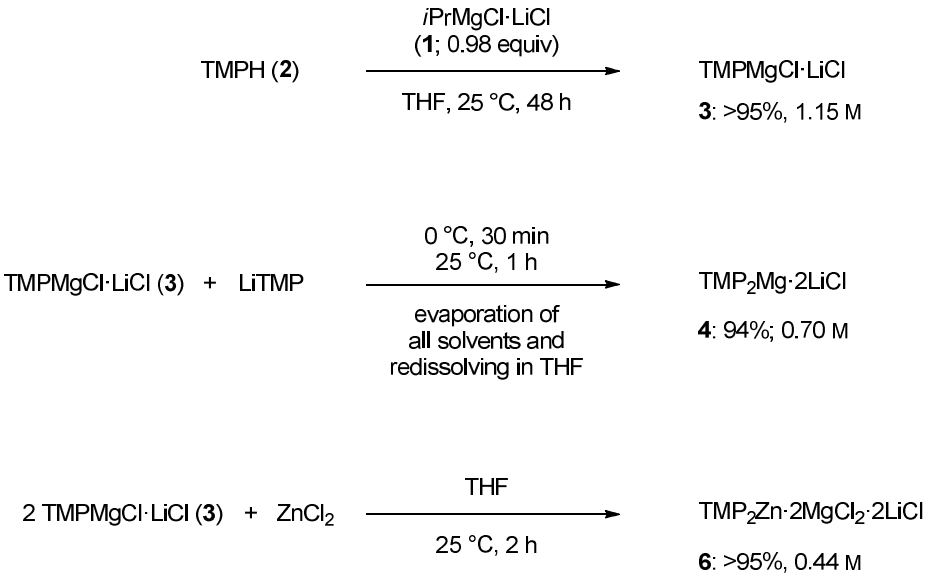
Recently, *Knochel* and coworkers found that the LiCl-complexed and solublized amide base TMPMgCl·LiCl (**3**) allows the smooth magnesiation of many activated aromatics and heteroaromatics.[141] The presence of LiCl is essential since it furnishes monomeric and therefore more reactive TMPMgCl·LiCl-moieties. Similarly the use of the sterically demanding amine TMPH (**2**) is essential, as the related base MgDA·LiCl proved to be dimeric.[142] Furthermore, the reagent **3** can be stored under inert gas atmosphere at 25 °C for several months without decomposition. For the metalation of less activated aromatic substrates, the highly reactive $TMP_2Mg·2LiCl$ (**4**) proved to be a powerful metalation agent. The only drawback is the stability of $TMP_2Mg·2LiCl$ (**4**) since it cannot be

[138] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667.
[139] M. R. Hickey, S. P. Allwein, T. D. Nelson, M. H. Kress, O. S. Sudah, A. J. Moment, S. D. Rodgers, M. Kaba, P. Fernandez, *Org. Process Res. Dev.* **2005**, *9*, 764.
[140] M. Bänziger, E. Küsters, L. La Vecchia, W. Marterer, J. Nozulak, *Org. Process Res. Dev.* **2003**, *7*, 904.
[141] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; c) N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715; d) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113;.
[142] D. R. Armstrong, P. García-Álvarez, A. R. Kennedy, R. E. Mulvey, J. A. Parkinson, *Angew. Chem.* **2010**, *122*, 3253; *Angew. Chem. Int. Ed.* **2010**, *49*, 3185.

stored at 25 °C without loss of reactivity.[131] Additionally, the metalation of more sensitive substrates can be accomplished by using the zinc base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**). Both $MgCl_2$ and LiCl are responsible for the high kinetic basicity and good solubility of this long-term stable reagent. This zincation protocol tolerates sensitive functionalities like aldehydes or nitro groups as well as heterocycles which are prone to undergo ring-opening. The zincations usually occur at convenient temperature and even at elevated temperature the tolerance towards functional groups remains remarkable.[143] Usually, these metalation procedures are carried out in 1-2 mmol scale. Extension of these metalation reagents to larger-scale experiments was investigated.

4.2 LARGER-SCALE BASE PREPARATION

For the large scale experiments, the amide bases are also prepared in bigger amounts. Therefore, TMPMgCl·LiCl (**3**) is provided by the reaction of *i*PrMgCl·LiCl (**1**; 1.31 M in THF, 850 mL, 1.11 mol) with TMPH (**2**; 161 g, 194 mL, 1.14 mol, 1.02 equiv, added at once to *i*PrMgCl·LiCl (**1**) at 25 °C) under inert gas atmosphere at 25 °C for 48 h with the possibility to degas the formed propane. A concentration of 1.15 M in THF (>95% yield) is obtained. Due to the high reactivity of $TMP_2Mg{\cdot}2LiCl$ (**4**), this base is prepared separately for each reaction by reacting TMPMgCl·LiCl (**3**; 87 mL, 100 mmol) with freshly prepared TMPLi (100 mmol, 1 M in hexane/THF). After evaporation of all solvents and redisolving the residue in THF, the concentration of $TMP_2Mg{\cdot}2LiCl$ (**4**) is determined to be 0.7 M in THF (94% yield). For the preparation of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**), TMPMgCl·LiCl (**3**; 348 mL, 400 mmol) is cooled to 0 °C and $ZnCl_2$ (1.0 M in THF, 200 mL, 200 mmol, 0.5 equiv) is added over a period of 15 min. After stirring this mixture for 2 h at 0 °C, the solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) is concentrated *in vacuo*. A concentration of 0.44 M in THF (>95% yield) is obtained (Scheme 32).

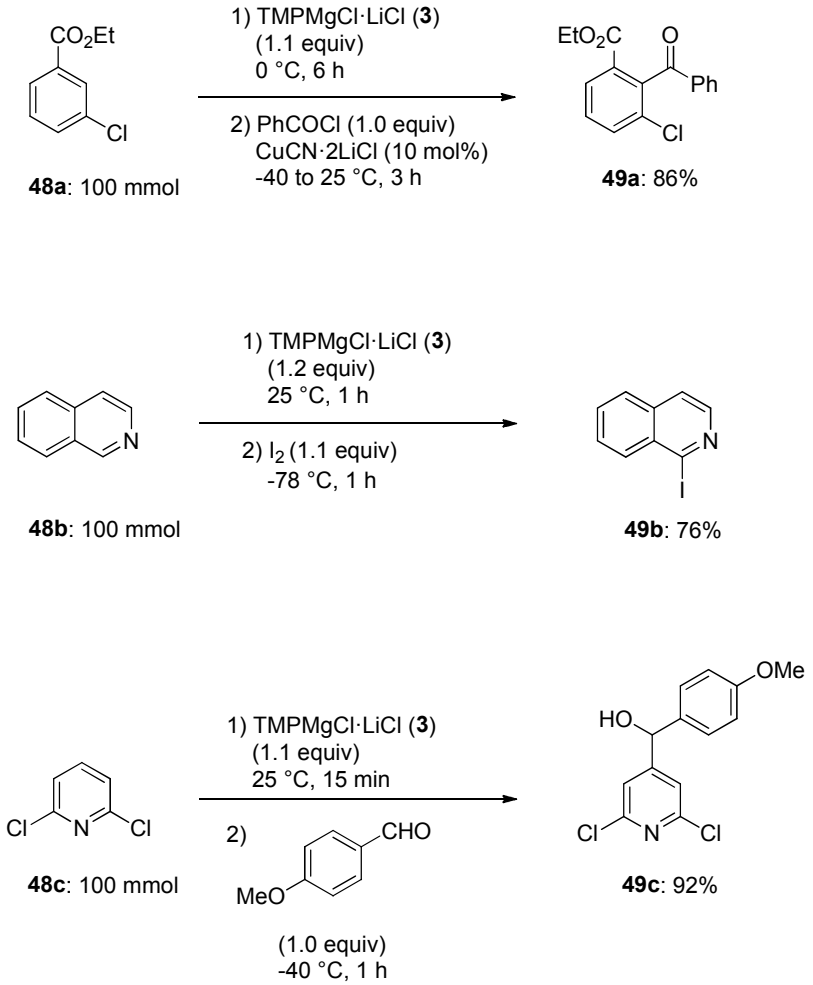


Scheme 32: Larger-scale preparation of the amide bases **3**, **4** and **6.**

[143] S.H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705;

4.3 LARGER-SCALE METALATIONS USING TMPMgCl·LiCl

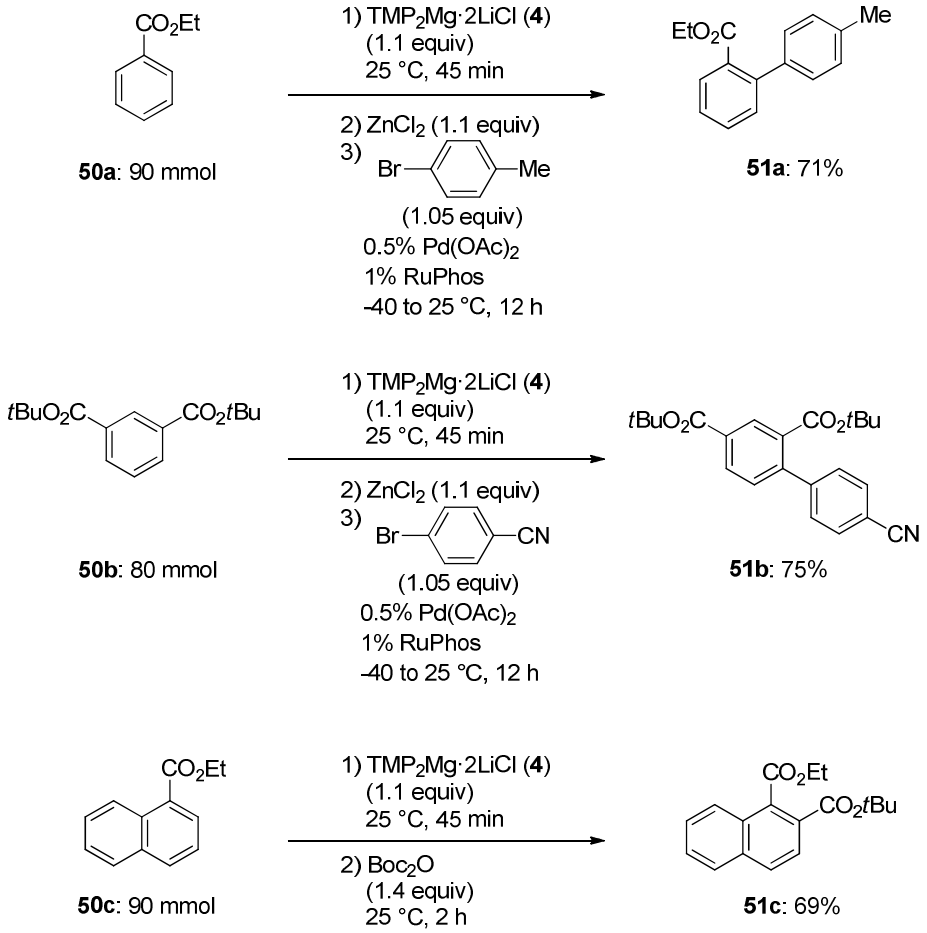
First, larger-scale metalations using TMPMgCl·LiCl (**3**; Scheme 33) were investigated. Ethyl 3-chlorobenzoate (**48a**; 18.5 g. 100 mmol) is added to a solution of TMPMgCl·LiCl (**3**; 1.15 M in THF, 96 mL, 110 mmol, 1.1 equiv) and metalation is performed at 0 °C for 6 h (same metalation rate like reactions in 2 mmol scale). The resulting mixture is cooled to -40 °C, and reacted with PhCOCl (14.2 g, 100 mmol, 1.0 equiv) in the presence of CuCN·2LiCl (1 M in THF, 10 mL, 10 mmol).[99] After slow warming to 25 °C within 3 h, the benzophenone **49a** is obtained in 86% yield. Moreover, isoquinoline (**48b**; 12.9 g, 100 mmol) is regioselectively metalated in position 2 using TMPMgCl·LiCl (**3**; 1.15 M in THF, 104 mL, 120 mmol, 1.2 equiv) within 1 h (compared to 2 h for 2 mmol scale) and the addition of the metalated species to a solution of I_2 in THF (1 M in THF, 110 mL, 110 mmol, 1.1 equiv) at -78 °C furnishes the expected iodide **49b** after 1 h in 76% yield. Similarly, 2,6-dichloropyridine (**48c**; 14.8 g, 100 mmol) is converted into the fully magnesiated species within 15 min at 25 °C (same metalation rate like reactions in 2 mmol scale). The alcohol **49c** is obtained in 92% yield after the reaction with 4-methoxybenzaldehyde (1.0 equiv).



Scheme 33: Metalation of ethyl 3-chlorobenzoate (**48a**), isoquinoline (**48b**) and 2,6-dichloropyridine (**48c**) using TMPMgCl·LiCl (**3**) and subsequent reactions with electrophiles.

4.4 LARGER-SCALE METALATIONS USING $TMP_2Mg·2LiCl$

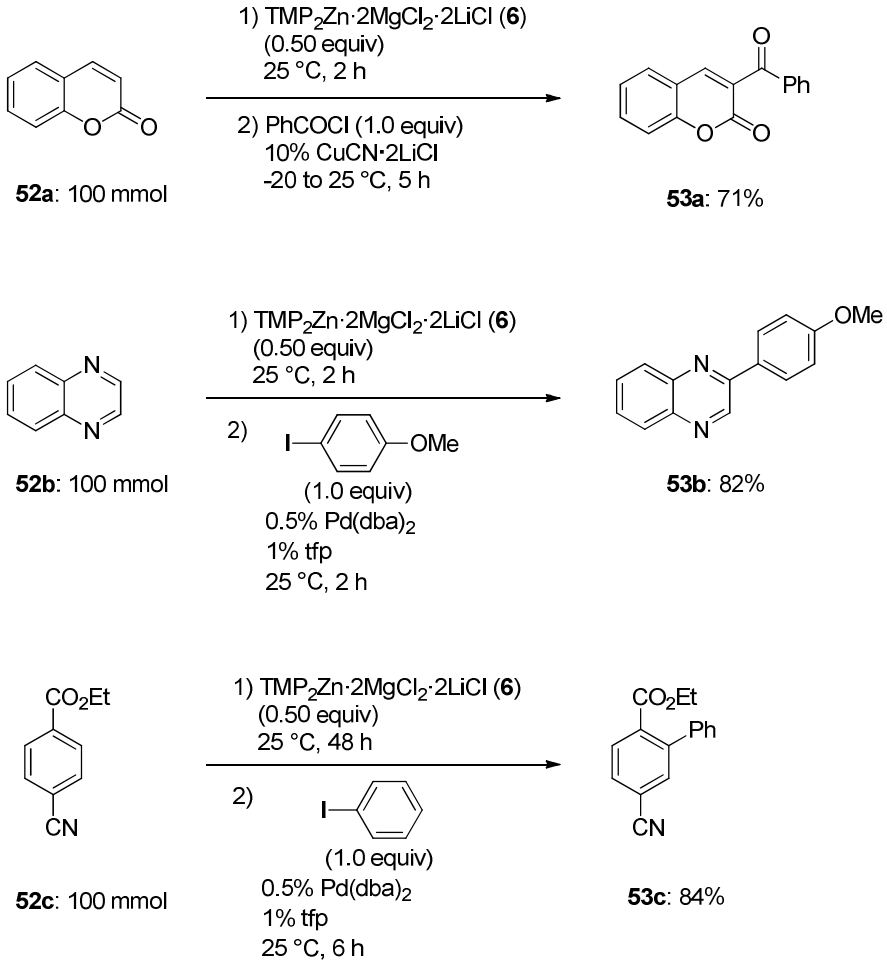
Furthermore, the larger-scale magnesiation of unactivated aromatics was performed by using the more reactive $TMP_2Mg·2LiCl$ (**4**) under the optimized conditions as shown in Scheme 34. Thus, a 500 mL *Schlenk*-flask is charged with freshly prepared $TMP_2Mg·2LiCl$ (**4**; 143 mL, 100 mmol). Ethylbenzoate (**50a**; 13.5 g, 90 mmol) is given to **4** in one portion at 25 °C. After 45 min metalation time (compared to 1 h for 2 mmol scale) and subsequent cooling to -40 °C, $ZnCl_2$ (100 mL, 100 mmol, 1.1 equiv) is added and the resulting mixture is stirred for 15 min. Then, a Pd-catalyzed cross-coupling reaction with 4-bromotoluene (1.0 equiv) using 0.5% $Pd(OAc)_2$ and 1% RuPhos as catalytic system leads to the biaryl **51a** 71% yield. Accordingly, the magnesiation of isophthalic acid di-*tert*-butyl ester (**50b**; 22.2 g 80 mmol) using $TMP_2Mg·2LiCl$ (**4**; 128 mL, 90 mmol, 1.1 equiv) is finished within 45 min at 25 °C (compared to 1 h for 2 mmol scale). Subsequently, after transmetalation with $ZnCl_2$ (90 mL, 90 mmol, 1.1 equiv) a Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (1.0 equiv) using 0.5% $Pd(OAc)_2$ and 1% RuPhos as catalytic system provides the biaryl **51b** in 75% yield. Additionally, the metalation of ethyl 1-naphtoate (**50c**; 18.0 g 90 mmol) is finished within 45 min at 25 °C using $TMP_2Mg·2LiCl$ (**4**; 143 mL, 100 mmol; compared to 1 h for 2 mmol scale) by applying this large scale protocol. After quenching with Boc_2O (1.4 equiv), the desired diester **51c** is isolated in 69% yield.



Scheme 34: Metalation of ethylbenzoate (**50a**), isophthalic acid di-*tert*-butyl ester (**50b**) and ethyl 1-naphtoate (**50c**) using $TMP_2Mg·2LiCl$ (**4**) and subsequent reactions with electrophiles**.**

4.5 LARGER-SCALE METALATIONS USING $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$

Finally, the larger-scale zincation was investigated (Scheme 35). Thus, a 250 mL *Schlenk*-flask is charged with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 114 mL, 50 mmol) and coumarin (**52a**; 14.6 g, 100 mmol) is given to **6** in one portion at 25 °C. After 2 h (compared to 4 h for 2 mmol scale), the metalation of coumarin is complete, and the resulting mixture is cooled to -20 °C. Then, CuCN·2LiCl (10 mL, 10 mmol, 10 mol%) is added, followed by benzoyl chloride (14.2 g, 100 mmol, 1.0 equiv). The acylation reaction proceeds while slowly warming the reaction mixture to 25 °C over 5 h. The desired benzoylated coumarin **53a** is obtained in 69% yield (compared to 75% in 2 mmol scale). Accordingly, the metalation of quinoxaline (**52b**; 13.5 g, 100 mmol) is finished within 3 h (compared to 6 h for 2 mmol scale). Subsequently, a Pd-catalyzed cross-coupling reaction with 4-iodoanisole (1.0 equiv) using 0.5% $Pd(dba)_2$ and 1% tfp as catalytic system furnishes the arylated quinoxaline **53b** in 82% yield (compared to 85% in 2 mmol scale). Interestingly, the metalation for **52a** and **52b** proceeds twice faster when carried out in 100 mmol scale. In contrast, the metalation of ethyl 4-cyanobenzoate (**52c**) takes 48 h at 25 °C (compared to 24 h for 2 mmol scale). The following Pd-catalyzed cross-coupling with iodobenzene (1.0 equiv) using 0.5% $Pd(dba)_2$ and 1% tfp as catalytic system leads to the biaryl **53c** in 84% yield (compared to 85% in 2 mmol scale).



Scheme 35: Metalation of coumarin (**52a**), quinoxaline (**52b**) and ethyl 4-cyanobenzoate (**52c**) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) and subsequent reactions with electrophiles.

To regenerate the TMPH (**2**), the aqueous layers of the above described reactions quenched with NH_4Cl and HCl are collected and treated with NaOH until TMPH (**2**) appears as organic layer above the aqueous phase. TMPH (**2**) can easily be separated and after distillation over CaH_2, it can be recovered in up to 75% yield.

5 HIGHLY SELECTIVE C-H ACTIVATIONS OF PYRIDINES AND RELATED N-HETEROCYCLES

5.1 INTRODUCTION

The regioselective functionalization of pyridines and quinolines is an important synthetic goal since many of these heterocycles have important biological properties. Thus, they find application where bioactivity is important, as in pharmaceutical drugs or crop protection products[144] and are of interest as new materials (Figure 8).[145]

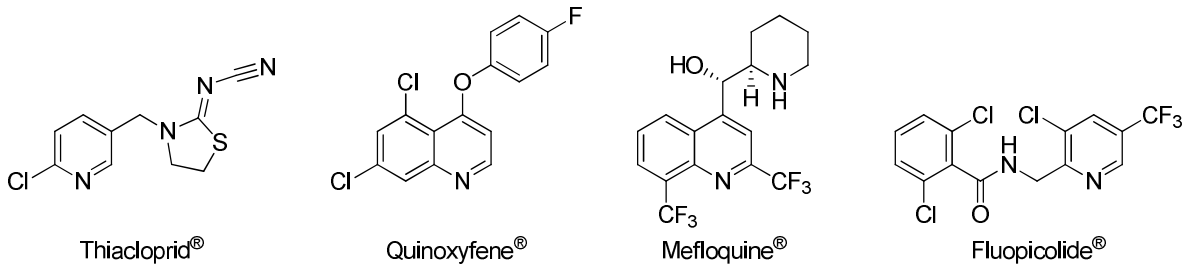


Figure 8: Selected pyridine and quinoline containing medication and pesticides.

The regioselective functionalization of these heterocyclic scaffolds has been achieved by directed metalations or metal-catalyzed C-H activations.[146] The stoichiometric lithiation of pyridines is complicated due to *Chichibabin*-dimerizations. An elegant solution has been proposed by *Kessar et al.* who showed that a complexation of pyridine with BF_3 allows a low temperature α-lithiation of pyridine[147] as well as some other amino derivatives.[148] However, attempts to magnesiate, zincate or aluminate unactivated pyridines with bases such as TMPMgCl·LiCl (**3**), $TMP_2Zn·2MgCl_2·2LiCl$ (**6**), TMPZnCl·LiCl (**5**) or [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) proved to be unsatisfactory. Thus, by using TMPMgCl·LiCl (**3**; 1.1 equiv, 25 °C) only a partial magnesiation was observed (less than 40%). Consequently, the *Kessar* protocol for performing such metalations using the TMP-bases **3**–**7** has been investigated for a convenient regioselective C-H activation of various polyfunctional pyridines and related heterocycles *via* a stepwise BF_3-activation followed by a metalation with the appropriate TMP-base.

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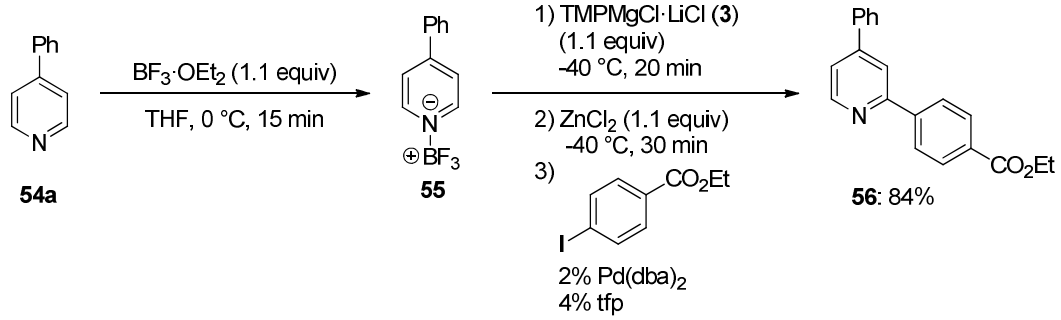
[146] a) S. Murai, *Activation of Unreactive Bonds and Organic Synthesis*, Springer, **1999**. b) A. R. Dick, M. S. Sanford, *Tetrahedron*, **2006**, *62*, 2439.

[147] S. V. Kessar, P. Singh, K. N. Singh, M. Dutt, *J. Chem. Soc., Chem. Commun.* **1991**, 570.

[148] a) S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, K. N. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568. b) S. V. Kessar, P. Singh, K. N. Singh, P. Venugopalan, A. Kaur, P. V. Bharatam, A. K. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 4506. c) S. V. Kessar, P. Singh, K. N. Singh, P. V. Bharatam, A. K. Sharma, S. Lata, A. Kaur, *Angew. Chem. Int. Ed.* **2008**, *47*, 4703.

5.2 REGIOSELECTIVITY SWITCH IN METALATIONS OF PYRIDINES AND RELATED N-HETEROCYCLES

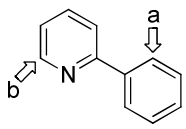
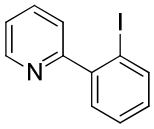
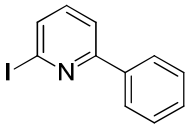
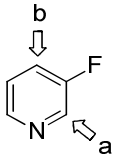
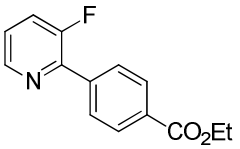
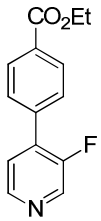
Thus, metalation of 4-phenylpyridine (**54a**) as test substrate led to unexpected observations. It was found that a precomplexation of **54a** with BF_3·OEt_2, which produces complex **55**, leads to a rapid deprotonation with TMPMgCl·LiCl (**3**; 1.1 equiv, -40 °C, 20 min). The generated metalated pyridine affords after transmetalation with $ZnCl_2$ and subsequent *Negishi* cross-coupling with ethyl 4-iodobenzoate the expected 2-arylated pyridine **56** in 84% yield (Scheme 36).

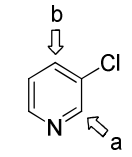
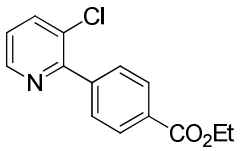
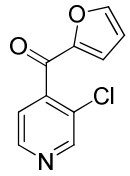
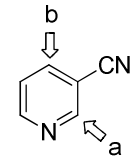
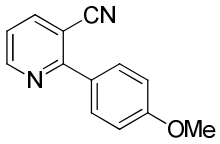
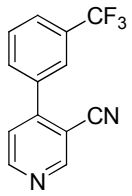
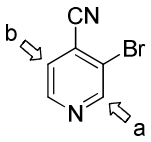
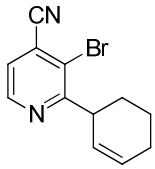
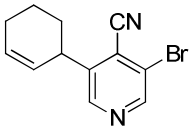
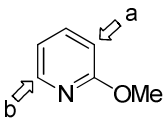
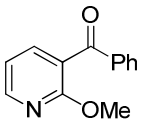
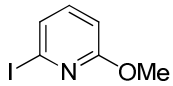
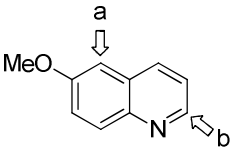
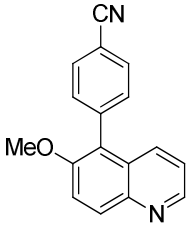
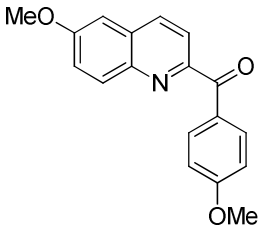


Scheme 36: BF_3-triggered metalation of 4-phenylpyridine (**54a**).

In a number of cases, this two step-metalation procedure allowed to switch the regioselectivity of the metalation completely, by using either TMP-derived bases **3**–**7** without BF_3·OEt_2 (metalation pathway a) or metalation of BF_3-precomplexed N-heterocycles (pathway b; Table 5) **.**

Table 5: Switchable, regioselective metalation of N-heterocycles with TMP-bases in the presence or absence of BF_3·OEt_2.

Entry	Substrate	TMP-base mediated metalation (pathway a)[m]	BF_3-triggered metalation (pathway b)[m]
1	 **54b**	 **57a**: 85%[a]	 **58a**:83%[h]
2	 **54c**	 **57b**: 72%[b, n]	 **58b**: 74%[b, n]

Entry	Substrate	TMP-base mediated metalation (pathway a)[m]	BF_3-triggered metalation (pathway b)[m]
3	 **54d**	 **57c**: 75%[c, n]	 **58c**: 78%[c, o]
4	 **54e**	 **57d**: 72%[d, n]	 **58d**: 79%[i, n]
5	 **54f**	 **57e**: 65%[e, p]	 **58e**: 63%[j, p]
6	 **54g**	 **57f**: 68%[f, o]	 **58f**: 75%[k]
7	 **54h**	 **57g**: 68%[g, n]	 **58g**: 94%[l, o]

Reaction conditions: [a] TMPMgCl·LiCl (**3**; 55 °C, 30 h); [b] TMPMgCl·LiCl (**3**; -78 °C, 30 min); [c] TMPMgCl·LiCl (**3**; -78 °C, 45 min); [d] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 25 °C, 12 h); [e] TMPMgCl·LiCl (**3**; -78 °C, 1 h); [f] [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**; 25 °C, 2 h); [g] [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**; -78 °C, 1 h); [h] TMPMgCl·LiCl (**3**; 0 °C, 30 h); [i] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; -30 °C, 30 min); [j] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; -78 °C, 1 h); [k] TMPMgCl·LiCl (**3**; 0 °C, 60 h); [l] TMPMgCl·LiCl (**3**; 0 °C, 1 h); [m] Yield of the analytically pure isolated product; [n] The product was obtained by palladium-catalyzed cross-coupling using 5% $Pd(dba)_2$ and 10% tfp; [o] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv); [p] Catalyzed by 5% of CuCN·2LiCl.

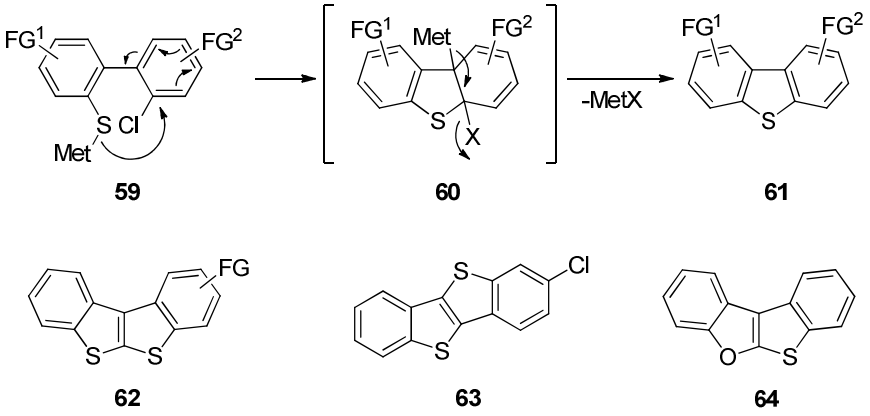
Thus, 2-phenylpyridine (**54b**) is selectively magnesiated with TMPMgCl·LiCl (**3**; 2 equiv, 55 °C, 30 h) in the *ortho*-position of the phenyl substituent leading after iodolysis to the aryl iodide **57a** (82% yield). In contrast, precomplexation with $BF_3{\cdot}OEt_2$ (1.1 equiv, 0 °C, 15 min) followed by the addition of

TMPMgCl·LiCl (**3**; 1.5 equiv, 0 °C, 30 h) is leading to a selective metalation in position 6 of the pyridine core, affording after iodolysis the iodopyridine **58a** (83% yield, Table 5, Entry 1). A number of substituted pyridines (**54c**-**g**; Entries 2-6) display this remarkable switch in selectivity. Thus, 3-fluoropyridine (**54c**) is magnesiated with TMPMgCl·LiCl (**3**; 1.1 equiv, -78 °C, 30 min), in position 2. After transmetalation with $ZnCl_2$ and *Negishi* cross-coupling with ethyl 4-iodobenzoate, the 2,3-disubstituted pyridine **57b** is obtained in 72% yield (Entry 2). Precomplexation with $BF_3{\cdot}OEt_2$ and metalation with TMPMgCl·LiCl (**3**; 1.1 equiv, -78 °C, 30 min) provides the 4-metalated pyridine which after cross-coupling with 1-iodo-3-(trifluoromethyl)benzene furnished the 3,4-disubstituted pyridine **58b** (74% yield; Entry 2). This complementary functionalization is observed as well for 3-chloropyridine (**54d**) and 3-cyanopyridine (**54e**) leading after similar reaction sequences to the 2,3-substituted pyridines **57c** and **57d** in 72-75% yield and to the 3,4-disubstituted pyridine **58c** and **58d** in 78-79% yield (Entries 3-4). The metalation of the electron-poor pyridine **54e** is especially remarkable since such sensitive heterocycles are prone to polymerization during metalations. Thus nicotinonitrile (**54e**) is selectively metalated in position 2 using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) furnishing after Negishi cross-coupling the 2,3-disubstituted pyridine **57d** in 72% yield whereas a precomplexation with $BF_3{\cdot}OEt_2$ and metalation with **6** (-30 °C, 30 min) provides after cross-coupling the 3,4-disubstituted product **58d** (79% yield; Entry 4). For electron-deficient disubstituted pyridines like 3-bromo-4-cyanopyridine (**54f**) the metalation is performed with TMPMgCl·LiCl (**3**; 1.1 equiv, -78 °C, 1 h) affording after copper-mediated allylation with 3-bromo-cyclohexene the 1,2,3-trisubstituted pyridine **57e** (65% yield; Entry 5). In contrast, by a precomplexation with $BF_3{\cdot}OEt_2$ (1.1 equiv, 0 °C, 15 min) and subsequent reaction with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**), a selective zincation occurs in position 4 providing after allylation the 3,4,5-trisubstituted pyridine **58e** (63% yield; Entry 5). Electron-rich pyridines such as 2-methoxypyridine (**54g**) can also be regioselectively deprotonated using in this case the aluminium base $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})\text{N}]_3\text{Al}{\cdot}3\text{LiCl}$ (**7**) which, in the absence of $BF_3{\cdot}OEt_2$, is leading after acylation to the 2,3-substituted pyridine **57f** (68% yield; Entry 6)). Precomplexation with $BF_3{\cdot}OEt_2$ followed by a metalation with TMPMgCl·LiCl (**3**) and iodolysis provides the 2,6-substituted iodo-pyridine **58f** (75% yield; Entry 6). This regioselectivity has been extended to functionalized quinoline derivatives. Thus, 6-methoxyquinoline (**54h**) is aluminated with $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})\text{N}]_3\text{Al}{\cdot}3\text{LiCl}$ (**7**) in position 5 affording after transmetalation with $ZnCl_2$ and subsequent *Negishi* cross-coupling the 5,6-disustituted quinoline **57g** in 68% yield whereas a precomplexation with $BF_3{\cdot}OEt_2$ followed by TMPMgCl·LiCl (**3**) leads after a copper-mediated acylation to the 2,6-disubstituted quinoline **58g** (94% yield; Entry 7).

6 NEW SYNTHESIS OF DIBENZOTHIOPHENES AND RELATED CLASSES OF S-HETEROCYCLES USING FUNCTIONALIZED DITHIOCARBAMATES

6.1 INTRODUCTION

Dibenzothiophenes, benzo[b]thiophenes, and benzo[c]thiophenes have found numerous applications as dyes, pharmaceuticals, agrochemicals, or as building blocks for the synthesis of conducting polymers.[149,150] Several straightforward syntheses of such S-heterocycles have been reported using various synthetic strategies.[151] Pd-catalyzed ring closures leading to S-heterocycles are especially difficult, but could be realized recently despite the deactivating effect of sulfur on transition metal catalysts.[152,153] In order to avoid this poison problem of thiols and thiolates on transition metals a ring closure procedure involving main-group thiophenolates such as **59** as precursors which by an addition-elimination reaction[154] may provide an intermediate such as **60** has been studied. After the elimination of Met-X various dibenzothiophenes of type **61** should result (Scheme 37)**.**



Scheme 37: Preparation of S-Heterocycles *via* a possible addition-elimination mechanism.

[149] a) M. D. Andrews, *Science of Synthesis*, Ed. E. J. Thomas, **2000**, *10*, 211; b) C. M. Rayner, M. A. Graham, *Science of Synthesis*, Ed. E. J. Thomas, **2000**, *10*, 155; c) T. L. Gilchrist, S. J. Higgins, *Science of Synthesis*, Ed. E. J. Thomas, **2000**, *10*, 185.

[150] For reviews on modern aspects of S-substituted aromatics and S-heterocycles see: M. Gingras, J.-C. Raimundo, I. M. Chabre, *Angew. Chem.* **2006**, *118*, 1718; *Angew. Chem. Int. Ed.* **2006**, *45*, 1686.

[151] a) I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem*. **2006**, *118*, 4585; *Angew. Chem. Int. Ed.* **2006**, *45*, 4473; b) R. Sanz, Y. Fernandez, M. P. Castroviejo, A. Perez, F. J. Fananas, *J. Org. Chem*. **2006**, *71*, 629; c) K. Sadorn, W. Sinananwanich, J. Areephong, C. Nerungsi, C. Wongma, C. Pakawatchai, T. Thongpanchang, *Tetrahedron Lett*. **2008**, *49*, 4519; d) Q. Zhao, L. Li, Y. Fang, D. Sun, C. Li, *J. Org. Chem.* **2009**, *74*, 459; e) K. Inamoto, Y. Arai, K. Hiroya, T. Doi, *Chem. Commun.* **2008**, 5529 ; f) T. Dahl, C. W. Tornoe, B. Bang-Andersen, P. Nielson, M. Jorgensen, *Angew. Chem*. **2008**, *120*, 1750; *Angew. Chem. Int. Ed.* **2008**, *47*, 1726; g) P. P. Singh, A. K. Yadav, H. Ila, H. Junjappa, *J. Org. Chem*. **2009**, *74*, 5496; h) O. Goyot, M. Gingras, *Tetrahedron Lett.* **2009**, *50*, 1977; i) J. T. Henssler, A. J. Matzger, *Org. Lett*. **2009**, *11*, 3144.

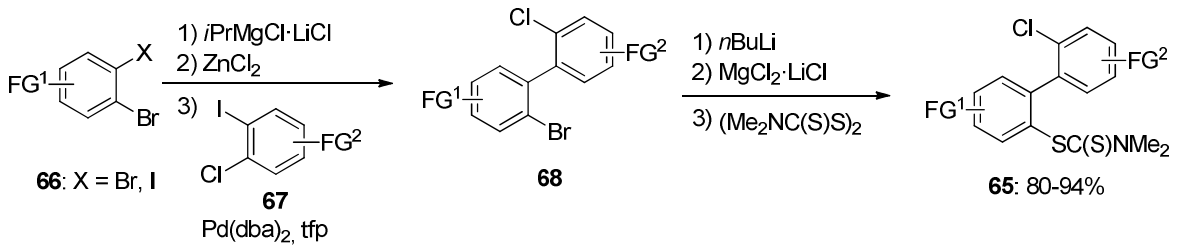
[152] a) C. S. Bryan, J. A. Braunger, M. Lautens, *Angew. Chem*. **2009**, *121*, 7198; *Angew. Chem. Int. Ed.* **2009**, *48*, 7064; b) J.-Y. Lee, P. H. Lee, *J. Org. Chem.* **2008**, *73*, 7413; c) M. A. Fernandez-Rodriguez, Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc*. **2006**, *128*, 2180; d) C. Mispelaere-Canivet, J.-F. Spindler, S. Perrio, P. Beslin, *Tetrahedron* **2005**, *61*, 5253; e) M. Murata, S. L. Buchwald, *Tetrahedron* **2004**, *60*, 7397.

[153] a) H. Morita, A. Tatami, T. Maeda, B. J. Kim, W. Kawashima, T. Yoshimura, H. Abe, T. Akasaka, *J. Org. Chem.* **2008**, *73*, 7159; b) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517; c) T. Otsubo, Y. Kono, N. Hozo, H. Miyamoto, Y. Aso, F. Ogura, T. Tanaka, M. Sawada, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2033; d) C. G. Bates, P. Saejueng, M. Q. Doherty, D. Venkataraman, *Org. Lett.* **2004**, *6*, 5005; e) S. L. Buchwald, Q. Fang, *J. Org. Chem.* **1989**, *54*, 2793; f) M. Black, J. I. Cadogan, H. McNab, *J. Chem. Soc.* **1990**, *5*, 395; g) V. H. Rawal, R. J. Jones, M. P. Cava, *J. Org. Chem.* **1987**, *52*, 19; h) T. Qi, W. Qiu, Y. Liu, H. Zhang, X. Gao, Y. Liu, K. Lu, C. Du, G. Yu, D. Zhu, *J. Org. Chem.* **2008**, *73*, 4638; i) J. L. Huppatz, W. H. F. Sasse, *Aust. J. Chem.* **1964**, *17*, 1406.

[154] For previous ring-closures involving a S_NAr of thiolates with electron-poor substrates leading to 6-membered S-heterocycles, see: a) B. Willy, T. J. J. Müller, *Synlett*, **2009**, 1255; b) B. Willy, W. Frank, T. J. J. Müller, *Org. Biomol. Chem*. **2010**, *8*, 90.

6.2 NEW PREPARATION OF S-HETEROCYCLES

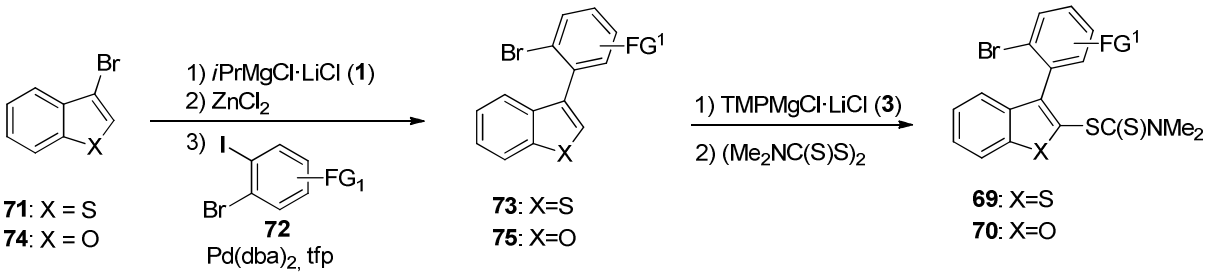
The synthesis of various classes of S-heterocycles of type **61**, and **62**[155] as well as 2-chlorobenzo[b] benzo[4,5]thieno[2,3-d]thiophene **63**[156] and the unknown benzo[4,5]thieno[2,3-b]benzofuran **64** has been accomplished according to Scheme 37, starting from readily available biaryls of type **65**. Thus, a Br-Mg or I-Mg exchange on aryl bromides or iodides of type **66** was first carried out with *i*PrMgCl·LiCl (**1**) and thentransmetalated with $ZnCl_2$. A subsequent Negishi cross-coupling with functionalized aryl iodides of type **67** then afforded the polysubstituted biphenyls **68**. These biphenyls do not undergo complete Br-Mg exchange because of steric hindrance. Br-Li exchange proved to be superior. After transmetalation with the THF soluble magnesium complex $MgCl_2$·LiCl,[157] the resulting arylmagnesium species were treated with tetramethylthiuram disulfide[158] providing biphenyl dithiocarbamates **65** (Scheme 38).



Scheme 38: Preparation of the starting biphenyl dithiocarbamates of type **65**.

This synthesis was also extended to the preparation of benzothiophenes **69** and benzofurans **70**. Thus, 3-bromobenzothiophene (**71**) was magnesiated with *i*PrMgCl·LiCl to the corresponding magnesium derivative which after transmetalation with $ZnCl_2$ and Negishi cross-coupling with various 2-bromoaryl iodides of type **72** resulted in the formation of the 3-arylated benzothiophenes of type **73** (Scheme 39). The magnesiation of compounds of type **73** with TMPMgCl·LiCl followed by trapping with $(Me_2NC(S)S)_2$ afforded the desired benzothienyl dithiocarbamates **69a**-**d** in 80-90% yield. Similarly, 3-bromobenzofuran (**74**) was converted using the same 2 step sequence to the benzofuryl dithiocarbamates **70** *via* the intermediates **75** (Scheme 39).

[155] S. Dayagi, I. Goldberg, U. Shmueli, *Tetrahedron*, **1970**, *26*, 411.
[156] a) H. Sashida, S. Yasuike, *J. Heterocyclic Chem*. **1998**, *35*, 725; b) S. Y. Zherdeva, A. Barudi, A. Y. Zheltov, B. I. Stepanov, *Zh. Org. Khim*. **1980**, *16*, 430; c) K. Takimiya, H. Ebata, K. Sakamoto, T. Izawa, T. Otsubo, Y. Kunugi, *J. Am. Chem. Soc*. **2006**, *128*, 12604.
[157] CH_2Cl_2 proved to be the best solvent for $(Me_2NC(S)S)_2$. Since the addition of $(Me_2NC(S)S)_2$ in CH_2Cl_2 to the lithium species resulted in the formation of undesired by-products a transmetalation to the corresponding Mg-species was advantageous.
[158] a) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett*, **2005**, 2691; b) A Krasovskiy, A. Gavryushin, P. Knochel, *Synlett*, **2006**, 792.



Scheme 39: Preparation of starting 3-benzothienyl and -furyl of type **69** and **70**.

The chloro-substituted dithiocarbamates **65** were converted with *t*BuOK to the corresponding potassium thiolates which undergo an addition-elimination ring closure according to Scheme 37 and provide the desired functionalized dibenzothiophenes of type **61** (Figure 9).

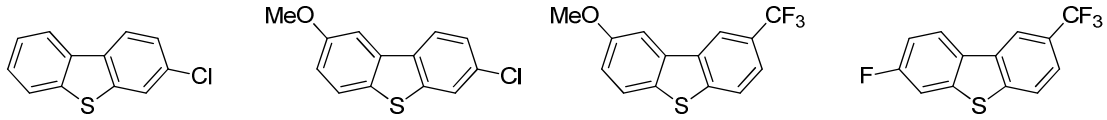
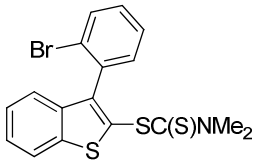
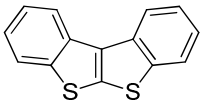


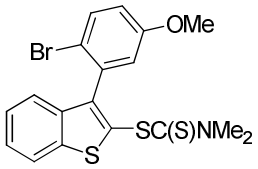
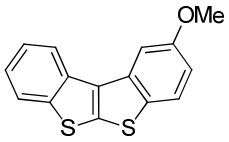
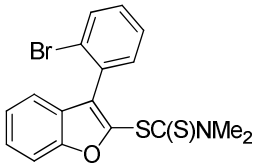
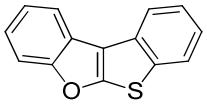
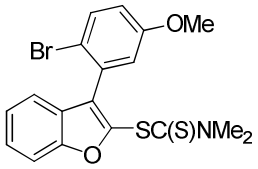
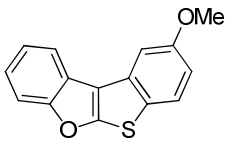
Figure 9: Synthesized dibenzothiophenes of type **61**.

Bromo-substituted precursors such as **69a**-**d** and **70a**-**b** can also be used in such a ring closure. Treatment with *n*BuLi leads to a complete cyclization within 30 min at -20 °C and furnishes the tetracylic heterocyclic products **62a**-**b** in 80-90% yield (Table 6, Entries 1-2) and **64a**-**b** in 72-76% yield (Entries 3-4). A possible mechanism may involve a Br-Li exchange followed by a substitution reaction of the intermediate aryllithiums on the dithiocarbamate group leading to the desired products and as well as to dimethyl-thiocarbamoyllithium ($LiC(S)NMe_2$),[159] which may decompose under these conditions. An alternative radical mechanism cannot be excluded.[160]

Table 6: Preparation of various S-heterocycles of type **62** and **64**

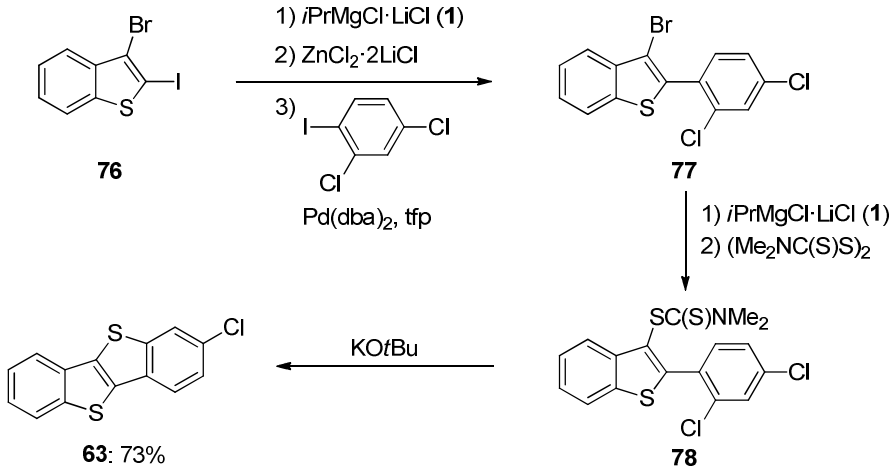
Entry	Substrate	T [°C][a]	Product[b]
1	 **69a**	-20 (0.5)[e]	 **62a**: 80%[b]

[159] a) D. Enders, D. Seebach, *Angew. Chem*. **1973**, *85*, 1104; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014; b) D. Seebach, W. Lubosch, D. Enders, *Chem. Ber*. **1976**, *109*, 1309.
[160] R. A. Rossi, A. B. Penenory, *Curr. Org. Synth*. **2006**, *3*, 121 and references therein.

Entry	Substrate	T [°C][a]	Product[b]
2	 **69b**	-20 (0.5)[e]	 **62b**: 90%[b]
3	 **70a**	-20 (0.5)[e]	 **64a**: 72%[b]
4	 **70b**	-20 (0.5)[e]	 **64b**: 76%[b]

[a] The reaction conditions for the ring closing reaction are given in parentheses (°C, h). [b] Isolated yield of analytically pure product. [c] KO*t*Bu (3 equiv) was used for the ring closure. [d] Microwave irradiation was used. [e] *n*BuLi (1.05 equiv) was used for the ring closure.

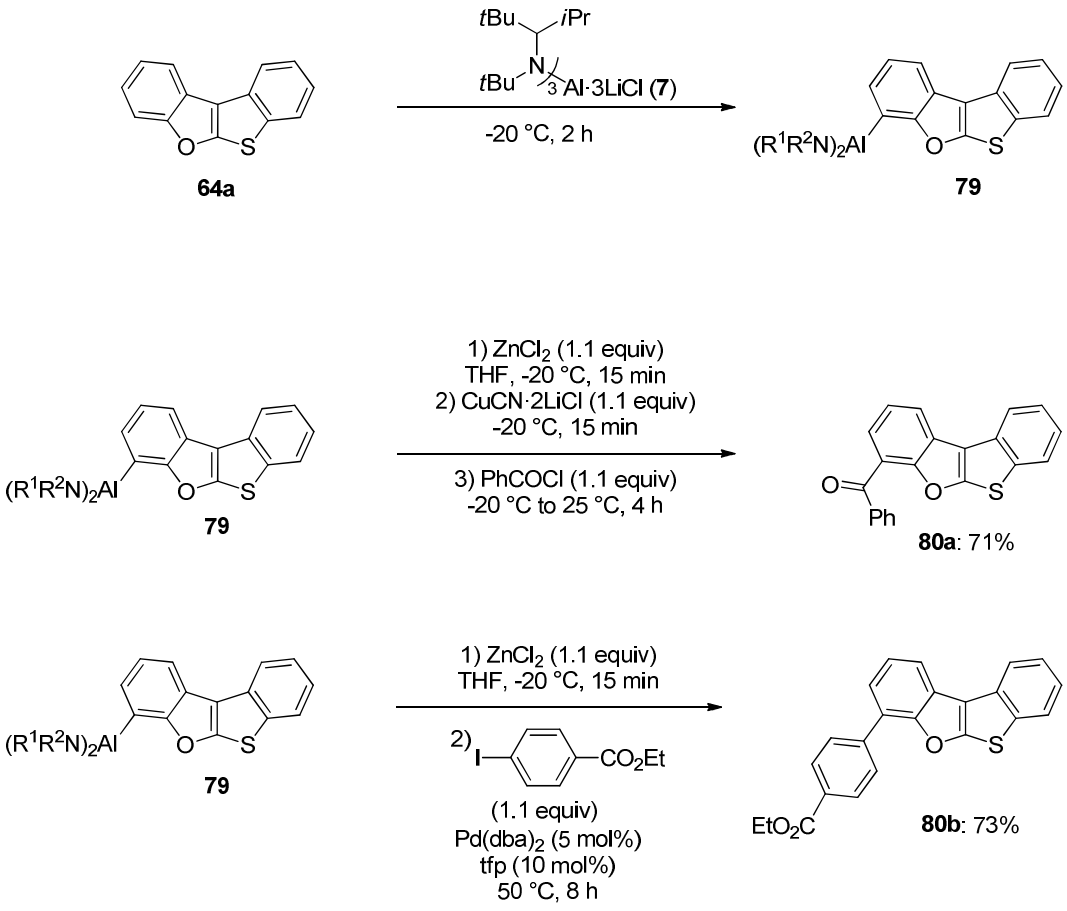
An isomeric structure of heterocycles of type **62** namely the substituted benzo[b]benzo[4,5]thieno [2,3-d]thiophene **63** could be prepared by a slight modification of this procedure (Scheme 37). Thus, a selective I-Mg exchange on 3-bromo-2-iodo-benzothiophene (**76**; *i*PrMgCl·LiCl (**1**; 1.1 equiv) -40 °C, 1 h) followed by a transmetalation with $ZnCl_2$ and *Negishi* cross-coupling with 2,4-dichloroiodobenzene **67a** provides the 2-arylated benzothiophene **77**. Br-Mg exchange of **77** using *i*PrMgCl·LiCl and subsequent quenching with $(Me_2NC(S)S)_2$ furnishes **78**. This dithiocarbamate undergoes a smooth ring closure using *t*BuOK leading to the tetracyclic heterocycle **63** (Scheme 40).



Scheme 40: Preparation of the S-heterocycle **63**.

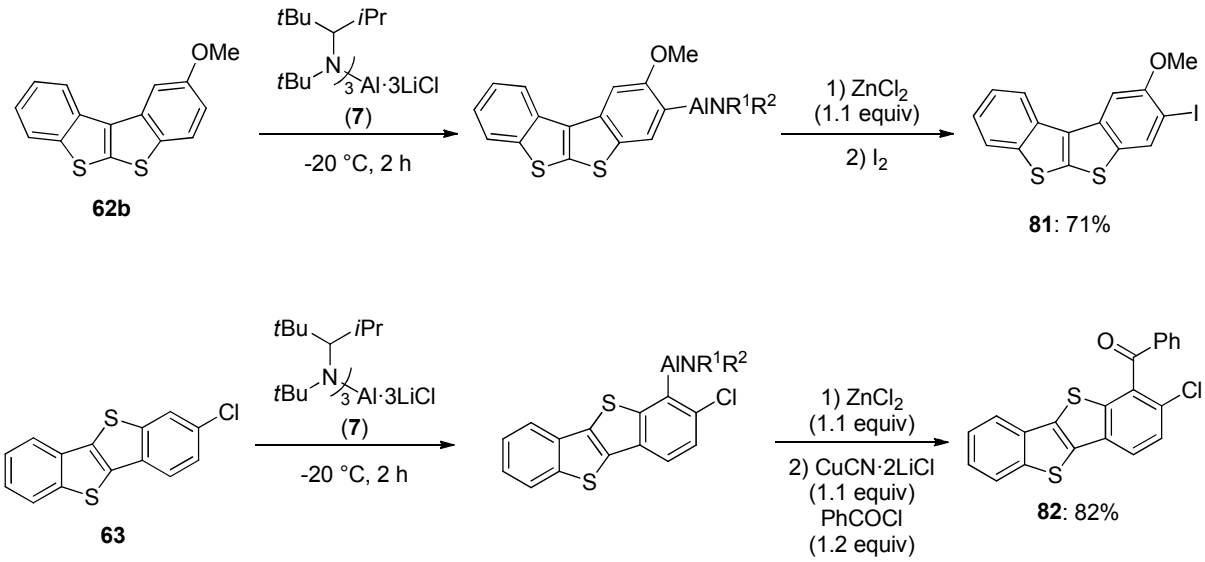
6.3 FUNCTIONALIZATION *VIA* ALUMINATION

The S-heterocycles prepared can be further functionalized by a regioselective alumination using the hindered aluminum amide [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**). Thus, the mixed O,S-tetracyclic compound (**64a**) was reacted with **7** (1.0 equiv, THF, -20 °C, 2 h) leading to a regiospecific alumination at the α-position to the furan unit due to a preferential complexation of the hindered aluminum base to the oxygen atom. The resulting aluminum organometallic **79** was acylated [i: $ZnCl_2$ (1.1 equiv); ii: CuCN·2LiCl (1.1 equiv); iii: PhCOCl (1.1 equiv, -20 to 25 °C, 4 h)] providing the ketone **80a** in 71% yield. Furthermore, Negishi cross-coupling of **79** [i: $ZnCl_2$ (1.1 equiv); ii: 5% $Pd(dba)_2$, 10% tfp, ethyl 4-iodobenzoate (1.1 equiv, 50 °C, 8 h)] led to the arylated product **80b** in 73% yield.



Scheme 41: Alumination and subsequent acylation or Negishi cross-coupling reaction leading to the substituted heterocyles **80a-b**.

Using the same base, it was possible to regiospecifically metalate the heterocycles **62b** and **63**. The substituents present in those substrates (e.g. a chloride or a methoxy group) direct fully the alumination affording after trapping either with iodine [i: **7** (1.0 equiv, 0 °C, 4 h); ii: $ZnCl_2$ (1.1 equiv); iii: I_2 (1.5 equiv , -20 to 25 °C, 0.5 h)] or acylation [i: **7** (1.0 equiv, -40 °C, 2 h); ii: $ZnCl_2$ (1.1 equiv); iii: CuCN·2LiCl (1.1 equiv); iv: PhCOCl (1.1 equiv, -20 to 25 °C, 4 h)] the substituted heterocycles **81** and **82** in 70-82% yield (Scheme 42).



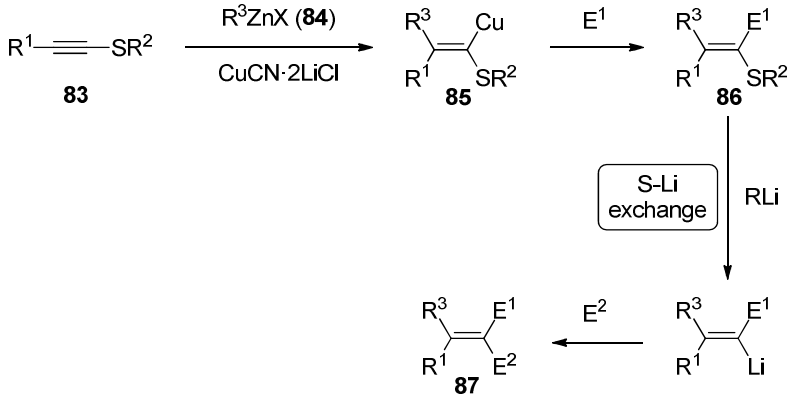
Scheme 42: Alumination and subsequent acylation or iodolysis leading to the substituted heterocyles **81-82**.

7 STEREOSELECTIVE SYNTHESIS OF TETRA-SUBSTITUTED ALKENES *VIA* A SEQUENTIAL CARBOCUPRATION AND A NEW SULFUR-LITHIUM EXCHANGE

7.1 INTRODUCTION

The stereoselective synthesis of tetrasubstituted alkenes is an important synthetic goal which may be achieved by carbometallation methods.[161] The *Normant*-carbocupration of terminal acetylenes allows the stereoselective preparation of trisubstituted alkenes with excellent *E*/*Z*-ratio.[162] However, in order to obtain tetrasubstituted alkenes, a carbometallation of an internal alkyne is required. This reaction is usually difficult due to steric hindrance and proceeds only if electron withdrawing groups are attached to the alkyne unit to facilitate the carbometallation step.

Therefore, using an alkynyl thioether such as **83** as activated alkyne has been envisoned. After a carbocupration of the alkyny thioether **83** with the organozinc reagent **84** in the presence of CuCN·2LiCl, the alkenylcopper species **85** should be obtained. Stereoselective quenching with an electrophile (E^1) should afford the tetrasubstituted alkenyl thioether **86**. Extensive experimentation showed that thioethers **86** do not ungergo Ni- or Pd- catalyzed cross couplings leading to products of type **87** (R = Me, Ph).[163] Thus, we have designed a new sulfur-lithium exchange (Scheme 43).



Scheme 43: Synthesis of tetrasubstituted olefins *via* a successive carbocupration and S-Li exchange.

Sulfur-lithium exchanges proceed only readily with sulfoxides[164] and these reactions are often complicated by radical side reactions. This new, direct sulfur-lithium exchange on an alkenyl thioether of type **86** involves the use of a bromobiphenyl R-group which by treatment with BuLi at

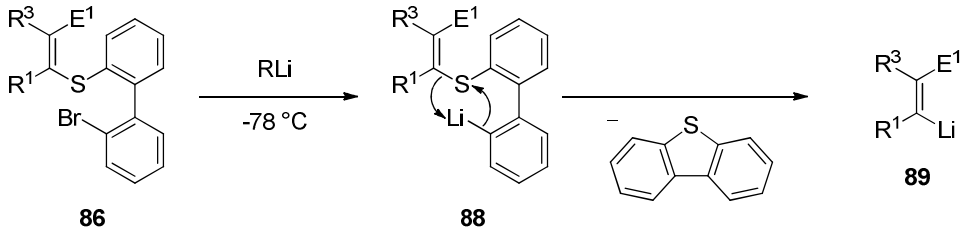
[161] a) K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670; b) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; c) C. Zhou, R. C. Larock, *Org. Lett.* **2005**, *7*, 259; d) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079; e) E. Shirakawa, D. Ikeda, S. Masui, M. Yoshida, T. Hayashi, *J. Am. Chem.Soc.* **2012**, *134*, 272; f) B. Dutta, N. Gilboa, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 5588; g) W. W. Ogilvie, A. B. Flynn, *Chem. Rev.* **2007**, *107*, 4698; h) A. Basheer, I. Marek, *Beilstein J. Org. Chem.* **2010**, *6*, No. 77; i) S. Achyutha Rao, P. Knochel, *J. Am. Chem. Soc.* **1991**, *113*, 5735.

[162] a) J. F. Normant, M. Bourgain, *Tetrahedron Lett.* **1971**, *27*, 2583; b) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841; c) . P. Knochel, Carbometallation of Alkenes and Alkynes. In *Comprehensive Organic Syntheses: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, Vol. 4, (Eds. Trost, B. M.; Fleming, I.; Semmelhack, M. F.), Pergamon Press, Oxford, U.K., **1992**.

[163] a) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; b) L. Melzig, A. Metzger, P. Knochel, *J. Org. Chem.* **2010**, *75*, 2131.

[164] T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561.

low temperatures undergoes first a fast bromine-lithium exchange leading to an intermediate biphenyllithium derivative of type **88** followed by an intramolecular ring closing sulfur-lithium exchange leading to the desired alkenyllithium **89** (Scheme 44).

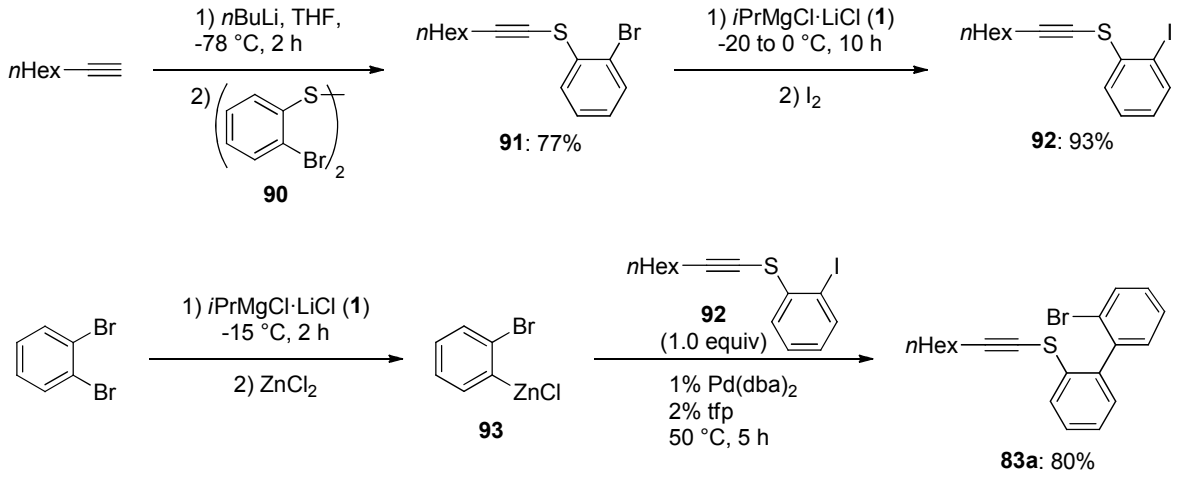


Scheme 44: Proposed mechanism for the sulfur-lithium exchange starting with the alkenyl thioether **86**.

Subsequent quenching with a different electrophile E^2 should afford the tetrasubstituted alkene of type **87** (Scheme 43).

7.2 CARBOCUPRATION

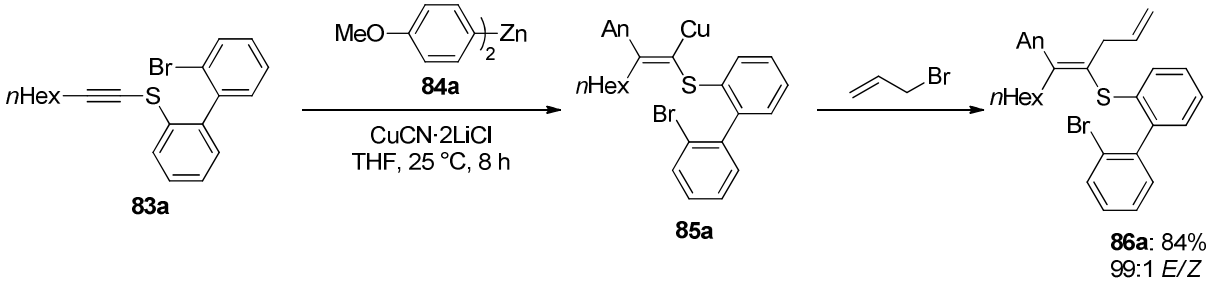
First, the alkynyl biphenyl thioether (**83a**) required for the carbometallation step was synthesized. Thus, octyne was deprotonated with *n*-butyllithium (1.1 equiv, THF, -78 °C, 2 h) followed by the addition of the diaryl disulfide[165] (**90**; 1.1 equiv, -78 to 25 °C, 3 h) providing the bromothioether **91** in 77% yield. Direct Pd-catalyzed *Negishi* cross-coupling of **91** with an arylzinc derivative failed. However, the bromide **91** could be readily converted to the corresponding iodide **92** by a bromine-magnesium exchange using *i*PrMgCl·LiCl (**1**) followed by iodolysis leading to the iodide **92** in 93% yield. Treatment of 1,2-dibromobenzene with *i*PrMgCl·LiCl (**1**) at -15 °C for 2 h followed by transmetallation with $ZnCl_2$ gives the required zinc reagent **93** which undergoes a *Negishi* cross-coupling with the iodide **92** at 50 °C (5 h) leading to the alkynyl thioether **83a** in 80 % yield (Scheme 45).



Scheme 45: Synthesis of precursor **83a**.

[165] T. J. Korn, P. Knochel, *Synlett* **2005**, 1185

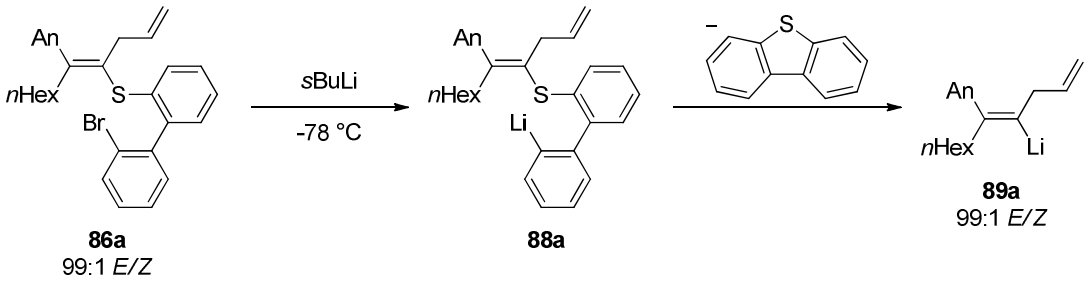
The harsh cross-coupling conditions may be due to the presence of the *ortho*-bromo substitution in the zinc reagent **93** which considerably reduces by inductive effects the nucleophilicity of this arylzinc reagent as well as to the sulfur atom of the electrophile which poisons the Pd-catalyst. With the thioether **83a** in hand, a *Normant*-carbocupration with di-*para*-anisylzinc (An_2Zn: **84a**) according to a procedure previously developed by *Knochel* could be performed.[166] Thus, the reaction of **83a** (1.0 equiv) with An_2Zn (**84a**; 1.5 equiv, THF) in the presence of CuCN·2LiCl (1.5 equiv) at 25 °C for 8 h produces the intermediate copper reagent **85a** which, after allylation with allyl bromide, provides the thioether **86a** in 84% yield and an *E*/*Z*-ratio of 99:1; (Scheme 46). The reaction of **85a** with other typical electrophiles is possible, but proceeds in moderate yields due to the low reactivity of copper reagent **85a**.



Scheme 46: Carbocupration of the thioether **83a** leading to the tetra-substituted alkene **86a**.

7.3 S-Li EXCHANGE

The bromothioether **86a** was then treated with *s*BuLi (1.3 equiv, -78 °C, 10 min) which leads to the formation of the intermediate aryllithium **88a** which undergoes the desired intramolecular sulfur-lithium exchange affording the alkenyllithium reagent **89a** (Scheme 47).

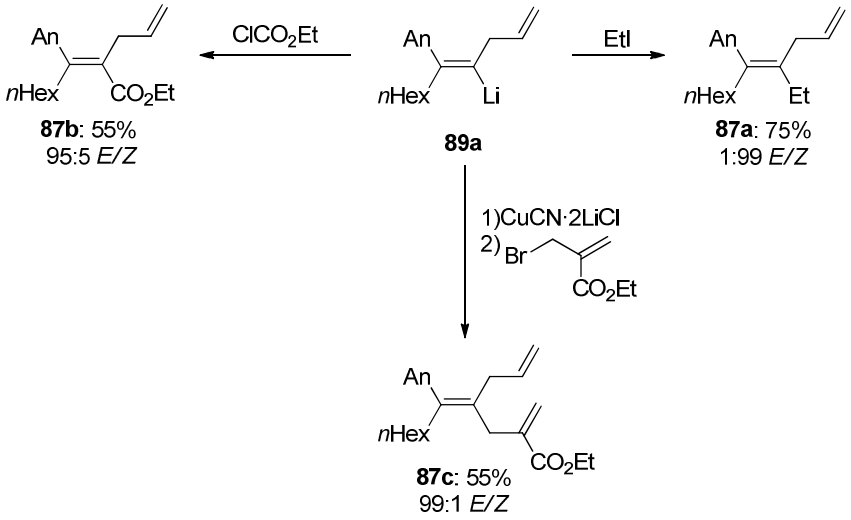


Scheme 47: Synthesis of the alkenyllithium reagent **89a** *via* S-Li exchange.

This alkenyllithium reagent was quenched with typical electrophiles with a high retention of the double bond geometry. Thus, the treatment of **89a** with ethyliodide (2 equiv, -78 °C, 15 min) provides the tetrasubstituted alkene **87a** in 75% yield and an *E*/*Z*-ratio of 1:99. Direct carboxylation by the reaction with ethyl chloroformate (1.1 equiv, -78 °C, 15 min) furnishes the corresponding unsaturated ethylester **87b** in 55% isolated yield and an *E*/*Z*-ratio of 95:5. Finally, a copper catalyzed

[166] C. Dunst, A. Metzger, E. A. Zaburdaeva, P. Knochel, *Synthesis* **2011**, 3453.

allylation with ethyl 2-(bromomethyl)acrylate (1.5 equiv, -78 to 0 °C, 2 h) affords the triene **87c** in 55% yield and an *E*/*Z*-ratio of 99:1 (Scheme 48).

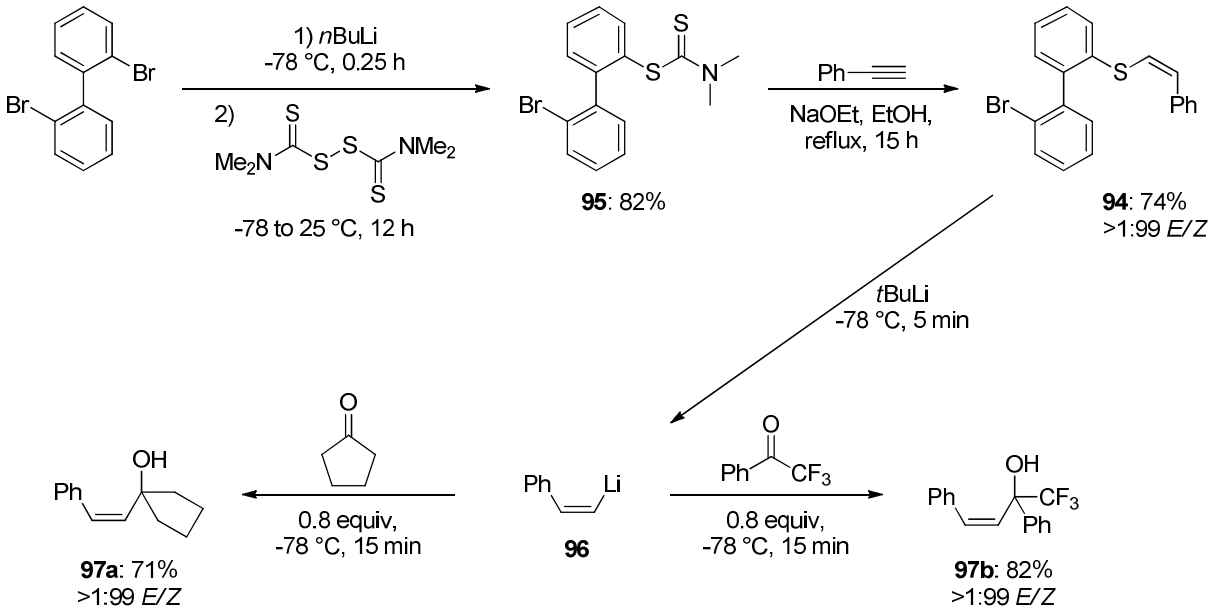


Scheme 48: Quenching of alkenyllithium **89a**
(Product ratios and diastereoselectivities were determined by ^{1}H- and 2D-NMR)

These quenching experiments demonstrate that this new method based on a successive carbocupration and sulfur-lithium exchange allows a stereoselective preparation of various tetrasubstituted alkenes. Since *Normant* has shown that various alkylcopper species add to alkynyl thioethers,[167] the use of a bromobiphenyl substituent (R^2) on the sulfur may allow a general stereoselective synthesis of tetrasubstituted alkenes.

In order to prove that this new sulfur-lithium exchange has further applications in the stereoselective synthesis of alkenes, *Z*-alkeny thioether **94** has been prepared starting from 2,2'-dibromobiphenyl. Thus, the performance of a bromine-lithium exchange with *n*BuLi (1.1 equiv, -78 °C, 0.25 h) followed by a quenching with tetramethylthiuram disulfide (1.1 equiv, -78 to 25 °C, 12 h) furnishes the dithiocarbamate **95** in 82% yield. Since the reduction to the free thiol is hard to achieve due to dibenzothiophene formation (*vide supra*), an *in situ* deprotection and stereoselective addition to phenylacetylene[168] has been performed (1.5 equiv, 1.25 equiv NaOEt, EtOH, reflux, 15 h) yielding the *Z*-alkenyl thioether **94** in 74% (Scheme 49).

[167] a) D. Masure, P. Coutrot, J. F. Normant, *Journal of Organomet. Chem.* **1982**, *226*, C55; b) A. Alexakis, G. Cahiez, J. F. Normant, *Tetrahedron* **1980**, *36*, 1961; c) J. F. Normant, J. C. Quirion, A. Alexakis, Y. Masuda, *Tetrahedron Lett.* **1989**, *30*, 3955
[168] W. E. Truce, J. A. Simms, *J. Am. Chem. Soc.* **1956**, *78*, 2756.



Scheme 49: Synthesis and quenching of *Z*-styryllithium (**96**).
(Product ratios and diastereoselectivities were determined by ^{1}H- and 2D-NMR)

Treatment of **93** with *t*BuLi (1.6 equiv, -78 °C, 10 min) provides directly the *Z*-styryllithium **96** which stereoselectively adds to α,α,α-trifluoroacetophenone (0.8 equiv, -78 °C, 0.5 h) and cyclopentanone (0.8 equiv, -78 °C, 0.5 h) to afford the expected tertiary allylic alcohols **97a-b** in 71-82% yield and *E*/*Z*-ratios of >1:99.

8 DIRECT Pd-CATALYZED CROSS-COUPLING OF FUNCTIONALIZED ORGANOALUMINUM REAGENTS

8.1 INTRODUCTION

Transition metal-catalyzed cross-couplings of organic halides with organometallics are one of the most important C-C bond forming reactions in organic synthesis.[169] The great impact of these synthetic transformations has been culminating in 2010's Nobel Prize award to *Heck*,[170] *Suzuki*[171] and *Negishi*.[106] Due to the low cost and toxicity of aluminum and to its exceptional chemoselectivity as well as Lewis acidity[172] a direct cross-coupling with these organometallics would be highly desirable. Whereas B,[173] Zn,[174] Sn[175] and Mg[176] reagents have been thoroughly elaborated, cross-coupling reactions of organoaluminums are rare, although alkenylalanes were used early on.[106a,b] In general, the cross-coupling of aluminum compounds was restricted to triorganoalanes such as $AlPh_3$[177] or $AlEt_3$,[178] in which case only one organic rest was transferred. However, the coupling of mixed organoalanes like $RAlEt_2$ or $RAl(i\text{Bu})_2$ (R = Ar, alkenyl or alkynyl) as well as organoaluminates e.g. $RAl(i\text{Bu})_3Li$ have been reported recently.[179] In these reactions, the unsaturated R group was always transferred selectively. The cross-coupling of alkyl, vinyl and allyl groups is also possible by using appropriate amino and oxygen-containing ligands.[180] Alternatively, the organoalanes needed transmetalation with zinc salts for an efficient cross-coupling.[106c-g]

[169] a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington, **2005**.

[170] a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518; b) R. F. Heck, *J. Am. Chem. Soc.* **1969**, *91*, 6707; c) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320.

[171] a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437; b) N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866; c) A. Suzuki, *Angew. Chem.* **2011**, *123*, 6854; *Angew. Chem. Int. Ed.* **2011**, *50*, 6722.

[172] a) C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward, A. Alexakis, *Angew. Chem.* **2010**, *122*, 7935; *Angew. Chem. Int. Ed.* **2010**, *49*, 7769; b) L. Gremaud, A. Alexakis, *Angew. Chem.* **2012**, *124*, 818; *Angew. Chem. Int. Ed.* **2012**, *51*, 794; c) X. Tang, D. Rawson, S. Woodward, *Synlett* **2010**, 636; d) Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem.* **2010**, *122*, 2661; *Angew. Chem. Int. Ed.* **2010**, *49*, 2607.

[173] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) M. R. Rivero, G. A. Molander, *Org. Lett.* **2002**, *4*, 107; c) L. Ackermann, H. K. Potukuchi, A. Althammer, R. Born, P. Mayer, *Org. Lett.* **2010**, *12*, 1004.

[174] a) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756; b) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380; c) C. Wang, T. Tobrman, Z. Xu, E. Negishi, *Org. Lett.* **2009**, *11*, 4092; d) A. Krasovskiy, C. Duplais, B. H. Lipshutz, *J. Am. Chem. Soc.* **2009**, *131*, 15592; e) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532; f) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.

[175] a) F. K. Sheffy, J. P. Godschalx, J. K. Stille, *J. Am. Chem. Soc.* **1984**, *106*, 4833; b) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; c) V. Farina, V. Krishnamurty, W. J. Scott, *Org. React.* **1997**, *50*, 1; d) D. A. Powell, T. Maki, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 510; e) J. R. Naber, S. L. Buchwald, *Adv. Synth. Catal.* **2008**, *350*, 957.

[176] a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222; b) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 17978; c) N. Yoshikai, H. Yatsuda, E. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 9590; d) O. Vechorkin, X. Hu, *Angew. Chem.* **2009**, *121*, 2981; *Angew. Chem. Int. Ed.* **2009**, *48*, 2937; e) L. Ackermann, H. K. Potukuchi, A. R. Kapdi, C. Schulzke, *Chem. Eur. J.* **2010**, *16*, 3300.

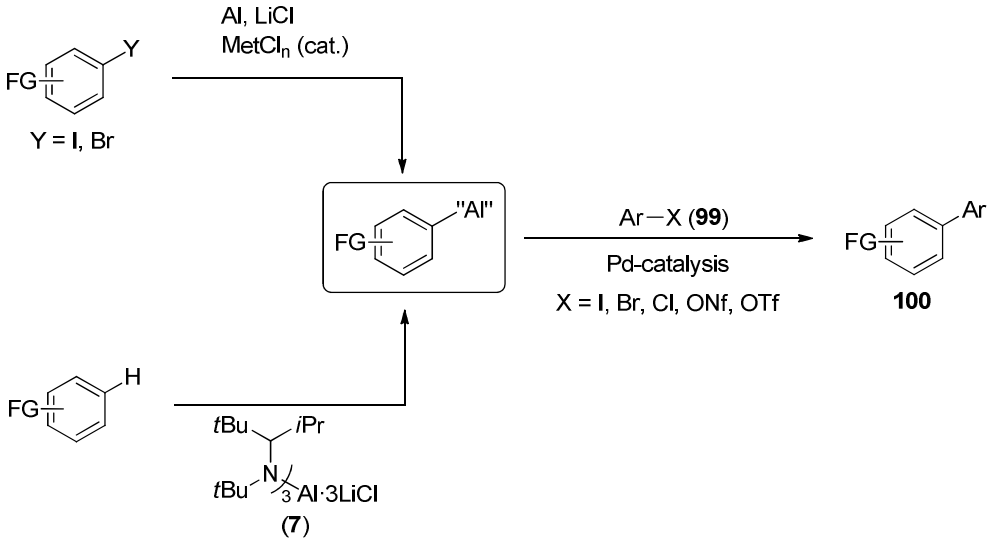
[177] a) N. A. Bumagin, A. B. Ponomaryov, I. P. Beletskaya, *J. Organomet. Chem.* **1985**, *291*, 129; b) S.-L. Ku, X.-P. Hui, C.-A. Chen, Y.-Y. Kuo, H.-M. Gau, *Chem. Commun.* **2007**, 3847; For a Fe-catalyzed version see: c) S. Kawamura, K. Ishizuka, H. Takaya, M. Nakamura, *Chem. Commun.* **2010**, *46*, 6054.

[178] E. Negishi, S. Gagneur in *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), John Wiley & Sons, New York, **2002**, pp. 597-618 and references therein.

[179] a) E. Negishi, T. Takahashi, A. O. King, *Org. Synth.* **1988**, *66*, 67; b) B. H. Lipshutz, G. Bülow, R. F. Lowe, K. L. Stevens, *Tetrahedron* **1996**, *52*, 7265; c) H. Gao, P. Knochel, *Synlett* **2009**, 1321; d) W.-T. Shu, S. Zhou, H.-M. Gau, *Synthesis* **2009**, 4075; e) D. B. Biradar, H.-M. Gau, *Chem. Commun.* **2011**, *47*, 10467; f) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921.

[180] a) J. Blum, D. Gelman, W. Baidossi, E. Shakh, A. Rosenfeld, Z. Aizenshtat, *J. Org. Chem.* **1997**, *62*, 8681; b) J. Blum, O. Berlin, D. Milstein, Y. Ben-David, B. Wassermann, S. Schutte, H. Schumann, *Synthesis* **2000**, 571; c) H. Schumann, J. Kaufmann, H.-G. Schmalz, A. Böttcher, B. Gotov, *Synlett* **2003**, 1783.

Recently, *Knochel* and coworkers reported a new and general preparation of functionalized organoaluminums by direct insertion of Al powder, leading to organoaluminum halides of the type R_2AlX and $RAlX_2$, abbreviated as $RAl_{2/3}X$.[181] They also developed an efficient directed alumination of aromatic and heterocyclic substrates using the hindered aluminum amide $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})\text{N}]_3\text{Al}\cdot 3\text{LiCl}$ (**7**, Scheme 50). These Al reagents were reluctant to undergo directly C-C bond formation and a transmetalation to the corresponding zinc species was always required for cross-coupling. Consequently, a new practical, direct cross-coupling procedure of these aluminum reagents with various unsaturated halides and pseudohalides would be desireable.



Scheme 50: Direct cross-coupling of organoaluminum reagents obtained by Al insertion or directed alumination.

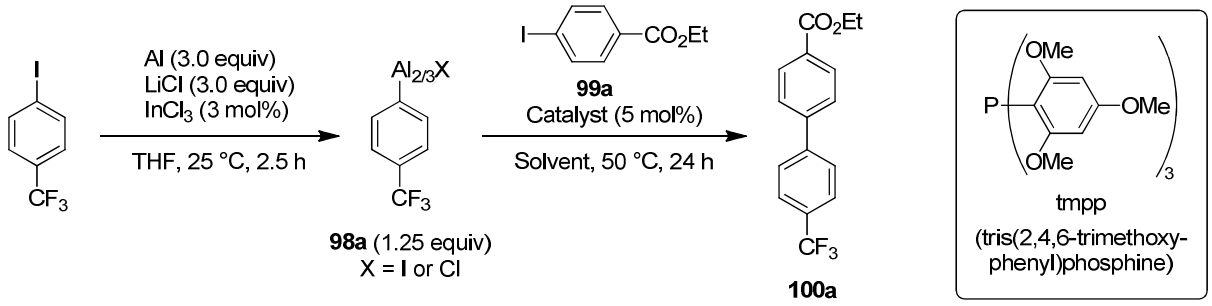
8.2 DIRECT CROSS-COUPLING OF ORGANOALUMINUM SESQUIHALIDES

Preliminary experiments for a direct cross-coupling of the organoaluminum sesquihalide **98a** with ethyl 4-iodobenzoate (**99a**) were conducted using PEPPSI-*i*Pr as catalyst in THF/NMP (2:1)[182] at 50 °C providing the biphenyl **100a** in the absence of a zinc salt in only 9% yield (Table 7, Entry 1). Other catalyst systems such as $Pd(OAc)_2$ and PCy_3, used for the coupling of $ArAlEt_2(THF)$,[106d] gave only a low conversion of 12% (Entry 2). Similarly, the preformed Pd-catalysts $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ showed unsatisfactory results (Entries 3-4). The use of *Buchwald*'s phosphine ligands S-Phos[183] and RuPhos[184] with various palladium salts equally resulted in an incomplete cross-coupling (Entries 5-6). Although the NHC-precursor *i*Pr·HCl[185] and $Pd(PhCN)_2Cl_2$ led to a full conversion, only 20-25% of product **100a** was formed due to several side-reactions (e.g. homo-coupling, reduction, Entries 7-8). In contrast,

[181] a) T. D. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313; b) L.-N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 9829; c) Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem.* **2010**, *122*, 8695; *Angew. Chem. Int. Ed.* **2010**, *49*, 8516; d) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440.
[182] This solvent system proved to be appropriate when a prior transmetalation with $Zn(OAc)_2$ was performed.
[183] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.
[184] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028.
[185] a) A. J. Arduengo, III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523; b) L. Jafarpour, E. D. Stevens, S. P. Nolan, *J. Organomet. Chem.* **2000**, *606*, 49.

the complex $Pd(tmpp)_2Cl_2$[186] gave full conversion of ethyl 4-iodobenzoate (**99a**) after 6 h at 50 °C and the biphenyl **100a** was obtained in 69% yield (Entry 9).[187] Further optimization by increasing the percentage of NMP (Entries 10-11) and testing several other polar co-solvents (NEP, DMPU, DMF, Entries 12-14) led to the best conditions, THF/DMF (1:2), which provided after 2 h at 50 °C the desired product **100a** in 89 % GC-yield and 83% isolated yield (Entry 14).[188]

Table 7: Screening of catalysts and solvent systems for the direct cross-coupling of organoaluminum sesquihalide **98a** at 50 °C.



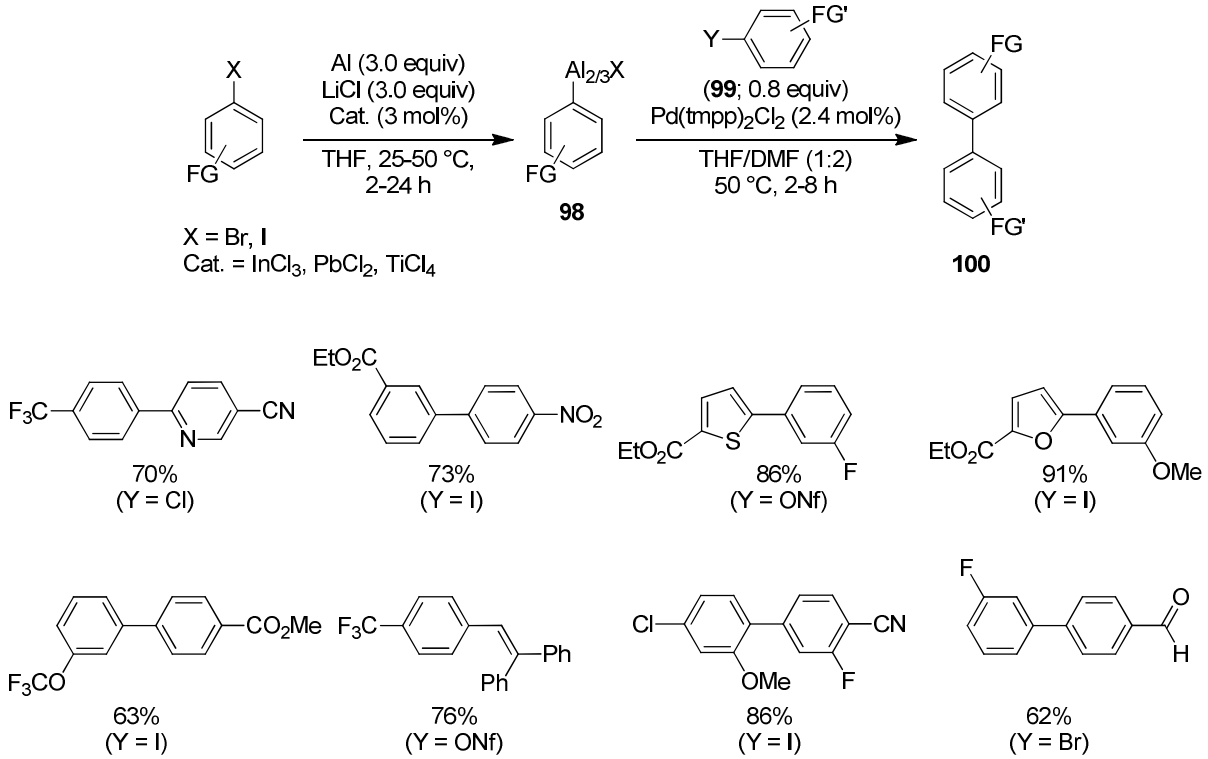
Entry	Catalyst	Solvent[a]	Conversion [%]	Yield [%][b]
1	PEPPSI-*i*Pr	A	16	(9)
2	$Pd(OAc)_2 + PCy_3$	A	12	(10)
3	$Pd(PPh_3)_2Cl_2$	A	11	(8)
4	$Pd(PPh_3)_4$	A	25	(21)
5	$Pd(OAc)_2$ + S-Phos	A	49	(10)
6	$Pd(dba)_2$ + RuPhos	A	72	(48)
7	$PdCl_2$ + *i*Pr·HCl	A	100	(25)
8	$Pd(PhCN)_2Cl_2$	A	100	(20)
9	$Pd(tmpp)_2Cl_2$	A	100	(69)[c]
10	$Pd(tmpp)_2Cl_2$	B	100	(71)
11	$Pd(tmpp)_2Cl_2$	C	100	(79)
12	$Pd(tmpp)_2Cl_2$	D	64	(61)
13	$Pd(tmpp)_2Cl_2$	E	81	(73)
14	$Pd(tmpp)_2Cl_2$	F	100	(89, 83[d])

[a] Solvents: A: THF/NMP (2:1); B: THF/NMP (1:1); C: THF/NMP (1:2), D: THF/NEP (1:2); E: THF/DMPU (1:2); F: THF/DMF (1:2). [b] Conversion of electrophile and GC-yield were determined by GC analysis with tetradecane as internal standard. [c] After 6 h at 50 °C >95 % conversion of the electrophile was achieved. [d] Isolated yield after 2 h at 50 °C.

To estimate the scope of this catalyst system, a variety of organoaluminum sesquihalides of type **98** were cross-coupled with a large number of aromatic, heteroaromatic and vinylic iodides, bromides, chlorides, triflates or nonaflates[189] of type **99** yielding biphenyls and styrenes of type **100**. Remarkably the method tolerates on the nucleophile all kinds of functional groups. The limiting

[186] a) K. R. Dunbar, J.-S. Sun, *J. Chem. Soc. Chem. Commun.* **1994**, 2387; b) K. Dunbar, S. C. Haefner, *Polyhedron* **1994**, *13*, 727.
[187] We also tried the tmpp ligand with several other Pd, Ni and Fe salts.
[188] In a further reaction, we found that with these conditions all three phenyl groups of $AlPh_3$·3LiCl can be transferred.
[189] a) I. M. Lyapkalo, M. Webel, H.-U. Reißig, *Eur. J. Org. Chem.* **2002**, 1015; b) J. Hörgermeier, H.-U. Reißig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868.

factor here is the oxidative insertion of aluminium metal in the carbon-halogen bond. Considering the electrophile, a broad range of sensitive functionalities, such as esters, aldehyde or a nitro group are tolerated (Scheme 51).



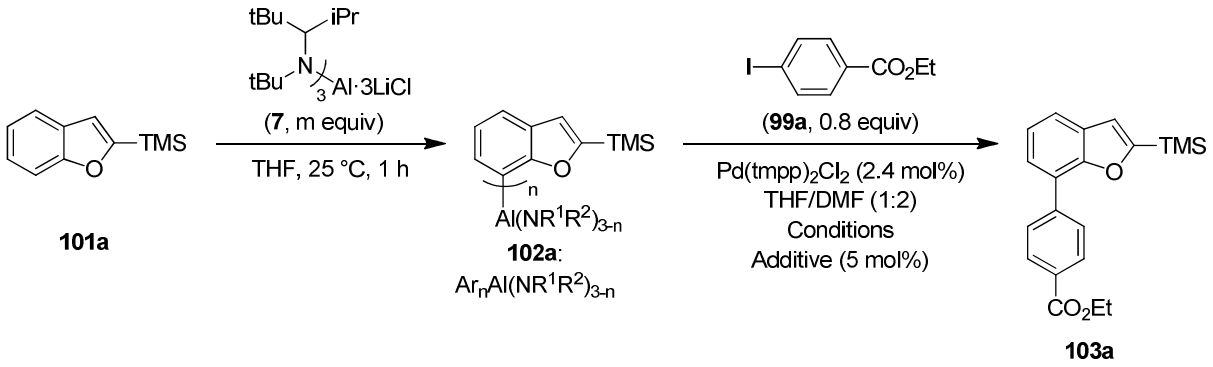
Scheme 51: Direct cross-coupling of organoaluminum sesquihalides of type **98** with electrophiles.

8.3 DIRECT CROSS-COUPLING AFTER ALUMINATION

The new, hindered Al base [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**, abbreviated as ($R^1R^2N)_3$Al) offers a unique regioselectivity in metalation reactions. This metalation provides Al reagents of the type Ar-Al($NR^1R^2)_2$. Although, these organometallics undergo Pd-catalyzed cross-couplings, a transmetalation with $ZnCl_2$ (1.1 equiv) was required for achieving good cross-coupling yields, also two equivalents of HNR^1R^2 were wasted. The atom economy of this reaction has been considerably improved, as the alumination of unsaturated substrates **101** with only 0.5 equiv [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) proceeds well at 25 °C within 0.5-2 h leading to *bis*-organoaluminum amides of type **102** (Ar_2Al(NR^1R^2), Table 9). Moreover, these Al reagents undergo smoothly a direct cross-coupling in the presence of 2.4% Pd(tmpp)$_2$Cl$_2$ at 80 °C for 12 h with 5% 4-fluorostyrene as cocatalyst, which is promoting the reductive elimination (Table 8).[190]

[190] a) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem.* **1998**, *110*, 2512; *Angew. Chem. Int. Ed.* **1998**, *37*, 2387; b) M. Piber, A. E. Jensen, M. Rottländer, P. Knochel, *Org. Lett.* **1999**, *1*, 1323; c) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79.

Table 8: Optimization of the direct cross-coupling of organoaluminum amide **102a**.



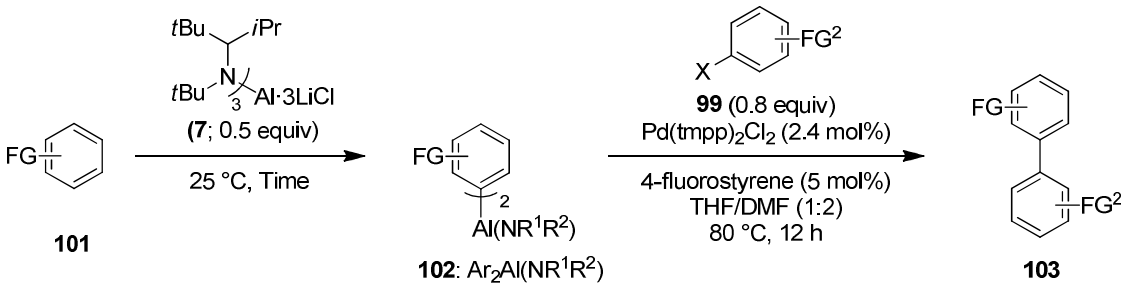
Entry	equiv **7** (m)	Conditions	n	Additive	Conversion of **99a**[a]	Yield of **103a**[a]
1	1.0	50 °C, 12 h	1	-	19%	-[b]
2	1.0	80 °C, 6 h	1	-	76%	50%
3	1.0	80 °C, 6 h	1	4-fluorostyrene	97%	61%
4	0.5	80 °C, 6 h	2	4-fluorostyrene	98%	79% (73%[c])

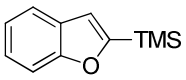
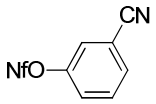
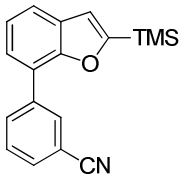
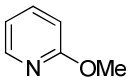
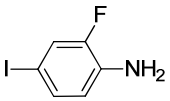
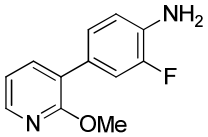
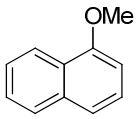
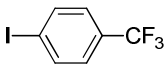
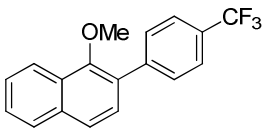
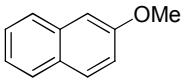
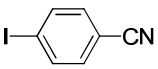
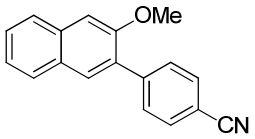
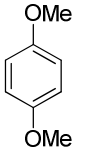
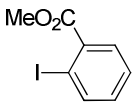
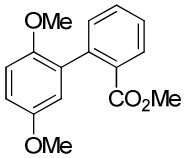
[a] Determined by GC analysis using tetradecane as internal standard. [b] Not determined. [c] Isolated yield of analytically pure product.

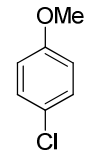
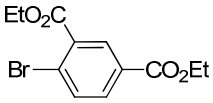
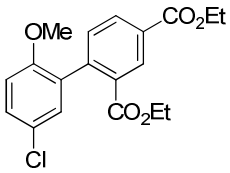
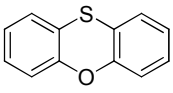
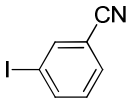
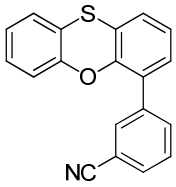
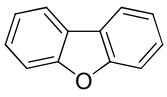
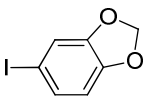
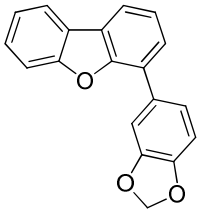
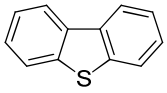
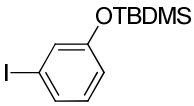
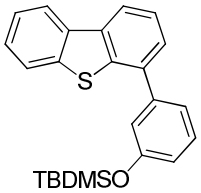
Using those modified conditions, the 2-silylated benzofuran **101a** was metalated rapidly with Al amide **7** (0.5 equiv) and the resulting diorganoalane was then cross-coupled with the aryl nonaflate **99b** (80 °C, 12 h) to give the heterocycle **103b** in 71% yield (Table 9, Entry 1). Remarkably, a free NH_2-group is readily tolerated in these cross-couplings. Alumination of 2-methoxypyridine (**101b**) using base **7** (0.5 equiv, 25 °C, 0.5 h) followed by cross-coupling with the iodoaniline **99c** (0.8 equiv) provides the biphenyl **103c** in 73% yield (Entry 2). No useful, regioselective metalation of 1-methoxynaphthalene (**101c**) in 2-position was reported so far,[191] however, by using the Al amide **7** (1.25 equiv, 25 °C, 12 h)[192] a smooth alumination occurs selectively at this position. The subsequent cross-coupling with aryl iodide **99d** gave the naphthalene **103d** in 89% yield (Entry 3). The alumination of 2-methoxynaphthalene (**101d**) with trisamide **7** is equally selective and the 2,3-disubstituted naphthalene **103e** is obtained after direct cross-coupling with 4-iodobenzonitrile (**99e**) in 88% yield (Entry 4). Other anisole derivatives such as 1,4-dimethoxybenzene (**101e**) or 4-chloroanisole (**101f**) are rapidly metalated and subsequent cross-coupling with iodide **99f** or bromide **99g** gave the products **103f-g** in 74-86% (Entries 5-6). Alumination of phenoxathiine (**101g**) with the Al base **7** (0.5 equiv) occurs *ortho* to oxygen and after cross-coupling the heterocycle **103h** was obtained in 76% yield (Entry 7). Furthermore, dibenzofuran (**101h**) and -thiophene (**101i**) were used after alumination in the direct cross-coupling with iodides **99i** and **99j** leading to the arenes **103i-j** in 63-72% yield (Entries 8-9).

[191] a) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975; b) J. Betz, W. Bauer, *J. Am. Chem. Soc.* **2002**, *124*, 8699.
[192] In this case, 1.25 equiv of Al-amide **7** was needed to achieve full conversion of the metalation.

Table 9: Alumination of aromatics and heteroaromatics with Al trisamide **7** and direct cross-coupling of the organoaluminum reagents **102** using $Pd(tmpp)_2Cl_2$.



Entry	Substrate / Time	Electrophile	Product / Yield[a]
1	 **101a**, 1 h	 **99b**	 **103b**: 71 %
2	 **101b**, 0.5 h	 **99c**	 **103c**: 73 %
3	 **101c**, 12 h[b]	 **99d**	 **103d**: 89 %
4	 **101d**, 1 h	 **99e**	 **103e**: 88 %
5	 **101e**, 1 h	 **99f**	 **103f**: 74 %

Entry	Substrate / Time	Electrophile	Product / Yield[a]
6	 **101f**, 1 h	 **99g**	 **103g**: 86 %
7	 **101g**, 1 h	 **99h**	 **103h**: 76 %
8	 **101h**, 1 h	 **99i**	 **103i**: 72 %
9	 **101i**, 2 h	 **99j**	 **103j**: 63 %

[a] Isolated yield of analytically pure product. [b] 1.25 equiv of aluminum base **7** was used for the metalation.

9 A CONVENIENT ALUMINATION OF FUNCTIONALIZED AROMATICS USING THE FRUSTRATED LEWIS PAIR Et_3Al AND TMPMgCl·LiCl

9.1 INTRODUCTION

Organoaluminum reagents are useful intermediates for the formation of new carbon-carbon bonds.[193] Compared to other main-group metals, aluminum is fairly inexpensive, non-toxic and its recovery is possible *via* aluminum hydroxide precipitation.[194] Furthermore, aluminum due to its Lewis-acid properties exhibits useful reactivities.[195] Especially, the alumination of electron-rich aromatics is of great synthetic interest, since the corresponding lithiation can require extensive cooling, whereas the metalation with standard Mg- and Zn-bases is sluggish with such aromatics. However, generally for an efficient metalation of these scaffolds lithium bases or bimetallic bases are required.[196]

Thus, the pioneering work of Uchiyama has shown that aluminum ate bases[197] such as "*i*Bu_3Al(TMP)Li"[198] (TMP=2,2,6,6-tetramethylpiperidyl) proved to be very useful for the directed alumination of various aromatics and some heterocycles.[199] Nevertheless, an excess of base (2.2 equiv) was needed to achieve full conversion. Recently, *Knochel* and coworkers have prepared the related base [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) which proved to regioselectively aluminate a range of aromatic and heteroaromatic scaffolds. Its metalation power and regioselectivity was

[193] a) T. L. May, J. A. Dabrowski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133,* 736; b) S. Saito, T. Nagahara, M. Shiozawa, M. Nakadai, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125,* 6200; c) H. Ito, T. Nagahara, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 1012; *Angew. Chem. Int. Ed.* **2004**, *43*, 994; d) C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward A. Alexakis, *Angew. Chem.* **2010**, *122*, 7935; *Angew. Chem. Int. Ed.* **2010**, *49*, 7769; e) D. Müller, M. Tissot, A. Alexakis, *Org. Lett.* **2011**, *13*, 3040; f) C. Hawner, K. Li, V. Cirriez A. Alexakis, *Angew. Chem.* **2008**, *120*, 9315; *Angew. Chem. Int. Ed.* **2010**, *47*, 9176; g) D. B. Biradar, H.-M. Gau, *Chem. Commun.* **2011**, *47*, 10467; h) T. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, **2**, 313; i) P. Wipf, S. Lim, *Angew. Chem.* **1993**, *105*, 1095; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068.

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[198] a) B. Conway, E. Hevia, J. García-Álvarez, D. V. Graham, A. R. Kennedy, R. E. Mulvey, *Chem. Commun.* **2007**, 5241; b) J. García-Álvarez, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, *Chem. Commun..* **2007**, 2402; c) B. Conway, J. García-Álvarez, E. Hevia, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Organometallics* **2009**, *28*, 6462; d) R. E. Mulvey, D. R. Armstrong, B. Conway, E. Crosby, A. R. Kennedy, S. D. Robertson, *Inorg. Chem.* **2011**, *50*, 12241.

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complementary to other TMP-bases such as TMPMgCl·LiCl (**3**), $TMP_2Mg·2LiCl$ (**4**), TMPZnCl·LiCl (**5**), $TMP_2Zn·2MgCl_2·2LiCl$ (**6**) and $TMP_2Mn·2MgCl_2·4LiCl$. Whereas most of these TMP-bases react readily with aromatics bearing electron-withdrawing substituents, [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) is able to metalate electron-rich oxygen substituted aromatics. Unfortunately, THF solutions of [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**) display only limited stability (2-3 days at -50 °C). A solution for the alumination of various functionalized aromatics may be the frustrated Lewis pair Et_3Al-TMPMgCl·LiCl (**104**). The dual catalysis of the Lewis acid Et_3Al and the Lewis base TMPMgCl·LiCl (**3**) has several preparative advantages. This Lewis pair displays good metalating power and a convenient practical handling. In contrast to previous reports, this new system and its *in situ* preparation avoids the problem of using an excess of the aluminum base in the metalation step. Furthermore, it could be disclosed that the use of $Zn(OPiv)_2$ (OPiv = pivalate) allows to minimize the excess of electrophile in subsequent reactions.

9.2 DESIGN OF THE PROCEDURE

In a first optimization step of this new directed alumination procedure, the most convenient aluminum source was searched for. Therefore, 4-chloroanisole (**105a**), which was used as a model aromatic substrate, was treated at 0 °C with various aluminum(III) reagents (1.1 equiv) followed by the addition of TMPMgCl·LiCl (**3**; 1.2 equiv) and consecutive warming to 25 °C.

Thus, if 4-chloroanisole (**105a**) was treated with TMPMgCl·LiCl (**3**) for 22 h at ambient temperature, 30% of *ortho* metalatation was obtained. However, the reaction did not proceed further. In the presence of the aluminum reagents $AlCl_3$, $MeAlCl_2$ and Me_2AlCl the conversion to the corresponding *ortho*-metalated compound of type **106** dropped to less than 5%. This was not surprising, as a standard transmetalation of TMPMgCl·LiCl (**3**) to tricoordinated aluminum compound is expected.[200a] The tentative structures of these aluminium reagents would be $Me_nCl_{2-n}Al(TMP)$ with n = 0-2, and no metalation activity is expected for these reagents. However, the use of trialkylaluminum reagents such as Me_3Al, Et_3Al and iBu_3Al greatly increased the metalation rate of **105a**. The observed rates proved to be comparable, but the combination of TMPMgCl·LiCl (**3**) with Et_3Al led to more complete conversions (Table 10).

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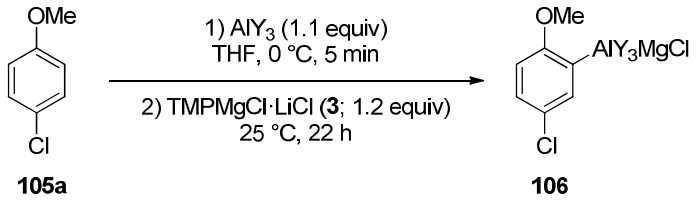
Table 10: Conversion of 4-chloroanisole (**105a**) to the aluminate species of type **106** in the course of the metalation with *in situ* prepared bases, using various aluminum sources.[a]



105a **106**

Time [h] / AlY_3	1 h	2 h	3 h	4 h	7 h	10 h	22 h
-	17	19	20	21	23	25	30
$AlCl_3$	<5	<5	<5	<5	<5	<5	<5
$MeAlCl_2$	<5	<5	<5	<5	<5	<5	<5
Me_2AlCl	<5	<5	<5	<5	<5	<5	<5
Me_3Al	32	44	58	61	69	74	76
Et_3Al	38	55	62	68	78	82	90
$i Bu_3Al$	31	45	57	62	69	76	81

[a] The conversion to the corresponding metal species was monitored *via* GC-analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

One possible mechanism, which would account for the better conversion with R_3Al additives compared to R_2AlX additives, would be the initial formation of the aluminate species $Et_3Al(TMP)MgCl{\cdot}LiCl$, similar to "$iBu_3Al(TMP)Li$", reported by *Uchiyama*.[75] This species would effectively deprotonate anisole **105a**. However, seminal studies of *Hevia*, *García-Álvarez*, *Robertson* and *Mulvey* demonstrated that solvent-separated ion-pair species and a dismutation process have to be considered for such aluminates. Also ligand exchanges have been reported on such aluminates.[198] Therefore, a multinuclear NMR study in order to clarify the nature of the species formed from the combination Et_3Al-TMPMgCl·LiCl (**104**) was performed. Thus, mixing equimolar amounts of Et_3Al with TMPMgCl·LiCl (**3**) at 25 °C in THF (0.5 M) furnishes approximately 80% unchainged TMPMgCl·LiCl (**3**) along with two new species (Figure 10).

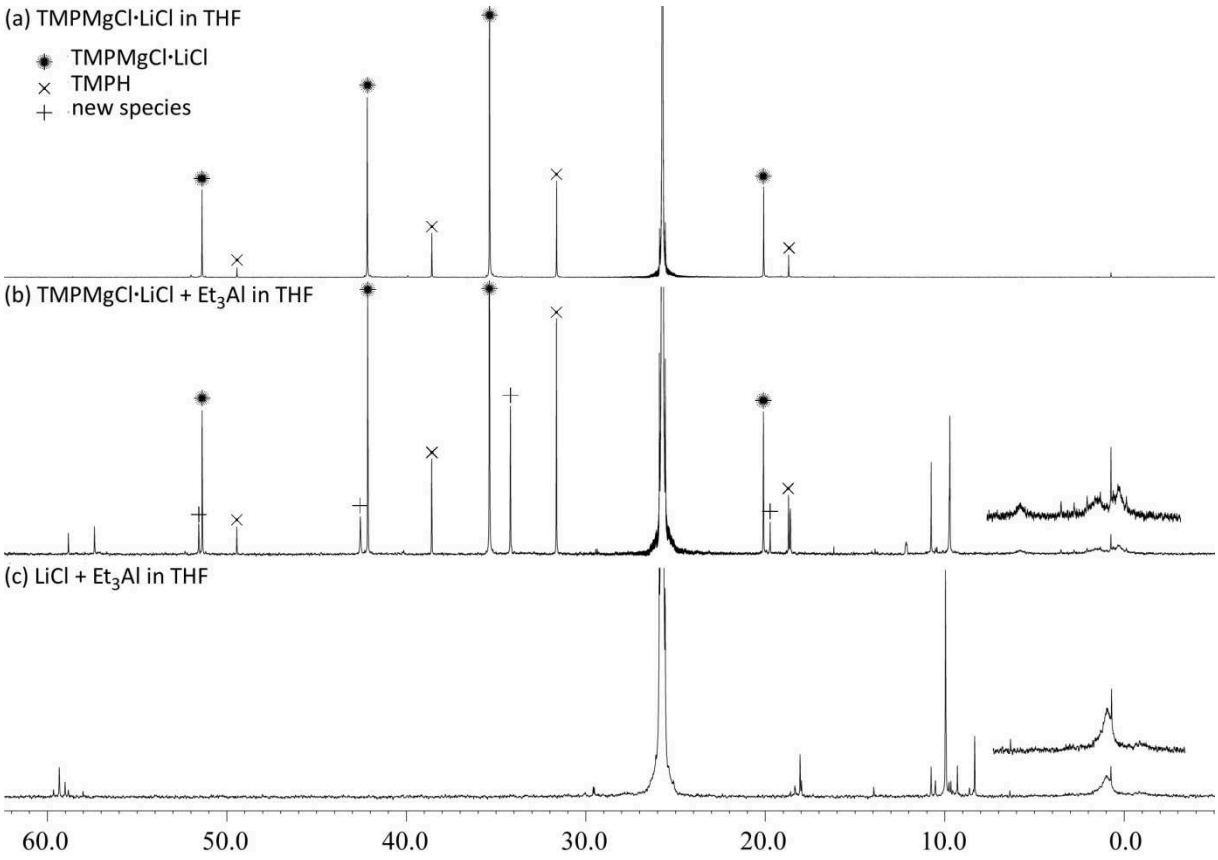
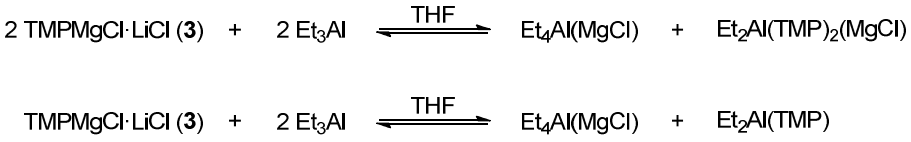


Figure 10: ^{13}C-NMR spectra of TMPMgCl·LiCl (**3**), Et_3Al-TMPMgCl·LiCl (**104**) and Et_3Al with LiCl.

One of these species was identified by means of ^{1}H, ^{13}C, ^{27}Al-NMR as $Et_4Al(MgCl)$,[201] whereas the second species clearly contains at least one TMP moiety (Figure 10). The formation of $Et_4Al(MgCl)$ along with a new TMP-containing compound in solution proves that an equilibration process took place. Furthermore, the existence of only one new TMP-containing compound in solution implies that there is no $Et_3Al(TMP)MgCl·LiCl$ present, since the observed formation of $Et_4Al(MgCl)$ can only be explained in connection with the two species $Et_2Al(TMP)·THF$ or $Et_2Al(TMP)_2MgCl·LiCl$[202] (Scheme 52).



Scheme 52: Putative equilibrations of Et_3Al-TMPMgCl·LiCl (**104**) in THF.

[201] a) H. Gizbar, Y. Westfried, O.Chusid, Y. Gofer, H. E. Gottlieb, V. Marks, D. Aurbach, *Organometallics* **2004**, *23*, 3826; b) B. Wrackmeyer, E. V. Klimkina, W. Milius, *Eur. J. Inorg. Chem.* **2009**, 3163.
[202] E. Crosbie, P. García-Álvarez, A. R. Kennedy, J. Klett, R. E. Mulvey, S. D. Robertson, *Angew. Chem.* **2010**, *122*, 9578; *Angew. Chem. Int. Ed.* **2010**, *49*, 9388.

Unfortunately, ^{27}Al-NMR does not allow to distinguish between these species due to similar expected chemical shifts (Figure 11a).[203] Figure 11a shows the expected broad signal for Et_3Al centered at 175 ppm along with the very sharp signal of $Et_4Al(MgCl)$ at 159 ppm.

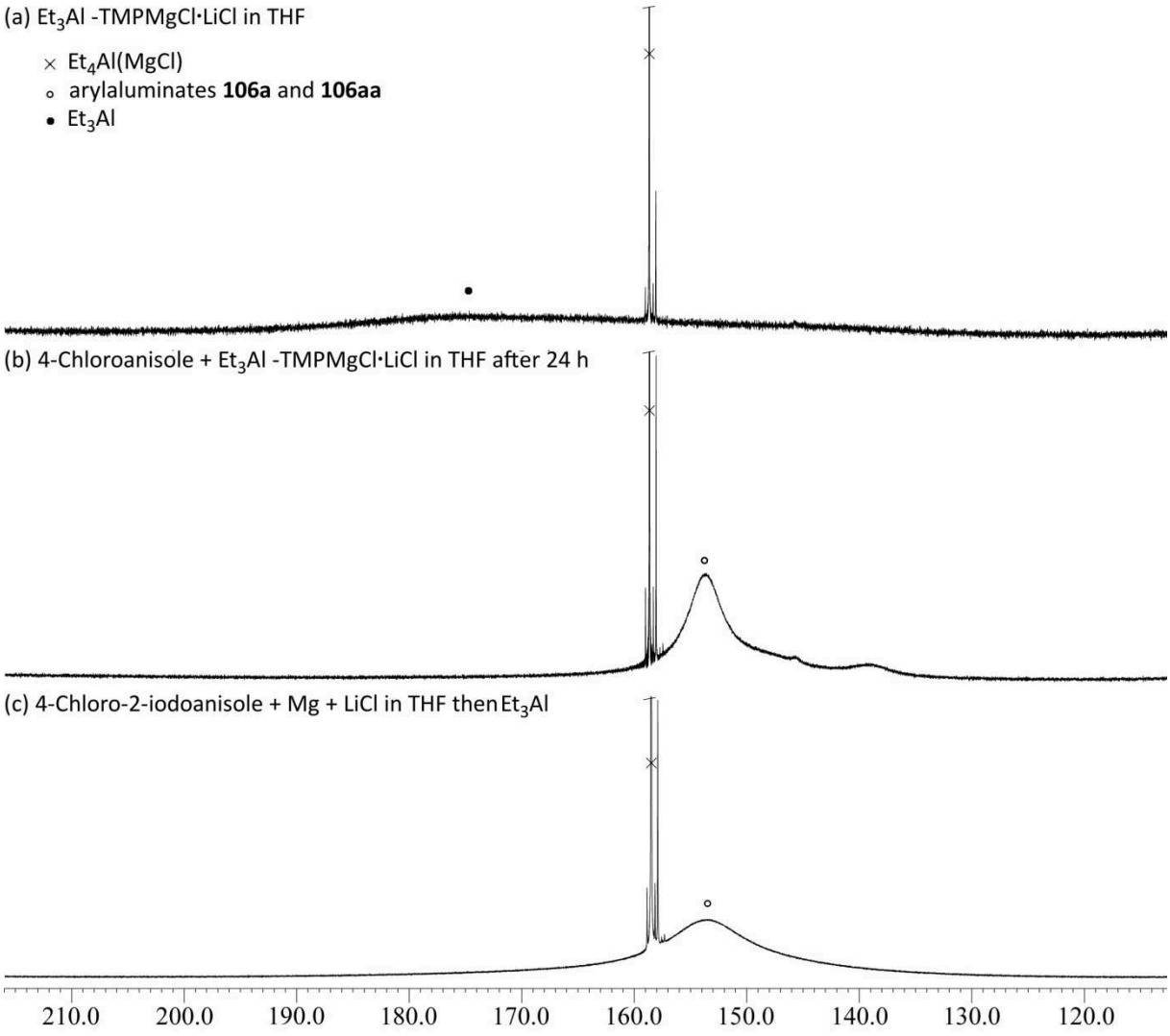


Figure 11: ^{27}Al-NMR spectra of Et_3Al-TMPMgCl·LiCl (**104**) and the arylaluminates **106a** and **106aa** prepared *via* deprotonation or Mg-insertion followed by transmetalation.

However, as shown in Table 10, Me_2AlTMP is not active in the metalation of **105a**. This is expected to be similar for Et_2AlTMP·THF (Scheme 52), whereas the formation of $Et_2Al(TMP)_2MgCl$·LiCl is for steric reasons less favored. Furthermore, *Hevia, García-Álvarez*, *Robertson* and *Mulvey* have shown that iBu$_4$Al(Li) is not active in metalations.[198] Therefore, we conclude that the active species in our system must be the Lewis-pair Et_3Al-TMPMgCl·LiCl (**104**). TMPMgCl·LiCl (**3**) along with Et_3Al represent in fact 80% of the reaction mixture. This coexistence of the Lewis acid Et_3Al and the Lewis base TMPMgCl·LiCl (**3**) during the course of the reaction implies that Et_3Al-TMPMgCl·LiCl (**104**) may be

[203] a) R. Benn, E. Janssen, H. Lehmkuhl, A. Rufińska, *J. Org. Chem.* **1987**,155; b) H. Feulner, N. Metzler, H. Nöth, *J. Organomet. Chem.* **1995**, 51; c) K. Knabel, I. Krossing, H. Nöth, H. Schwenk-Kircher, M. Schmidt-Amelunxen, T. Seifert, *Eur. J. Inorg. Chem.* **1998**, 1095.

regarded as a frustrated Lewis pair. There is a very slow and incomplete reaction taking place between **3** and Et_3Al (Scheme 52 and Figure 10).

In order to shed some light on the organometallic species produced after the metalation, we have deprotonated 4-chloroanisole (**105a**) with a stoichiometric mixture of Et_3Al-TMPMgCl·LiCl (**104**) at ambient temperature. After 24 h reaction time we have investigated the reaction mixture by ^{1}H, ^{13}C, ^{27}Al and ^{7}Li-NMR. The ^{13}C-NMR spectrum recorded at 25 °C shows clearly the presence of three organoaluminum species, which are identified as **106a**, **106aa** and $AlEt_4(MgCl)$ (Scheme 53). The same three species are formed independently, by transmetalation of the corresponding Grignard reagent (5-chloro-2-methoxyphenyl)magnesium iodide with Et_3Al. (Figure 11 and Figure 12)

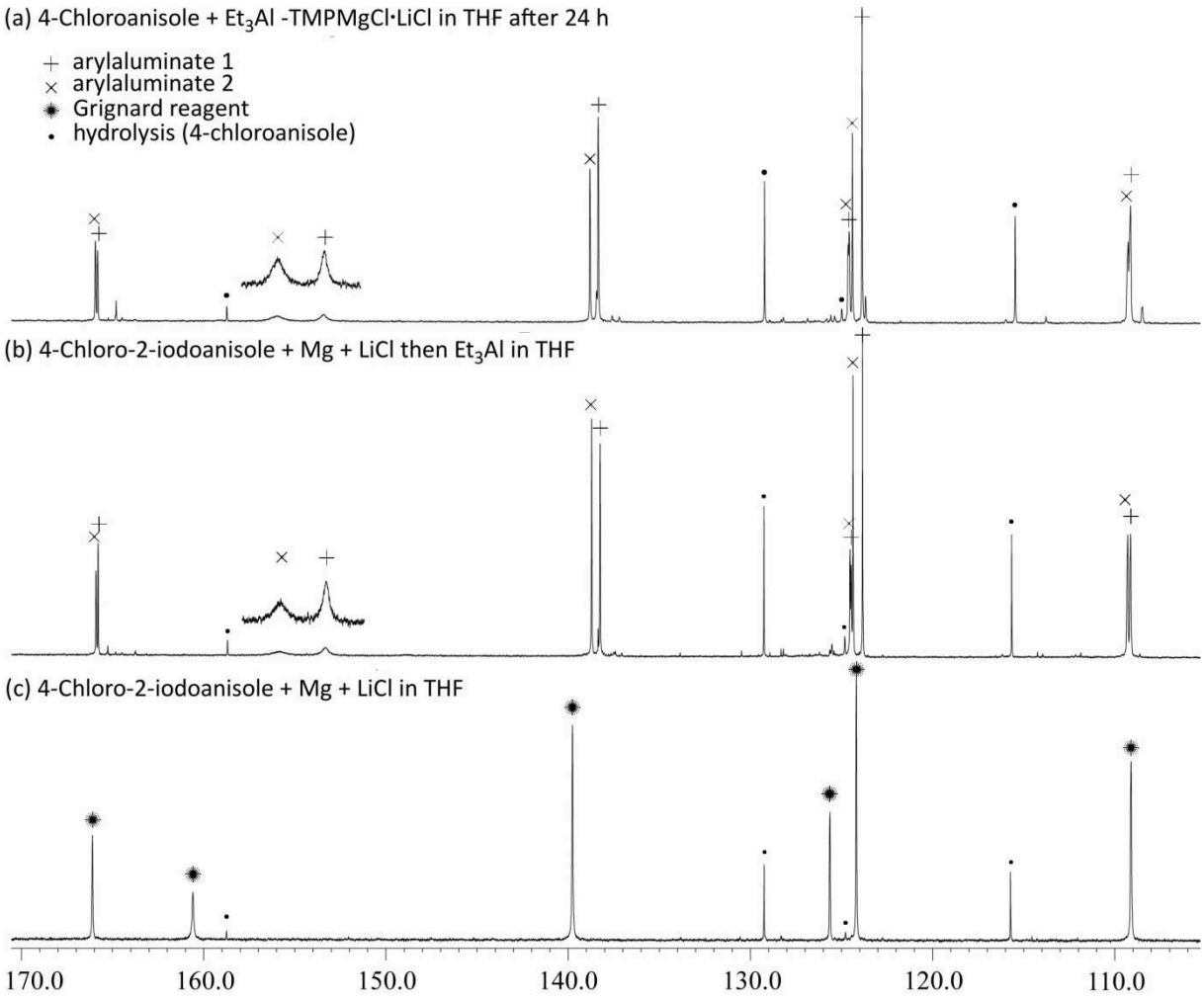
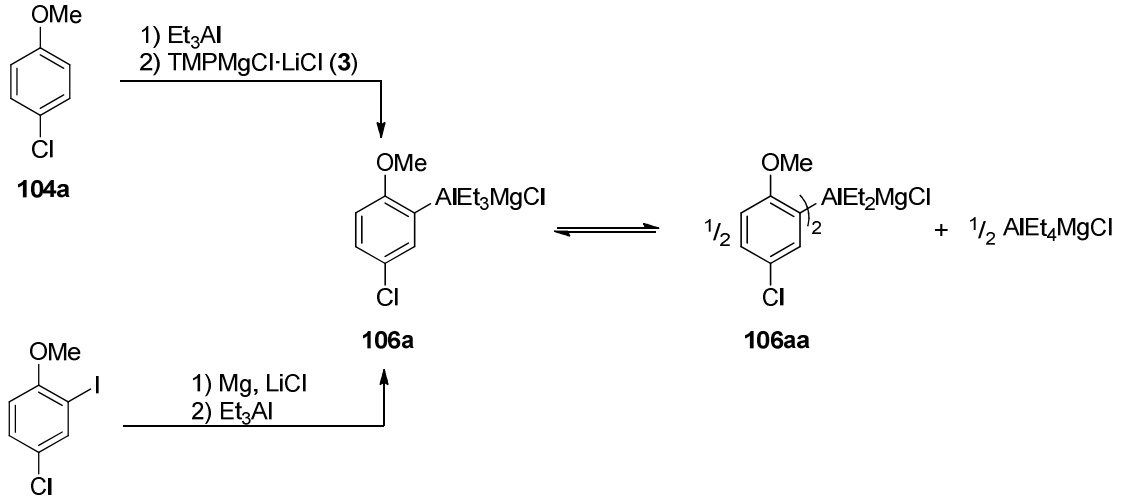


Figure 12: ^{13}C-NMR spectra of the arylaluminates **106a** and **106aa** prepared *via* deprotonation or Mg-insertion followed by transmetalation and the corresponding Grignard reagent.

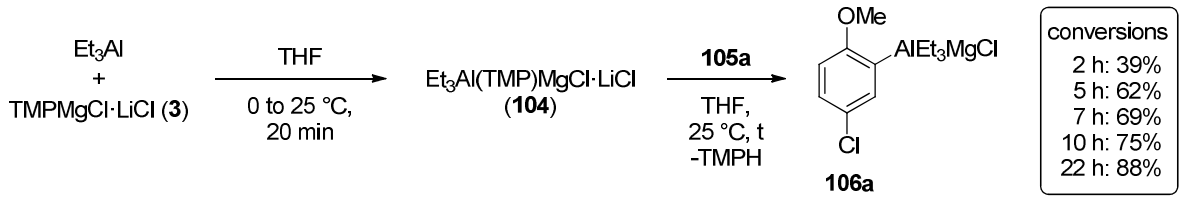
The Grignard reagent was prepared *via* oxidative insertion of magnesium in the presence of LiCl in 4-chloro-2-iodo-1-methoxybenzene (Scheme 53).[204] Thus, it can be concluded that the reaction proceeds *via* deprotonation by the TMP anion rather than by an alkyl ligand.



Scheme 53: Postulated equilibration of the arylaluminate **106a**.

In particular the absence of the ^{13}C-NMR signals of the Grignard reagent and generation of the same species simply by addition of Et_3Al to the Grignard reagent supports the identity of these organoaluminum species. Further indication is provided by the ^{27}Al-NMR spectrum (Figure 11). It shows a new broad signal at 153 ppm, which is attributed to the two organoaluminum species **106a** and **106aa**. Due to the similar environment of Al in these species (surrounded by 4 carbon atoms) similar chemical shifts are anticipated. Due to the expected broadness of the signals they cannot be resolved. In all these reactions Li^+ did obviously not change its environment. All solutions in which Li^+ is present showed the same signal: a singlet at 3.2 ppm.

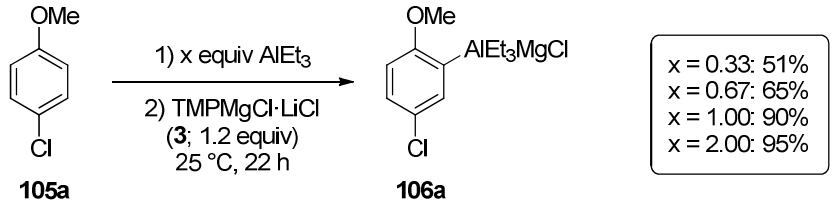
Further preliminary experiments proved that *in situ* generation of Et_3Al-TMPMgCl·LiCl (**104**) was advantageous, since Et_3Al-TMPMgCl·LiCl (**104**) slowly decomposes in THF. Additionally, the conversion of 4-chloroanisole (**105a**) to the aluminate species (**106a**) is slightly higher for the *in situ* preparation (Scheme 54 and Table 10).



Scheme 54: Alumination of 4-chloroanisole (**105a**) with preformed $Et_3Al(TMP)MgCl·LiCl$ (**104**).

[204] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem.* **2008**, *120*, 6907; *Angew. Chem. Int. Ed*. **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

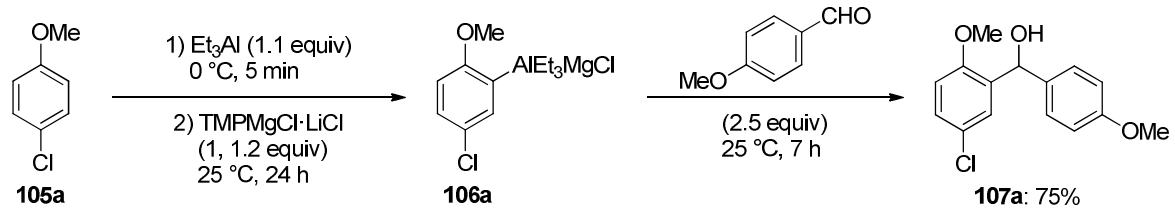
In the next step, the stoichiometry of Et_3Al was optimized. Therefore, 4-chloroanisole (**105a**) was treated with various amounts of Et_3Al and reacted with 1.1 equiv of TMPMgCl·LiCl (**3**) for 22 h at 25 °C. If Et_3Al is used in substoichiometric amounts only low conversions (51-65%) are obtained, whereas an excess of Et_3Al does not further improve the metalation rate (Scheme 55). Hence, the best conditions require the use of stoichiometric amounts of Et_3Al.



Scheme 55: Metalation of 4-chloroanisole (**105a**) using various amounts of $AlEt_3$.

9.3 ALUMINATION AND REACTIONS WITH ELECTROPHILES AFTER TRANSMETALATION USING $ZnCl_2$

With these optimized reaction conditions, we were able to aluminate a broad range of electron-rich as well as electron-poor aromatics and have reacted the resulting aluminates with various electrophiles e.g. addition to aldehydes, acylations, allylations and cross-couplings with aryl iodides (Table 2). Thus, 4-chloroanisole (**105a**) is smoothly metalated at 25 °C within 24 h. The resulting aryltriethylaluminate **106a** subsequently reacts with *p*-anisaldehyde to give the desired alcohol **107a** in 75% yield (Scheme 56).



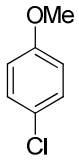
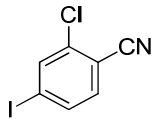
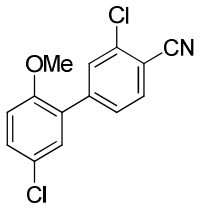
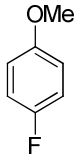
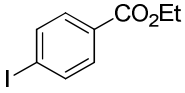
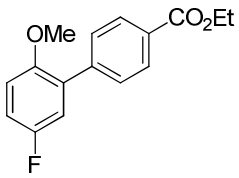
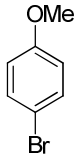
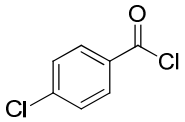
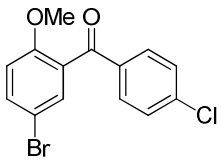
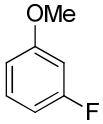
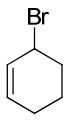
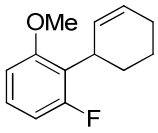
Scheme 56: Regioselective functionalization of 4-chloroanisole (**105a**) *via* alumination.

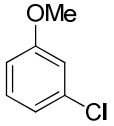
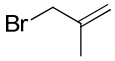
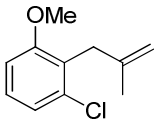
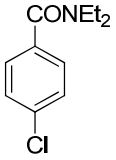
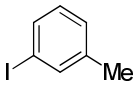
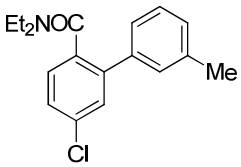
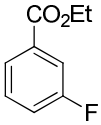
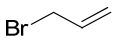
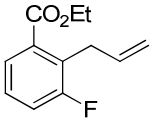
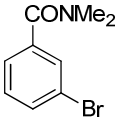
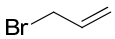
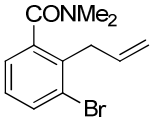
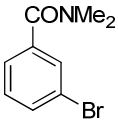
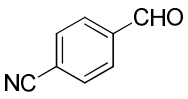
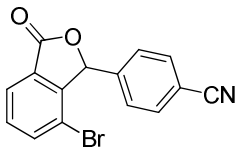
This new procedure proved to be quite general. By treating a variety of aromatics of type **105** with Et_3Al followed by TMPMgCl·LiCl (**3**) a range of functionalized aluminates was prepared in a convenient temperature range (-5 to 25 °C). After quenching with typical electrophiles, the expected products of type **107** were isolated in 70–83% yield (Table 11).

Accordingly, aluminate **106a** can also be smoothly transmetalated to zinc using $ZnCl_2$ and undergoes a Pd-catalyzed Negishi cross-coupling with 2-chloro-4-iodobenzonitrile (2.5 equiv) with 2% $Pd(dba)_2$ and 4% tfp (tfp = tri(2-furyl)phosphine) leading to the desired biphenyl **107b** in 70% yield (Table 11, Entry 1,). Also, 4-fluoroanisole (**105b**) and 4-bromoanisole (**105c**) are completely metalated at 25 °C within 15 h and 28 h, respectively. After transmetalation with $ZnCl_2$ (2.2 equiv) the corresponding organometallics react with ethyl 4-iodobenzoate (2.5 equiv) and Pd-catalysis or with 4-chlorobenzoyl

chloride (2.5 equiv) mediated by CuCN·2LiCl[99] (1.1 equiv) affording biphenyl **107c** and ketone **107d** in 77-79% yield (Entries 2-3). Since 3-fluoroanisole (**105d**) is prone to undergo a β-elimination, it is metalated at lower temperature (-5 °C). Under these conditions, full metalation is achieved within 20 min. Following transmetalation to zinc and a copper-catalyzed allylation with 3-bromocyclohexene provides the desired product **107e** in 87% yield (Entry 4). In contrast, 3-chloroanisole (**105e**) was metalated at 25 °C within 1 h, subsequent allylation with methallyl bromide gives the anisole derivative **107f** in 85% yield (Entry 5). Also the electron poor arenes **105f-h** are metalated at slightly lower temperatures. Accordingly, the *para*-substituted amide **105f** is aluminated at 0 °C within 3 h. After Negishi cross-coupling with 3-iodotoluene (2.5 equiv) the biphenyl **107g** is obtained in 73% yield (Entry 6). The *meta*-substituted ester **105g** and amide **105h** are metalated at 0 °C within 1 h. The resulting aryl-aluminates are allylated or reacted with 4-cyanobenzaldehyde affording the 2-allylated products **107h**-**i** and the lactone **107j** in 74-83% yield (Entries 7-9).

Table 11: Alumination of aromatics and subsequent quenching with electrophiles (2.5 equiv).

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
1	 **105a**	25, 24		 **107b:** 70%[b]
2	 **105b**	25, 15		 **107c:** 77%[b]
3	 **105c**	25, 28		 **107d:** 79%[c]
4	 **105d**	-5, 0.3		 **107e:** 87%[d]

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
5	 **105e**	25, 1		 **107f:** 85%
6	 **105f**	0, 3		 **107g:** 73%
7	 **105g**	0, 1		 **107h:** 81%
8	 **105h**	0, 1		 **107i:** 74%
9	 **105h**	0, 1		 **107j:** 83%

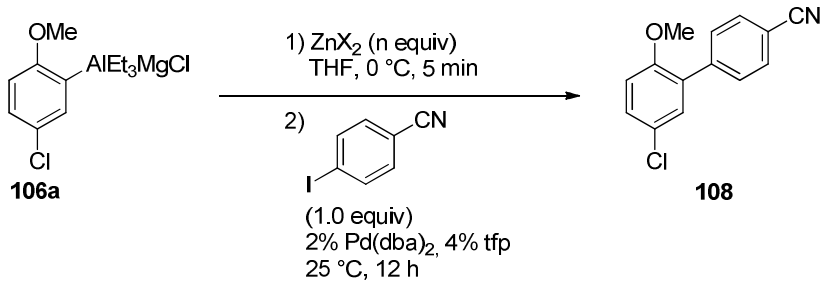
[a] Isolated yield of analytically pure product. [b] Obtained after transmetalation with $ZnCl_2$ (2.2 equiv) by palladium-catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp. [c] A transmetalation with $ZnCl_2$ (2.2 equiv) and CuCN·2LiCl (1.1 equiv) was performed. [d] Obtained after transmetalation with $ZnCl_2$ (2.2 equiv) by 5% CuCN·2LiCl catalyzed allylation.

9.4 ALUMINATION OF ELECTRON RICH AROMATICS AND REACTIONS WITH ELECTROPHILES AFTER TRANSMETALATION USING $Zn(OPiv)_2$

Nevertheless, this smooth alumination still had a drawback. For achieving high yields, it was necessary to use an excess of the electrophile (2.5 equiv). Preliminary results showed that a direct cross-coupling of the intermediate aluminates using $[Pd(tmpp)_2Cl_2]$ (tmpp = tris(2,4,6-trimethoxyphenyl)phosphine) leads only to low yields of the desired biphenyl (15%). Therefore the the nature and amount of the zinc reagent used for the transmetalation has been screened (Table 12). If 2 equiv of $ZnCl_2$ are used for the transmetalation, the biphenyl **108** was isolated in 38% yield, whereas with 5 equiv of $ZnCl_2$, the yield increases to 58% (Table 12, Entries 1-2). In contrast, the use

of 2 or 5 equiv of $ZnCl_2 \cdot 2LiCl$ gives mainly 4-ethylbenzonitrile and only small amounts of **108** (Entries 3-4). Finally $Zn(OPiv)_2$ provides the best results. Remarkably, 2 equiv of $Zn(OPiv)_2$ were sufficient for providing **108** in 70% yield, while the use of 5 equiv did not further improve the yield of **108** (Entries 5-6).

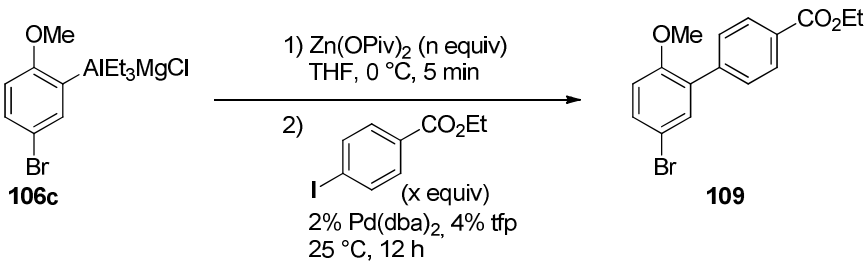
Table 12: Screening of various Zn-salts for the transmetalation step.



Entry	ZnX_2	equiv (n)	Yield of **7** (%)
1	$ZnCl_2$	2	38
2	$ZnCl_2$	5	58
3	$ZnCl_2 \cdot 2LiCl$	2	<5
4	$ZnCl_2 \cdot 2LiCl$	5	<5
5	$Zn(OPiv)_2$	2	70
6	$Zn(OPiv)_2$	5	67

In the next step, the stoichiometry of $Zn(OPiv)_2$ and the electrophile was further optimized. Therefore it was attempted to reduce the amount of $Zn(OPiv)_2$ and investigated if the use of an excess of electrophile has still an impact on the reaction yield (Table 13).

Table 13: Influence of the stoichiometry of $Zn(OPiv)_2$ and the electrophile

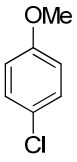
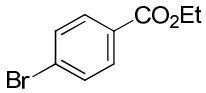
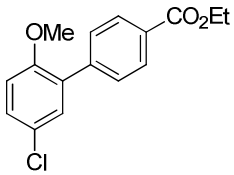


Entry	equiv $Zn(OPiv)_2$ (n)	equiv ethyl 4-iodobenzoate (x)	Yield of **109** (%)
1	1.1	1.2	47
2	1.1	2.4	51
3	2.2	1.2	78
4	2.2	2.4	75

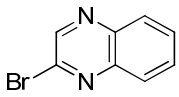
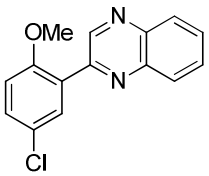
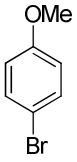
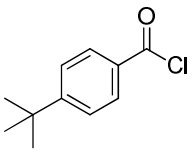
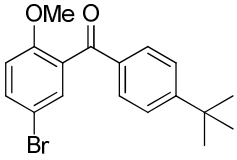
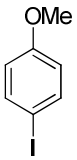
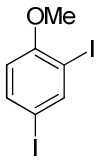
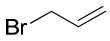
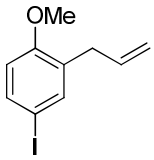
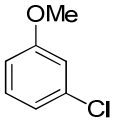
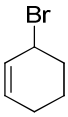
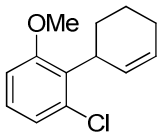
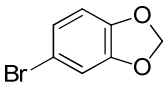
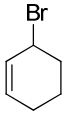
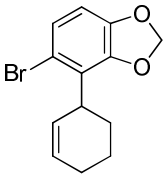
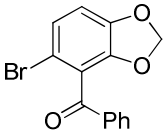
Interestingly, a large excess of ethyl 4-iodobenzoate did not significantly improve the yield of **109** in the Negishi cross-coupling, whereas the amount of $Zn(OPiv)_2$ greatly influenced the reaction yield. The best results were obtained with 2.2 equiv of $Zn(OPiv)_2$ and 1.2 equiv of the electrophile (Table 13, Entry 3).

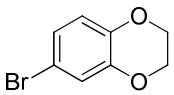
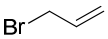
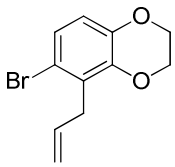
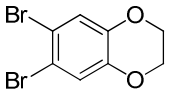
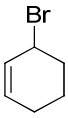
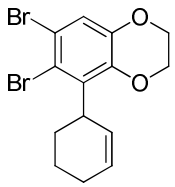
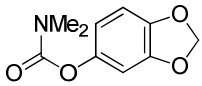
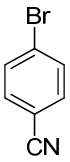
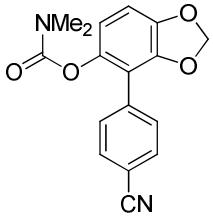
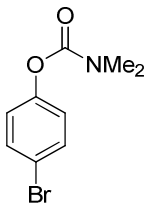
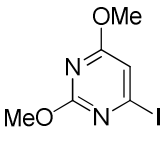
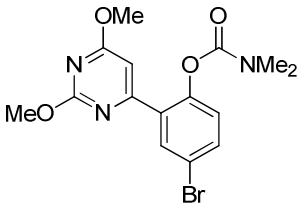
Having these optimized conditions in hand, metalations of various electron-rich substrates were carried out, yielding the products **110a-k** in 51-91% (Table 14). Thus, 4-chloroanisole (**105a**) is metalated at 25 °C within 24 h. After transmetalation with $Zn(OPiv)_2$ a Negishi cross-coupling with ethyl 4-bromobenzoate and 2-bromoquinoxaline leads to the desired products **110a** and **110b** in 71-73% yield (Table 14, Entries 1-2). Similarly 4-bromoanisole (**105c**) is metalated at 25 °C within 28 h and a subsequent CuCN·2LiCl-mediated acylation gives the ketone **110c** in 68% (Entry 3). 4-Iodoanisole (**105i**) is iodolyzed and allylated after alumination, providing diiodoarene **110d** and the 2-allylated anisole **110e** in 83-89% yield (Entries 4-5). Furthermore, 3-chloroanisole (**105e**) is smoothly aluminated and allylated, giving the anisole derivative **110f** in 77% yield (Entry 6). Also, dioxygenated substrates are readily metalated following this procedure. Thus, 5-bromo-1,3-benzodioxole (**105j**) is aluminated at 0 °C within 30 min. Subsequent allylation with 3-bromocyclohexene or benzoylation furnished the expected arenes **110g** and **110h** in 51-91% yield (Entries 7-8). Similarly, 6-bromo-2,3-dihydro-1,4-benzodioxine (**105k**) and 6,7-bromo-2,3-dihydro-1,4-benzodioxine (**105l**) are efficiently aluminated at 0 °C and readily allylated with a CuCN·2LiCl-catalysis affording the desired functionalized dihydrobenzodioxines **110i** and **110j** in 72-80% yield (Entries 9-10). Interestingly, the dimethylcarbamate protected phenols **105m–n** are smoothly aluminated without undergoing anionic *ortho-Fries* rearrangement[205] yielding after Pd-catalyzed cross-coupling the biphenyls **110k-l** in 74-77% (Entries 11-12).

Table 14: Metalation of electron-rich aromatics and reaction with electrophiles (1.2 equiv) after transmetalation with $Zn(OPiv)_2$ (2.2 equiv).

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
1	 **105a**	25, 24		 **110a:** 73%[b]

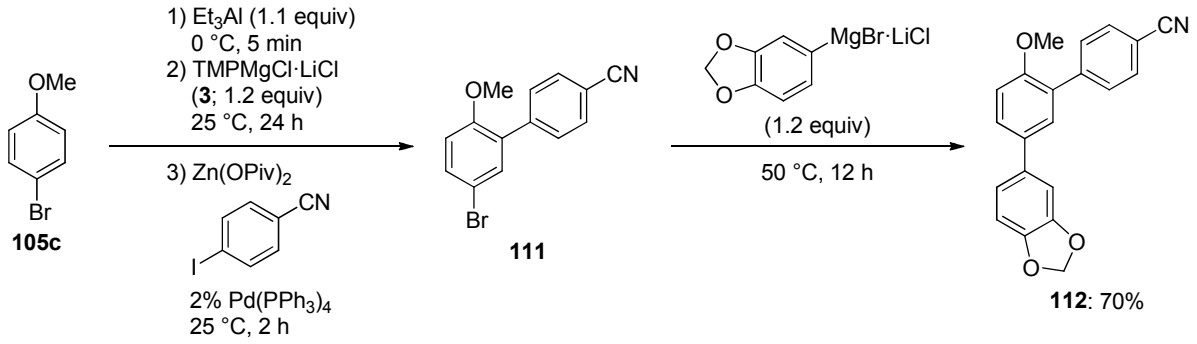
[205] a) L. S. Melvin, *Tetrahedron Lett.* **1981**, 3375; b) M. Sibi, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1937; c) T. K. Macklin, J. Panteleev, V. Snieckus, *Angew. Chem.* **2008**, *120*, 2127; *Angew. Chem. Int. Ed.* **2008**, *47*, 2097; d) K. J. Singh, D. B. Collum, *J. Am. Chem. Soc.* **2006**, *128*, 13753; e) J. C. Riggs, K. J. Singh, M. Yun, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 13709; f) J. P. H. Charmant, A. M. Dyke, G. C. Lloyd-Jones, *Chem. Commun.* **2003**, 380; g) F. Ding, Y. Zhang, B. Qu, G. Li, V. Farina, B. Z. Lu, C. H. Senanayake, *Org. Lett.* **2008**, *10*, 1067.

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
2	**105a** 	25, 24		 **110b:** 71%[b]
3	 **105c**	25, 28		 **110c:** 69%[c]
4	 **105i**	25, 30	I_2	 **110d:** 83%
5	**105i**	25, 30		 **110e:** 89%[d]
6	 **105e**	25, 1		 **110f:** 77%[d]
7	 **105j**	0, 0.5		 **110g:** 91%[d]
8	**105j**	0, 0.5	PhCOCl	 **110h:** 51%[c]

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
9	 **105k**	0, 0.5		 **110i:** 80%[d]
10	 **105l**	0, 0.5		 **110j:** 72%[d]
11	 **105m**	0, 0.5		 **110k:** 74%[d]
12	 **105n**	0, 2		 **110l:** 77%[b]

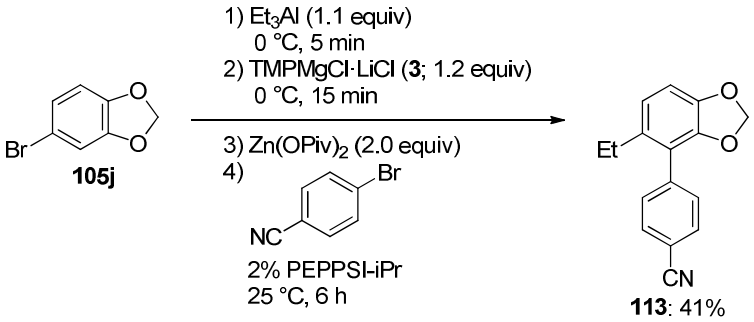
[a] Isolated yield of analytically pure product. [b] Obtained after transmetalation with $Zn(OPiv)_2$ (2.0 equiv) by palladium-catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp. [c] Obtained after transmetalation with $Zn(OPiv)_2$ (2.0 equiv) by palladium-catalyzed cross-coupling using 2% $Pd(PPh_3)_4$. [d] A transmetalation with $Zn(OPiv)_2$ (2.2 equiv) and CuCN·2LiCl (1.1 equiv) was performed. [e] Obtained after transmetalation with $Zn(OPiv)_2$ (2.2 equiv) by 5% CuCN·2LiCl catalyzed allylation.

Furthermore, selective cross-couplings can be performed. The choice of the Pd-catalyst is essential for achieving a chemoselective reaction. Therefore, the use of 2% $Pd(PPh_3)_4$ as catalyst leaves the bromo-substituent in *para*-position untouched during a cross-coupling with 4-iodobenzonitrile providing the biphenyl **111** at 25 °C. By addition of 1.2 equiv of (3,4-methylenedioxy)phenyl-magnesium bromide to the same reaction vessel, a second cross-coupling takes place at 50 °C, affording the polyfunctional terphenyl **112** in 70% yield (Scheme 57).



Scheme 57: One-pot preparation of a polyfunctional terphenyl (**112**) by two consecutive selective cross-couplings.

In contrast, use of [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-*i*Pr)[206] leads selectively first to the formation of the desired bromo-biphenyl at 25 °C. It undergoes directly a second cross-coupling with an ethyl group from the aluminum reagent Et_3Al, giving the alkylated biphenyl **113** in 41% yield (Scheme 58).

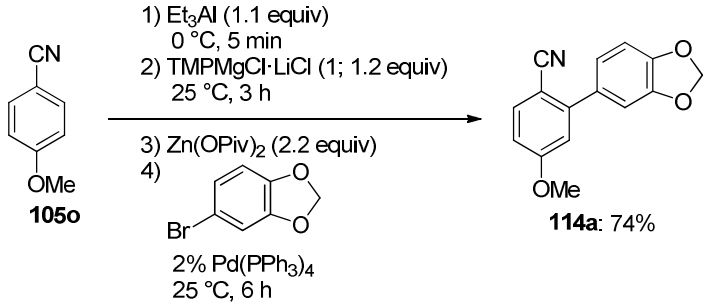


Scheme 58: Selective one-pot arylation and alkylation

[206] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; c) J. Nasielski, N. Hadei, G. Achonduh, E. A. B. Kantchev, C. J. O'Brien, A. Lough, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844; d) H. N. Hunter, N. Hadei, V. Blagojevic, P. Patschinski, G. T. Achonduh, S. Avola, D. K. Bohme, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 7845; e) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem.* **2011**, *123*, 9372; *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.

9.5 ALUMINATION OF ELECTRON POOR AROMATICS AND REACTIONS WITH ELECTROPHILES AFTER TRANSMETALATION USING $Zn(OPiv)_2$

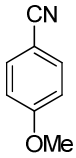
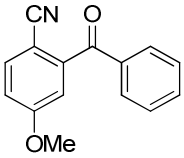
This methodology was also applied to arenes bearing electron-withdrawing groups and heterocycles. Therefore, 4-methoxybenzonitrile (**105o**) is readily aluminated at 25 °C and subsequent cross-coupling with 5-bromo-1,3-benzodioxole affords the desired biphenyl **114a** in 74% yield (Scheme 59)

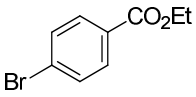
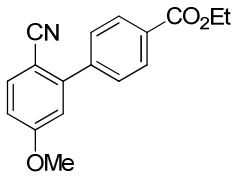
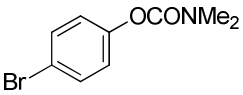
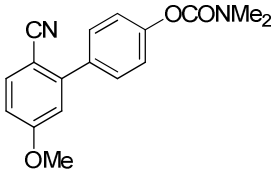
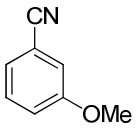
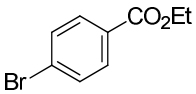
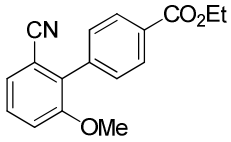
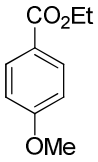
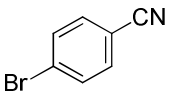
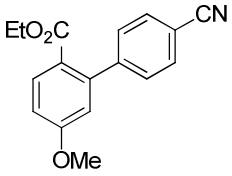
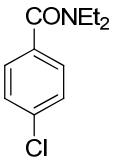
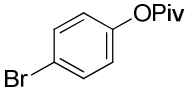
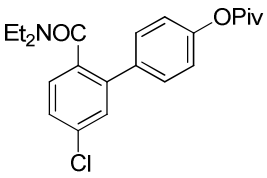
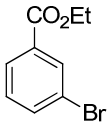
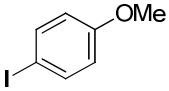
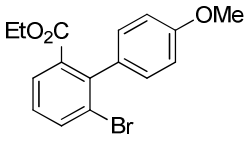
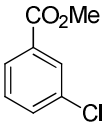
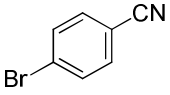
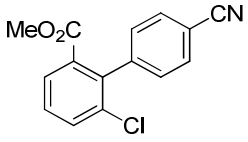


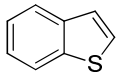
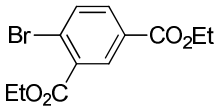
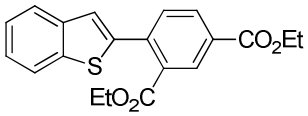
Scheme 59: Metalation of 4-methoxybenzonitrile (**105o**).

Performing the same reaction sequence, alumination of **105o** and transmetalation with $Zn(OPiv)_2$ affords 2-zincated 4-methoxybenzonitrile, which is acylated in the presence of CuCN·2LiCl providing the functionalized ketone **114b** in 72% yield (Table 15, Entry 1). Similarly, it undergoes Pd-catalyzed cross-couplings with ethyl 4-bromobenzoate or 4-bromophenyl dimethylcarbamate giving the biphenyls **114c**-**d** 67-75% yield (Entries 2-3). The isomeric 3-methoxybenzonitrile (**105o**) and ethyl 4-methoxybenzoate (**105p**) are correspondingly metalated and cross-coupled, leading to the highly functionalized biphenyls **114e**-**f** in 62-73% yield (Entries 4-5). The carbamate **105f**, ethyl ester **105q** and methyl ester **105r** are smoothly aluminated at 0 °C, giving after Pd-catalyzed cross-coupling, the arenes **114g**-**i** in 65-82% yield (Entries 6-8). This methodology is also applicable to heteroarenes. Hence, benzothiophene (**105s**) is metalated at 25 °C within 1 h and undergoes after transmetalation with $Zn(OPiv)_2$ a Pd-catalyzed cross-coupling with diethyl 4-bromoisophthalate affording the 2-arylated benzothiophene **114j** in 74% yield (Entry 9).

Table 15: Metalation of electron poor substrates and reaction with electrophiles (1.2 equiv) after transmetalation with $Zn(OPiv)_2$ (2.2 equiv).

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
1	 **105o**	25, 3	PhCOCl	 **114b:** 72%[b]

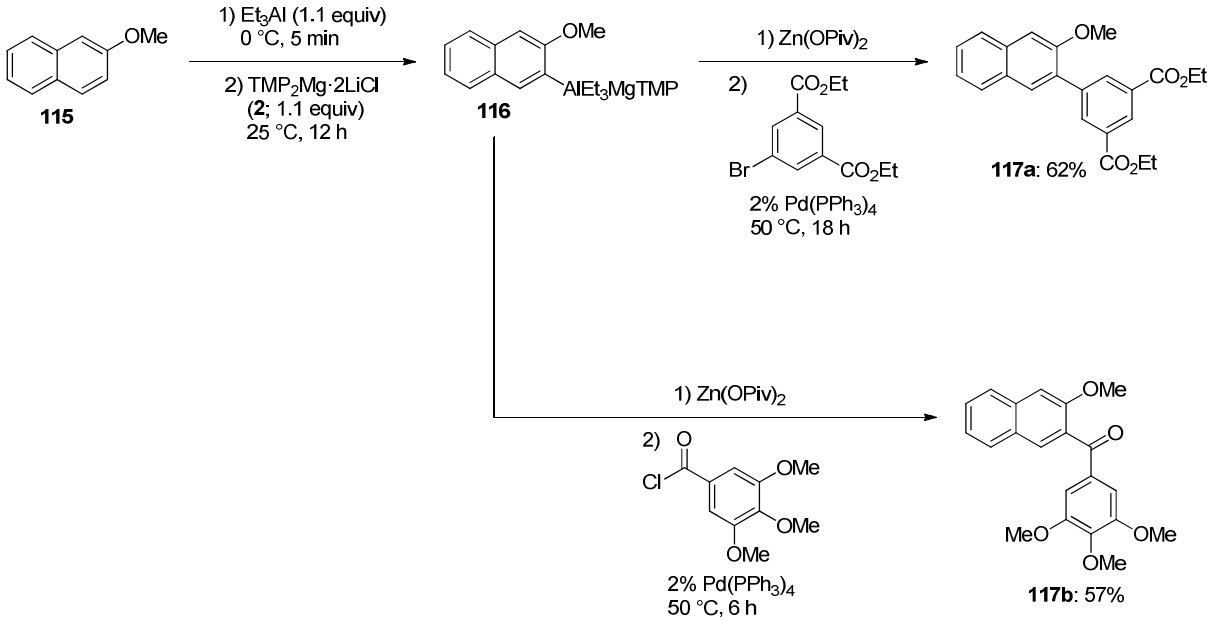
Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
2	**105o**	25, 3		 **114c:** 67%[c]
3	**105o**	25, 3		 **114d:** 75%[c]
4	 **105p**	25, 2		 **114e:** 62%[c]
5	 **105q**	25, 2		 **114f:** 73%[c]
6	 **105f**	0, 3		 **114g:** 82%[c]
7	 **105r**	0, 1		 **114h:** 65%[d]
8	 **105t**	0, 1		 **114i:** 73%[c]

Entry	Substrate	t [°C], T [h]	Electrophile	Product / Yield[a]
9	 **105t**	25, 1		 **114j:** 74%[c]

[a] Isolated yield of analytically pure product. [b] A transmetalation with $Zn(OPiv)_2$ (2.2 equiv) and CuCN·2LiCl (1.1 equiv) was performed. [c] Obtained after transmetalation with $Zn(OPiv)_2$ (2.0 equiv) by palladium-catalyzed cross-coupling using 2% $Pd(PPh_3)_4$. [d] Obtained after transmetalation with $Zn(OPiv)_2$ (2.0 equiv) by palladium-catalyzed cross-coupling using 2% $Pd(dba)_2$ and 4% tfp.

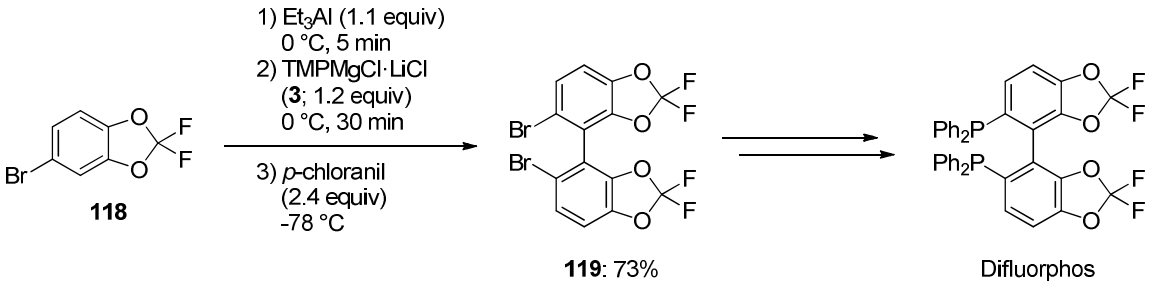
9.6 EXTENSION OF THE ALUMATION BY USING TMP_2Mg·2LiCl (4)

The method can also be extended to the alumination of more electron-rich arenes like 2-methoxynaphthalene (**115**) by replacing TMPMgCl·LiCl (**3**) with TMP_2Mg·2LiCl (**4**). In the metalation of **115** with *in situ* prepared Et_3Al-TMPMgCl·LiCl (**104**) only low conversions to the corresponding aryl aluminate species were obtained. Hence, the naphthalene derivative **115** is smoothly metalated by Et_3Al and TMP_2Mg·2LiCl (**2**) at 25 °C within 12 h. The resulting aluminate **116** undergoes a Pd-catalyzed Negishi cross-coupling or acylation after transmetalation with $Zn(OPiv)_2$ leading to the desired products **117a**-**b** in 57-62% yield (Scheme 60).



Scheme 60: Metalation of 2-methoxynaphthalene (**115**) using Et_3Al and TMP_2Mg·2LiCl (**4**)

Finally, the homocoupling[207] of the aluminate derived from 5-bromo-2,2-difluorobenzo[1,3]dioxole (**118**) proceeds readily in the presence of *p*-chloranil (2.4 equiv, -78 °C, 2 h) to afford the bis-naphthol **119**, a known precursor for Difluorphos,[208] the electron deficient analog of SEGPHOS[209] (Scheme 61).



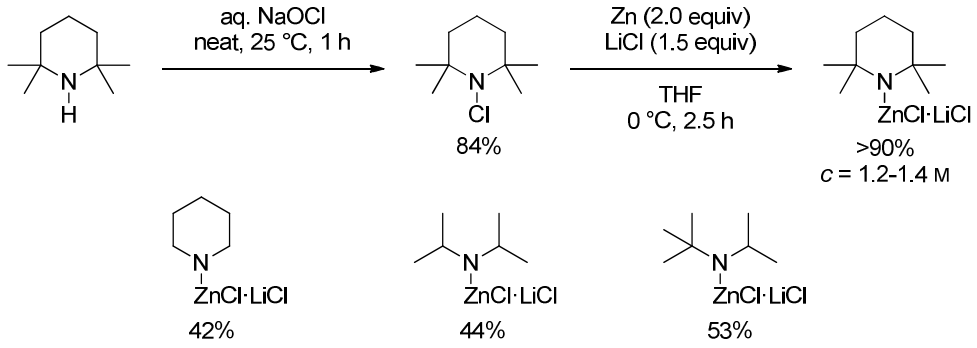
Scheme 61: Preparation of a Difluorphos precursor using *in situ* prepared Et_3Al-TMPMgCl·LiCl (**104**).

[207] A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem.* **2006**, *118*, 5132; *Angew. Chem. Int. Ed.* **2006**, 45,5010.
[208] a) S. Jeulin, S. S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, P. Dellis, *Angew. Chem.* **2004**, *116*, 324; *Angew. Chem. Int. Ed.* **2004**, *43*, 320; b) F. Leroux, J. Gorecka, M. Schlosser, *Synthesis* **2004**, 326; c) X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195; d) V. S. Chan, M. Chiu, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6021.
[209] a) T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**; *343*, 264; b) H. Smizu, I Nagasaki, K. Matsumura, N. Sayo, T. Saito, *Acc. Chem. Res.* **2007,** *40,* 1385; c) J. R. Zbieg, J. Moran, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 10582; d) P. Mauleón, J. L. Krinsky, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 4513.

10 SUMMARY

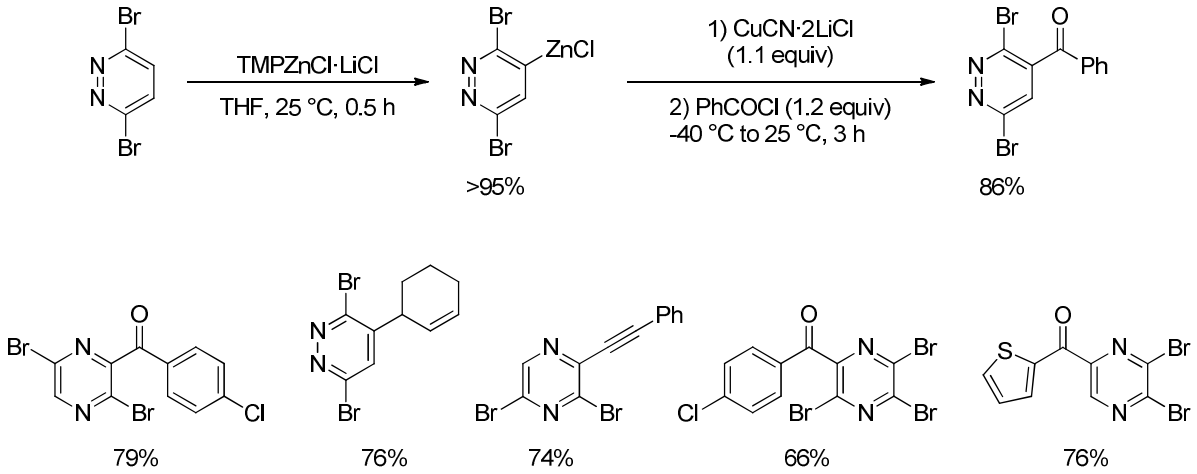
This work was focused on the chemo- and regioselective generation of functionalized aryl and heteroaryl organometallic reagents *via* directed metalation. For this purpose magnesiations, zincations and aluminations in combination with preactivation methods and frustrated Lewis pairs have been employed.

A fast, efficient and easy to perform synthesis of the zinc base TMPZnCl·LiCl *via* zinc insertion into a nitrogen-chlorine bond under mild conditions in high yields has been developed.



Scheme 62: New synthesis of TMPZnCl·LiCl and other zinc amides.

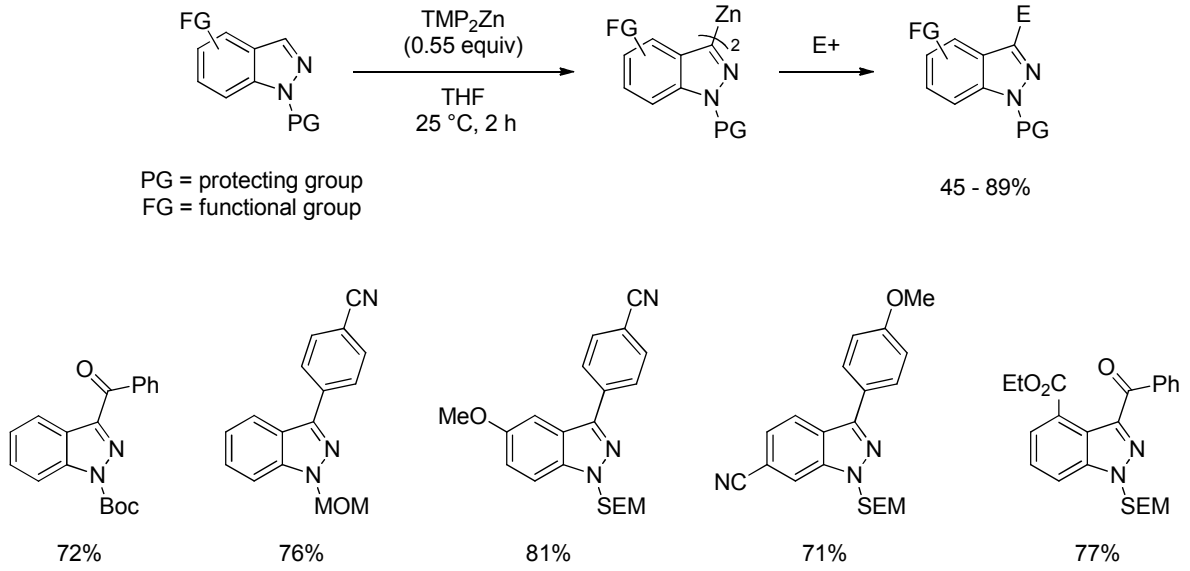
Remarkably this base is kinetically highly active and can be used for the successive chemo- and regioselective functionialization of sensitive dibromodiazine scaffolds.



Scheme 63: New synthesis of TMPZnCl·LiCl and functionalization of dibromodiazines.

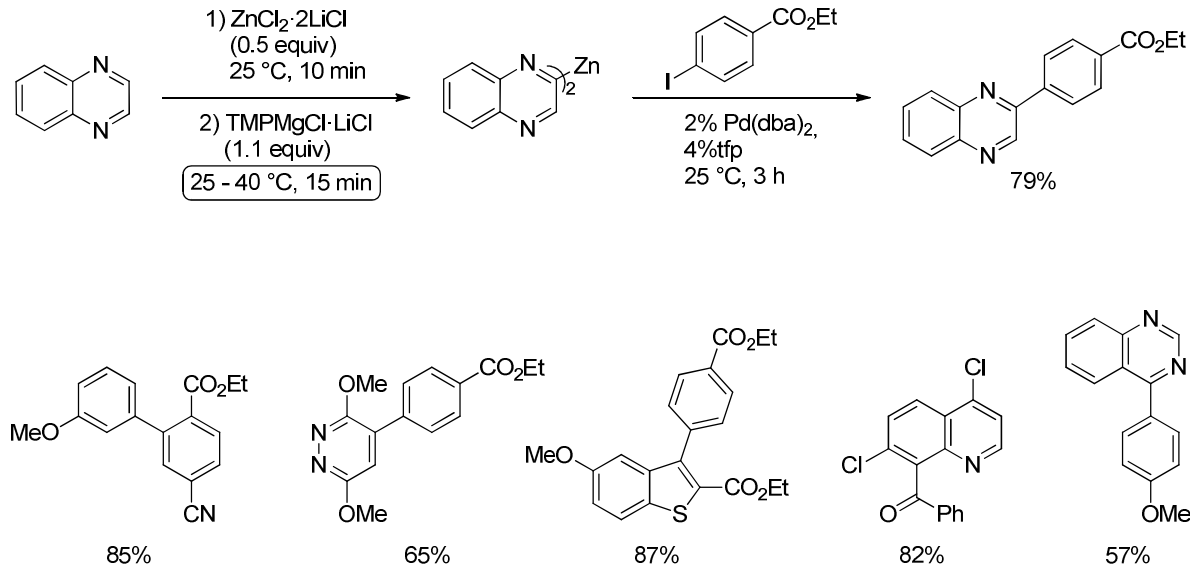
The resulting polyhalogenated diazines can be further regioselectively functionalized *via* metalations, transition metal-catalyzed cross-couplings or ring closing providing highly functionalized halogenated diazines in good yields

Furthermore, a simple, mild and efficient method for the metalation of N1-protected indazoles in position 3 with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) has been established. The resulting indazolylzincs could subsequently be reacted with electrophiles, especially in *Negishi* cross-couplings with various aryl iodides.



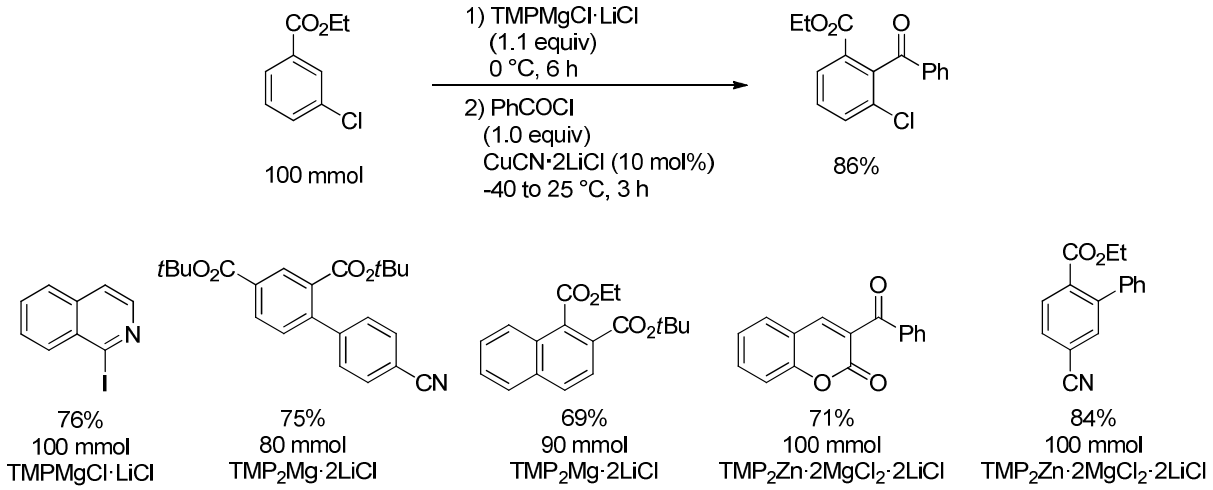
Scheme 64: Zincation of Indazoles and subsequent reaction with electrophiles.

Moreover, a new and efficient process for the preparation of functionalized diorganozincs *via* metalation involving the sequential addition of $ZnCl_2{\cdot}nLiCl$ and TMPMgCl·LiCl (**3**) has been established. This practical method combines fast metalations with an excellent functional group tolerance (compatibility with a methyl ester, an aldehyde and various electron-deficient heterocycles). The new procedure involves a metalation rate increase up to 50 times for only 10-15 °C temperature increase, indicating a reaction pathway including a Lewis acid activation of the organic substrate, followed by a magnesiation and a fast transmetalation with $ZnCl_2$.



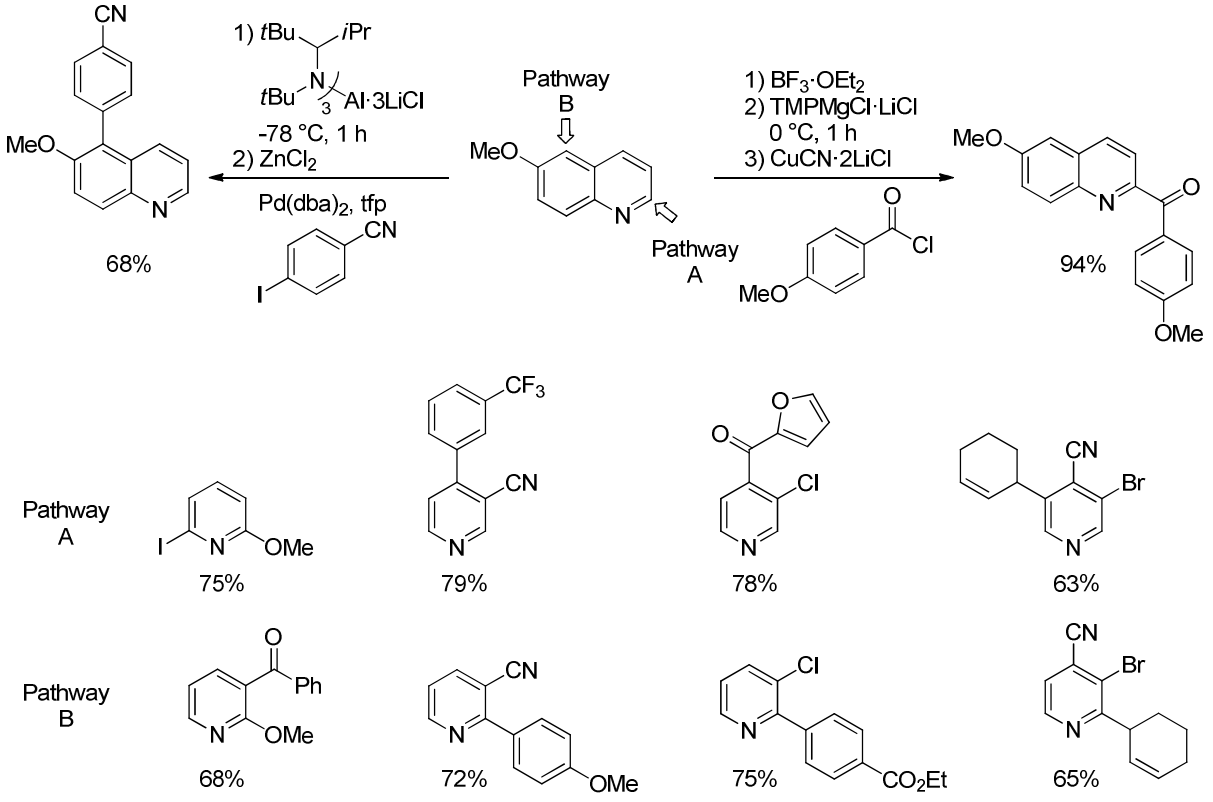
Scheme 65: Accelerated zincation with the new sequential procedure.

In addition, it could be shown that metalation processes using TMPMgCl·LiCl (**3**), $TMP_2Mg·2LiCl$ (**4**) and $TMP_2Zn·2MgCl_2·2LiCl$ (**6**) can readily and safely be carried out at multigram scale. The metalation step occurs typically with enhanced rate, acylation reactions can be carried out with 10 mol% CuCN·2LiCl and the catalyst loading of cross-coupling reactions can be lowered to 0.5% of Pd-catalyst.



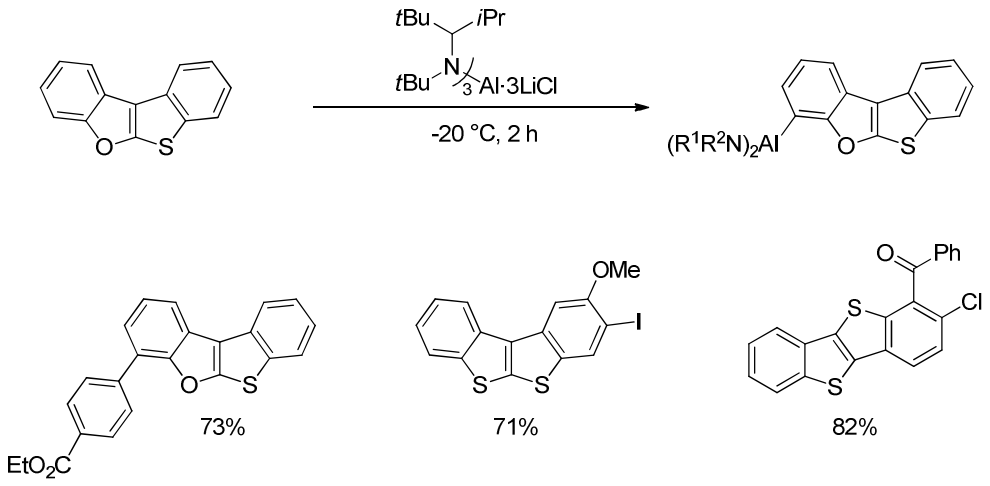
Scheme 66: Larger-scale metalations.

Moreover, the regioselective functionalization of various heterocycles was investigated. Thus, the metalation of various *N*-heterocycles with or without $BF_3·OEt_2$ using hindered Mg-, Zn- or Al-bases (**3**, **6** or **7**) allows for a complementary switch in the regioselectivity of the metalation. After reaction with a variety of electrophiles a range of new polyfunctional N-heterocycles is obtained.



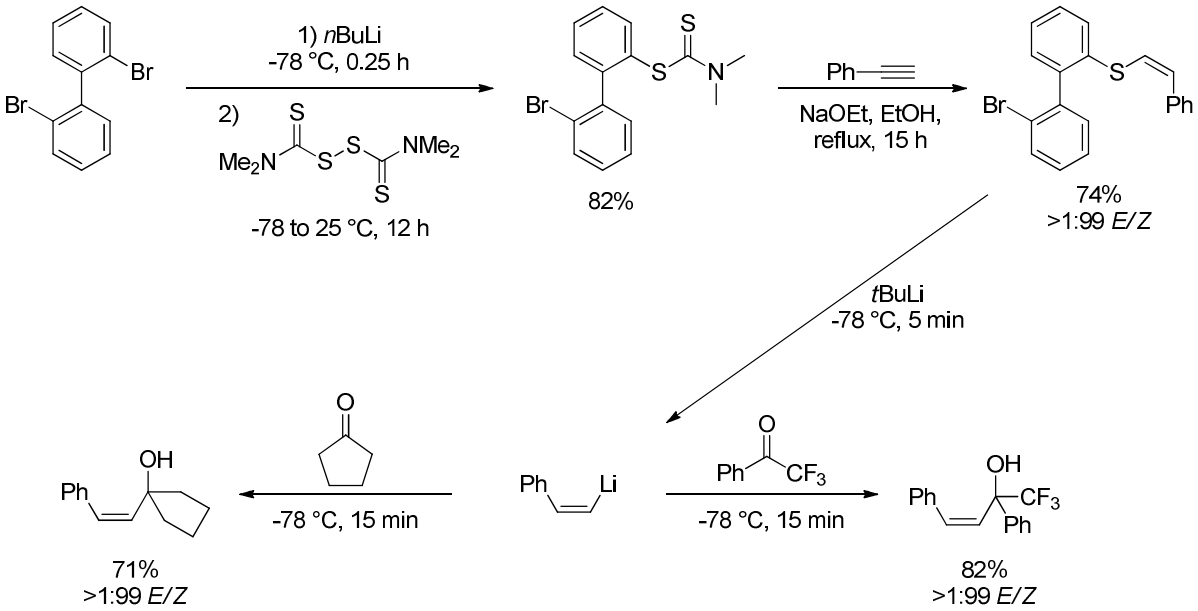
Scheme 67: Complete switch in the regioselectivity of the metalation with or without $BF_3·OEt_2$.

Also condensed tetracyclic S-heteroaromatics can be regioselectively functionalized using the hindered aluminum trisamide (**7**).



Scheme 68: Regioselective alumination of condensed S-heterocycles.

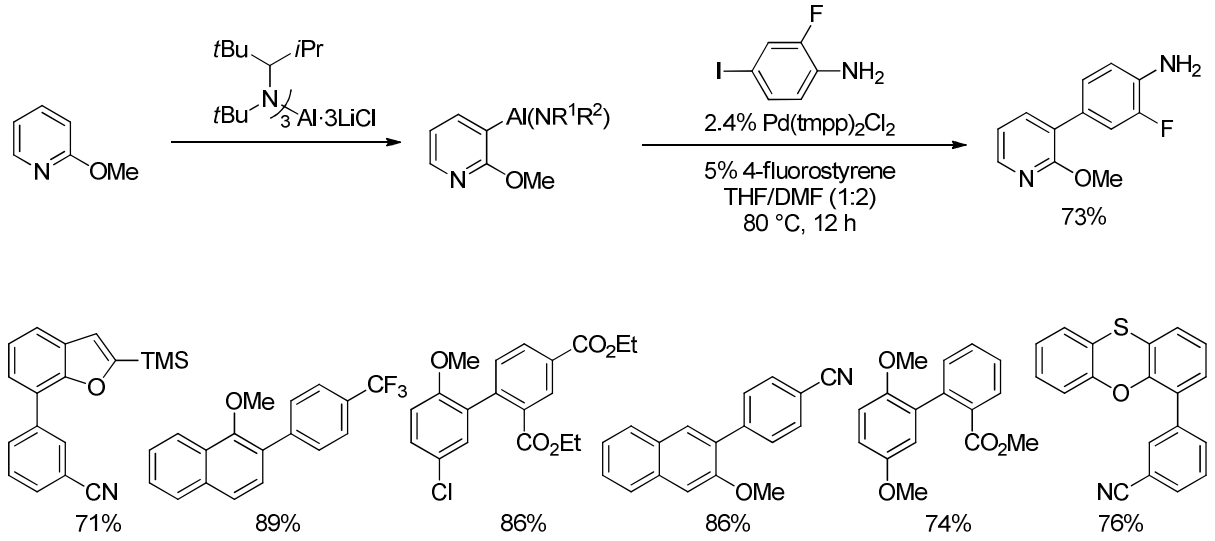
Besides, the synthesis of tetrasubstituted olefins with excellent *E*/*Z*- stereoselectivities up to 99:1 has been reported. Therfore a sequential carbocupration and a new sulfur-lithium exchange involving an alkenyl thioether bearing a 2'-bromobiphenyl substituent which triggers efficiently the sulfur-lithium exchange have been employed. Extension to the stereoselective preparation of *Z*-styryllithium has been shown.



Scheme 69: Preparation of *Z*-styryllithium and reaction with electrophiles.

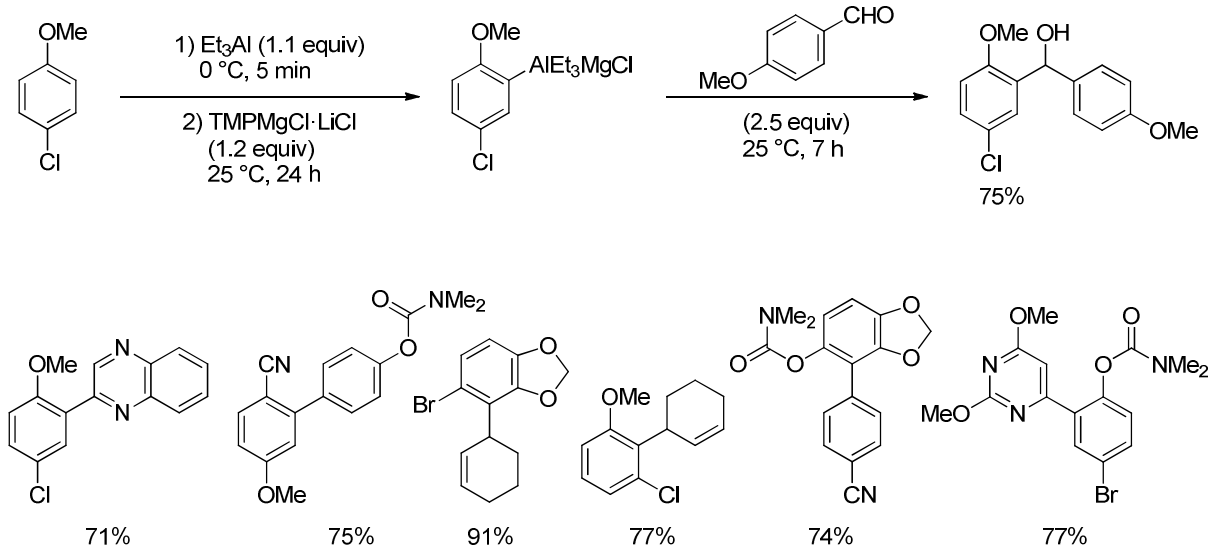
In addition, a new efficient, direct cross-coupling of functionalized organoaluminum reagents without the need for a transmetalation has been developed. This methodology allows a practical C-C bond formation starting from bis-organoaluminum amides prepared by an improved directed alumination with only 0.5 equiv of a sterically hindered aluminum trisamide. Previously, the alumination had to

be performed using 1 equiv of base. It could be shown that aryl and heteroaryl iodides, bromides, nonaflates and in special cases chlorides and triflates are good electrophiles for such cross-couplings and that free NH_2-groups, aldehydes, ketones, ester and nitro-functions are well tolerated.



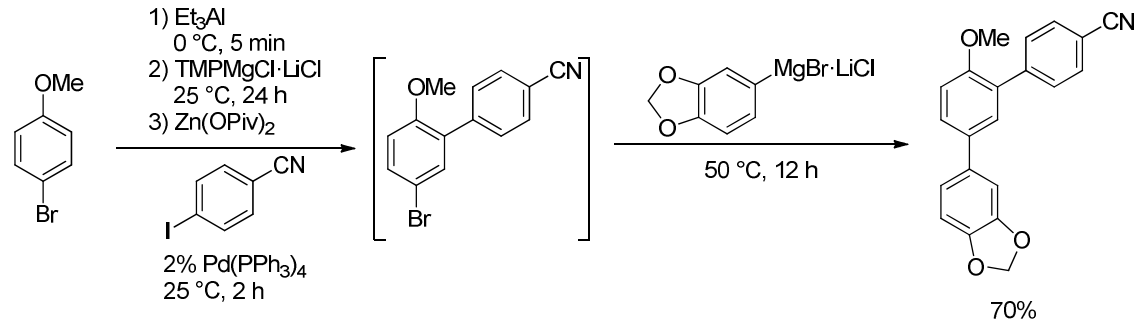
Scheme 70: Improved alumination and subsequent direct cross-coupling.

Finally, a new alumination procedure involving the *in situ* preparation of the frustrated Lewis pair Et_3Al-TMPMgCl·LiCl *via* sequential addition of Et_3Al and TMPMgCl·LiCl was developed. This method combines chemo- and regioselective metalations with good functional group tolerance, storable reagents and overcomes the need for an excess of base and electrophile. This practical procedure gives access to new organometallics not readily available by halogen-metal exchange reactions or previously reported metalation procedures using TMP-bases. After transmetalation of the resulting aluminates with $Zn(OPiv)_2$ subsequent reactions with only slight excess of electrophile is possible.



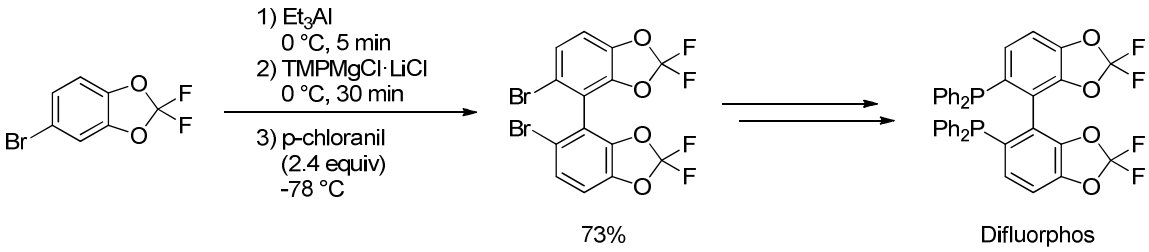
Scheme 71: Alumination *via* sequential addition of Et_3Al and TMPMgCl·LiCl and obtained products after transmetalation with $Zn(OPiv)_2$.

The method allows also the one-pot preparation of polyfunctional terphenyls by alumination and two consecutive selective cross-couplings.



Scheme 72: One-pot preparation of a polyfunctional terphenyl by alumination and two consecutive selective cross-couplings.

Oxidative homocoupling of the resulting aluminates allows for an selective preparation of the desired biphenyls, without transfer of an ethyl group being observed. Therefore, as an application a known precursor for Difluorphos was prepared in one step.



Scheme 73: Preparation of a Difluorphos precursor using *in situ* prepared Et_3Al-TMPMgCl·LiCl.

C. EXPERIMENTAL

1 GENERAL CONSIDERATIONS

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

1.1 SOLVENTS

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

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

1,4-Dioxane was refluxed over CaH_2 and distilled from CaH_2.

DME was predried over $CaCl_2$ and distilled from Na/benzophenone ketyl under argon.

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

DMPU was predried over CaH_2 (4 h) and distilled off.

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

EtOAc was predried over CaH_2 (4 h) and distilled off.

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

NEP was refluxed over CaH_2 and distilled from CaH_2.

NMP was refluxed over CaH_2 and distilled from CaH_2.

Pyridine was dried over KOH and distilled.

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

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

Triethylamine was dried over KOH and distilled.

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

1.2 REAGENTS

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

BF_3·OEt_2 was distilled under Ar prior to use.

TMPH was distilled from CaH_2 under Ar prior to use.

$ZnCl_2$ in THF (1.0 M)

$ZnCl_2$ (27.3 g, 200 mmol) was placed in a 250 mL Schenk tube equipped with a magnetic stirring bar and a septum. The salt is heated at 150 °C in an oil bath for 4 h under high vacuum. Then, after cooling to 25 °C absolute THF was added till a total volume of 200 mL was reached. Afterwards, the septum was replaced by a glass stopper and the suspension was left stirring over night at 25 °C. After 12 h, the salts had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities were allowed to settle down by that way). The solution was stored under argon upon use.

$ZnCl_2$·LiCl in THF (1.0 M)

LiCl (8.5 g, 200 mmol) was placed in a 250 mL Schenk tube equipped with a magnetic stirring bar and a septum. The salt is heated at 400 °C using a heatgun for 15 min under high vacuum. After cooling to room temperature $ZnCl_2$ (27.3 g, 200 mmol) was added and the salts were heated at 150 °C in an oil bath for 4 h under high vacuum. Then, after cooling to 25 °C absolute THF was added till a total volume of 200 mL was reached. Afterwards, the septum was replaced by a glass stopper and the suspension was left stirring over night at 25 °C. After 12 h, the salts had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities were allowed to settle down by that way). The solution was stored under argon upon use.

$ZnCl_2$·2LiCl in THF (1.0 M)

LiCl (17.0 g, 400 mmol) was placed in a 250 mL Schenk tube equipped with a magnetic stirring bar and a septum. The salt is heated at 400 °C using a heatgun for 15 min under high vacuum. After cooling to room temperature $ZnCl_2$ (27.3 g, 200 mmol) was added and the salts were heated at 150 °C in an oil bath for 4 h under high vacuum. Then, after cooling to 25 °C absolute THF was added till a total volume of 200 mL was reached. Afterwards, the septum was replaced by a glass stopper and the suspension was left stirring over night at 25 °C. After 12 h, the salts had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little

particles and insoluble impurities were allowed to settle down by that way). The solution was stored under argon upon use.

CuCN·2LiCl in THF (1.0 M)

LiCl (17.0 g, 400 mmol) was placed in a 250 mL Schenk tube equipped with a magnetic stirring bar and a septum. The salt is heated at 650 °C using a heatgun for 15 min under high vacuum. After cooling to room temperature CuCN (17.9 g, 200 mmol) was added and the salts were heated at 150 °C in an oil bath for 4 h under high vacuum. Then, after cooling to 25 °C absolute THF was added till a total volume of 200 mL was reached. Afterwards, the septum was replaced by a glass stopper and the suspension was left stirring over night at 25 °C. After 12 h, the salts had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities were allowed to settle down by that way). The solution was stored under argon upon use.

$MgCl_2$·LiCl in THF (0.50 M)

LiCl (424 mg, 10 mmol) was placed in a 50 mL Schenk tube equipped with a magnetic stirring bar and a septum. The salt is heated at 400 °C using a heatgun for 15 min under high vacuum. Then, Mg turnings (243 mg, 10 mmol) were added, followed by absolute THF (5 mL). Afterwards, 1,2-dichloroethane (0.79 mL, 10 mmol) was added in one portion. The reaction was started by gentle warming of the reaction mixture. Once the reaction is started the mixture is cooled by the further addition of THF (15 mL). After complete dissolving of LiCl the stirring was stopped and the solution was was left for some more time to become completely clear (little particles and insoluble impurities are allowed to settle down by that way). The solution was stored under argon upon use.

$Zn(OPiv)_2$

Pivalic acid (30.6 g, 34.5 mL, 300 mmol) was placed in a dry and argon-flushed 500 mL *Schlenk*-flask, equipped with a magnetic stirring bar and a pressure-relief valve, and dissolved in absolute THF (150 mL). The solution was cooled to 0 °C and a solution of diethylzinc (18.8 g, 15.6 mL, 152 mmol) in absolute THF (150 mL) was added dropwise over a period of 30 min (gas formation and partial precipitation of the product was observed). After slowly warming to 22 °C under vigorous stirring, the solvent was removed *in vacuo* and $Zn(OPiv)_2$ was obtained as a colorless solid in quantitative yield. $Zn(OPiv)_2$ was stored under argon although no sensitivity towards air or moisture was observed.

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

PhMgCl was purchased as a solution in THF from Rockwood Lithium GmbH.

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

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

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

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

The content of organometallic reagent was determined either by the method of *Paquette* using *i*PrOH and 1,10-phenanthroline as indicator (organolithium reagents)[210] or the method of *Knochel* using I_2 (organomagnesium or -zinc reagents)[211] prior to use.

TMP metal bases were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.3 ANALYTICAL DATA

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

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

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

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

NMR spectra were recorded on *Varian* Mercury 200, *Bruker* AC 300, WH 400, or AMX 600 instruments. Chemical shifts are reported as *δ*-values in ppm relative to the solvent peak. For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), m (multiplet), q (quartet), quint (quintet), sxt (sextet), as well as br (broad).

[210] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[211] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

1.4 CHROMATOGRAPHY

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

- Phosphormolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12.0 mL) in water (230 mL).
- Iodine absorbed on silica gel.
- $KMnO_4$ (0.3 g), K_2CO_3 (20 g) and KOH (0.3 g) in water (300 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

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

2 NEW PREPARATION OF TMPZnCl·LiCl BY Zn INSERTION INTO TMPCl. APPLICATION TO THE FUNCTIONALIZATION OF DIBROMODIAZINES

2.1 TYPICAL PROCEDURES

Typical procedure for the zincation of dibromodiazines with TMPZnCl·LiCl (5) (TP 1):

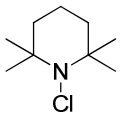
A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding dibromodiazine (2.0 mmol) in dry THF (2.0 mL) as well as 50 µL of tetradecane (internal standard for GC analysis). After setting the desired temperature (Table 1 and Table 2), TMPZnCl·LiCl (**5**) (1.1 mmol) was added dropwise and stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the Pd-catalyzed cross-coupling reaction of organozinc reagents (TP 2):

In a dry argon-flushed Schlenk flask, equipped with a septum and a magnetic stirring bar, the heteroaromatic bromide or iodide (1.0 mmol) was dissolved in THF (1.0 mL) and the Pd-source (0.02 mmol, 2 mol%) as well as the phosphineligand (0.04 mmol, 4 mol%) were added. After the corresponding zinc reagent (0.8 mmol, 0.8 equiv) was added dropwise and the reaction mixture was stirred for the given time at the indicated temperature until GC-analysis showed full conversion.

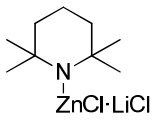
2.2 PREPARATION OF STARTING MATERIALS

Preparation of TMPCl (9)



This compound was prepared from commercially available TMPH and aq sodium hypochlorite according to the procedure reported by Rabalais *et al*.[212]

Preparation of TMPZnCl·LiCl (5):



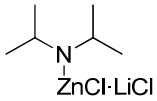
[212] N. Bodor, J. J. Kaminski, S. D. Worley, R. J. Colton, T. H. Lee, J. W. Rabalais, *J. Pharm. Sci.* **1974**, *63*, 1387.

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) and dried for 5 min at 400 °C (heat gun) under high vacuum. Then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) under high vacuum. THF (10 mL) was added and the zinc was activated with *i*Bu_2AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-2,2,6,6-tetramethylpiperidine (**9**, 8.75 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added *via* syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 min. Then the excess of zinc was allowed to sediment and the solution was titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.15 M in THF (92%) was obtained.

Preparation of piperidyl-ZnCl·LiCl:

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) and dried for 5 min at 400 °C (heat gun) under high vacuum. Then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) under high vacuum. THF (10 mL) was added and the zinc was activated with *i*Bu_2AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-piperidine[213] (5.98 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added *via* syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 min. Then the excess of zinc was allowed to sediment and the solution was titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.53 M in THF (42%) was obtained.

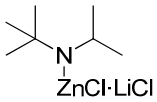
Preparation of diisopropylamino-ZnCl·LiCl:



[213] A. M. Socha, N. Y. Tan, J. K. Sello, K. L. Laplante, *Bioorg. Med. Chem.* **2010**, *18*, 7193.

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) and dried for 5 min at 400 °C (heat gun) under high vacuum. Then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) under high vacuum. THF (10 mL) was added and the zinc was activated with *i*Bu_2AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-diisopropylamine[214] (6.78 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added *via* syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 min. Then the excess of zinc was allowed to sediment and the was solution titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.55 M in THF (44%) was obtained.

Preparation of *tert*Butylisopropylamino-ZnCl·LiCl:

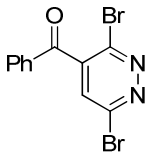


A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (3.18 g, 75 mmol) and dried for 5 min at 400 °C (heat gun) under high vacuum. Then zinc powder (6.5 g, 100 mmol) was added and again dried for 5 min at 400 °C (heat gun) under high vacuum. THF (10 mL) was added and the zinc was activated with *i*Bu_2AlH (0.07 mL, 0.5 mmol). After 5 min of stirring the zinc was further activated with 1,2-dibromoethane (0.22 mL, 0.5 mmol) and the reaction mixture was heated until ebullition occured. After cooling to 25 °C, trimethylsilyl chloride (0.06 mL, 0.01 mmol) and I_2 (0.5 mL, 1 M in THF, 0.5 mmol) were added and the mixture was cooled to 0 °C. 1-Chloro-tertbutylisopropylamine[215] (7.48 g, 50 mmol) was diluted with THF to a total volume of 30 mL and added *via* syringe pump at a rate of 0.25 mL/min. After the addition the reaction was stirred for further 30 min. Then the excess of zinc was allowed to sediment and the solution was titrated with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.66 M in THF (53%) was obtained.

[214] O. I. Kolodiazhnyi, O. R. Golovatyi, *Phosphorus, Sulfur and Silicon Relat. Elem.* **1995**, *102*, 133.
[215] K. Smith, M. Butters, B. Nay, *Tetrahedron Lett.* **1988**, *29*, 1319.

2.3 FUNCTIONALIZATION OF DIBROMODIAZINES

Synthesis of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (15a)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**13a**; 476 mg, 2.0 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.28 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **15a** (588 mg, 86%) as a colorless solid.

m.p.: 148.8 – 149.9 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.39 (s, 1H), 7.92 – 7.88 (m, 2H), 7.81 – 7.76 (m, 1H), 7.62 – 7.58 (m, 2H).

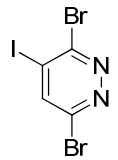
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 189.8, 148.0, 143.3, 142.0, 135.4, 133.7, 131.4, 130.2, 129.3.

MS (70 eV, EI) *m/z* (%): 343 (7), 341 (13), 339 (6) [M^+], 199 (3), 105 (100), 77 (43), 50 (5), 43 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 1663, 1656, 1591, 1490, 1451, 1342, 1320, 1305, 1250, 1169, 1162, 1128, 1086, 1077, 1023, 999, 960, 943, 911, 854, 809, 799, 748, 713, 695, 687, 652 .

HRMS (EI) for **$C_{11}H_6Br_2N_2O$** (339.8847): 339.8841.

Synthesis of 3,6-dibromo-4-iodopyridazine (15b)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**13a**; 476 mg, 2.0 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to 0 °C, then a solution of I_2 (761 mg, 3 mmol) in THF (6 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was

purified by flash column chromatography (pentane:diethyl ether = 49:1) to give **15b** (515 mg, 71%) as a colorless solid.

m.p.: 154.9 – 156.2 °C.

^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 8.67 (s, 1H).

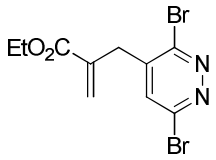
^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 154.8, 145.5, 142.8, 112.2.

MS (70 eV, EI) *m/z* (%): 365 (43), 363 (100) [M^+], 361 (43), 210 (34), 208 (82), 206 (35), 129 (39), 127 (43), 126 (30), 77 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3085, 1725, 1668, 1587, 1563, 1528, 1496, 1469, 1419, 1396, 1321, 1286, 1260, 1190, 1160, 1146, 1091, 1074, 1038, 1028, 997, 962, 937, 881, 830, 811, 769, 745, 727, 670, 657.

HRMS (EI) for **$C_4HBr_2IN_2$** (361.7551): 361.7687.

Synthesis of ethyl 2-((3,6-dibromopyridazin-4-yl)methyl)acrylate (15c)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**13a**; 476 mg, 2.0 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **15c** (513 mg, 73%) as a colorless solid.

m.p.: 60.4 – 61.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.45 (s, 1H), 6.47 (s, 1H), 5.74 (d, *J* = 0.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

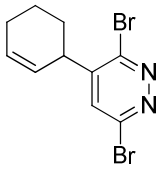
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.5, 150.9, 147.4, 143.1, 134.8, 132.6, 129.9, 61.5, 36.8, 14.1.

MS (70 eV, EI) *m/z* (%): 348 (2) [M^+], 305 (11), 271 (20), 243 (95), 241 (100), 177 (16), 161 (11), 117 (17), 90 (14), 85 (15), 71 (20), 63 (12), 57 (27), 55 (11), 43 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3059, 2978, 1707, 1632, 1553, 1465, 1371, 1360, 1326, 1306, 1290, 1221, 1207, 1146, 1123, 1078, 1024, 1017, 969, 944, 888, 858, 822, 747, 729, 677.

HRMS (EI) for **$C_{10}H_{10}Br_2N_2O_2$** (347.9109): 347.9108.

Synthesis of 3,6-dibromo-4-(cyclohex-2-en-1-yl)pyridazine (15d)



According to **TP 1**, the metalation of 3,6-dibromopyridazine (**13a**; 476 mg, 2.0 mmol) was completed within 15 min at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **15d** (485 mg, 76%) as a colorless solid.

m.p.: 50.4 – 51.4 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.62 (s, 1H), 6.08 – 6.02 (m, 1H), 5.63 – 5.57 (m, 1H), 3.64 – 3.57 (m, 1H), 2.09 – 1.97 (m, 3H), 1.60 – 1.48 (m, 3H).

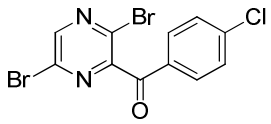
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 150.9, 149.2, 147.8, 132.0, 131.4, 125.4, 39.2, 27.7, 24.2, 19.6.

MS (70 eV, EI) *m/z* (%): 319 (29), 317 (56), 315 (30) [M^+], 302 (11), 263 (18), 239 (15), 157 (41), 130 (15), 102 (22), 81 (22), 79 (16), 77 (17), 67 (13), 61 (15), 57 (13), 53 (10), 45 (13), 43 (100), 40 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3023, 2922, 2859, 2829, 1548, 1493, 1455, 1444, 1427, 1391, 1351, 1339, 1321, 1299, 1288, 1274, 1248, 1115, 1085, 1076, 1056, 1038, 1016, 992, 910, 878, 844, 819, 758, 747, 723, 681, 664.

HRMS (EI) for **$C_{10}H_{10}Br_2N_2$** (315.9211): 315.9208.

Synthesis of (4-chlorophenyl)(3,6-dibromopyrazin-2-yl)methanone (15e)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**13b**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (0.31 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **15e** (596 mg, 79%) as an off white solid.

m.p.: 130.8 – 132.8 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 8.95 (s, 1H), 7.96 (dt, *J* = 9.0, 2.4 Hz, 2H), 7.67 (dt, *J* = 9.0, 2.4 Hz, 2H).

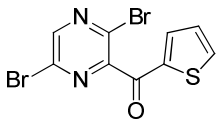
^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 189.2, 151.2, 149.3, 140.4, 138.3, 135.0, 132.3, 132.1, 129.4.

MS (70 eV, EI) *m/z* (%): 377 (5), 375 (8) [M^+], 139 (8), 138 (100), 111 (30), 75 (12), 44 (7), 43 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3116, 3061, 1663, 1656, 1590, 1583, 1490, 1451, 1342, 1320, 1304, 1249, 1168, 1162, 1127, 1086, 1078, 1022, 999, 960, 943, 911, 855, 808, 798, 748, 711, 695, 686.

HRMS (EI) for **$C_{11}H_5Br_2ClN_2O$** (373.8547): 373.8464.

Synthesis of (3,6-dibromopyrazin-2-yl)(thiophen-2-yl)methanone (15f)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**13b**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (0.26 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **15f** (450 mg, 65%) as an off white solid.

m.p.: 106.2 – 108.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 1H), 7.84 (d, *J* = 4.1 Hz, 1H), 7.65 (d, *J* = 3.3 Hz, 1H), 7.22 – 7.16 (m, 1H).

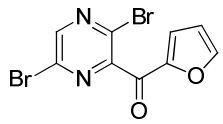
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 181.4, 151.1, 148.3, 140.8, 137.6, 137.2, 136.9, 136.1, 128.7.

MS (70 eV, EI) *m/z* (%): 348 (13), 346 (7) [M^+], 319 (2), 112 (6), 110 (100), 83 (6), 56 (3), 45 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 2920, 1633, 1509, 1410, 1403, 1376, 1368, 1350, 1256, 1237, 1175, 1168, 1156, 1131, 1085, 1059, 1039, 946, 916, 907, 858, 802, 759, 743, 682.

HRMS (EI) for **$C_9H_4Br_2N_2OS$** (345.8411): 345.8408.

Synthesis of (3,6-dibromopyrazin-2-yl)(furan-2-yl)methanone (15g)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**13b**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (0.26 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **15g** (352 mg, 53%) as an off white solid.

m.p.: 139.2 – 140.4 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.95 (s, 1H), 8.24 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.58 (dd, *J* = 3.7, 0.6 Hz, 1H), 6.85 – 6.84 (m, 1H).

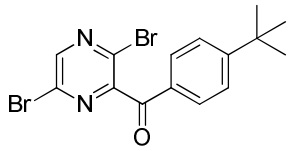
^{13}C-NMR (100 MHz, DMSO-d_6) δ: (ppm) 176.4, 151.0, 150.3, 149.6, 149.4, 138.1, 135.2, 125.6, 113.6.

MS (70 eV, EI) *m/z* (%): 333 (11), 331 (25) [M^+], 329 (12), 305 (12), 303 (26), 301 (13), 96 (13), 95 (54), 94 (100), 43 (65).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3125, 3069, 1648, 1558, 1500, 1460, 1403, 1376, 1361, 1282, 1238, 1167, 1153, 1135, 1081, 1058, 1032, 964, 918, 904, 880, 801, 773, 743, 657.

HRMS (EI) for **$C_9H_4Br_2N_2O_2$** (329.8640): 329.8587.

Synthesis of (4-(tert-butyl)phenyl)(3,6-dibromopyrazin-2-yl)methanone (15h)



According to **TP 1**, the metalation of 2,5-dibromopyrazine (**13b**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-(*tert*-butyl)benzoyl chloride (0.31 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **15h** (567 mg, 71%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (s, 1H), 7.84 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.61 (dt, *J* = 8.8, 2.0 Hz, 2H), 1.31 (s, 9H).

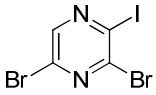
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 189.7, 158.7, 152.1, 149.0, 138.4, 134.9, 131.1, 130.3, 126.2, 35.2, 30.6.

MS (70 eV, EI) *m/z* (%): 399 (19), 397 (39), 395 (20) [M^+], 384 (45), 382 (95), 380 (45), 264 (20), 236 (27), 162 (90), 161 (100), 146 (32), 118(48), 115 (26), 91 (30), 77 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 2903, 2867, 1670, 1602, 1565, 1462, 1410, 1365, 1313, 1250, 1171, 1134, 1107, 1048, 952, 907, 849, 817, 775, 723, 705, 652.

HRMS (EI) for **$C_{15}H_{14}Br_2N_2O$** (395.9473): 395.9462.

Synthesis of 3,5-dibromo-2-iodopyrazine (15i)



According to **TP 1**, the metalation of 2,6-dibromopyrazine (**13c**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to 0 °C, then a solution of I_2 (761 mg, 3 mmol) in THF (6 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **15i** (604 mg, 83%) as a colorless solid.

m.p.: 115.6 – 117.6 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.68 (s, 1H).

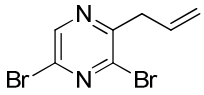
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 147.1, 145.3, 136.7, 123.9.

MS (70 eV, EI) *m/z* (%): 365 (41), 363 (100), 361 (41) [M^+], 238 (45), 236 (87), 234 (46), 184 (16), 177 (13), 129 (17), 126 (29), 77 (13), 71 (11), 57 (18), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1782, 1496, 1477, 1374, 1344, 1294, 1261, 1255, 1192, 1162, 1136, 1120, 1103, 1022, 1010, 893, 803, 734.

HRMS (EI) for **$C_4HBr_2IN_2$** (361.7551): 361.7563.

Synthesis of 2-allyl-3,5-dibromopyrazine (15j)



According to **TP 1**, the metalation of 2,6-dibromopyrazine (**13c**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and allylbromide (0.21 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **15i** (499 mg, 90%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.82 (s, 1H), 6.03 – 5.93 (m, 1H), 5.15 – 5.12 (m, 1H), 5.13 (dq, *J* = 28.0, 1.6 Hz, 1H), 3.65 (dt, *J* = 6.43, 1.56 Hz, 2H).

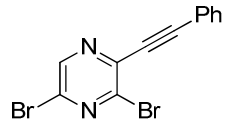
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 154.1, 145.9, 145.2, 139.2, 135.4, 132.9, 117.9.

MS (70 eV, EI) *m/z* (%): 278 (52), 277 (100), 275 (24) [M^+], 274 (55), 251 (13), 198 (10), 118 (20), 91 (10), 90 (14), 57 (16), 43 (14), 40 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1638, 1525, 1501, 1428, 1407, 1367, 1328, 1309, 1262, 1246, 1210, 1174, 1142, 1123, 1082, 1047, 989, 919, 898, 858, 849, 782, 711.

HRMS (EI) for **$C_7H_6Br_2N_2$** (275.8898): 275.8872.

Synthesis of 3,5-dibromo-2-(phenylethynyl)pyrazine (15k)



According to **TP 1**, the metalation of 2,6-dibromopyrazine (**13c**; 476 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and (bromoethynyl)benzene[216] (434 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **15k** (502 mg, 74%) as an off white solid.

m.p.: 128.7 – 130.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.59 (s, 1H), 7.62 – 7.66 (m, 2H), 7.46 – 7.36 (m, 3H).

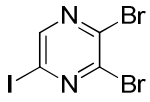
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 145.0, 141.3, 140.0, 136.1, 132.2, 130.1, 128.6, 121.1, 98.5, 85.1.

MS (70 eV, EI) *m/z* (%): 335 (1) [M^+], 88 (5), 73 (5), 70 (10), 61 (14), 60 (5), 45 (13), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2222, 1568, 1486, 1440, 1415, 1330, 1270, 1192, 1169, 1158, 1119, 1069, 1055, 1020, 997, 916, 897, 871, 775, 759, 689, 653.

HRMS (EI) for **$C_{12}H_6Br_2N_2$** (335.8898): 335.88925.

Synthesis of 2,3-dibromo-5-iodopyrazine (15l)



According to **TP 1**, the metalation of 2,3-dibromopyrazine (**13d**; 476 mg, 2.0 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to 0 °C, then a solution of iodine (761 mg, 3 mmol) in THF (6 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **15l** (514 mg, 71%) as a colorless solid.

[216] J. P. Marino, H. N. Nguyen, *J. Org. Chem.* **2002**, *67*, 6841

m.p.: 117.5 – 119.9 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.72 (s, 1H).

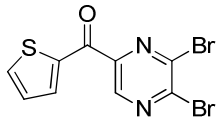
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 146.8, 146.2, 137.0, 122.9.

MS (70 eV, EI) *m/z* (%): 365 (3), 363 (1) [M^+], 321 (24), 319 (73), 317 (68), 194 (25), 190 (100), 165 (25), 163 (19), 69 (12), 57 (49), 56 (18), 55 (17), 44 (26), 43 (16), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1496, 1477, 1374, 1345, 1292, 1263, 1195, 1172, 1137, 1113, 1093, 1029, 1015, 894, 810, 800, 737.

HRMS (EI) for **$C_4HBr_2IN_2$** (363.7766): 363.7538.

Synthesis of (5,6-dibromopyrazin-2-yl)(thiophen-2-yl)methanone (15m)



According to **TP 1**, the metalation of 2,3-dibromopyrazine (**13d**; 476 mg, 2.0 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (0.26 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **15m** (527 mg, 76%) as an off white solid.

m.p.: 144.5 – 146.9 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (s, 1H), 8.26 (dd, *J* = 3.9, 1.3 Hz, 1H), 8.22 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.34 (dd, *J* = 4.9, 3.9 Hz, 1H).

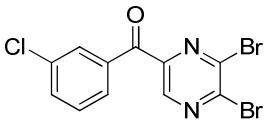
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 180.3, 146.2, 146.0, 142.9, 140.6, 139.3, 138.4, 137.5, 128.8.

MS (70 eV, EI) *m/z* (%): 347 (18), 345 (9) [M^+], 319 (4), 111 (100), 83 (6), 57 (2), 56 (2), 33 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3111, 1636, 1601, 1530, 1507, 1500, 1407, 1356, 1313, 1264, 1227, 1215, 1187, 1158, 1141, 1071, 1048, 1042, 1028, 936, 930, 897, 864, 802, 775, 767, 739, 717.

HRMS (EI) for **$C_9H_4Br_2N_2OS$** (345.8411): 345.8409.

Synthesis of (3-chlorophenyl)(5,6-dibromopyrazin-2-yl)methanone (15n)



According to **TP 1**, the metalation of 2,3-dibromopyrazine (**13d**; 476 mg, 2.0 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-chlorobenzoyl chloride (0.27 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **15n** (424 mg, 56%) as a colorless solid.

m.p.: 155.9 – 157.2 °C.

^{1}H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 8.94 (s, 1H), 8.09 (t, *J* = 1.8 Hz, 1H), 8.02 – 7.97 (m, 1H), 7.64 – 7.59 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H).

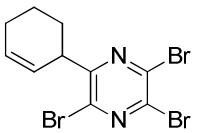
^{13}C-NMR (75 MHz, DMSO-d$_6$) δ (ppm): 188.2, 146.8, 143.3, 143.2, 141.4, 136.4, 134.8, 133.9, 130.7, 129.8, 129.0.

MS (70 eV, EI) *m/z* (%): 373 (1) [M^+], 138 (12), 111 (5), 88 (5), 73 (5), 70 (10), 61 (14), 45 (11), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3085, 1720, 1667, 1587, 1563, 1528, 1496, 1469, 1418, 1395, 1320, 1259, 1190, 1170, 1160, 1145, 1090, 1074, 1038, 1028, 997, 970, 961, 937, 881, 829, 810, 769, 746, 727, 670, 657.

HRMS (EI) for **$C_{11}H_5Br_2ClN_2O$** (373.8457): 373.8438.

Synthesis of 2,3,5-tribromo-6-(cyclohex-2-en-1-yl)pyrazine (15o)



According to **TP 1**, the metalation of 2,3,5-tribromopyrazine (**13e**; 634 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (463 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl

/ NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **15o** (437 mg, 55%) as an off white solid.

m.p.: 70.9 – 72.8 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 5.95 – 5.78 (m, 1H), 5.61 (dd, *J* = 10.0, 1.3 Hz, 1H), 3.83 (dt, *J* = 5.4, 2.7 Hz, 1H), 2.11 – 1.94 (m, 3H), 1.81 (td, *J* = 10.2, 5.1 Hz, 1H), 1.69 – 1.52 (m, 2H).

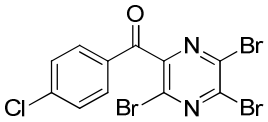
^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 158.6, 140.2, 137.7, 137.0, 128.8, 126.3, 40.1, 27.3, 24.0, 20.7.

MS (70 eV, EI) *m/z* (%): 399 (16), 397 (42), 395 (47), 393 (19) [M^+], 370 (16), 368 (46), 366 (50), 364 (15), 356 (15), 354 (16), 343 (36), 341 (39), 331 (45), 329 (41), 318 (51), 316 (100), 314 (53), 288 (16), 81 (16), 79 (22), 77 (28), 67 (93), 57 (16), 53 (19), 43 (31), 41 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3023, 2945, 2897, 2830, 1683, 1493, 1448, 1429, 1355, 1313, 1255, 1185, 1174, 1142, 1130, 1080, 1055, 1015, 931, 897, 863, 810, 720.

HRMS (EI) for **$C_{10}H_9Br_3N_2$** (393.8316): 393.8311.

Synthesis of (4-chlorophenyl)(3,5,6-tribromopyrazin-2-yl)methanone (15p)



According to **TP 1**, the metalation of 2,3,5-tribromopyrazine (**13e**; 634 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (0.27 mL, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **15p** (598 mg, 66%) as a yellowish solid.

m.p.: 156.9 – 159.8 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 8.00 (dt, *J* = 9.0, 2.3 Hz, 2H), 7.68 (dt, *J* = 9.0, 2.3 Hz, 2H).

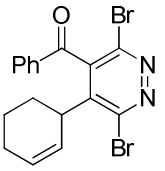
^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 188.9, 148.9, 143.0, 141.0, 140.5, 132.9, 132.5, 132.2, 129.4.

MS (70 eV, EI) *m/z* (%): 452 (1) [M^+], 139 (100), 111 (19), 75 (9), 70 (5), 61 (8), 45 (7), 43 (60).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2921, 2852, 1678, 1585, 1571, 1504, 1486, 1404, 1355, 1279, 1240, 1180, 1165, 1140, 1090, 1069, 1012, 956, 843, 823, 768, 752, 729, 685, 667.

HRMS (EI) for **$C_{11}H_4Br_3ClN_2O$** (451.7562): 451.7569.

Synthesis of [3,6-dibromo-5-(cyclohex-2-en-1-yl)pyridazin-4-yl](phenyl)methanone (16a)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**; 342 mg, 1.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.05 mL, 0.05 mmol) and 3-bromocyclohexene (193 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **16a** (335 mg, 72%) as a colorless solid.

m.p.: 56.9 – 59.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.87 – 7.58 (m, 3H), 7.55 – 7.45 (m, 2H), 5.59 – 5.43 (m, 1H), 5.17 – 5.02 (m, 1H), 3.92 – 3.66 (m, 1H), 1.99 – 1.42 (m, 6H).

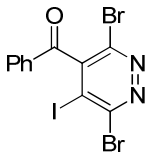
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 190.9, 144.5, 144.3, 135.9, 135.0, 134.5, 131.3, 129.7, 129.2, 129.0, 124.7, 41.6, 24.5, 24.0, 21.7.

MS (70 eV, EI) *m/z* (%): 422 (13), 420 (8) [M^+], 165 (12), 127 (12), 125 (11), 113 (17), 111 (26), 109 (14), 105 (55), 99 (22), 97 (36), 95 (19), 91 (12), 85 (59), 83 (36), 81 (23), 79 (14), 77 (61), 71 (76), 69 (40), 61 (16), 57 (100), 55 (47), 43 (63), 41 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3024, 2925, 2860, 2829, 1671, 1594, 1581, 1495, 1448, 1324, 1227, 1221, 1177, 1141, 1073, 1037, 1000, 955, 910, 804, 783, 770, 759, 706, 684, 661.

HRMS (EI) for **$C_{17}H_{14}Br_2N_2O$** (419.9473): 419.9480.

Synthesis of (3,6-dibromo-5-iodopyridazin-4-yl)(phenyl)methanone (16b)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**; 342 mg, 1.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, then a solution of I_2 (381 mg, 1.5 mmol) in THF (3 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **16b** (314 mg, 67%) as a colorless solid.

m.p.: 230.9 – 232.1 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.98 (d, *J* = 7.2 Hz, 2H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 2H).

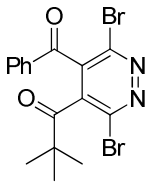
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 191.2, 156.0, 147.8, 140.1, 135.7, 131.6, 130.0, 129.7, 110.8.

MS (70 eV, EI) *m/z* (%): 467 (12), 465 (5) [M^+], 105 (100), 77 (46), 50 (5), 42 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1667, 1590, 1580, 1494, 1456, 1449, 1318, 1311, 1297, 1227, 1180, 1169, 1161, 1096, 1054, 1025, 998, 955, 938, 809, 795, 761, 735, 705, 680, 658.

HRMS (EI) for **$C_{11}H_5Br_2IN_2O$** (465.7813): 465.7802.

Synthesis of 1-(5-benzoyl-3,6-dibromopyridazin-4-yl)-2,2-dimethylpropan-1-one (16c)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**; 342 mg, 1.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and pivaloyl chloride (145 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude

product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **16c** (244 mg, 57%) as a colorless solid.

m.p.: 116.8 – 119.9 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 7.90 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.80 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.59 (dd, *J* = 8.3, 7.5 Hz, 2H), 1.12 (s, 9H).

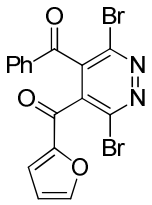
^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 207.6, 190.4, 143.4, 142.2, 140.7, 137.0, 136.1, 133.6, 130.4, 129.5, 44.0, 26.9.

MS (70 eV, EI) *m/z* (%): 423 (1) [M$^+$], 376 (43), 371 (50), 369 (100), 2351 (25), 233 (23), 209 (10), 77 (40), 56 (94), 43 (11), 41 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2923, 1795, 1691, 1667, 1592, 1478, 1463, 1447, 1396, 1368, 1361, 1320, 1270, 1232, 1165, 1146, 1049, 1025, 995, 955, 841, 821, 800, 774, 756, 705, 683, 669.

HRMS (EI) for **$C_{16}H_{14}Br_2N_2O_2$** (423.9422): 423.9427.

Synthesis of (5-benzoyl-3,6-dibromopyridazin-4-yl)(furan-2-yl)methanone (16d)



According to **TP 1**, the metalation of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**; 342 mg, 1.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and 2-furoyl chloride (156 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **16d** (271 mg, 62%) as an off white solid.

m.p.: 173.3 – 174.1 °C

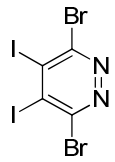
^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 8.16 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.88 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.76 – 7.71 (m, 2H), 7.56 – 7.52 (m, 2H), 6.79 (dd, *J* = 3.8, 1.7 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 189.3, 175.0, 151.6, 149.4, 144.0, 143.6, 139.2, 137.6, 135.8, 135.8, 133.5, 130.2, 129.3, 114.0.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1671, 1646, 1595, 1561, 1505, 1449, 1396, 1385, 1330, 1318, 1304, 1238, 1142, 1082, 1047, 1037, 1019, 1000, 983, 903, 883, 822, 805, 784, 772, 726, 705, 682, 668.

HRMS (ESI) for **$C_{16}H_9Br_2N_2O_3^+$** (434.8902): 434.8974.

Synthesis of 3,6-dibromo-4,5-diiodopyridazine (16e)



According to **TP 1**, the metalation of 3,6-dibromo-4-iodopyridazine (**15b**; 364 mg, 1.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, then a solution of I_2 (381 mg, 1.5 mmol) in THF (3 mL) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a sat. aq $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **16e** (361 mg, 74%) as a yellowish solid.

m.p.: 143.3 – 145.7 °C

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): .

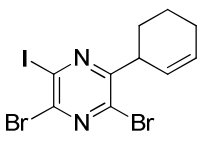
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 152.0, 127.1.

MS (70 eV, EI) *m/z* (%): 492 (49), 489 (100) [M^+], 487 (50), 336 (22), 334 (46), 332 (24), 255 (11), 253 (39), 209 (32), 207 (68), 205 (35), 176 (14), 128 (15), 126 (56), 57 (10), 42 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2925, 2870, 1661, 1503, 1476, 1427, 1402, 1321, 1272, 1261, 1217, 1139, 1118, 1043, 984, 919, 890, 886, 859, 783, 723, 701, 654.

HRMS (EI) for **$C_4{}^{79}Br^{81}Br^{127}I_2N_2$** (489.6518): 489.6492.

Synthesis of 2,6-dibromo-3-(cyclohex-2-en-1-yl)-5-iodopyrazine (16f)



According to **TP 1**, the metalation of 3,5-dibromo-2-iodopyrazine (**15i**; 364 mg, 1.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.05 mL, 0.05 mmol) and 3-bromocyclohexene (193 mg, 1.2 mmol) were added. The mixture was allowed to warm to 25 °C and stirred for 5 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl / NH_3 (25% in H_2O) = 9:1 (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 19:1) to give **16f** (312 mg, 70%) as a colorless solid.

m.p.: 64.4 – 65.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 5.97 – 5.88 (m, 1H), 5.67 – 5.60 (m, 1H), 3.94 – 3.85 (m, 1H), 2.16 – 2.03 (m, 3H), 1.95 – 1.84 (m, 1H), 1.80 – 1.65 (m, 2H).

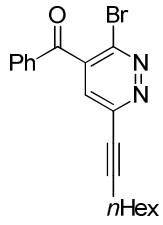
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.6, 143.6, 138.0, 129.6, 125.9, 119.9, 40.7, 27.8, 24.5, 21.2.

MS (70 eV, EI) *m/z* (%): 443 (7) [M^+], 377 (7), 177 (10), 70 (13), 67 (13), 61 (18), 57 (14), 45 (16), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3018, 2947, 2886, 2829, 1449, 1428, 1352, 1336, 1312, 1287, 1252, 1240, 1195, 1174, 1138, 1127, 1079, 1051, 1040, 988, 930, 896, 859, 804, 723.

HRMS (EI) for **$C_{10}H_9Br_2IN_2$** (441.8177): 441.8171.

Synthesis of [3-bromo-6-(oct-1-yn-1-yl)pyridazin-4-yl](phenyl)methanone (17a)



According to **TP 2** (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**; 342 mg, 1.0 mmol, in 1 mL THF) was reacted with 1-octyne (0.18 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), CuI (19 mg, 10 mmol) and NEt_3 (0.55 mL, 4 mmol). After 3 h at 50 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **17a** (298 mg, 80%) as a yellowish solid.

m.p.: 44.4 – 45.8 °C

^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 8.06 (s, 1H), 7.87 – 7.83 (m, 2H), 7.77 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.61 – 7.56 (m, 2H), 2.54 (t, *J* = 6.9 Hz, 2H), 1.63 – 1.53 (m, 2H), 1.47 – 1.37 (m, 2H), 1.32 – 1.25 (m, 4H), 0.89 – 0.83 (m, 3H).

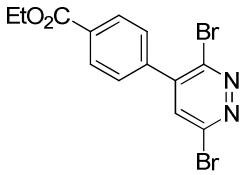
^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 190.6, 147.4, 141.3, 139.6, 135.2, 133.9, 130.1, 129.3, 129.2, 98.4, 76.8, 30.7, 27.9, 27.4, 21.9, 18.6, 13.9.

MS (70 eV, EI) *m/z* (%): 370 (6) [M^+], 314 (18), 312 (19), 301 (13), 299 (12), 291 (9), 104 (100), 77 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3053, 2931, 2857, 2229, 1667, 1595, 1579, 1450, 1378, 1338, 1247, 1183, 1157, 1078, 999, 908, 858, 793, 757, 711, 701, 684, 669.

HRMS (EI) for **$C_{19}H_{19}BrN_2O$** (370.0681): 370.0681.

Synthesis of ethyl 4-(3,6-dibromopyridazin-4-yl)benzoate (17b)



According to **TP 2** 3,6-dibromo-4-iodopyridazine (**15b**; 364 mg, 1.0 mmol, in 1 mL THF) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide[217] (0.8 mmol), $Pd(dba)_2$ (11 mg, 0.02 mmol) and tfp (9 mg, 0.04 mmol). After 3 h at 25 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **17b** (173 mg, 56%) as a colorless solid.

m.p.: 135.7 – 136.8 °C

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.18 (s, 1H), 8.08 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.72 (dt, *J* = 8.5, 1.8 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

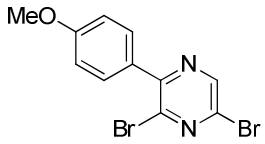
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 165.1, 148.2, 147.7, 143.6, 139.0, 133.2, 130.9, 129.6, 129.1, 61.1, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2987, 1706, 1609, 1551, 1472, 1447, 1409, 1344, 1321, 1275, 1234, 1184, 1127, 1113, 1104, 1039, 1026, 1016, 1012, 903, 863, 823, 775, 748, 713, 703.

HRMS (ESI) for **$C_{13}H_{11}Br_2N_2O_2^+$** (384.9109): 384.9181.

[217] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

Synthesis of 3,5-dibromo-2-(4-methoxyphenyl)pyrazine (17c)



According to **TP 2** 3,5-dibromo-2-iodopyrazine (**15i**; 364 mg, 1.0 mmol, in 1 mL THF) was reacted with 4-methoxyphenylzinc iodide[217] (0.8 mmol), $Pd(dba)_2$ (11 mg, 0.02 mmol) and tfp (9 mg, 0.04 mmol). After 3 h at 25 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **17c** (136 mg, 49%) as a colorless solid.

m.p.: 173.3 – 174.1 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.63 (s, 1H), 7.74 (dt, *J* = 9.4, 2.8 Hz, 2H), 7.00 (dt, *J* = 9.4, 2.8 Hz, 2H), 3.87 (s, 3H).

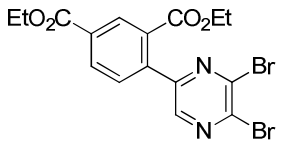
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.9, 153.3, 144.7, 137.6, 135.3, 131.0, 128.2, 113.7, 55.4.

MS (70 eV, EI) *m/z* (%): 345 (30), 343 (72), 341 (30) [M^+], 264 (38), 177 (14), 161 (12), 133 (19), 83 (10), 71 (14), 70 (14), 69 (10), 61 (18), 57 (23), 55 (12), 45 (12), 43 (100), 41 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1671, 1646, 1595, 1561, 1505, 1449, 1396, 1385, 1330, 1318, 1304, 1238, 1142, 1082, 1047, 1037, 1019, 1000, 983, 903, 883, 822, 805, 784, 772, 726, 705, 682, 668.

HRMS (EI) for **$C_{11}H_8Br_2N_2O$** (341.9003): 341.8998.

Synthesis of diethyl 4-(5,6-dibromopyrazin-2-yl)isophthalate (17d)



According to **TP 2** 2,3-dibromo-5-iodopyrazine (**15l**; 364 mg, 1.0 mmol, in 1 mL THF) was reacted with 2,4-bis(ethoxycarbonyl)phenylzinc bromide[217] (0.8 mmol), $Pd(dba)_2$ (11 mg, 0.02 mmol) and tfp (9 mg, 0.04 mmol). After 6 h at 25 °C, the reaction mixture was quenched with sat. aq Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **17d** (290 mg, 79%) as a colorless solid.

m.p.: 135.3 – 137.1 °C

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (s, 1H), 8.33 (dd, *J* = 1.8, 0.4 Hz, 1H), 8.25 (dt, *J* = 8.1, 1.9 Hz, 1H), 7.92 (dd, *J* = 8.1, 0.5 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

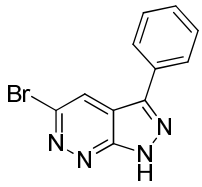
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 166.7, 164.9, 151.6, 142.8, 141.6, 141.2, 138.7, 132.5, 132.3, 131.7, 131.4, 130.6, 61.9, 61.9, 14.5, 14.2.

MS (70 eV, EI) *m/z* (%): 455 (2) [M^+], 430 (7), 428 (12), 426 (7), 412 (10), 70 (12), 61 (16), 45 (15), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2903, 1709, 1569, 1537, 1483, 1445, 1391, 1302, 1277, 1261, 1232, 1167, 1147, 1123, 1109, 1092, 1044, 1032, 1016, 926, 853, 827, 791, 771, 754, 726, 702, 670.

HRMS (EI) for **$C_{16}H_{14}Br_2N_2O_4$** (455.9320): 455.9305.

Synthesis of 5-bromo-3-phenyl-1*H*-pyrazolo[3,4-*c*]pyridazine (120a)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (3,6-dibromopyridazin-4-yl)(phenyl)methanone (**15a**; 342 mg, 1.0 mmol) in EtOH (10 mL). $N_2H_4 \cdot H_2O$ (0.3 mL, 3 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C, CH_2Cl_2 (100 mL) was added and the organic layer was washed with brine (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **121a** as a yellow solid (205 mg, 75%).

m.p.: 258.3 – 259.4 °C

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.84 (d, *J* = 0.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.45 (td, *J* = 7.3, 1.2 Hz, 1H).

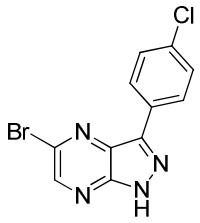
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 155.4, 142.3, 137.9, 131.2, 129.1, 129.0, 126.6, 123.7, 116.1.

MS (70 eV, EI) *m/z* (%): 275 (98), 273 (100) [M^+], 140 (45), 104 (10), 77 (14), 64 (15), 43 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3091, 2994, 2919, 1583, 1509, 1456, 1432, 1388, 1287, 1253, 1187, 1139, 1064, 1002, 926, 909, 880, 830, 796, 756, 742, 688, 666.

HRMS (EI) for **$C_{11}H_7BrN_4$** (273.9854): 273.9722.

Synthesis of 5-bromo-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (122b)



A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (4-chlorophenyl)(3,6-dibromopyrazin-2-yl)methanone (**15e**; 376 mg, 1.0 mmol) in EtOH (10 mL). $N_2H_4 \cdot H_2O$ (0.3 mL, 3 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C, CH_2Cl_2 (100 mL) was added and the organic layer was washed with brine (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH giving **123b** as a yellow solid (260 mg, 84%).

m.p.: 246.3 – 248.5 °C

^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 8.76 (s, 1H), 8.30 (dt, *J* = 8.9, 2.5 Hz, 2H), 7.60 (dt, *J* = 8.9, 2.6 Hz, 2H).

^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 145.6, 144.6, 140.2, 135.0, 133.8, 131.2, 130.6, 129.5, 128.0.

MS (70 eV, EI) *m/z* (%): 311 (5), 309 (23), 307 (15) [M^+], 58 (33), 43 (100), 42 (8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3177, 3138, 3015, 1812, 1583, 1570, 1513, 1463, 1440, 1365, 1333, 1302, 1287, 1210, 1185, 1111, 1085, 1016, 996, 936, 907, 837, 829, 790, 775, 756, 699, 664.

HRMS (EI) for **$C_{11}H_6BrClN_4$** (307.9464): 307.9458.

3 REGIOSELECTIVE ZINCATION OF INDAZOLES USING TMP_2Zn AND *NEGISHI* CROSS-COUPLING WITH ARYL AND HETEROARYL IODIDES

3.1 TYPICAL PROCEDURES

Typical procedure for the zincation of Indazoles with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (TP 3):

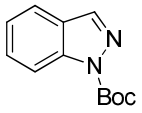
A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding indazole (2.0 mmol) in dry THF (2 mL) as well as 50 µL of tetradecane (internal standard for GC analysis). After setting the desired temperature (Table 1), the zinc base (1.1 mmol) was added dropwise and and the reaction mixture was stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure for the SEM-protection of Indazoles (TP 4):

To an ice-bath cooled mixture of the indazole **23** (20 mmol)**,** tetra-butylammonium bromide (0.01 equiv), aq potassium hydroxide (50 percent, 15 mL), dichloromethane (20 mL) and 2-(trimethylsilyl)ethoxymethyl chloride (22 mmol, 1.1 equiv) was added dropwise. The mixture was stirred for 3 h, poured into water (50 mL) and extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with water (50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. In order to separate the (N-1 and N-2)-SEM-indazoles the residual oil was purified by flash column chromatography on silica eluting with ether/pentane to give the title compound.

3.2 PREPARATION OF STARTING MATERIALS

Synthesis of *tert*-butyl 1*H*-indazole-1-carboxylate (23a):



To a stirred solution of 1*H*-indazole (1.18 g, 10 mmol), MeCN (20 mL) and DMAP (25 mg, 0.2 mmol) was added Boc_2O (2.6 g, 12 mmol). Bubbling was then observed. After 3 h, the solvent was evaporated *in vacuo* and the remaining residue was partitioned between diethyl ether (100 mL) and H_2O (50 mL). The aq phase was extracted with diethyl ether (3 × 75 mL). The organic layer was washed with sat. aq $NaHCO_3$ (75 mL), brine (75 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **23** (2.07 g, 95%) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.40 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.62–7.55 (m, 1H), 7.39–7.33 (m, 1H), 1.63 (s, 9H).

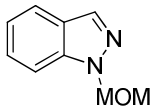
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 148.6, 139.9, 138.9, 129.0, 125.6, 123.7, 121.6, 114.0, 84.4, 27.7.

MS (70 eV, EI) *m/z* (%): 218 (3) [M^+], 119 (10), 118 (100), 97 (12), 91 (20), 85 (20), 83 (13), 71 (27), 69 (12), 57 (49), 56 (18), 55 (17), 44 (26), 43 (16), 41 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2934, 1755, 1732, 1613, 1504, 1478, 1469, 1458, 1429, 1381, 1370, 1343, 1317, 1289, 1281, 1246, 1200, 1157, 1142, 1112, 1040, 1028, 1010, 966, 946, 908, 874, 842, 765, 746, 642, 621.

HRMS (EI) for **$C_{12}H_{14}N_2O_2$** (218.1055): 218.1035.

Synthesis of 1-(methoxymethyl)-1*H*-indazole (23b):



1*H*-indazole (2.36 g, 20 mmol) was dissolved in 50 mL of *N*,*N*-dimethylformamide, and sodium hydride (60 percent in oil, 1.0 g, 25 mmol) was added under ice-cooling, followed by stirring for 30 min. To the reaction mixture was added chloromethyl methyl ether (1.76 g, 22 mmol) followed by stirring at room temperature for 30 min. To the reaction mixture was added water (50 mL) and the mixture was extracted with ethyl acetate (3 × 75 mL). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was purified and separated by silica gel column chromatography (pentane:diethyl ether = 10:1), to give **23b** (2.60 g, 80%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 5.71 (s, 2H), 3.30 (s, 3H).

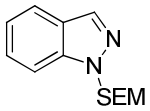
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 139.8, 134.2, 126.9, 124.8, 121.4, 121.1, 109.5, 79.4, 56.5.

MS (70 eV, EI) *m/z* (%):162 (47) [M^+], 132 (31), 131 (100), 104 (10), 103 (10), 77 (20), 45 (52), 43 (35).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 1617, 1500, 1466, 1423, 1369, 1316, 1216, 1173, 1132, 1103, 1071, 1006, 973, 906, 835, 740.

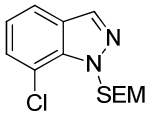
HRMS (EI) for **$C_9H_{10}N_2O$** (162.0793): 162.0791.

Synthesis of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (23c):



This compound was prepared from commercially available 1*H*-indazole and 2-(trimethylsilyl)ethoxymethyl chloride according to the procedure reported by Luo *et al*.[218]

Synthesis of 7-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (23d)



Prepared according to **TP 4** from 7-chloro-1*H*-indazole[219]. Purification by silica gel column chromatography (pentane:diethyl ether = 10:1) gave **23d** (3.51 g, 62%) as orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 5.72 (s, 2H), 3.59 – 3.49 (m, 2H), 0.91 – 0.82 (m, 2H), -0.08 (s, 9H).

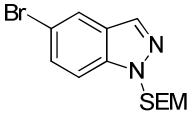
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 140.7, 132.6, 127.4, 126.6, 124.1, 121.0, 108.3, 78.0, 66.6, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 282 (1) [M^+], 209 (13), 166 (15), 73 (22), 70 (11), 61 (18), 15 (16), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1614, 1496, 1446, 1365, 1303, 1248, 1169, 1118, 1078, 927, 832, 775, 757, 732, 693.

HRMS (EI) for **$C_{13}H_{19}ClN_2OSi$** (282.0955): 282.0950.

Synthesis of 5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (23e)



[218] G. Luo, L. Chen, G. Dubowchik, *J. Org. Chem.* **2006**, *71*, 5392.
[219] C. Rüchardt, V. Hassmann, *Liebigs Ann. Chem.* **1980**, *6*, 908.

Prepared according to **TP 4** from 5-bromo-1*H*-indazole.[220] Purification by silica gel column chromatography (pentane:diethyl ether = 10:1) gave **23e** (5.30 g, 81%) as orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.94 (s, 1H), 7.87 (s, 1H), 7.51 – 7.43 (m, 2H), 5.71 (s, 2H), 3.56 – 3.47 (m, 2H), 0.91 – 0.82 (m, 2H), -0.08 (s, 9H).

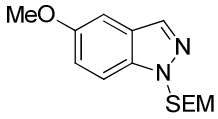
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 138.4, 133.1, 129.8, 126.3, 123.5, 114.5, 111.2, 77.9, 66.5, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 328 (1) [M^+], 211 (7), 87 (5), 73 (13), 70 (11), 61 (18), 45 (15), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2895, 1485, 1440, 1419, 1370, 1300, 1248, 1189, 1076, 1050, 989, 938, 912, 857, 832, 786, 760, 693, 664.

HRMS (EI) for **$C_{13}H_{19}BrN_2OSi$** (326.0450): 326.0441.

Synthesis of 5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (23f)



Prepared according to **TP 4** from 5-methoxy-1*H*-indazole.[221] Purification by silica gel column chromatography (pentane:diethyl ether = 10:1) gave **23f** (4.40 g, 79%) as orange solid.

m.p.: 56.8 – 58.5 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.99 (s, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.07 (dd, *J* = 9.0, 2.3 Hz, 1H), 5.67 (s, 2H), 3.78 (s, 3H), 3.50 – 3.44 (m, 2H), 0.80 – 0.74 (m, 2H), -0.14 (s, 9H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 154.4, 135.4, 133.2, 124.6, 118.2, 110.9, 100.2, 76.8, 65.4, 55.3, 17.1, -1.4.

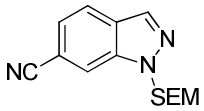
MS (70 eV, EI) *m/z* (%): 278 (23) [M^+], 233 (14), 220 (32), 178 (18), 162 (32), 148 (12), 121 (34), 73 (100), 61 (13), 45 (11), 43 (78).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 1738, 1600, 1507, 1451, 1374, 1305, 1225, 1153, 1100, 1075, 1030, 916, 832, 768, 719.

[220] M. Boulouard, P. Schumann-Bard, S. Butt-Gueulle, E. Lohou, S. Stiebing, V. Collot, S. Rault, *Bioorg. Med. Chem. Lett.* **2007,** *17*, 3177
[221] S. K. V. Vernekar, H. Y. Hallaq, G. Clarkson, M. Lochner, A. J. Thompson, L. Silvestr, S. C. R. Lummis, *J. Med. Chem.* **2010**, *53*, 2324.

HRMS (EI) for **$C_{14}H_{22}N_2O_2Si$** (278.1451): 278.1452.

Synthesis of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-6-carbonitrile (23g)



Prepared according to **TP 4** from 1*H*-indazole-6-carbonitrile.[222] Purification by silica gel column chromatography (pentane:diethyl ether = 4:1) gave **23g** (3.72 g, 68%) as orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.13 (s, 1H), 8.10 (s, 1H), 7.68 – 7.58 (m, 2H), 5.75 (s, 2H), 3.57 – 3.50 (m, 2H), 0.91 – 0.83 (m, 2H), -0.09 (s, 9H).

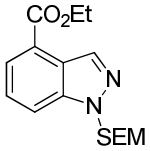
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 140.5, 134.6, 128.9, 127.4, 124.4, 119.4, 111.0, 105.0, 78.0, 66.8, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 273 (1) [M^+], 200 (11), 157 (13), 156 (16), 73 (17), 70 (13), 61 (20), 45 (16), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2926, 2902, 2218, 1620, 1503, 1449, 1425, 1386, 1371, 1356, 1296, 1249, 1175, 1140, 1092, 1076, 990, 914, 817, 752, 696.

HRMS (EI) for **$C_{14}H_{19}N_3OSi$** (273.1297): 273.1294.

Synthesis of ethyl 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-4-carboxylate (23h)



1*H*-indazole-4-carboxylate[223] (2.362 g, 20 mmol) was dissolved in 50 mL of *N*,*N*-dimethylformamide, and sodium hydride (60 percent in oil, 1.0 g, 25 mmol) was added under ice-cooling, followed by stirring for 30 min. To the reaction mixture was added chloromethyl methyl ether (1.76 g, 22 mmol) followed by stirring at room temperature for 30 min. To the reaction mixture was added water (50 mL) and the mixture was extracted with ethyl acetate (3 × 75 mL). The organic layer was washed

[222] MERCK and CO., INC., *Patent: WO2006/86255 A2*, **2006**.
[223] D. G. Batt, J. J. Petraitis, G. C. Houghton, D. P. Modi, G. A. Cain, M. H. Corjay, S. A. Mousa, P. J. Bouchard, M. S. Forsythe, P. P. Harlow, F. A. Barbera, S. M. Spitz, R. R. Wexler, P. K. Jadhav, *J. Med. Chem.* **2000**, *43*, 41.

with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The residue was purified and separated by silica gel column chromatography (pentane:diethyl ether = 4:1), to give **23h** (3.59 g, 56%) as yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.44 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.57 (dd, *J* = 8.3, 7.3 Hz, 1H), 5.82 (s, 2H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.54 – 3.45 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.85 – 0.72 (m, 2H), -0.14 (s, 9H).

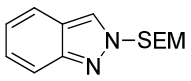
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 165.4, 140.1, 134.0, 126.1, 124.3, 122.3, 122.2, 115.4, 76.9, 65.7, 60.9, 17.1, 14.2, -1.4.

MS (70 eV, EI) *m/z* (%): 320 (1) [M^+], 204 (14), 203 (17), 190 (5), 145 (5), 88 (5), 75 (10), 73 (16), 70 (11), 61 (16), 45 (16), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2897, 1714, 1609, 1449, 1417, 1372, 1305, 1270, 1249, 1169, 1150, 1120, 1079, 1029, 964, 936, 856, 834, 752, 693.

HRMS (EI) for **$C_{16}H_{24}N_2O_3Si$** (320.1556): 320.1557.

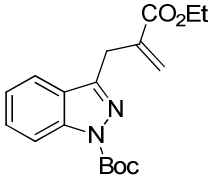
Synthesis 2-((2-(trimethylsilyl)ethoxy)methyl)-2*H*-indazole (23i):



This compound was prepared from commercially available 1*H*-indazole and 2-(Trimethylsilyl)ethoxymethyl chloride according to the procedure reported by Luo *et al*.[1]

3.3 ZINCATION OF INDAZOLES AND TRAPPING WITH ELECTROPHILES

Synthesis of *tert*-butyl 3-[2-(ethoxycarbonyl)prop-2-en-1-yl]-1*H*-indazole-1-carboxylate (25a):



According to **TP 3**, the metalation of *tert*-butyl 1*H*-indazole-1-carboxylate (**23a**; 436 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.1 mL, 0.1 mmol) and ethyl 2-(bromomethyl)acrylate (463 mg, 2.4 mmol) were added. The

mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **25a** (548 mg, 89%) as a yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.61 (d, *J* = 7.5 Hz, 1H), 7.54 (td, *J* = 7.8, 1.6 Hz, 1H), 7.33 – 7.25 (m, 2H), 6.32 (d, *J* = 1.6 Hz, 1H), 5.87 (s, 1H), 4.54 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.39 (s, 9), 1.21 (t, *J* = 7.2 Hz, 3H).

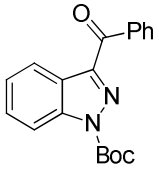
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 165.8, 153.2, 145.1, 135.8, 133.4, 133.1, 127.8, 127.0, 116.9, 113.2, 81.7, 60.9, 50.4, 28.1, 14.0.

MS (70 eV, EI) *m/z* (%): 257 (7), 231 (15), 230 (100), 229 (17), 202 (17), 185 (13), 184 (31), 183 (40), 157 (22), 156 (60), 155 (50), 144 (11), 131 (31), 129 (29), 118 (11), 103 (11), 102 (11), 57 (64), 56 (11), 55 (22), 44(17), 41 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2935, 1705, 1638, 1598, 1576, 1491, 1452, 1424, 1367, 1307, 1258, 1237, 1150, 1107, 1047, 1023, 956, 940, 856, 818, 762, 657, 646, 608.

HRMS (EI) for **$C_{18}H_{22}N_2O_4$** (330.1580): 330.1562.

Synthesis of *tert*-butyl 3-benzoyl-1*H*-indazole-1-carboxylate (25b):



According to **TP 3**, the metalation of *tert*-butyl 1*H*-indazole-1-carboxylate (**23a**, 436 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:2) to give **25b** (465 mg, 72%) as a colorless solid.

m.p.: 111.0 – 113.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.81 (d, *J* = 7.1 Hz, 2H), 7.75 (d, *J* = 9.1 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.51–7.42 (m, 3H), 1.23 (s, 9H).

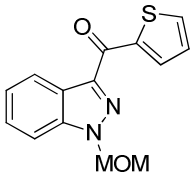
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 171.9, 151.9, 141.5, 136.2, 133.6, 133.3, 131.9, 130.2, 128.6, 128.3, 128.2, 116.2, 113.3, 84.7, 27.4.

MS (70 eV, EI) *m/z* (%): 223 (3), 222 (22), 144 (5), 119 (2), 106 (6), 105 (100), 78 (2), 77 (29), 57 (6), 56 (4), 55 (2), 51 (6), 50 (2), 44 (5), 41 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3110, 2982, 2927, 1736, 1663, 1578, 1544, 1471, 1447, 1370, 1358, 1324, 1308, 1236, 1207, 1178, 1155, 1150, 1136, 1114, 1086, 1026, 999, 978, 949, 898, 874, 849, 832, 815, 796, 770, 757, 741, 716, 689, 624, 616, 603.

HRMS (EI) for **$C_{19}H_{18}N_2O_3$** (322.1317): 322.1305.

Synthesis of [1-(methoxymethyl)-1*H*-indazol-3-yl](thiophen-2-yl)methanone (25c):



According to **TP 3**, the metalation of 1-(methoxymethyl)-1*H*-indazole (**23b,** 324 mg, 2.0 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and thiophene-2-carbonyl chloride (322 mg, 2.2 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25e** (532 mg, 76%) as a colorless solid.

m.p.: 87.9 – 89.3 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.54 (d, *J* = 3.1 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 4.5 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.30 (m, 1H), 5.93 (s, 2H), 3.31 (s, 3H).

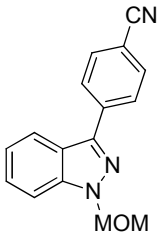
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 178.9, 141.9, 141.3, 140.6, 135.8, 135.4, 128.6, 127.7, 124.2, 123.5, 122.0, 111.0, 79.6, 56.5.

MS (70 eV, EI) *m/z* (%): 273 (15), 272 (100) [M^+], 244 (10), 243 (43), 145 (41), 129 (26), 111 (92), 103 (12), 45 (70), 44 (30), 43 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932, 1738, 1609, 1513, 1472, 1419, 1348, 1312, 1217, 1154, 1126, 1079, 1051, 1003, 916, 868, 812, 781, 753, 723, 718, 686.

HRMS (EI) for **$C_{14}H_{12}N_2O_2S$** (272.0619): 272.0613.

Synthesis of 4-[1-(methoxymethyl)-1*H*-indazol-3-yl]benzonitrile (25d):



According to **TP 3**, the metalation of 1-(methoxymethyl)-1*H*-indazole (**23b,** 324 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 8 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25d** (398 mg, 76%) as a colorless solid.

m.p.: 102.6 – 104.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 5.76 (s, 2H), 3.36 (s, 3H).

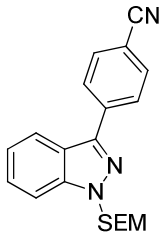
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 142.9, 141.4, 137.9, 132.6, 127.8, 127.2, 122.6, 122.3, 120.8, 118.9, 111.4, 110.2, 79.7, 56.7.

MS (70 eV, EI) *m/z* (%): 264 (7), 263 (42) [M^+], 233 (28), 232 (100), 205 (3), 190 (5), 129 (4), 102 (5), 77 (4), 45 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2940, 2226, 1738, 1608, 1520, 1489, 1372, 1317, 1234, 1142, 1090, 1016, 956, 911, 848, 768, 745, 666.

HRMS (EI) for **$C_{16}H_{13}N_3O$** (263.1059): 263.1051.

Synthesis of 4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazol-3-yl)benzonitrile (25e):



According to **TP 3**, the metalation of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23c,** 497 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 8 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **4e** (532 mg, 76%) as a colorless solid.

m.p.: 105.4 – 106.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.95 – 7.90 (m, 2H), 7.86 – 7.81 (m, 2H), 7.80 – 7.74 (m, 1H), 7.67 – 7.62 (m, 1H), 7.40 – 7.32 (m, 1H), 7.20 – 7.14 (m, 1H), 5.69 (s, 2H), 3.90 – 3.83 (m, 2H), 0.99 – 0.93 (m, 2H), 0.00 (s, 9H).

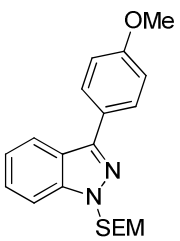
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 148.2, 134.5, 134.1, 132.7, 130.2, 127.8, 127.1, 123.5, 121.5, 119.9, 118.5, 112.2, 79.5, 67.9, 18.0, -1.4.

MS (70 eV, EI) *m/z* (%): 349 (5) [M^+], 306 (13), 304 (15), 291 (38), 290 (36), 277 (16), 276 (71), 234 (14), 233 (100), 232 (62), 219 (14), 148 (22), 138 (11), 73 (79).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3397, 3126, 3075, 2218, 1691, 1602, 1578, 1518, 1458, 1396, 1304, 1273, 1158, 1122, 1010, 933, 884, 853, 833, 754.

HRMS (EI) for **$C_{20}H_{23}N_3OSi$** (349.1610): 349.1601.

Synthesis of 3-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (25f):



According to **TP 3**, the metalation of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23c,** 497 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodoanisole (515 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25f** (575 mg, 81%) as a colorless solid.

m.p.: 85.6 – 87.3 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.67 – 7.63 (m, 3H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.10 – 7.04 (m, 1H), 5.65 (s, 2H), 3.84 (s, 3H), 3.73 – 3.65 (m, 2H), 0.88 – 0.80 (m, 2H), -0.09 (s, 9H).

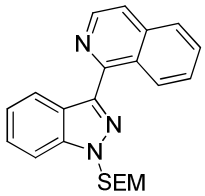
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 159.7, 147.4, 135.8, 130.8, 126.5, 121.9, 121.1, 120.6, 120.3, 117.5, 114.6, 78.7, 66.6, 55.3, 17.3, -1.4.

MS (70 eV, EI) *m/z* (%): 355 (10), 354 (47) [M^+], 311 (10), 309 (26), 297 (14), 296 (54), 295 (48), 282 (11), 281 (71), 239 (12), 238 (83), 237 (100), 224 (33), 223 (12), 209 (13), 152 (15), 148 (15), 140 (17), 75 (15), 61 (16), 43 (80).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052, 3006, 2935, 1739, 1609, 1504, 1472, 1361, 1270, 1248, 1177, 1085, 1015, 940, 860, 834, 795, 755, 732, 652.

HRMS (EI) for **$C_{20}H_{26}N_2O_2Si$** (354.1764): 354.1751.

Synthesis of 1-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazol-3-yl)isoquinoline (25g):



According to **TP 3**, the metalation of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23c,** 497 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 2-iodoisoquinoline (561 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25g** (464 mg, 76%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.10 (d, *J* = 8.6 Hz, 1H), 8.73 (d, *J* = 5.8 Hz, 1H), 8.36 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H) 7.76 – 7.56 (m, 4H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.36 – 7.27 (m, 1H), 5.92 (s, 2H), 3.76 – 3.68 (m, 2H), 1.01 – 0.92 (m, 2H), -0.04 (s, 9H).

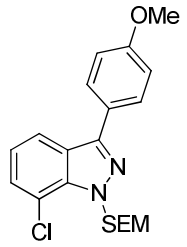
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 152.2, 143.9, 141.9, 140.8, 137.1, 130.1, 128.0, 127.7, 127.1, 127.1, 127.0, 124.8, 123.2, 122.4, 120.5, 109.6, 78.1, 66.6, 17.8, -1.4.

MS (70 eV, EI) *m/z* (%): 376 (10), 375 (30) [M^+], 316 (21), 303 (18), 302 (69), 259 (55), 258 (100), 244 (10), 151 (17), 128 (23), 73 (33).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2951, 1554, 1493, 1303, 1248, 1237, 1152, 1129, 1121, 1075, 1050, 943, 915, 857, 826, 798, 778, 743, 693.

HRMS (EI) for **$C_{22}H_{25}N_3OSi$** (375.1767): 375.1765.

Synthesis of 7-chloro-3-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (25h):



According to **TP 3**, the metalation of 7-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23d**, 564 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodoanisole (515 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25h** (552 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.76 (s, 2H), 3.87 (s, 3H), 3.64 – 3.59 (m, 2H), 0.94 – 0.86 (m, 2H), -0.06 (s, 9H).

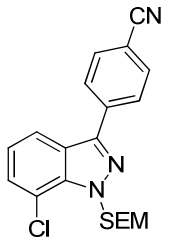
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.8, 145.4, 142.2, 131.8, 127.3, 127.3, 125.1, 122.2, 120.6, 113.2, 108.6, 78.0, 66.6, 55.3, 17.8, -1.5.

MS (70 eV, EI) *m/z* (%): 390 (17), 389 (11), 388 (50) [M^+], 343 (16), 332 (15), 331 (14), 330 (43), 329 (14), 317 (12), 315 (34), 273 (29), 272 (32), 271 (100), 258 (12), 73 (67).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2896, 1613, 1563, 1529, 1486, 1338, 1290, 1245, 1211, 1174, 1111, 1076, 1032, 962, 915, 831, 783, 765, 750, 726, 692.

HRMS (EI) for **$C_{20}H_{25}ClN_2O_2Si$** (388.1374): 388.1370.

Synthesis of 4-(7-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazol-3-yl)benzonitrile (25i):



According to **TP 3**, the metalation of 7-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23d**, 564 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 8 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25h** (658 mg, 86%) as a colorless solid.

m.p.: 46.6 – 48.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 5.76 (s, 2H), 3.64 – 3.58 (m, 2H), 0.93 – 0.87 (m, 2H), -0.06 (s, 9H).

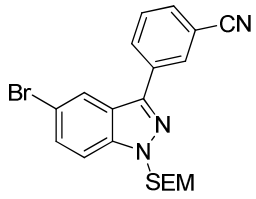
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 143.7, 142.3, 137.5, 131.5, 131.2, 127.8, 126.8, 123.0, 120.3, 118.9, 111.9, 108.9, 78.2, 66.9, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 383 (10) [M^+], 340 (10), 338 (10), 327 (14), 326 (12), 325 (38), 324 (10), 312 (13), 310 (36), 269 (19), 268 (27), 267 (58), 266 (60), 155 (10), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2224, 1606, 1485, 1339, 1297, 1244, 1153, 1108, 1068, 962, 923, 830, 777, 758, 744, 692.

HRMS (EI) for **$C_{20}H_{22}ClN_3OSi$** (383.1221): 383.1217.

Synthesis of 3-(5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazol-3-yl)benzonitrile (25j):



According to **TP 3**, the metalation of 5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23e**, 654 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 3-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25j** (533 mg, 62%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 – 8.09 (m, 3H), 7.72 – 7.66 (m, 1H), 7.65 – 7.50 (m, 3H), 5.76 (s, 2H), 3.64 – 3.55 (m, 2H), 0.94 – 0.85 (m, 2H), -0.07 (s, 9H).

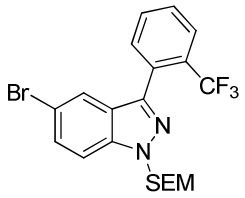
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 141.7, 140.0, 134.2, 131.6, 131.4, 130.8, 130.3, 129.7, 123.7, 123.2, 118.6, 115.7, 113.3, 111.8, 78.2, 66.8, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 429 (9), 427 (9) [M^+], 371 (31), 370 (20), 369 (28), 368 (12), 356 (19), 354 (18), 313 (32), 312 (40), 311 (33), 310 (37), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1584, 1468, 1446, 1394, 1340, 1296, 1236, 1162, 1150, 1078, 1052, 1038, 874, 858, 824, 774, 766, 756, 728, 698, 676.

HRMS (EI) for **$C_{20}H_{22}BrN_3OSi$** (427.0716): 427.0711.

Synthesis of 5-bromo-3-[2-(trifluoromethyl)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (25k):



According to **TP 3**, the metalation of 5-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23e**, 654 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 1-iodo-2-(trifluoromethyl)benzene (598 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 10 h. The reaction mixture was

quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **25k** (587 mg, 62%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (d, *J* = 7.8 Hz, 1H), 7.86 – 7.78 (m, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.71 – 7.61 (m, 3H), 5.82 (s, 2H), 3.55 – 3.48 (m, 2H), 0.84 – 0.78 (m, 2H), -0.12 (s, 9H).

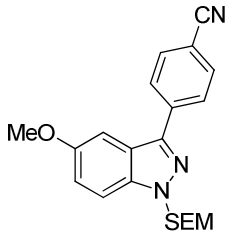
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 141.5, 138.8, 132.5, 130.1 (q, $^3J_{C\text{-}F}$ = 1.9 Hz), 129.7, 129.4, 128.2 (q, $^2J_{C\text{-}F}$ = 30.1 Hz), 126.7 (q, $^3J_{C\text{-}F}$ = 5.2 Hz), 124.9, 124.3 (q, $^1J_{C\text{-}F}$ = 273.8 Hz), 124.2, 122.3, 114.2, 112.5, 77.2, 65.6, 17.2, -1.6.

MS (70 eV, EI) *m/z* (%): 472 (5), 470 (6) [M^+], 427 (10), 425 (9), 354 (36), 345 (17), 343 (15), 222 (7), 127 (7), 75 (7), 74 (9), 73 (100), 61 (7), 43 (38).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 1470, 1368, 1316, 1244, 1172, 1130, 1108, 1081, 922, 834, 812, 806, 784, 765, 699.

HRMS (EI) for **$C_{20}H_{22}BrF_3N_2OSi$** (470.0637): 470.0634.

Synthesis of 4-(5-methoxy-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazol-3-yl)benzonitrile (25l):



According to **TP 3**, the metalation of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (**23f**, 556 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **25l** (552 mg, 71%) as a colorless solid.

m.p.: 69.1 – 70.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 9.1 Hz, 1H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.15 (dd, *J* = 9.1, 2.2 Hz, 1H), 5.74 (s, 2H), 3.89 (s, 3H), 3.62 – 3.56 (m, 2H), 0.92 – 0.87 (m, 2H), -0.08 (s, 9H).

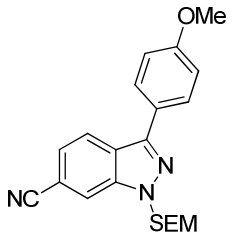
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.0, 141.8, 138.3, 137.2, 132.6, 127.5, 122.7, 119.0, 111.3, 111.0, 111.0, 100.3, 78.1, 66.6, 55.8, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 380 (11), 379 (34) [M^+], 334 (16), 322 (18), 321 (55), 320 (15), 306 (24), 263 (42), 262 (66), 249 (10), 219 (10), 178 (22), 73 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 1670, 1592, 1580, 1550, 1448, 1420, 1314, 1290, 1256, 1158, 1132, 1096, 1054, 1022, 972, 924, 808, 752, 700, 682, 668.

HRMS (EI) for **$C_{21}H_{25}N_3O_2Si$** (379.1716): 379.1711.

Synthesis of 3-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-6-carbonitrile (25m):



According to **TP 3**, the metalation of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-6-carbonitrile (**23g**, 546 mg, 2.0 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by 4-iodoanisole (515 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 10 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **25m** (537 mg, 71%) as a colorless solid.

m.p.: 77.9 – 79.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 1H), 7.84 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 5.78 (s, 2H), 3.87 (s, 3H), 3.63 – 3.58 (m, 2H), 0.98 – 0.87 (m, 2H), -0.06 (s, 9H).

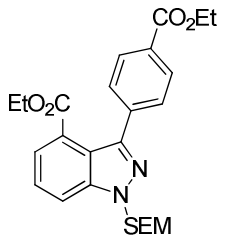
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 145.1, 139.9, 128.8, 124.7, 124.6, 123.6, 122.7, 119.1, 115.2, 114.5, 109.9, 78.1, 66.8, 55.4, 17.7, -1.5.

MS (70 eV, EI) *m/z* (%): 380 (13), 379 (37) [M^+], 334 (13), 322 (18), 321 (68), 320 (20), 306 (39), 263 (36), 262 (69), 249 (13), 153 (12), 75 (10), 73 (100), 61 (10), 44 (19), 43 (70).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936, 2227, 1610, 1529, 1481, 1416, 1378, 1350, 1300, 1246, 1178, 1135, 1087, 1034, 968, 914, 832, 810, 770, 762, 715, 661.

HRMS (EI) for **$C_{21}H_{25}N_3O_2Si$** (379.1716): 379.1714.

Synthesis of ethyl 3-[4-(ethoxycarbonyl)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-4-carboxylate (25n):



According to **TP 3**, the metalation of ethyl 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-4-carboxylate (**23h**, 640 mg, 2.0 mmol) was completed within 12 h at 50 °C. A solution of $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (46 mg, 0.2 mmol) in THF (2 mL) was added, followed by ethyl 4 iodobenzoate (607 mg, 2.2 mmol). The reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **25n** (424 mg, 45%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.11 – 8.02 (m, 3H), 7.67 – 7.55 (m, 4H), 5.89 (s, 2H), 4.35 (q, *J* = 6.9 Hz, 2H), 3.81 (q, *J* = 7.2 Hz, 2H), 3.62 – 3.55 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.84 – 0.78 (m, 2H), 0.74 (t, *J* = 7.1 Hz, 3H), -0.13 (s, 9H)

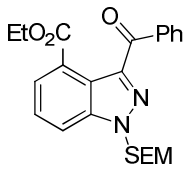
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 167.0, 166.0, 144.4, 142.0, 139.5, 129.5, 129.3, 129.0, 127.0, 125.9, 124.4, 118.4, 114.9, 77.5, 66.4, 61.3 (2x), 17.6, 14.6, 13.6, -1.0.

MS (70 eV, EI) *m/z* (%): 468 (10) [M^+], 423 (25), 410 (19), 409 (13), 348 (19), 347 (100), 346 (91), 334 (10), 73 (72), 71 (11), 59 (11), 57 (19), 43 (28), 42 (14), 41 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 1714, 1606, 1464, 1368, 1270, 1248, 1208, 1175, 1111, 1099, 1023, 984, 922, 858, 834, 780, 752, 706.

HRMS (EI) for **$C_{25}H_{32}N_2O_5Si$** (468.2080): 468.2068.

Synthesis of ethyl 3-benzoyl-1-{[2-(trimethylsilyl)ethoxy]methyl]-1*H*-indazole-4-carboxylate (25o):



According to **TP 3**, the metalation of ethyl 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole-4-carboxylate (**23h**, 640 mg, 2.0 mmol) was completed within 12 h at 50 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **25o** (653 mg, 77%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 8.16 (d, *J* = 8.0 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.75 – 7.65 (m, 3H), 7.55 (t, *J* = 7.8 Hz, 2H), 5.92 (s, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.60 – 3.54 (m, 2H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.84 – 0.79 (m, 2H), -0.12 (s, 9H).

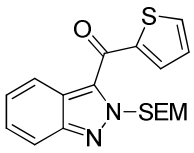
^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 188.9, 165.9, 142.8, 140.8, 136.8, 133.6, 129.7, 128.6, 127.2, 124.9, 124.6, 114.9, 77.5, 66.1, 60.8, 17.1, 13.6, -1.5.

MS (70 eV, EI) *m/z* (%): 424 (3) [M^+], 379 (24), 352 (26), 323 (15), 309 (20), 308 (91), 262 (27), 249 (12), 247 (11), 153 (17), 77 (37), 73 (100), 71 (27), 59 (40), 57 (36), 45 (30), 43 (64).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1720, 1663, 1599, 1463, 1371, 1276, 1189, 1173, 1139, 1070, 1050, 1027, 938, 880, 835, 752, 713, 694.

HRMS (EI) for **$C_{23}H_{28}N_2O_4Si$** (424.1818): 424.1806.

Synthesis of thienyl(2-{[2-(trimethylsilyl)ethoxy]methyl}-2*H*-indazol-3-yl)methanone (25p):



According to **TP 3**, the metalation of 2-{[2-(trimethylsilyl)ethoxy]methyl}-2*H*-indazole (**23i**; 497 mg, 2.0 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was further stirred for 2 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried

over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:2) to give **25p** (577 mg, 81%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85 – 7.80 (m, 2H), 7.70 (dd, *J* = 3.7 Hz, 1.2 Hz, 1H), 7.55 (dt, *J* = 8.6 Hz, 1.1 Hz, 1H), 7.34 (ddd, *J* = 8.9 Hz, 6.6 Hz, 1.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 6.07 (s, 2H), 3.60 (m, 2H), 0.83 (m, 2H), -0.13 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 177.8, 147.7, 144.3, 135.4, 135.4, 131.4, 128.1, 126.6, 124.8, 122.9, 120.7, 118.8, 80.7, 67.4, 17.7, -1.6.

MS (70 eV, EI) *m/z* (%):358 (2) [M^+], 286 (19), 285 (100), 256 (59), 243 (8), 145 (15), 111 (19), 97 (11), 73 (48).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2895, 1619, 1514, 1459, 1411, 1354, 1330, 1306, 1268, 1247, 1220, 1090, 1044, 995, 944, 914, 825, 754, 719, 690.

HRMS (EI) for **$C_{18}H_{22}N_2O_2SSi$** (358.1171): 358.1167.

4 ACCELERATED ZINCATIONS FOR AN EFFICIENT AND MILD FUNCTIONALIZATION OF AROMATICS AND HETEROCYCLES

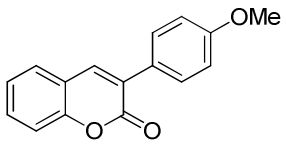
4.1 TYPICAL PROCEDURES

Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with TMPMgCl·LiCl (3) using $ZnCl_2$, $ZnCl_2$·LiCl or $ZnCl_2$·2LiCl (TP 5)

In a dry argon-flushed 25 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material (2.0 mmol) was dissolved in THF (1 mL), and $ZnCl_2$ (respectively $ZnCl_2$·LiCl or $ZnCl_2$·2LiCl; 1 M solution in THF, 1.0 mL, 1.0 mmol) was added. TMPMgCl·LiCl (**3**; 1.2 M in THF, 1.85 mL, 2.2 mmol) was added dropwise and the resulting mixture was stirred at 25 °C for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots which were quenched with I_2 in dry THF using tetradecane as internal standard.

4.2 ZINCATION OF AROMATICS AND HETEROAROMATICS AND SUBSEQUENT REACTIONS WITH ELECTROPHILES

Synthesis of 3-(4-methoxyphenyl)-2*H*-chromen-2-one (28):



According to **TP 5**, the metalation of coumarin (**26**; 292 mg, 2.0 mmol) was completed within 5 min at 25 °C using $ZnCl_2$·LiCl (1.0 mL, 1.0 mmol). A solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 1-iodo-4-methoxybenzene (515 mg, 2.2 mmol) and the resulting mixture was stirred at 25 °C for 3 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **28** (414 mg, 82%) as a colorless solid.

m.p.: 140.5–142.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.75 (s, 1H), 7.69 – 7.64 (m, 2H), 7.36 – 7.27 (m, 4H), 6.99 – 6.94 (m, 2H), 3.84 (s, 3H).

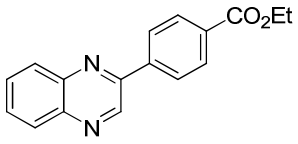
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.8, 160.1, 153.3, 138.5, 131.0, 129.8, 127.8, 127.7, 127.0, 124.4, 119.8, 116.4, 113.9, 55.4.

MS (70 eV, EI) *m/z* (%): 254 (2) 253 (14), 252 (100) [M^+], 237 (3), 224 (4), 210 (3), 209 (14), 181 (7), 152 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 2944, 2834, 1715, 1699, 1607, 1573, 1512, 1490, 1461, 1451, 1330, 1306, 1290, 1250, 1212, 1180, 1158, 1128, 1120, 1113, 1031, 962, 952, 937, 917, 870, 830, 820, 782, 757, 741, 716, 640, 618.

HRMS (EI) for **$C_{16}H_{12}O_3$** (252.0786): 252.0782.

Synthesis of ethyl 4-(quinoxalin-2-yl)benzoate (31):



According to **TP 5**, the metalation of quinoxaline (**29**; 260 mg, 2.0 mmol) was completed within 15 min at 25 °C using $ZnCl_2$·2LiCl (1.0 mL, 1.0 mmol). A solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (607 mg, 2.2 mmol) and the resulting mixture was stirred at 25 °C for 3 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **31** (440 mg, 79%) as a colorless solid.

m.p.: 88.8–90.9 °C.

^{1}H-NMR (300 Hz, $CDCl_3$) δ (ppm): 9.34 (s, 1H), 8.30 – 8.11 (m, 6H), 7.84 – 7.75 (m, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

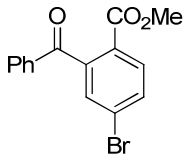
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.1, 150.7, 143.1, 142.3, 141.8, 140.7, 131.8, 130.6, 130.3, 130.1, 129.8, 129.2, 127.4, 61.3, 14.3

MS (70 eV, EI) *m/z* (%): 279 (17), 278 (100) [M^+], 250 (36), 234 (23), 233 (87), 206 (14), 205 (35), 102 (13), 76 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 1713, 1607, 1541, 1467, 1445, 1432, 1405, 1363, 1337, 1310, 1293, 1271, 1233, 1213, 1183, 1126, 1099, 1048, 1017, 988, 978, 958, 914, 895, 875, 861, 852, 840, 796, 772, 758, 752, 740, 720, 711, 698, 668, 637, 615.

HRMS (EI) for **$C_{17}H_{14}N_2O_2$** (278.1055): 278.1030.

Synthesis of methyl 2-benzoyl-4-bromobenzoate (34a):



According to **TP 5**, the metalation of methyl 4-bromobenzoate (**32a**; 428 mg, 2.0 mmol) was completed within 12 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.28 mL, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 6:1) to give **34a** (542 mg, 85%) as a yellow solid.

m.p.: 125 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.94 (d, J = 8.75 Hz, 1H), 7.78 – 7.70 (m, 3H), 7.65 – 7.56 (m, 2H), 7.49 – 7.44 (m, 2H), 3.63 (s, 3H).

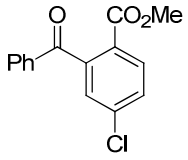
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 195.3, 165.6, 143.4, 136.6, 133.5, 132.8, 131.7, 130.7, 129.3, 128.7, 127.9, 127.6, 52.4.

MS (70 eV, EI) *m/z* (%): 319 (21), 317 (21) [M^+], 288 (14), 286 (14), 242 (60), 240 (61), 105 (100), 77 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072, 1666, 1582, 1555, 1455, 1433, 1381, 1270, 1192, 1177, 1140, 1092, 948, 907, 859, 831, 788, 759, 701, 687.

HRMS (EI) for **$C_{15}H_{11}BrO_3$** (317.9892): 317.9884.

Synthesis of methyl 2-benzoyl-4-chlorobenzoate (34b):



According to **TP 5**, the metalation of methyl 4-chlorobenzoate (**32b**; 340 mg, 2.0 mmol) was completed within 20 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.28 mL, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 20 h. Then, the

reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 6:1) to give **34b** (473 mg, 86%) as a colorless solid.

m.p.: 98.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.75 (m, 2H), 7.52 – 7.59 (m, 2H), 7.42 – 7.46 (m, 2H), 7.37 (d, *J* = 2.1 Hz, 1H), 3.61 (s, 3H).

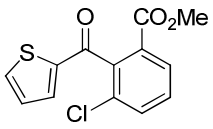
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 195.4, 165.4, 143.3, 139.1, 136.6, 133.4, 131.6, 129.7, 129.2, 128.6, 127.8, 127.4, 52.3.

MS (70 eV, EI) *m/z* (%): 274 (26) [M^+], 243 (21), 197 (80), 152 (10), 105 (100), 77 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1717, 1668, 1595, 1585, 1564, 1452, 1434, 1388, 1317, 1280, 1272, 1257, 1181, 1157, 1142, 1104, 1074, 1026, 1001, 979, 952, 934, 929, 902, 860, 849, 834, 807, 786, 768, 711, 700, 693, 671, 660, 645, 634, 629, 624, 620, 612, 608.

HRMS (EI) for **$C_{15}H_{11}ClO_3$** (274.0397): 274.0393.

Synthesis of methyl 3-chloro-2-(thiophene-2-carbonyl)benzoate (34c):



According to **TP 5**, the metalation of methyl 3-chlorobenzoate (**32c**; 340 mg, 2.0 mmol) was completed within 5 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 2-thiophene acid chloride (365 mg, 2.5 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 20 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **34c** (443 mg, 82%) as a colorless solid.

m.p.: 134.7 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.01 (d, *J* = 9.1 Hz, 1H), 7.69 (d, *J* = 4.8 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.07 (dd, *J* = 4.8, 3.8 Hz, 1H), 3.73 (s, 3H).

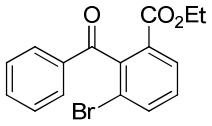
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 186.4, 164.9, 144.1, 139.9, 138.3, 134.4, 134.0, 133.7, 132.0, 130.2, 128.9, 128.1, 52.6.

MS (70 eV, EI) *m/z* (%): 208 (35) [M^+], 251 (15), 249 (36), 221 (11), 197 (25), 111 (100), 59 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1722, 1653, 1586, 1567, 1517, 1455, 1434, 1412, 1349, 1274, 1235, 1207, 1159, 1112, 1083, 1049, 1034, 971, 882, 867, 861, 848, 817, 765, 746, 736, 722, 680, 674, 662, 645, 639, 634, 631, 621, 608, 605.

HRMS (EI) for **$C_{13}H_9ClO_3S$** (279.9961): 279.9963.

Synthesis of ethyl 2-benzoyl-3-bromobenzoate (34d):



According to **TP 5**, the metalation of ethyl 3-bromobenzoate (**32d**; 460 mg, 2.0 mmol) was completed within 4 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.28 mL, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 5 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 8:1) to give **34d** (606 mg, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 (dt, *J* = 8.3, 1.6 Hz, 2H), 7.69 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.54 – 7.58 (m, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.41 – 7.46 (m, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 1.03 (t, *J* = 7.1 Hz, 3H).

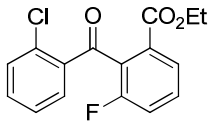
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 195.1, 165.1, 143.2, 136.6, 133.4, 132.6, 131.7, 130.5, 129.3, 128.6, 128.0, 127.4, 61.7, 13.5.

MS (70 eV, EI) *m/z* (%): 334 (32), 332 (32) [M^+], 290 (20), 289 (565), 288 (22), 287 (55), 257 (68), 255 (70), 229 (88), 227 (88), 181 (11), 180 (15), 152 (33), 151 (12), 106 (13), 105 (100), 77 (56).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1712, 1676, 1598, 1583, 1555, 1474, 1471, 1450, 1444, 1383, 1362, 1318, 1310, 1281, 1267, 1243, 1178, 1156, 1135, 1116, 1097, 1074, 1024, 1020, 1000, 965, 948, 898, 859, 842, 826, 815, 805, 778, 759, 712, 697, 689, 681, 662, 654, 641, 633, 626, 622, 619, 612, 603.

HRMS (EI) for **$C_{16}H_{13}BrO_3$** (332.0048): 332.0034.

Synthesis of ethyl 2-(2-chlorobenzoyl)-3-fluorobenzoate (34e):



According to **TP 5**, the metalation of ethyl 3-fluorobenzoate (**32e**; 336 mg, 2.0 mmol) was completed within 2 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 2-chlorobenzoyl chloride (0.31 mL, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 5 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 8:1) to give **34e** (574 mg, 94%) as a yellowish solid.

m.p.: 104.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.84 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.77 –7.72 (m, 1H), 7.54 – 7. 43 (m, 3H), 7.35 – 7.27 (m, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).

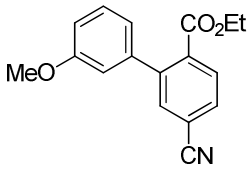
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 190.6, (d, $^3J_{C\text{-}F}$ = 1.3 Hz), 164.9, 159.1 (d, $^1J_{C\text{-}F}$ = 248 Hz), 135.2, 134.0, 133.4, 132.4, 131.6, 131.1 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 130.8 (d, $^2J_{C\text{-}F}$ = 8.3 Hz), 130.5, 126.7, 126.2 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 120.0 (d, $^2J_{C\text{-}F}$ = 22 Hz), 61.9, 13.8.

MS (70 eV, EI) *m/z* (%): 306 (5) [M^+], 272 (17), 271 (88), 261 (34), 243 (10), 195 (23), 170 (10), 168 (11), 167 (100), 141 (25), 139 (75), 111 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1712, 1686, 1608, 1587, 1575, 1566, 1482, 1468, 1452, 1444, 1431, 1367, 1292, 1265, 1239, 1191, 1165, 1152, 1125, 1112, 1070, 1056, 1043, 1023, 960, 953, 928, 863, 826, 809, 776, 758, 742, 683, 675, 651, 637, 618, 612.

HRMS (EI) for **$C_{16}H_{12}ClFO_3$** (306.0459): 306.0452.

Synthesis of ethyl 5-cyano-3'-methoxy-biphenyl-2-carboxylate (34f):



According to **TP 5**, the metalation of ethyl 4-cyanobenzoate (**32f**; 370 mg, 2.0 mmol) was completed within 4 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). A solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 3-iodo-anisole (598 mg, 2.2 mmol) and the

resulting mixture was stirred at 25 °C for 3 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 6:1) to give **34f** (490 mg, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.34 – 7.28 (m, 1H), 6.86 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 6.87 – 6.81 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H).

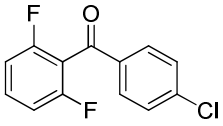
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 167.4, 159.5, 142.9, 140.3, 135.6, 133.9, 130.6, 130.1, 129.4, 120.6, 117.9, 114.6, 113.8, 113.7, 61.6, 55.3, 13.6.

MS (70 eV, EI) *m/z* (%): 282 (21), 281 (100) [M^+], 253 (12), 237 (21), 236 (65), 210 (14), 209 (77), 206 (12), 193 (21), 179 (11), 177 (12), 165 (13), 164 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2229, 1713, 1598, 1586, 1485, 1464, 1442, 1419, 1402, 1392, 1321, 1305, 1281, 1270, 1249, 1225, 1172, 1166, 1143, 1102, 1082, 1052, 1030, 994, 985, 923, 906, 892, 875, 855, 794, 781, 770, 755, 728, 697, 645, 627, 622, 617, 613.

HRMS (EI) for **$C_{17}H_{13}NO_3$** (281.1052): 281.1048.

Synthesis of (4-chlorophenyl)(2,6-difluorophenyl)methanone (34g):



According to **TP 5**, the metalation of 1,3-difluorobenzene (**32g**; 228 mg, 2.0 mmol) was completed within 6 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (0.31 mL, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 12 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 29:1) to give **34g** (402 mg, 80%) as a colorless solid.

m.p.: 75.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.80 (d, *J* = 8.6 Hz, 2H), 7.43-7.48 (m, 3H), 6.98-7.03 (m, 2H).

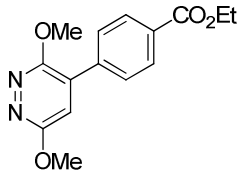
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 187.6, 159.7 (dd, $^1J_{C\text{-}F}$=252 Hz, $^3J_{C\text{-}F}$=7.7 Hz), 140.8, 135.2, 132.2 (t, $J_{C\text{-}F}$=9.8 Hz), 130.9, 129.1, 116.5, 112.0 (dd, $^2J_{C\text{-}F}$=22 Hz, $^3J_{C\text{-}F}$=4.2 Hz).

MS (70 eV, EI) *m/z* (%): 254 (18), 252 (52) [M^+], 141 (53), 141 (38), 139 (100), 113 (13), 111 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1670, 1623, 1586, 1574, 1556, 1488, 1461, 1401, 1311, 1286, 1272, 1233, 1182, 1172, 1151, 1144, 1113, 1091, 1057, 1022, 1015, 999, 977, 957, 926, 880, 846, 830, 814, 789, 769, 751, 731, 715, 695, 680, 667, 662, 656, 636, 628, 607.

HRMS (EI) for **$C_{13}H_7ClF_2O$** (252.0153): 252.0147.

Synthesis of ethyl 4-(3,6-dimethoxypyridazin-4-yl)benzoate (34h):



According to **TP 5**, the metalation of 3,6-dimethoxypyridazine (**33a**; 278 mg, 2.0 mmol) was completed within 5 h at 25 °C using $ZnCl_2$ (1.0 mL, 1.0 mmol). A solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (607 mg, 2.2 mmol) and the resulting mixture was stirred at 25 °C for 7 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **34h** (374 mg, 65%) as a colorless solid.

m.p.: 96.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 6.96 (s, 1H), 4.40 (q, *J* = 7.3 Hz, 2H), 4.08 (s, 6H), 1.40 (t, *J* = 7.2 Hz, 3H).

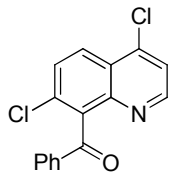
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.0, 162.6, 156.3, 137.8, 133.1, 131.1, 129.6, 129.0, 119.5, 61.2, 54.9, 54.7, 14.3.

MS (70 eV, EI) *m/z* (%): 289 (10), 288 (54) [M^+], 287 (100), 259 (29), 243 (17), 215 (10), 129 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 1705, 1604, 1571, 1469, 1412, 1368, 1274, 1251, 1215, 1186, 1131, 1106, 1001, 895, 862, 773, 709.

HRMS (EI) for **$C_{15}H_{16}N_2O_4$** (288.1110): 288.1083.

Synthesis of (4,7-dichloroquinolin-8-yl)(phenyl)methanone (34i):



According to **TP 5**, the metalation of 4,7-dichloroquinoline (**33b**; 396 mg, 2.0 mmol) was completed within 5 min at 25 °C using $ZnCl_2$·LiCl (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 12 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **34i** (497 mg, 82%) as a colorless solid.

m.p.: 128.9 – 130.6 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ (ppm): 8.67 (d, *J* = 4.8 Hz, 1H), 8.29 (dd, *J* = 9.1, 1.0 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.70 (q, *J* = 9.1 Hz, 1H), 7.58 (td, *J* = 7.4, 1.0 Hz, 1H), 7.49 (d, *J* = 4.8 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H).

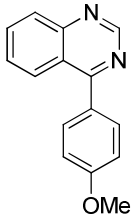
^{13}C-NMR ($CDCl_3$, 150 MHz) δ (ppm): 194.5, 151.2, 147.7, 142.7, 137.6, 136.5, 133.9, 132.9, 129.7, 128.9, 128.7, 126.1, 125.1, 121.8.

MS (70 eV, EI) *m/z* (%): 301 (5) [M^+], 276 (10), 275 (15), 274 (61), 273 (24), 272 (100), 238 (22), 223 (4), (195 (4), 160 (5), 77 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3096, 3066, 1676, 1595, 1581, 1558, 1481, 1451, 1393, 1316, 1280, 1265, 1206, 1180, 1159, 1142, 1087, 1072, 1057, 1024, 1000, 962, 938, 934, 895, 850, 836, 828, 794, 754, 710, 690, 683, 657, 616, 606.

HRMS (EI) for **$C_{16}H_9Cl_2NO$** (301.0061): 301.0049.

Synthesis of 4-(4-methoxyphenyl)quinazoline (34j):



According to **TP 5**, the metalation of quinazoline (**33c**; 260 mg, 2.0 mmol) was completed within 1 h at 25 °C using $ZnCl_2$·LiCl (1.0 mL, 1.0 mmol). A solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 1-iodo-4-methoxybenzene (515 mg, 2.2 mmol) and the resulting mixture was stirred at 50 °C for 12 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:ethyl acetate = 1:1) to give **34j** (270 mg, 57%) as a colorless solid.

m.p.: 135.8–137.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.36 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.92 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H), 7.81 (ddd, J = 9.2, 2.9, 2.5 Hz, 2H), 7.62 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.11 (ddd, *J* = 9.2, 2.9, 2.5 Hz, 2H), 3.93 (s, 3H).

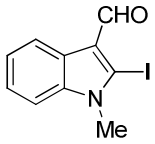
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 167.8, 161.3, 154.6, 151.1, 133.5, 131.7, 129.5, 128.8, 127.5, 127.1, 123.1, 114.1, 55.4.

MS (70 eV, EI) *m/z* (%): 237 (10), 236 (74) [M^+], 235 (100), 227 (12), 225 (10), 224 (11), 221 (10), 220 (17), 205 (49), 193 (10), 192 (35), 44 (84).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 3002, 2933, 2835, 1600, 1578, 1533, 1486, 1425, 1290, 1271, 1248, 1227, 1183, 1132, 1031, 958, 846, 811, 796, 757, 729, 671, 654, 631, 608.

HRMS (EI) for **$C_{15}H_{12}N_2O$** (236.0950): 236.0909.

Synthesis of 2-iodo-1-methyl-1H-indole-3-carbaldehyde (34k):



According to **TP 5**, the metalation of 1-methyl-1*H*-indole-3-carbaldehyde (**33d**; 318 mg, 2.0 mmol) was completed within 1 h at 25 °C using $ZnCl_2$·LiCl (1.0 mL, 1.0 mmol). A solution of I_2 (759 mg, 3 mmol) in THF (6 mL) was added at 0 °C, and the reaction mixture was warmed slowly to 25 °C over 1 h. Then, the reaction mixture was quenched with sat. aq NaS_2O_3 solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **34k** (445 mg, 78%) as a colorless solid.

m.p.: 135.8–137.2 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ (ppm): 9.83 (s, 1H), 8.32 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.30 – 7.25 (m, 2H), 3.84 (s, 3H).

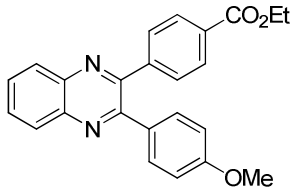
^{13}C-NMR ($CDCl_3$, 150 MHz) δ (ppm): 187.6, 139.3, 126.3, 124.1, 122.9, 120.8, 119.2, 110.0, 100.6, 34.7.

MS (70 eV, EI) *m/z* (%): 286 (10), 285 (100) [M^+], 284 (85), 157 (10), 129 (12), 114 (8), 89 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2932, 2802, 1773, 1638, 1630, 1620, 1611, 1579, 1483, 1458, 1379, 1369, 1345, 1317, 1249, 1176, 1132, 1083, 1035, 1012, 822, 795, 752, 736, 630.

HRMS (EI) for **$C_{10}H_8INO$** (284.9651): 284.9646.

Synthesis of ethyl 4-[3-(4-methoxyphenyl)quinoxalin-2-yl]benzoate (34l):



According to **TP 5**, the metalation of ethyl 4-quinoxalin-2-ylbenzoate (**31**; 546 mg, 2.0 mmol) was completed within 2 h at 25 °C using $ZnCl_2$·2LiCl (1.0 mL, 1.0 mmol). A solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 1-iodo-4-methoxybenzene (515 mg, 2.2 mmol) and the resulting mixture was stirred at 25 °C for 12 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **34l** (434 mg, 57%) as a yellowish solid.

m.p.: 90.3–93.3 °C

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.16 (ddd, *J* = 7.1, 5.0, 2.2 Hz, 2H), 8.0 (ddd, *J* = 8.5, 1.8, 1.6 Hz, 2H), 7.81 – 7.72 (m, 2H), 7.61 (ddd, *J* = 8.6, 1.9, 1.7 Hz, 2H), 7.44 (ddd, *J* = 9.3, 2.9, 2.5 Hz, 2H), 6.85 (ddd, *J* = 9.3, 3.0, 2.6 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H).

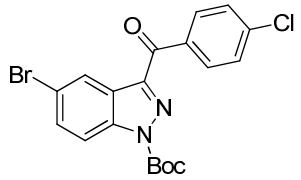
^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.3, 160.4, 152.8, 152.3, 143.7, 141.3, 140.9, 131.3, 130.8, 130.5, 130.3, 129.9, 129.8, 129.5, 129.2, 129.0, 113.9, 61.1, 55.3, 14.3.

MS (70 eV, EI) *m/z* (%): 385 (28), 384 (100) [M^+], 383 (20), 356 (13), 355 (15), 311 (39), 209 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 2492, 2370, 2239, 1706, 1605, 1512, 1476, 1462, 1443, 1366, 1343, 1308, 1274, 1254, 1244, 1223, 1176, 1146, 1127, 1109, 1053, 1022, 978, 862, 854, 841, 822, 813, 777, 746, 726, 715, 698, 676, 656, 646, 628, 608.

HRMS (EI) for **$C_{24}H_{20}N_2O_3$** (384.1474): 384.1472.

Synthesis of tert-butyl 5-bromo-3-(4-chlorobenzoyl)-1H-indazole-1-carboxylate (34m):



According to **TP 5**, the metalation of tert-butyl 5-bromo-1H-indazole-1-carboxylate (**33e**; 594 mg, 2.0 mmol) was completed within 5 min at 25 °C using $ZnCl_2$·2LiCl (1.0 mL, 1.0 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (420 mg, 2.4 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred for 12 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **34m** (647 mg, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.35 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 1.19 (s, 9H).

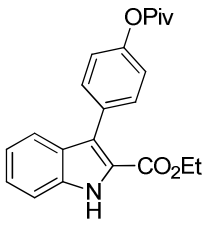
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 170.4, 150.7, 140.4, 137.5, 136.8, 135.7, 134.3, 132.2, 129.7, 128.5, 121.7, 114.7, 113.9, 84.7, 26.9.

MS (70 eV, EI) *m/z* (%): 335 (10), 333 (8) [M-Boc$^+$], 138 (100), 111 (22), 75 (8), 57 (13), 44 (10), 43 (36), 41 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2935, 2235, 1740, 1687, 1590, 1487, 1458, 1393, 1370, 1342, 1316, 1232, 1178, 1144, 1088, 1044, 1030, 1013, 889, 839, 817, 804, 768, 751, 726, 690, 659.

HRMS (EI) for **$C_{14}H_8BrClN_2O$** [M-Boc$^+$] (333.9509): 333.9487.

Synthesis of ethyl 3-[4-(pivaloyloxy)phenyl]-1*H*-indole-2-carboxylate (37):



According to **TP 5**, the metalation of 1-tert-butyl 2-ethyl 1*H*-indole-1,2-dicarboxylate (**35**; 578 mg, 2.0 mmol) was completed within 30 min at 25 °C using $ZnCl_2$·2LiCl (1.0 mL, 1.0 mmol). A solution of PEPPSI-*i*Pr (27 mg, 0.04 mmol) and 4-bromophenyl pivalate (566 mg, 2.2 mmol) in THF (2 mL) was added and the reaction mixture was heated to 50 °C for 2 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **37** (592 mg, 81%) as a colorless solid.

m.p.: 168.3–170.2 °C

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ (ppm): 11.94 (s, 1H), 7.56 – 7.45 (m, 4H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.33 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H).

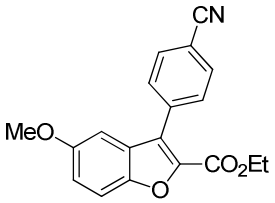
^{13}C-NMR (100 MHz, DMSO-d$_6$) δ (ppm): 176.4, 161.2, 149.7, 136.1, 131.4, 131.0, 126.7, 125.1, 122.8, 121.5, 121.0, 120.5, 120.4, 112.7, 60.3, 38.6, 26.8, 14.0.

MS (70 eV, EI) *m/z* (%): 366 (20), 365 (72) [M^+], 340 (11), 28 (79), 235 (100), 206 (17), 177 (20), 164 (10), 161 (14), 151 (10), 57 (50), 40 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3327, 2981, 1746, 1676, 1536, 1499, 1479, 1451, 1383, 1331, 1250, 1199, 1165, 1114, 1022, 987, 927, 899, 854, 815, 798, 781, 745, 686, 652.

HRMS (EI) for **$C_{22}H_{23}NO_4$** (365.1627): 365.1624.

Synthesis of ethyl 3-(4-cyanophenyl)-5-methoxybenzofuran-2-carboxylate (40):



According to **TP 5**, the metalation of ethyl 5-methoxybenzofuran-2-carboxylate (**38**; 440 mg, 2.0 mmol) was completed within 30 min at 25 °C using $ZnCl_2$·2LiCl (1.0 mL, 1.0 mmol). A solution of

PEPPSI-*i*Pr (27 mg, 0.04 mmol) and 4-bromobenzonitrile (401 mg, 2.2 mmol) in THF (2 mL) was added and the reaction mixture was heated to 50 °C for 1 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **40** (482 mg, 75%) as a colorless solid.

m.p.: 175.5–176.5 °C

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.97 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.18 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

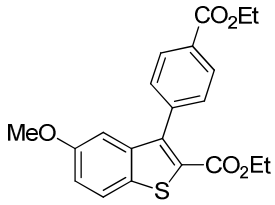
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 158.5, 156.7, 148.7, 140.8, 135.3, 132.1, 131.0, 127.4, 126.7, 118.7, 118.3, 113.2, 111.0, 102.2, 61.1, 55.7, 13.8.

MS (70 eV, EI) *m/z* (%): 322 (19), 321 (76) [M^+], 293 (40), 276 (19), 249 (24), 220 (9), 177 (17), 151 (10), 70 (10), 61 (14), 45 (14), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2985, 2226, 2168, 2166, 1712, 1611, 1569, 1502, 1473, 1440, 1396, 1376, 1327, 1279, 1242, 1200, 1172, 1150, 1108, 1025, 977, 918, 858, 835, 807, 775, 730, 672.

HRMS (EI) for **$C_{19}H_{15}NO_4$** (321.1001): 321.0994.

Synthesis of ethyl 3-[4-(ethoxycarbonyl)phenyl]-5-methoxybenzo[*b*]thiophene-2-carboxylate (43):



According to **TP 5**, the metalation of ethyl 5-methoxybenzo[*b*]thiophene-2-carboxylate (**41**; 472 mg, 2.0 mmol) was completed within 30 min at 25 °C using $ZnCl_2$·2LiCl (1.0 mL, 1.0 mmol). A solution of PEPPSI-*i*Pr (27 mg, 0.04 mmol) and ethyl 4-bromobenzoate (504 mg, 2.2 mmol) in THF (2 mL) was added and the reaction mixture was heated to 50 °C for 1 h. Then, the reaction mixture was quenched with sat. aq NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **43** (669 mg, 87%) as a colorless solid.

m.p.: 180.2–182.9 °C

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 8.07 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.22 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 4.35 (q, *J* = 7.3 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 165.6, 161.6, 157.8, 141.3, 140.0, 139.1, 132.1, 130.1, 129.8, 129.4, 128.9, 124.0, 118.4, 105.5, 61.2, 60.8, 55.3, 14.2, 13.7.

MS (70 eV, EI) *m/z* (%): 387 (15), 385 (22), 384 (100) [M^+], 356 (13), 339 (16), 311 (11), 267 (8), 195 (11), 186 (13), 44 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2993, 1712, 1597, 1529, 1496, 1453, 1403, 1359, 1309, 1269, 1212, 1183, 1115, 1087, 1057, 1020, 971, 899, 840, 806, 764, 732, 707, 690, 668, 655.

HRMS (EI) for **$C_{21}H_{20}O_5S$** (384.1031): 384.1032.

5 SCALEABLE PREPARATION OF FUNCTIONALIZED ORGANOMETALLICS *VIA* DIRECTED ORTHO METALATION USING Mg- AND Zn-AMIDE BASES

5.1 LARGER-SCALE PREPARATION OF THE BASES

Preparation of TMPMgCl·LiCl (3)

A dried and nitrogen-flushed 2 L Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with *i*PrMgCl·LiCl (**1**; 1.31 M in THF, 850 mL, 1.11 mol). Then 2,2,6,6-tetramethylpiperidine (**2**; 161 g, 194 mL, 1.14 mol, 1.02 equiv) is added at once, and the mixture is stirred until gas evolution ceases (48 h). Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use shows a concentration of 1.15 M.

Preparation of $TMP_2Mg·2LiCl$ (4)

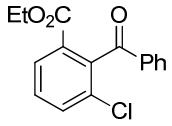
A flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with 100 mL of dry THF cooled in a -40 °C cooling bath and stirred for 15 min at this temperature. Then 2,2,6,6-tetramethylpiperidine (**2**; 14.1 g, 100 mmol) is added at once *via* syringe. After stirring for 15 min at -40 °C, *n*BuLi (45.5 mL, 2.22 M in hexanes, 100 mmol) is added at once *via* syringe. The resulting mixture is stirred at -40 °C for 5 min and stirred at 0 °C for further 30 min. Then, TMPMgCl·LiCl (**3;** 87 mL, 1.15 M in THF, 100 mmol) is added *via* syringe in one portion (addition time <1 min). The mixture is stirred at 0 °C for 30 min and at 25 °C for another 1 h. The solvents are removed *in vacuo*. The resulting pale-brown solid is redissolved in dry THF (100 − 120 mL) and stirred for 10 min at 25 °C. Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use shows a concentration of 0.70 M.

Preparation of $TMP_2Zn·2MgCl_2·2LiCl$ (6)

A flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $ZnCl_2$ (1.0 M in THF, 200 mL, 200 mmol, 0.5 equiv) and cooled to 0 °C. Then, TMPMgCl·LiCl (**3**; 348 mL, 400 mmol) is added over a period of 15 min. After stirring this mixture for 2 h at 0 °C, the solution of $TMP_2Zn·2MgCl_2·2LiCl$ (**6**) is concentrated *in vacuo*. Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use shows a concentration of 0.44 M.

5.2 LARGER-SCALE METALATIONS

Synthesis of ethyl 2-benzoyl-3-chlorobenzoate (49a)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of TMPMgCl·LiCl (**3**; 96 mL, 110 mmol) and cooled to 0 °C. Then, ethyl 3-chlorobenzoate (**48a**; 18.5 g, 100 mmol) is added and the mixture is stirred for 6 h at 0 °C. The resulting mixture is cooled to -40 °C and CuCN·2LiCl (1 M in THF, 10 mL, 10 mmol) as well as PhCOCl (14.2 g, 100 mmol, 1.0 equiv) were added. After slow warming to 25 °C within 3 h, the reaction mixture is quenched with a mixture of a sat. aq NH_4Cl solution (150 mL) and aq HCl (2 M, 100 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane:ethyl acetate) to give **49a** as a colorless solid (24.8 g, 86%).

m.p.: 108.6−109.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (m, 1H), 7.81 (m, 2H), 7.68 − 7.44 (m, 5H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H).

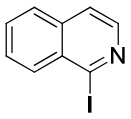
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 194.5, 164.8, 140.7, 136.9, 136.8, 134.2, 133.6, 132.0, 130.9, 130.1, 129.2, 128.9, 62.1, 13.8

MS (70 eV, EI) *m/z* (%): 290 (19), 288 (43) [M^+], 242 (32), 211 (73), 211 (26), 185 (32), 183 (100), 152 (10), 151 (13), 105 (87), 77 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1706, 1672, 1584, 1564, 1430, 1366, 1284, 1202, 1152, 1074, 1028, 928, 866, 764, 744, 734, 702, 652, 618.

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0569.

Synthesis of 2-iodoisoquinoline (49b)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of TMPMgCl·LiCl (**3**; 104 mL, 120 mmol). Isoquinoline (**48b**;

12.9 g, 100 mmol) is added, and the mixture is stirred for 1 h at 25 °C. Then, the reaction mixture is cannulated slowly to a solution of I_2 in THF (1 M in THF, 110 mL, 110 mmol, 1.1 equiv) at -78 °C. The resulting mixture is stirred for 1 h at −78 °C and then quenched with a sat. aq $Na_2S_2O_3$ solution (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **49b** (19.4 g, 76%) as a yellowish solid.

m.p.: 73.9−75.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (d, *J* = 5.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.72 − 7.62 (m, 3H), 7.54 (d, *J* = 5.6 Hz, 1H).

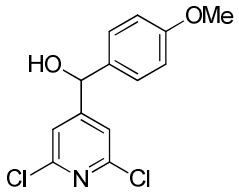
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 143.0, 136.1, 132.8, 131.9, 131.1, 129.0, 127.4, 127.2, 121.3.

MS (70 eV, EI) *m/z* (%): 255 (39) [M^+], 129 (10), 128 (100), 127 (5), 101 (17), 77 (7), 75 (8), 51 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3047, 1992, 1904, 1834, 1774, 1619, 1576, 1539, 1490, 1443, 1363, 1316, 1302, 1251, 1219, 1173, 1136, 1038, 954, 871, 822, 808, 787, 776, 751, 654, 637.

HRMS (EI) for **C_9H_6IN** (254.9545): 254.9535.

Synthesis of (2,6-dichloropyridin-4-yl)(4-methoxyphenyl)methanol (49c)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of TMPMgCl·LiCl (**3**; 96 mL, 110 mmol). 2,6-dichloropyridine (**48c**; 14.8 g, 100 mmol) is added, and the mixture is stirred for 15 min at 25 °C. The resulting mixture is cooled to −40 °C, and 4-methoxybenzaldehyde (13.6 g, 100 mmol, 1.0 equiv) is added. The resulting mixture is stirred for 1 h at -40°C, then quenched with brine (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane:ethyl acetate) to give **49c** as a colorless solid (26.1 g, 92%).

m.p.: 90.6−93.8 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.26 (d, *J* = 0.75 Hz, 2H), 7.21 − 7.18 (m, 2H), 6.88 − 6.86 (m, 2H), 5.67 (s, 1H), 3.78 (s, 3H), 2.67 (br s, 1H).

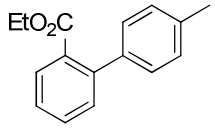
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 159.9, 158.8, 150.5, 133.6, 128.2, 120.3, 114.5, 73.9, 55.3.

MS (70 eV, EI) *m/z* (%): 285 (55), 283 (35) [M^+], 176 (13), 174 (20), 137 (100), 135 (12), 109 (69), 94 (17), 77 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3340, 3100, 3000, 2835, 1739, 1584, 1554, 1544, 1508, 1464, 1426, 1378, 1362, 1303, 1240, 1167, 1150, 1113, 1098, 1069, 1030, 993, 920, 834, 828, 813, 774, 768, 736, 680, 666, 630, 610.

HRMS (EI) for **$C_{13}H_{11}Cl_2NO_2$** (283.0167): 283.0164.

Synthesis of ethyl 4'-methylbiphenyl-2-carboxylate (51a)



In a flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (**4**; 110 mL, 100 mmol) is provided. Ethyl benzoate (**50a**; 13.5 g, 90 mmol) is added, and the reaction mixture is stirred for 45 min at 25 °C. The resulting solution is cooled to −40 °C, and $ZnCl_2$ (100 mL, 100 mmol, 1.1 equiv) is added, and the resulting mixture is stirred for 15 min. Then, $Pd(OAc)_2$ (101 mg, 0.45 mmol), RuPhos (420 mg, 0.9 mmol) and 4-bromotoluene (16.2 g, 95 mmol, 1.05 equiv) are added. After warming to 25 °C and stirring for 12 h at 25 °C, the reaction is quenched with a mixture of a sat. aq NH_4Cl solution (150 mL) and aq HCl (2 M, 100 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **51a** as pale-yellow oil (15.4 g, 71%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.89 – 7.87(m, 1H), 7.54 – 7.52 (m, 1H), 7.45 – 7.43 (m, 2H), 7.33 – 7.25 (m, 4H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).

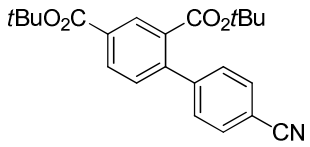
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 168.9, 142.5, 138.6, 136.8, 131.5, 131.1, 130.7, 129.7, 128.8, 128.4, 127.0, 60.9, 21.2, 13.8.

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

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

HRMS (EI) for **$C_{16}H_{16}O_2$** (240.1150): 240.1142.

Synthesis of di-*tert*-butyl 4'-cyanobiphenyl-2,4-dicarboxylate (51b)



In a flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (**4**; 100 mL, 90 mmol) is provided. Di-*tert*-butylisophthalate (**50b**; 22.2 g, 80 mmol) is added, and the reaction mixture is stirred for 45 min at 25 °C. The resulting solution is cooled to -40 °C, and $ZnCl_2$ (90 mL, 90 mmol, 1.1 equiv) is added. The resulting mixture is stirred for 15 min. Then, $Pd(OAc)_2$ (90 mg, 0.4 mmol), RuPhos (373 mg, 0.8 mmol) and 4-bromobenzonitrile (15.3 g, 84 mmol, 1.05 equiv) are added. After warming to 25 °C and stirring for 12 h at 25 °C, the reaction mixture is quenched with a mixture of a sat. aq NH_4Cl solution (150 mL) and aq HCl (2 M, 100 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane:ethyl acetate) to give **51b** as a yellow solid (22.8 g, 75%).

m.p.: 158.5−158.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.44 (d, *J* = 1.5 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 1.61 (s, 9H), 1.37 (s, 9H).

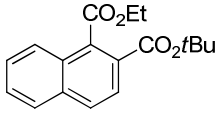
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 164.5, 146.0, 143.9, 132.6, 132.0, 131.8, 131.7, 131.1, 130.3, 129.2, 118.7, 111.4, 82.2, 81.8, 28.2, 27.6.

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

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

HRMS (EI) for **$C_{23}H_{25}NO_4$** (379.1784): 379.1785.

Preparation of 2-*tert*-butyl 1-ethyl naphthalene-1,2-dicarboxylate (51c)



In a flame-dried and nitrogen-flushed 500 mL Schlenk flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $TMP_2Mg{\cdot}2LiCl$ (**4**; 110 mL, 100 mmol) is added

followed by ethyl 1-naphthoate (**50c**; 18.0 g, 90 mmol), and the reaction mixture is stirred for 45 min at 25 °C. Boc_2O (28.0 g, 130 mmol, 1.44 equiv) is added in one portion at 25 °C, and the reaction mixture was stirred for 2 h. A mixture of a sat. aq NH_4Cl solution (150 mL) and aq HCl (2 M, 100 mL) is added, and the mixture is extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane:ethyl acetate) to give **51c** as a colorless solid (12.4 g, 69%).

m.p.: 70.5−70.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.95 – 7.89 (m, 4H), 7.61 – 7.57 (m, 2H), 4.58 (q, *J* = 7.3 Hz, 2H), 1.64 (s, 9H), 1.46 (t, *J* = 7.2 Hz, 3H).

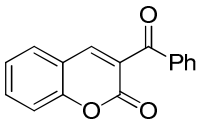
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 169.0, 165.1, 134.9, 134.4, 134.3, 129.4, 129.3, 128.1, 127.5, 127.0, 125.9, 125.2, 82.2, 61.7, 28.1, 14.1.

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

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

HRMS (EI) for **$C_{18}H_{20}O_4$** (300.1362): 300.1358.

Synthesis of 3-benzoyl-2H-chromen-2-one (53a)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 114 mL, 100 mmol). Coumarin (**52a**; 14.6 g, 100 mmol) is added neatly, and the mixture is stirred for 2 h at 25 °C. The resulting mixture is cooled to -20 °C, then CuCN·2LiCl (1 M in THF, 10 mL, 10 mmol) and PhCOCl (14.2 g, 100 mmol, 1.0 equiv) were added. After slow warming to 25 °C within 5 h, the reaction mixture is quenched with a mixture of a sat. aq NH_4Cl solution (300 mL) and conc. aq NH_3 solution (50 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane:ethyl acetate) to give **53a** as an off white solid (17.8 g, 71%).

m.p.: 136.0−137.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.10 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 2), 7.67 − 7.57 (m, 3H), 7.51 − 7.44 (m, 2H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H).

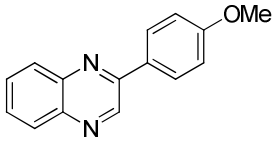
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.6, 158.4, 154.8, 145.3, 136.2, 133.8, 133.6, 129.5, 129.2, 128.6, 127.0, 125.0, 118.2, 116.9.

MS (70 eV, EI) *m/z* (%): 251 (13), (250) (100) [M^+], 222 (24), 221 (59), 173 (21), 105 (98), 77 (61), 51 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 1712, 1656, 1607, 1595, 1580, 1563, 1487, 1453, 1449, 1445, 1363, 1318, 1305, 1297, 1264, 1237, 1214, 1182, 1164, 1144, 1120, 1073, 1041, 1026, 1000, 962, 952, 946, 937, 920, 865, 857, 816, 793, 769, 759, 754, 736, 696, 681.

HRMS (EI) for **$C_{16}H_{10}O_3$** (250.0630): 250.0605.

Preparation of 2-(4-methoxyphenyl)quinoxaline (53b)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 114 mL, 100 mmol). Quinoxaline (**52b**; 13.0 g, 100 mmol) is added and the mixture is stirred for 3 h at 25 °C. Then, $Pd(dba)_2$ (280 mg; 0.5 mmol), tfp (230 mg; 1 mmol) and 4-iodoanisole (23.4 g, 100 mmol, 1.00 equiv) are added and the reaction mixture is stirred for 2 h at 25 °C. The reaction mixture is quenched with a sat. aq NH_4Cl solution (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*heptane:ethyl acetate) to give **53b** as a colorless solid (19.4 g, 82%).

m.p.: 100.2−101.9 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 9.28 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 8.12 (t, *J* = 8.1 Hz, 2H), 7.77 − 7.67 (m, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H).

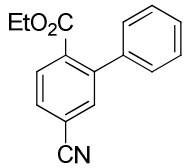
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 161.5, 151.4, 143.0, 142.3, 141.1, 130.3, 129.4, 129.2, 129.1, 129.1, 129.0, 114.6, 55.5.

MS (70 eV, EI) *m/z* (%): 236 (100) [M^+], 233 (14), 221 (17), 209 (12), 166 (8), 118 (8), 57 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 3005, 2930, 2833, 1602, 1576, 1536, 1488, 1427, 1291, 1270, 1246, 1226, 1181, 1130, 1030, 957, 847, 810, 795, 758, 728, 670, 655, 630, 609.

HRMS (EI) for **$C_{15}H_{12}N_2O$** (236.0950): 236.0945.

Synthesis of Ethyl 5-cyanobiphenyl-2-carboxylate (53c)



A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 114 mL, 100 mmol). Ethyl 4-cyanobenzoate (**52c**; 17.5 g, 100 mmol) is added, and the mixture is stirred for 48 h at 25 °C. Then, $Pd(dba)_2$ (280 mg, 0.5 mmol), tfp (230 mg, 1 mmol) and iodobenzene (20.4 g, 100 mmol, 1.00 equiv) are added, and the reaction mixture is stirred for 5 h at 25 °C. The reaction mixture is quenched with a mixture of a sat. aq NH_4Cl solution (150 mL) and aq HCl (2 M, 100 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by flash column chromatography (pentane:ether 7:1) to give **53c** as a yellowish oil (21.1 g, 84%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 − 8.13 (m, 1H), 7.91 − 7.89 (m, 1H), 7.77 − 7.70 (m, 2H), 7.47 − 7.40 (m, 2H), 7.34 − 7.29 (m, 2H), 4.10 (q, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 167.4, 143.2, 139.1, 135.5, 134.0, 132.2, 130.2, 130.1, 128.4, 128.2, 116.3, 114.8, 61.6, 13.6.

MS (70 eV, EI) *m/z* (%): 251 (35) [M^+], 223 (11), 207 (16), 206 (100), 178 (16), 177 (16), 151 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3098, 3052, 2990, 2980, 2938, 2904, 2232, 1712, 1674, 1602, 1578, 1568, 1558, 1504, 1480, 1472, 1444, 1398, 1366, 1350, 1318, 1280, 1250, 1186, 1158, 1138, 1124, 1106, 1076, 1048, 1020, 968, 920, 902, 872, 854, 842, 788, 764, 710, 696, 668, 642, 630, 614, 604, 580, 566.

HRMS (EI) for **$C_{16}H_{13}NO_2$** (251.0946): 251.0941.

6 HIGHLY SELECTIVE C-H ACTIVATIONS OF PYRIDINES AND RELATED N-HETEROCYCLES

6.1 TYPICAL PROCEDURES

Typical Procedure for the metalation of heteroaromatics with hindered metal amide bases (TP 6)

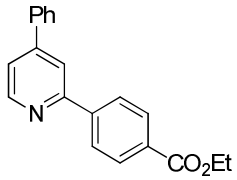
A dry and argon flushed 50 mL Schlenk-Tube, equipped with a magnetic stirring bar was charged with a solution of the corresponding N-heteroarene (2.0 mmol) in dry THF (2 mL) and then cooled to the indicated temperature. The indicated hindered metal amide base in the amount of the given equivalents, titrated prior to use, was added dropwise and the reaction mixture was stirred at the indicated temperature for the given time. Complete metalation was detected by GC analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

Typical Procedure for the BF_3-triggered metalation of heteroaromatics with hindered metal amide bases (TP 7)

A dry and argon flushed 50-mL Schlenk-Tube, equipped with a magnetic stirring bar was charged with a solution of the corresponding N-heteroarene (2.0 mmol) in dry THF (10 mL) and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol,) was added dropwise and stirred for 15 min at the same temperature. The reaction mixture was cooled to the given temperature followed by dropwise addition of the indicated hindered metal amide base in the amount of the given equivalents, titrated prior to use and stirring the reaction mixture at the indicated temperature for the given time. Complete metalation was detected by GC analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

6.2 FUNCTIONALZATION OF PYRIDINES AND RELATED N-HETEROCYCLES

Synthesis of ethyl 4-(4-phenylpyridin-2-yl)benzoate (56):



A mixture of 4-phenylpyridine (**54a**; 310 mg, 2 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M solution in THF, 2.5 mL, 3 mmol) according to **TP 7** (-40 °C, 20 min). $ZnCl_2$ (1 M in THF, 2.2 mL, 2.2 mmol) was added at -40 °C and stirred for 30 min. $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (36 mg, 0.2 mmol) dissolved in THF (2 mL) were then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (441 mg, 1.6 mmol) dissolved

in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. After GC analysis of a hydrolyzed aliquot showed full conversion sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) were added and the layers were separated followed by extraction using diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (*n*pentane:diethyl ether = 4:1) furnished the product **56** as a pale yellowish solid (407 mg, 84% yield).

m.p.: 72.5-78.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.76 (d, *J* = 5.1 Hz, 1H), 8.10 – 8.19 (m, 4H), 7.96 – 7.98 (m, 1H), 7.66 – 7.71 (m, 2H), 7.43 – 7.54 (m, 4H), 4.41 (q, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

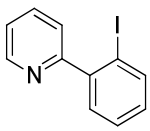
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 156.7, 150.0, 149.8, 143.1, 138.1, 130.9, 130.0, 129.3, 129.2, 127.1, 126.9, 121.0, 119.2, 61.1, 14.3.

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

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

HRMS (EI) for **$C_{20}H_{17}O_2N$** (303.1259): 303.1250.

Synthesis of 2-(2-iodophenyl)pyridine (57a):



According to **TP 6**, 2-Phenylpyridine (**54b**; 310 mg, 2 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 3.3 mL, 4 mmol) (55 °C, 30 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq NH_4Cl solution (9 mL), conc. aq NH_3 (1 mL) and sat. aq $Na_2S_2O_3$ (2 mL) followed by extraction with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl = ether, 4:1) furnished the compound **57a** as a yellowish oil (478 mg, 85% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.70 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.81 – 7.72 (m, 1H), 7.52 – 7.38 (m, 3H), 7.33 – 7.27 (m, 1H), 7.11 – 7.03 (m, 1H).

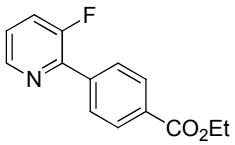
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.6, 149.0, 144.8, 139.7, 136.1, 130.3, 129.7, 128.2, 124.5, 122.5, 96.6.

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

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

HRMS (EI) for **$C_{11}H_8IN$** (280.9701): 280.9682.

Synthesis of ethyl 4-(3-fluoropyridin-2-yl)benzoate (57b):



According to **TP 6**, 3-Fluoropyridine (**54c**; 196 mg, 2.0 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 1.8 mL, 2.2 mmol) (-78 °C, 30 min). $ZnCl_2$ (1 M in THF, 2.2 mL, 2.2 mmol) was added and the mixture was stirred for 30 min at the same temperature. $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (36 mg, 0.2 mmol) dissolved in THF (4 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (442 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and was stirred for 12 h at the same temperature. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) followed by extraction with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 4:1) furnished the compound **57b** as a yellow oil (282 mg, 72% yield).

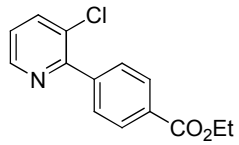
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.56 – 8.52 (m, 1H), 8.17 – 8.15 (m, 1H), 8.14 – 8.12 (m, 1H), 8.08 – 8.05 (m, 1H), 8.05 – 8.02 (m, 1H), 7.56 – 7.48 (m, 1H), 7.35 – 7.28 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 ppm (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3, 157.7 (d, $^1J_{C\text{-}F}$ = 261.6 Hz), 145.3 (d, $^3J_{C\text{-}F}$ = 5.4 Hz), 144.9 (d, $^2J_{C\text{-}F}$ = 10.8 Hz), 139.1 (d, $^3J_{C\text{-}F}$ = 5.4 Hz), 131.0, 129.6, 128.7 (d, *J* = 6.2 Hz), 124.6 (d, $^2J_{C\text{-}F}$ = 20.6 Hz), 124.3 (d, $^3J_{C\text{-}F}$ = 4.1 Hz), 61.1, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3066, 2982, 2362, 2338, 1940, 1712, 1610, 1596, 1578, 1512, 1442, 1402, 1368, 1312, 1268, 1248, 1186, 1096, 1060, 1034, 1016, 864, 838, 800, 786, 742, 730, 698, 640, 630.

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

Synthesis of ethyl 4-(3-fluoropyridin-2-yl)benzoate (57c):



According to **TP 6**, 3-chloropyridine (**54d**; 113 mg, 1.0 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 0.92 mL, 1.1 mmol) (-78 °C, 45 min). $ZnCl_2$ (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise at -78 °C and stirred for 30 min at the same temperature. $Pd(dba)_2$ (57 mg, 0.1 mmol) and tfp (36 mg, 0.2 mmol) dissolved in THF (2 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aq NH_4Cl solution (4.5 mL) and conc. aq NH_3 (0.5 mL) followed by extraction with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 3:1) furnished the compound **57c** as a yellow solid (157 mg, 75% yield).

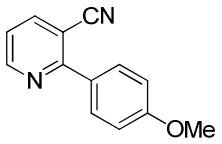
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.64 – 8.59 (m, 1H), 8.18 – 8.11 (m, 2H), 7.86 – 7.76 (m, 3H), 7.31 – 7.26 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 155.4, 147.5, 142.1, 138.4, 130.7, 130.3, 129.4, 129.2, 123.6, 61.1, 14.3.

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

HRMS (ESI) for **$C_{14}H_{13}ClNO_2$ ($M+H^+$)** (262.0635): 262.0627.

Synthesis of 2-(4-methoxyphenyl)nicotinonitrile (57d):



According to **TP 6**, nicotinonitrile (**54e**; 208 mg, 2.0 mmol) was reacted with $TMP_2Zn·2MgCl_2·2LiCl$ (**6**; 0.8 M in THF, 2.75 mL, 2.2 mmol) (25 °C, 12 h). $Pd(dba)_2$ (56 mg, 5 mol%) and tfp (46 mg, 10 mol%) dissolved in THF (4 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl 4-iodoanilsole (221 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aq NH_4Cl solution (4.5 mL) and conc. aq NH_3 (0.5 mL) followed by extraction with diethyl

ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*-pentane/ethyl acetate, 3:1) furnished the compound **57d** as a yellow solid (286 mg, 85% yield).

m.p.: 138.1-139.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.82 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.93 (ddd, *J* = 9.4, 3.0, 2.6 Hz, 2H), 7.29 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.03 (ddd, *J* = 9.4, 3.0, 2.6 Hz, 2H), 3.87 (s, 3H).

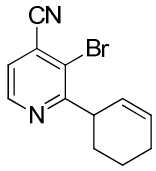
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 161.3, 160.4, 152.5, 141.9, 130.4, 129.5, 120.9, 117.9, 114.1, 106.7, 55.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3064, 2846, 2224, 1606, 1582, 1572, 1554, 1516, 1458, 1432, 1312, 1252, 1192, 1182, 1114, 1038, 1018, 836, 826, 812, 788, 776, 722, 632, 616.

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

HRMS (EI) for **$C_{13}H_{10}N_2O$** (210.0793): 210.0790.

Synthesis of 3-bromo-2-cyclohexylisonicotinonitrile (57e):



According to **TP 6**, 3-bromoisonicotinonitrile (**54f**; 366 mg, 2.0 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 1.85 mL, 2.2 mmol,) (-78 °C, 1 h). CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol,) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (258 mg, 1.6 mmol) was added at -78 °C. The reaction mixture was warmed slowly to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 5:1) furnished the compound **57e** as a yellowish oil (274 mg, 65% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.63 (d, *J* = 4.9 Hz, 1H), 7.84 (d, *J* = 4.9 Hz, 1H), 5.98 – 5.90 (m, 1H), 5.68 – 5.61 (m, 1H), 4.15 – 4.08 (m, 1H), 2.17 – 2.00 (m, 3H), 1.89 – 1.78 (m, 1H), 1.72 – 1.53 (m, 2H).

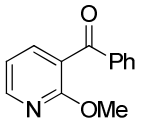
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 148.3, 129.0, 127.1, 124.6, 124.3, 122.2, 115.5, 42.6, 28.4, 24.5, 21.3.

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

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

HRMS (EI) for **$C_{12}H_{11}BrN_2$** (262.0106): 262.0115.

Synthesis of (2-methoxypyridin-3-yl)(phenyl)methanone (57f):



According to **TP 6**, 2-methoxypyrdine (**54g**; 218 mg, 2.0 mmol) was reacted with [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**; 0.3 M in THF, 6.67 mL, 2.0 mmol) (25 °C, 2 h). The reaction mixture was cooled to -40 °C and a solution of $ZnCl_2$ (1 M in THF, 2.2 mL, 2.2 mmol) was added followed by the addition of CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol). After stirring for 20 min at the same temperature benzoyl chloride (308 mg, 1.6 mmol) was added, the reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 5:1) furnished the compound **57f** as a white solid (341 mg, 80% yield).

m.p.: 80.2-81.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.31 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.71 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.47 – 7.40 (m, 2H), 7.00 (dd, *J* = 7.3, 5.1 Hz, 1H), 3.87 (s, 3H).

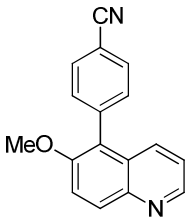
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 194.7, 161.1, 149.2, 138.9, 137.2, 133.3, 129.7, 128.4, 122.7, 116.5, 53.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 1654, 1596, 1576, 1468, 1448, 1406, 1322, 1312, 1302, 1284, 1256, 1232, 1180, 1152, 1104, 1014, 952, 944, 930, 858, 830, 816, 784, 770, 706, 686, 646.

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

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

Synthesis of 4-(6-methoxyquinolin-5-yl)benzonitrile (57g):



According to **TP 6**, 6-methoxyquinoline (**54h**; 318 mg, 2.0 mmol) was reacted with [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**; 0.3 M in THF, 6.67 mL, 2.0 mmol) (-78 °C, 1 h). $ZnCl_2$ (1 M in THF, 2.2 mL, 2.2 mmol) was added dropwise at -78 °C and stirred for 30 min at the same temperature. $Pd(dba)_2$ (56 mg, 5 mol%) and P(*o*-fur)$_3$ (46 mg, 10 mol%) dissolved in THF (4 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of 4-iodobenzonitrile (503 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) followed by extraction with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:ethyl acetate = 4:1) furnished the compound **57g** as a white solid (354 mg, 68% yield).

m.p.: 183.4-185.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.77 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.82 – 7.73 (m, 4H), 7.41 – 7.37 (m, 2H), 7.14 (d, *J* = 2.8 Hz, 1H), 3.97 (s, 3H).

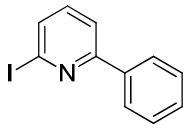
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 157.2, 148.0, 143.8, 141.7, 140.2, 135.3, 131.8, 131.3, 130.1, 123.1, 121.7, 119.1, 111.2, 106.0, 55.7.

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

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

HRMS (EI) for **$C_{17}H_{12}N_2O$** (260.0950): 260.0943.

Synthesis of 2-iodo-6-phenylpyridine (58a):



According to **TP 7**, a mixture of 2-phenylpyridine (**54b**; 310 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 2.5 mL, 3 mmol) (0 °C, 30 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq NH_4Cl solution (9 mL), conc. aq NH_3 (1 mL) and sat. aq $Na_2S_2O_3$ (2 mL) followed by extraction with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 40:1) furnished the compound **58a** as a yellowish solid (467 mg, 83% yield).

m.p.: 81.7-82.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.99 – 7.93 (m, 2H), 7.67 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.63 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.49 – 7.38 (m, 3H), 7.37 (t, *J* = 7.8 Hz, 1H).

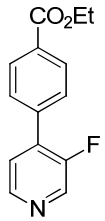
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.0, 138.0, 137.7, 133.1, 129.5, 128.8, 126.9, 119.3, 118.2.

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

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

HRMS (EI) for **$C_{11}H_8NI$** (280.9701): (280.9693).

Synthesis of ethyl 4-(3-fluoropyridin-4-yl)benzoate (58b):



According to **TP 7**, a mixture of 3-fluoropyridine (**54c**; 97 mg, 1 mmol) and $BF_3{\cdot}OEt_2$ (156 mg, 1.1 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 0.92 mL, 1.1 mmol) (-78 °C, 30 min). $ZnCl_2$ (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise at -78 °C and stirred for 30 min at the same temperature. $Pd(dba)_2$ (28 mg, 0.05 mmol) and tfp (23 mg, 0.10 mmol) dissolved in THF (2 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of ethyl

4-iodobenzoate (221 mg, 0.8 mmol) dissolved in THF (1 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aq NH_4Cl solution (4.5 mL) and conc. aq NH_3 (0.5 mL) followed by extraction with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 3:1) furnished the compound **58b** as a yellow solid (145 mg, 74% yield).

m.p.: 60.4-62.9 °C.

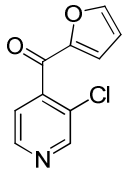
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.56 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.18 – 8.10 (m, 2H), 7.70 – 7.63 (m, 2H), 7.45 – 7.37 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 156.5 (d, $^1J_{C\text{-}F}$ = 258.2 Hz), 145.0 (d, $^3J_{C\text{-}F}$ = 5.4 Hz), 139.0 (d, $^2J_{C\text{-}F}$ = 25.8 Hz), 137.1 (d, $^3J_{C\text{-}F}$ = 1.3 Hz), 135.2 (d, $^2J_{C\text{-}F}$ = 10.6 Hz), 131.2, 130.0, 128.8 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 124.1, 61.3, 14.3.

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

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

Synthesis of (3-chloropyridin-4-yl)(2-furyl)methanone (58c):



According to **TP 7**, a mixture of 3-chloropyridine (**54d**; 228 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 1.1 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 1.8 mL, 2.2 mmol) (-78 °C, 45 min). CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 2-furoyl chloride (209 mg, 1.6 mmol) was added at -78 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 1:1) furnished the compound **58c** as a brown oil (259 mg, 78% yield).

m.p.: 64.3-65.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 8.61 (d, *J* = 4.9 Hz, 1H), 7.71 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.37 (dd, *J* = 4.9, 0.7 Hz, 1H), 7.14 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.61 (dd, *J* = 3.7, 0.8 Hz, 1H).

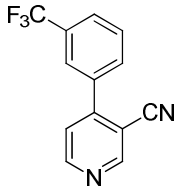
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 179.3, 151.1, 150.0, 148.8, 147.4, 144.6, 128.8, 122.6, 122.1, 113.1.

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

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

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

Synthesis of 4-[3-(trifluoromethyl)phenyl]nicotinonitrile (58d):



According to **TP 7**, a mixture of nicotinonitrile (**54e**; 208 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 0.71 M in THF, 3.1 mL, 2.2 mmol) (-30 °C, 30 min). $Pd(dba)_2$ (56 mg, 0.1 mmol) and tfp (43 mg, 0.2 mmol) dissolved in THF (4 mL) was then transferred *via* cannula to the reaction mixture, followed by the addition of 1-iodo-3-(trifluoromethyl)benzene (435 mg, 1.6 mmol) dissolved in THF (2 mL). The reaction mixture was warmed to 25 °C and stirred for 12 h at the same temperature. The reaction mixture was quenched with sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) followed by extraction with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 1:2) furnished the compound **58d** as a white solid (313 mg, 78% yield).

m.p.: 125.6-128.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.98 (s, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 7.87 – 7.75- (m, 3H), 7.73 – 7.64 (m, 1H), 7.49 (d, *J* = 5.2 Hz, 1H).

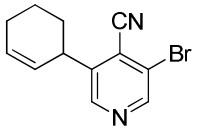
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 154.0, 153.1, 150.7, 136.2, 131.8 (q, *J* = 33.0 Hz), 131.7 (q, *J* = 1.3 Hz), 129.8, 127.0 (q, *J* = 3.7 Hz), 125.3 (q, *J* = 3.8 Hz), 123.7, 123.6 (q, *J* = 272.6 Hz), 116.1, 108.7.

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

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

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

Synthesis of 3-bromo-5-cyclohex-2-en-1-ylisonicotinonitrile (58e):



According to **TP 7**, a mixture of 3-bromoisonicotinonitrile (**54f**; 366 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**; 0.71 M in THF, 3.1 mL, 2.2 mmol) (-78 °C, 1 h). CuCN·2LiCl (1 M in THF, 1.1 mL, 1.1 mmol) was added and the reaction mixture was stirred for 30 min at the same temperature before 3-bromocyclohexene (258 mg, 1.6 mmol) was added. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 5:1) furnished the compound **58e** as a yellowish oil (266 mg, 63% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.72 (s, 1H), 8.56 (s, 1H), 6.13 – 5.97 (m, 1H), 5.70 – 5.55 (m, 1H), 3.90 – 3.72 (m, 1H), 2.26 – 2.02 (m, 3H), 1.80 – 1.47 (m, 3H).

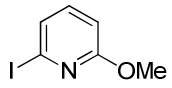
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 150.4, 149.7, 148.3, 145.6, 131.3, 125.8, 122.7, 113.9, 38.8, 31.0, 24.6, 20.5.

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

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

HRMS (EI) for **$C_{12}H_{11}BrN_2$** (262.0106): 262.0114.

Synthesis of 2-iodo-6-methoxypyridine (58f):



According to **TP 7**, a mixture of 2-methoxypyridine (**54g**; 218 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.8 mL, 2.2 mmol, 1.2 M in THF) (0 °C, 60 h). The reaction mixture was cooled to -30 °C and a solution of iodine (1 g, 4 mmol) in THF (4 mL) was added and slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq NH_4Cl solution (9 mL), conc. aq NH_3 (1 mL) and sat. aq $Na_2S_2O_3$ (2 mL) followed by extraction with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*pentane:diethyl ether = 150:1) furnished the compound **58f** as a yellowish solid (353 mg, 75% yield).

m.p.: 49.1-50.3 °C.

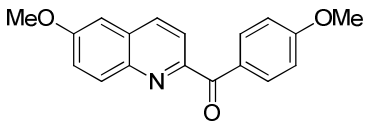
^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.67 (dd, *J* = 8.2, 0.9 Hz, 1H), 3.90 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 163.4, 139.6, 127.5, 113.7, 109.9, 54.1.

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

HRMS (ESI) for **C_6H_7INO ($M+H^+$)** (235,9572): 235.9566.

Synthesis of (4-methoxyphenyl)(6-methoxyquinolin-2-yl)methanone (58g):



According to **TP 7**, a mixture of 6-methoxyquinoline (**54h**; 318 mg, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) was reacted with TMPMgCl·LiCl (**3**; 1.2 M in THF, 1.83 mL, 2.2 mmol) (0 °C, 1 h). The reaction mixture was cooled to -40 °C and CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min at the same temperature. Then, 4-methoxybenzoyl chloride (273 mg, 1.6 mmol) was added at -40 °C. The reaction mixture was slowly warmed to 25 °C and was stirred at this temperature for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (9 mL) and conc. aq NH_3 (1 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration, the solvents were evaporated *in vacuo*. Purification by flash column chromatography (*n*-pentane/ethyl acetate, 2:1) furnished the compound **58g** as a white solid (441 mg, 94% yield).

m.p.: 138.1-139.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.27 (ddd, *J* = 9.4, 2.8, 2.4 Hz, 2H), 8.21 (d, *J* = 8.6 Hz, 1H), 8.12 (d, *J* = 9.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.13 (d, *J* = 2.8 Hz, 1H), 6.98 (ddd, *J* = 9.4, 2.8, 2.4 Hz, 2H), 3.97 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.8, 163.6, 159.3, 152.8, 142.4, 135.7, 133.9, 131.7, 130.2, 129.2, 123.2, 121.4, 113.5, 104.9, 55.7, 55.5.

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

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

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

7 NEW SYNTHESIS OF DIBENZOTHIOPHENES AND RELATED CLASSES OF HETEROCYCLES USING FUNCTIONALIZED DITHIOCARBAMATES

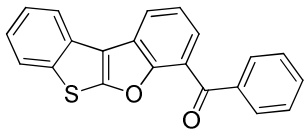
7.1 TYPICAL PROCEDURES

Typical Procedure for the metalation (TP 8):

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 0.3 M in THF, 1 mL, 0.3 mmol, 1.0 equiv). The heteroaromatic substrate (0.3 mmol) in THF (1 mL) was added dropwise at the respective temperature (T_1). The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at the respective temperature (T_2). The completion of the reaction of the reaction was checked by GC analysis of reaction aliquots quenched with sat. aq NH_4Cl solution.

7.2 ALUMINATIONS OF THE HETEROCYCLES

Synthesis of benzo[4,5]thieno[2,3-*b*]benzofuran-4-yl(phenyl)methanone (80a)



Benzo[4,5]thieno[2,3-*b*]benzofuran (**64a**; 67 mg, 0.3 mmol) was metalated according to **TP 8:** T_1 = -20 °C, 2 h; T_2 = -20 °C, 4 h. Before the addition of benzoylchloride (46 mg, 0.33 mmol), a solution of $ZnCl_2$ (1 M in THF, 0.33 mL, 0.33 mmol, 15 min, -20 °C) and subsequently a solution of CuCN·2LiCl (1 M in THF, 0.33 mL, 0.33 mmol, 15 min, -20 °C) were added. After warming to 25 °C over 4 h, the reaction mixture was quenched with methanol (0.1 mL) and after concentration *in vacuo* directly transferred to flash column chromatography (pentane:ethylacetate = 50:1) yielding benzo[4,5]thieno[2,3-*b*]benzofuran-4-yl(phenyl)methanone (**80a**; 70 mg, 71%) as a colorless solid.

m.p.: 154.9 – 156.3 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 8.11 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.61 (m, 1H), 7.57 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.53 – 7.46 (m, 4H), 7.39 – 7.35 (m, 1H).

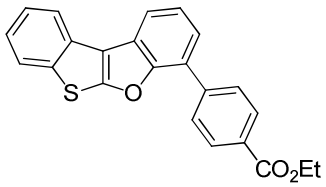
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 193.6, 160.1, 157.9, 138.6, 137.6, 133.2, 130.2, 130.0, 128.4, 125.5, 125.3, 125.1, 124.1, 124.0, 123.6, 123.3, 122.5, 121.4, 119.6.

MS (70 eV, EI) *m/z* (%): 372 (100) [M^+], 344 (17), 327 (10), 271 (7), 163 (6), 135 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2922, 2852, 1664, 1608, 1594, 1560, 1514, 1492, 1464, 1448, 1434, 1410, 1394, 1320, 1306, 1286, 1274, 1250, 1226, 1196, 1180, 1162, 1154, 1058, 1032, 1018, 956, 938, 910, 896, 848, 830, 804, 780, 750, 738, 724, 714, 686, 672

HRMS (EI) for **$C_{21}H_{12}O_2S$** (328.0558): 328.0555.

Synthesis of ethyl 4-(benzo[4,5]thieno[2,3-*b*]benzofuran-4-yl)benzoate (80b)



Benzo[4,5]thieno[2,3-*b*]benzofuran (**64a**; 67 mg, 0.3 mmol) was metalated according to **TP 8:** T_1 = -20 °C, 2 h; T_2 = 50 °C, 8 h. Before the addition of ethyl 4-iodobenzoate (0.33 mmol, 91 mg), a solution of $ZnCl_2$ (1 M in THF, 0.33 mL, 0.33 mmol, 5 min, -20 °C) and subsequently $Pd(dba)_2$ (9 mg, 0.015 mmol) and tfp (7 mg, 0.03 mmol) were added. The reaction mixture was quenched with methanol (0.1 mL) and after concentration *in vacuo* directly transferred to flash column chromatography (pentane:ethylacetate = 50:1) yielding ethyl 4-(benzo[4,5]thieno[2,3-*b*]benzofuran-4-yl)benzoate (**80b**; 82 mg, 73%) as a colorless solid.

m.p.: 147.5 – 148.8 °C.

^{1}H-NMR (600 MHz, THF-d_8) δ (ppm): 8.20 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.93 (dd, *J* = 7.1, 1,7 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.39 – 7.35 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

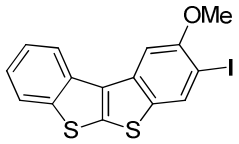
^{13}C-NMR (150 MHz, THF-d_8) δ (ppm): 166.4, 159.3, 157.7, 140.5, 138.5, 130.3, 129.9, 129.8, 128.7, 125.5, 125.2, 124.8, 124.1, 124.0, 123.9, 123.5, 121.5, 120.0, 119.0, 61.0, 14.4.

MS (70 eV, EI) *m/z* (%): 372 (100) [M^+], 344 (17), 327 (10), 271 (7), 163 (6), 135 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3056, 2984, 2902, 1708, 1606, 1560, 1510, 1494, 1480, 1462, 1442, 1434, 1424, 1408, 1388, 1366, 1338, 1310, 1268, 1252, 1242, 1226, 1182, 1156, 1120, 1102, 1068, 1054, 1018, 974, 962, 936, 902, 878, 864, 856, 826, 792, 766, 754, 738, 728, 704, 690, 662.

HRMS (EI) for **$C_{23}H_{16}O_3S$** (372.0820): 372.0815.

Synthesis of 3-iodo-2-methoxybenzo[*b*]benzo[4,5]thieno[3,2-*d*]thiophene (81)



2-Methoxybenzo[*b*]benzo[4,5]thieno[3,2-*d*]thiophene (**62b**; 81 mg, 0.3 mmol) was metalated according to **TP 8:** T_1 = -20 °C, 1 h; T_2 = -20 °C, 20 min. Before the addition of the I_2 (127 mg, 0.5 mmol) in THF, a solution of $ZnCl_2$ (1 M in THF, 0.33 mL, 0.33 mmol, 5 min, -20 °C) was added. The reaction mixture was quenched with sat. aq NaS_2O_3 solution (2.5 mL) and water (2.5 mL). The aqueous layer was extracted with ethylacetate (4 x 5 mL). The combined organic extracts were washed with 2 M HCl (5 mL), dried over $MgSO_4$ and after filtration concentrated *in vacuo*. The crude residue was purified by flash column chromatography (pentane:ethylacetate = 50:1) yielding 3-iodo-2-methoxybenzo[*b*]benzo[4,5]thieno[3,2-*d*]thiophene (**81**; 84 mg, 71%) as colorless crystals

m.p.: 210 °C (decomp).

^{1}H-NMR (400 MHz, THF-d_8) δ (ppm): 8.40 (d, *J* = 7.8 Hz, 1H), 8.35 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.55 – 7.48 (m, 1H), 7.42 – 7.37 (m, 1H), 4.07 (s, 3H).

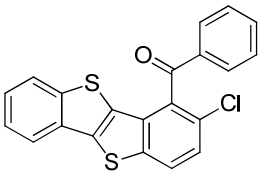
^{13}C-NMR (100 MHz, THF-d_8) δ (ppm): 157.4, 144.6 142.5, 137.9, 135.4, 135.3, 134.1, 134.1, 125.7, 124.9, 124.1, 122.0, 103.4, 83.1, 56.9.

MS (70 eV, EI) *m/z* (%): 396 (100) [M^+], 353 (8), 254 (13), 239 (9), 226 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2926, 1728, 1584, 1468, 1446, 1394, 1340, 1296, 1272, 1258, 1236, 1186, 1162, 1150, 1096, 1078, 1052, 1038, 974, 928, 874, 858, 846, 824, 774, 766, 756, 728, 698, 676.

HRMS (EI) for **$C_{15}H_9IOS_2$** (395.9139): 395.9139.

Synthesis of (3-chlorobenzo[*b*]benzo[4,5]thieno[2,3-*d*]thiophen-4-yl)(phenyl)methanone (82)



3-Chlorobenzo[*b*]benzo[4,5]thieno[2,3-*d*]thiophene (**63**; 82 mg, 0.3 mmol) was metalated according to **TP 8:** T_1 = -20 °C, 2 h; T_2 = -20 °C, 4 h. Before the addition of benzoylchloride (0.33 mmol, 46 mg), a solution of $ZnCl_2$ (1 M in THF, 0.33 mL, 0.33 mmol, 15 min, -20 °C) and subsequently a solution of CuCN·2LiCl (1 M in THF, 0.33 mL, 0.33 mmol, 15 min, -20 °C) were added. After warming to 25 °C over 4 h, the reaction mixture was quenched with methanol (0.1 mL) and after concentration *in vacuo*

directly transferred to flash column chromatography (pentane:ethylacetate = 50:1) yielding (3-chlorobenzo[b]benzo[4,5]thieno[2,3-d]thiophen-4-yl)(phenyl)methanone (**82**; 93 mg, 82%) as a colorless solid.

m.p.: 218.8 – 220.1 °C.

^{1}H-NMR (400 MHz, THF-d_8) δ (ppm): 8.06 (d, *J* = 8.6 Hz, 1H), 8.02 – 7.97 (m, 1H), 7.90 – 7-82 (m, 3H), 7.66 – 7.60 (m, 2H), 7.51 – 7.40 (m, 4H).

^{13}C-NMR (100 MHz, THF-d_8) δ (ppm): 193.5, 143.4, 142.6, 136.9, 135.9, 135.0, 134.8, 133.5, 133.4, 130.5, 130.4, 129.8, 128.5, 127.7, 126.6, 126.1, 125.0, 124.2, 122.5.

MS (70 eV, EI) *m/z* (%): 378 (100) [M^+], 343 (4), 301 (9), 273 (10), 238 (6), 105 (32), 77 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960, 1910, 1790, 1670, 1592, 1580, 1550, 1484, 1448, 1420, 1340, 1322, 1314, 1290, 1256, 1178, 1158, 1132, 1096, 1068, 1054, 1022, 998, 972, 940, 924, 808, 752, 738, 726, 700, 682, 668.

HRMS (EI) for **$C_{21}H_{11}ClOS_2$** (377.9940): 377.9929.

8 STEREOSELECTIVE SYNTHESIS OF TETRA-SUBSTITUTED ALKENES *VIA* A SEQUENTIAL CARBOCUPRATION AND A NEW SULFUR-LITHIUM EXCHANGE

8.1 TYPICAL PROCEDURES

Typical procedure for the carbocupration of alkynyl sulfides with functionalized diorganozinc reagents (TP 9)

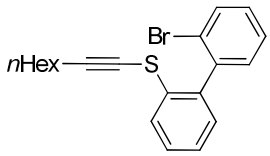
A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with the diorganozinc reagent of type $R_2Zn{\cdot}2MgX_2{\cdot}2LiCl$ (1.5 equiv) and cooled to -20 °C. CuCN·2LiCl (1.5 equiv) was added dropwise and the resulting mixture was stirred for 30 min. Then, the alkynyl sulfide was added, warmed to 25 °C and stirred for the indicated time. The carbocupration progress was monitored by GC analysis of the reaction aliquots, which where quenched with sat. aq NH_4Cl solution and conc. aq NH_3 = 9:1 using tetradecane as internal standard.

Typical procedure for the sulfur-lithium exchange (TP 10)

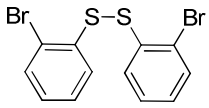
In a dry and argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar 2'-bromobiphenyl thioether (1 mmol) was dissolved in THF (10 mL) and the solution cooled to -78 °C. Then the organolithium was added and the reaction mixture was stirred for 10 min.

8.2 SYNTHESIS OF STARTING MATERIALS

Synthesis of 2'-bromobiphenyl-2-yl oct-1-yn-1-yl sulfide (83a)



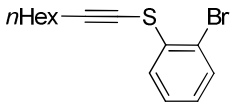
A: Synthesis of 1,1'-disulfanediylbis(2-bromobenzene) (90)



This compound was prepared from commercially available 2-bromothiophenole according to the procedure reported by Wilson and Tarbell.[224]

[224] H. F. Wilson, D. S. Tarbell, *J. Am. Chem. Soc.* **1950**, *72*, 5200.

B: Synthesis of 1-bromo-2-(oct-1-yn-1-ylsulfanyl)benzene (91)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-octyne (1.1 g, 10 mmol) in THF (10 mL). *n*BuLi (4.4 mL, 11 mmol) was slowly added at -78 °C and the resulting solution was stirred for 2 h. Then, 1,1'-disulfanediylbis(2-bromobenzene) (**90**, 4.1 g, 11 mmol) was added at this temperature and the resulting mixture was warmed to 25 °C over 3 h. The reaction mixture was quenched with sat. aq Na_2CO_3 (100 mL) and the resulting mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (pentane) yielded 1-bromo-2-(oct-1-yn-1-ylsulfanyl)benzene (**91**, 1.63 g, 77%) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.65 – 7.62 (m, 2H), 7.50 – 7.46 (m, 1H), 7.23 – 7.19 (m, 1H), 2.51 (t, *J* = 6.9 Hz, 2H), 1.58 – 1.50 (m, 2H), 1.42 – 1.35 (m, 2H), 1.26 – 1.27 (m, 4H), 0.87 – 0.83 (m, 3H).

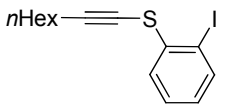
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 134.0, 132.8, 128.8, 128.0, 126.2, 118.4, 102.9, 63.3, 30.7, 28.0, 27.9, 22.0, 19.5, 13.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2928, 2856, 1575, 1446, 1428, 1255, 1104, 1036, 1018, 743, 726, 710.

MS (70 eV, EI) *m/z* (%): 298 (50), 296 (45) [M^+], 229 (20), 227 (31), 225 (11), 190 (14), 188 (25), 188 (14), 183 (25), 181 (26), 175 (16), 174 (42), 173 (19), 160 (14), 149 (17), 148 (95), 147 (100), 146 (20), 145 (13), 141 (27), 115 (12), 109 (51), 108 (20), 108 (14), 107 (17), 102 (32), 93 (14), 81 (14), 79 (33), 71 (23), 69 (12), 67 (70), 55 (13), 44 (10), 44 (15).

HRMS (EI) for **$C_{14}H_{17}BrS$**: (296.0234): 296.0225.

C: Synthesis of 1-iodo-2-(oct-1-yn-1-ylsulfanyl)benzene (92)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-bromo-2-(oct-1-yn-1-ylsulfanyl)benzene (**91**, 2.1 g, 10 mmol) and cooled to -20 °C. *i*PrMgCl·LiCl (**1**, 17 mL, 11 mmol) was added at -20 °C and the resulting mixture was warmed to 0 °C over 10 h. Then, a solution of I_2 (5.6 g, 22 mmol) in THF (20 mL) was added and the resulting mixture was stirred at this temperature for 15 min. The reaction mixture was quenched with sat. aq $Na_2S_2O_3$ (100 mL) and the resulting mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by

flash column chromatography (pentane + 2 vol-% NEt_3) yielded 1-iodo-2-(oct-1-yn-1-ylsulfanyl)benzene (**92**, 2.41 g, 93%) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.81 (dd, *J* = 7.8 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.52 – 7.47 (m, 1H), 7.04 – 7.00 (m, 1H), 2.51 – 2.48 (m, 2H), 1.57 – 1.50 (m, 2H), 1.42 – 1.35 (m, 2H), 1.30 – 1.25 (m, 4H), 0.87 – 0.83 (m, 3H).

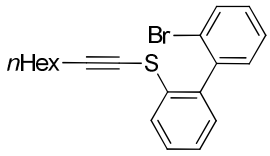
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 139.2, 137.6, 129.3, 127.9, 125.6, 102.6, 94.0, 65.0, 30.7, 28.0, 27.9, 22.0, 19.5, 13.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2926, 2856, 1568, 1558, 1440, 1424, 1378, 1324, 1254, 1094, 1036, 1008, 938, 742, 702, 644.

MS (70 eV, EI) *m/z* (%): 344 (90) [M^+], 275 (23), 273 (20), 236 (39), 174 (15), 173 (17), 148 (43), 147 (100), 146 (31), 141 (25), 128 (13), 109 (47), 109 (16), 108 (17), 108 (19), 102 (22), 81 (15), 79 (27), 71 (16), 69 (13), 67 (58), 57 (14), 55 (19), 43 (13), 41 (17).

HRMS (EI) for **$C_{14}H_{17}IS$**: (344.0096) 344.0101.

D: Synthesis of 2'-bromobiphenyl-2-yl oct-1-yn-1-yl sulfide (83a)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with *i*PrMgCl·LiCl (**1**, 9.4 mL, 12.6 mmol) and cooled to -20 °C. 1,2-Dibromobenzene (2.8 g, 12 mmol) was slowly added at this temperature and stirred at -15 °C for 2 h. Then, $ZnCl_2$ (1 M in THF, 12.6 mL, 12.6 mmol) was added and the resulting mixture was stirred at this temperature for 20 min. The resulting solution was cannulated to a new *Schlenk*-flask equipped with 1-iodo-2-(oct-1-yn-1-ylsulfanyl)benzene (**92**, 2.8 g, 12 mmol) in THF (12 mL), $Pd(dba)_2$ (115 mg, 0.12 mmol) and tfp (93 mg, 0.24 mmol) and stirred at 50 °C for 5 h. The reaction mixture was then quenched with sat. aq NH_4Cl (100 mL) and the resulting mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (pentane + 2 vol-% NEt_3) to give **83a** (2.3 g, 80%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82 – 7.79 (m, 1H), 7.71 – 7.67 (m, 1H), 7.47 – 7.35 (m, 2H), 7.31 – 7.24 (m, 3H), 7.16 – 7.13 (m, 1H), 2.24 (t, *J* = 6.9 Hz, 2H), 1.65 – 1.56 (m, 2H), 1.50 – 1.40 (m, 2H), 1.36 – 1.29 (m, 4H), 0.94 – 0.89 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 139.8, 138.4, 133.5, 132.8, 131.2, 129.8, 129.7, 128.8, 127.3, 125.8, 125.7, 123.8, 100.6, 64.6, 31.3, 28.6, 28.5, 22.5, 20.3, 14.0.

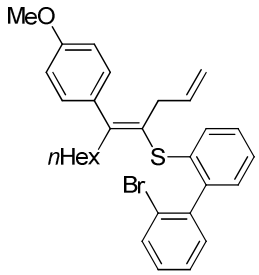
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3052, 2952, 2926, 2855, 1582, 1561, 1453, 1434, 1421, 1377, 1324, 1159, 1118, 1078, 1052, 1035, 1027, 1002, 942, 748, 729, 686, 658.

MS (70 eV, EI) *m/z* (%): 372 (5) [M^+], 294 (20), 293 (100), 221 (11), 184 (21).

HRMS (EI) for **$C_{20}H_{21}BrS$** (372.0547) 372.0539.

8.3 CARBOCUPRATION AND SULFUR-LITHIUM EXCHANGE

Synthesis of 2-{[(1*E*)-1-allyl-2-(4-methoxyphenyl)oct-1-en-1-yl]thio}-2'-bromobiphenyl (86a)



Prepared according to **TP 9** from 2'-bromobiphenyl-2-yl oct-1-yn-1-yl sulfide (**83a**, 373 mg, 1 mmol) and bis(4-methoxyphenyl)zinc[225] (**84a**, 4 mL, 1.5 mmol) [carbometalation conditions: 25 °C, 8 h]. Then, the reaction mixture was cooled to -40 °C and allyl bromide (0.29 mL, 3 mmol) was added. The solution was stirred for 30 min at this temperature followed by 30 min at 0 °C. The reaction mixture was quenched with sat. aq NH_4Cl solution and conc. aq NH_3 = 9:1 (100 mL) and the resulting mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **86a** (367 mg, 84%, *E/Z* = 99:1) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.68 (d, *J* = 7.9 Hz, 1H), 7.41 – 7.16 (m, 7H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.79 – 5.65 (m, 1H), 4.90 – 4.75 (m, 2H), 3.80 (s, 3H), 2.71 (d, *J* = 6.1 Hz, 2H), 2.46 (d, *J* = 4.1 Hz, 2H), 1.28 – 1.15 (m, 8H), 0.81 (t, *J* = 6.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.4, 149.6, 141.9, 141.4, 136.6, 135.1, 134.2, 132.6, 131.5, 130.4, 129.8, 129.1, 128.3, 127.5, 126.9, 125.8, 123.9, 115.4, 113.4, 107.5, 55.2, 38.3, 37.1, 31.6, 29.0, 28.1, 22.5, 14.1.

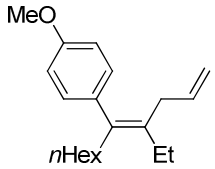
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2926, 2855, 1582, 1561, 1453, 1434, 1421, 1377, 1323, 1159, 1118, 1078, 1052, 1027, 1002, 942, 863, 748, 729, 686, 658.

[225] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem.* **2010**, *122*, 4769; *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.

MS (70 eV, EI) *m/z* (%): 523 (26), 522 (78), 521 (26), 520 (70) [M^+], 442 (24), 441 (65), 216 (10), 215 (55), 187 (35), 186 (18), 185 (19), 184 (15), 174 (14), 173 (87), 171 (11), 161 (46), 159 (23), 158 (12), 147 (20), 145 (13), 121 (100).

HRMS (EI) for **$C_{30}H_{33}BrOS$**: (520.1435) 520.1432.

Synthesis of 1-[(1*Z*)-2-ethyl-1-hexylpenta-1,4-dien-1-yl]-4-methoxybenzene (87a)



Prepared according to **TP 10** from 2-{[(1*E*)-1-allyl-2-(4-methoxyphenyl)oct-1-en-1-yl]thio}-2'-bromobiphenyl (**86a**, 436 mg, 1 mmol) and *s*BuLi (1.35 mL, 1.1 mmol). After 10 min iodethane (312 mg, 2.0 mmol) was added and the solution was stirred for 15 min. The reaction mixture was quenched with sat. aq NH_4Cl solution (25 mL) and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (pentane + 2 vol-% NEt_3) yielded **87a** (151 mg, 75%, *E/Z* = 1:99) as a yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.03 – 7.01 (m, 2H), 6.86 – 6.83 (m, 2H), 5.75 – 5.68 (m, 1H), 4.97 – 4.92 (m, 2H), 3.82 (s, 3H), 2.61 (d, *J* = 6.3 Hz, 2H), 2.32 (t, *J* = 7.1 Hz, 2H), 2.18 (q, *J* = 7.5 Hz, 2H), 1.31 – 1.20 (m, 8H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.86 (m, *J* = 7.1 Hz, 3H).

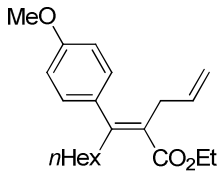
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 157.7, 137.8, 136.8, 136.0, 134.6, 129.7, 114.8, 113.2, 55.1, 37.1, 34.2, 31.8, 29.3, 28.4, 23.8, 22.6, 14.1, 13.4

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2926, 2872, 2856, 1636, 1608, 1508, 1458, 1442, 1374, 1286, 1242, 1174, 1104, 1038, 994, 908, 832, 810, 742, 704.

MS (70 eV, EI) *m/z* (%): 287 (15), 286 (61) [M^+], 257 (24), 202 (17), 201 (100), 187 (29), 184 (35), 174 (11), 173 (55), 172 (13), 161 (15), 160 (15), 159 (40), 158 (16), 147 (14), 145 (13), 128 (13), 121 (65), 115 (13), 91 (13), 57 (13), 55 (12), 43 (16), 43 (14), 41 (15).

HRMS (EI) for **$C_{20}H_{30}O$**: (286.2297) 286.2290.

Synthesis of ethyl (2*E*)-2-allyl-3-(4-methoxyphenyl)non-2-enoate (87b)



Prepared according to **TP 10** from 2-(((1*E*)-1-Allyl-2-(4-methoxyphenyl)oct-1-en-1-yl)thio)-2'-bromobiphenyl (**86a**, 436 mg, 1 mmol) and *s*BuLi (1.35 mL, 1.1 mmol). After 10 min ethyl chloroformate (119 mg, 1.1 mmol) was added and the solution was stirred for 15 min. The reaction mixture was quenched with sat. aq NH_4Cl solution (25 mL) and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (pentane + 2 vol-% NEt_3) yielded **87b** (135 mg, 55%, *E/Z* = 95:5) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.10 – 7.07 (m, 2H), 6.95 – 6.92 (m, 2H), 5.76 – 5.66 (m, 1H), 4.98 – 4.90 (m, 2H), 4.15 (t, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 3.01 – 2.92 (m, 2H), 2.79 (d, *J* = 5.9 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 – 1.12 (m, 8H), 0.81 – 0.78 (m, 3H).

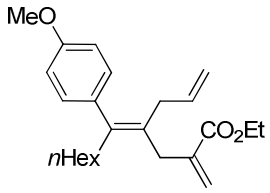
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 169.1, 158.9, 148.7, 136.4, 132.9, 129.0, 127.6, 116.1, 114.1, 60.4, 55.5, 36.1, 35.5, 31.4, 28.9, 28.1, 22.4, 14.5, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2928, 2858, 1712, 1608, 1510, 1462, 1442, 1366, 1284, 1244, 1208, 1176, 1134, 1112, 1080, 1032, 1010, 994, 912, 834, 810, 752, 700, 668.

MS (70 eV, EI) *m/z* (%): 331 (18), 330 (100) [M^+], 329 (20), 285 (45), 260 (40), 257 (40), 245 (55), 227 (41), 214 (52), 199 (34), 199 (43), 187 (36), 186 (52), 185 (37), 173 (57), 172 (50), 171 (67), 159 (28), 158 (24), 147 (19), 145 (20), 134 (22), 128 (22), 121 (78), 108 (26).

HRMS (EI) for **$C_{21}H_{30}O_3$**: (330.2195) 330.2179.

Synthesis of ethyl (4*E*)-4-allyl-5-(4-methoxyphenyl)-2-methyleneundec-4-enoate (87c)



Prepared according to **TP 10** from 2-{[(1*E*)-1-allyl-2-(4-methoxyphenyl)oct-1-en-1-yl]thio}-2'-bromobiphenyl (**86a**, 436 mg, 1 mmol) and *s*BuLi (1.35 mL, 1.1 mmol). After 10 in CuCN·2LiCl (1.1 mL, 1.1 mmol) was added and the resulting solution was stirred for 30 min. Then, ethyl

2-(bromomethyl)acrylate (452 mg, 1.5 mmol) was added and the mixture was warmed to 0 °C over 2 h. The reaction mixture was quenched with sat. aq NH_4Cl solution (25 mL) and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (pentane+ 2 vol-% NEt_3) yielded **87c** (157 mg, 55%, *E/Z* = 99:1) as a yellow oil.

^{1}H-NMR (600 MHz, C_6D_6) δ (ppm): 7.12 – 7.10 (m, 2H), 6.87 – 6.84 (m, 2H), 6.46 (q, *J* = 1.7 Hz, 1H), 5.84 – 5.77 (m, 1H), 5.63 (q, *J* = 1.7 Hz, 1H), 5.08 – 5.03 (m, 2H), 4.09 (t, *J* = 7.1 Hz, 2H), 3.52 (t, *J* = 1.8 Hz, 2H), 3.38 (s, 3H), 2.78 (d, *J* = 6.3 Hz, 2H), 2.45 – 2.41 (m, 2H), 1.41 – 1.36 (m, 2H), 1.27 – 1.16 (m, 6H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H).

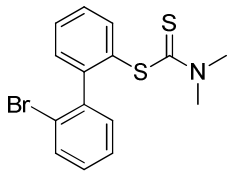
^{13}C-NMR (150 MHz, C_6D_6) δ (ppm): 166.8, 158.5, 140.9, 139.1, 137.3, 135.1, 129.5, 129.3, 128.0, 124.0, 115.4, 113.6, 60.4, 54.4, 37.8, 34.8, 32.8, 31.8, 29.3, 28.3, 22.7, 13.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927, 1716, 1608, 1510, 1464, 1283, 1243, 1175, 1134, 1034, 944, 833.

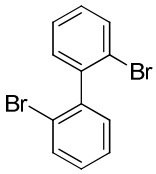
MS (70 eV, EI) *m/z* (%): 370 (100) [M^+], 285 (20), 257 (48), 239 (49), 211 (27), 185 (25), 173 (27), 172 (15), 171 (20), 159 (15), 147 (12), 122 (24), 121 (100), 59 (14), 43 (14), 41 (15).

HRMS (EI) for **$C_{24}H_{34}O_3$**: (370.2508) 370.2504.

Synthesis of 2'-bromo-[1,1'-biphenyl]-2-yl dimethylcarbamodithioate (95)



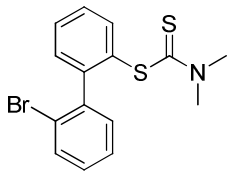
A: Synthesis of 2,2'-dibromo-1,1'-biphenyl



This compound was prepared from commercially available 1,2-dibromobenzene according to the procedure reported by Holmes *et al*.[226]

[226] K. L. Chan, S. E. Watkins, C. S. K. Mak, M. J. McKiernan, C. R. Towns, S. I. Pascua, A. B. Holmes, *Chem. Commun.* **2005**, 5766.

B: Synthesis of 2'-bromo-[1,1'-biphenyl]-2-yl dimethylcarbamodithioate (95)



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with 2,2'-dibromo-1,1'-biphenyl (7.8 g, 25 mmol) in THF (125 mL) and cooled to -78 °C. A solution of *n*BuLi in hexanes (13.75 mL, 27.5 mmol) was added dropwise and the resulting mixture was stirred for 15 min. Then tetramethylthiuram disulfide (6.61 g, 27.5 mmol) was added in one portion and the suspension slowly warmed to 25 °C over 12 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution (100 mL), extracted with CH_2Cl_2 (3 × 200 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by recrystallisation from heptane:CH_2Cl_2 to give **95** (7.25 g, 82 %) as colorless crystals.

m.p.: 150.7 – 152.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60 (dt, *J* = 7.7, 1.6 Hz, 2H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.48 (td, *J* = 7.6, 1.5 Hz, 1H), 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.20 (dd, *J* = 7.7, 1.7 Hz, 1H), 3.42 (s, 3H), 3.25 (s, 3H).

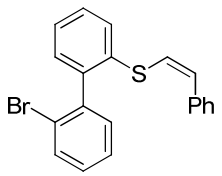
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 197.0, 146.4, 141.4, 138.4, 131.8, 131.1, 130.6, 130.2, 129.0, 128.7, 126.6, 123.6, 45.4, 42.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1496, 1454, 1431, 1374, 1243, 1144, 1055, 1025, 1004, 979, 944, 860, 764, 751, 720, 693, 655.

MS (70 eV, EI) *m/z* (%): 351 (1) [M^+], 272 (46), 184 (16), 152 (7), 139 (7), 88 (100), 73 (5), 43 (7).

HRMS (EI) for **$C_{15}H_{14}BrNS_2$**: (350.9751) 350.9733.

Synthesis of (*Z*)-(2'-bromo-[1,1'-biphenyl]-2-yl)(styryl)sulfane (94)



2'-bromo-[1,1'-biphenyl]-2-yl dimethylcarbamodithioate (**95**, 7.05 g., 20 mmol) was added to a freshly prepared solution of NaOEt in EtOH, made from sodium (2.37 g, 25 mmol) and absolute

ethanol (25 mL). Freshly distilled phenylacetylene (3.0 g., 30 mmol) was then added and, after 15 h at reflux, the resulting solution was poured into water (100 mL), extracted with extracted with CH_2Cl_2 (3 × 200 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane+ 1 vol-% NEt_3) yielded **94** (157 mg, 74%, *E/Z* > 1:99) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.43 (dd, *J* = 5.7, 1.5 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.35 (d, *J* = 6.1 Hz, 2H), 7.32 – 7.22 (m, 4H), 6.59 (d, *J* = 10.5 Hz, 1H), 6.48 (d, *J* = 10.5 Hz, 1H).

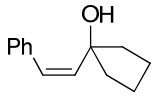
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 142.2, 141.2, 136.3, 135.8, 132.6, 131.3, 130.9, 130.3, 129.2, 128.9, 128.7, 128.1, 127.9, 127.1, 127.0, 127.0, 125.9, 123.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 3019, 1594, 1562, 1490, 1455, 1422, 1354, 1082, 1055, 1027, 1003, 944, 943, 909, 846, 750, 725, 689, 659.

MS (70 eV, EI) *m/z* (%): 366 (7) [M^+], 287 (100), 209 (16), 184 (39), 52 (16), 139 (11), 103 (55), 77 (22), 43 (43).

HRMS (EI) for **$C_{20}H_{15}BrS$**: (366.0078) 366.0075.

Synthesis of (*Z*)-1-styrylcyclopentanol (97a)



Prepared according to **TP 10** from (*Z*)-(2'-bromo-[1,1'-biphenyl]-2-yl)(styryl)sulfane (**94**, 367 mg, 1 mmol) and *t*BuLi (1.6 mL, 1.6 mmol). After 10 min cyclopentanone (67 mg, 0.8 mmol) was added and the resulting solution was stirred for 15 min. Then, the reaction mixture was quenched with sat. aq $NaHCO_3$ solution (25 mL) and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (aluminum oxide, pentane) yielded **97a** (107 mg, 71%, *E/Z* > 1:99) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.53 (d, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 12.7 Hz, 1H), 5.80 (d, *J* = 12.7 Hz, 1H), 4.59 – 4.46 (s, 1H), 1.77 – 1.45 (m, 8 H)

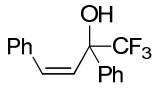
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 138.6, 137.3, 129.6, 128.8, 127.4, 126.5, 79.4, 40.6, 23.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2870, 1492, 1447, 1183, 1071, 1028, 991, 945, 915, 886, 840, 767, 694.

MS (70 eV, EI) *m/z* (%): 188 (3) [M^+], 145 (3), 105 (3), 91 (7), 88 (5), 70 (10), 61 (14), 45 (13), 43 (100).

HRMS (EI) for **$C_{13}H_{16}O$**: (188.1201) 188.1193.

Synthesis of (*Z*)-1,1,1-trifluoro-2,4-diphenylbut-3-en-2-ol (97b)



Prepared according to **TP 10** from (*Z*)-(2'-bromo-[1,1'-biphenyl]-2-yl)(styryl)sulfane (**94**, 367 mg, 1 mmol) and *t*BuLi (1.6 mL, 1.6 mmol). After 10 min α,α,α-trifluoroacetophenone (139 mg, 0.8 mmol) was added and the resulting solution was stirred for 15 min. Then, the reaction mixture was quenched with sat. $NaHCO_3$ solution (25 mL) and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (aluminum oxide, pentane) yielded **97b** (183 mg, 82%, *E/Z* > 1:99) as a yellow oil.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.54 (d, *J* = 7.0 Hz, 2H), 7.28 – 7.23 (m, 4H), 7.16 – 7.12 (s, 1H), 7.08 – 7.02 (m, 3H), 6.82 (d, *J* = 12.9 Hz, 1H), 6.29 (d, *J* = 12.9 Hz, 1H), 3.31 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 137.8, 135.8, 135.2, 130.4, 128.5, 128.0, 127.9, 127.8, 127.7, 127.6, 126.3 (q, *J* = 288.2 Hz), 75.7 (q, *J* = 28.6 Hz).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1494, 1449, 1277, 1253, 1183, 1151, 1125, 1071, 1030, 986, 946, 911, 761, 730, 694.

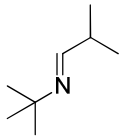
MS (70 eV, EI) *m/z* (%): 278 (3) [M^+], 209 (39), 131 (16), 105 (10), 103 (13), 77 (17), 61 (9), 45 (11), 43 (100).

HRMS (EI) for **$C_{16}H_{13}F_3O$**: (278.0918) 278.0916.

9 DIRECT Pd-CATALYZED CROSS-COUPLING OF FUNCTIONALIZED ORGANOALUMINUM REAGENTS

9.1 PREPARATION OF STARTING MATERIALS

Synthesis of *N*-*tert*-butyl(2-methylpropylidene)amine

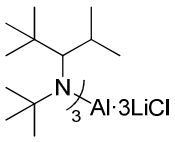


This compound was prepared from commercially available *tert*-butylamine and isobutyraldehyde according to the procedure reported by *Dowd*[227] and distilled twice at atmospheric pressure prior usage.

Preparation of $AlCl_3$-Solution in THF

In an argon flushed 100 mL *Schlenk*-flask, THF (60 mL) was cooled to -78 °C and dry $AlCl_3$ (2.67 g, 20 mmol) was added in small portions over a period of 20 min. The resulting mixture was stirred at -78 °C for 1 h and then slowly warmed to 0 °C within 4 h.[228]

Preparation of the Base aluminum *tris*-(*tert*-Butyl-(1-isopropyl-2,2-dimethyl-propyl)-amide) *tris*(Lithium Chloride) ([(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl ;7)



In a dry and argon flushed 50 mL *Schlenk*-tube, equipped with a septum and magnetic stirring bar, *N*-*tert*-butyl(2-methylpropylidene)amine (191 mg, 1.5 mmol) was dissolved in THF (1.5 mL). This solution was cooled to –78 °C and *t*BuLi (1.5 M in pentane, 1 mL, 1.5 mmol) was added dropwise and stirred at this temperature for 1 h, then slowly warmed to 0 °C within 4 h. Afterwards, a freshly prepared solution of $AlCl_3$ (0.5 mmol, 1.5 mL) in THF was added at -60 °C and the mixture was stirred for 2 h.

[227] G. Stork, S. R. Dowd, *Org. Synth*. **1974**, *54*, 46.
[228] H. Nöth, R. Rurländer, P. Wolfgardt, Peter, *Z. Naturforschung, Part B* **1982**, *37*, 29.

9.2 TYPICAL PROCEDURES

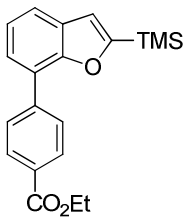
Typical Procedure for Alumination and Subsequent, Direct Cross-Coupling (TP 11)

The fresh aluminum *tris*-(*tert*-butyl-(1-*iso*propyl-2,2-dimethyl-propyl)-amide) *tris*(lithium chloride) ([(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl; **7**) solution (0.5 mmol) was concentrated *in vacuo* to a final volume of approximately 1.5 mL and used without titration. The corresponding arene (1.0 mmol) was added neat and the mixture was stirred at 25 °C for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots, quenched with iodine or allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

The thus prepared organoaluminum reagent (1.0 mmol) was added to a solution of Pd(tmpp)$_2$Cl$_2$ (30 mg, 0.02 mmol) and the electrophile (0.8 mmol) in DMF (2.0 mL). Afterwards, 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) was added and the mixture was stirred at 80 °C for 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (7.5 mL) and water (2.5 mL) were added and the aq layer was extracted with Et_2O or EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo,* purification by flash column chromatography afforded the expected products.

9.3 DIRECTED ALUMINATION AND SUBSEQUENT CROSS-COUPLING

Synthesis of ethyl 4-[2-(trimethylsilyl)benzofuran-7-yl]benzoate (103a)



Benzofuran-2-yltrimethylsilane (**101a**; 381 mg, 2.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)N]$_3$Al·3LiCl (**7**; 1.0 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with ethyl 4-iodobenzoate (**99a**; 442 mg, 1.6 mmol), Pd(tmpp)$_2$Cl$_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (0.1 M in DMF, 1.0 mL, 0.10 mmol) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 49:1) afforded the desired product **103a** (396 mg, 73 %) as a colorless solid.

m.p.: 83-85 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.14 (m, *J* = 8.6 Hz, 2H), 7.97 (m, *J* = 8.4 Hz, 2H), 7.55 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.46 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.30 – 7.20 (m, 1H), 7.00 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.33 (s, 9H).

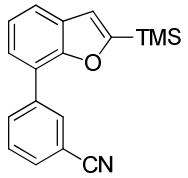
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.6, 163.9, 155.3, 141.4, 129.7, 129.2, 129.1, 128.4, 124.1, 123.8, 123.0, 121.1, 116.1, 60.9, 14.4, -1.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974, 2958, 2906, 1706, 1666, 1610, 1539, 1478, 1474, 1440, 1394, 1367, 1316, 1284, 1268, 1252, 1246, 1217, 1190, 1181, 1156, 1128, 1111, 1100, 1065, 1056, 1025, 969, 962, 937, 905, 880, 841, 795, 762, 745, 714, 696.

MS (70 eV, EI) *m/z* (%): 339 (26), 338 (100) [M^+], 323 (18), 293 (10), 251 (15), 235 (28).

HRMS (EI) for **$C_{20}H_{22}O_3Si$** (338.1338): 338.1329.

Synthesis of 3-[2-(trimethylsilyl)benzofuran-7-yl]benzonitrile (103b)



Benzofuran-2-yltrimethylsilane (**101a**; 381 mg, 2.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 1.0 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with 3-cyanophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**99b**; 642 mg, 1.6 mmol), Pd(tmpp)$_2Cl_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (0.1 M in DMF, 1.0 mL, 0.10 mmol,) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 49:1) afforded the desired product **103b** (329 mg, 71 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (s, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 0.38 (s, 9H).

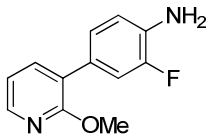
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 164.1, 155.0, 138.1, 132.6, 132.0, 130.7, 129.3, 129.2, 123.5, 123.1, 122.7, 121.4, 118.9, 116.2, 112.7, -1.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3067, 2959, 2900, 2230, 1598, 1577, 1536, 1488, 1468, 1429, 1394, 1320, 1288, 1269, 1250, 1227, 1168, 1158, 1109, 1064, 964, 913, 838, 800, 779, 757, 744, 689.

MS (70 eV, EI) *m/z* (%): 292 (13), 291 (55) [M^+], 277 (19), 276 (100), 260 (18).

HRMS (EI) for **$C_{18}H_{17}NOSi$** (291.1079): 291.1074.

Synthesis of 2-Fluoro-4-(2-methoxypyridin-3-yl)aniline (103c)



2-Methoxypyridine (**101b**; 381 mg, 2.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 1.0 mmol) with stirring for 30 min at 25 °C. The subsequent cross-coupling with 2-fluoro-4-iodoaniline (**99c**; 380 mg, 1.6 mmol), $Pd(tmpp)_2Cl_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (0.1 M in DMF, 1.0 mL, 0.10 mmol) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:EtOAc = 5:1) afforded the desired product **103c** (256 mg, 73 %) as a colorless solid.

m.p.: 71-73 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (d, *J* = 3.2 Hz, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 6.0 Hz, 1H), 6.81 (t, *J* = 8.7 Hz, 1H), 3.98 (s, 3H), 3.82 (br s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 160.7, 151.1 (d, $^1J_{C\text{-}F}$ = 238 Hz), 145.1, 137.8, 134.0 (d, $^2J_{C\text{-}F}$ = 13 Hz), 127.1 (d, $^3J_{C\text{-}F}$ = 7 Hz), 125.1 (d, $^4J_{C\text{-}F}$ = 3 Hz), 123.6 (d, $^4J_{C\text{-}F}$ = 2 Hz), 117.1, 116.4 (d, $^3J_{C\text{-}F}$ = 4 Hz), 116.0 (d, $^2J_{C\text{-}F}$ = 20 Hz), 53.5.

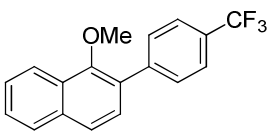
^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm): -135.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3483, 3359, 3227, 1646, 1582, 1526, 1464, 1451, 1396, 1332, 1312, 1301, 1244, 1224, 1180, 1167, 1147, 1110, 1071, 1024, 1016, 904, 870, 824, 807, 790, 776, 770, 714, 700, 668, 658.

MS (70 eV, EI) *m/z* (%): 219 (14), 218 (100) [M^+], 201 (11), 189 (14), 175 (12), 148 (12).

HRMS (EI) for **$C_{12}H_{11}FN_2O$** (218.0855): 218.0849.

Synthesis of 1-methoxy-2-[4-(trifluoromethyl)phenyl]naphthalene (103d)



1-Methoxynaphthalene (**67c**; 158 mg, 1.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 1.25 mmol) with stirring for 12 h at 25 °C. The subsequent cross-coupling with 1-iodo-4-(trifluoromethyl)benzene (**99d**; 218 mg, 0.8 mmol), $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.1 M in DMF, 0.5 mL, 0.05 mmol,) in DMF (4.5 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 99:1) afforded the desired product **103d** (216 mg, 89 %) as colorless crystals.

m.p.: 91-95 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.27 (d, *J* = 7.5 Hz, 1H), 7.91 – 7.70 (m, 6H), 7.61 – 7.48 (m, 3H), 3.61 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 155.3, 142.4, 134.7, 129.7, 129.2 (q, $^2J_{C\text{-}F}$ = 32 Hz), 128.4, 128.2, 127.94 (q, ^1J(C,F) = 272 Hz), 127.91, 127.86, 126.7, 126.5, 125.3 (q, ^3J(C,F) = 4 Hz), 124.3, 122.6, 61.4.

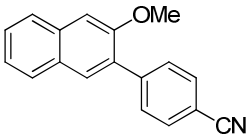
^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm): -62.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 3014, 2960, 2935, 2845, 1616, 1597, 1578, 1501, 1464, 1448, 1407, 1365, 1344, 1321, 1289, 1249, 1210, 1156, 1119, 1108, 1100, 1070, 1053, 1018, 982, 958, 871, 859, 844, 814, 797, 755, 744, 718, 696, 689.

MS (70 eV, EI) *m/z* (%): 303 (22), 302 (100) [M^+], 287 (35), 286 (10), 219 (10), 218 (51), 189 (19).

HRMS (EI) for **$C_{18}H_{13}F_3O$** (302.0918): 302.0912.

Synthesis of 4-(3-methoxynaphthalen-2-yl)benzonitrile (103e)



2-Methoxynaphthalene (**101d**; 158 mg, 1.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 0.50 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with 4-iodobenzonitrile (**99e**; 183 mg, 0.8 mmol), Pd(tmpp)$_2$Cl$_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.1 M in DMF, 0.5 mL, 0.05 mmol) in DMF (2.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 9:1) afforded the desired product **103e** (183 mg, 88 %) as a colorless solid.

m.p.: 125-127 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.80 (dd, *J* = 7.9, 4.6 Hz, 2H), 7.75 (s, 1H), 7.72 (s, 4H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.26 (s, 1H), 3.94 (s, 3H).

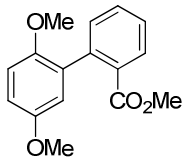
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 154.6, 143.2, 134.4, 131.7, 130.4, 130.3, 130.2, 128.6, 127.8, 127.0, 126.4, 124.3, 119.1, 110.7, 106.0, 55.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 3011, 2226, 1629, 1605, 1512, 1497, 1469, 1446, 1429, 1407, 1360, 1334, 1309, 1271, 1252, 1197, 1172, 1125, 1037, 1023, 949, 896, 863, 855, 839, 827, 815, 741, 716, 702.

MS (70 eV, EI) *m/z* (%): 260 (21), 259 (100) [M^+], 244 (14), 243 (10), 216 (20), 214 (15), 190 (10).

HRMS (EI) for **$C_{18}H_{13}NO$** (259.0997): 259.0990.

Synthesis of methyl 2',5'-dimethoxybiphenyl-2-carboxylate (103f)



1,4-Dimethoxybenzene (**101e**; 138 mg, 1.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 0.50 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with methyl 2-iodobenzoate (**99f**; 210 mg, 0.8 mmol), Pd(tmpp)$_2$Cl$_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.1 M in DMF, 0.5 mL, 0.05 mmol) in DMF (2.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 3:1) afforded the desired product **103f** (161 mg, 74 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.87 (dd, *J* = 6.7, 0.9 Hz, 1H), 7.55 (td, *J* = 7.7, 1.1 Hz, 1H), 7.44 – 7.31 (m, 2H), 6.91 – 6.78 (m, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H).

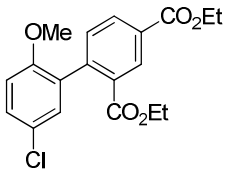
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 168.5, 153.6, 150.3, 138.5, 131.6, 131.5, 131.4, 131.2, 129.3, 127.2, 116.1, 113.0, 111.2, 55.8, 55.7, 51.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3027, 3010, 2955, 2932, 2905, 2834, 1723, 1584, 1572, 1501, 1487, 1462, 1443, 1435, 1415, 1308, 1291, 1279, 1267, 1248, 1226, 1207, 1178, 1162, 1149, 1128, 1088, 1048, 1023, 964, 957, 920, 876, 806, 800, 776, 744, 734, 720, 711, 666.

MS (70 eV, EI) *m/z* (%): 273 (13), 272 (100) [M$^+$], 241 (39), 226 (12), 198 (25), 183 (14).

HRMS (EI) for **$C_{16}H_{16}O_4$** (272.1049): 272.1048.

Synthesis of diethyl 5'-chloro-2'-methoxybiphenyl-2,4-dicarboxylate (103g)



1-Chloro-4-methoxybenzene (**101f**; 285 mg, 2.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 1.0 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with diethyl 4-bromobenzene-1,3-dicarboxylate (**99g**; 482 mg, 1.6 mmol), Pd(tmpp)$_2$Cl$_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (0.1 M in DMF, 1.0 mL, 0.10 mmol) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash chromatography (*i*hexane:Et_2O = 2:1) afforded the desired product **103g** (501 mg, 86 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 1.7 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

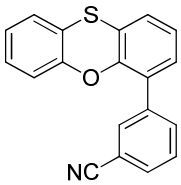
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 167.0, 165.6, 154.7, 141.7, 132.3, 132.1, 131.5, 131.3, 130.7, 129.9, 129.5, 128.8, 125.6, 111.4, 61.3, 61.0, 55.5, 14.3, 13.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 2939, 2905, 2842, 1716, 1610, 1563, 1501, 1481, 1464, 1443, 1410, 1393, 1366, 1302, 1227, 1175, 1139, 1109, 1100, 1082, 1024, 928, 886, 856, 833, 808, 790, 772, 739, 710, 687, 657.

MS (EI, 70 eV) m/z (%): 364 (34), 363 (22), 362 (100) [M^+], 333 (14), 331 (34), 319 (11), 317 (30), 305 (28), 304 (15), 303 (75), 289 (13), 275 (17), 274 (11), 230 (12), 208 (11).

HRMS (EI) for **$C_{19}H_{19}ClO_5$** (362.0921): 362.0909.

Synthesis of 3-phenoxathiin-4-ylbenzonitrile (103h)



Phenoxathiin (**101g**; 200 mg, 1.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 0.50 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with 3-iodobenzonitrile (**99h**; 183 mg, 0.8 mmol), $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.1 M in DMF, 0.5 mL, 0.05 mmol) in DMF (2.0 mL) was conducted at 80 °C for 12 h, after addition of a further portion of $Pd(tmpp)_2Cl_2$ (15 mg, 0.012 mmol) full conversion was achieved after further 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:EtOAc = 49:1) afforded the desired product **103h** (184 mg, 76 %) as a colorless solid.

m.p.: 168-171 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.85 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.71 – 7.65 (m, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.01 (m, 6H), 6.86 (d, *J* = 8.2 Hz, 1H).

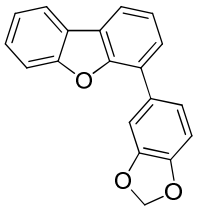
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 152.1, 149.1, 138.4, 133.9, 133.1, 130.9, 129.2, 129.0, 128.8, 127.9, 127.2, 126.9, 125.0, 124.6, 122.1, 120.7, 118.8, 117.5, 112.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062, 3038, 2960, 2923, 2854, 2227, 1601, 1578, 1508, 1488, 1471, 1458, 1438, 1398, 1263, 1222, 1216, 1199, 1080, 1070, 1052, 1027, 923, 891, 864, 819, 806, 784, 744, 713, 693, 685.

MS (70 eV, EI) *m/z* (%): 302 (19), 301 (100) [M^+], 300 (9), 272 (6), 269 (7).

HRMS (EI) for **$C_{19}H_{11}NOS$** (301.0561): 301.0550.

Synthesis of 4-(1,3-benzodioxol-5-yl)dibenzo[*b*,*d*]furan (103i)



Dibenzo[*b*,*d*]furan (**101h**; 168 mg, 1.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 0.50 mmol) with stirring for 1 h at 25 °C. The subsequent cross-coupling with 5-iodo-1,3-benzodioxole (**99i**; 198 mg, 0.8 mmol), Pd(tmpp)$_2Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.1 M in DMF, 0.5 mL, 0.05 mmol) in DMF (2.0 mL) showed full conversion after further 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 99:1) afforded the desired product **103i** (167 mg, 72 %) as a colorless solid.

m.p.: 79-81 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 7.7 Hz, 1H), 7.91 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.44 – 7.33 (m, 3H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.1, 153.2, 147.9, 147.3, 130.4, 127.2, 126.5, 125.6, 124.9, 124.2, 123.2, 122.7, 122.5, 120.6, 119.3, 111.8, 109.3, 108.6, 101.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 2360, 2338, 1506, 1481, 1453, 1409, 1351, 1338, 1257, 1230, 1193, 1178, 1170, 1092, 1039, 932, 913, 882, 852, 841, 815, 790, 745, 737, 720, 713, 694, 668.

MS (70 eV, EI) *m/z* (%): 289 (23), 288 (100) [M^+], 287 (13), 229 (15), 202 (8), 200 (7), 144 (6).

HRMS (EI) for **($C_{19}H_{12}O_3$)** (288.0786): 288.0778.

Synthesis of *tert*-butyl(3-(dibenzo[*b*,*d*]thiophen-4-yl)phenoxy)dimethylsilane (103j)

Dibenzo[*b*,*d*]thiophene (**101i**; 184 mg, 1.0 mmol) was metalated according to **TP 11** using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**7**; 0.50 mmol) with stirring for 2 h at 25 °C. The subsequent cross-coupling with *tert*-butyl(3-iodophenoxy)dimethylsilane (**99j**; 267 mg, 0.8 mmol), Pd(tmpp)$_2$$Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.1 M in DMF, 0.5 mL, 0.05 mmol) in DMF (2.0 mL) showed full conversion after further 12 h at 80 °C. Purification by flash column chromatography (*i*hexane:Et_2O = 99:1) afforded the desired product **103j** (195 mg, 63 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.21 – 8.15 (m, 2H), 7.87 – 7.84 (m, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.51 – 7.46 (m, 3H), 7.42 – 7.33 (m, 2H), 7.26 (s, 1H), 6.95 (d, *J* = 6.9 Hz, 1H), 1.05 (s, 9H), 0.30 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 156.0, 142.0, 139.6, 138.5, 136.9, 136.2, 135.8, 129.8, 126.8, 126.7, 125.0, 124.3, 122.6, 121.7, 121.3, 120.4, 119.9, 119.8, 25.7, 18.2, -4.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 2954, 2928, 2885, 2856, 1598, 1582, 1574, 1492, 1473, 1462, 1442, 1427, 1380, 1361, 1329, 1298, 1259, 1250, 1220, 1176, 1160, 1116, 1102, 1082, 1050, 1030, 1017, 1000, 945, 880, 836, 801, 780, 747, 726, 716, 698, 670.

MS (70 eV, EI) *m/z* (%): 391 (16), 390 (48) [M^+], 335 (14), 334 (37), 333 (100), 317 (27), 258 (15), 167 (11).

HRMS (EI) for **$C_{24}H_{26}OSSi$** (390.1474): 390.1460.

10 A CONVENIENT ALUMINATION OF FUNCTIONALIZED AROMATICS USING THE FRUSTRATED LEWIS PAIR Et_3Al AND TMPMgCl·LiCl

10.1 TYPICAL PROCEDURES

Typical procedure for the alumination of polyfunctionalized aromatics using *in situ* generated Et_3Al(TMP)MgCl·LiCl (TP 12)

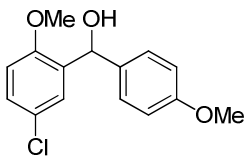
A flame-dried and argon-flushed Schlenk tube equipped with a rubber septum and a magnetic stirring bar was charged with a solution of the aromatic substrate (2.0 mmol) in dry THF (2 mL) as well as 50 µL of tetradecane (internal standard for GC analysis). The mixture was cooled to 0 °C, Et_3Al (251 mg, 2.2 mmol, 1.1 equiv) was added at 0 °C and the mixture was stirred for 10 min. Then TMPMgCl·LiCl (**3**; 1.2 M in THF, 2.0 mL, 2.4 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at the given temperature for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

Typical procedure for the alumination of polyfunctionalized aromatics using Et_3Al and TMP_2Mg·2LiCl (TP 13)

A flame-dried and argon-flushed Schlenk tube equipped with a rubber septum and a magnetic stirring bar was charged with a solution of the aromatic substrate (2.0 mmol) in dry THF (2 mL) as well as 50 µL of tetradecane (internal standard for GC analysis). The mixture was cooled to 0 °C, Et_3Al (251 mg, 2.2 mmol, 1.1 equiv) was added at 0 °C and the mixture was stirred for 10 min. Then, TMP_2Mg·2LiCl (**4**; 0.6 M in THF, 4.0 mL, 2.4 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at the given temperature for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard

10.2 ALUMINATION OF AROMATICS AND SUBSEQUENT REACTION WITH ELECTROPHILES

Synthesis of (5-chloro-2-methoxyphenyl)(4-methoxyphenyl)methanol (107a)



According to **TP 12**, the metalation of 4-chloroanisole (**105a**; 284 mg, 2.0 mmol) was completed within 24 h at 25 °C. The reaction mixture was cooled to 0 °C and then 4-methoxy benzaldehyde (680 mg, 5 mmol) was added. The mixture was allowed to warm to 25 °C and stirred for 7 h. The

reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 5:1) to give **107a** (418 mg, 75%) as an off white solid.

m.p.: 88.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.27 (m, 3H), 7.21 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.99 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.72 (br. s, 1H).

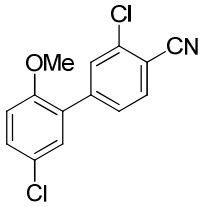
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.0, 155.1, 134.8, 134.0, 128.1, 127.8, 127.3, 125.9, 113.7, 111.9, 71.0, 55.7, 55.2.

MS (70 eV, EI) *m/z* (%): 280 (23), 279 (13), 278 (71) [M^+], 262 (21), 261 (15), 260 (54), 247 (20), 245 (19), 171 (33), 170 (10), 169 (100), 166 (14), 155 (16), 137 (39), 135 (58), 121 (31), 117 (11), 109 (51), 108 (36), 77 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3324, 3004, 2932, 2836, 1713, 1608, 1586, 1511, 1482, 1464, 1441, 1422, 1408, 1338, 1302, 1290, 1246, 1196, 1172, 1126, 1110, 1093, 1060, 1029, 1019, 1008, 939, 906, 896, 844, 828, 809, 794, 776, 735, 710, 702, 674, 654, 642, 625, 611, 606, 602.

HRMS (EI) for **$C_{15}H_{15}ClO_3$** (278.0710): 278.0694.

Synthesis of 3,5'-dichloro-2'-methoxy-[1,1'-biphenyl]-4-carbonitrile (107b)



According to **TP 12**, the metalation of 4-chloroanisole (**105a**; 284 mg, 2.0 mmol) was completed within 24 h at 25 °C. The reaction mixture was cooled to 0 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (23 mg, 2 mol%) and tfp (19 mg, 4 mol%) in THF (2 mL) was added, followed by 2-chloro-4-iodobenzonitrile (1.32 g, 5.0 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 25:1) to give **107b** (390 mg, 70%) as a colorless solid.

m.p.: 120.8 – 122.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 2.1 Hz, 1H), 7.66 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H).

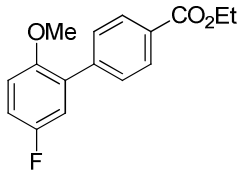
13C-NMR (100 MHz, $CDCl_3$) δ (ppm): 154.8, 136.6, 135.6, 134.8, 134.7, 130.0, 129.7, 129.5, 128.4, 126.0, 116.0, 113.1, 112.6, 55.9.

MS (70 eV, EI) *m/z* (%): 277 (74) [M^+], 262 (13), 229 (29), 227 (100), 198 (11), 164 (19), 61 (13), 45 (11), 43 (74).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2229, 1591, 1494, 1477, 1465, 1439, 1382, 1369, 1276, 1253, 1235, 1178, 1157, 1140, 1102, 1064, 1061, 1039, 1025, 1014, 888, 879, 832, 821, 804, 736, 717, 712, 702.

HRMS (EI) for **$C_{14}H_9Cl_2NO$** (277.0061): 277.0057.

Synthesis of ethyl 5'-fluoro-2'-methoxy-[1,1'-biphenyl]-4-carboxylate (107c)



According to **TP 12**, the metalation of 4-chloroanisole (**105b**; 284 mg, 2.0 mmol) was completed within 15 h at 25 °C. The reaction mixture was cooled to 0 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (1.38 g, 5.0 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 29:1) to give **107c** (420 mg, 77%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.60 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.11 – 7.00 (m, 2H), 6.92 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

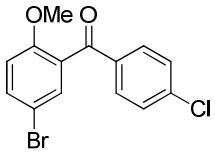
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4, 157.0 (d, $^1J_{C\text{-}F}$ = 238.9 Hz), 152.6 (d, $^4J_{C\text{-}F}$ = 2.3 Hz), 141.9 (d, $^4J_{C\text{-}F}$ = 1.5 Hz), 130.7 (d, $^3J_{C\text{-}F}$ = 7.2 Hz), 129.3, 129.2, 129.2, 117.1(d, $^2J_{C\text{-}F}$ = 23.1 Hz), 115.0 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 112.4 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 60.9, 56.1, 14.3.

MS (70 eV, EI) m/z (%): 275 (15), 274 (100) [M^+], 246 (21), 203 (17), 229 (87), 187 (25), 186 (50), 157 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2982, 2941, 2906, 2837, 1710, 1608, 1596, 1567, 1516, 1492, 1465, 1444, 1424, 1398, 1367, 1312, 1269, 1254, 1233, 1178, 1100, 1038, 1019, 896, 881, 856, 806, 777, 746, 728, 718, 702, 656, 636, 620, 611.

HRMS (EI) for **$C_{16}H_{15}FO_3$** (274.1005): 274.1001.

Synthesis of (5-bromo-2-methoxyphenyl)(4-chlorophenyl)methanone (107d)



According to **TP 12**, the metalation of 4-bromoanisole (**105c**; 372 mg, 2.0 mmol) was completed within 28 h at 25 °C. The reaction mixture was cooled to 0 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) and 4-chlorobenzoyl chloride (874 mg, 5.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 14:1) to give **107d** (515 mg, 79%) as a colorless solid.

m.p.: 85.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71 (ddd, *J* = 8.7, 2.4, 2.2 Hz, 2H), 7.56 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.45 (d, *J* = 2.7 Hz, 1H), 7.40 (ddd, *J* = 8.9, 2.3, 2.1 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H).

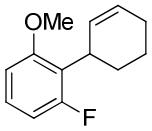
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 193.5, 156.3, 139.7, 135.6, 134.7, 132.0, 131.1, 130.1, 128.7, 113.3, 113.0, 55.9.

MS (70 eV, EI) *m/z* (%): 328 (33), 327 (40), 326 (87), 325 (26), 324 (85) [M^+], 309 (29), 308 (12), 307 (18), 291 (32), 289 (27), 119 (19), 228 (10), 227 (47), 214 (78), 212 (87), 209 (28), 202 (13), 201 (77), 199 (72), 172 (23), 170 (22), 157 (18), 155 (16), 139 (100), 134 (10), 113 (25), 111 (90), 77 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1721, 1668, 1662, 1587, 1570, 1483, 1460, 1452, 1438, 1402, 1390, 1370, 1310, 1294, 1262, 1240, 1180, 1157, 1147, 1122, 1109, 1091, 1022, 1015, 975, 952, 947, 935, 918, 894, 881, 862, 851, 830, 812, 768, 762, 744, 730, 714, 702, 690, 684, 665, 627, 620, 612.

HRMS (EI) for **$C_{14}H_{10}BrClO_2$** (323.9553): 323.9545.

Synthesis of 2-cyclohex-2-enyl-1-fluoro-3-methoxybenzene (107e)



According to **TP 12**, the metalation of 3-fluoroanisole (**105d**; 372 mg, 2.0 mmol) was completed within 20 min at -5 °C. The reaction mixture was cooled to -20 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (810 mg, 5.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 1000:1) to give **107e** (360 mg, 87%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 7.16 – 7.10 (m, 1H), 6.69 – 6.63 (m, 2H), 5.80 – 5.73 (m, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.83 (s, 3H), 2.22 – 2.04 (m, 2H), 1.95 – 1.80 (m, 3H), 1.76 – 1.66 (m, 1H).

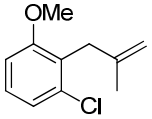
^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 162.2 (d, $^1J_{C\text{-}F}$ = 245.4 Hz), 158.6 (d, $^3J_{C\text{-}F}$ = 9.5 Hz), 130.5(d, $^4J_{C\text{-}F}$ = 1.4 Hz), 127.1 (d, $^3J_{C\text{-}F}$ = 10.9 Hz), 125.6 (d, $^4J_{C\text{-}F}$ = 2.0 Hz), 121.7 (d, $^2J_{C\text{-}F}$ = 15.1 Hz), 108.5 (d, $^2J_{C\text{-}F}$ = 23.3 Hz), 106.4 (d, $^3J_{C\text{-}F}$ = 2.8 Hz), 55.9 (d, $^4J_{C\text{-}F}$ = 0.6 Hz), 32.2 (d, $^4J_{C\text{-}F}$ = 1.4 Hz), 28.4 (d, $^4J_{C\text{-}F}$ = 1.7 Hz), 24.7, 23.1.

MS (70 eV, EI) *m/z* (%): 207 (15), 206 (100) [M^+], 205 (14), 191 (41), 178 (35), 177 (20), 165 (33), 163 (26), 152 (33), 150 (13), 149 (35), 174 (25), 146 (16), 139 (28), 137 (22), 135 (11), 133 (18), 125 (24), 115 (12), 109 (46), 81 (16), 79 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3021, 2932, 2859, 2837, 1611, 1584, 1469, 1439, 1349, 1334, 1327, 1303, 1292, 1266, 1234, 1222, 1187, 1164, 1136, 1083, 1045, 987, 941, 928, 899, 876, 846, 779, 727, 643, 615.

HRMS (EI) for **$C_{13}H_{15}FO$** (206.1107): 206.1100.

Synthesis of 1-chloro-3-methoxy-2-(2-methylallyl)benzene (107f)



According to **TP 12**, the metalation of 3-chloroanisole (**105d**; 372 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to 0 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL,

4.0 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and metallyl bromide (670 mg, 5.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 100:1) to give **107f** (335 mg, 85%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.14 (t, *J* = 8.1 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.80 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.72 – 4.79 (m, 1H), 4.42 – 4.46 (m, 1H), 3.83 (s, 3H), 3.51 (s, 2H), 1.83 (dd, *J* = 1.3, 0.6 Hz, 3H).

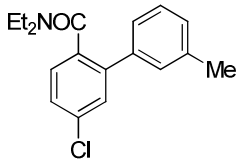
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.7, 143.1, 135.6, 127.5, 126.8, 121.6, 110.0, 108.9, 55.9, 34.5, 23.0.

MS (70 eV, EI) *m/z* (%): 198 (14), 196 (30) [M^+], 167 (15), 166 (100), 157 (13), 156 (13), 155 (43), 136 (15), 127 (13), 125 (37), 111 (10), 97 (15), 91 (15), 85 (16), 83 (17), 77 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3079, 2937, 2837, 1652, 1591, 1577, 1462, 1435, 1374, 1312, 1263, 1230, 1216, 1181, 1080, 1043, 1004, 929, 922, 886, 840, 823, 767, 722, 659, 649, 626, 620.

HRMS (EI) for **$C_{11}H_{13}ClO$** (196.0655): 196.0635.

Synthesis of 5-chloro-*N*,*N*-diethyl-3'-methylbiphenyl-2-carboxamide (107g)



According to **TP 12**, the metalation of 4-chloro-*N,N*-diethylbenzamide (**105f**; 413 mg, 2.0 mmol) was completed within 3 h at 0 °C. The reaction mixture was cooled to -20 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 3-iodotoluene (1.09 g, 5.0 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **107g** (417 mg, 85%) as an off white solid.

m.p.: 54.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 1.9 Hz, 1H), 7.36 (d, *J* = 1.9 Hz, 1H), 7.33 (s, 1H), 7.28 (t, *J* = 2.9 Hz, 3H), 7.21 – 7.15 (m, 1H), 3.86 – 3.71 (m, 1H), 3.05 – 2.88 (m, 2H), 2.74 – 2.58 (m, 1H), 2.38 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H).

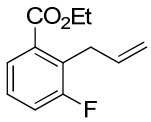
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 169.6, 140.4, 138.4, 138.0, 134.8, 134.6, 129.4, 129.4, 128.8, 128.5, 128.4, 127.5, 125.8, 42.4, 38.5, 21.4, 13.4, 11.9.

MS (70 eV, EI) *m/z* (%): 303 (6), 302 (14), 301 (18) [M^+], 300 (34), 272 (4), 232 (6), 231 (31), 230 (17), 229 (100), 217 (3), 215 (9), 210 (6), 201 (4), 199 (2), 195 (5), 194 (6), 193 (3), 186 (7), 167 (8), 166 (49), 165 (52), 164 (6), 163 (6), 151 (4), 139 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3243, 3042, 2968, 2929, 2868, 1894, 1625, 1590, 1516, 1458, 1439, 1424, 1377, 1363, 1348, 1316, 1294, 1251, 1219, 1184, 1129, 1100, 1083, 1069, 1052, 998, 947, 890, 867, 820, 787, 763, 701, 656.

HRMS (EI) for **$C_{18}H_{20}ClNO$** (301.1233): 301.1219.

Synthesis of ethyl 2-allyl-3-fluorobenzoate (107h)



According to **TP 12**, the metalation of ethyl 3-fluorobenzoate (**105g**; 336 mg, 2.0 mmol) was completed within 3 h at 0 °C. The reaction mixture was cooled to -20 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and allyl bromide (605 mg, 5.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 50:1) to give **107h** (337 mg, 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.67 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7. 29 – 7. 15 (m, 2H), 6.07 – 5.92 (m, 1H), 5.06 – 5.01 (m, 1H), 5.02 - 4.97 (m, 1H), 4.41 - 4.33 (m, 2H), 3.80 - 3.74 (m, 2H), 1.39 (t, *J* = 7.3 Hz, 3H).

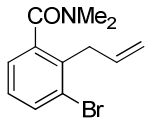
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7 (d, *J* = 3.4 Hz), 161.3 (d, *J* = 245.2 Hz), 135.9, 132.3 (d, *J* = 4.2 Hz), 128.4 (d, *J* = 17.1 Hz), 127.2 (d, *J* = 9.0 Hz), 126.0 (d, *J* = 3.6 Hz), 118.7 (d, *J* = 23.6 Hz), 115.4, 61.1, 29.7 (d, *J* = 4.8 Hz), 14.2.

MS (70 eV, EI) *m/z* (%):209 (10), 208 (61) [M^+], 194 (8), 193 (64), 180 (15), 179 (13), 166 (9), 165 (85), 164 (22), 163 (73), 162 (56), 161 (21), 152 (16), 151 (10), 151 (8), 149 (15), 135 (56), 134 (50), 133 (100), 123 (9), 115 (32), 109 (24), 108 (10), 107 (16), 83 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3081, 2982, 2939, 1719, 1637, 1610, 1456, 1366, 1260, 1195, 1139, 1095, 1024, 995, 957, 914, 754.

HRMS (EI) for **$C_{12}H_{13}FO_2$** (208.0900): 208.0887.

Synthesis of 2-allyl-3-bromo-*N*,*N*-dimethylbenzamide (107i)



According to **TP 12**, the metalation of 3-bromo-*N*,*N*-dimethylbenzamide (**105h**; 456 mg, 2.0 mmol) was completed within 3 h at 0 °C. The reaction mixture was cooled to -20 °C, $ZnCl_2$ (1.0 M solution in THF, 4.0 mL, 4.0 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and allyl bromide (605 mg, 5.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 3:1) to give **107i** (337 mg, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 – 7.53 (m, 1H), 7.12 – 7.05 (m, 2H), 5.95 – 5.82 (m, 1H), 5.06 – 4.96 (m, 2H), 3.68 – 3.45 (m, 2H), 3.09 (s, 3H), 2.75 (s, 3H).

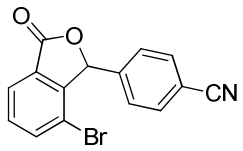
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 170.0, 138.6, 135.8, 134.4, 133.3, 127.8, 126.0, 125.2, 116.1, 39.0, 37.3, 34.6.

MS (70 eV, EI) *m/z* (%): 269 (10), 267 (12) [M^+], 254 (23), 252 (21), 224 (90), 222 (100), 197 (17), 195 (13), 144 (50), 115 (80).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 3012, 2926, 1629, 1589, 1558, 1497, 1431, 1392, 1266, 1233, 1216, 1177, 1144, 1128, 1071, 993, 915, 831, 793, 757, 753, 746.

HRMS (EI) for **$C_{12}H_{14}BrNO$** (267.0259): 267.0238.

Synthesis of 4-(7-bromo-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzonitrile (107j)



According to **TP 12**, the metalation of 3-bromo-*N*,*N*-dimethylbenzamide (**105h**; 456 mg, 2.0 mmol) was completed within 3 h at 0 °C. The reaction mixture was cooled to 0 °C and then 4-cyano benzaldehyde (655 mg, 5 mmol) was added. The mixture was allowed to warm to 25 °C and stirred for 7 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 5:1) to give **107j** (521 mg, 83%) as a colorless solid.

m.p.: 154.8 – 155.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.69 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.38 (dt, *J* = 8.4, 1.8 Hz, 2H), 6.35 (s, 1H).

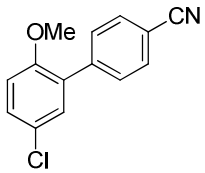
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 147.2, 139.1, 138.2, 132.6, 131.9, 129.3, 128.3, 125.0, 118.1, 117.7, 113.6, 82.1.

MS (70 eV, EI) *m/z* (%): 315 (100), 313 (99) [M^+], 312 (10), 213 (30), 211 (31), 206 (13), 190 (77), 188 (26), 185 (85), 183 (96), 177 (18), 163 (12), 157 (11), 155 (11), 130 (13), 102 (12), 75 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3069, 2235, 1779, 1603, 1578, 1506, 1456, 1414, 1330, 1303, 1275, 1264, 1251, 1194, 1179, 1163, 1124, 1114, 1057, 1040, 1022, 999, 995, 887, 858, 830, 819, 770, 750, 737, 722.

HRMS (EI) for **$C_{15}H_8BrNO_2$** (312.9738): 312.9716.

Synthesis of 5'-chloro-2'-methoxy-[1,1'-biphenyl]-4-carbonitrile (108)



According to **TP 12**, the metalation of 4-chloroanisole (**105a**; 284 mg, 2.0 mmol) was completed within 24 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.07 g, 4.0 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 4-iodobenzonitrile (458 mg, 2.0 mmol) and the solution was stirred for 12 h. The reaction mixture was quenched with a

mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **108** (342 mg, 70%) as a colorless solid.

m.p.: 126.3 – 127.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (dt, *J* = 8.8, 1.8 Hz, 2H), 7.61 (dt, *J* = 8.6, 1.8 Hz, 2H), 7.34 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 3.82 (s, 3H).

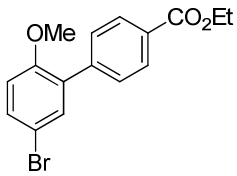
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 155.0, 141.9, 131.8, 130.2, 130.1, 130.1, 129.4, 126.0, 118.9, 112.6, 111.0, 55.9.

MS (70 eV, EI) *m/z* (%): 245 (14), 243 (73) [M^+], 228 (18), 193 (100), 164 (53), 151 (10), 138 (17), 86 (13), 75 (13), 73 (14), 63 (27), 50 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 3008, 2980, 2936, 2924, 2866, 2829, 1580, 1437, 1375, 1345, 1326, 1311, 1281, 1242, 1223, 1199, 1194, 1151, 1106, 1058, 1046, 1021, 957, 938, 930, 902, 891, 878, 864, 832, 825, 801, 729, 723, 691.

HRMS (EI) for **$C_{14}H_{10}ClNO$** (243.0451): 243.0457.

Synthesis of ethyl 5'-bromo-2'-methoxy-[1,1'-biphenyl]-4-carboxylate (109)



According to **TP 12**, the metalation of 4-bromoanisole (**105c**; 372 mg, 2.0 mmol) was completed within 28 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (458 mg, 2.4 mmol) and the solution was stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **109** (525 mg, 78%) as a colorless solid.

m.p.: 88.2 – 89.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (ddd, *J* = 8.1, 1.9, 1.7 Hz, 2H), 7.57 (ddd, *J* = 8.0, 1.9, 1.4 Hz, 2H), 7.47 - 7.42 (m, 2H), 6.88 (d, *J* = 9.4 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 1.42 (t, 3 H)

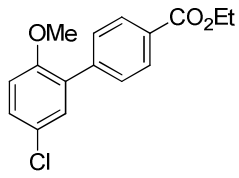
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4, 155.6, 141.7, 133.2, 131.8, 131.6, 129.4, 129.4, 129.3, 113.1, 113.1, 60.9, 55.8, 14.3.

MS (70 eV, EI) *m/z* (%): 336 (99), 334 (100) [M^+], 308 (17), 306 (116), 291 (75), 289 (70), 248 (24), 246 (21), 182 (16), 168 (30), 139 (35), 97 (10), 69 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980, 2935, 2838, 1706, 1608, 1574, 1512, 1485, 1458, 1440, 1412, 1386, 1366, 1312, 1277, 1260, 1234, 1180, 1142, 1112, 1098, 1020, 1014, 887, 860, 848, 817, 806, 776, 740, 726, 703, 652.

HRMS (EI) for **$C_{16}H_{15}BrO_3$** (334.0205): 334.0196.

Synthesis of ethyl 5'-chloro-2'-methoxy-[1,1'-biphenyl]-4-carboxylate (110a)



According to **TP 12**, the metalation of 4-chloroanisole (**105a**; 284 mg, 2.0 mmol) was completed within 24 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by ethyl 4-bromobenzoate (549 mg, 2.4 mmol) and the solution was stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **110a** (424 mg, 73%) as a colorless solid.

m.p.: 52.8 – 54.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (ddd, *J* = 8.0, 1.9, 1.4 Hz, 2H), 7.57 (ddd, *J* = 8.0, 1.9, 1.4 Hz, 2H), 7.33 – 7.25 (m, 2H), 6.92 (d, *J* = 9.4 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H).

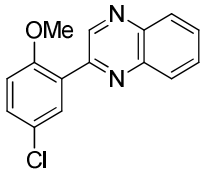
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4, 155.1, 141.8, 131.2, 130.4, 129.4, 129.4, 129.3, 128.8, 125.8, 112.6, 60.9, 55.9, 14.4.

MS (70 eV, EI) *m/z* (%): 292 (29), 290 (100) [M^+], 262 (11), 247 (24), 245 (54), 202 (22), 168 (12), 139 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2906, 1705, 1608, 1562, 1512, 1486, 1478, 1437, 1387, 1311, 1266, 1234, 1181, 1145, 1139, 1123, 1099, 1018, 908, 879, 856, 850, 830, 802, 773, 742, 725, 699, 661.

HRMS (EI) for **$C_{16}H_{15}ClO_3$** (290.0710): 290.0705.

Synthesis of 2-(5-chloro-2-methoxyphenyl)quinoxaline (110b)



According to **TP 12**, the metalation of 4-chloroanisole (**105a**; 284 mg, 2.0 mmol) was completed within 24 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 2-bromoquinoxaline (502 mg, 2.4 mmol) and the solution was stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **110b** (384 mg, 71%) as a yellowish solid.

m.p.: 142.7 – 143.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.33 (s, 1H), 8.17 – 8.08 (m, 2H), 7.92 (d, *J* = 2.7 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.41 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H).

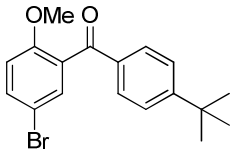
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 156.0, 150.6, 146.8, 142.5, 141.2, 131.2, 130.9, 129.9, 129.7, 129.5, 129.1, 127.8, 126.6, 112.8, 56.0.

MS (70 eV, EI) *m/z* (%): 272 (36), 270 (100) [M^+], 255 (27), 253 (75), 243 (14), 241 (45), 213 (15), 207 (13), 205 (23), 178 (17), 131 (50), 103 (19), 77 (22), 75 (13), 69 (13), 57 (21), 50 (14), 43 (61).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1548, 1487, 1479, 1463, 1443, 1419, 1265, 1246, 1225, 1182, 1153, 1132, 1127, 1100, 1060, 1019, 966, 954, 931, 919, 891, 880, 804, 796, 764, 756, 731, 710, 681.

HRMS (EI) for **$C_{15}H_{11}ClN_2O$** (270.0560): 270.0553.

Synthesis of (5-bromo-2-methoxyphenyl)(4-(*tert*-butyl)phenyl)methanone (110c)



According to **TP 12**, the metalation of 4-bromoanisole (**105c**; 372 mg, 2.0 mmol) was completed within 28 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) and 4-*tert*-butylbenzoyl chloride (472 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 24:1) to give **110c** (478 mg, 69%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (dt, *J* = 8.8, 1.9 Hz, 2H), 7.55 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.47 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.43 – 7.40 (m, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 3.74 (s, 3H), 1.35 (s, 9H).

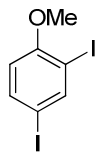
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 194.2, 157.2, 156.2, 134.3, 134.0, 131.6, 131.0, 129.9, 125.4, 113.2, 112.7, 56.0, 35.2, 31.1.

MS (70 eV, EI) *m/z* (%): 348 (55), 346 (55) [M^+], 333 (95), 331 (100), 329 (16), 291 (91), 289 (90), 275 (12), 212 (72), 210 (30), 201 (38), 172 (12), 170 (12), 165 (11), 161 (86), 157 (11), 155 (13), 151 (12), 146 (12), 133 (23), 118 (22), 115 (18), 105 (10), 91 (24), 77 (16), 63 (12), 57 (16), 43 (39), 41 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 2903, 2867, 1664, 1602, 1590, 1564, 1480, 1460, 1439, 1408, 1390, 1363, 1313, 1290, 1262, 1240, 1190, 1181, 1157, 1124, 1105, 1022, 950, 884, 851, 811, 778, 698, 666.

HRMS (EI) for **$C_{18}H_{19}BrO_2$** (346.0568): 346.0563.

Synthesis of 2,4-diiodo-1-methoxybenzene (110d)



According to **TP 12**, the metalation of 4-iodoanisole (**105i**; 468 mg, 2.0 mmol) was completed within 30 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. Then a solution of iodine (2.54 g, 10 mmol) in THF (10 mL) was added dropwise. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was

quenched with sat. aq $Na_2S_2O_3$ solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 1000:1) to give **110d** (596 mg, 83%) as a colorless solid.

m.p.: 68.3 – 69.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.05 (d, *J* = 2.2 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.59 (d, *J* = 8.6 Hz, 1H), 3.86 (s, 3H).

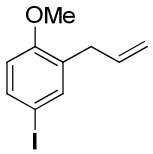
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 158.2, 146.6, 138.2, 112.8, 87.4, 83.2, 56.4.

MS (70 eV, EI) *m/z* (%): 360 (100) [M^+], 345 (31), 218 (21), 63 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2965, 1863, 1738, 1565, 1465, 1433, 1408, 1371, 1279, 1266, 1247, 1186, 1146, 1084, 1036, 1009, 935, 871, 801, 697, 660.

HRMS (EI) for **$C_7H_6I_2O$** (359.8508): 359.8505.

Synthesis of 2-allyl-4-iodo-1-methoxybenzene (110e)



According to **TP 12**, the metalation of 4-iodoanisole (**105i**; 468 mg, 2.0 mmol) was completed within 30 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and allyl bromide (290 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 1000:1) to give **110e** (487 mg, 89%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 1H), 6.02 – 5.87 (m, 1H), 5.11 – 5.08 (m, 1H), 5.07 – 5.03 (m, 1H), 3.81 (s, 3H), 3.33 (d, *J* = 6.4 Hz, 2H).

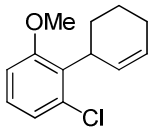
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 157.2, 138.2, 138.2, 136.0, 131.4, 116.1, 112.6, 82.8, 55.5, 33.8.

MS (70 eV, EI) *m/z* (%): 272 (5) [M^+-H], 263 (36), 261 (53), 233 (11), 146 (38), 135 (10), 132 (30), 131 (27), 121 (10), 118 (18), 115 (20), 103 (18), 100 (25), 91 (26), 89 (13), 78 (13), 77 (26), 76 (13), 70 (11), 63 (17), 61 (15), 57 (10), 50 (12), 45 (12), 43 (100), 41 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3000, 2934, 2902, 2834, 1637, 1585, 1484, 1460, 1438, 1394, 1319, 1299, 1281, 1241, 1188, 1172, 1136, 1122, 1028, 993, 913, 882, 852, 801, 725, 653.

HRMS (EI) for **$C_{10}H_{10}IO$** [M^+-H] (272.9776): 272.9756.

Synthesis of 1-chloro-2-cyclohex-2-en-1-yl-3-methoxybenzene (110f)



According to **TP 12**, the metalation of 3-chloroanisole (**105e**; 285 mg, 2.0 mmol) was completed within 1 h at 25 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (386 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 1000:1) to give **110f** (344 mg, 77%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.10 (t, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.75 – 5.68 (m, 1H), 5.62 – 5.56 (m, 1H), 4.23 – 4.10 (m, 1H), 3.79 (s, 3H), 2.21 – 1.96 (m, 3H), 1.95 – 1.87 (m, 1H), 1.83 – 1.66 (m, 2H).

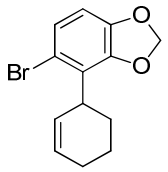
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 134.8, 131.8, 130.5, 127.3, 127.3, 125.0, 122.4, 109.8, 55.8, 26.9, 24.6, 24.6, 23.3.

MS (70 eV, EI) *m/z* (%): 224 (33), 222 (100) [M^+], 207 (24), 194 (15), 187 (26), 179 (13), 170 (13), 168 (43), 159 (73), 155 (22), 153 (25), 144 (34), 141 (16), 128 (21), 127 (17), 125 (39), 115 (37), 89 (16), 79 (12), 77 (18), 43 (37), 41 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3019, 2930, 2833, 1587, 1572, 1459, 1432, 1348, 1247, 1222, 1151, 1039, 984, 931, 900, 851, 837, 774, 730, 718, 690.

HRMS (EI) for **$C_{13}H_{15}ClO$** (222.0811): 222.0811.

Synthesis of 5-bromo-4-(cyclohex-2-en-1-yl)benzo[1,3]dioxole (110g)



According to **TP 12**, the metalation of 5-bromo-1,3-benzodioxole (**105j**; 402 mg, 2.0 mmol) was completed within 30 min at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (386 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 100:1) to give **110g** (510 mg, 91%) as a colorless solid.

m.p.: 68.8 – 70.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.04 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 5.94 (dd, *J* = 4.1, 1.4 Hz, 2H), 5.85 – 5.77 (m, 1H), 5.69 – 5.62 (m, 1H), 3.93 – 3.83 (m, 1H), 2.23 – 2.02 (m, 2H), 1.99 – 1.61 (m, 4H).

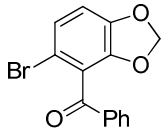
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 147.2, 146.6, 128.9, 127.2, 127.1, 125.4, 115.7, 107.6, 101.2, 39.7, 27.6, 24.7, 22.6.

MS (70 eV, EI) *m/z* (%): 282 (97), 281 (100) [M^+], 228 (23), 226 (24), 201 (20), 171 (15), 160 (16), 143 (59), 135 (17), 128 (15), 115 (57), 102 (14), 89 (10), 79 (11), 77 (11), 63 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3021, 2906, 2830, 1822, 1587, 1505, 1449, 1442, 1409, 1343, 1336, 1293, 1237, 1223, 1190, 1159, 1130, 1102, 1056, 1043, 1026, 969, 962, 929, 898, 873, 860, 824, 797, 760, 723, 715, 677.

HRMS (EI) for **$C_{13}H_{13}BrO_2$** (280.0099): 280.0083.

Synthesis of (5-bromobenzo[1,3]dioxol-4-yl)(phenyl)methanone (110h)



According to **TP 12**, the metalation of 5-bromo-1,3-benzodioxole (**105j**; 402 mg, 2.0 mmol) was completed within 30 min at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (337 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 50:1) to give **110h** (313 mg, 51%) as a colorless solid.

m.p.: 116.3 – 117.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.90 (dd, *J* = 8.6, 1.4 Hz, 2H), 7.63 (tt, *J* = 7.5, 1.9 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 5.98 (s, 2H).

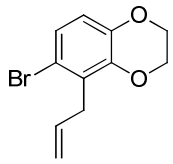
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 191.8, 147.4, 146.1, 135.9, 134.1, 129.9, 128.8, 125.7, 122.5, 110.4, 110.3, 102.4.

MS (70 eV, EI) *m/z* (%): 306 (76), 304 (75) [M^+], 229 (32), 227 (28), 195 (24), 167 (14), 139 (17), 105 (100), 91 (20), 77 (52), 51 (12), 43 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2898, 1666, 1620, 1592, 1577, 1494, 1449, 1441, 1400, 1337, 1317, 1274, 1234, 1171, 1156, 1095, 1039, 1027, 1006, 999, 928, 879, 871, 861, 813, 800, 750, 739, 714, 693, 674, 668.

HRMS (EI) for **$C_{14}H_9BrO_3$** (303.9735): 303.9729.

Synthesis of 5-allyl-6-bromo-2,3-dihydrobenzo[1,4]dioxine (110i)



According to **TP 12**, the metalation of 6-bromo-2,3-dihydrobenzo[1,4]dioxine (**105k**; 430 mg, 2.0 mmol) was completed within 30 min at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and allyl bromide (290 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 100:1) to give **110i** (407 mg, 80%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.04 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 6.00 – 5.85 (m, 1H), 5.09 – 5.04 (m, 1H), 5.02 (t, *J* = 1.5 Hz, 1H), 4.30 – 4.22 (m, 4H), 3.53 (dt, *J* = 6.1, 1.7 Hz, 2H).

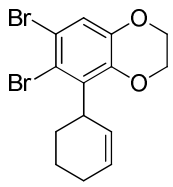
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 142.8, 142.3, 134.6, 128.1, 124.6, 116.4, 115.8, 115.4, 64.3, 64.0, 33.6.

MS (70 eV, EI) *m/z* (%): 256 (87), 254 (100) [M^+], 175 (98), 174 (12), 149 (19), 132 (11), 119 (69), 91 (41), 89 (15), 83 (17), 71 (14), 69 (20), 65 (19), 63 (19), 57 (21), 55 (19), 43 (53), 41 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977, 2925, 2876, 1637, 1589, 1488, 1464, 1452, 1429, 1378, 1305, 1279, 1260, 1242, 1200, 1132, 1091, 1058, 984, 912, 890, 857, 821, 796, 759, 701, 671.

HRMS (EI) for **$C_{11}H_{11}BrO_2$** (253.9942): 253.9762.

Synthesis of 6,7-dibromo-5-(cyclohex-2-en-1-yl)-2,3-dihydrobenzo[1,4]dioxine (110j)



According to **TP 12**, the metalation of 6,7-dibromo-2,3-dihydrobenzo[1,4]dioxine (**105l**; 588 mg, 2.0 mmol) was completed within 30 min at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) and 3-bromocyclohexene (386 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 100:1) to give **110j** (540 mg, 72%) as a colorless solid.

m.p.: 42.8 – 44.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.10 (s, 1H), 5.77 – 5.64 (m, 1H), 5.61 – 5.53 (m, 1H), 4.23 – 4.21 (m, 5H), 2.20 – 2.01 (m, 2H), 2.01 – 1.61 (m, 4H).

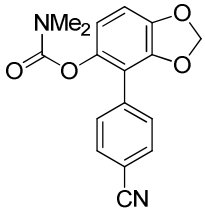
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 143.5, 143.4, 135.4, 129.8, 129.6, 119.8, 119.6, 116.5, 64.1, 63.7, 26.7, 24.6, 24.5, 23.1.

MS (70 eV, EI) *m/z* (%): 376 (47), 374 (96), 372 (47) [M^+], 322 (12), 320 (25), 318 (13), 229 (15), 227 (14), 214 (76), 186 (100), 173 (19), 158 (13), 130 (23), 128 (14), 115 (11), 102 (16), 79 (11), 77 (10), 43 (40).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 3009, 2924, 2866, 1644, 1580, 1467, 1451, 1437, 1375, 1345, 1326, 1311, 1300, 1281, 1242, 1223, 1199, 1194, 1151, 1106, 1077, 1058, 1047, 1020, 957, 938, 930, 902, 891, 878, 864, 741, 729, 723, 689.

HRMS (EI) for **$C_{14}H_{14}Br_2O_2$** (371.9361): 371.9352.

Synthesis of 4-(4-cyanophenyl)benzo[1,3]dioxol-5-yl dimethylcarbamate (110k)



According to **TP 12**, the metalation of benzo[1,3]dioxol-5-yl dimethylcarbamate (**105m**; 418 mg, 2.0 mmol) was completed within 30 min at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 4-bromobenzonitrile (437 mg, 2.4 mmol) and the solution was stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **110k** (460 mg, 74%) as an off white solid.

m.p.: 140.2 – 141.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (ddd, *J* = 8.2, 2.3, 1.6 Hz, 2H), 7.61 (ddd, *J* = 8.2, 2.3, 1.6 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.01 (s, 2H), 2.92 (s, 3H), 2.86 (s, 3H).

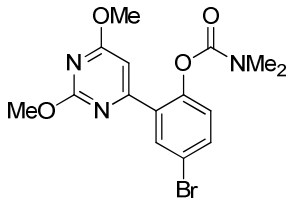
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 154.5, 145.6, 145.2, 142.7, 136.8, 131.8, 130.4, 118.8, 116.4, 115.9, 111.4, 108.0, 101.9, 36.7, 36.2.

MS (70 eV, EI) *m/z* (%): 310 (16) [M^+], 154 (4), 72 (100), 43 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2926, 1725, 1608, 1503, 1451, 1402, 1384, 1358, 1310, 1271, 1240, 1220, 1162, 1089, 1047, 1022, 965, 935, 899, 853, 827, 796, 783, 749, 732, 723, 661.

HRMS (EI) for **$C_{17}H_{14}N_2O_4$** (310.0954): 310.0947.

Synthesis of 4-bromo-2-(2,6-dimethoxypyrimidin-4-yl)phenyl dimethylcarbamate (110l)



According to **TP 12**, the metalation of 4-bromophenyl dimethylcarbamate (**105n**; 488 mg, 2.0 mmol) was completed within 3 h at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 4-iodo-2,6-dimethoxypyrimidine (638 mg, 2.4 mmol) and the solution was stirred for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (dichloromethane:ethyl acetate = 9:1) to give **110l** (590 mg, 77%) as an off white solid.

m.p.: 100.3 – 101.3 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.96 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.79 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 2.98 (s, 3H), 2.84 (s, 3H).

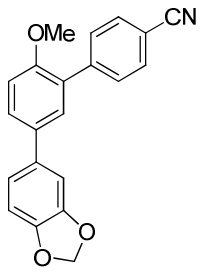
^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 171.7, 164.8, 162.4, 153.1, 148.3, 133.5, 132.5, 132.4, 126.4, 117.9, 100.6, 54.5, 54.0, 36.4, 36.0.

MS (70 eV, EI) *m/z* (%): 383 (4), 381 (4) [M^+], 339 (8), 337 (8), 322 (7), 310 (11), 308 (10), 239 (7), 237 (7), 72 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941, 1736, 1723, 1594, 1574, 1554, 1477, 1450, 1399, 1373, 1348, 1281, 1256, 1248, 1201, 1157, 1133, 1082, 1065, 1028, 1020, 1004, 965, 883, 853, 833, 822, 797, 785, 747, 737, 695, 684, 660.

HRMS (EI) for **$C_{15}H_{16}BrN_3O_4$** (381.0324): 381.0312.

Synthesis of 5'-(benzo[1,3]dioxol-5-yl)-2'-methoxy-[1,1'-biphenyl]-4-carbonitrile (112)



According to **TP 12**, the metalation of 4-bromoanisole (**105c**; 372 mg, 2.0 mmol) was completed within 28 h at 25 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol) and the solution was stirred for 2 h. (3,4-methylenedioxy)phenylmagnesium bromide (0.5 M in THF, 4.8 mL, 2.4 mmol) was added dropwise and the solution was heated to 50 °C for 12 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **112** (461 mg, 70%) as a colorless solid.

m.p.: 153.7 – 154.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.70 (d, *J* = 2.8 Hz, 4H), 7.53 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.09 - 7.02 (m, 3H), 6.88 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.01 (s, 2H), 3.87 (s, 3H).

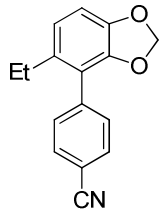
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 155.6, 148.2, 146.9, 143.2, 134.6, 134.0, 131.8, 130.2, 129.1, 128.9, 128.1, 120.1, 119.1, 111.7, 110.6, 108.6, 107.3, 101.1, 55.7.

MS (70 eV, EI) *m/z* (%): 329 (100) [M^+], 284 (29), 256 (39), 227 (12), 201 (5), 164 (5), 100 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2224, 1603, 1482, 1468, 1442, 1389, 1340, 1264, 1248, 1215, 1183, 1176, 1152, 1109, 1051, 1026, 1009, 934, 916, 903, 894, 842, 825, 814, 804, 796, 776, 746, 732, 705, 652.

HRMS (EI) for **$C_{21}H_{15}NO_3$** (329.1052): 329.1046.

Synthesis of 4-(5-ethylbenzo[1,3]dioxol-4-yl)benzonitrile (113)



According to **TP 12**, the metalation of 5-bromo-1,3-benzodioxole (**105j**; 402 mg, 2.0 mmol) was completed within 30 min at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of PEPPSI-*i*Pr (27 mg, 2 mol %) in THF (2 mL) was added, followed by 4-bromobenzonitrile (437 mg, 2.4 mmol) and the solution was stirred for 6 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 24:1) to give **113** (207 mg, 41%) as a colorless solid.

m.p.: 128.2 – 129.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74 (ddd, *J* = 8.0, 2.2, 1.4 Hz, 2H), 7.48 (ddd, *J* = 8.3, 2.2, 1.7 Hz, 2H), 6.82 (s, 2H), 5.92 (s, 2H), 2.47 (q, *J* = 7.5 Hz, 2H), 1.04 (t, *J* = 7.5 Hz, 3H).

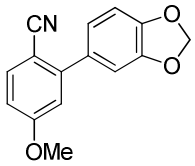
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 145.3, 145.1, 140.3, 135.4, 132.1, 130.7, 121.5, 121.5, 118.8, 111.4, 108.3, 101.0, 25.5, 15.9.

MS (70 eV, EI) *m/z* (%): 252 (15), 251 (73) [M^+], 236 (26), 206 (100), 178 (31), 151 (13), 43 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2968, 2909, 2872, 1605, 1505, 1467, 1445, 1396, 1371, 1346, 1266, 1225, 1203, 1175, 1131, 1097, 1072, 1055, 1036, 1016, 936, 924, 920, 893, 845, 831, 809, 762, 755, 726, 652.

HRMS (EI) for **$C_{16}H_{13}NO_2$** (251.0946): 251.0944.

Synthesis of 2-(benzo[1,3]dioxol-5-yl)-4-methoxybenzonitrile (114a)



According to **TP 12**, the metalation of 4-methoxybenzonitrile (**105o**; 266 mg, 2.0 mmol) was completed within 3 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 5-bromo-1,3-benzodioxole (482 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114a** (375 mg, 74%) as a colorless solid.

m.p.: 138.3 – 139.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.61 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.96 – 6.86 (m, 2H), 6.01 (s, 2H), 3.89 (s, 3H).

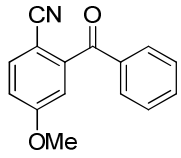
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 159.7, 147.4, 147.3, 134.2, 132.9, 131.5, 129.9, 122.9, 119.1, 111.5, 109.9, 108.3, 104.2, 101.2, 55.8.

MS (70 eV, EI) *m/z* (%): 254 (17), 253 (100) [M^+], 208 (49), 194 (6), 180 (24), 152 (10), 125 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2902, 2842, 1608, 1599, 1489, 1441, 1434, 1337, 1275, 1264, 1247, 1234, 1193, 1161, 1132, 1103, 1046, 1031, 1017, 940, 926, 918, 897, 860, 839, 810, 805, 743, 734, 723, 717, 686.

HRMS (EI) for **$C_{15}H_{11}NO_3$** (253.0739): 253.0729.

Synthesis of 2-benzoyl-4-methoxybenzonitrile (114b)



According to **TP 12**, the metalation of 4-methoxybenzonitrile (**105o**; 266 mg, 2.0 mmol) was completed within 3 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (336 mg, 2.4 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114b** (342 mg, 72%) as a colorless solid.

m.p.: 134.6 – 136.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.16 – 8.10 (m, 1H), 7.78 (dd, *J* = 8.6, 2.2 Hz, 2H), 7.66 – 7.57 (m, 2H), 7.52 – 7.43 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 1H), 3.81 (s, 3H).

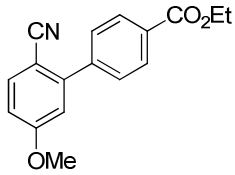
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 193.8, 160.3, 136.7, 135.9, 133.7, 133.2, 130.1, 129.7, 128.5, 118.3, 112.1, 104.3, 56.0.

MS (70 eV, EI) *m/z* (%): 237 (71) [M^+], 222 (14), 220 (31), 206 (10), 160 (98), 146 (41), 117 (30), 105 (100), 102 (17), 77 (74), 43 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3071, 2839, 2557, 1683, 1651, 1604, 1595, 1572, 1495, 1453, 1448, 1439, 1413, 1318, 1273, 1201, 1186, 1162, 1128, 1112, 1073, 1026, 1014, 1001, 980, 975, 931, 898, 839, 808, 751, 732, 705, 684, 667.

HRMS (EI) for **$C_{15}H_{11}NO_2$** (237.0790): 237.0785.

Synthesis of ethyl 2'-cyano-5'-methoxy-[1,1'-biphenyl]-4-carboxylate (114c)



According to **TP 12**, the metalation of 4-methoxybenzonitrile (**105o**; 266 mg, 2.0 mmol) was completed within 3 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by ethyl 4-bromobenzoate (549 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114c** (375 mg, 67%) as a colorless solid.

m.p.: 104.3 – 105.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11 (dt, *J* = 8.3, 1.9 Hz, 2H), 7.67 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.61 (d, *J* = 2.2 Hz, 1H), 7.55 (dt, *J* = 8.3, 1.9 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

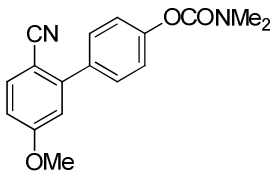
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 159.7, 140.7, 134.3, 133.7, 130.9, 129.8, 129.4, 129.3, 118.9, 111.7, 104.4, 61.0, 55.9, 14.3.

MS (70 eV, EI) *m/z* (%): 281 (51) [M^+], 253 (24), 236 (100), 208 (5), 193 (40), 164 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978, 2913, 2842, 1708, 1610, 1601, 1515, 1492, 1481, 1445, 1419, 1392, 1364, 1313, 1267, 1187, 1170, 1146, 1125, 1116, 1104, 1043, 1039, 1023, 1008, 925, 895, 858, 852, 818, 775, 747, 736, 702.

HRMS (EI) for **$C_{17}H_{15}NO_3$** (281.1052): 281.1045.

Synthesis of 2'-cyano-5'-methoxy-[1,1'-biphenyl]-4-yl dimethylcarbamate (114d)



According to **TP 12**, the metalation of 4-methoxybenzonitrile (**105o**; 266 mg, 2.0 mmol) was completed within 3 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 4-bromophenyl dimethylcarbamate (586 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **114d** (446 mg, 75%) as an off white solid.

m.p.: 149.5 – 151.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.46 (ddd, *J* = 8.8, 2.7, 2.1 Hz, 2H), 7.18 (ddd, *J* = 8.8, 2.7, 2.1 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 3.87 (s, 3H), 3.13 (s, 3H), 3.04 (s, 3H).

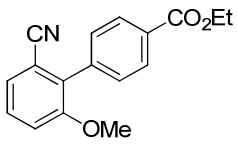
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 159.7, 154.7, 151.1, 134.2, 133.1, 133.0, 131.2, 130.2, 121.5, 119.1, 111.5, 104.1, 55.8, 36.7, 36.4.

MS (70 eV, EI) *m/z* (%): 296 (19) [M^+], 72 (100), 43 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2922, 2851, 1883, 1722, 1599, 1515, 1492, 1457, 1444, 1387, 1280, 1268, 1248, 1215, 1177, 1146, 1104, 1061, 1040, 1015, 942, 892, 874, 860, 839, 817, 808, 745, 711, 681.

HRMS (EI) for **$C_{17}H_{16}N_2O_3$** (296.1161): 296.1156.

Synthesis of ethyl 2'-cyano-6'-methoxy-[1,1'-biphenyl]-4-carboxylate (114e)



According to **TP 12**, the metalation of 3-methoxybenzonitrile (**105p**; 266 mg, 2.0 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of

$Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by ethyl 4-bromobenzoate (549 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114e** (348 mg, 62%) as a colorless solid.

m.p.: 103.4 – 104.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.16 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.51 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.21 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

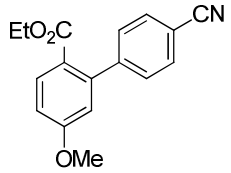
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.2, 156.8, 138.8, 133.6, 130.4, 130.1, 129.7, 129.4, 125.1, 117.8, 115.4, 113.7, 61.0, 56.0, 14.3.

MS (70 eV, EI) *m/z* (%): 281 (51) [M^+], 253 (22), 236 (100), 209 (10), 193 (43), 164 (13), 138 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2223, 1727, 1720, 1611, 1578, 1564, 1469, 1436, 1405, 1362, 1299, 1269, 1195, 1185, 1171, 1126, 1118, 1102, 1069, 1027, 1015, 1005, 963, 908, 855, 790, 771, 766, 731, 712, 703, 697, 653.

HRMS (EI) for **$C_{17}H_{15}NO_3$** (281.1052): 281.1047.

Synthesis of ethyl 4'-cyano-5-methoxy-[1,1'-biphenyl]-2-carboxylate (114f)



According to **TP 12**, the metalation of ethyl 4-methoxybenzoate (**105q**; 360 mg, 2.0 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to 0 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 4-bromobenzonitrile (437 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114f** (410 mg, 73%) as a colorless solid.

m.p.: 70.0 – 71.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 8.8 Hz, 1H), 7.69 (dt, *J* = 8.6, 1.8 Hz, 2H), 7.40 (dt, *J* = 8.6, 1.8 Hz, 2H), 6.98 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H).

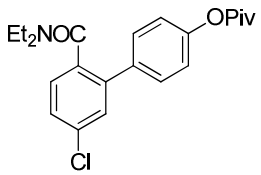
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 166.8, 161.9, 146.9, 143.6, 132.9, 131.6, 129.2, 122.1, 118.9, 116.1, 113.2, 110.9, 60.7, 55.6, 13.8.

MS (70 eV, EI) *m/z* (%): 281 (51) [M^+], 253 (22), 236 (100), 209 (10), 193 (43), 164 (13), 138 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2984, 2842, 1706, 1604, 1573, 1554, 1487, 1461, 1388, 1365, 1299, 1285, 1246, 1216, 1179, 1141, 1134, 1108, 1036, 1027, 1014, 892, 857, 846, 830, 776, 710, 682.

HRMS (EI) for **$C_{17}H_{15}NO_3$** (281.1052): 281.1047.

Synthesis of 5'-chloro-2'-(diethylcarbamoyl)-[1,1'-biphenyl]-4-yl pivalate (114g)



According to **TP 12**, the metalation of 4-chloro-*N,N*-diethylbenzamide (**105f**; 413 mg, 2.0 mmol) was completed within 3 h at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 4-bromophenyl pivalate (617 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 2:1) to give **114g** (634 mg, 82%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (dt, *J* = 8.8, 2.5 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.31 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.08 (dt, *J* = 8.8, 2.5 Hz, 2H), 3.79 – 3.64 (m, 1H), 3.09 – 2.98 (m, 1H), 2.96 – 2.85 (m, 1H), 2.72 – 2.60 (m, 1H), 1.37 (s, 9H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.1 Hz, 3H).

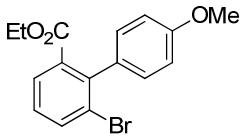
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 176.9, 169.4, 151.1, 139.2, 135.8, 134.8, 134.7, 129.7, 129.3, 128.5, 127.8, 121.6, 42.3, 39.1, 38.6, 27.1, 13.4, 12.0.

MS (70 eV, EI) *m/z* (%): 389 (12), 388 (21), 387 (36) [M^+], 305 (17), 304 (29), 303 (42), 302 (60), 233 (22), 231 (63), 196 (14), 168 (22), 139 (29), 85 (11), 72 (15), 57 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2934, 2873, 1749, 1713, 1624, 1592, 1556, 1511, 1459, 1427, 1396, 1381, 1363, 1287, 1220, 1202, 1167, 1102, 1030, 1014, 943, 898, 877, 854, 828, 801, 784, 768, 717, 656.

HRMS (EI) for **$C_{22}H_{26}ClNO_3$** (387.1601): 387.1593.

Synthesis of ethyl 6-bromo-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (114h)



According to **TP 12**, the metalation of ethyl 3-bromobenzoate (**105r**; 458 mg, 2.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(dba)_2$ (23 mg, 0.04 mmol) and tfp (19 mg, 0.08 mmol) in THF (2 mL) was added, followed by 4-iodoanisole (562 mg, 2.5 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114h** (433 mg, 65%) as a colorless solid.

m.p.: 84.0 – 85.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.57 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.47 – 7.42 (m, 2H), 6.90 – 6.86 (m, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

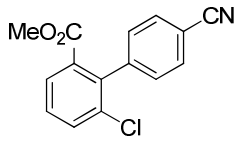
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4, 155.6, 141.7, 133.2, 131.8, 131.6, 129.4, 129.4, 129.3, 113.1, 113.1, 60.9, 55.8, 14.3.

MS (70 eV, EI) *m/z* (%): 336 (39), 334 (100) [M^+], 308 (19), 289 (80), 246 (27), 182 (17), 168 (37), 139 (46), 97 (13), 69 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2992, 2933, 1711, 1605, 1558, 1487, 1473, 1458, 1434, 1387, 1373, 1364, 1291, 1266, 1183, 1147, 1122, 1108, 1100, 1024, 1011, 906, 876, 861, 808, 777, 740, 735, 705, 654.

HRMS (EI) for **$C_{16}H_{15}BrO_3$** (334.0205): 334.0198.

Synthesis of methyl 6-chloro-4'-cyano-[1,1'-biphenyl]-2-carboxylate (114i)



According to **TP 12**, the metalation of methyl 3-chlorobenzoate (**105s**; 341 mg, 2.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 4-bromobenzonitrile (437 mg, 2.4 mmol) and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **114i** (398 mg, 73%) as a colorless solid.

m.p.: 105.2 – 106.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.88 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.62 (s, 3H).

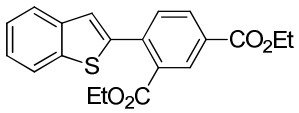
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.6, 143.2, 139.2, 134.3, 133.1, 132.4, 131.7, 129.8, 129.3, 128.6, 118.8, 111.6, 52.3.

MS (70 eV, EI) *m/z* (%): 273 (13), 271 (40) [M^+], 242 (36), 240 (100), 204 (14), 177 (54), 150 (10), 43 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2949, 1721, 1715, 1608, 1585, 1566, 1508, 1451, 1426, 1402, 1266, 1252, 1201, 1181, 1146, 1110, 1093, 1007, 975, 851, 840, 831, 824, 772, 764, 740, 727.

HRMS (EI) for **$C_{15}H_{10}ClNO_2$** (271.0400): 271.0398.

Synthesis of diethyl 4-(benzo[b]thiophen-2-yl)isophthalate (114j)



According to **TP 12**, the metalation of benzothiophene (**105t**; 268 mg, 2.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by diethyl 4-bromoisophthalate (722 mg, 2.4 mmol)

and the solution was stirred for 10 h. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **114j** (523 mg, 74%) as a colorless solid.

m.p.: 78.4 – 80.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.44 (dd, *J* = 1.9, 0.6 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.82 – 7.77 (m, 1H), 7.65 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.33 – 7.43 (m, 2H), 7.32 (d, *J* = 0.8 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H).

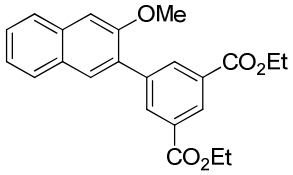
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 167.8, 165.4, 141.1, 140.4, 139.9, 138.3, 132.6, 131.6, 131.3, 130.6, 130.3, 124.6, 124.6, 123.8, 123.7, 122.1, 61.6, 61.4, 14.3, 13.8.

MS (70 eV, EI) *m/z* (%): 354 (100) [M^+], 326 (11), 309 (31), 281 (17), 254 (10), 237 (15), 208 (19), 165 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3065, 2976, 2929, 1711, 1607, 1459, 1439, 1389, 1365, 1334, 1299, 1284, 1244, 1182, 1169, 1135, 1110, 1088, 1066, 1022, 1012, 948, 939, 874, 856, 842, 833, 769, 758, 730, 725, 680, 659.

HRMS (EI) for **$C_{20}H_{18}O_4S$** (354.0926): 354.0921.

Synthesis of diethyl 5-(3-methoxynaphthalen-2-yl)isophthalate (117a)



According to **TP 13**, the metalation of 2-methoxynaphthalene (**115**; 316 mg, 2.0 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by diethyl 5-bromoisophthalate (722 mg, 2.4 mmol) and the solution was stirred for 18 h at 50 °C. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **117a** (468 mg, 74%) as a colorless solid.

m.p.: 97.5 – 98.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.71 (t, *J* = 1.7 Hz, 1H), 8.48 (d, *J* = 1.7 Hz, 2H), 7.85 – 7.77 (m, 3H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.26 (s, 1H), 4.46 (q, *J* = 7.0 Hz, 4H), 3.95 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 6H).

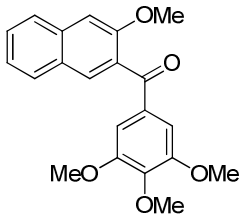
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 154.9, 139.1, 135.0, 134.4, 130.7, 130.4, 130.2, 129.3, 128.7, 127.8, 126.8, 126.4, 124.2, 105.9, 61.3, 55.6, 14.4.

MS (70 eV, EI) *m/z* (%): 354 (100) [M^+], 326 (11), 309 (31), 281 (17), 254 (10), 237 (15), 208 (19), 165 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981, 1713, 1630, 1596, 1503, 1467, 1441, 1424, 1393, 1367, 1339, 1321, 1306, 1230, 1198, 1174, 1114, 1102, 1056, 1020, 921, 906, 869, 839, 832, 758, 752, 726, 696, 682.

HRMS (EI) for **$C_{21}H_{20}O_5$** (352.1311): 352.1306.

Synthesis of (3-methoxynaphthalen-2-yl)(3,4,5-trimethoxyphenyl)methanone (117b)



According to **TP 13**, the metalation of 2-methoxynaphthalene (**115**; 316 mg, 2.0 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to -20 °C, $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and stirred for 15 min. The mixture was allowed to warm to 25 °C and a solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added, followed by 3,4,5-trimethoxybenzoyl chloride (552 mg, 2.4 mmol) and the solution was stirred for 6 h at 50 °C. The reaction mixture was quenched with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 4:1) to give **117b** (403 mg, 57%) as a colorless solid.

m.p.: 114.2 – 115.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82 (s, 2H), 7.80 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.54 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.25 (s, 1H), 7.15 (s, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.82 (s, 6H).

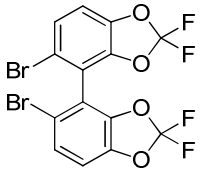
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 194.7, 155.0, 152.9, 142.8, 135.3, 132.8, 130.4, 129.4, 128.3, 127.9, 127.7, 126.6, 124.4, 107.6, 106.2, 60.9, 56.3, 55.7.

MS (70 eV, EI) *m/z* (%): 352 (100) [M^+], 335 (15), 195 (32), 185 (36), 181 (47), 171 (76), 127 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2973, 2940, 2838, 1663, 1627, 1582, 1500, 1457, 1430, 1411, 1335, 1325, 1252, 1234, 1202, 1170, 1152, 1127, 1098, 1045, 1021, 998, 961, 909, 877, 862, 849, 837, 792, 770, 762, 750, 743, 705, 653.

HRMS (EI) for **$C_{21}H_{20}O_5$** (352.1311): 352.1306.

Synthesis of 5,5'-dibromo-2,2,2',2'-tetrafluoro-4,4'-bibenzo[1,3]dioxole (119)



According to **TP 12**, the metalation of 5-bromo-2,2-difluorobenzo[1,3]dioxole (**118**; 474 mg, 2.0 mmol) was completed within 1 h at 0 °C. The reaction mixture was cooled to -78 °C, then *p*-chloranil (590 mg, 2.4 mmol) in dry THF (14 mL), was added slowly over a period of 90 min. The reaction mixture was allowed to reach -50 °C and was further stirred for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture and it was filtered through Celite, washed with diethyl ether thoroughly, and the filtrate was washed with a mixture of sat. aq NH_4Cl solution (30 mL) and aq HCl (2 M, 10 mL). The organic phase was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 99:1) to give **119** (346 mg, 73%) as a colorless solid.

m.p.: 130.0 – 131.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 1.8 Hz, 2H), 7.30 (d, *J* = 1.8 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 144.6, 140.2, 131.5 (t, $^1J_{C\text{-}F}$ = 258.7 Hz), 126.4, 117.2, 116.0, 113.6.

MS (70 eV, EI) *m/z* (%): 474 (43), 472 (98), 470 (44) [M^+], 314 (15), 312 (32), 310 (18), 124 (27), 70 (11), 62 (18), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3137, 3094, 1692, 1635, 1586, 1455, 1446, 1403, 1331, 1247, 1227, 1157, 1070, 1031, 929, 896, 868, 845, 713, 707, 679.

HRMS (EI) for **$C_{14}H_4Br_2F_4O_4$** (469.8412): 469.8408.

D. APPENDIX

1 LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
An	di-*para*-anisyl
aq	aq
Ar	aryl
ATR	attenuated total reflection (IR)
Bn	benzyl
Boc	*tert*butyl carbonate
Bu	butyl
calc.	calculated
conc.	concentrated
Cy	cyclohexyl
dba	trans,trans-dibenzylideneacetone
DBE	1,2-dibromoethane
dest.	distilled
DA	Diisopropylamide
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DoI	directed *ortho* insertion
δ	chemical shifts in parts per million
E	electrophile
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectrometry
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium diisopropylamide
M	molarity
m	meta
m.p.	melting point
Me	methyl

Met	metal
min	minute
mmol	millimole
MOM	methoxymethyl
MS	mass spectrometry
NEP	*N*-ethyl-2-pyrrolidine
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	ortho
p	para
PEPPSI-*i*Pr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PG	protecting group
Piv	pivaloyl
Ph	phenyl
R	organic substituents
Ru-Phos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
rt	room temperature
sat	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBDMS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
Tf	triflate
tfp	tris-(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Tos	4-toluenesulfonyl