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NEW PREPARATION METHODS AND REACTIONS OF ORGANOMETALLIC REAGENTS OF MG, ZN AND AL FOR THE FUNCTIONALIZATION OF AROMATICS AND HETEROAROMATICS AND REGIOSELECTIVE FUNCTIONALIZATIONS OF AROMATICS AND HETEROCYCLES BEARING A BIS(SILYL)METHYL GROUP

von

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aus Gummersbach

2015

Erklärung

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Eidesstattliche Versicherung

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München, 18. Februar 2015

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Thomas Klatt

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Communications and Full Papers

1) T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel: "$InCl_3$-Catalyzed Synthesis of 1,2-Dimetallic Compounds by Direct Insertion of Aluminum or Zinc Powder" *Angew. Chem. Int. Ed.* **2012**, *51*, 9926−9930; *Angew. Chem.* **2012**, *124*, 10064−10068.
2) T. Klatt, K. Groll, P. Knochel: "Generation of Functionalized Aryl and Heteroaryl Aluminum Reagents by Halogen-Lithium Exchange" *Chem. Commun.* **2013**, *49*, 6953−6955. *(Chosen as Chem. Comm. Hot Article)*
3) T. Klatt, T. D. Blümke, M. A. Ganiek, P. Knochel: "Synthesis of 1,2-Dimetallic Compounds via Direct Insertion of Zinc Powder in the Presence of $InCl_3$: Synthesis of ortho-Bis-functionalized Aromatics" *Synthesis* **2014**, *46*, 290−294.
4) T. Klatt, D. Sustac Roman, T. León, P. Knochel: "TMP-Magnesium and TMP-Zinc Bases for the Regioselective Metalation of the Cinnoline Scaffold" *Org. Lett.* **2014**, *16*, 1232−1235.
5) V. Werner, T. Klatt, M. Fuji, Y. Apeloig, P. Knochel: "Preparation and Regioselective Metalation of *Bis*(trimethylsilyl)methyl-Substituted Aryl Derivatives for the Generation of Highly Functionalized Arenes" *Chem. Eur. J.* **2014**, *20*, 8338-8342.
6) T. Klatt, V. Werner, M. G. Maximova, D. Didier, Y. Apeloig, P. Knochel: "Preparation and Regioselective Magnesiation or Lithiation of Bis(trimethylsilyl)methyl-Substituted Heteroaryls for the Generation of Highly Functionalized Heterocycles" *Chem. Eur. J.*, *accepted,* DOI: 10.1002/chem.201500627.

Reviews

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3) T. Klatt, P. Knochel: "The preparation and cross-coupling reaction of organoaluminum compounds" in *The Chemistry of Organoaluminum Compounds* (Eds.: L. Micouin, I. Marek), Wiley **2015**, *manuscript in preparation.*

"It doesn't matter how beautiful your theory is,
it doesn't matter how smart you are.
If it doesn't agree with experiment, it's wrong."

- Richard P. Feynman

Meiner Familie

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A. INTRODUCTION

1. OVERVIEW

As we enter the 21st century, we have wealth and technology unmatched in human experience, and the fortunate few who live in the world's developed nations are almost inevitably propelled toward a future enriched by advances in computers, communication, and life sciences.[1]

In the same moment, however, we are facing new challenges and threads. We will be confronted by so called ‘mega trends’ that shape what is to come. A main issue is the increase of the world population especially in developing and emerging countries. Simultaneously, more and more people for whom these glittering opportunities of the new centuries were beyond reach so far, claim access to western standards, creating an increased demand on food, goods and healthcare. This development puts an enormous strain on limited resources, such as organic materials or energy.

As we have the privilege of technological and scientific progress combined with the neceressary knowledge, we should shoulder the responsibility to make use of these capabilities, adressing solutions regarding the growing demand meeting limited resources.[2]

In this context, chemistry is present in many areas. Agrochemical industry develops fertilizers, herbicides, fungicides and insecticides increasing the harvested area not only due to multiple cropping but also by more efficient cultivation, therefore raising the amount of crops being harvested per acre.[3] Pharmaceutical chemistry is providing us with drugs rising life expectancy and, hopefully, quality. In addition, novel materials used for heat insulation, solar energy or to prepare organic LEDs (OLED), which lead to a reduction in energy consumption, are of interest.

In order to find ways to lessen the burden on earth’s resources, the chemical sector needs innovations for more efficient and sustainable ways in the area of organic synthesis. As a key issue, the formation of new carbon-carbon bonds is central to organic synthetic methodology. Whereas a broad range of electrophilic reaction partners are available for organic synthesis, the choice of polyfunctional nucleophiles is more difficult, and organometallic intermediates have proven to be excellent nucleophilic intermediates for the formation of new carbon-carbon bonds. The availability of highly functionalized organometallics is of special interest, since it allows the

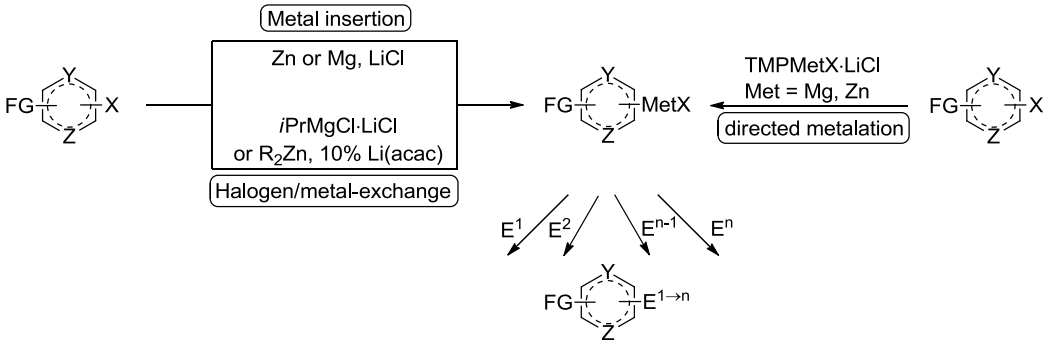
[1] J. Carter, Challenges for Humanity: A Beginning, *National Geographic*, **2002**.
[2] S. Kuznets, *Amer. Econ. Rev.* **1973**, *63*, 247.
[3] Food and Agriculture Organization of the United Nations (FAO), *World Agriculture Towards 2030/2050*. The 2012 Revision.

formation of complex organic target molecules avoiding complex protection/deprotection steps. This introduction shall focus on organometallics derived from magnesium and zinc, as these are well-established reagents. Their low toxicity as well as their low price, are essential characteristics of these two metals, which have allowed to fully exploit the exceptional compatibility of these organometallics. Furthermore, in the presence of catalysts and appropriate reaction conditions (solvent, temperature, concentration) carbon-carbon bonds can be made with great efficiency. Additionally, zinc and magnesium organometallics are compatible with strong Lewis acid catalysts (formation of frustrated Lewis pairs)[4] which considerably expands the synthetic scope of these reactive intermediates.

1.1 PREPARATION OF POLYFUNCTIONAL ZINC AND MAGNESIUM ORGANOMETALLICS

Over the last thirty years, a range of simple preparation methods of polyfunctional organozinc and -magnesium has been found.[5] As substrates, it is possible to use readily available organic halides,[6] as well as molecules bearing relatively acidic protons such as ketones, esters,[7] nitriles,[8] alkynes, or aromatic and heterocyclic scaffolds bearing H-C(sp^2) bonds.[9] Thus, three preparation methods will be described in detail: (1) the LiCl-promoted insertion of magnesium or zinc to various organic halides, (2) the bromine/magnesium-exchange reaction triggered by *i*PrMgCl·LiCl and (3) the directed metalation of numerous aromatic and heterocyclic substrates using sterically hindered TMP-bases of magnesium and zinc complexed by LiCl. Also, the resulting polyfunctional zinc and magnesium reagents readily form new carbon-carbon bonds by reactions with various electrophiles, leading to a broad range of polyfunctional organic molecules (Scheme 1).

[4] D. W. Stefan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46.
[5] a) P. Knochel, J. F. Normant, *Tetrahedron Lett*. **1986**, *27*, 1039. b) P. Knochel, J. F. Normant, *Tetrahedron Lett*. **1986**, *27*, 1043.
[6] C. Jubert, P. Knochel, *J. Org. Chem.* **1992**, *57*, 5425.
[7] S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690.
[8] a) F. F. Fleming, Z. Zhang, P. Knochel, *Org. Lett.* **2004**, *6*, 501. b) F. F. Fleming, Z. Zhang, W. Liu, P. Knochel, *J. Org. Chem.* **2005**, *70*, 2200. c) D. Nath, M. C. Skilbeck, I. Coldham, F. F. Fleming, *Org. Lett.* **2014**, *16*, 62.
[9] D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1475.



Scheme 1: General methods for the preparation of polyfunctional zinc and magnesium organometallics.

1.1.1 SELECTIVE INSERTIONS OF MAGNESIUM AND ZINC INTO ORGANIC HALIDES

Zinc powder is a moderately good reducing reagent and reacts readily only with alkyl iodides[10] and benzylic halides.[11] Aryl iodides undergo the insertion of zinc only in polar solvents, such as DMA.[12] The use of the highly activated zinc introduced by Rieke[13] improves remarkably the zinc insertion rate, but requires the generation of highly active zinc powder. The group of *Knochel* has found that the presence of LiCl considerably facilitates the rates of zinc metal insertion in aryl iodides and electron-poor aryl or heteroaryl bromides.[14] The roles of LiCl may be multiple, but notably this salt has an exceptional ability to solubilize organometallics and metal salts in common organic solvents, such as THF. Early on, Li_2CuCl_4 (Kochi catalyst)[15] and $CuCN \cdot 2LiCl$[16] have been found to be very valuable sources of copper(I) for numerous carbon-carbon bond formations. Similarly, numerous salts can dissolve in THF in the presence of LiCl by forming

[10] a) M. C. P. Yeh, P. Knochel, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390. b) M. C. P. Yeh, P. Knochel, L. E. Santa, *Tetrahedron Lett.* **1988**, *29*, 3887. c) M. C. P. Yeh, P. Knochel, W. M. Butler, S. C. Berk, *Tetrahedron Lett.* **1988**, *29*, 6693. d) M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1988**, *29*, 2395. e) M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4799. f) P. Knochel, T. S. Chou, H. G. Chen, M. C. P. Yeh, M. J. Rozema, *J. Org. Chem.* **1989**, *54*, 5202. g) T. N. Majid, M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 5069. h) M. C. P. Yeh, H. G. Chen, P. Knochel, *Org. Synth.* **1992**, *70*, 195. i) P. Knochel, T. S. Chou, C. Jubert, D. Rajagopal, *J. Org. Chem.* **1993**, *58*, 588. j) P. Knochel, N. Millot, A. Rodriguez, C. E. Tucker, *Organic Reactions* **2001**, *58*, 417.

[11] a) S. C. Berk, P. Knochel, M. C. P. Yeh, *J. Org. Chem.* **1988**, *53*, 5789. b) H. G. Chen, C. Hoechstetter, P. Knochel, *Tetrahedron Lett.* **1989**, *30*, 4795. c) S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053.

[12] T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413.

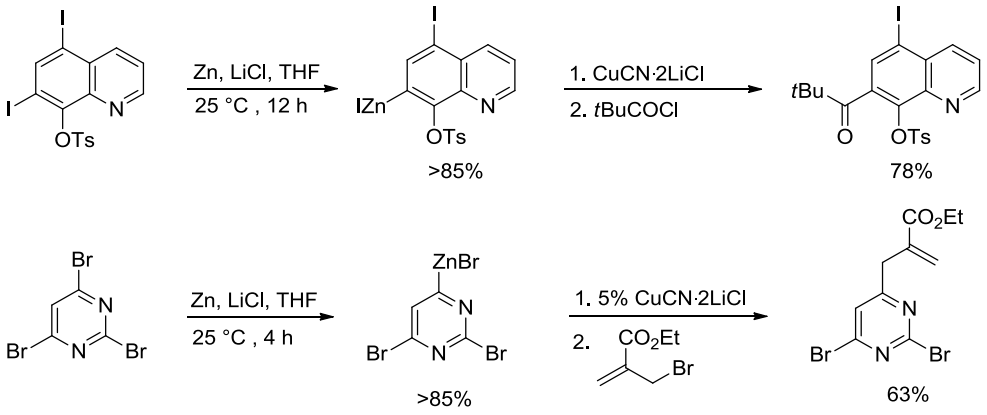
[13] a) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3672. b) R. D. Rieke, *Science* **1989**, *246*, 1260. c) J. Lee, R. Verlarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

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

[15] R. P. Eswein, E. S. Howald, R. A. Howald, D. P. Keeton, *Inorg. Nucl. Chem.* **1967**, 437.

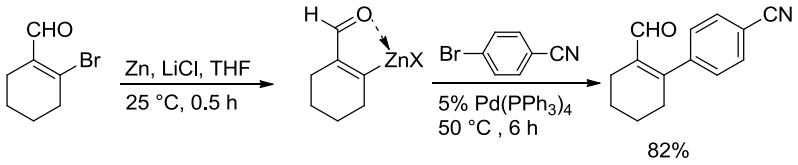
[16] a) T. Stemmler, J. E. Penner-Hahn, P. Knochel, *J. Am. Chem. Soc*. **1993**, *115*, 348. b) T. L. Stemmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Böhme, G. Frenking, *J. Am. Chem. Soc.* **1995**, *117*, 12489.

adducts such as $MnCl_2 \cdot 2LiCl$[17] or $ZnCl_2 \cdot 2LiCl$.[18] Thus, LiCl probably accelerates the magnesium or zinc insertion by removing the newly generated organometallics from the metal magnesium or zinc surface and therefore regenerates the active metal sites at the surface. This activation is quite general and has been used for other metals such as indium,[19] manganese,[20] and aluminum.[19b,21]



Scheme 2: Regioselective zinc insertion in the presence of LiCl.

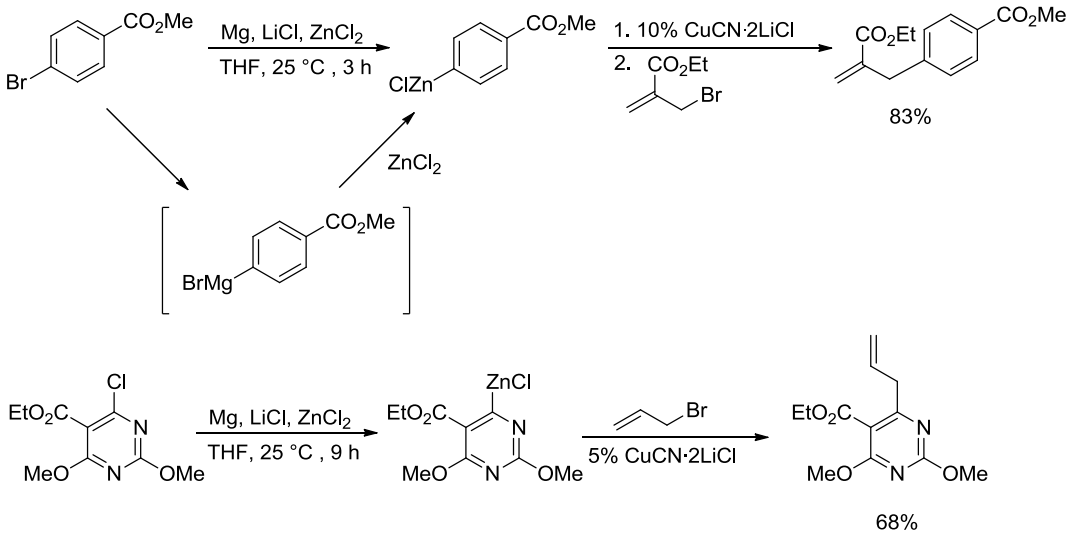
Thus, a highly regioselective room temperature zinc insertion is achieved by treating a heterocyclic diiodide or tribromide (Scheme 2) with zinc powder in the presence of LiCl, providing the functionalized zincated building blocks in high yields.[22,23] Quenching the resulting organocuprate with an acid chloride or an allylic halide in the presence of CuCN·2LiCl provides the expected heterocycles in 63-78% yield (Scheme 2).The exceptional mild insertion conditions allow an insertion in β-unsaturated aldehydes leading to the corresponding zinc species. After cross-coupling, the expected unsaturated aldehyde is obtained in 82% yield (Scheme 3).[24]



Scheme 3: Regio- and stereoselective insertion of zinc to α,β-unsaturated aldehydes.

[17] a) I. Klement, H. Stadtmüller, P. Knochel, G. Cahiez, *Tetrahedron Lett.* **1997**, *38*, 1927. b) T. Stüdemann, M. Ibrahim-Ouali, G. Cahiez, P. Knochel, *Synlett* **1998**, 143. c) C. Boucley, G. Cahiez, S. Carini, M. Comes-Franchini, P. Knochel, S. Pollicino, A. Ricci, *J. Organomet. Chem*. **2001**, *624,* 223. d) G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109,* 1434. e) S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[18] Z. Dong, G. C. Clososki, S. H. Wunderlich, A. Unsinn, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 457.
[19] a) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236. b) T. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nature Chemistry* **2010**, *2*, 313.
[20] a) Z. Peng, B. A. Haag, P. Knochel, *Org. Lett.* **2010**, *12*, 5398. b) Z. Peng, P. Knochel, *Org. Lett*. **2011**, *13*, 3198.
[21] K. Groll, T. D. Blümke, A. Unsinn, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 11157.
[22] N. Boudet, S. Sase, P. Sinha, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129,* 12358.
[23] D. Soorukram, N. Boudet, V. Malakhov, P. Knochel, *Synthesis* **2007**, 3915.
[24] C. Sämann, M. A. Schade, S. Yamada, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 9495.

Since the moderate reduction power of zinc metal precludes insertions into electron-rich aryl bromides, zinc was replaced by a stronger reducing metal magnesium.[25] The presence of $ZnCl_2$ and LiCl led to a synergetic activation of the metal and converts immediately the intermediate arylmagnesium derivative into the corresponding zinc reagent.



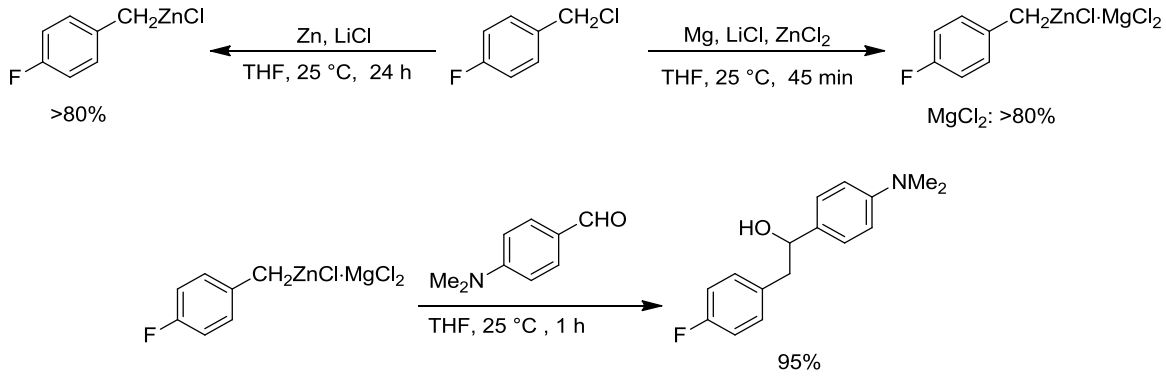
Scheme 4: Magnesium insertions in the presence of $ZnCl_2$ and LiCl.

This insertion reaction can be performed at room temperature in THF and is complete within 3 h. A copper(I)-catalyzed allylation converts this zinc reagent into the allylated product in 83% yield. This method now allows the conversion of electron-deficient heterocyclic chlorides, such as an uracil derivative, to the corresponding zinc reagent. After allylation, the uracil derivative is obtained in 68% yield (Scheme 4).[24] The use of LiCl also allows the direct insertion of indium,[26] manganese, and aluminum[27] to aryl iodides and in some cases to aryl bromides.

The insertion of zinc to benzylic chlorides has a broad scope and represents a unique method for preparing polyfunctional benzylic organometallics.[28] Furthermore, the use of Mg in conjunction with $ZnCl_2$ and LiCl for performing this insertion shortens considerably the reaction time.[29] Thus, 4-fluorobenzyl chloride requires ca. 24 h at room temperature for a complete zinc insertion,

[25] P. Knochel, Carbometallation of Alkenes and Alkynes. in *Comprehensive Organic Synthesis*, Vol. 4, (Ed. B. M. Trost), Pergamon Press: **1991**.
[26] C. Retherford, M. C. P. Yeh, I. Schipor, H.-G. Chen, P. Knochel, *J. Org.Chem.* **1989**, *54*, 5200.
[27] C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482.
[28] a) P. Auvray, P. Knochel, J. Vaissermann, J. F. Normant, *Bull. Soc. Chim. Fr.* **1990**, 813. b) P. Knochel, *Angew. Chem.* **1992**, *104*, 1486. c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107. d) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian. J.* **2008**, *3*, 1678. e) A. Metzger, C. Argyo, P. Knochel, *Synthesis* **2010**, 882.
[29] A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun.* **2008**, 5824.

leading to the corresponding zinc reagent in >80% yield. By using Mg, $ZnCl_2$, and LiCl, the insertion occurs quickly and the zinc reagent is prepared within 45 min at the same temperature.



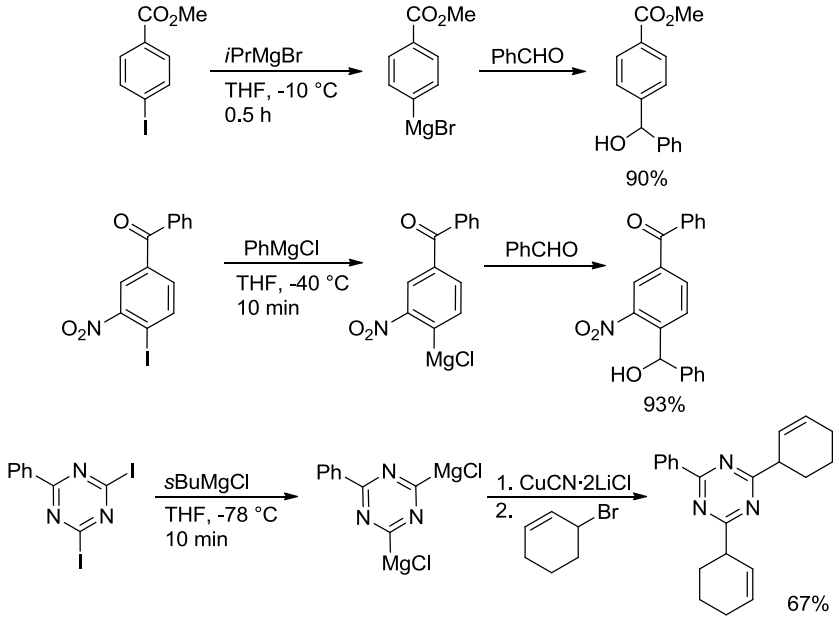
Scheme 5: Insertions of zinc or Mg, $ZnCl_2$ to benzylic chlorides in the presence of LiCl.

Furthermore, the resulting benzylic zinc reagent is complexed by $MgCl_2$. The Lewis acid boosts the reactivity of this benzylic zinc reagent, and its addition to an aldehyde is complete within 1 h at 25 °C to produce the corresponding alcohol, whereas, in the absence of $MgCl_2$, a conversion of only 23% is obtained after 20 h at 25 °C (Scheme 5).[30] Allylic zinc reagents display an even higher reactivity toward various electrophiles due to the polar character of this carbon-zinc bond.[31]

[30] a) A. Metzger, S. Bernhardt, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665. b) S. Bernhardt, A. Metzger, P. Knochel, *Synthesis* **2010**, 3802.
[31] a) P. Auvray, P. Knochel, J. F. Normant, *Tetrahedron* **1988**, *44*, 6095. b) P. Knochel, M. C. P. Yeh, C. Xiao, *Organometallics* **1989**, *8*, 2831.

1.1.2 PREPARATION OF MAGNESIUM OR ZINC ORGANOMETALLICS *VIA* A HALOGEN-MAGNESIUM EXCHANGE

The iodine-magnesium exchange is an excellent method for converting aryl iodides to the corresponding magnesium species.[32] For example, methyl 4-iodobenzoate reacts with *i*PrMgBr in THF at −10 °C and leads within 30 min to the corresponding Grignard reagent in >95% yield.[33] After the reaction with benzaldehyde, this arylmagnesium bromide affords the benzylic alcohol in 90% yield.



Scheme 6: The iodine-magnesium exchange on functionalized aromatics and heterocycles.

Unfortunately, the iodine-magnesium exchange is usually a slow reaction. The presence of electron-withdrawing substituents on the aromatic ring[34] or the use of electron-poor heterocycles[20a] facilitates the exchange reaction, furnishing the corresponding magnesium derivatives in good yields. The resulting organometallic reagents can be quenched with various electrophiles (Scheme 6).

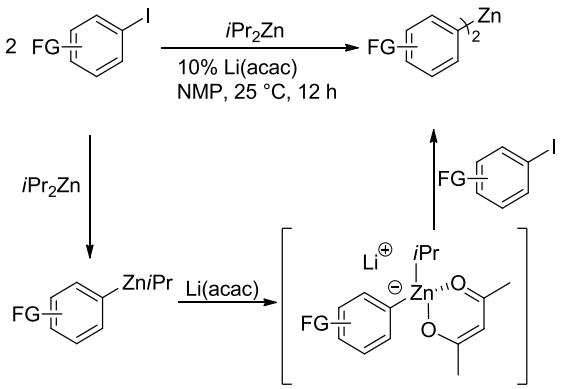
---

[32] a) Y. Kai, P. Knochel, S. Kwiatkowski, J. D. Dunitz, J. F. M. Oth, D. Seebach, H. O. Kalinowski, *Helv. Chim. Acta* **1982**, *65*, 137. b) P. Knochel, D. Seebach, *Tetrahedron Lett*. **1982**, *23*, 3897. c) P. Knochel, J. F. Normant, *Tetrahedron Lett*. **1984**, *25*, 1475. d) H. G. Chen, P. Knochel, *Tetrahedron Lett*. **1988**, *29*, 6701. e) P. Knochel, C. Xiao, M. C. P. Yeh, *Tetrahedron Lett*. **1988**, *29*, 6697.

[33] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V.-A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302. b) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V.-A. Vu, P. Knochel, *Synthesis* **2002**, 565. c) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.

[34] a) P. Knochel, D. Seebach, *Tetrahedron Lett*. **1981,** *22*, 3223. b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002***, 41*, 1610.

The bromine-magnesium exchange is much more sluggish and proceeds readily only if chelating groups in the ortho position assist the bromine-magnesium exchange reaction.[35,36] This reduced scope of the bromine-magnesium exchange reaction led *Knochel* to explore the catalysis of a halogen-metal exchange. Thus, in the search for improving the iodine-zinc exchange reaction on aromatic iodides, the group of *Knochel* found that the addition of Li(acac) to iPr$_2$Zn considerably accelerates the iodine-zinc exchange tentatively *via* a zincate in which a nucleophilic isopropyl-group is present. This extra nucleophilicity accelerates a second iodine-zinc exchange, furnishing a diarylzinc compound (Scheme 7).[37]

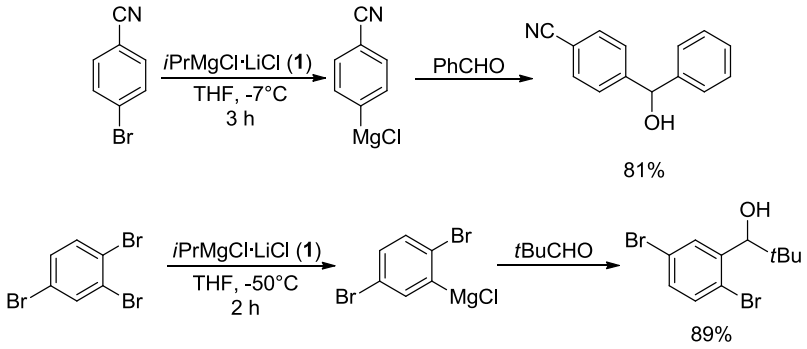


Scheme 7: Li(acac)-catalyzed iodine-zinc exchange.

This catalysis could be extended to the bromine-magnesium exchange using LiCl as a promoter instead of Li(acac). Thus, the use of iPrMgCl·LiCl (**1**) leads to a dramatic rate acceleration of the bromine-magnesium exchange and allows now the performance of such exchange reactions under especially mild reaction conditions. Thus, 4-bromobenzonitrile reacts with iPrMgCl·LiCl (**1**) at –7 °C to provide the corresponding magnesium reagent, which after quenching with benzaldehyde gives the desired alcohol in 81% yield (Scheme 8). Similarly, a highly regioselective bromine-magnesium exchange is observed with a tribromide. The exchange reaction with iPrMgCl·LiCl (**1**) proceeds at –50 °C and leads to the corresponding Grignard reagent, which reacted with pivaldehyde to the corresponding alcohol in 89% yield (Scheme 8).[38] The role of LiCl is to favor the formation of the magnesiated intermediate iPrMgCl$_2^-$ Li$^+$, which

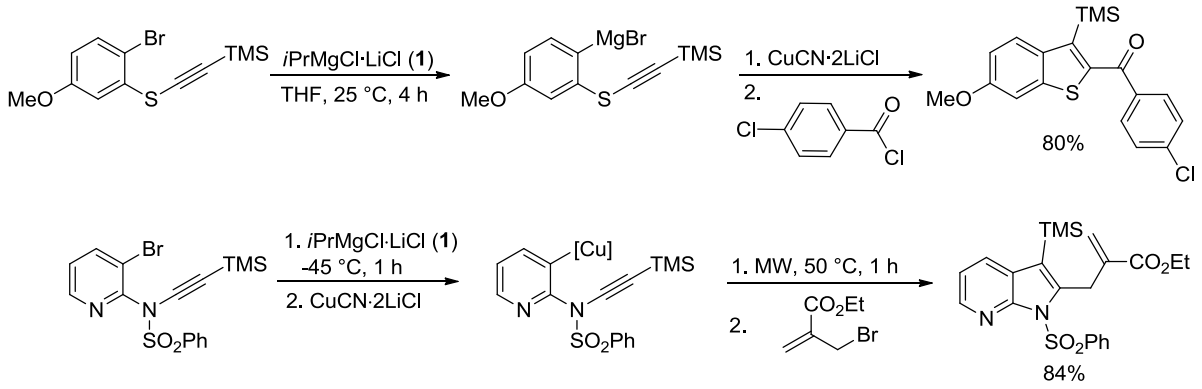
[35] M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449.
[36] M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618.
[37] a) S. Achyutha Rao, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 7575. b) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017. c) L.-Z. Gong, P. Knochel, *Synlett* **2005**, 267.
[38] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

should display a higher nucleophilicity compared to *i*PrMgCl. This exchange procedure has a broad scope and has found many applications.[39]



Scheme 8: LiCl-accelerated bromine-magnesium exchange.

Thus, the LiCl-assisted bromine-magnesium exchange is compatible with a range of functional groups and heterocycles, and therefore allows for the preparation of highly functionalized Grignard reagents. The treatment of an alkynyl thioether with *i*PrMgCl·LiCl (**1**) leads to the corresponding Grignard reagent, which undergoes an intramolecular carbocupration in the presence of CuCN·2LiCl. Quenching with an acid chloride provides the substituted benzothiophene in 80% yield (Scheme 9).[40]



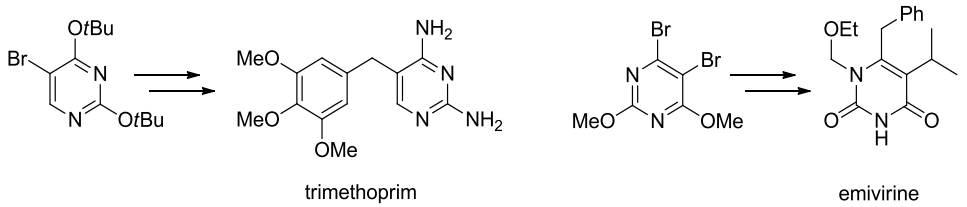
Scheme 9: Synthesis of functionalized benzothiophenes and aza-indoles *via* intramolecular carbocupration.

Similarly, a range of indoles and more importantly 7-, 6-, 5-, or 4-aza-indoles can be prepared using *i*PrMgCl·LiCl. A bromine-magnesium exchange at an alkynylamine and transmetalation to the corresponding copper reagent leads to an intramolecular *anti*-carbocupration under

[39] H. G. Chen, J. L. Gage, S. D. Barrett, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 1829.
[40] T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

microwave irradiation at 50 °C for 1 h. Finally, quenching the cyclic copper intermediate with an allylic bromide provides the desired 7-azaindole in 84% overall yield (Scheme 9).[41]

Finally, the bromine-magnesium exchange has been applied to the synthesis of various biologically active compounds, such as the antibiotic *trimethoprim*[42] and anti-AIDS drug *emivirine* (Scheme 10).[43]



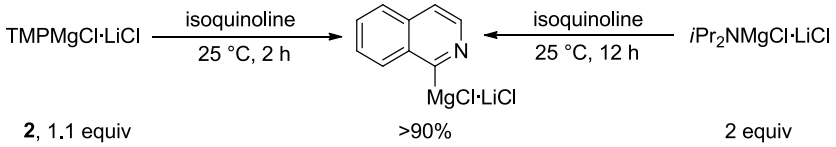
Scheme 10: Preparation of biologically active molecules using a bromine-magnesium exchange.

1.1.3 DIRECTED METALATION WITH METALLIC TMP-BASES

Pioneered by *Hauser*,[44] various metallic amides have been used to regioselectively metalate unsaturated substrates.[45] The regioselective C-H activation of aromatics and heterocyclic compounds using lithium bases has been popularized by *Snieckus*,[46] *Quéguiner*,[47] and *Schlosser*.[48] However, the ionic character and reactivity of the carbon-lithium bond complicates the use of such bases with polyfunctional molecules bearing sensitive functionalities. The group of *Knochel* has developed some LiCl-solubilized metallic TMP-bases,[49] allowing a highly chemoselective and regioselective metalation of a broad range of unsaturated substrates. Especially useful are TMPMgCl·LiCl (**2**),[50] TMPZnCl·LiCl (**3**)[51] and $TMP_2Zn·2MgCl_2·2LiCl$

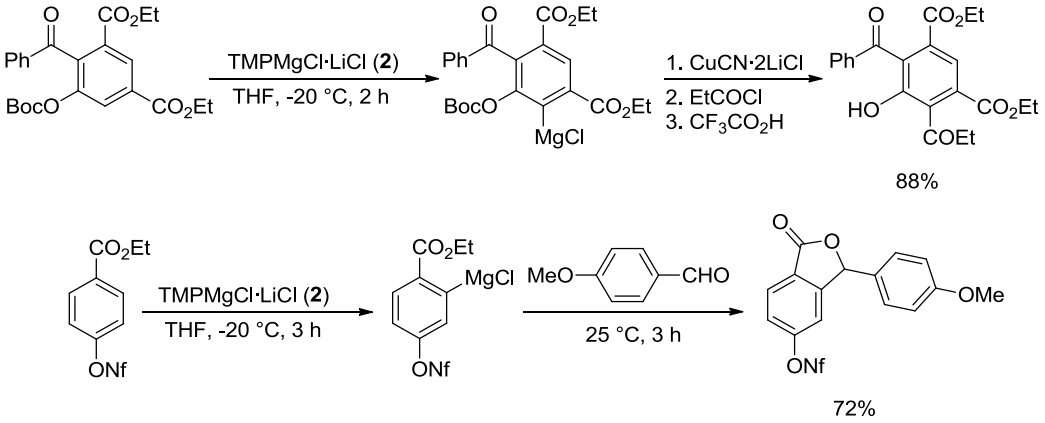
[41] A. Frischmuth, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10084.
[42] C. C. Kofink, P. Knochel, *Org. Lett.* **2006**, *8*, 4121.
[43] N. Boudet, P. Knochel, *Org. Lett.* **2006**, *8*, 3737.
[44] a) L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758. b) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295. c) P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[45] a) A. Harrison-Marchand, F. Mongin, *Chem. Rev.* **2013**, *113*, 7470. b) F. Mongin, A. Harrison-Marchand, *Chem. Rev.* **2013**, *113*, 7563.
[46] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879. b) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
[47] a) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489–4505; b) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059. c) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, 37, 595.
[48] a) M. Schlosser, J. H. Choi, S. Takagishi, *Tetrahedron* **1990**, *46*, 5633. b) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975. c) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376. d) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827.
[49] B. A. Haag, M. Mosrin, I. Hiriyakkanavar, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[50] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

(**4**).[52] The high steric hindrance of the TMP-moiety is essential for a high kinetic activity of these bases. Consequently, the less sterically hindered bases *i*Pr$_2$NMgCl·LiCl is considerably less effective for deprotonations.



Scheme 11: Relative kinetic basicity of TMPMgCl·LiCl (**2**) and *i*Pr$_2$NMgCl·LiCl.

Thus, the treatment of isoquinoline with *i*Pr$_2$NMgCl·LiCl at 25 °C is sluggish and takes long reaction times. Furthermore, it requires two equivalents of base for a complete metalation, providing the 2-magnesiated isoquinoline. On the other hand, the use of TMPMgCl·LiCl (**2**) leads to a complete magnesiation within 2 h at 25 °C (Scheme 11).[52] The discrepancy between the two bases can be explained best by the higher aggregation of *i*Pr$_2$NMgCl·LiCl compared to TMPMgCl·LiCl (**2**).

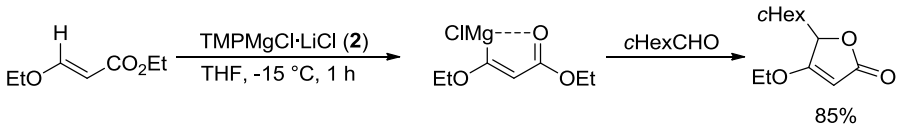


Scheme 12: Selective magnesiations with TMPMgCl·LiCl (**2**).

Because of its high kinetic basicity, TMPMgCl·LiCl (**2**) is able to deprotonate polyfunctional aromatics, such as the highly functionalized arenes, under mild conditions (Scheme 12, –20 °C, 2 h). Under these conditions, an ester, a carbonate, and an aryl ketone remain untouched during the magnesiation. The resulting magnesium reagent can be acylated in the presence of

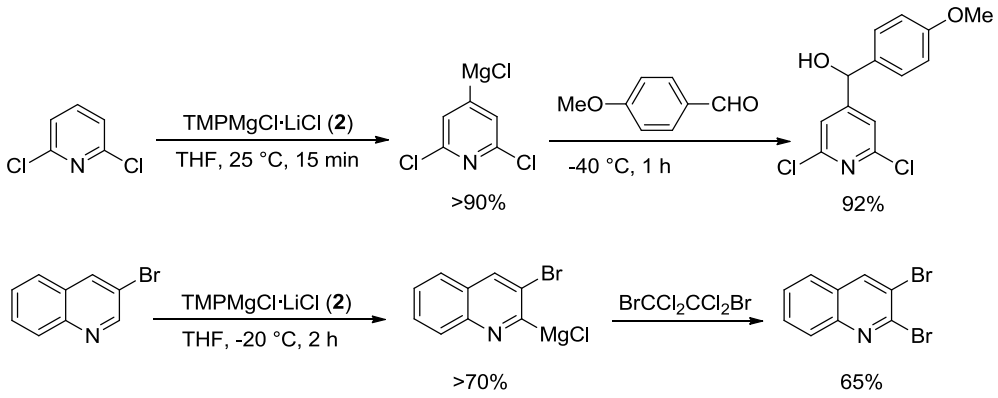
[51] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. b) T. Bresser, M. Mosrin, G. Monzón, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686. c) F. Crestey, P. Knochel, *Synthesis* **2010**, 1097. d) T. Bresser, G. Monzón, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299. e) T. Bresser, M. Mosrin, G. Monzón, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686. f) F. Crestey, P. Knochel, *Synthesis* **2010**, 1097. g) T. Bresser, G. Monzón, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299.
[52] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

CuCN·2LiCl, leading to the pentasubstituted phenol derivative in 88% yield (Scheme 12).[53] Highly electrophilic functional groups, such as a nonaflate (ONf = $OSO_2C_4F_9$),[54] are also well-tolerated. The magnesiation of the corresponding benzoate with TMPMgCl·LiCl (**2**) proceeds readily at −20 °C and after addition of an aldehyde at 25 °C the resulting lactone is isolated in 72%.[55]



Scheme 13: Directed magnesiation with TMPMgCl·LiCl.

TMPMgCl·LiCl (**2**) can also be used to metalate cyclic unsaturated systems, such as an unsaturated ester. A regioselective magnesiation provides the chelated magnesium derivative in >90% yield. Trapping with *c*HexCHO provides a lactone in 85% yield (Scheme 13).



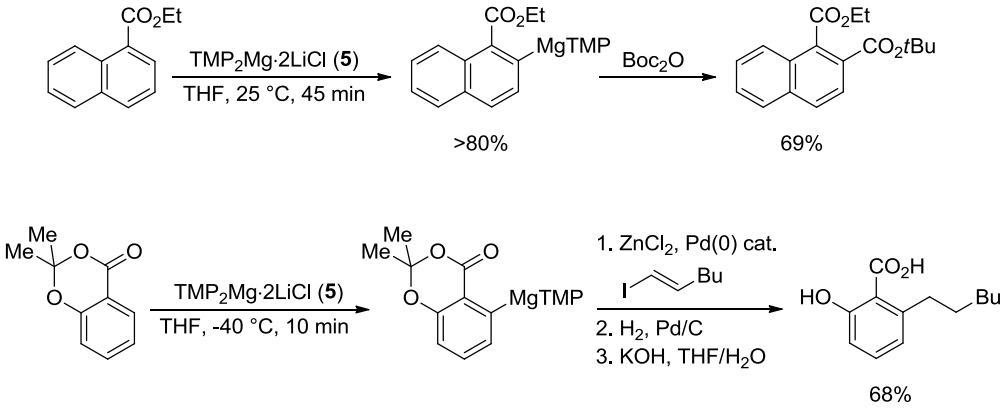
Scheme 14: Magnesiation of *N*-heterocycles with TMPMgCl·LiCl (**2**).

A broad range of furans,[56] thiophenes,[57] pyrroles, pyrazoles,[58] and thienothiophenes[59] can be functionalized in this way. The magnesiation of pyridines can also be achieved with TMPMgCl·LiCl (**2**) and the reaction of 2,6-dichloropyridine with TMPMgCl·LiCl (**2**) at 25 °C leads regioselectively to a 4-magnesiated pyridine. Trapping the Grignard reagent with an aldehyde furnishes the resulting alcohol in 92% yield.[60] The metalation of 3-bromo quinoline is

[53] W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673.
[54] a) J. Högermeier, H.-U. Reissig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868. b) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541. c) J. Högermeier, H.-U. Reissig, *Adv. Synth. Catal.* **2009**, *351*, 2747.
[55] G. Monzón, P. Knochel, *Synlett* **2010**, 304.
[56] F. M. Piller, P. Knochel, *Synthesis* **2011**, 1751.
[57] F. M. Piller, P. Knochel, *Org. Lett*. **2009**, *11*, 445.
[58] C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.
[59] T. Kunz, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 866.
[60] S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev*. **2010**, *14*, 339.

readily achieved with TMPMgCl·LiCl (**2**), providing the 2-magnesiated derivative. After bromination with $(BrCl_2C)_2$, the corresponding dibromoquinoline is obtained in 65% yield (Scheme 14).[61]

In some cases, TMPMgCl·LiCl (**2**) is not strong enough to ensure a fast magnesiation reaction. In these cases, the use of $TMP_2Mg·2LiCl$ (**5**) is required. This base allows a room-temperature magnesiation of ethyl naphthenoate leading to the corresponding magnesium derivative. After ester formation with Boc_2O, the expected diester is obtained in 69% yield (90 mmol scale reaction).[60,62] Also, a salicylate is smoothly magnesiated at –40 °C. After *Negishi* alkenylation with *E*-iodohexene, hydrogenation and saponification, the salicylic acid derivative found in *pelargonium sidoides*, is obtained in 68% yield (Scheme 15).

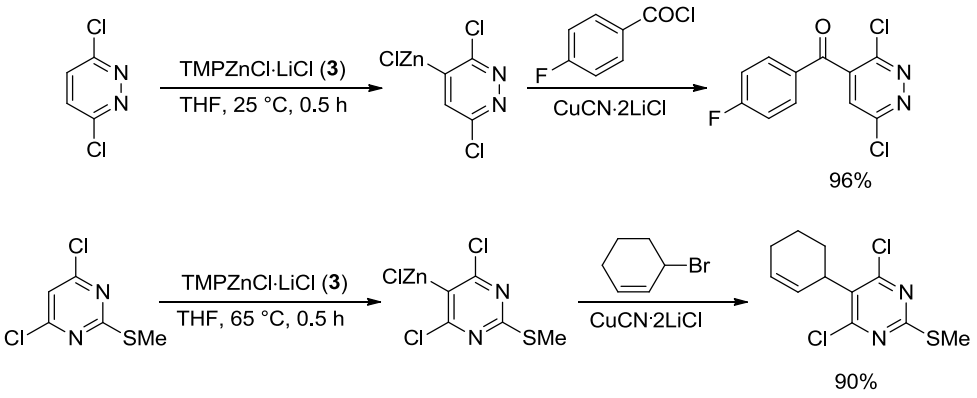


Scheme 15: $TMP_2Mg·2LiCl$ (**5**) for the magnesiation of reluctant substrates.

The metalation with TMP-magnesium bases produces magnesium-derivatives, and it is the stability and reactivity of the newly formed carbon-magnesium bond that dictates the reaction condition for the metalation and sets the reaction conditions for the magnesiation. Therefore, it is advantageous to use a TMP-zinc base for the metalation.[63] TMPZnCl·LiCl (**3**),[51] and to a lesser extent $TMP_2Zn·2MgCl_2·2LiCl$ (**4**), proved to be highly versatile bases for the zincation of numerous aromatics and heterocycles. Since organozinc species, all of which have an excellent functional group compatibility, are produced directly, it is possible to choose a broad range of conditions for the metalation step, and an exact control of the temperature is not necessary when using TMPZnCl·LiCl (**3**). This base can be used to metalate a dichloropyridazine at 25 °C,

[61] N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525.
[62] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46,* 7681.
[63] a) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115. b) C. E. Tucker, P. Knochel, *Synthesis* **1993**, 530.

leading to the corresponding zinc reagent within 30 min. Subsequent acylation with an acid chloride provides the corresponding ketone in almost quantitative yield. Also, such zincations can readily be performed at high temperature. Thus, a trisubstituted pyrimidine is zincated at 65 °C. Subsequent allylation provides the product in 90% yield (Scheme 16).[51]

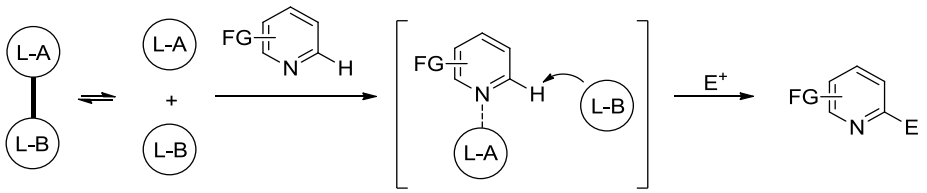


Scheme 16: Zincation of *N*-heterocycles with TMPZnCl·LiCl (**3**).

1.1.4 LEWIS ACID AND BASES COMPATIBILITY – FRUSTRATED BASE PAIRS FOR THE METALATION OF N-HETEROCYCLES

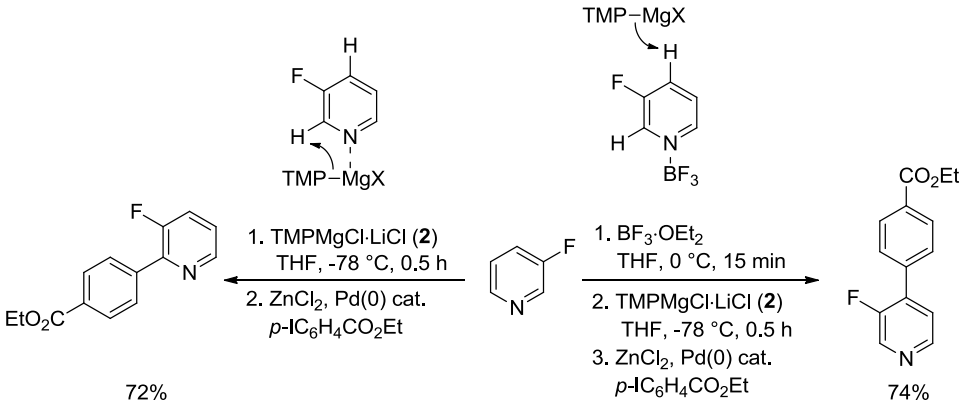
A Lewis acid-base reaction is often a labile equilibrium, especially if the steric hindrance of both (or at least one) reaction partner is large. This phenomena, although described in the literature by *Brown*[64] and *Wittig*[65] more than sixty years ago, has received much attention only recently due to the pioneer contributions of *Stefan* and *Erker*.[66,67] Thus, a Lewis acid and a Lewis base (Scheme 17) may reversibly form a Lewis pair, but after the addition of a *N*-heterocyclic derivative, the Lewis acid may acidify all aromatic positions by a coordination at the heterocyclic N-atom. Simultaneously, the Lewis-base may play the role of a Brønsted base and abstract the kinetically more acidic proton of the resulting complex of the *N*-heterocycle with the Lewis acid *via* a transition state, illustrated below. The resulting metalated pyridine can then be quenched by an electrophile, providing 2-substituted products (Scheme 17).[68]

[64] H. C. Brown, H. I. Schlesinger, S. Z. Cardon, *J. Am. Chem. Soc.* **1942**, *64*, 325.
[65] G. Wittig, H. Schloeder, *Liebigs Ann. Chem.* **1955**, *592*, 38.
[66] a) G. C. Welch, R. R. San Juan, J. D. Musada, D. W. Stephan, *Science* **2006**, *314*, 1124. b) G. C. Welch, D. W. Stephan, *J. Am. Chem. Soc.* **2007**, *129*, 1880.
[67] For an excellent review, see: D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2012**, *51*, 46.
[68] P. Knochel, K. Karaghiosoff, S. Manolikakes, Selective C-H Activations Using Frustrated Lewis Pairs. Applications in Organic Synthesis, In Frustrated Lewis Pairs II. Topics in Current Chemistry, Vol. 334, (Eds.: G. Erker, D. W. Stephan) Springer: Berlin, **2013**.



Scheme 17: Frustrated Lewis pairs for accelerated metalations.

Serendipitously, the group of *Knochel* found that the strong Lewis base TMPMgCl·LiCl (**2**) is compatible with the strong Lewis acid $BF_3 \cdot OEt_2$ at temperatures below –20 °C.[69] This behavior has been exploited for performing an orthogonal regioselective functionalization of various 3-substituted pyridines. Thus, the magnesiation of 3-fluoropyridine with TMPMgCl·LiCl (**2**) proceeds *via* the formation of a complex which directs the metalation in position 2, providing a 2-arylated pyridine after a Negishi cross-coupling in 72% yield. Alternatively, the treatment of 3-fluoropyridine with $BF_3 \cdot OEt_2$[70] followed by TMPMgCl·LiCl (**2**) occurs *via* a different complex. In this complex, the metalation at position 2 is blocked by the BF_3 moiety and the magnesiation proceeds only at position 4, leading to a 4-arylated pyridine after a Negishi cross-coupling in 74% yield (Scheme 18).[71]

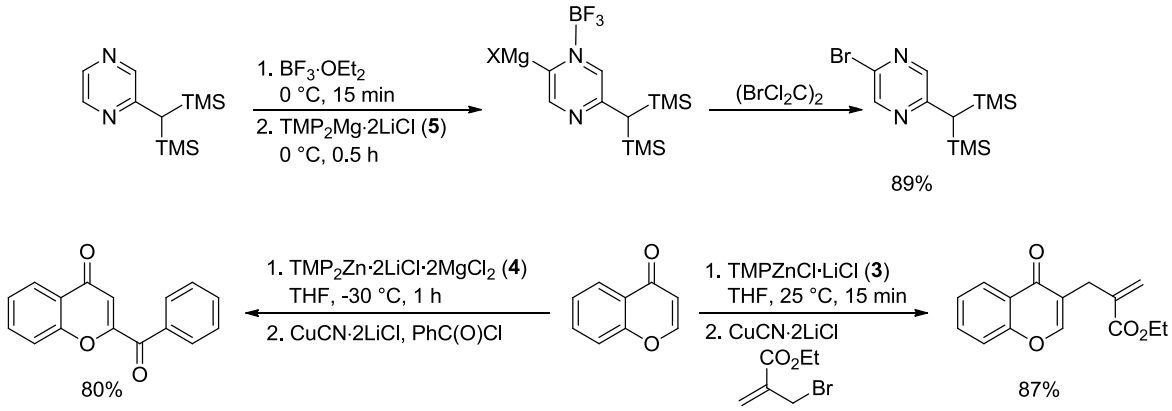


Scheme 18: Orthogonal regioselective magnesiation of 3-fluoropyridine.

This behavior can be extended to a number of substituted pyridines. Thus, nicotine is cleanly metalated in position 6 with the frustrated Lewis pair $BF_3 \cdot TMPMgCl \cdot LiCl$.[72] The nature of the

[69] M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
[70] For BF_3-catalysis in the presence of Grignard reagents, see: Brieden, W.; Ostwald, R.; Knochel, P. *Angew. Chem.* **1993**, *105*, 629.
[71] S. M. Manolikakes, M. Jaric, K. Karaghiosoff, P. Knochel, *Chem. Commun.* **2013**, *49*, 2124.
[72] M. Jaric, B. A. Haag, S. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306.

metal (Met) in the metalated species has been examined[71,73,74] and may depend on the metalated pyridine studied. Intermediates may either be trifluoroboronates[71] or magnesium derivatives.[71]



Scheme 19: Metalation of heterocycles with frustrated Lewis pairs.

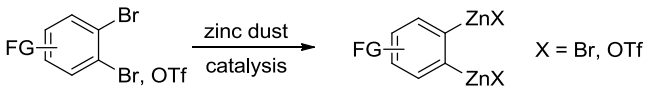
Bis(silyl)methyl-substituted pyrazines, are readily magnesiated with the Lewis pair $BF_3 \cdot OEt_2$ and $TMP_2Mg \cdot 2LiCl$ (**5**). Subsequent bromination furnishes the corresponding heterocyclic bromide in 89% yield (10 mmol scale).[75] Similarly, oxygenated heterocycles, such as chromone, may be metalated either in position 2 or position 3, depending on the nature of the Lewis base used (TMPZnCl·LiCl (**3**) or the frustrated pair $TMP_2Zn \cdot 2LiCl \cdot 2MgCl_2$ (**4**); Scheme 19).

The observed regioselectivity can be explained by assuming that $MgCl_2$ complexes the carbonyl oxygen center, leading to a metalation in position 2 (steric hindrance at position 3).[74] Thus, the zincation of chromone with TMPZnCl·LiCl (**3**) produces the desired product after a copper-catalyzed allylation in 87% yield. Alternatively, the metalation of chromone with the frustrated Lewis pair $TMP_2Zn \cdot 2LiCl \cdot 2MgCl_2$ (**4**) produces the 2-acylated chromone after a copper-mediated benzoylation in 80% yield.

[73] a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302; b) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.
[74] L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc*. **2012**, *134*, 13584.
[75] K. Groll, S. M. Manolikakes, X. Mollat du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776.

1.2 OBJECTIVES

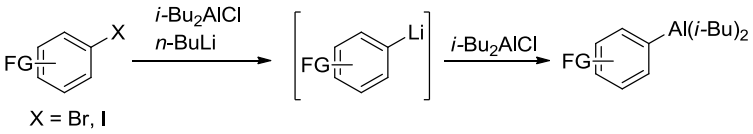
We planned to develop a practical and scalable synthetic procedure for the preparation of 1,2-dimetallic species by the direct insertion of zinc powder into aryl halides. The preparation methods of such species are quite limited and rather problematic. Therefore, a convenient procedure would be of high value.[76]



Scheme 20: Preparation of 1,2-dimetallics by direct insertion of zinc powder.

In addition, the thus prepared organozinc reagents should be readily used for subsequent reactions. By quenching the reactive 1,2-dimetallic species with various electrophiles a wide range of interesting compounds should be accessible.

In a second project the preparation of functionalized arylaluminum compounds was of high interest as this has been a challenge for several years. Even though a few methods have been reported, their functional group tolerance is rather limited and long reaction times are usually required. Using *Barbier*-type conditions we planned to apply a halogen-lithium exchange allowing an *in situ* trapping of the unstable lithiated intermediates with an aluminum source.

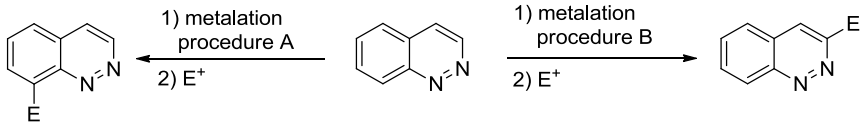


Scheme 21: Generation of functionalized arylaluminum reagents.

Additionally, we wanted to develop reaction conditions allowing for the direct reaction of these organometallics without the need of further transmetalation to the corresponding zinc reagent.

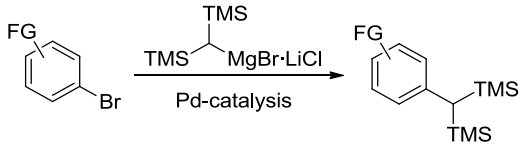
In another project, we aimed for the functionalization *via* regioselective metalation of a benzodiazine such as the cinnoline. Its unique moiety of condensed rings bearing two chemically distinguishable nitrogen atoms should allow a selective metalation depending on the choice of base.[77]

[76] This project was developed in cooperation with T. D. Blümke, see: T. D. Blümke, Disseratation, LMU München **2012**.
[77] This project was developed in cooperation with D. Sustac Roman.



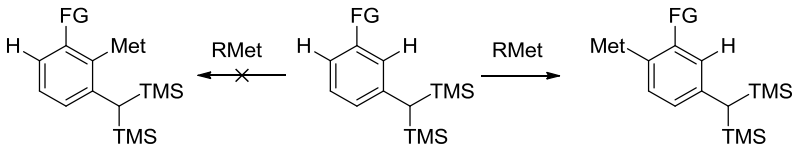
Scheme 22: Regioselective metalation of the cinnoline scaffold.

Our next goal was to find suitable ways to prepare bis(trimethylsilyl)methyl (BTSM)-substituted aryl derivatives. The group of *Knochel* reported recently the cross-coupling between a BTSM-Grignard reagent and a pyrazine chloride. Based on these experiments, we wanted to extend the preparation method to aryl bromides bearing functional groups.[78]



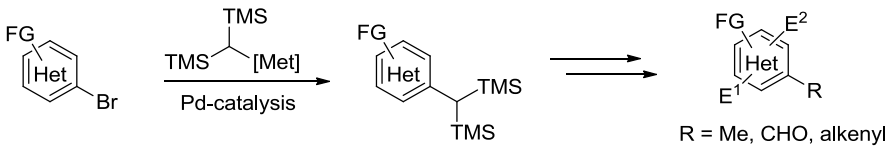
Scheme 23: Preparation of BTSM-substituted aryl derivatives *via* cross-coupling reactions.

We further decided to investigate the regioselective metalation of such *meta*-substituted arenes. We envisioned that due to the sterical hindrance caused by the bulky bis(silyl)methyl-group a deprotonation with an appropriate base should occur exclusively in the sterically less hindered *ortho*-position of the directing group.



Scheme 24: Regioselective metalation of substrates bearing a bulky BTSM-substituent.

Furthermore, we wanted to extend this method for the generation of highly functionalized BTSM-substituted heteroaryls.[78] To this point no cross-coupling procedure was known which allows the generation of BTSM-substituted heterocycles that carry a sensitive functional group. Therefore procedures using different organometallic reagents should be investigated.



Scheme 25: Preparation and functionalization of BTSM-substituted heteroaryl derivatives.

[78] This project was developed in cooperation with V. Werner, see: V. Werner, Disseratation, LMU München **2015**.

Finally, we wanted to use the unique features of the resulting substituted heterocycles for regioselective metalations. Additional properties of this bulky group are various possible subsequent transformations. Deprotection furnishes a benzylic methyl-group, while oxidation is known to lead to the corresponding aldehyde. Also, this group is known to be converted into stilbene derivatives in the presence of carbonyl-groups. Hence, this strategy allows the generation of highly functionalized heterocycles.

B. RESULTS AND DISCUSSION

1 SYNTHESIS OF 1,2-DIMETALLIC COMPOUNDS *VIA* DIRECT INSERTION OF ZINC POWDER IN THE PRESENCE OF $InCl_3$

1.1 INTRODUCTION

Organozinc reagents are important for organic synthesis and the interest in their unique chemical properties has increased during the past two decades.[79] Due to their high functional group tolerance and reactivity in transition metal-catalyzed reactions, such as *Negishi* cross-couplings, they have found numerous synthetic applications.[80,81] Aryl- and benzylic zinc reagents are accessible under mild conditions by direct insertion of commercially available zinc dust (activated with 1,2-dibromoethane and chlorotrimethylsilane) into the corresponding aryl bromides or benzyl chlorides in the presence of LiCl.[14] However, this method fails for the preparation of aryl dimetallics.

Dimetallics are organometallics containing two carbon-metal bonds in the same molecule that often show special reactivity patterns and offer unique synthetic applications.[82] The chemical properties of such organometallics depend on the nature of the two metals and their topological proximity.[83] The preparation of organometallics bearing two adjacent carbon-metal bonds (1,2-

[79] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117. b) P. Knochel, N. Millot, A. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417. c) P. Knochel, in *Handbook of Functionalized Organometallics*; Wiley-VCH: Weinheim, **2005**.

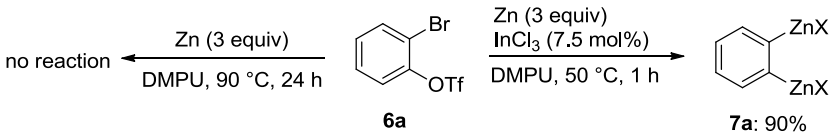
[80] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821. b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. c) G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118. d) E. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, Z. Huang, Z., in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd. (Eds.: A. de Meijere, F. Diederich, F.), Wiley-VCH, Weinheim, **2004**.

[81] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028. b) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532. c) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2010**, *49*, 2014. d) N. Hadei, G. T. Achonduh, C. Valente, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2011**, *50*, 3896.

[82] a) F. Bickelhaupt, *Angew. Chem.* **1987**, *99*, 1020. b) K. Fujita, Y. Ohnuma, H. Yasuda, H. Tani, *J. Organomet. Chem.* **1976**, *113*, 210. c) *Handbook of Functionalized Organometallics*, (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; d) O. Baron, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44,* 3133. e) I. Marek, *Chem. Rev.* **2000**, *100*, 2887. f) I. Marek, *Tetrahedron* **2002**, *58*, 9463. g) M. Sada, S. Komagawa, M. Uchiyama, M. Kobata, T. Mizuno, K. Utimoto, K. Oshima, S. Matsubara, *J. Am. Chem. Soc*. **2010**, *132*, 17452. h) H. Yoshino, N. Toda, M. Kobata, K. Ukai, K. Oshima, K. Utimoto, S. Matsubara, *Chem. Eur. J*. **2006**, *12*, 721. For unique properties of other mixed metal systems see: i) R. E. Mulvey, V. L. Blair, W. Clegg, A. R. Kennedy, J. Klett, L. Russo, *Nat. Chem.* **2010**, *2*, 588. j) V. L. Blair, L. M. Carrella, W. Clegg, B. Conway, R. W. Harrington, L. M. Hogg, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Angew. Chem. Int. Ed.* **2008**, *47*, 6208. k) D. R. Armstrong, W. Clegg, P. Garcia-Alvarez, A. R. Kennedy, M. D. McCall, L. Russo, E. Hevia, *Chem. Eur. J.* **2011**, *17*, 8333.

[83] a) C. E. Tucker, S. Achyutha Rao, P. Knochel, *J. Org. Chem.* **1990**, *55*, 5446. b) J. J. Eisch, A. Piotrowski, *Tetrahedron Lett*. **1983**, *24*, 2043. c) F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611. d) S. H. Pine, R. Zahler, P. A. Evans, R. H. Grubbs, *J. Am. Chem. Soc*. **1980**, *102*, 3270. e) S. H. Pine, G. S. Shen, H. Hoang, *Synthesis* **1991**, 165. f) P. Knochel, N. Jeong, M. J. Rozema, M. C. P. Yeh, *J. Am. Chem. Soc.* **1989**, *111*, 6474. g) P. Knochel, S. Achyutha Rao, *J. Am. Chem. Soc.* **1990**, *112*, 6146.

dimetallics) is in general difficult[84] and transmetallations or trapping of arynes have led to 1,2-dimetallics derived from a few metals such as boron[85], aluminum[86], tin[87] and silicon[88]. However, the direct insertion of a metal into a 1,2-dihalide such as 1,2-dibromobenzene would be the most straightforward and atom-economical method to generate a 1,2-dimetallic. Unfortunately, all attempts for this preparation strategy so far have proved to be highly problematic.[89,90] To this point, the best results for a direct insertion have been obtained using a zinc insertion into aromatic iodides in a polar solvent.[91] The works of *Takai*[92] and others[93] have shown that activation of the metal surface is important for insertion reactions into different unsaturated aryl halides. It was shown that salts such as $InCl_3$ can activate several metals very effectively for direct insertion reactions, and we have envisioned a novel $InCl_3$-catalyzed insertion of aluminum or zinc into substituted arenes to afford 1,2-dimetallics.



Scheme 26: Reaction of the bromo-triflate **6a** with Zn powder in the absence and in the presence of catalytic amounts of $InCl_3$.

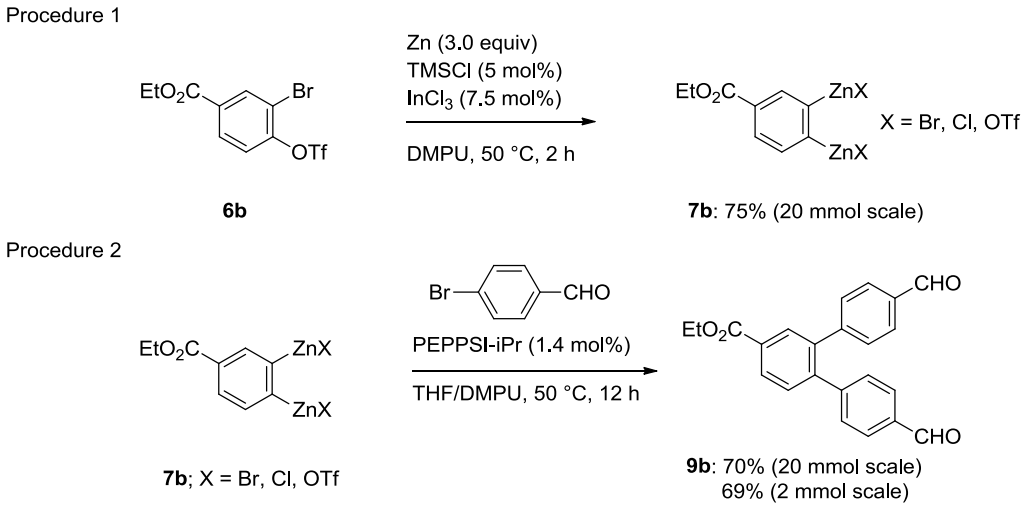
We found that the insertion of zinc dust is greatly enhanced by catalytic amounts of $InCl_3$ (7.5 mol%; Scheme 1), allowing the generation of 1,2-dimetallics from cheap unsaturated 1,2-

[84] a) A. Maercker, U. Girreser, *Tetrahedron*, **1994**, *50*, 8019. b) A. Maercker, U. Girreser, *Angew. Chem.* **1990**, *102*, 718. c) A. Maercker, M. Kemmer, H. Wang, D.-H. Dong, M. Szwarc, *Angew. Chem. Int. Ed.* **1998**, *37*, 2136.
[85] a) H. Yoshida, K. Okada, S. Kawashima, K. Tanino, J. Ohshita, *Chem. Commun*. **2010**, *46*, 1763. b) J. J. Eisch, B. W. Kotowicz, *Eur. J. Inorg. Chem*. **1998**, 761.
[86] J. J. Eisch, K. Mackenzie, H. Windisch, C. Krüger, *Eur. J. Inorg. Chem*. **1999**, 153.
[87] a) H. Yoshida, K. Tanino, J. Ohshita, A. Kunai, *Angew. Chem. Int. Ed.* **2004**, *43*, 5042. b) H. Yoshida, K. Tanino, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 5678. c) For another route to tin dimetallics see: T. N. Mitchell, K. Böttcher, P. Bleckmann, B. Costisella, C. Schwittek, C. Nettelbeck, *Eur. J. Org. Chem*. **1999**, 2413.
[88] H. Yoshida, J. Ikadai, M. Shudo, J. Ohshita, A. Kunai, *J. Am. Chem. Soc.* **2003**, *125*, 6638.
[89] a) M. A. G. M. Tinga, G. Schat, O. S. Akkerman, F. Bickelhaupt, E. Horn, H. Kooijman, W. J. J. Smeets, A. L. Smeets, A. L. Spek, *J. Am. Chem. Soc*. **1993**, *115*, 2808. b) G. Wittig, *Angew. Chem. Int. Ed.* **1957**, *69*, 245. c) F. A. Hart, F. G. Mann, *J. Chem. Soc*. **1957**. 3939. d) S. Achyutha Rao, M. Periasamy, *Tetrahedron Lett*. **1988**, *29*, 1583.
[90] a) L. S. Chen, C. J. Chen, C. Tamborski, *J. Organomet. Chem.* **1980**, *193*, 283. b) G. Wittig, *Angew. Chem. Int. Ed*. **1965**, *4*, 731. c) H. G. Richey, Jr. (Ed.), *Grignard Reagents, New Developments*, Wiley-VCH, Weinheim, **2000**.
[91] M. Amano, A. Saiga, R. Ikegami, T. Ogata, K. Tagaki, *Tetrahedron Lett.* **1998**, *39*, 8667.
[92] a) K. Takai, Y. Ikawa, *Org. Lett.* **2002**, *4*, 1727. b) K. Takai, T. Ueda, T. Hayashi, T. Moriwake, *Tetrahedron Lett.* **1996**, *37*, 7049.
[93] a) T. D. Blümke, Z. Peng, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516. b) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440. c) K. Uneyama, N. Kamaki, A. Moriya, S. Torii, *J. Org. Chem.* **1985**, *50*, 5396. d) H. Tanaka, T. Nakahara, H. Dhimane, S. Torii, *Tetrahedron Lett.* **1989**, *30*, 4161. e) H. Tanaka, K. Inoue, U. Pokorski, M. Taniguchi, S. Torii, *Tetrahedron Lett.* **1990**, *31*, 3023.

dibromides, as well as readily available 1,2-bromo triflates.[94] We decided to investigate these organometallic zinc reagents towards their functional group tolerance, as well as their scale-up.

1.2 GENERATION OF 1,2-DIZINC REAGENTS AND SUBSEQUENT REACTIONS

1,2-Dimetallic zinc reagents were accessible under mild reaction conditions starting from 1,2-dibromides or 1,2-bromo triflates. Thus, the addition of the ester-functionalized triflate **6b** to zinc dust (3 equiv) and $InCl_3$ (7.5 mol%) in DMPU furnished the expected dizinc reagent **7b** in 75% yield.[95] The described insertion reaction was also performed on a 20 mmol scale and proceeds smoothly in 2 h at 50 °C (Scheme 27, Procedure 1). The resulting dizinc reagent **7b** reacted well with 4-bromobenzaldehyde (**8a**) in a twofold Pd-catalyzed cross-coupling reaction in the presence of 1.4 mol% PEPPSI-*i*Pr,[96] affording the ester **9b** in 69% yield on a 2 mmol scale.

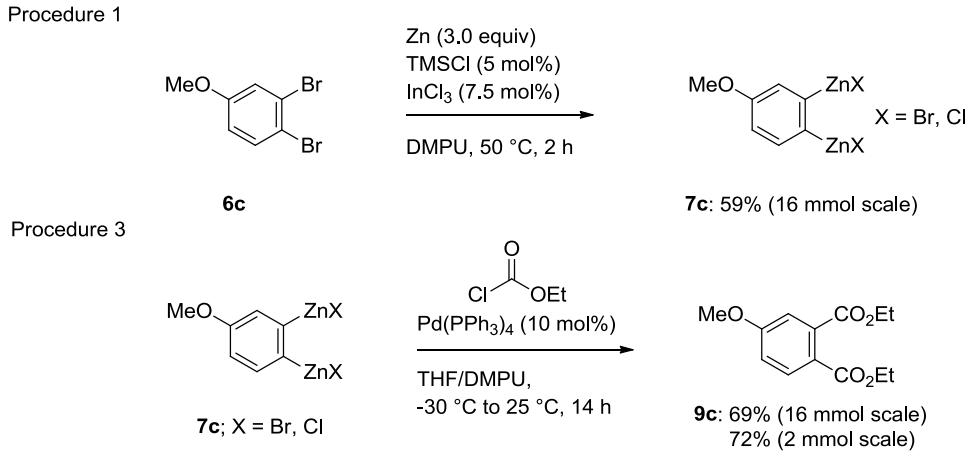


Scheme 27: Typical procedures for the preparation of 1,2-dizinc reagents *via* $InCl_3$-catalyzed insertion of Zn powder into aromatic 1,2-bromo-triflates (Procedure 1) and subsequent functionalization *via* cross-coupling (Procedure 2).

Upscaling was easily possible leading to a similar yield of 70%, on larger scale (Scheme 27, Procedure 2). The unprotected aldehyde was perfectly compatible with the reaction conditions. Furthermore, the electron-rich aromatic dibromide **6c** underwent a smooth insertion, furnishing

[94] T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9926.
[95] The yield was determined by GC analysis of iodolyzed reaction aliquots in THF.
[96] a) M. G. Organ, S. Calimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem. Int. Ed.* **2009**, *48*, 2383. b) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkins, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743. 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.

the 1,2-dizinc reagent **7c** in 59% yield (Scheme 28, Procedure 1). 1,2-Dimetallics bearing electron donating groups are generally more difficult to obtain than reagents bearing electron-withdrawing substituents. After subsequent Pd-catalyzed acylation with ethyl chloroformate (**8b**), the diester **9c** was obtained in 72% yield on a 2 mmol scale, and in 69% yield on a 16 mmol scale (Scheme 28, Procedure 3).

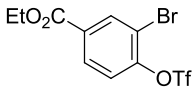
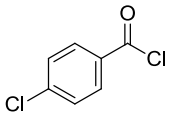
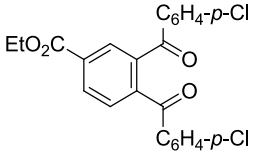
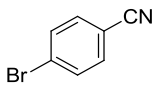
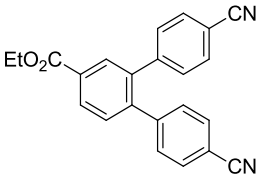
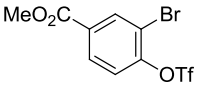
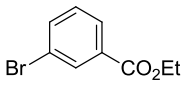
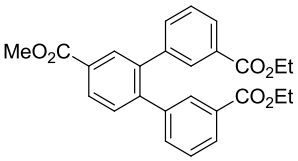
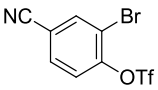
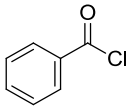
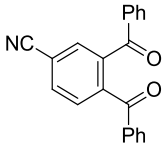
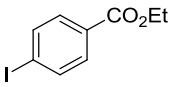
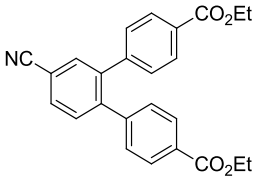
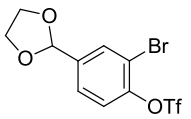
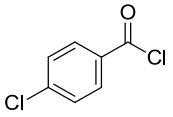
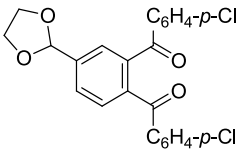


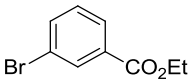
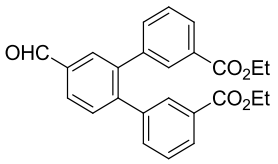
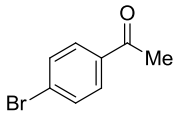
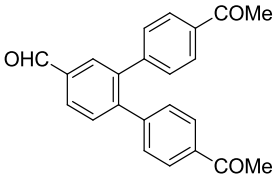
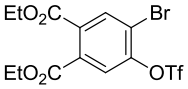
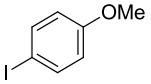
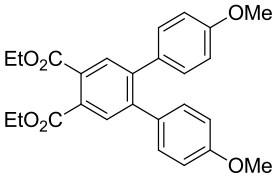
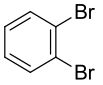
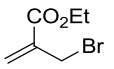
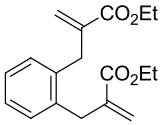
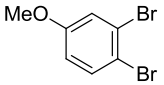
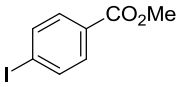
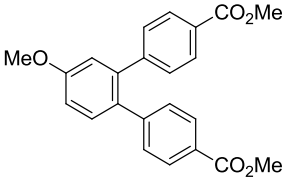
Scheme 28: Typical procedures for the preparation of 1,2-dizinc reagents *via* $InCl_3$-catalyzed insertion of Zn powder into aromatic 1,2-dibromides (Procedure 1) and subsequent functionalization *via* acylation (Procedure 3).

Interestingly, only Pd-catalyzed acylations were found to proceed smoothly and attempts to perform acylation reactions in the presence of Cu(I)-salts resulted in extensive decomposition of the organometallic species. Similarly, the dizinc reagent **7b** underwent a smooth acylation reaction with 4-chlorobenzoyl chloride (**8c**) in the presence of 10 mol% $Pd(PPh_3)_4$ (Table 1, entry 1). It should be noted that other Pd-catalysts are not as efficient for performing such acylation reactions. A cross-coupling with 4-bromobenzonitrile (**8d**) led to the corresponding *ortho*-substituted product **9e** in 63-64% yield (entry 2).

Even a sensitive methyl ester (**6d**) was tolerated under these reaction conditions, and a *Negishi* cross-coupling of the corresponding 1,2-dimetallic reagent **7c** with ethyl 3-bromobenzoate (**8e**) furnished the triester **9f** in 61-63% yield (entry 3). Remarkably, using these synthetic procedures, a nitrile functionality (**6e**) could be tolerated and the corresponding dimetallic reagent **7d** was obtained in 57% yield. After subsequent Pd-catalyzed acylation with benzoyl chloride, the diketone **9g** was isolated in 63% yield (entry 4).

Table 1: $InCl_3$-catalyzed Zn insertion into substrates **1** and subsequent functionalization leading to products **4**.

Entry	Substrate	Time[a] Yield[b]	Electrophile[c]	Product[d]	Yield (%)
1		2 h 75%			65% (10 mmol scale) 54% (2 mmol scale)
	6b		**8c**: (2.0 equiv)	**9d**	
2	**6b**				64% (20 mmol scale) 63% (2 mmol scale)
			8d: (2.0 equiv)	**9e**	
3		2 h 70%			63% (20 mmol scale) 61% (2 mmol scale)
	6d		**8e**: (2.0 equiv)	**9f**	
4		2 h 57%			68% (40 mmol scale) 63% (2 mmol scale)
	6e		**8f**: (2.0 equiv)	**9g**	
5	**6e**				53% (20 mmol scale) 55% (2 mmol scale)
			8g: (2.0 equiv)	**9h**	
6		2 h 60%			61% (20 mmol scale) 62% (2 mmol scale)
	6f		**8c**: (2.0 equiv)	**9i**	

7	**6f**		 **8e**: (2.0 equiv)	 **9j**	58% (15 mmol scale) [e] 54% (2 mmol scale)[e]
8	**6f**		 **8h**: (2.0 equiv)	 **9k**	59% (15 mmol scale)[e] 60% (2 mmol scale)[e]
9	 **6g**	2 h 45%	 **8i**: (2.0 equiv)	 **9l**	64% (10 mmol scale) 69% (2 mmol scale)
10	 **6h**	2 h 59%	 **8j**: (2.0 equiv)	 **9m**	63% (20 mmol scale) 61% (2 mmol scale)
11	 **6c**	2 h 59%	 **8k**: (2.0 equiv)	 **9n**	71% (15 mmol scale) 68% (2 mmol scale)

[a] Reaction time for completion at 50 °C. [b] Yield determined by GC-analysis of iodolyzed reaction aliquots. [c] Up to 2.0 equiv of electrophile were used. [d] Yield of isolated analytically pure compounds. [e] Yield including a deprotection step.

Cross-coupling of the organometallic reagent **7d** with ethyl 4-iodobenzoate (**8g**) afforded the desired product **9h** in 53-55% yield (entry 5). An aldehyde was not compatible with the *insertion* reaction conditions; however, after protection as an acetal, the bromo triflate **6f** reacted well with zinc powder and led to the 1,2-dizinc reagent **7e** in 60% yield. This dimetallic reagent was smoothly acylated with 4-chlorobenzoyl chloride (**8c**), affording the diketone **9i** in 61-62% yield (entry 6). Furthermore, *Negishi* cross-coupling of this dizinc reagent with ethyl 3-bromobenzoate (**8e**) or the methyl ketone **8h**, followed by acidic acetal cleavage, furnished the expected products

9j-k in 54-60% yield (entries 7-8). Also, a dimetallic species bearing two ester groups (**7f**) could be generated, and after cross-coupling with 4-iodoanisole (**8i**), the highly functionalized terphenyl **9l** was obtained in 69% and 64% yield, respectively (entry 9). Similarly, 1,2-dizinc reagents can be derived from aromatic 1,2-dibromides. Thus, 1,2-dibromobenzene **6h** or the electron-rich 1,2-dibromoansiole **6c** were both converted to the corresponding 1,2-dizinc reagents **7f-g** in 59% yield. The hereby obtained reagents were allylated (10 mol% CuCN·2LiCl)[10a] with ethyl 2-(bromomethyl)acrylate[97] (**8j**) or underwent a *Negishi* cross-coupling with an aryl bromide **8k**, providing the bis-(acrylate) **9m** and the terphenyl **9n** in 61-68% yield (entries 10-11).

[97] a) J. Villiéras, M. Rambaud, *Synthesis* **1982**, 924. b) J. Villiéras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.

2 GENERATION OF FUNCTIONALIZED ARYL AND HETEROARYL ALUMINUM REAGENTS BY HALOGEN/LITHIUM EXCHANGE

2.1 INTRODUCTION

Besides its low toxicity and price, aluminum is a metal which has many attractive features. Especially owing to its broad functional group tolerance, efforts have been made over the past years to develop general preparations of arylaluminum compounds.[98] Recently, *Knochel* has reported for the first time a convenient generation of functionalized arylaluminum sesquihalides by catalyzed direct insertion of Al powder to aryl halides.[93a,99] In addition, cross-couplings of these new aryl and heteroaryl organometallics obtained by direct alumination could be achieved very efficiently.[21,100] Although this novel aluminum insertion is quite atom-economical,[101] its functional group tolerance is rather limited, and long reaction times are usually required. Therefore, we decided to prepare arylaluminums by a Br/Li exchange followed by a transmetalation with an aluminum halide.

However, the generation of functionalized aryllithiums is only possible at very low temperature (-100 °C)[102,103] unless *Barbier*-type conditions are used. Thus, *Vedsø* has developed a practical preparation of arylboronic esters by *in situ* trapping of unstable lithio intermediates, which were obtained by *ortho*-metalation of the corresponding arenes.[104] In a similar manner, we were interested in examining a reaction involving a Br/Li exchange in the presence of *i*-Bu_2AlCl

[98] 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**, *4*, 636; d) Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem*. **2010**, *122*, 2661; *Angew. Chem. Int. Ed*. **2010**, *49*, 2607. See also: e) Preparation of Organoalanes for Organic Synthesis, P. Knochel, T. D. Blümke, K. Groll, Y.-H. Chen in Topics in Organometallic Chemistry, Vol. 41: Modern Organoaluminum Reagents, (Eds. S. Woodward, S. Dagorne), Springer-Verlag, Berlin/Heidelberg, **2013**.

[99] See also: L.-N. Guo, H. Gao, P. Mayer, P. Knochel, *Chem. Eur. J*. **2010**, *16*, 9829.

[100] See also: 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. d) R. E. Mulvey, F. Mongin, M. Uchyama and Y. Kondo, *Angew. Chem. Int. Ed.,* **2007**, *46*, 3802. e) S. H. Wunderlich, P. Knochel, *Angew. Chem*. **2009**, *121*, 1530; *Angew. Chem. Int. Ed*. **2009**, *48*, 1501.

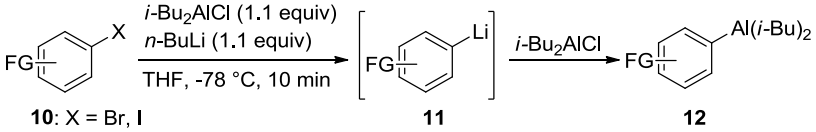
[101] B. M. Trost, *Science* **1991**, *254*, 1471.

[102] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187. b) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704.

[103] a) T. Ishikawa, A. Ogawa, T. Hirao, *J. Am. Chem. Soc*. **1998**, *120*, 5124. b) C. Hawner, K. Li, V. Cirriez, A. Alexakis, *Angew. Chem*. **2008**, *120*, 8334; *Angew. Chem. Int. Ed*. **2008**, *47*, 8211. c) J. Westermann, U. Imbery, A.-T. Nguyen, K. Nickisch, *Eur. J. Inorg. Chem*. **1998**, *2*, 295.

[104] J. Kristensen, M. Lysén, P. Vedsø, M. Begtrup, *Org. Lett.* **2001**, *3*, 1435.

(Scheme 29).[105,106] Therefore, we decided to investigate the general synthesis of aryl and heteroaryl aluminum reagents at -78 °C, as well as their direct reactions with various electrophiles without the need of a further transmetalation step.[80,107]



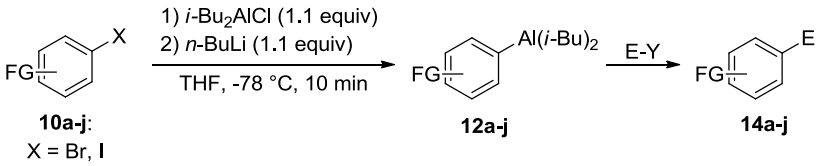
Scheme 29: Hal/Li exchange-Li/Al-transmetalation sequence.

2.2 BARBIER-TYPE TRAPPING AND SUBSEQUENT REACTIONS OF ALUMINUM REAGENTS

Thus, a mixture of *i*-Bu_2AlCl (1.1 equiv) and 3-bromobenzonitrile (**10a**) reacted at -78 °C with *n*-BuLi (1.1 equiv, 10 min), furnishing the expected aluminum reagent **12a** in 81% yield.[108] This arylaluminum reagent readily underwent a cross-coupling reaction with ethyl 4-iodobenzoate (**13a**) in the presence of 2.5 mol% Pd_2dba_3 and 10 mol% P(*t*-Bu)$_3$, affording the biaryl **14a** in 65% yield (Table 2, entry 1).[109] The *ortho*-substituted 2-bromobenzonitrile (**10b**) provided the corresponding arylaluminum reagent **12b**, which was smoothly acylated (10% CuCN·2LiCl)[10a] leading to the ketone **14b** (entry 2). Similarly, 4-bromobenzonitrile (**10c**) was converted into the corresponding aluminum reagent **12c** in 80% yield, and after Cu(I)-mediated 1,4-addition with cyclohexenone (**13c**) in the presence of TMSCl (2.5 equiv), the ketone **14c** was isolated in 51% yield (entry 3). Benzamide **10d** was transformed into aluminum reagent **12d** in 75% yield. Reagent **3d** was then reacted with 3-bromocyclohexene (**13d**) to furnish product **14d** in 73% yield (entry 4).

[105] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040. b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem.* **2008**, *120*, 6907; *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[106] Transmetalation to the corresponding Zinc species in the presence of 1.1 equiv $ZnCl_2$ under comparable reaction conditions lead to lower conversion and yield of the organometalic compound.
[107] H. Gao, P. Knochel, *Synlett* **2009**, 1321.
[108] The yield was determined by GC analysis of iodolyzed reaction aliquots in THF.
[109] A cross-coupling reaction catalyzed by Pd(tmpp)Cl_2 did not lead to satisfactory results.

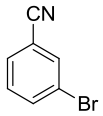
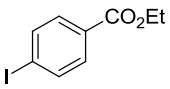
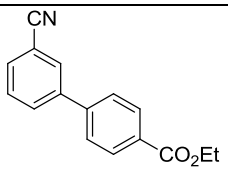
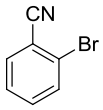
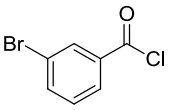
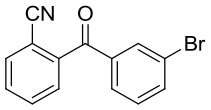
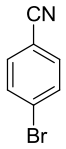
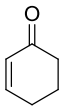
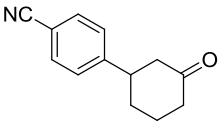
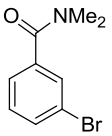
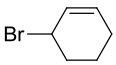
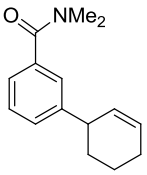
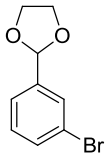
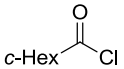
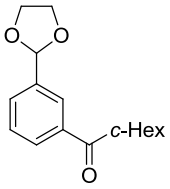
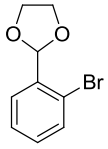
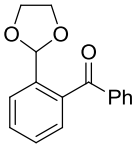
Table 2: Preparation of arylaluminum reagents and subsequent reactions with electrophiles.

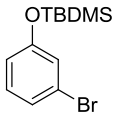
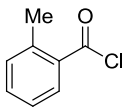
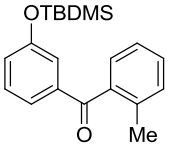
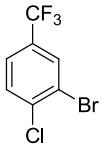
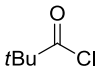
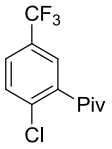
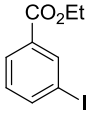
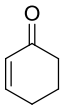
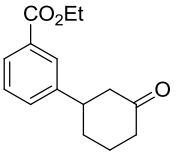
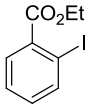
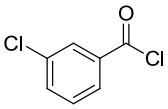
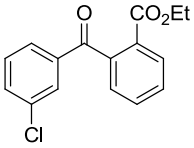


10a-j: X = Br, I

12a-j

14a-j

Entry	Substrate[a]	Electrophile	Product, Yield[b]
1			
	10a: (81%)	**13a**	**14a**: 65%[c]
2			
	10b: (64%)	**13b**	**14b**: 72%[d]
3			
	10c: (80%)	**13c**	**14c**: 51%[e]
4			
	10d: (75%)	**13d**	**14d**: 73%[e]
5			
	10e: (71%)	**13e**	**14e**: 78%[d]
6			
	10f: (83%)	**13f**	**14f**: 73%[d]

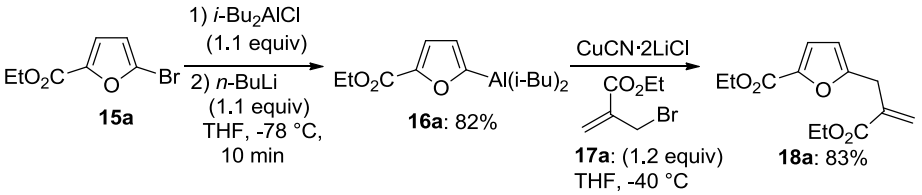
7			
	10g: (81%)	**13g**	**14g**: 75%[d]
8			
	10h: (64%)	**13h**	**14h**: 67%[d]
9			
	10i: (65%)	**13c**	**14i**: 73%[e]
10			
	10j: (72%)	**13j**	**14j**: 81%[d]

[a] Yield of aluminum reagent in parentheses was determined by GC-analysis of iodolyzed reaction aliquots. [b] Yield of isolated analytically pure compounds. [c] 2.5 mol% Pd_2dba_3 was used. [d] 20 mol% CuCN·2LiCl was added. [e] 1.0 equivalent CuCN·2LiCl was added.

Although aldehydes were not tolerated under the insertion conditions, the corresponding acetal **1e** reacted well in the Br/Li exchange reaction and led to the aluminum reagent **3e** in 71% yield. A Cu-catalyzed acylation with cyclohexanecarbonyl chloride **13e** provided the ketone **14e** in 78% yield (entry 5). Using the same conditions, several other aryl bromides (**10f-h)** carrying substituents such as an acetal, silyl ether or trifluoromethyl group, could be converted to highly functionalized products (**14f-h**) in good yields (entries 6-8).

However, for aryl bromides bearing a sensitive ester function, the Br/Li exchange was unsatisfactory as the respective butylketone was formed as the major reaction product. Nevertheless, performing the halogen/lithium exchange on aryl iodides (**10i-j**), the corresponding arylaluminum reagents (**12i-j**) bearing an ethyl ester could be prepared in 65-72% yield. Subsequent Cu(I)-mediated 1,4-addition or acylation reaction could be carried out in 73-81% yield (entries 9-10).

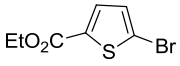
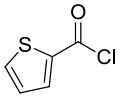
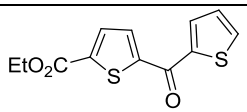
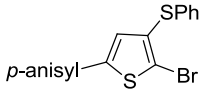
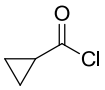
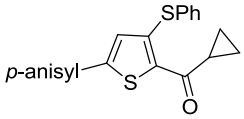
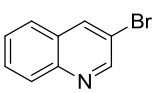
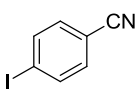
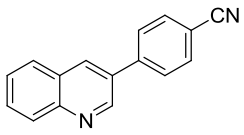
Remarkably, in the case of electron-rich heteroaryl bromides bearing a furan or thiophene moiety, sensitive ester functions could be tolerated, and the corresponding bromides (**15a-b**) were smoothly converted to the functionalized aluminum reagents (**16a-b**) (Scheme 30; Table 3, entry 1).



Scheme 30: Preparation of aluminum reagent **16a** and subsequent allylation reaction.

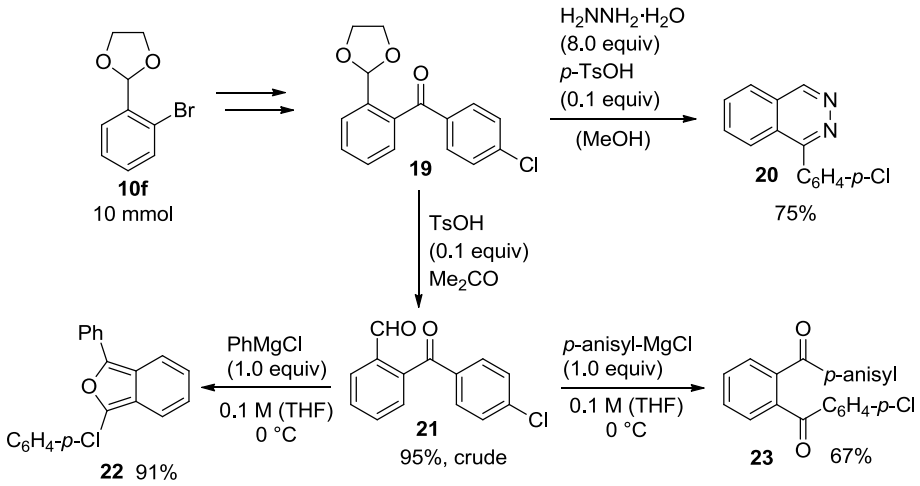
The hereby obtained heteroaryl aluminum reagents **16a-b** provided the corresponding products (**15a-b**) after subsequent Cu(I)-mediated allylation or acylation reaction in 68-83% yield (Scheme 30; Table 3, entry 1). The trisubstituted bromothiophene **15c**, was converted to the aluminum species **7c** in 93% yield, and after acylation, the ketone **18c** was obtained in 85% yield (entry 2).

Table 3: Preparation of functionalized heteroarylaluminum reagents and subsequent reaction with electrophiles.

Entry	Substrate[a]	Electrophile	Product, Yield[b]
1			
	15b: (72%)	**17b**	**18b**: 68%[c]
2			
	15c: (93%)	**17c**	**18c**: 85%[c]
3			
	15d: (63%.)	**17d**	**18d**: 73%[d]

[a] Yield of aluminum reagent in parentheses was determined by GC-analysis of iodolyzed reaction aliquots. [b] Yield of isolated analytically pure compounds. [c] 20 mol% CuCN·2LiCl was added. [d] 2.5 mol% Pd_2dba_3 was used.

Also, *N*-heterocycles have proven to be good substrates for an alumination reaction. Thus, starting from 3-bromoquinoline (**15d**), a Br/Li exchange and subsequent transmetalation afforded the aluminum compound **16d**. Pd-catalyzed cross-coupling with 4-iodobenzonitrile (**17d**) furnished **18d** in 73% yield (entry 3).



Scheme 31: Synthesis of the substituted phthalazine **20**, isobenzofuran **22** and diketone **23** starting from the acylation product **19**.

In addition, the generation of aluminum reagent **12f** was performed on a 10 mmol scale in 84% yield. Cu(I)-mediated acylation with 4-chlorobenzoyl chloride afforded the ketone **19** in 75% yield (Scheme 3). Starting from acetal **19**, the substituted phthalazine **20** could be obtained after treatment with hydrazine in the presence of catalytic amounts of *p*-toluenesulfonic acid in 75% yield. After deprotection and aqueous workup of **19**, the crude aldehyde **21** reacted smoothly with PhMgCl affording the isobenzofuran **22** in 91% yield.[110] Interestingly, under the same reaction conditions, addition of an electron-rich anisyl Grignard reagent to the aldehyde **21** furnished the diketone **23** in 67% yield (Scheme 31).

[110] J. Jacq, B. Bessieres, C. Einhorn, J. Einhorn, *Organic & Biomolecular Chemistry* **2010**, *8*, 4927.

3 TMP-MAGNESIUM AND TMP-ZINC BASES FOR THE REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD

3.1 INTRODUCTION

Due to their bioactivity, nitrogen-containing heterocycles are privileged structures in organic chemistry. They are present in numerous natural products, pharmaceuticals and agrochemicals.[111] Amongst them, 1,2-benzodiazines or cinnolines have found various applications in materials and optics,[112] and have important anti-cancer,[113] anti-inflammatory and anti-fungal properties.[114] Consequently, the functionalization of these heterocyclic scaffolds is of special synthetic importance.[115]

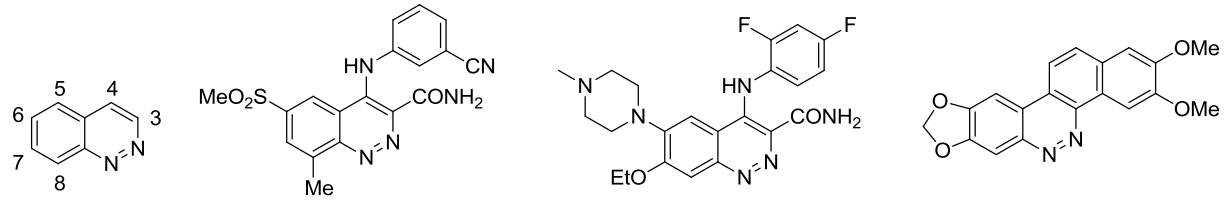


Figure 1: Cinnoline (**24**) and bioactive derivatives.

The construction of the cinnoline (**24**) ring and especially its derivatives involves lengthy syntheses and the handling of diazonium species.[112,116] More recently, copper-catalyzed preparations of cinnolines have been reported by *Willis*[117] and *Ge*.[118]

There are only a few reports describing the direct metalation of cinnolines. *Quéguiner* showed that 3-, 4-chloro- and 3-, 4-methoxycinnolines can be lithiated with 2,2,6,6-tetramethylpiperidyl-

[111] T. Eicher, S. Hauptmann, A. Speicher, in *The Chemistry of Heterocycles 2nd Ed*., Wiley-VCH, Weinheim, **2003**.
[112] V. Gautheron Chapoulaud, N. Plé, A. Turck, G. Quéguiner, *Tetrahedron* **2000**, *56*, 5499.
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[115] a) R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev*. **2004**, *104*, 2667. b) D. Zhao, Q. Wu, X. Huang, F. Song, T. Lv, J. You, *Chem. -Eur. J*. **2013**, *19*, 6239.
[116] a) D. B. Kimball, A. G. Hayes, M. M. Haley, *Org. Lett*. **2000**, *2*, 3825. b) D. B. Kimball, T. J. R. Weakley, M. M. Haley, *J. Org. Chem*. **2002**, *67*, 6395. c) D. B. Kimball, T. J. R. Weakley, R. Herges, M. M. Haley, *J. Am. Chem. Soc*. **2002**, *124*, 13463.
[117] C. J. Ball, J. Gilmore, M. C. Willis, *Angew. Chem. Int. Ed*. **2012**, *51*, 5718.
[118] G. Zhang, J. Miao, Y. Zhao, H. Ge, *Angew. Chem. Int. Ed*. **2012**, *51*, 8318.

lithium (TMP-Li) or lithium diisopropylamide (LDA).[119] The resulting heteroaryllithium species are sensitive intermediates, which require handling at low temperature to avoid decomposition by competitive nucleophilic addition reactions.[120]

Recently, we have reported a range of sterically hindered TMP-magnesium bases such as $TMP_2Mg\cdot 2LiCl$ (**5**) for the selective magnesiation of unsaturated substrates.[50,62] Also TMP-zinc bases, such as $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**4**),[52,121] were developed for the selective zincation of heterocycles.[122] Furthermore, we have shown that these bases are compatible with strong Lewis acids, such as $BF_3\cdot OEt_2$, forming frustrated Lewis pairs (FLP).[69,71,72] This considerably expands the synthetic scope of the original Zinc and Mg-TMP bases.

Herein, we report that the cinnoline scaffold can be regioselectively metalated using these new TMP-bases **4** and **5**. Preliminary results showed that the reaction of cinnoline (**24**) with $TMP_2Mg\cdot 2LiCl$ (**5**; 1.0 equiv, −78 °C, 10 min) leads to a preferential magnesiation at position 3 accompanied by substantial amounts of metalation at position 8 (ratio = 4:1). However, the addition of $BF_3\cdot OEt_2$ (1.1 equiv) to **24** prior to the magnesiation with $TMP_2Mg\cdot 2LiCl$ (**2**; 1.1 equiv) leads to a highly selective metalation at position 3 (> 98:2).

3.2 REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD IN POSITION 3

Thus, treatment of cinnoline (**24**) with $BF_3\cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) and $TMP_2Mg\cdot 2LiCl$ (**5**; 1.1 equiv, −78 °C, 10 min; procedure A) results in C(3)-selective magnesiation and after transmetalation with $ZnCl_2$, a Pd-catalyzed Negishi cross-coupling[80] with ethyl 4-bromobenzoate (**25a**) furnishes the 3-substituted cinnoline **26a** in 74% yield (Table 4, entry 1). Other aryl bromides and iodides bearing electron-donating or electron-withdrawing substituents reacted as well, affording the 3-arylated cinnolines **26b-e** in 63-75% yield (entries 2-5).

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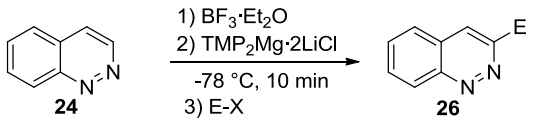
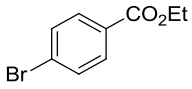
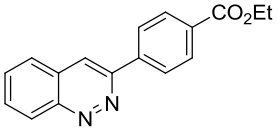
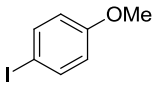
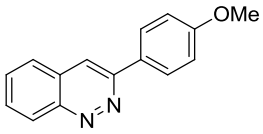
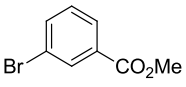
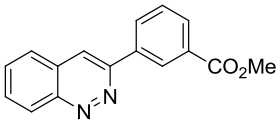
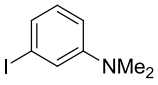
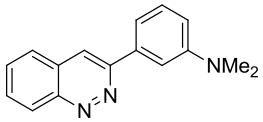
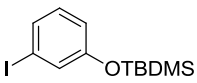
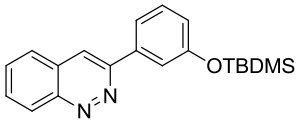
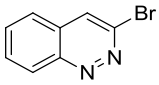
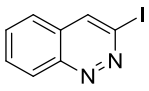
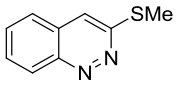
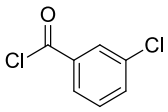
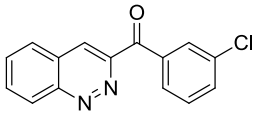
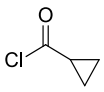
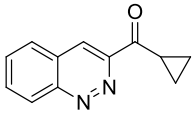
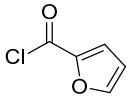
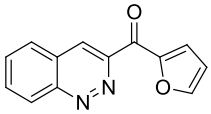
[120] a) Z.-B. Dong, W.-H. Zhu, Z.-G. Zhang, M.-Z. Li, *J. Org. Chem.* **2010**, 775. b) F. Chevallier, F. Mongin, *Chem. Soc. Rev*. **2008**, *37*, 595. c) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059. d) G. Quéguiner, *J. Heterocycl. Chem*. **2000**, *37*, 615. See also: e) J. Clayden, in *Chemistry of Organolithium Compounds*, Vol. 1, (Eds. Z. Rappoport, I. Marek), Wiley: Chichester, **2004**.
[121] a) A. Unsinn, S. H. Wunderlich, P. Knochel, P. *Adv. Synth. Catal*. **2013**, *355*, 989. b) A. Unsinn, P. Knochel, *Chem. Commun*. **2012**, *48*, 2680.
[122] a) M. Mosrin, P. Knochel, *Chem.-Eur. J.* **2009**, *15*, 1468. For a Review see: b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed*. **2011**, *50*, 9794. See also: c) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. d) R. E. Mulvey, *Acc. Chem. Res*. **2009**, *42*, 743.

Table 4: Preparation of C(3)-substituted cinnolines by magnesiation and subsequent quenching with electrophiles.



24 **26**

Entry	Electrophile	Product, Yield[a]
1		
	25a	**26a**: 74%[b]
2		
	25b	**26b**: 75%[c]
3		
	25c	**26c**: 69%[b]
4		
	25d	**26d**: 73%[c]
5		
	25e	**26e**: 63%[c]
6	$(CBrCl_2)_2$	
		26f: 55%
7	I_2	
		26g: 51%

8	$MeSO_2SMe$	 **26h**: 51%
9	 **25f**	 **26i**: 53%[d]
10	 **25g**	 **26j**: 58%[d]
11	 **25h**	 **26k**: 53%[d]

[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 5 mol% $Pd(PPh_3)_4$ and 0.8 equiv of electrophile. [c]Pd-catalyzed cross-coupling using 2 mol% $Pd(dba)_2$, 4 mol% P(*o*-furyl)$_3$[123] and 0.8 equiv of electrophile. [d]CuCN·2LiCl (1.1 equiv) was used.

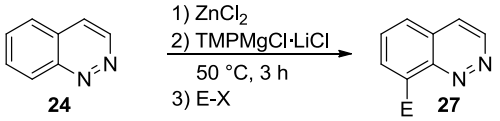
The halogenation of the metalated cinnoline with either $(CBrCl_2)_2$ or iodine provides the bromocinnoline **26f** in 55% yield or the iodocinnoline **26g** in 51% yield (entries 6-7). Quenching the magnesiated species with $MeSO_2Me$ furnishes the thioether **26h** in 51% yield (entry 8). Additionally, after transmetalation with $ZnCl_2$ the corresponding zincated cinnoline is readily acylated in the presence of CuCN·2LiCl[10a] (1.1 equiv). The use of acyl chlorides bearing aryl-, alkyl- or heteroaryl substituents affords the corresponding ketones **26i-k** in 53-58% yield (entries 9-11).

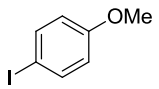
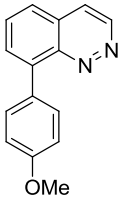
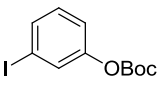
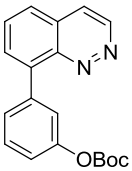
[123] a) V. Farina, S. R. Baker, D. A. Benigni, C. Sapino Jr., *Tetrahedron Lett*. **1988**, *29*, 5739. b) V. Farina, S. R. Baker, D. A. Benigni, S. I. Hauck, C. Sapino Jr., *J. Org. Chem*. **1990**, *55*, 5833.

3.3 REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD IN POSITION 8

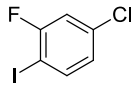
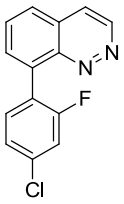
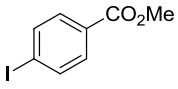
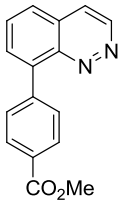
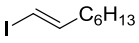
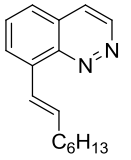
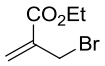
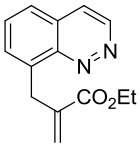
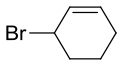
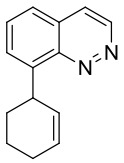
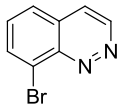
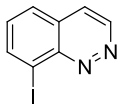
Complementary to the C(3)-selective magnesiation, a regioselective zincation of cinnoline (**1**) in position 8 can also be achieved. Thus, metalation of **24** with putative $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[124] (**4**; 1 equiv, 50 °C, 3 h) furnishes the 8-zincated cinnoline intermediate with high regioselectivity (95:5).[125] Subsequent cross-coupling with 4-iodoanisole (**25b**) leads to the 8-arylated cinnoline **27a** in 84% yield (Table 5, entry 1). Further examples, illustrating this metalation sequence and cross-coupling with aryl iodides substituted in *para*-, *meta*- and *ortho*-position proceeds in 60-70% yield (entries 2-4). A cross-coupling with (*E*)-iodooctene (**25l**) leads to the cinnoline **27e** in 65% yield (*E*:*Z* > 99:1; entry 5). Copper(I)-mediated allylation with ethyl 2-(bromomethyl)acrylate[97] (**25m**) or 3-bromocyclohexene (**25n**) affords the allylated cinnolines **27f-g** in 53-61% yield (entries 6-7). Bromination and iodination of the 8-zincated cinnoline furnishes the sensitive halogenated derivatives **27h-i** in 46-52% yield (entries 8-9).

Table 5: 8-Substituted products obtained by regioselective zincation and subsequent reaction with electrophiles.



Entry	Electrophile	Product, Yield[a]
1	 **25b**	 **27a**: 84%[b]
2	 **25i**	 **27b**: 70%[b]

[124] For the *in situ* zincation cinnoline **24** was premixed with $ZnCl_2$ (1.0 equiv) followed by the addition of TMPMgCl·LiCl (2.0 equiv).
[125] Zincation with the *in situ* generated base leads to slightly higher yields of the metalated species than by using the preformed base.

3		
	25j	**27c**: 65%[b]
4		
	25k	**27d**: 60%[b]
5		
	25l	**27e**: 65%, *E*:*Z* > 99:1[b]
6		
	25m	**27f**: 61%[c]
7		
	25n	**27g**: 53%[c]
8	Br_2·dioxane	
		27h: 46%
9	I_2	
		27i: 52%

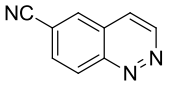
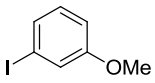
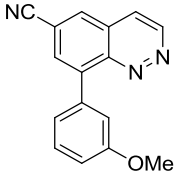
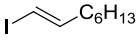
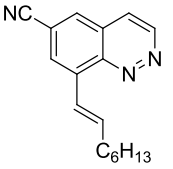
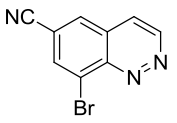
[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 2 mol% $Pd(dba)_2$, 4 mol% P(*o*-furyl)$_3$ and 0.8 equiv of electrophile. [c]CuCN·2LiCl (1.1 equiv) was used.

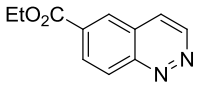
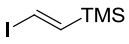
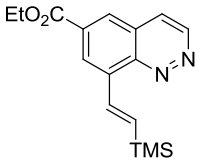
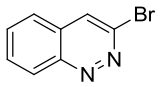
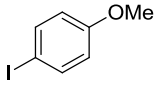
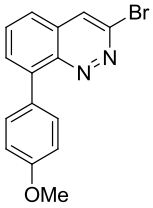
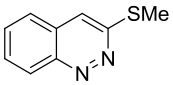
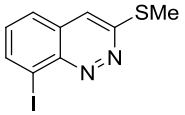
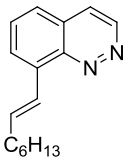
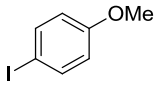
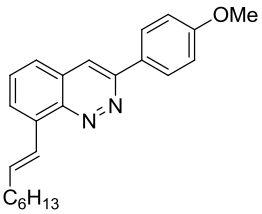
3.4 REGIOSELECTIVE SUBSEQUENT METALATION OF SUBSTITUTED CINNOLINE DERIVATIVES

Functionalized cinnolines bearing a cyano or an ester group such as **28a-b** can be readily prepared[116b] and zincated using *in situ* generated $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**4**; 1.0 equiv, 25 °C, 1 h; procedure B).

Using this procedure, 6-cyanocinnoline (**28a**) undergoes regioselective metalation at position 8. The resulting zinc species reacts with various electrophiles to afford the functionalized cinnoline derivatives **29a**-**c** in 59-72% yield (Table 6, entries 1-3). The mild metalation conditions also tolerate the presence of an ester group in substrate **28b**. After metalation and subsequent cross-coupling with the alkenyl iodide **25p**, the 6,8-disubstituted cinnoline **29d** is obtained in 57% yield (entry 4).

Table 6: Preparation of disubstituted cinnoline derivatives.

Entry	Substrate	Electrophile	Product, Yield[a]
1			
	28a	**25o**	**29a**: 72%[b]
2	**28a**		
		25l	**29b**: 68%, *E*:*Z* > 99:1[b]
3	**28a**	$Br_2 \cdot$dioxane	
			29c: 59%

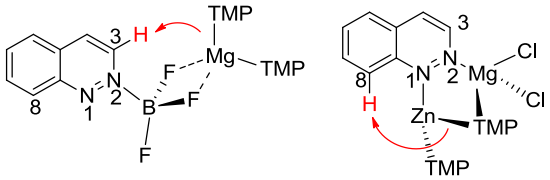
4	 **28b**	 **25p**	 **29d**: 57%, *E*:*Z* = 99:1[c]
5	 **26f**	 **25b**	 **29e**: 65%[b]
6	 **26h**	I_2	 **29f**: 48%
7	 **27e**	 **25b**	 **29g**: 68%, *E*:*Z* > 99:1[b]

[a]Isolated yield of analytically pure product. [b]Pd-catalyzed cross-coupling using 2 mol% $Pd(dba)_2$, 4 mol% P(*o*-furyl)$_3$ and 0.8 equiv of electrophile. [c]Pd-catalyzed cross-coupling using 2 mol% $Pd(dba)_2$, 4 mol% P(*o*-furyl)$_3$ and 0.7 equiv of electrophile.

Finally, a double functionalization *via* successive metalation can be achieved and the 3-functionalized cinnolines (**26f**, **26h**; see Table 1) can be readily zincated (procedure B) affording the corresponding 3,8-disubstituted cinnolines (**29e-f**) in 48-65% yield (entries 5-6). Additionally, 8-substituted cinnoline **27e** undergoes a second metalation and a subsequent cross-coupling with 4-iodoanisole (**25b**) to furnish the corresponding disubstituted cinnoline **29g** in 68% yield (entry 7).

The observed regioselectivity in the case of a metalation at position 3 is best explained by assuming a complexation of BF_3 at the most sterically accessible nitrogen N(2) (Scheme 32).

This coordination acidifies the proton in position 3 sufficiently so that a deprotonation occurs exclusively in this position.



Scheme 32: $BF_3 \cdot OEt_2$ and $MgCl_2$-triggered selective metalations of cinnoline (**25**) at positions 3 and 8 using $TMP_2Mg \cdot 2LiCl$ (**5**) and $TMP_2Zn \cdot MgCl_2 \cdot 2LiCl$ (**4**).

By using the much less active $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**4**), position 3 is now only activated by $MgCl_2$ (instead of $BF_3 \cdot OEt_2$) due to complexation at N(2). This may not be sufficient activation to initiate the deprotonation at position 3 and coordination of zinc from **5** at N(1) directs the zincation at position 8 (Scheme 32).[74]

4 PREPARATION AND REGIOSELECTIVE METALATION OF BIS(TRIMETHYLSILYL)-METHYL-SUBSTITUTED ARYL AND HETEROARYL DERIVATIVES

4.1 INTRODUCTION

The regioselective functionalization of aromatics and especially heterocycles is an important synthetic task since substituted arenes are essential building blocks of biologically active compounds used as pharmaceuticals and agrochemicals.[126] Furthermore, silyl-substituents experience an increasing interest for numerous applications in organic chemistry.[127] Besides various strategies that have been elaborated for performing regioselective lithiations,[128] the group of *Snieckus* pioneered the application of the $(Me_3Si)_2CH$-group (bis(trimethylsilyl)methyl; BTSM)[129] showing that this group triggers the directed lithiation of benzamides with great efficiency.[130] This bulky silicon group has also been successfully used as remote control for the synthesis of isolable atropisomeric amides[131] or for *Wittig* rearrangements and *Prins* cyclizations.[132] Additionally, the BTSM-group recently found a number of synthetic applications in organic synthesis[133] due to its unique synthetic features (steric hindrance combined with facile transformations).

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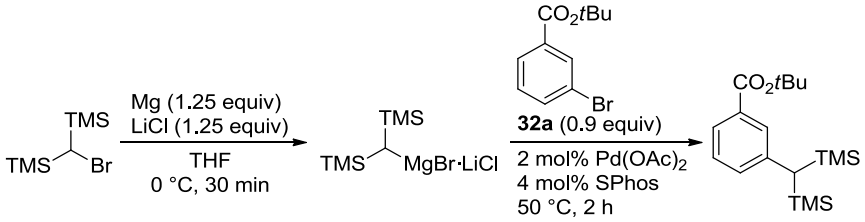
[126] L. Ackermann in *Modern Arylation Methods*, (Ed: L. Ackermann), Wiley, Weinheim, **2009**.
[127] a) S. E. Denmark, J. H.-C. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 2978 b) S. E. Denmark, J. D. Baird, *Chem. Eur. J.* **2006**, *12*, 4954. c) R. Dobrovetsky, D. Bravo-Zhivotovskii, B. Tumanskii, M. Botonshansky, Y. Apeloig, *Angew. Chem. Int. Ed.* **2010**, *49*, 7086. d) D. Bravo-Zhivotovskii, R. Dobrovetsky, D. Nemirovsky, V. Molev, M. Bendikov, G. Molev, M. Botoshansky, Y. Apeloig, *Angew. Chem. Int. Ed.* **2008**, *47*, 4343; e) T. Robert, M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 5216. f) L. B. Delvos, D. J. Vyas, M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 4650. g) K. Itami, K. Mitsudo, J. Yoshida, *Angew. Chem. Int. Ed.* **2001**, *40*, 2337. h) K. Itami, T. Nokami, J. Yoshida, *Angew. Chem. Int. Ed.* **2001**, *40*, 1074. i) H. Miyazoe, S. Yamago, J. Yoshida, *Angew. Chem. Int. Ed.* **2000**, *39*, 3559. j) C. Z. Rotsides, C. Hu, K. A. Woerpel, *Angew. Chem. Int. Ed.* **2013**, *52*, 13033. k) L. E. Bourque, P. A. Cleary, K. A. Woerpel, *J. Am. Chem. Soc.* **2007**, *129*, 12602; l) V. T. Tran, K. A. Woerpel, *J. Org. Chem.* **2013**, *78*, 6609. l) A. K. Franz, K. A. Woerpel, *Acc. Chem. Res.* **2000**, *33*, 813.
[128] M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[129] a) I. Fleming, C. D. Floyd, *J. Chem. Soc. Perkin Trans. 1* **1981**, 969. b) A. G. Brook, J. J. Chrusciel, *Organometallics* **1984**, *3*, 1317. c) M. Lautens, R. N. Ben, P. H. M. Delanghe, *Angew. Chem.* **1994**, *106*, 2557; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2448. d) D. M. Hodgson, S. F. Barker, L. H. Mace, J. R. Moran, *Chem. Commun.* **2001**, 153. for its use in metalation reactions see: e) D. P. M. Pleynet, J. L. Dutton, A. P. Johnson, *Tetrahedron* **1999**, *55*, 11903. f) C. Palomo, J. M. Aizpurua, I. Ganboa, A. Benito, L. Cuerdo, R. M. Fratila, A. Jimenez, I. Loinaz, J. I. Miranda, K. R. Pytlewska, A. Micle, A. Linden, *Org. Lett.* **2004**, *6*, 4443.
[130] a) R. J. Mills, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1565. b) R. J. Mills, N. J. Taylor, V. Snieckus, *J. Org. Chem.* **1989**, *54*, 4372.
[131] X.-F. Bai, W.-H. Deng, Z. Xu, F.-W. Li, Y. Deng, C.-G. Xia, L.-W. Xu, *Chem. Asian J.* **2014**, *9*, 1108.
[132] a) X. Lin, X. Ye, X. Sun, Y. Zhang, L. Gao, Z. Song, *Org. Lett.* **2014**, *16*, 1084. b) J. Lu, Z, Song, Y. Zhang, Z. Gan, H. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 5367. c) X. Sun, J. Lei, C. Sun, Z. Song, L. Yan, *Org. Lett.* **2012**, *14*, 1094. d) L. Gao, X. Lin, J. Lei, Z. Song, Z. Lin, *Org. Lett.* **2012**, *14*, 158. e) Z. Song, Z. Lei, L. Gao, X. Wu, L. Li, *Org. Lett.* **2010**, *12*, 5298.
[133] Y. Wu, L. Li, H. Li, L. Gao, H. Xie, Z. Zhang, Z. Su, C. Hu, Z. Song, *Org. Lett.* **2014**, *16*, 1880.

We therefore decided to investigate a simple way to introduce the BTSM-substituent on an aromatic system using a Kumada-Corriu cross-coupling reaction[134] between $(Me_3Si)_2CHMgBr{\cdot}LiCl$ (**30**)[135] and various aryl bromides. Furthermore, we aimed for a regioselective magnesiation or lithiation of these functionalized aromatics. As a highlight we were interested in developing a regioselective switch (in the presence or absence of the BTSM-group) and demonstrated several transformations of the BTSM-group.

In addition, we wanted to extend this method for the preparation of various BTSM-substituted heterocycles, as well as their selective metalation and further functionalization. In addition, a range of transformations of the BTSM-group has been performed demonstrating the versatility of this protecting group.[136]

4.2 PREPARATION OF BTSM-SUBSTITUTED ARYL DERIVATIVES

Thus, $(Me_3Si)_2CHMgBr{\cdot}LiCl$ was prepared by the reaction of $(Me_3Si)_2CHBr$ (**31**, 1.0 equiv) with magnesium turnings (1.25 equiv) in the presence of LiCl (1.25 equiv) furnishing the desired Grignard reagent **30** within 30 min at 0 °C. Titration of the organomagnesium reagent with iodine in THF indicated a concentration of 0.6 M (80% yield).



31 **30**: 80% **33a**: 97%

Scheme 33: Preparation of **33a** and subsequent cross-coupling reaction.

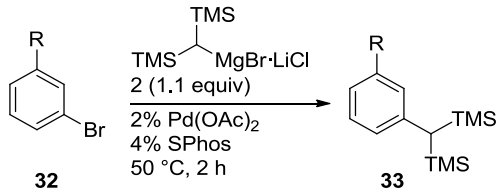
In preliminary experiments, $(Me_3Si)_2CHMgBr{\cdot}LiCl$ (**30**) underwent a smooth Kumada-Corriu cross-coupling reaction with *tert*-butyl 3-bromobenzoate (**32a**, 0.9 equiv, 50 °C, 2 h) using

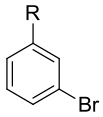
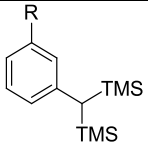
[134] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374. b) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Commun.* **1972**, 144a.
[135] a) H. J. Breuning, W. Kanig, A. Soltani-Neshan, *Polyhedron* **1983**, *2*, 291. b) D. R. Williams, Á. I. Morales-Ramos, C. M. Williams, *Org. Lett.* **2006**, *8*, 4393.
[136] For other silyl protecting groups see: a) A. V. Gulevich, F. S. Melkonyan, D. Sarkar, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 5528. b) D. Sarkar, F. S. Melkonyan, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed*. **2013**, *52*, 10800.

2 mol% $Pd(OAc)_2$ and 4 mol% SPhos,[137] and the BTSM-substituted benzoic ester (**33a**) was obtained in 97% yield (Scheme 1).

This cross-coupling procedure could be extended to a range of aromatic bromides bearing either electron-donating or electron-withdrawing substituents. Thus, the *meta*-substituted aryl bromides **32b**-**4f** underwent the cross-coupling reaction with the Grignard reagent **30** and the corresponding BTSM-functionalized aromatic derivatives (**33b-33f**) were isolated in 88-95% yield (Table 7, entries 1-5). Also the *para*-substituted methyl 4-bromobenzoate (**32g**) was converted into the corresponding cross-coupling product **33g** in 89% yield (entry 6). Even a keto-function could be tolerated in this cross-coupling and the bromobenzophenone **32h** was converted to **33h** in 72% yield (entry 7). Also, the unprotected aniline derivative **32i** furnished the corresponding cross-coupling product **33i** by using 3 equivalents of the Grignard reagent **30** and toluene as cosolvent (THF:toluene = 1:2, 80 °C, 24 h). The resulting aniline **33i** was isolated in 60% yield (entry 8).[138]

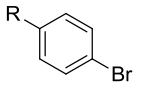
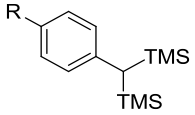
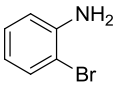
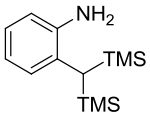
Table 7: Products of type **33** obtained by Kumada-Corriu cross-coupling reaction of various aryl bromides with **2**.



Entry	Electrophile	Product[a]
		
1	**32b**: R = F	**33b**: 92%
2	**32c**: R = CF_3	**33c**: 91%
3	**32**: R = CO_2Et	**33d**: 91%
4	**32e**: R = OMe	**33e**: 95%

[137] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871. b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685. c) R. A. Altmann, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115. d) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

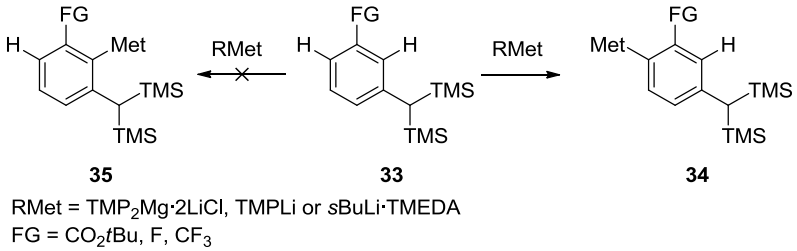
[138] This experiment was performed by V. Werner and are given here for the sake of completeness.

5	**32**: R = NMe_2	**33f**: 88%
		
6	**32g**: R = CO_2Me	**33g**: 89%
7	**32**: R = COPh	**33h**: 72%
8		
	32i	**33i**: 60%[b]

[a] Isolated yields of analytically pure product. [b] The cross-coupling was performed by using 2.5 equivalents of **2** in a 2:1 mixture of THF/toluene at 80 °C for 24 h.

4.3 METALATION AND TRANSFORMATION OF BTSM-SUBSTITUTED ARYL DERIVATIVES

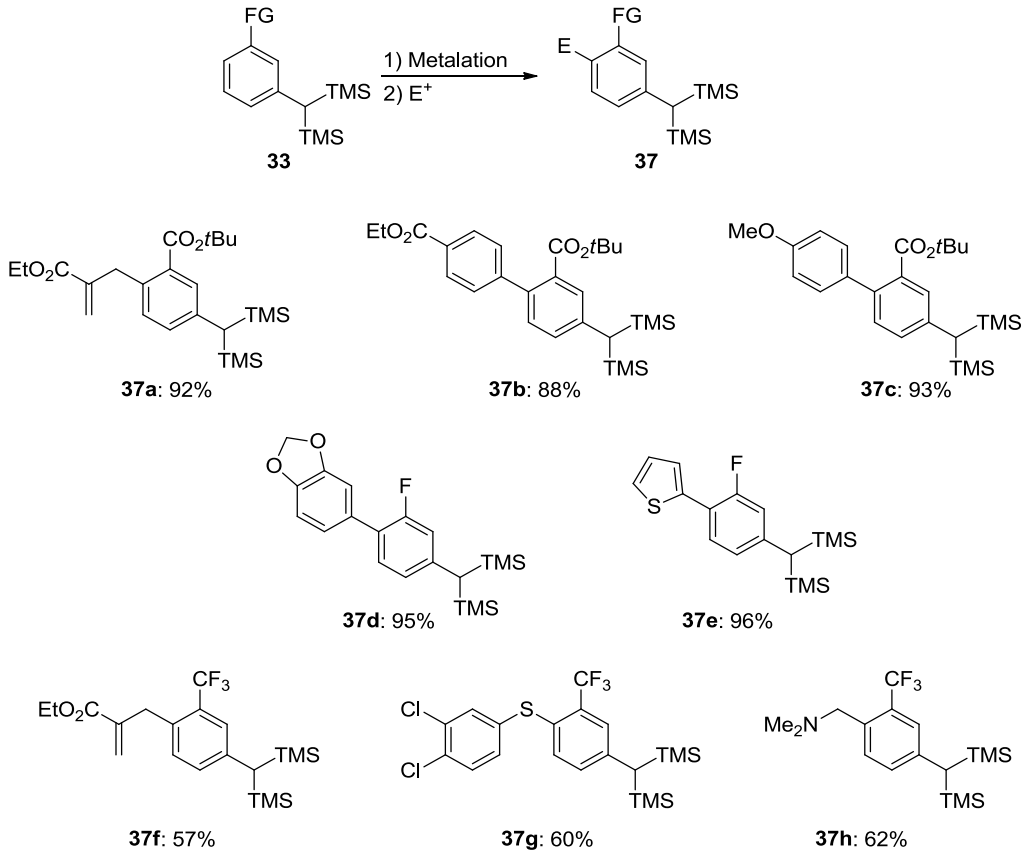
The prepared BTSM-substituted aromatics of type **5** were submitted to metalation reactions using various Li- or Mg-bases. In all cases, a regioselective metalation at the least hindered position of the aromatic substrate **33** was observed, leading to the lithiated or magnesiated species **34**, and not to the more sterically hindered organometallic **35** (Scheme 34).



Scheme 34: Regioselective metalation of aromatics of type **33** using various Li- or Mg-bases.

For the metalation of the benzoate **33a** bearing a sensitive ester function, the use of TMPMgCl·LiCl (**2**)[50] did not lead to complete conversion. Therefore, the stronger base $TMP_2Mg·2LiCl$ (**5**)[62] was applied for a selective metalation. Thus, treatment of **33a** with $TMP_2Mg·2LiCl$ (**5**, 1.5 equiv) in THF (25 °C, 2 h) led to the Grignard reagent **34a** and then transmetalated with $ZnCl_2$ (1.5 equiv). In the presence of CuCN·2LiCl (1.5 equiv), a reaction

with ethyl (2-bromomethyl)acrylate[97] (**36a**) gave the allylated product **37a** in 92% yield (entry 4). The less sensitive substrate **33b** was conveniently lithiated with TMPLi (2 equiv) in THF (-60 °C, 1 h) leading to the aryllithium reagent **34b** (Scheme 35). For the metalation of **33c**, *s*BuLi (1.5 equiv) and TMEDA (1.5 equiv) in hexane[139] (-30 °C, 1.5 h) led to the *ortho*-lithiated species **34c**. These lithiated species reacted with a range of electrophiles (after or without transmetalation to the corresponding zinc or magnesium species) in cross-coupling reactions, allylation reactions or reacted with sulfur electrophiles or *N*,*N*-dimethylenemethaniminium trifluoroacetate (**36h**).[140,141]

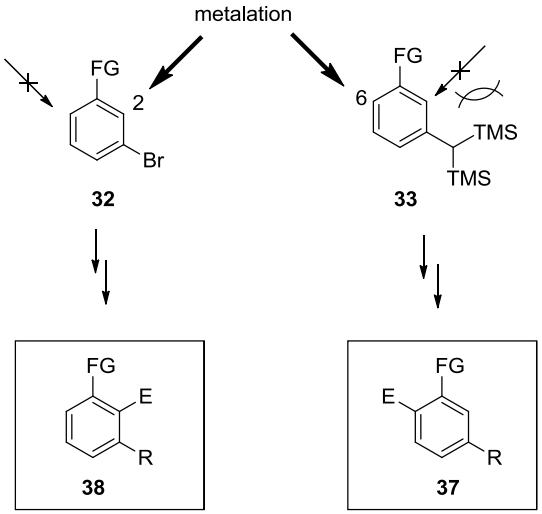


Scheme 35: Products of type **37** obtained by metalation of substrates of type **33** followed by reaction with different electrophiles.

The presence or absence of the BTSM-group allows to switch the regioselectivity of the metalation. Thus, an aryl bromide of type **32** (FG is an electron-withdrawing substituent) is preferentially metalated in position 2 leading to products of type **38** after quenching with an

[139] S. O. de Silva, M. Watanabe, V. Snieckus, *J. Org. Chem.* **1979**, *44*, 4802.
[140] G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed*. **1976**, *15*, 239.
[141] These reactions were performed by V. Werner and is given here for the sake of completeness.

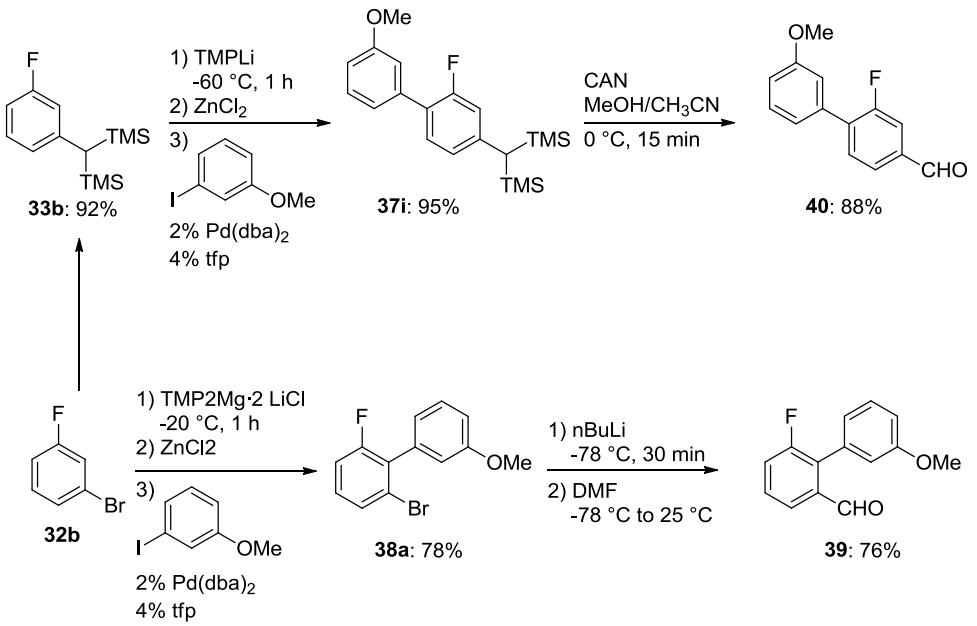
electrophile E (Scheme 3). On the other hand, the metalation of substrate **33** proceeds at the least sterically hindered position 6, leading to products of type **37** after quenching with an electrophile. In this sequence the final group R present in **37** or **38** is either a BTSM-group or a formyl group (CHO).



Scheme 36: Regioselective metalation of substrates of type **32** and **33**.

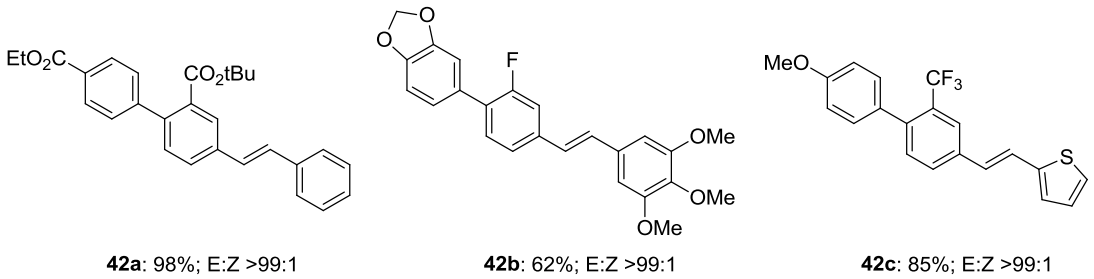
Treatment of **32b** with $TMP_2Mg \cdot 2LiCl$ (**5**; 1.1 equiv, -20 °C, 1 h) led to a 2-magnesiated intermediate which after transmetalation with $ZnCl_2$ (1.2 equiv) reacted in a Pd-catalyzed cross-coupling with 3-iodo-anisole furnishing the biphenyl **38a** in 78% yield. A Br/Li-exchange was then performed on the arene **38a** with *n*BuLi (1.1 equiv) in THF (-78 °C, 30 min) affording a lithiated species which was trapped with DMF (2.0 equiv) to give the benzaldehyde **39** in 76% yield. Complementary, the metalation of **33b** with TMPLi (2.0 equiv, -60 °C, 1 h) followed by a transmetalation with $ZnCl_2$ (2.1 equiv) and subsequent Negishi cross-coupling afforded the biphenyl **37i** in 95% yield. Oxidation of **37l** with CAN (5.0 equiv, 0 °C) according to the methodology developed by *Palomo*[142] in a 3:1 mixture of methanol/acetonitrile (0 °C, 10 min) furnished the benzaldehyde derivative **40** in 88% yield. The resulting aldehydes **39** and **40** have a complementary regioisomeric substitution pattern (Scheme 37).

[142] a) J. Lasarte, C. Palomo, J. P. Picard, J. Dunogues, J. M. Aizpurua, *J. Chem. Soc. Chem. Commun.* **1989**, 72. b) C. Palomo, J. M. Aizpurua, M. Legido, A. Mielgo, R. Galarza, *Chem. Eur. J.* **1997**, *3*, 1432.



Scheme 37: Generation of the orthogonal functionalized benzaldehydes **39** and **40**.

Finally, in order to show the utility of the BTSM-group, several polyfunctional BTSM-substituted arenes were converted to the corresponding stilbene derivatives of type **42** *via* Peterson-olefinations[143] of various biphenyls such as **37b** and **37d** using benzaldehyde (**41a**), 3,4,5-trimethoxybenzaldehyde (**41b**) or thiophene-2-carbaldehyde (**41c**; 1.2 equiv) in the presence of 10% tetra-*n*-butylammonium fluoride (TBAF)[144] in THF (-20 °C, 15 min, Scheme 38).[145]



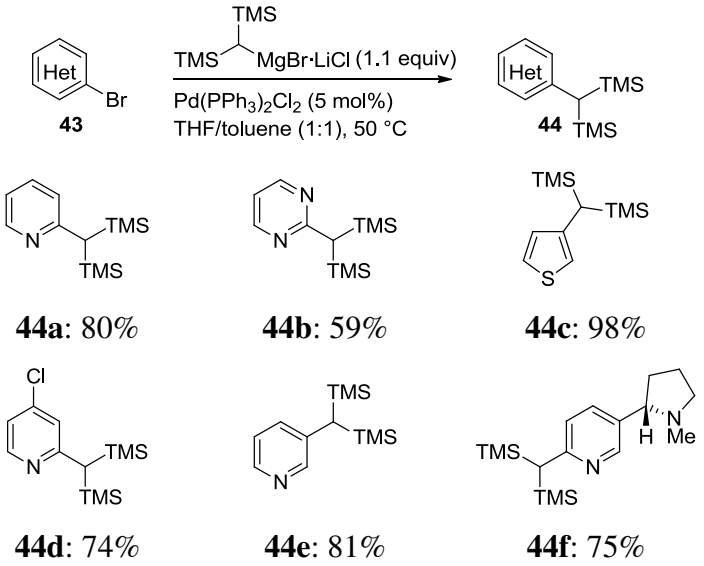
42a: 98%; E:Z >99:1 **42b**: 62%; E:Z >99:1 **42c**: 85%; E:Z >99:1

Scheme 38: Peterson olefination of substrates of type **37** to stilbene derivatives of type **42**.

[143] For a review on the Peterson olefination see: L. F. van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195.
[144] C. Palomo, J. M. Aizpurua, J. M. García, I. Ganboa, F. P. Cossio, B. Lecea, C. López, *J. Org. Chem.* **1990**, *55*, 2498.
[145] These reactions were performed by V. Werner and are given here for the sake of completeness.

4.4 PREPARATION OF BTSM-SUBSTITUTED HETEROARYL DERIVATIVES

Following these experiments we focused on the extension of this methodology for the preparation of heterocyclic BTSM-substituted substrates. Thus, the reaction of the Grignard reagent $(Me_3Si)_2CHMgBr{\cdot}LiCl$[146] (**30**; 1.1 equiv, 50 °C, 12 h) with 2-bromopyridine (**43a**) using 5 mol% $Pd(PPh_3)_2Cl_2$ furnished the corresponding BTSM-substituted pyridine (**44a**) in 80% yield. This protocol was extended to a range of heteroaromatic bromides (**43b-f**) such as pyrimidines, thiophenes, differently substituted pyridines or even a nicotine derivative. The resulting silylated heterocycles **44b-f** were obtained in 59-98% yield (Scheme 39).



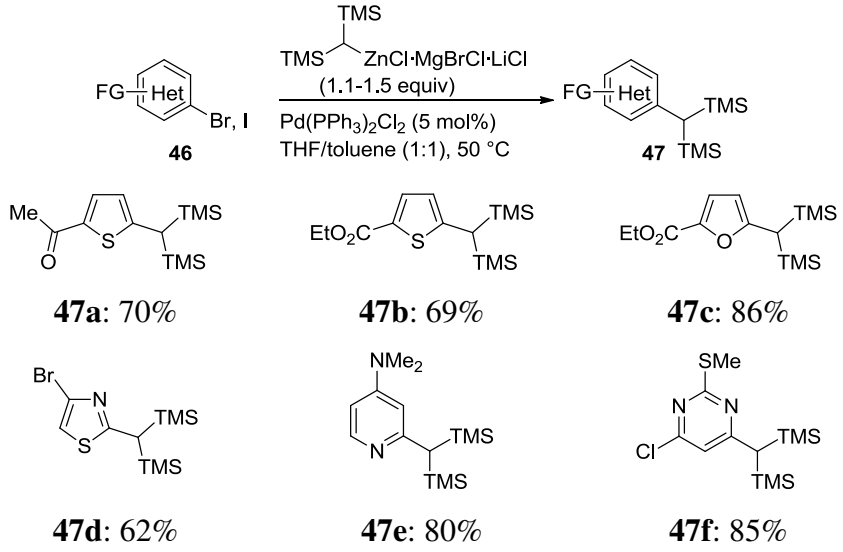
Scheme 39: Isolated yields of analytically pure products of type **44** obtained by Kumada-Corriu[134] cross-coupling reaction of various heteroaryl bromides with **30**.

However, when these reaction conditions were used for heteroaryl iodides or heteroarenes containing electron-withdrawing functional groups, the cross-coupling did not lead to satisfactory results and mostly homocoupling products were obtained. We found that these undesired side-reactions can be avoided by using the zinc reagent $(Me_3Si)_2CHZnCl{\cdot}MgBrCl{\cdot}LiCl$ (**45**) which was readily prepared by transmetalation of the Grignard reagent **30** with $ZnCl_2$ (1 equiv, 25 °C, 5 min).[147]

[146] $(Me_3Si)_2CHMgBr{\cdot}LiCl$ was prepared by the reaction of $(Me_3Si)_2CHBr$ (1.0 equiv) with magnesium turnings (1.25 equiv) in the presence of LiCl (1.25 equiv) furnishing the desired Grignard reagent **30** within 30 min at 0 °C. Titration of the organomagnesium reagent with iodine in THF indicated a concentration of 0.6 M (80% yield).

[147] The corresponding zinc reagent derived by zinc insertion (analogue Ref. 7) can be prepared easily but is not stable towards storage and less reactive than the species derived by transmetalation from the Grignard reagent.

Consequently, this new zinc reagent (**45**; 1.1-1.5 equiv) underwent a Negishi[80a,148] cross-coupling using 5 mol% $Pd(PPh_3)_2Cl_2$ with bromo- or iodo-thiophenes containing sensitive acetyl or ester functions smoothly leading to the BTSM-substituted thiophenes (**47a-b**) in 69-70% yield (Scheme 40). Also a furan bearing an ester function was tolerated and the BTSM-furan **47c** was isolated in 86% yield. In addition, using this mild zinc reagent, dibromides undergo a regioselective cross-coupling[149] furnishing the thiazol **47d** in 62% yield. Also 2-bromo-4-(dimethylamino)-pyridine (**46e**) was exposed to the cross-coupling conditions, as well as the substituted pyrimidyl bromide (**5f**) leading to the corresponding products (**47e-f**) in 80-85% yield.



Scheme 40: Isolated yields of analytically pure products of type **47** obtained by Negishi cross-coupling reaction of various heteroaryl bromides and iodides with **45**.

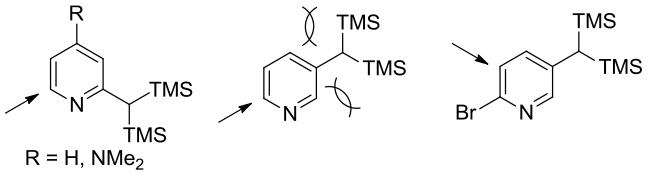
4.5 METALATION OF BTSM-SUBSTITUTED HETEROARYL DERIVATIVES

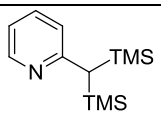
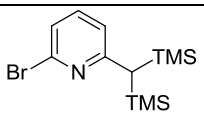
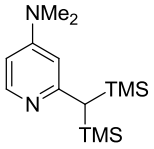
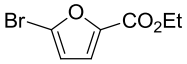
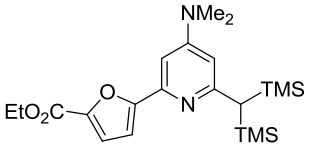
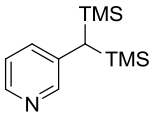
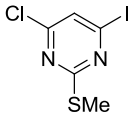
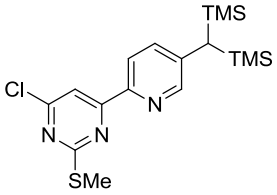
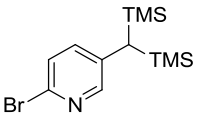
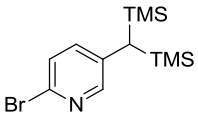
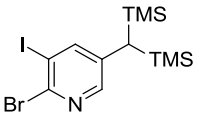
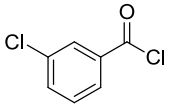
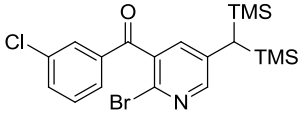
The resulting *N*-heteroaromatics of type **44** and **47** were metalated using the frustrated Lewis pair (FLP)[4] of $BF_3{\cdot}OEt_2$ and $TMP_2Mg{\cdot}2LiCl$ (**5**).[62,150] Interestingly, we observed a regioselective metalation of the heteroarene in all cases. Thus, 2-BTSM-pyridine (**44a**) was magnesiated selectively at position 6 of the pyridine core (Table 8, entry 1). The same selectivity was observed when the pyridine moiety carried an additional substituent (-NMe_2) in position 4 and

[148] E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[149] S. Schröter, C. Stock, T. Bach, *Tetrahedron* **2005**, *61*, 2245.
[150] T. Klatt, D. Sustac Roman, T. León, P. Knochel, *Org. Lett.* **2014**, *16*, 1232.

after subsequent cross-coupling reaction the corresponding DMAP derivative (4**8b**) was isolated in 75% yield (entry 2).

Table 8: Products of type **48** obtained by metalation of pyridine derivatives of type **44** and **47** followed by reaction with different electrophiles.



Entry	Substrate	Electrophile	Product[a]
1		$(CBrCl_2)_2$	
	44a		**48a**: 60%[b]
2			
	47e		**48b**: 75%[c], [d]
3			
	44e		**48c**: 65%[c], [e]
4		$(CBrCl_2)_2$	
	44e		**48d**: 68%[c]
5		I_2	
	48d		**48e**: 82%[f]
6			
	48d		**48f**: 60%[f], [g]

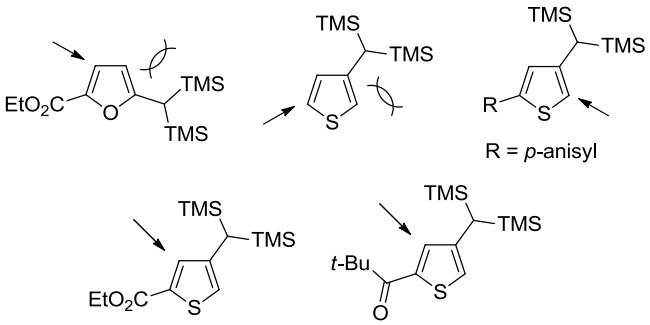
[a] Isolated yields of analytically pure product. [b] Metalation conditions: $BF_3 \cdot OEt_2$ (1.1 equiv), 0 °C, 15 min, $TMP_2Mg \cdot 2LiCl$ (1.1 equiv), 0 °C, 30 min. [c] Metalation conditions: $BF_3 \cdot OEt_2$ (1.1 equiv), 0 °C, 15 min, $TMP_2Mg \cdot 2LiCl$ (1.1 equiv), 0 °C, 15 min. [d] Cross-coupling conditions: $ZnCl_2$, 2 mol% $Pd(OAc)_2$, 4% SPhos, 50 °C, 12 h. [e] Cross-coupling conditions: $ZnCl_2$, 2 mol% $Pd(dba)_2$, 4 mol% tfp, 50 °C, 12 h. [f] Metalation conditions: $TMP_2Mg \cdot 2LiCl$ (1.5 equiv), 0 °C, 25 h. [g] CuCN·2LiCl (1.5 equiv) was added.

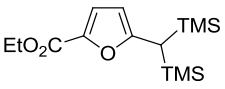
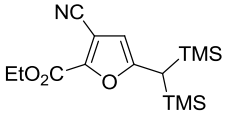
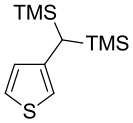
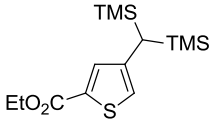
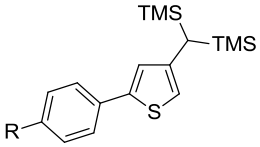
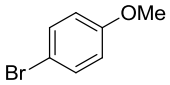
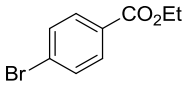
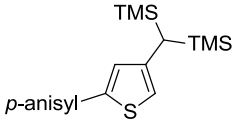
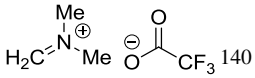
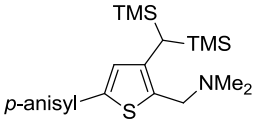
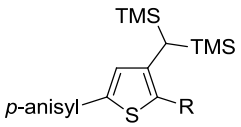
The 3-BTSM pyridine (**44e**) is an especially interesting substrate for metalations as a wide range of 3-functionalized pyridines are already known to be deprotonated in position 2 or 4 depending on the metalation protocol.[13a,c] However, in this case the bulky BTSM-group directs the metalation of the 3-substituted pyridine **44e** at position 6 when exposed to the Lewis pair $BF_3 \cdot OEt_2$ and $TMP_2Mg \cdot 2LiCl$ (**5**) leading to the pyridines **48c-d** in 65-68% yield (entries 3-4). Interestingly, a second metalation of the disubstituted pyridine **48d** can be performed using $TMP_2Mg \cdot 2LiCl$ (**5**)[151] occuring at the non-activated position 5 due to the bulky silyl substituent in position 3. Subsequent iodination or acylation led to the trisubstituted pyridines (**48e-f**) in 60-82% yield (entries 5-6).

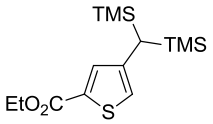
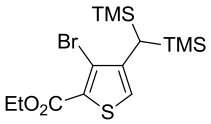
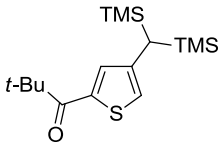
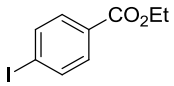
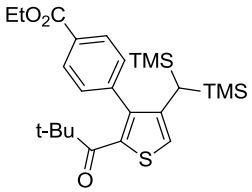
In a similar way, BTSM-substituted furans and thiophenes were metalated with various Li- or Mg-bases. Thus, the metalation of the furan **47c** with TMPMgCl (**2**; 1.1 equiv, 0 °C, 15 min) occurs selectively at the position more easily accessible next to the ester and not *ortho* to the bulky BTSM-group. After quenching of the magnesiated furan with tosyl cyanide, the corresponding nitrile (**49a**) was isolated in 87% yield (Table 9, entry 1). A more general metalation procedure is illustrated by the functionalization of 3-BTSM substituted thiophene (**44c**). The BTSM-group prevents lithiation at position 2 and 4 (*n*-BuLi, 1.1 equiv, -30 °C, 30 min) and a lithiation only at the less sterically hindered position 5 is observed. This lithiated thiophene reacts smoothly with a range of electrophiles, such as ethyl chloroformate or, after transmetalation with $ZnCl_2$, in a Negishi cross-coupling with aryl halides carrying electron-donating or electron-withdrawing[152] substituents leading to the products (**49b-d**) in excellent yields of 88-91% (Table 9, entries 2-4).

[151] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem.* **2011**, *123*, 9968; *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[152] This experiment was performed by V. Werner and is given here for the sake of completeness.

Table 9: Products of type **3** and **6** obtained by metalation of furan and thiophene derivatives followed by reaction with different electrophiles.



Entry	Substrate	Electrophile	Product[a]
1		TsCN	
	47c		**49a**: 87%[b]
2		$ClCO_2Et$	
	44c		**49b**: 88%[c]
			
3	**44c**		**49c**: R = OMe: 91%[c], [d]
4	**44c**		**49d**: R = CO_2Et: 91%[c], [d]
5			
	49c		**49e**: 72%[e]
			
6	**49c**	$(CBrCl_2)_2$	**49f**: R = Br: 71%[e]
7	**49c**	$ClCO_2Et$	**49g**: R = CO_2Et: 62%[e]

8	 **49b**	$(CBrCl_2)_2$	 **49h**: 81%[f]
9	 **49i**		 **49j**: 85%[g], [h]

[a] Isolated yields of analytically pure product. [b] Metalation conditions: TMPMgCl·LiCl (1.1 equiv), 0 °C, 15 min. [c] Metalation conditions: *n*-BuLi (1.1 equiv), -30 °C, 30 min. [d] The cross-coupling was performed using 2 mol% $Pd(OAC)_2$ and 4 mol% SPhos. [e] Metalation conditions: TMPLi (1.1 equiv), -60 °C, 45 min. [f] Metalation conditions: TMPMgCl·LiCl (1.1 equiv), 0 °C, 75 min. [g] Metalation conditions: $TMP_2Mg·2LiCl$ (1.1 equiv), 0 °C, 1 h. [h] The cross-coupling was performed using 2% $Pd(dba)_2$ and 4% tfp.

When the disubstituted thiophene (**49c**) was exposed to a second lithiation (TMPLi, 1.1 equiv, -60 °C, 45 min), it occurred as expected at the remaining acidic α-position to the sulfur unit and the metalated species was quenched with a variety of electrophiles in 62-72% yield (entries 5-7).[153] Interestingly, in the case of ester or ketone substituted thiophenes (**49b**) and (**49i**) the magnesiation using TMPMgCl·LiCl (0 °C, 75 min) or $TMP_2Mg·2LiCl$ (0 °C, 1 h) occurred exclusively *ortho* to the functional group and after subsequent quenching by bromination or cross-coupling the corresponding 2,3,4-trisubstituted products (**49h**) and (**49j**) were isolated in 81-85% yield (entries 8-9).[153]

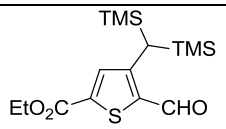
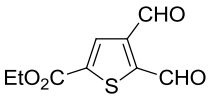
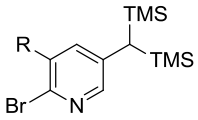
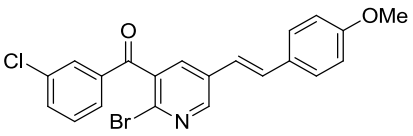
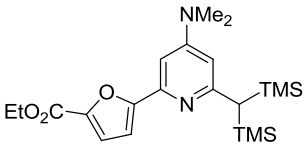
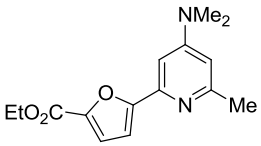
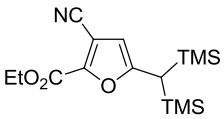
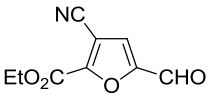
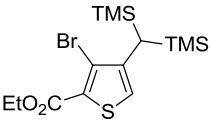
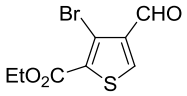
4.6 TRANSFORMATION AND FUNCTIONALIZATION OF BTSM-SUBSTITUTED HETEROARYL DERIVATIVES

As shown by Palomo,[142,144] the BTSM group can be transformed into a methyl, formyl or styryl group.[154] Thus, the dialdehyde (**50a**) was prepared by oxidation of **49k** with CAN (5.0 equiv, 25 °C, 2 d) in a mixture of acetonitrile and methanol (Table 10, entry 1). The BTSM group can

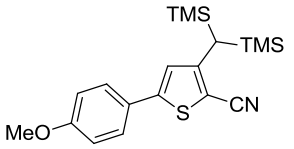
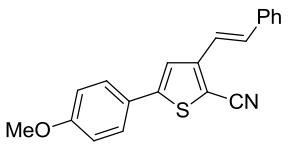
[153] These experiments were performed by V. Werner and are given here for the sake of completeness.
[154] For further functionalizations of benzylic TMS groups see: a) N. Sugita, S. Hayashi, F. Hino, T. Takanami, *J. Org. Chem.* **2012**, *77*, 10488. b) M. Leiendecker, C.-C. Hsiao, L. Guo, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 12912.

also undergo a Peterson olefination illustrated by the reaction of **48f** and anisaldehyde in the presence of 10% TBAF in THF (-20 °C, 15 min) leading to the stilbene derivative (**50b**) in 92% yield (entry 2).[16d] Another transformation is illustrated by the deprotection of the masked benzylic position of **48b** using TBAF·H_2O (1.0 equiv, 0 °C, 30 min) yielding the picoline derivative (**50c**) in 90% yield (entry 3). Furthermore, using the described oxidation methodology the furyl and thiophenyl carbaldehydes (**50d-e**) were prepared in 92-93% yield (entries 4-5). In addition the nitrile **49l** underwent a smooth olefination reaction with benzaldehyde (-20 °C, 15 min) furnishing the substituted thiophene (**50f**) in 95% yield (entry 6).[155]

Table 10: Products of type **50** obtained after transformation of the BTSM group.

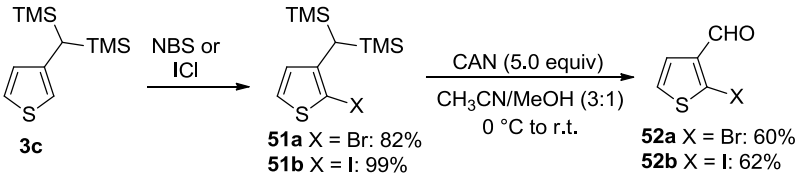
Entry	Substrate	Product[a]
1		
	49k	**50a**: 91%[b]
2		
	48f	**50b**: 92%[c]
3		
	48b	**50c**: 90%[d]
4		
	49a	**50d**: 92%[e]
5		
	49h	**50e**: 93%[e]

[155] This experiment was performed by V. Werner and is given here for the sake of completeness.

6		
	49l	**50f**: 95%[c]

[a] Isolated yields of analytically pure product. [b] Oxidation performed using 5.0 equiv CAN in CH_3CN/MeOH. [c] Reaction performed using 10% TBAF. [d] Reaction performed using 1 equiv TBAF·H_2O. [e] Oxidation performed using 5 equiv CAN in CH_3CN/H_2O.

While the described metalation methodology led exclusively to a functionalization at position 5 of the BTSM-substituted thiophene (**44c**) (see Table 9), the halogenation using NBS (1.0 equiv, DMF, 0 °C, 2 h) or ICl (1.5 equiv, THF, -78 °C, 30 min) lead to 2,3-disubstituted bromo- or iodothiophenes (**51a-b**) which were isolated in 82-99% yield (Scheme 41).[156] These thiophenes were transformed into the corresponding carbaldehydes (**52a-b**), thereby offering access to an orthogonal functionalization.[157]

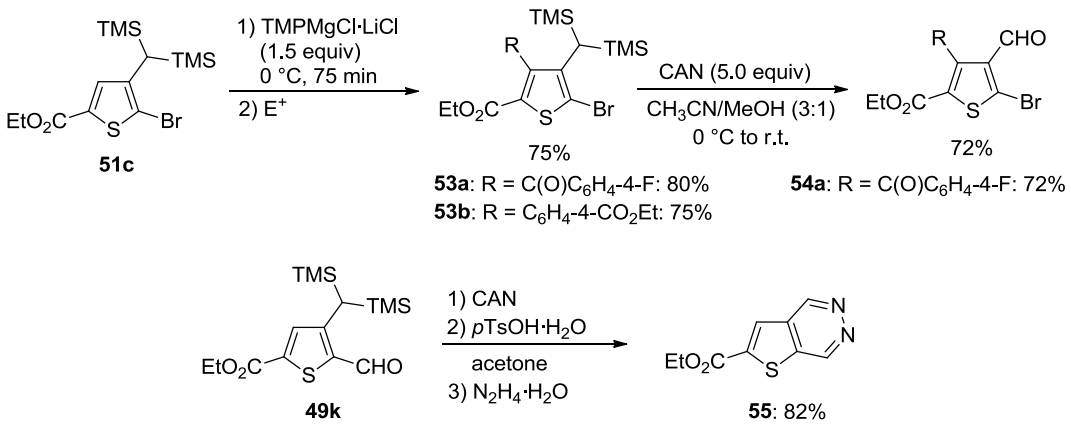


Scheme 41: Halogenation of **44c** and subsequent oxidation of the reaction products with CAN.

Additionally, the further functionalization of trisubstituted thiophenes has been realized, thus achieving a full functionalization of the thiophene scaffold. Hence, the trisubstituted thiophene (**51c**) was magnesiated using TMPMgCl·LiCl (**2**; 1.5 equiv) and after acylation or cross-coupling reaction the fully substituted thiophenes (**53a-b**) were isolated in 75-80% yield (Scheme 4). According to the oxidation protocol with CAN (*vide supra*) the thiophene (**53a**) was transformed into the corresponding carbaldehyde (**54a**) in 72% yield (Scheme 42).[157]

[156] a) R. Wu, J. S. Schumm, D. L. Pearson, J. M. Tour, *J. Org. Chem.* **1996**, *61*, 6906. b) S. S. Gunathilake, H. D. Magurudeniya, P. Huang, H. Nguyen, E. A. Rainbolt, M. C. Stefan, M. C. Biewer, *Polym. Chem.* **2013**, *4*, 5216. c) S. K. Sontag, J. A. Bilbrey, N. E. Huddleston, G. R. Sheppard, W. D. Allen, J. Locklin, *J. Org. Chem.* **2014**, *79*, 1836. d) J. Marshall, B. C. Schroeder, H. Bronstein, I. Meager, S. Rossbauer, N. Yaacobi-Gross, E. Buchaca-Domingo, T. D. Anthopoulos, N. Stingelin, P. Beavis, M. Heeney, *Macromolecules* **2014**, *47*, 89. e) J. Eras, C. Galvez, F. Garcia, *J. Heterocyclic Chem.* **1984**, *21*, 215. f) K.-H. Lee, K. Morino, A. Sudo, T. Endo, *J. Polym. Sci. Pol. Chem.* **2011**, *49*, 1190.

[157] These experiments were performed by V. Werner and are given here for the sake of completeness.



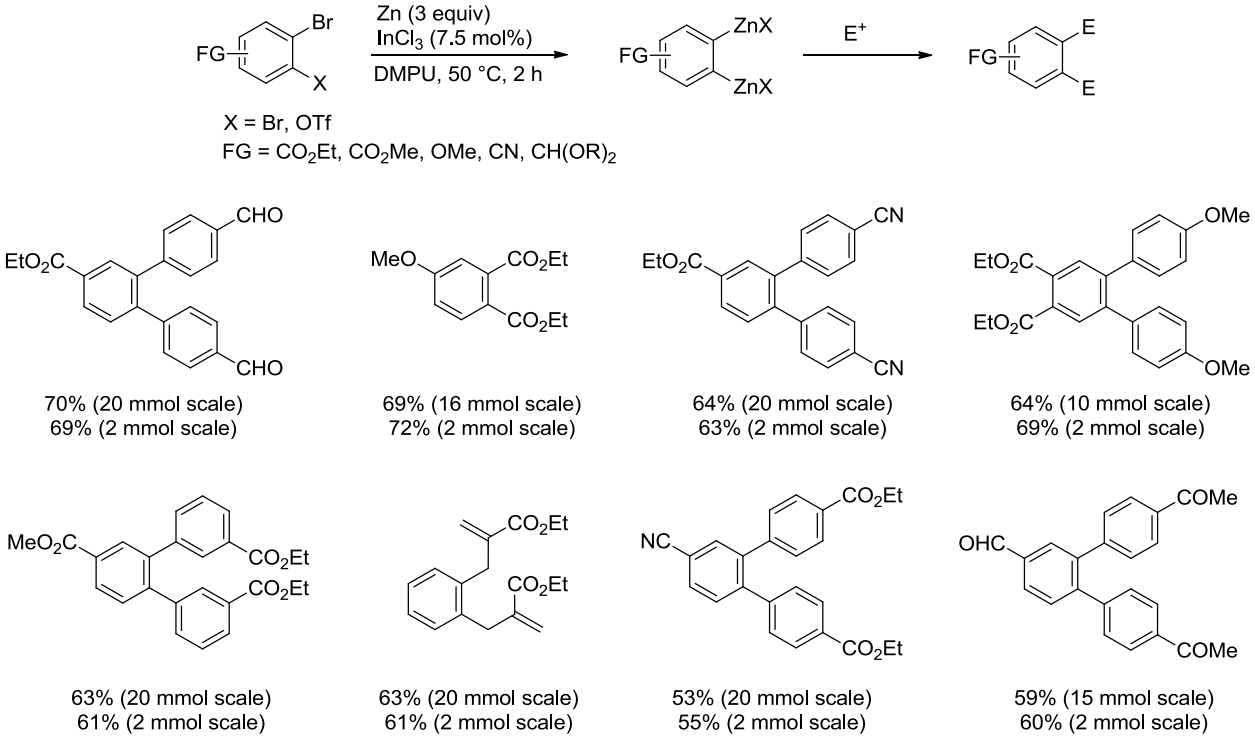
Scheme 42: Full functionalization of the thiophene scaffold and cyclization with hydrazine.

Furthermore, the precursor (**49k**) of the sensitive dialdehyde **50a** was used in a multistep-reaction, starting with a CAN-oxidation of (**49k**) (see Table 10, entry 1) followed by an *in situ* deprotection (10% *p*TsOH·H_2O, acetone, 1 h) of the obtained diacetal. The crude dialdehyde **50a** was then converted by a ring-closing reaction with hydrazine (3 equiv, 30 min) into an ester substituted thieno[2,3-*d*]pyridazine (**55**) in 82% yield.

5 SUMMARY

5.1 SYNTHESIS OF 1,2-DIMETALLIC COMPOUNDS *VIA* DIRECT INSERTION OF ZINC POWDER IN THE PRESENCE OF $InCl_3$

A straightforward and efficient direct insertion of zinc powder promoted by catalytic amounts of $InCl_3$ was demonstrated. The preparation of various functionalized 1,2-dizinc species using commercially available metal powder, aromatic dibromides and readily available 1,2-bromo triflates under mild reaction conditions was performed.

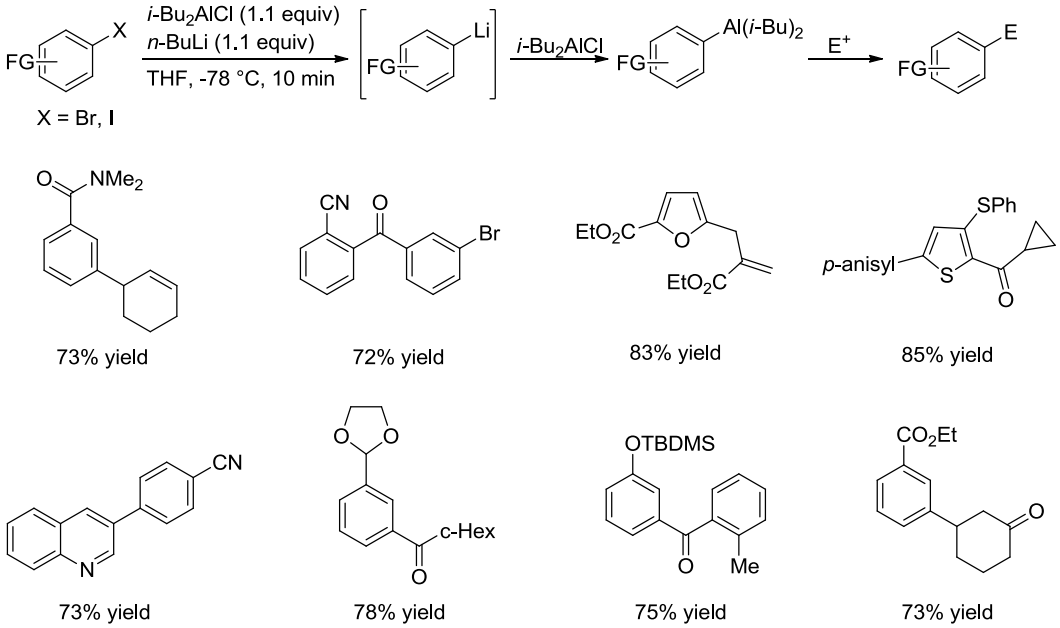


Scheme 43: Preparation of aromatic 1,2-dimetallics and subsequent bis-functionalizations.

The chemical properties of these organometallic reagents and the topological proximity of the two metals allow a novel approach to a variety of *ortho*-bis-functionalized aromatics. We have developed readily scalable experimental procedures (2-20 mmol scale) using standard laboratory glassware and usual laboratory techniques.

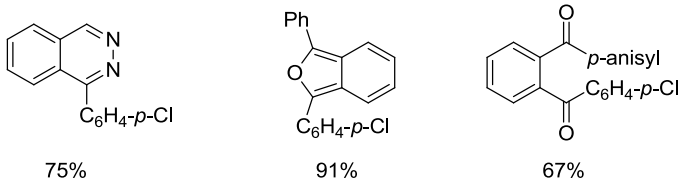
5.2 GENERATION OF FUNCTIONALIZED ARYL AND HETEROARYL ALUMINUM REAGENTS BY HALOGEN/LITHIUM EXCHANGE

Aryl aluminum reagents bearing functional groups such as nitriles or benzamides, as well as heteroaryl aluminum reagents bearing an ester group can readily be prepared by Br/Li exchange reactions in the presence of *i*-Bu_2AlCl. Complementary to this, arylaluminum reagents bearing a sensitive ester group can be prepared by the performance of an I/Li exchange of the corresponding aryl iodides.



Scheme 44: Preparation of arylaluminum reagents and subsequent reactions with electrophiles.

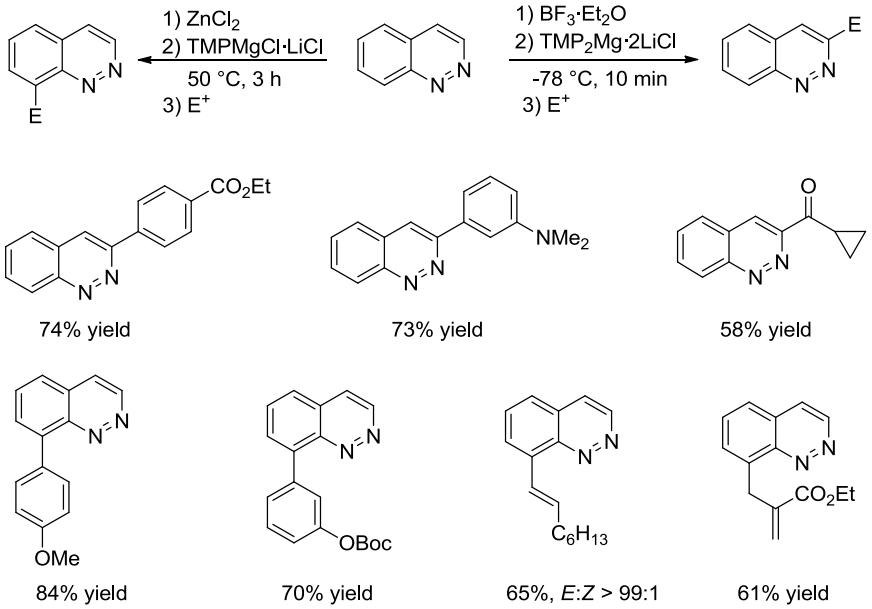
These new reagents undergo Pd-catalyzed cross-couplings or Cu-catalyzed allylations, acylations and 1,4-Michael additions without further transmetalation to the corresponding zinc species. In addition, the preparation method was performed on a 10 mmol scale and the resulting product was used for the generation of a substituted phthalazine, as well as the preparation of an isobenzofuran or diketone.



Scheme 45: Preparation of a substituted phthalazine, isobenzofuran and diketone.

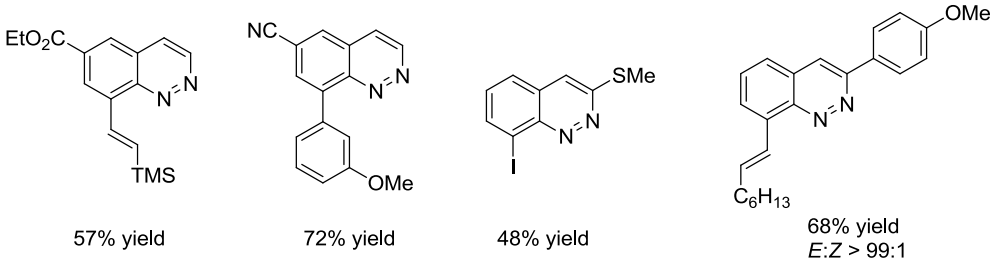
5.3 TMP-MAGNESIUM AND TMP-ZINC BASES FOR THE REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD

A new general method for the regioselective metalation of the cinnoline scaffold by implementation of two complementary metalation procedures A ($BF_3 \cdot OEt_2$ and $TMP_2Mg \cdot 2LiCl$ (**2**)) and B ($TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**)) allowing either a magnesiation at C(3) or a selective zincation at C(8) was developed.



Scheme 46: Obtained substituted cinnolines after subsequent quenching of the metalated species.

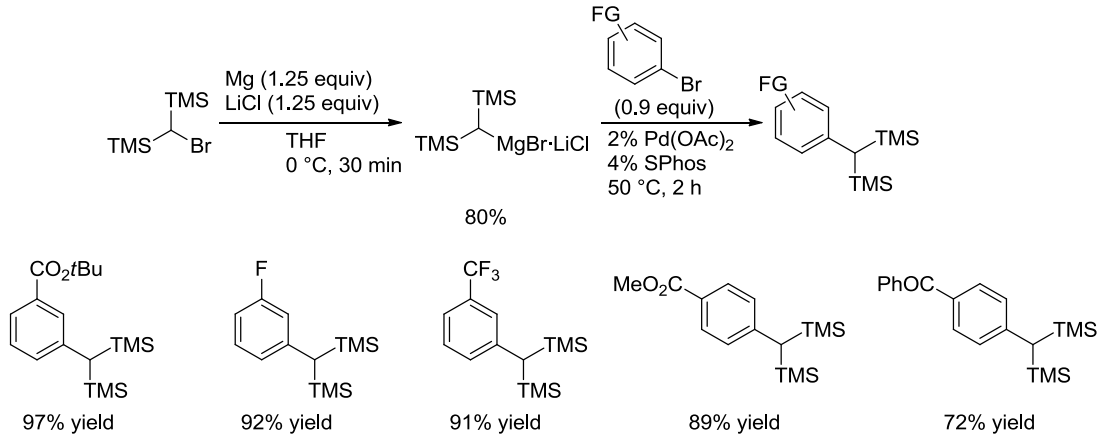
Additionally, a second selective metalation of prefunctionalized cinnoline derivatives can be performed, leading to highly functionalized compounds. Even functionalized cinnolines bearing a cyano or an ester group in position 6 can be zincated by a procedure using *in situ* generated $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**) furnishing 6,8-disubstituted cinnoline derivatives.



Scheme 47: Preparation of 3,8- and 6,8-disubstituted cinnoline derivatives.

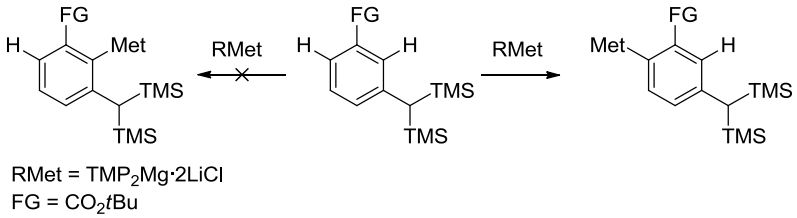
5.4 PREPARATION AND REGIOSELECTIVE METALATION OF BIS(TRIMETHYLSILYL)-METHYL-SUBSTITUTED ARYL DERIVATIVES

We have developed a simple procedure for the preparation of BTSM-functionalized arenes using a Kumada-Corriu cross-coupling. A range of functional groups, such as esters, ketones or amino groups were tolerated in the cross-coupling reactions.



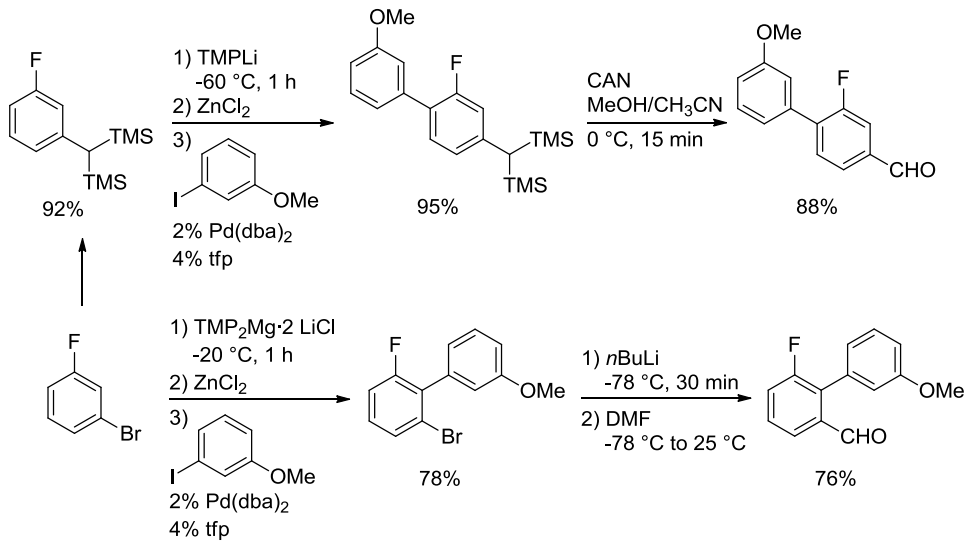
Scheme 48: Preparation of BTSM-functionalized arenes.

The bulky BTSM-group allows the regioselective metalation of various substrates as well as the synthesis of orthogonally functionalized compounds. Transformation of the BTSM-group to aldehydes or *E*-stilbenes has been performed confirming that the BTSM-group is a versatile substituent of aromatics allowing highly regioselective lithiations or magnesiations.



Scheme 49: Regioselectivity of the metalation of a *meta*-substituted BTSM-functionalized arene.

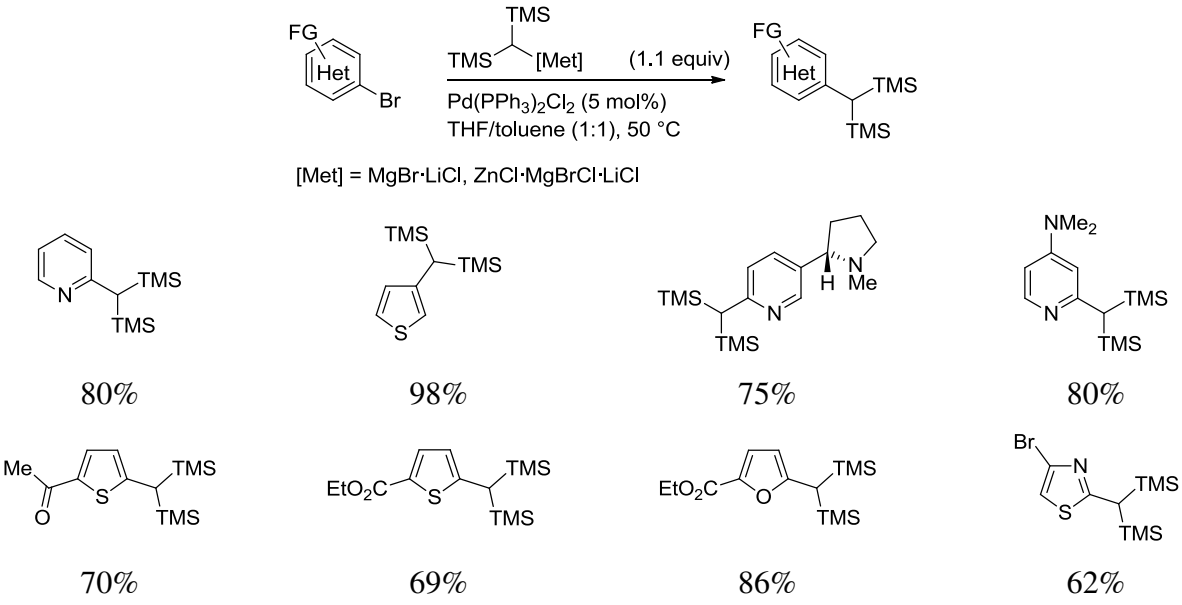
The presence or absence of the BTSM-group allows to switch the metalation regioselectivity. Thus, a functionalized aryl bromide (FG is an electron-withdrawing substituent in *meta*-position) is preferentially metalated in position 2. On the other hand, the metalation of the BTSM-functionaliazed substrates proceeds at the least sterically hindered position 6. In the presented sequence this was used for the preparation of orthogonally substituted aldehydes after appropriate quenching and functionalization reactions.



Scheme 50: Generation of orthogonally substituted aldehydes.

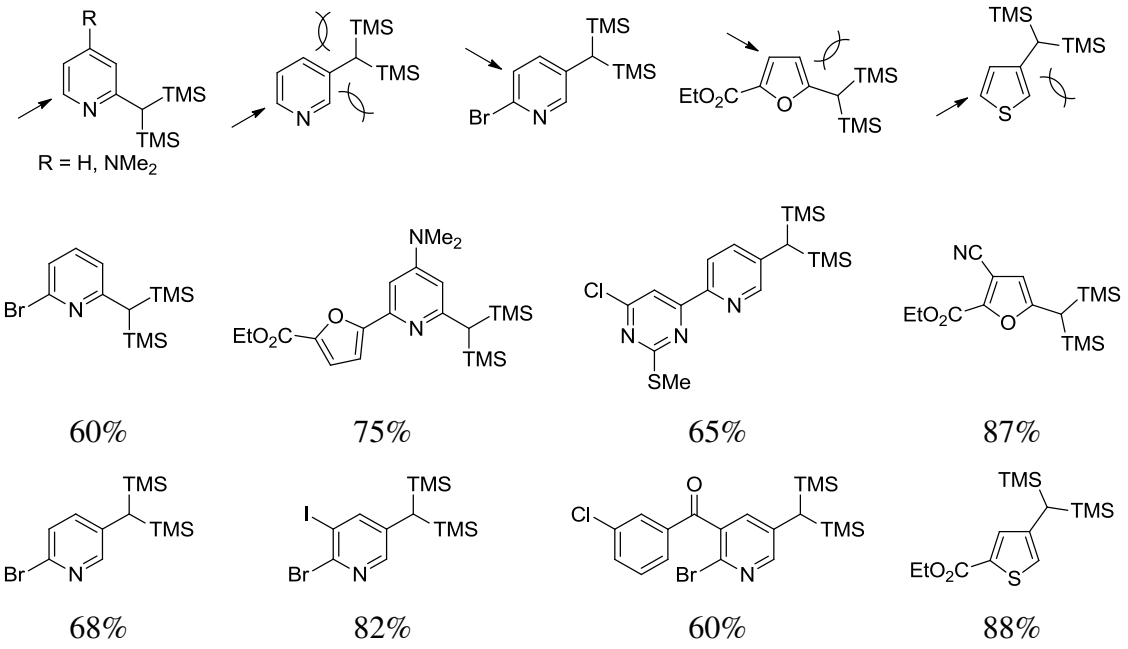
5.5 PREPARATION AND REGIOSELECTIVE METALATION OF BIS(TRIMETHYLSILYL)-METHYL-SUBSTITUTED HETEROARYL DERIVATIVES

We have also developed a simple procedure for the preparation of functionalized BTSM substituted heteroaryls using either a Kumada-Corriu or Negishi cross-coupling tolerating a broad scope of functional groups such as esters, ketones or even aldehydes.



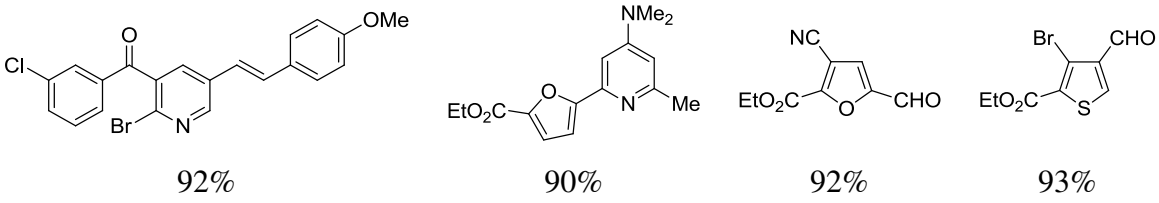
Scheme 51: Preparation of BTSM-subsituted heterocycles.

Due to the bulky silyl group the resulting BTSM-heterocycles were metalated with different Li- or Mg-bases in a site-selective manner und quenched with a variety of electrophiles furnishing heterocycles in good yields.



Scheme 52: Generation of highly functionalized heteroaryls by regioselective metalations.

These highly substituted heterocycles were exposed to transformation procedures leading to the corresponding methyl, formyl or styryl substituted heteroaryls.



Scheme 53: Generation of functionalized heteroaryls after transformation of the BTSM-group.

C. EXPERIMENTAL

1 GENERAL CONSIDERATIONS

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

1.1 SOLVENTS

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

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

$CHCl_3$ was predried over $CaCl_2$ and distilled from CaH_2.

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

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

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

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

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

NEt_3 was dried over KOH and distilled.

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

1.2 REAGENTS

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

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

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

TMPMgCl·LiCl was prepared according to a literature procedure.[50]

TMP_2Mg·2LiCl was prepared according to a literature procedure.[62]

TMP_2Zn·2$MgCl_2$·2LiCl was prepared according to a literature procedure.[52]

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

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (200 mmol, 27.3 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, 200 mL dry THF were added and stirring was continued until the salt was dissolved.

1.3 CONTENT DETERMINATION OF ORGANOMETALLIC REAGENTS

Organozinc and organomagnesium reagents were titrated with I_2 in THF.[158]

Organolithium reagents were titrated with dry 2-propanol and 1,10-phenanthroline as indicator in THF.[159]

TMPMgCl·LiCl, **TMP_2Mg·2LiCl** and **TMP_2Zn·2$MgCl_2$·2LiCl** were titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.[50,52,62]

1.4 CHROMATOGRAPHY

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from MERCK.

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

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

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

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

Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

1.5 ANALYTICAL DATA

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

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

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

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

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

2 SYNTHESIS OF 1,2-DIMETALLIC COMPOUNDS *VIA* DIRECT INSERTION OF ZINC POWDER IN THE PRESENCE OF $InCl_3$

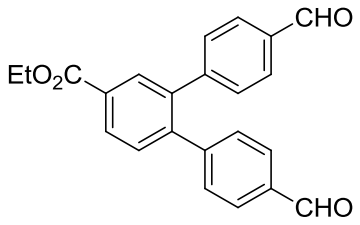
2.1 TYPICAL PROCEDURES

Typical procedure for the preparation of aromatic 1,2-dizinc reagents from aromatic 1,2-dibromides or *ortho*-bromo triflates; Typical Procedure 1:

$InCl_3$ (7.5 mol%) was placed in an argon-flushed Schlenk-flask and dried for 5 min by heating with a heat gun (450 °C) under high vacuum. Zinc powder (3 equiv) was added under argon, and the drying process was repeated for 5 min. The flask was evacuated and backfilled with argon three times before DMPU (1-2 mL/mmol) was added, along with the internal standard (heptadecane). TMSCl (3 mol%) was added, and the reaction mixture was heated with a heat gun until ebullition occurred. When the reaction mixture had been cooled to room temperature (20 °C), the triflate or bromide (1 equiv) was added in one portion and the reaction mixture was stirred at 50 °C. The progress of the insertion reaction was monitored by GC analysis of hydrolysed reaction aliquots quenched with HCl (2 M) or saturated aqueous NH_4Cl solution until a conversion of >95% was reached. The zinc powder was allowed to settle down, and the remaining solution containing the zinc reagent was used for further reactions.

2.2 GENERATION OF 1,2-DIZINC REAGENTS AND SUBSEQUENT REACTIONS

Synthesis of ethyl 4,4''-diformyl-[1,1':2',1''-terphenyl]-4'-carboxylate (9b); Typical Procedure 2:



The zinc reagent **7b** was prepared according to **TP1** from ethyl 3-bromo-4-((trifluoromethyl)sulfonyl)-oxy)benzoate (**6b**, 7.54 g, 20 mmol), zinc-powder (3.92 g, 60 mmol) and $InCl_3$ (0.33 g, 1.5 mmol). The reaction was carried out in 20 mL DMPU at 50 °C for 2 h. Iodolysis indicated a yield of 75% dimetallic reagent (15 mmol). The solution containing the zinc

reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of 4-bromobenzaldehyde (**8a**, 7.40 g, 40 mmol) and PEPPSI-*i*Pr (0.19 g, 0.28 mmol) in THF (20 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 50 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 5:1) afforded **9b** as a white solid (3.76 g, 10.5 mmol, 70%).

m.p. (°C): 123-126.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 9.58 (s, 1 H), 9.58 (s, 1 H), 8.27-8.24 (m, 1 H), 8.18 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.12 (dd, *J* = 8.0 Hz, *J* = 0.4 Hz, 1 H), 6.88-6.84 (m, 4 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 1.08 (t, *J* = 7.1 Hz, 3 H).

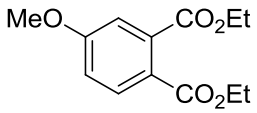
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 190.6, 190.6, 165.7, 146.0, 145.9, 143.7, 140.0, 135.8, 135.6, 132.0, 131.2, 131.0, 130.5, 130.4, 129.6, 129.5, 129.4, 61.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2926, 2849, 2748, 1716, 1696, 1602, 1574, 1568, 1517, 1473, 1424, 1400, 1387, 1366, 1302, 1286, 1266, 1235, 1211, 1169, 1140, 1106, 1043, 1020, 1010, 1003, 918, 895, 838, 828, 767, 748, 735, 723, 702, 666.

MS (EI, 70 eV): *m/z* (%) = 359 (20), 358 (100), 313 (40), 285 (10), 229 (40), 228 (33), 227 (11), 226 (11).

HRMS (EI) for **$C_{23}H_{18}O_4$** (358.1205): 358.1196 (M^+).

Synthesis of diethyl 4-methoxyphthalate (9c); Typical Procedure 3:



The zinc reagent **7c** was prepared according to **TP1** from 1,2-dibromo-4-methoxybenzene (**6c**, 4.25 g, 16 mmol), zinc-powder (3.14 g, 36 mmol) and $InCl_3$ (0.20 g, 1.2 mmol). The reaction was carried out in 16 mL DMPU at 50 °C for 2 h. Iodolysis indicated a yield of 59% dimetallic reagent (9.44 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask and cooled to -30 °C. $Pd(PPh_3)_4$ (1.85 g, 1.6 mmol) was added at -30 °C before ethyl chloroformate (**8b**, 3.47 g, 32 mmol) was added subsequently. The reaction mixture was stirred at -30 °C for 1 h and slowly warmed to 20 °C before being

quenched with HCl (2 M, 16 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9c** as colorless oil (1.64 g, 6.51 mmol, 69%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.76 (d, *J* = 8.6 Hz, 1 H), 7.12 (d, *J* = 2.5 Hz, 1 H), 6.57 (dd, *J* = 8.6 Hz, *J* = 2.7 Hz, 1 H), 4.26 (q, *J* = 7.0 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.05 (s, 3 H), 1.10 (t, *J* = 7.1 Hz, 3 H), 1.03 (t, *J* = 7.1 Hz, 3 H).

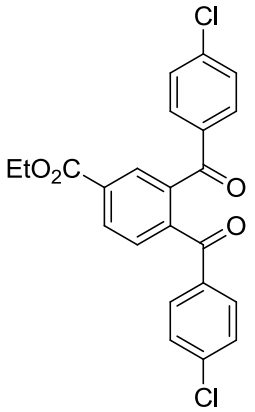
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 168.1, 166.3, 162.2, 137.0, 131.7, 123.5, 115.7, 113.8, 61.5, 61.0, 54.9, 14.1, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2939, 1714, 1602, 1573, 1500, 1464, 1446, 1423, 1390, 1366, 1324, 1274, 1229, 1182, 1173, 1115, 1067, 1030, 930, 924, 849, 803, 779, 702, 672.

MS (EI, 70 eV): *m/z* (%) = 252 (29), 207 (25), 180 (10), 179 (100).

HRMS (EI) for **$C_{13}H_{16}O_5$** (252.0998): 252.0999 (M^+).

Synthesis of ethyl 3,4-bis(4-chlorobenzoyl)benzoate (9d):



The zinc reagent **7b** was prepared according to **TP1** from ethyl 3-bromo-4-((trifluoromethyl)sulfonyl)-oxy)benzoate (**6b**, 3.77 g, 10 mmol), zinc powder (1.96 g, 30 mmol) and $InCl_3$ (165 mg, 0.75 mmol). The reaction was carried out in 10 mL DMPU at 50 °C for 2 h. Iodolysis indicated a yield of 75% dimetallic reagent (7.50 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask and cooled to -30 °C. $Pd(PPh_3)_4$ (1.16 g, 1.0 mmol) was added at -30 °C before 4-chlorobenzoyl chloride (**8c**, 3.50 g, 20 mmol) was added subsequently. The reaction mixture was stirred at -30 °C for 1 h and slowly warmed to 20 °C before being quenched with HCl (2 M, 10 mL). Flash

column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9d** as an amber solid (2.08 g, 4.88 mmol, 65%).

m.p. (°C): 125-127.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.29 (d, *J* = 1.7 Hz, 1 H), 8.06 (dd, *J* = 7.9, *J* = 1.5 Hz, 1 H), 7.44 - 7.36 (m, 4 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 6.95 - 6.91 (m, 2 H), 6.87 - 6.82 (m, 2 H), 4.13 - 4.06 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H).

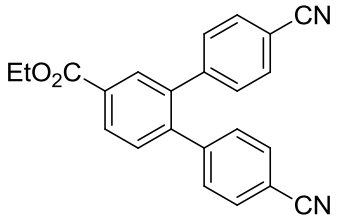
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 194.5, 194.1, 165.2, 144.5, 140.6, 140.2, 140.1, 135.8, 135.6, 132.8, 131.9, 131.8, 131.8, 130.8, 129.8, 129.3, 129.3, 62.0, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2990, 2959, 2937, 2898, 1717, 1659, 1655, 1583, 1570, 1480, 1448, 1400, 1356, 1308, 1270, 1253, 1124, 1110, 1091, 1012, 974, 930, 917, 871, 847, 777, 747, 686, 667.

MS (EI, 70 eV): *m/z* (%) = 430 (20), 429 (14), 428 (51), 427 (18), 426 (75), 391 (19), 381 (12), 317 (24), 316 (14), 315 (73), 287 (12), 152 (10), 139 (100), 111 (40).

HRMS (EI) for **$C_{23}H_{16}Cl_2O_4$** (426.0426): 426.0420 (M^+).

Synthesis of ethyl 4,4''-dicyano-[1,1':2',1''-terphenyl]-4'-carboxylate (9e):



The zinc reagent **7b** was prepared according to **TP1** from ethyl 3-bromo-4-((trifluoromethyl)sulfonyl)-oxy)benzoate (**6b**, 7.54 g, 20 mmol), zinc powder (3.92 g, 60 mmol) and $InCl_3$ (0.33 g, 1.5 mmol). The reaction was carried out in 20 mL DMPU at 50 °C for 2 h. Iodolysis indicated a yield of 75% dimetallic reagent (15 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of 4-bromobenzonitrile (**8d**, 7.40 g, 40 mmol) and PEPPSI-*i*Pr (0.19 g, 0.28 mmol) in THF (20 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with

HCl (2 M, 50 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 5:1) afforded **9e** as a white solid (3.38 g, 9.60 mmol, 64%).

m.p. (°C): 69-72.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.00 - 8.25 (m, 2 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.63 - 6.88 (m, 4 H), 6.36 - 6.63 (m, 4 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 1.07 (t, *J* = 7.1 Hz, 3 H).

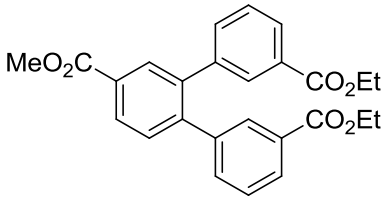
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 165.5, 144.0, 144.0, 142.9, 139.2, 132.0, 132.0, 131.9, 131.4, 130.9, 130.3, 130.2, 129.7, 118.4, 118.4, 112.0, 111.8, 61.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2905, 2227, 1714, 1604, 1573, 1505, 1477, 1465, 1446, 1415, 1392, 1366, 1303, 1263, 1235, 1179, 1107, 1043, 1016, 1005, 920, 896, 859, 835, 772, 753, 740, 730, 698, 671, 658.

MS (EI, 70 eV): *m/z* (%): 353 (21), 352 (100), 324 (47), 308 (33), 307 (99), 280 (19), 279 (69), 278 (27), 252 (14), 251 (28), 44 (10).

HRMS (EI) for **$C_{23}H_{16}N_2O_2$** (352.1212): 352.1203 (M^+).

Synthesis of 3,3''-diethyl 4'-methyl [1,1':2',1''-terphenyl]-3,3'',4'-tricarboxylate (9f):



The zinc reagent **7d** was prepared according to **TP1** from methyl 3-bromo-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (**6d**, 7.26 g, 20 mmol), zinc powder (3.92 g, 60 mmol) and $InCl_3$ (0.33 g, 1.5 mmol). The reaction mixture was stirred in DMPU (20 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 70% dimetallic reagent (14 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of ethyl 3-bromobenzoate (**8e**, 9.16 g, 40 mmol) and PEPPSI-*i*Pr (0.19 g, 0.28 mmol) in THF (20 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 50 mL). Flash column chromatographical purification on silica gel (pentane/diethyl ether = 4:1) afforded **9f** as a colorless oil (3.82 g, 8.83 mmol, 63%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.27 (d, *J* = 1.4 Hz, 1 H), 8.13-8.08 (m, 3 H), 7.98-7.94 (m, 2 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 7.01-6.94 (m, 2 H), 6.89-6.82 (m, 2 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 4.03 (q, *J* = 7.2 Hz, 2 H), 3.55 (s, 3 H), 0.99 (t, *J* = 6.3 Hz, 3 H), 0.95 (t, *J* = 6.4 Hz, 3 H).

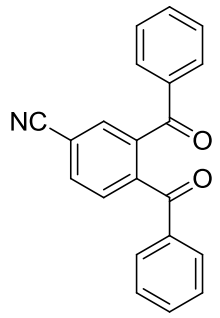
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 166.3, 165.8, 165.8, 144.2, 140.9, 140.8, 140.3, 134.3, 134.2, 132.0, 131.3, 131.3, 131.2, 131.1, 131.0, 130.5, 129.4, 128.7, 128.5, 128.4, 128.3, 60.9, 60.8, 51.8, 14.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 2981, 2906, 2280, 1716, 1605, 1584, 1475, 1464, 1435, 1391, 1367, 1303, 1269, 1236, 1222, 1192, 1170, 1106, 1082, 1056, 1034, 1019, 1000, 911, 862, 814, 777, 753, 703, 685, 670.

MS (EI, 70 eV): *m/z* (%): 433 (24), 432 (100), 419 (15), 418 (61), 388 (10), 387 (34), 373 (16), 314 (10), 313 (18), 255 (12), 242 (12), 228 (26), 227 (23), 226 (37).

HRMS (EI) for **$C_{26}H_{24}O_6$** (432.1573): 432.1567 (M^+).

Synthesis of 3,4-dibenzoylbenzonitrile (9g):



The zinc reagent **7e** was prepared according to **TP1** from 2-bromo-4-cyanophenyl trifluoromethanesulfonate (**6e**, 13.2 g, 40 mmol), zinc powder (7.84 g, 120 mmol) and $InCl_3$ (0.66 g, 3.0 mmol). The reaction mixture was stirred in DMPU (40 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 57% dimetallic reagent (22.8 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask and cooled to -30 °C. $Pd(PPh_3)_4$ (3.32 g, 2.0 mmol) was added at -30 °C before benzoyl chloride (**8f**, 11.2 g, 80 mmol) was added subsequently. The reaction mixture was stirred at -30 °C for 1 h and slowly warmed to 20 °C before being quenched with HCl (2 M, 40 mL). Flash column

chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9g** as an offwhite solid (4.84 g, 15.5 mmol, 68%).

m.p. (°C): 99-104.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.45 - 7.59 (m, 4 H), 6.98 - 7.06 (m, 3 H), 6.79 - 6.97 (m, 6 H).

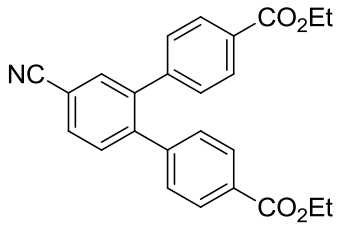
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 194.9, 194.0, 144.4, 141.3, 137.2, 137.0, 133.7, 133.7, 132.8, 130.5, 130.4, 130.0, 129.0, 128.9, 117.9, 114.5, 110.8,

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2926, 2855, 2230, 1760, 1658, 1594, 1578, 1558, 1491, 1482, 1448, 1397, 1372, 1317, 1312, 1293, 1273, 1226, 1212, 1196, 1176, 1159, 1121, 1103, 1072, 1063, 1025, 1017, 1000, 976, 964, 935, 925, 852, 834, 797, 765, 757, 716, 707, 697, 690, 682, 656.

MS (EI, 70 eV): *m/z* (%): 312 (20), 311 (74), 235 (17), 177 (10), 151 (11), 105 (91), 77 (60).

HRMS (EI) for **$C_{21}H_{13}NO_2$** (311.0946): 311.0938 (M^+).

Synthesis of diethyl 4'-cyano-[1,1':2',1''-terphenyl]-4,4''-dicarboxylate (9h):



The zinc reagent **7e** was prepared according to **TP1** from 2-bromo-4-cyanophenyl trifluoromethanesulfonate (**6e**, 6.60 g, 20 mmol), zinc powder (3.92 g, 60 mmol) and $InCl_3$ (0.33 g, 1.5 mmol). The reaction mixture was stirred in DMPU (20 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 57% dimetallic reagent (11.4 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of ethyl 4-iodobenzoate (**8g**, 11.0 g, 40 mmol) and PEPPSI-*i*Pr (0.19 g, 0.28 mmol) in THF (20 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 50 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9h** as a colorless oil (2.42 g, 6.05 mmol, 53%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.97-7.93 (m, 4 H), 7.14 (d, *J* = 1.4 Hz, 1 H), 7.04 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1 H), 6.80-6.70 (m, 5 H). 4.08 (q, *J* = 7.2 Hz, 2 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 0.97 (t, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 7.1 Hz, 3 H).

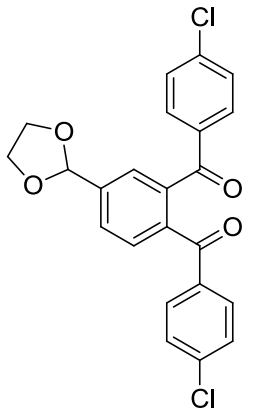
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 165.7, 165.6, 143.9, 143.6, 143.5, 140.7, 134.0, 131.3, 131.3, 131.2, 130.4, 130.3, 129.9, 129.8, 129.7, 118.4, 112.7, 61.0, 61.0, 14.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 2982, 2281, 2231, 1711, 1610, 1569, 1550, 1477, 1465, 1446, 1414, 1406, 1390, 1367, 1330, 1310, 1269, 1179, 1099, 1045, 1019, 1005, 966, 903, 858, 835, 812, 774, 751, 730, 710, 662.

MS (EI, 70 eV): *m/z* (%): 400 (29), 399 (100), 355 (14), 354 (62), 340 (17), 326 (11), 298 (10), 255 (10), 254 (48), 253 (18), 177 (17), 161 (11), 97 (10), 85 (16), 71 (20), 57 (27).

HRMS (EI) for **$C_{25}H_{21}NO_4$** (399.1471): 399.1460 (M^+).

Synthesis of (4-(1,3-dioxolan-2-yl)-1,2-phenylene)bis((4-chlorophenyl)methanone) (9i):



The zinc reagent **7f** was prepared according to **TP1** from 2-bromo-4-(1,3-dioxolan-2-yl)phenyl trifluoromethanesulfonate (**6f**, 7.54 g, 20 mmol), zinc powder (3.92 g, 60 mmol) and $InCl_3$ (0.33 g, 1.5 mmol). The reaction mixture was stirred in DMPU (20 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 60% dimetallic reagent (12 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask and cooled to -30 °C. $Pd(PPh_3)_4$ (3.32 g, 2.0 mmol) was added at -30 °C before 4-chlorobenzoyl chloride (**8c**, 7.00 g, 50 mmol) was added subsequently. The reaction mixture was stirred at -30 °C for 1 h and slowly warmed to 20 °C before being quenched with saturated aqueous NH_4Cl solution (40 mL).

Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9i** as an offwhite solid (3.15 g, 7.32 mmol, 61%).

m.p. (°C): 156.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.73 (d, *J* = 1.6 Hz, 1 H), 7.48 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1 H), 7.44 - 7.37 (m, 4 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 6.93 - 6.83 (m, 4 H), 5.60 (s, 1 H), 3.57 - 3.36 (m, 4 H).

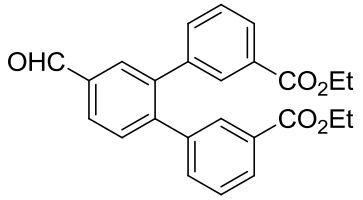
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 194.8, 194.7, 141.6, 141.3, 140.9, 139.8, 139.8 , 136.2, 136.1, 131.9, 131.9, 130.0, 129.2, 129.2, 129.0, 128.3, 103.2, 65.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 3053, 2981, 2953, 2873, 1661, 1642, 1586, 1572, 1490, 1482, 1420, 1404, 1381, 1306, 1284, 1275, 1264, 1212, 1179, 1162, 1156, 1114, 1106, 1088, 1024, 1013, 992, 987, 976, 964, 958, 940, 929, 897, 888, 872, 857, 851, 837, 786, 757, 744, 724, 690, 683, 657.

MS (EI, 70 eV): *m/z* (%): 430 (12), 429 (13), 428 (55), 427 (39), 426 (74), 425 (26), 319 (12), 317 (15), 315 (39), 288 (11), 245 (25), 244 (11), 243 (58), 152 (25), 141 (36), 139 (100), 111 (53), 75 (13), 73 (41) , 45 (12), 44 (11).

HRMS (EI) for **$C_{23}H_{16}Cl_2O_4$** (426.0426): 426.0421 (M^+).

Synthesis of diethyl 4'-formyl-[1,1':2',1''-terphenyl]-3,3''-dicarboxylate (9j):



The zinc reagent **7f** was prepared according to **TP1** from 2-bromo-4-(1,3-dioxolan-2-yl)phenyl trifluoromethanesulfonate (**6f**, 5.66 g, 15 mmol), zinc powder (2.94 mg, 45 mmol) and $InCl_3$ (0.25 g, 1.13 mmol). The reaction mixture was stirred in DMPU (15 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 60% dimetallic reagent (9.0 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of 1-(4-bromophenyl)ethanone (**8h**, 5.97 g, 30 mmol) and PEPPSI-*i*Pr

(0.14 g, 0.21 mmol) in THF (15 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 30 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9j** as a colorless oil (2.10 g, 5.21 mmol, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.12 (s, 1 H), 8.00 - 7.90 (m, 6 H), 7.64 (d, *J* = 8.3 Hz, 1 H), 7.30 - 7.27 (m, 1 H), 7.26 - 7.20 (m, 3 H), 4.33 (qd, *J* = 7.1 Hz, *J* = 1.2 Hz, 4 H), 1.35 (td, *J* = 7.1 Hz, 1.5 Hz, 6 H).

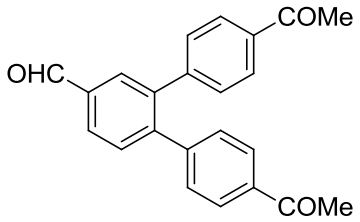
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 191.6, 166.1, 166.0, 145.5, 140.5, 140.0, 140.0, 135.8, 134.1, 134.0, 131.8, 131.3, 130.7, 130.6, 130.6, 130.5, 128.9, 128.6, 128.4, 128.1, 128.1, 61.0, 61.0, 14.2, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2980, 2904, 2832, 2726, 1713, 1698, 1599, 1583, 1561, 1465, 1444, 1428, 1390, 1366, 1301, 1286, 1238, 1223, 1170, 1105, 1082, 1055, 1032, 1017, 999, 918, 848, 837, 818, 794, 771, 755, 701, 695, 681, 672.

MS (EI, 70 eV): m/z (%) = 403 (28), 402 (100), 358 (16), 357 (56), 329 (12), 327 (12), 313 (22), 285 (10), 284 (18), 283 (28), 256 (10), 255 (23), 230 (11), 229 (64), 228 (38), 227 (44), 226 (45), 224 (10), 113 (16), 57 (12).

HRMS (EI) for $C_{25}H_{22}O_5$ (402.1467): 402.1463 (M^+).

Synthesis of 4,4''-diacetyl-[1,1':2',1''-terphenyl]-4'-carbaldehyde (9k):



The zinc reagent **7f** was prepared according to **TP1** from 2-bromo-4-(1,3-dioxolan-2-yl)phenyl trifluoromethanesulfonate (**6f**, 5.66 g, 15 mmol), zinc powder (2.94 g, 45 mmol) and $InCl_3$ (0.25 g, 1.13 mmol). The reaction mixture was stirred in DMPU (15 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 60% dimetallic reagent (9.0 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of 1-(4-bromophenyl)ethanone (**8h**, 5.97 g, 30 mmol) and PEPPSI-*i*Pr

(0.14 g, 0.21 mmol) in THF (15 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 40 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9k** as a colorless oil (1.82 g, 5.32 mmol, 59%).

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 9.77 (s, 1 H), 7.72-7.56 (m, 6 H), 7.15-7.11 (m, 1 H), 6.96-6.88 (m, 4 H), 2.01 (s, 3 H), 1.99 (s, 3 H).

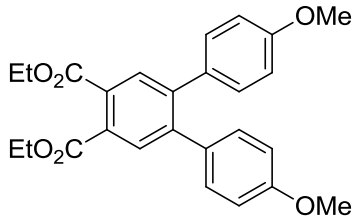
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 195.9, 195.9, 190.7, 145.1, 144.6, 144.6, 140.6, 136.6, 136.5, 136.4, 131.9, 131.5, 130.0, 130.0, 128.9, 128.5, 128.4, 26.0, 26.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 3002, 2922, 2831, 2726, 2362, 2280, 1697, 1678, 1599, 1570, 1554, 1514, 1476, 1423, 1402, 1383, 1356, 1330, 1263, 1174, 1126, 1112, 1077, 1042, 1014, 1004, 956, 902, 881, 823, 772, 742, 728, 708, 690, 672, 660.

MS (EI, 70 eV): *m/z* (%): 343 (16), 342 (51), 328 (25), 327 (100), 229 (11), 228 (14), 43 (21).

HRMS (EI) for **$C_{23}H_{18}O_3$** (342.1256): 342.1256 (M^+).

Synthesis of diethyl 4,4''-dimethoxy-[1,1':2',1''-terphenyl]-4',5'-dicarboxylate (9l):



The zinc reagent **7g** was prepared according to **TP1** from diethyl 4-bromo-5-(((trifluoromethyl)sulfonyl)oxy)phthalate (**6g**, 4.49 g, 10 mmol), zinc powder (1.96 g, 30 mmol) and $InCl_3$ (0.17 g, 0.75 mmol). The reaction mixture was stirred in DMPU (10 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 45% dimetallic reagent (4.50 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of 1-iodo-4-methoxybenzene (**8i**, 4.68 g, 20 mmol) and PEPPSI-*i*Pr (0.1 g, 0.14 mmol) in THF (10 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 25 mL). Flash column chromatographical purification on silica gel (pentane/diethyl ether = 4:1) afforded **9l** as a white solid (1.25 g, 2.88 mmol, 64%).

m.p. (°C): 108-110.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.94 (s, 2 H), 7.00-6.94 (m, 4 H), 6.62-6.57 (m, 4 H), 4.26 (q, *J* = 7.2 Hz, 4 H), 3.20 (s, 6 H), 1.10 (t, *J* = 7.2 Hz, 6 H).

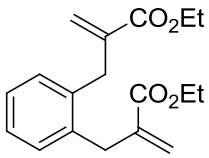
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 167.4, 159.4, 143.0, 132.7, 131.9, 131.7, 131.2, 114.0, 61.5, 54.6, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 3011, 2948, 2832, 2360, 1730, 1710, 1673, 1652, 1607, 1577, 1554, 1518, 1512, 1491, 1482, 1461, 1439, 1416, 1378, 1368, 1316, 1292, 1276, 1246, 1233, 1174, 1133, 1114, 1092, 1072, 1051, 1032), 1022, 1010, 1002, 969, 959, 938, 930, 912, 870, 855, 846, 833, 815, 804, 793, 785, 774, 747, 688, 677.

MS (EI, 70 eV): *m/z* (%): 435 (27), 434 (100), 361 (22).

HRMS (EI) for **$C_{26}H_{26}O_6$** (434.1729): 434.1727 (M^+).

Synthesis of diethyl 2,2'-(1,2-phenylenebis(methylene))-diacrylate (9m):



The zinc reagent **7h** was prepared according to **TP1** from 1,2-dibromobenzene (**6h**, 7.54 g, 20 mmol), zinc powder (3.92 g, 60 mmol) and $InCl_3$ (0.33 g, 1.50 mmol). The reaction mixture was stirred in DMPU (20 mL) at 50 °C for 2 h. Iodolysis indicated a yield of 59% dimetallic reagent (11.8 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask and cooled to -30 °C. CuCN·2LiCl (1 M in THF, 2.0 mL, 2.0 mmol) was added at -30 °C before ethyl 2-(bromomethyl)acrylate (**8j**, 7.72 g, 40 mmol) was added subsequently. The reaction mixture was stirred at -30 °C for 1 h and slowly warmed to 20 °C before being quenched with HCl (2 M, 20 mL). Flash column chromatographical purification on silica gel (*i*hexane/diethyl ether = 4:1) afforded **9m** as colorless oil (2.25 g, 7.43 mmol, 63%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.09-7.01 (m, 4 H), 6.27-6.25 (m, 2 H), 5.14-5.11 (m, 2 H), 3.95 (q, *J* = 7.2 Hz, 4 H), 3.71-3.67 (m, 4 H), 0.91 (t, *J* = 7.1 Hz, 6 H).

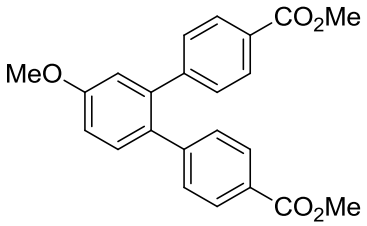
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 166.6, 140.5, 137.6, 130.5, 127.1, 125.6, 60.6, 35.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2907, 1712, 1632, 1492, 1478, 1446, 1428, 1404, 1392, 1368, 1330, 1300, 1275, 1250, 1201, 1176, 1130, 1095, 1025, 948, 871, 859, 846, 818, 786, 756, 734, 692, 669.

MS (EI, 70 eV): *m/z* (%): 257 (26), 256 (32), 229 (19), 228 (100), 211 (15), 210 (38), 199 (17), 183 (29), 182 (51), 181 (10), 156 (16), 155 (81), 154 (56), 153 (34), 143 (22), 141 (15), 129 (31), 128 (36), 115 (20).

HRMS (EI) for **$C_{18}H_{22}O_4$** (302.1518): 302.1519 (M^+).

Synthesis of dimethyl 4'-methoxy-[1,1':2',1''-terphenyl]-4,4''-dicarboxylate (9n):



The zinc reagent **7c** was prepared according to **TP1** from 1,2-dibromo-4-methoxybenzene (**6c**, 3.98 g, 15 mmol), zinc powder (2.94 mg, 45 mmol) and $InCl_3$ (0.25 g, 1.13 mmol). The reaction was carried out in 15 mL DMPU at 50 °C for 2 h. Iodolysis indicated a yield of 59% dimetallic reagent (8.85 mmol). The solution containing the zinc reagent was separated from the remaining zinc powder and transferred to a new flask containing a solution of methyl 4-iodobenzoate (**8k**, 788 g, 30 mmol) and PEPPSI-*i*Pr (0.14 g, 0.21 mmol) in THF (15 mL). The reaction mixture was stirred at 50 °C for 12 h before being quenched with HCl (2 M, 40 mL). Flash column chromatographical purification on silica gel (pentane/diethyl ether = 5:1) afforded **9n** as a white solid (2.37 g, 6.29 mmol, 71%).

m.p. (°C): 123-124.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.01-7.93 (m, 4 H), 7.15 (d, *J* = 8.1 Hz, 1 H), 7.07-7.01 (m, 4 H), 6.91 (d, *J* = 2.6 Hz, 1 H), 6.81 (m, 1 H), 3.46 (s, 3 H), 3.44 (s, 3 H), 3.34 (s, 3 H).

^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 166.5, 166.4, 160.0, 146.2, 145.9, 141.3, 132.5, 132.1, 130.2, 130.1, 129.7, 129.7, 129.3, 128.8, 116.3, 114.0, 55.0, 51.5, 51.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3007, 2953, 2842, 1711, 1597, 1578, 1566, 1558, 1517, 1486, 1458, 1451, 1441, 1432, 1404, 1394, 1366, 1319, 1279, 1240, 1221, 1191, 1178, 1115, 1100, 1050, 1029, 1016, 1002, 984, 971, 959, 882, 864, 858, 837, 824, 774, 743, 732, 720, 711, 668, 656.

MS (EI, 70 eV): *m/z* (%) = 377 (21), 376 (100), 345 (15), 258 (10).

HRMS (EI) for **$C_{23}H_{20}O_5$** (376.1311): 376.1306 (M^+).

3 GENERATION OF FUNCTIONALIZED ARYL AND HETEROARYL ALUMINUM REAGENTS BY HALOGEN/LITHIUM EXCHANGE

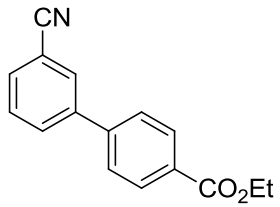
3.1 TYPICAL PROCEDURES

Typical Procedure for the preparation of aryl aluminum reagents (TP1):

A dry and argon-flushed 20 mL Schlenk-tube equipped with a magnetic stirring bar was charged with the aryl halide (1.5 mmol), THF (2.5 mL) and the internal standard (undecane) and cooled to -78 °C. A solution of *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) was added, and the resulting mixture was stirred for 10 min before a solution of *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 5 min and then allowed to warm to room temperature. The reaction was monitored by GC-analysis of reaction aliquots quenched with iodine in dry THF.

3.2 BARBIER-TYPE TRAPPING AND SUBSEQUENT REACTIONS OF ALUMINUM REAGENTS

Synthesis of ethyl 3'-cyano-[1,1'-biphenyl]-4-carboxylate (14a)

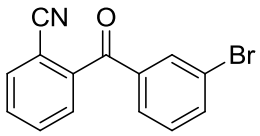


The aluminum reagent **12a** was prepared according to **TP1** from 3-bromobenzonitrile (**10a,** 273 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 81% organometallic reagent (**12a**, 1.21 mmol). A solution of ethyl 4-iodobenzoate (**13a**, 414 mg, 1.5 mmol), Pd_2dba_3 (34 mg, 0.0375 mmol), P(*t*-Bu)$_3$ (1 M in toluene, 0.15 mL, 0.15 mmol) in THF (1 mL) was added. The resulting mixture was stirred at 50 °C for 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 x 15 mL) and

dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14a** as colorless oil (198 mg, 65%).

The analytical data matches the one reported in the literature.[160]

Synthesis of 2-(3-bromobenzoyl)benzonitrile (14b)



The aluminum reagent **12b** was prepared according to **TP1** from 2-bromobenzonitrile (**10b,** 273 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 64% organometallic reagent (**12b**, 0.96 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and 3-bromobenzoyl chloride (**13b**, 362 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14b** as a yellowish oil (198 mg, 72%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94 (t, *J* = 1.8 Hz, 1 H), 7.88 - 7.83 (m, 1 H), 7.79 - 7.74 (m, 1 H), 7.73 - 7.67 (m, 3 H), 7.65 - 7.61 (m, 1 H), 7.38 (t, *J* = 7.9 Hz, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 192.4, 140.8, 137.9, 136.8, 134.5, 133.1, 132.4, 131.9, 130.4, 130.1, 129.0, 123.1, 117.0, 112.1.

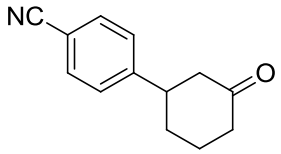
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 3067, 2959, 2922, 2853, 2225, 1914, 1850, 1657, 1588, 1558, 1482, 1465, 1450, 1412, 1301, 1261, 1158, 1068, 996, 953, 897, 886, 812, 785, 759, 726, 699, 664.

[160] S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380.

MS (EI, 70 eV): *m/z* (%) = 287 (47), 285 (42), 207 (11), 206 (75), 185 (95), 183 (100), 157 (32), 155 (34), 130 (73), 102 (52), 76 (43), 75 (36), 74 (10), 50 (25), 41 (10).

HRMS (EI) for **$C_{14}H_8BrNO$** (284.9789): 284.9780 (M^+).

Synthesis of 4-(3-oxocyclohexyl)benzonitrile (14c)



The aluminum reagent **12c** was prepared according to **TP1** from 4-bromobenzonitrile (**10c,** 273 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 80% organometallic reagent (**12c**, 1.2 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) was added, followed by a solution of cyclohexenone (**13c**, 216 mg, 2.25 mmol) and chlorotrimethylsilane (611 mg, 5.63 mmol) and 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14c** as a yellowish oil (122 mg, 51%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.00 (m, 2 H), 6.44 (m, 2 H), 2.30 - 2.16 (m, 3 H), 1.83 - 1.73 (m, 2 H), 1.49 - 1.43 (m, 1 H), 1.30 - 1.26 (m, 1 H), 1.20 - 1.11 (m, 1 H), 1.05 - 0.97 (m, 1 H).

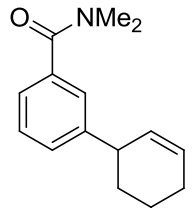
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 207.1, 149.3, 132.3, 127.4, 118.8, 111.1, 47.9, 44.2, 40.8, 32.0, 25.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3045, 2940, 2866, 2225, 1707, 1606, 1505, 1447, 1416, 1345, 1314, 1249, 1224, 1177, 1100, 1071, 1056, 1025, 997, 972, 902, 832.

MS (EI, 70 eV): *m/z* (%) = 200 (15), 199 (62), 157 (12), 156 (100), 143 (43), 142 (30), 130 (16), 129 (48), 128 (19), 116 (23), 115 (11), 102 (13), 84 (30), 74 (16), 59 (27), 55 (10), 45 (16), 44 (20), 43 (10), 42 (13), 41 (18).

HRMS (EI) for **$C_{13}H_{13}NO$** (199.0997): 199.0991 (M^+).

Synthesis of *N*,*N*-dimethyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxamide (14d)



The aluminum reagent **12d** was prepared according to **TP1** from 3-bromo-*N*,*N*-dimethylbenzamide (**10d,** 342 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 75% organometallic reagent (**12d**, 1.13 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) and 3-bromocyclohexene (**13d**, 290 mg, 1.8 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14d** as a yellowish oil (188 mg, 73%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.35 - 7.21 (m, 4 H), 5.94 - 5.86 (m, 1 H), 5.69 (dq, *J* = 10.2, 2.2 Hz, 1 H), 3.46 - 3.38 (m, 1 H), 3.10 (s, 3 H), 2.97 (s, 3 H), 2.11 - 1.97 (m, 3 H), 1.78 - 1.69 (m, 1 H), 1.67 - 1.50 (m, 2 H).

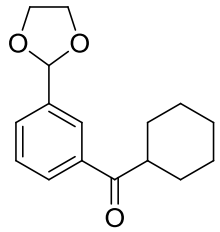
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 172.1, 147.0, 136.4, 129.7, 129.1, 128.9, 128.3, 126.5, 124.8, 41.8, 39.7, 35.4, 32.6, 25.1, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031, 2934, 2860, 2837, 2244, 1624, 1603, 1582, 1503, 1447, 1408, 1398, 1270, 1261, 1174, 1081, 1059, 921, 900, 802, 741, 712, 671.

MS (EI, 70 eV): *m/z* (%) = 229 (45), 228 (24), 186 (14), 185 (100), 129 (14), 128 (16), 115 (15).

HRMS (EI) for **$C_{15}H_{19}NO$** (229.1467): 229.1451 (M^+).

Synthesis of (3-(1,3-dioxolan-2-yl)phenyl)(cyclohexyl)methanone (14e)



The aluminum reagent **3e** was prepared according to **TP1** from 2-(3-bromophenyl)-1,3-dioxolane (**10e,** 344 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 71% organometallic reagent (**12e**, 1.07 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and cyclohexanecarbonyl chloride (**13e**, 242 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14e** as a yellowish oil (216 mg, 78%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.32 (t, *J* = 1.8 Hz, 1 H), 7.84 (ddd, *J* = 7.9, 1.5, 1.4 Hz, 1 H), 7.60 (ddd, *J* = 7.6, 1.4, 1.2 Hz, 1 H), 7.13 (t, *J* = 7.7 Hz, 1 H), 3.63 - 3.55 (m, 2 H) 5.69 (s, 1 H), 3.50 - 3.42 (m, 2 H), 3.03 - 2.96 (m, 1 H), 1.79 - 1.74 (m, 2 H), 1.63 - 1.57 (m, 2 H), 1.54 - 1.46 (m, 3 H), 1.15 - 1.05 (m, 3 H).

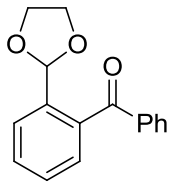
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 202.3, 139.7, 137.1, 130.9, 129.1, 128.8, 126.9, 103.5, 65.2, 45.6, 29.7, 26.3, 26.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 2853, 1721, 1677, 1604, 1588, 1448, 1373, 1289, 1254, 1241, 1189, 1162, 1132, 1075, 1027, 974, 942, 911, 805, 779, 715, 694, 666.

MS (EI, 70 eV): *m/z* (%) = 260 (3), 259 (4), 193 (10), 187 (15), 178 (13), 177 (100), 73 (34).

HRMS (EI) for $\mathbf{C_{16}H_{20}O_3}$ (260.1412): 260.1377 (M^+).

Synthesis of (2-(1,3-dioxolan-2-yl)phenyl)(phenyl)methanone (14f)



The aluminum reagent **12f** was prepared according to **TP1** from 2-(2-bromophenyl)-1,3-dioxolane (**10f,** 344 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 83% organometallic reagent (**12f**, 1.25 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and benzoyl chloride (**13f**, 232 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14f** as a yellowish oil (231 mg, 73%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.91 - 7.87 (m, 2 H), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.15 - 7.06 (m, 3 H), 7.04 - 6.96 (m, 3 H), 6.25 (s, 1 H), 3.41 - 3.36 (m, 2 H), 3.23 - 3.23 (m, 1 H), 3.25 - 3.21 (m, 2 H).

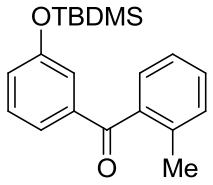
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 196.8, 139.5, 138.5, 137.9, 132.8, 130.4, 129.7, 128.5, 128.3, 128.2, 127.1, 101.6, 65.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 3026, 2960, 2888, 2766, 1663, 1596, 1579, 1473, 1448, 1394, 1313, 1267, 1209, 1151, 1112, 1071, 1025, 970, 926, 848, 804, 764, 758, 700, 687.

MS (EI, 70 eV): *m/z* (%) = 253 (12), 210 (23), 209 (83), 194 (19), 182 (19), 182 (57), 181 (52), 165 (33), 153 (16), 152 (26), 149 (52), 148 (16), 133 (15), 105 (100), 104 (12), 78 (13), 77 (54), 76 (12), 73 (17), 45 (10).

HRMS (EI) for $\mathbf{C_{16}H_{14}O_3}$ (254.0943): 254.0924 (M^+).

Synthesis of (3-((*tert*-butyldimethylsilyl)oxy)phenyl)(*o*-tolyl)methanone (14g)



The aluminum reagent **12g** was prepared according to **TP1** from (3-bromophenoxy)(*tert*-butyl)dimethylsilane (**10g,** 431 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78□ °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 81% organometallic reagent (**12g**, 1.22 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and 2-methylbenzoyl chloride (**13g**, 255 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14g** as a colorless oil (298 mg, 75%).

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.65 - 7.63 (m, 1 H), 7.38 (dt, *J* = 7.2, 1.5 Hz, 1 H), 7.18 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.10 - 7.04 (m, 1 H), 6.99 - 6.89 (m, 4 H), 2.25 (s, 3 H), 0.92 (s, 9 H), 0.07 (s, 6 H).

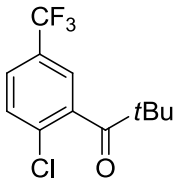
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 197.2, 156.4, 140.1, 139.4, 137.1, 131.2, 130.2, 129.9, 128.8, 125.3, 125.1, 123.9, 121.2, 25.8, 20.0, 18.4, -4.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3023, 2955, 2929, 2891, 2857, 2388, 2279, 2269, 1664, 1595, 1578, 1479, 1472, 1433, 1362, 1330, 1292, 1276, 1253, 1227, 1139, 1106, 1003, 980, 904, 892, 837, 827, 779, 740, 684.

MS (EI, 70 eV): *m/z* (%) = 326 (37), 270 (31), 269 (100), 119 (56), 91 (23).

HRMS (EI) for **$C_{20}H_{26}O_2Si$** (326.1702): 326.1687 (M^+).

Synthesis of 1-(2-chloro-5-(trifluoromethyl)phenyl)-2,2-dimethylpropan-1-one (14h)



The aluminum reagent **12h** was prepared according to **TP1** from 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**10h,** 389 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 64% organometallic reagent (**12h**, 0.96 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and pivaloyl chloride (**13h**, 199 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14h** as a colorless oil (170 mg, 67%).

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.24 (d, *J* = 2.2 Hz, 1 H), 6.95 - 6.90 (m, 1 H), 6.83 - 6.78 (m, 1 H), 1.02 - 0.99 (m, 9 H).

^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 208.0, 141.6, 134.0 (q, *J* = 1 Hz), 130.7, 128.8 (q, *J* = 32 Hz), 126.6 (q, *J* = 4 Hz), 124.1 (q, *J* = 273 Hz), 123.4 (q, *J* = 4 Hz), 45.1, 26.6.

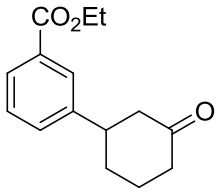
^{19}F-NMR (211 MHz, C_6D_6): δ / ppm = -62.49.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971, 2907, 2871, 2365, 2330, 2278, 2269, 1704, 1609, 1581, 1479, 1401, 1330, 1286, 1266, 1184, 1173, 1134, 1084, 978, 901, 832, 810, 714.

MS (EI, 70 eV): *m/z* (%) = 264 (1), 209 (22), 207 (43), 57 (100), 41 (32).

HRMS (EI) for **$C_{12}H_{12}ClF_3O$** (264.0529): 264.0532 (M^+).

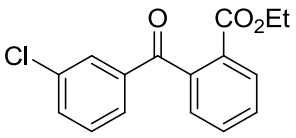
Synthesis of ethyl 3-(3-oxocyclohexyl)benzoate (14i)



The aluminum reagent **12i** was prepared according to **TP1** from ethyl 3-iodobenzoate (**10i,** 414 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 65% organometallic reagent (**12i**, 0.98 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) was added, followed by a solution of cyclohexenone (**13c**, 216 mg, 2.25 mmol) and chlorotrimethylsilane (611 mg, 5.63 mmol) and 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14i** as a yellowish oil (175 mg, 73%).

The analytical data matches the one reported in the literature.[161]

Synthesis of ethyl 2-(3-chlorobenzoyl)benzoate (14j)



The aluminum reagent **12j** was prepared according to **TP1** from ethyl 2-iodobenzoate (**10j,** 414 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 72% organometallic reagent (**3j**, 1.08 mmol). The reaction mixture was cooled to -40 °C, then

[161] G. Varchi, A. Ricci, G. Cahiez, P. Knochel, *Tetrahedron* **2000**, *56*, 2727.

CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and 3-chlorobenzoyl chloride (**13j**, 289 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14j** as a colorless oil (253 mg, 81%).

^{1}H-NMR (300 MHz, C_6D_6): δ / ppm = 7.98 (t, *J* = 1.8 Hz, 1 H), 7.94 - 7.89 (m, 1 H), 7.49 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.09 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1 H), 7.05 - 7.00 (m, 3 H), 6.75 (t, *J* = 7.9 Hz, 1 H), 3.78 (q, *J* = 7.1 Hz, 2 H), 0.72 (t, *J* = 7.2 Hz, 3 H).

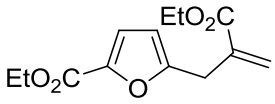
^{13}C-NMR (75 MHz, C_6D_6): δ / ppm = 194.7, 165.6, 141.6, 139.8, 135.1, 132.7, 132.3, 130.3, 130.1, 130.1, 129.7, 129.3, 127.9, 127.7, 61.5, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2982, 2936, 2903, 2872, 1713, 1675, 1596, 1571, 1466, 1445, 1424, 1366, 1275, 1253, 1153, 1126, 1079, 1041, 1014, 957, 944, 896, 854, 771, 763, 735, 709, 685, 673.

MS (EI, 70 eV): *m/z* (%) = 288 (15), 245 (11), 243 (34), 177 (53), 152 (19), 149 (100), 139 (22), 111 (14).

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0552 (M^+).

Synthesis of ethyl 5-(2-(ethoxycarbonyl)allyl)furan-2-carboxylate (18a)

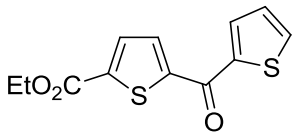


The aluminum reagent **16a** was prepared according to **TP1** from ethyl 5-bromofuran-2-carboxylate (**15a,** 329 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78□ °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 82% organometallic reagent (**16a**, 1.23 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) and ethyl 2-(bromomethyl)acrylate (**17a**, 347 mg, 1.8 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **18a** as a yellowish oil (258 mg, 83%).

The analytical data matches the reported one in the literature.[105c]

Synthesis of ethyl 5-(thiophene-2-carbonyl)thiophene-2-carboxylate (18b)



The aluminum reagent **16b** was prepared according to **TP1** from ethyl 5-bromothiophene-2-carboxylate (**15b,** 353 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 72% organometallic reagent (**16b**, 1.08 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and thiophene-2-carbonyl chloride (**17b**, 242 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **18b** as a yellow solid (196 mg, 68%).

m.p. (°C): 73-75.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.54 (d, *J* = 3.9 Hz, 1 H), 7.39 (dd, *J* = 3.8, 1.1 Hz, 1 H), 7.26 (d, *J* = 4.3 Hz, 1 H), 6.91 - 6.86 (m, 1 H), 6.54 - 6.51 (m, 1 H), 4.00 (q, *J* = 7.1 Hz, 2 H), 0.94 (t, *J* = 7.1 Hz, 3 H).

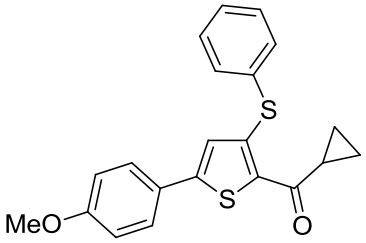
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 178.1, 161.4, 147.5, 143.1, 139.9, 134.0, 133.5, 133.1, 132.4, 128.0, 61.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2979, 2945, 1712, 1603, 1584, 1524, 1520, 1412, 1346, 1288, 1247, 1230, 1212, 1172, 1101, 1092, 1084, 1052, 1039, 1003, 865, 834, 790, 751, 743, 726, 703.

MS (EI, 70 eV): *m/z* (%) = 266 (41), 238 (13), 221 (49), 111 (100), 97 (11), 85 (18), 83 (11), 83 (10), 71 (28), 69 (14), 57 (46), 56 (10), 55 (18), 43 (40), 42 (10), 41 (18).

HRMS (EI) for **$C_{12}H_{10}O_3S_2$** (266.0071): 266.0079 (M^+).

Synthesis of cyclopropyl(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)methanone (18c)



The aluminum reagent **16c** was prepared according to **TP1** from 2-bromo-5-(4-methoxyphenyl)-3-(phenylthio)thiophene (**15c,** 566 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 93% organometallic reagent (**16c**, 1.40 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and cyclopropanecarbonyl chloride (**17c**, 172 mg, 1.65 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 (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **18c** as a yellow solid (435 mg, 85%).

m.p. (°C): 174-181.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.50 - 7.47 (m, 2 H), 7.18 - 7.14 (m, 3 H), 7.03 - 6.95 (m, 3 H), 6.69 - 6.62 (m, 2 H), 3.26 (s, 3 H), 2.28 - 2.22 (m, 1 H), 1.36 - 1.30 (m, 2 H), 0.65 - 0.60 (m, 2 H).

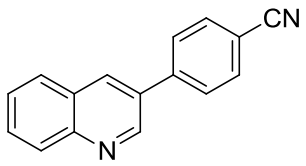
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 194.3, 160.0, 147.2, 142.3, 138.4, 135.0, 133.9, 129.9, 129.3, 127.1, 126.6, 123.2, 114.7, 54.9, 19.2, 11.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3087, 3070, 3017, 3005, 2969, 2935, 2841, 1627, 1606, 1538, 1501, 1438, 1427, 1411, 1293, 1254, 1217, 1176, 1121, 1111, 1084, 1031, 1019, 998, 993, 951, 897, 833, 821, 808, 751, 708, 704, 695, 673.

MS (EI, 70 eV): m/z (%) = 368 (13), 367 (25), 366 (100), 325 (23), 309 (14), 221 (11), 151 (10), 69 (14), 41 (13).

HRMS (EI) for **$C_{21}H_{18}O_2S_2$** (366.0748): 366.0747 (M^+).

Synthesis of 4-(quinolin-3-yl)benzonitrile (18d)

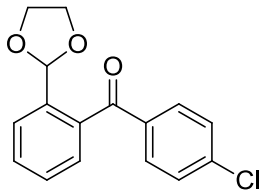


The aluminum reagent **16d** was prepared according to **TP1** from 3-bromoquinoline (**15d,** 312 mg, 1.5 mmol), *i*-Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 63% organometallic reagent (**16d**, 0.95 mmol). A solution of 4-iodobenzonitrile (**17d**, 344 mg, 1.5 mmol), Pd_2dba_3 (34 mg, 0.0375 mmol), P(*t*-Bu)$_3$ (1 M in toluene, 0.15 mL, 0.15 mmol) in NMP (2 mL) was added. The resulting mixture was stirred at 50 °C for 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **18d** as a yellow solid (159 mg, 73%).

The analytical data matches the reported one in the literature.[162]

[162] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205.

Synthesis of (2-(1,3-dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (19)



The aluminum reagent **12f** was prepared according to an upscaled **TP1** from 2-(2-bromophenyl)-1,3-dioxolane (**10f,** 2.29 g, 10 mmol), *i*-Bu_2AlCl (1 M in THF, 11 mL, 11 mmol) and *n*-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol). The reaction was carried out in THF (10 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 84 % organometallic reagent (**12f**, 8.4 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2 mL, 2 mmol) and 4-chlorobenzoyl chloride (**13f**, 1.93 g, 11 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 (35 mL), extracted with Et_2O (3 x 100 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **19** as a yellowish solid (1.82 g, 75%).

m.p. (°C): 86.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.71 (d, *J* = 8.4 Hz, 1 H), 7.62 - 7.58 (m, 2 H), 7.16 - 7.12 (m, 1 H), 7.02 - 6.96 (m, 4 H), 6.15 (s, 1 H), 3.39 - 3.33 (m, 2 H), 3.30 - 3.23 (m, 2 H).

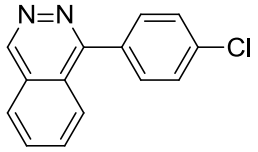
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 195.5, 139.2, 138.9, 137.8, 136.7, 131.7, 129.9, 128.8, 128.4, 128.1, 127.2, 101.6, 65.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 3062, 3036, 2989, 2961, 2895, 2859, 2758, 1671, 1662, 1584, 1569, 1482, 1470, 1446, 1396, 1305, 1287, 1267, 1211, 1177, 1150, 1112, 1087, 1075, 1064, 1011, 972, 954, 940, 927, 852, 781, 773, 758, 744, 671.

MS (EI, 70 eV): *m/z* (%) = 289 (22), 288 (14), 287 (61), 246 (14), 245 (39), 244 (38), 243 (100), 209 (20), 181 (50), 165 (11), 153 (11), 152 (42), 149 (40), 148 (13), 139 (60), 111 (27), 105 (16), 104 (11), 77 (12), 76 (15), 75 (12), 73 (10).

HRMS (EI) for **$C_{16}H_{13}ClO_3$** (288.0553): 288.0522 (M^+).

Synthesis of 1-(4-chlorophenyl)phthalazine (20)



(2-(1,3-Dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**19**, 577 mg, 2 mmol) was dissolved in MeOH (20 mL). Hydrazine hydrate (801 mg, 16 mmol) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) were added and the resulting mixture was stirred under reflux. After stirring for 14 h, the reaction mixture was concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **20** as a greenish solid (361 mg, 75%).

m.p. (°C): 156-157.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.54 (s, 1 H), 8.06 - 8.01 (m, 2 H), 7.95 - 7.86 (m, 2 H), 7.71 - 7.67 (m, 2 H), 7.56 - 7.50 (m, 2 H).

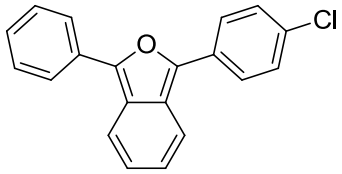
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.0, 150.7, 135.9, 134.5, 133.1, 132.6, 131.4, 128.9, 127.1, 127.0, 125.9, 125.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 3059, 3032, 2976, 1615, 1591, 1540, 1485, 1408, 1379, 1352, 1292, 1267, 1225, 1180, 1132, 1105, 1085, 1015, 993, 952, 945, 880, 834, 812, 797, 762, 733, 716, 667, 662.

MS (EI, 70 eV): *m/z* (%) = 242 (18), 241 (39), 240 (51), 239 (100), 206 (12), 205 (74), 177 (16), 176 (21), 88 (13), 75 (13).

HRMS (EI) for **$C_{14}H_9ClN_2$** (240.0454): 240.0418 (M^+).

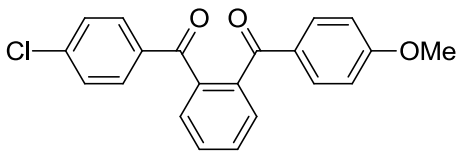
Synthesis of 1-(4-chlorophenyl)-3-phenylisobenzofuran (22)



(2-(1,3-Dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**19**, 577 mg, 2 mmol) was dissolved in acetone (10 mL) and *p*-toluenesulfonic acid monohydrate (38 mg,0.2 mmol) was added at room temperature. After stirring for 1 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution (15 mL), extracted with Et_2O (3 x 50 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo* and the crude aldehyde **21** was obtained as a colorless oil (465 mg, 1.9 mmol). A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer, was charged with **21** (465 mg, 1.9 mmol) in anhydrous THF (15 mL). A solution of anisyl Grignard (1.1 M in THF, 1.73 mL, 1.9 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Then, an aqueous solution of HCl (4 M, 10 mL) was slowly added at 0 °C. The mixture (still under argon) was warmed to room temperature and stirred for 1 h, then extracted with ether (3 x 50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (dichloromethane:ethyl acetate = 1:1) to give **22** as a yellow solid (527 mg, 91%).

The analytical data matches the reported one in the literature.[110]

Synthesis of (2-(4-chlorobenzoyl)phenyl)(4-methoxyphenyl)methanone (23)



(2-(1,3-Dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**19**, 577 mg, 2 mmol) was dissolved in acetone (10 mL) and *p*-toluenesulfonic acid monohydrate (38 mg,0.2 mmol) was added at room temperature. After stirring for 1 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution (15 mL), extracted with Et_2O (3 x 50 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo* and the crude aldehyde **21** was obtained as a colorless oil

(465 mg, 1.9 mmol). A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer, was charged with **21** (465 mg, 1.9 mmol) in anhydrous THF (15 mL). A solution of PhMgCl (1.7 M in THF, 1.1 mL, 1.9 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Then, an aqueous solution of HCl (4 M, 10 mL) was slowly added at 0 °C. The mixture (still under argon) was warmed to room temperature and stirred for 1 h, then extracted with ether (3 x 50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$, brine and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **23** as a yellowish solid (447 mg, 67%).

m.p. (°C): 138-140.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.66 (m, 4 H), 7.61 - 7.55 (m, 4 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 3.82 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 195.6, 195.1, 163.7, 140.2, 139.6, 139.5, 135.7, 132.4, 131.2, 130.5, 130.3, 130.0, 129.6, 129.4, 128.7, 113.7, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2961, 2926, 2836, 1770, 1742, 1665, 1655, 1596, 1584, 1567, 1509, 1459, 1438, 1397, 1313, 1282, 1254, 1173, 1150, 1088, 1033, 1013, 936, 923, 839, 831, 787, 782, 748, 734, 684, 679.

MS (EI, 70 eV): *m/z* (%) = 352 (28), 351 (18), 350 (71), 243 (21), 240 (11), 239 (64), 211 (10), 152 (14), 139 (13), 136 (10), 135 (100), 111 (12), 92 (10), 77 (17).

HRMS (EI) for **$C_{21}H_{15}ClO_3$** (350.0710): 350.0707 (M^+).

4 TMP-MAGNESIUM AND TMP-ZINC BASES FOR THE REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD

4.1 TYPICAL PROCEDURES

Typical Procedure A for the magnesiation of cinnoline (TP 1):

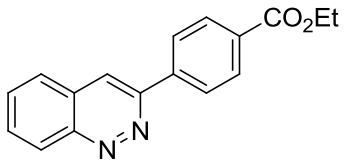
A dry, argon-flushed 25 mL Schlenk-flask was charged with cinnoline **24** (130 mg, 1.0 mmol) and dry THF (4 mL). The solution was cooled to 0 °C and dry $BF_3 \cdot Et_2O$ (0.14 mL, 1.1 mmol) was added dropwise. The reaction mixture was stirred for 15 min, then cooled to -78 °C, and $TMP_2Mg \cdot 2LiCl$ (1.1 mmol) was added dropwise. The completion of the metalation was checked by using GC analysis of reaction aliquots quenched with a solution of I_2 in THF (reaction was >95% conversion in 5 min).

Typical Procedure B for the zincation of cinnoline (TP 2):

A dry, argon-flushed 25 mL Schlenk flask was charged with cinnoline **24** (130 mg, 1.0 mmol) and dry THF (4 mL). A 1.0 M solution of $ZnCl_2$ (1.0 mL, 1.0 mmol) in THF was added at room temperature, followed by the immediate addition of TMPMgCl·LiCl (2.0 mmol). The reaction mixture was then heated at 50 °C. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF (reaction was complete in 3 h).

4.2 REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD IN POSITION 3

Synthesis of ethyl 4-(cinnolin-3-yl)benzoate (26a)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. A solution of $Pd(PPh_3)_4$ (45 mg, 0.04 mmol), and ethyl 4-bromobenzoate (141 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred at 50 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 7:3) to give **26a** as a yellow solid (127 mg, 74%).

m.p. (°C): 178.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.50 (m, 1 H), 8.36 - 8.32 (m, 2 H), 8.21 - 8.18 (m, 2 H), 7.35 (d, *J* = 0.78 Hz, 1 H), 7.21 - 7.18 (m, 2 H), 7.12 - 7.08 (m, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 1.08 - 1.04 (t, *J* = 7.2 Hz, 3 H).

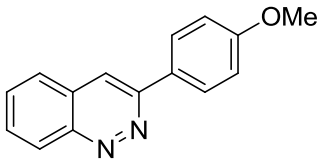
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.1, 152.3, 150.5, 141.6, 131.8, 130.8, 130.5, 130.3, 130.3, 127.6, 127.1, 126.1, 118.7, 61.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2985, 2947, 2899, 2229, 1719, 1712, 1620, 1610, 1584, 1478, 1416, 1396, 1366, 1354, 1293, 1269, 1241, 1187, 1179, 1123, 1114, 1105, 1020, 963, 911, 861, 851, 793, 772, 752, 699, 675.

MS (EI, 70 eV): *m/z* (%) = 279 (22), 278 (100), 251 (13), 250 (68), 233 (18), 223 (10), 222 (58), 205 (15), 178 (12), 177 (40), 176 (45), 151 (19), 150 (12), 88 (29), 44 (10).

HRMS (EI) for **$C_{17}H_{14}N_2O_2$** (278.1055): 278.1044 (M^+).

Synthesis of 3-(4-methoxyphenyl)cinnoline (26b)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. A solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and 4-iodoanisole (144 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **26b** as a brown solid (109 mg, 75%).

m.p. (°C): 107.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (d, *J* = 8.3 Hz, 1 H), 8.25 - 8.18 (m, 2 H), 8.09 (s, 1 H), 7.86 - 7.69 (m, 3 H), 7.12 - 7.05 (m, 2 H), 3.90 (s, 3 H).

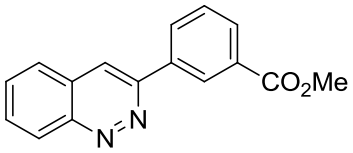
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.0, 153.4, 149.7, 131.3, 130.0 (2), 129.6, 128.7, 127.0, 126.8, 117.8, 114.6, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2836, 1603, 1510, 1438, 1257, 1243, 1172, 1119, 1034, 1019, 896, 830, 745, 752, 675.

MS (EI, 70 eV): *m/z* (%) = 237 (18), 236 (100), 209 (13), 208 (79), 193 (16), 166 (12), 165 (79), 164 (12), 163 (12), 104 (13).

HRMS (EI) for **$C_{15}H_{12}N_2O$** (236.0950): 236.0936 (M^+).

Synthesis of methyl 3-(cinnolin-3-yl)benzoate (26c)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. A solution of $Pd(PPh_3)_4$ (45 mg, 0.04 mmol), and methyl 3-bromobenzoate (132 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred at 50 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 7:3) to give **26c** as a yellow solid (110 mg, 69%).

m.p. (°C): 105-107.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.84 - 8.79 (m, 1 H), 8.58 - 8.51 (m, 2 H), 8.22 (s, 1 H), 8.14 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.85 - 7.71 (m, 2 H), 7.62 (t, *J* = 7.9 Hz, 1 H), 3.96 (s, 3 H).

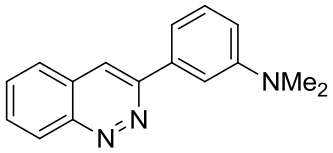
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.9, 152.5, 150.1, 137.3, 131.8, 131.6, 131.1, 130.7, 130.5, 129.9, 129.3, 128.2, 127.1, 126.5, 119.2, 52.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3032, 2945, 2924, 2846, 1720, 1605, 1582, 1446, 1429, 1335, 1288, 1263, 1214, 1179, 1136, 1106, 1087, 1050, 967, 912, 829, 804, 797, 778, 751, 738, 692.

MS (EI, 70 eV): *m/z* (%) = 265 (38), 264 (100), 237 (13), 236 (76), 233 (15), 207 (10), 206 (63), 205 (16), 178 (16), 177 (65), 176 (80), 165 (15), 151 (29), 150 (14), 127 (12), 102 (17), 89 (15), 88 (58), 75 (13), 69 (13), 57 (19), 55 (18), 43 (16), 43 (16), 43 (42), 41 (16).

HRMS (EI) for **$C_{16}H_{12}N_2O_2$** (264.0899): 264.0886 (M^+).

Synthesis of 3-(cinnolin-3-yl)-*N*,*N*-dimethylaniline (26d)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. A solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and 3-iodo-*N*,*N*-dimethylaniline (152 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 6:4) to give **26d** as a brown solid (112 mg, 73%).

m.p. (°C): 108-110.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 - 8.50 (m, 1 H), 8.12 (s, 1 H), 7.83 (d, *J* = 8.9 Hz, 1 H), 7.80 - 7.66 (m, 3 H), 7.48 - 7.43 (m, 1 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 6.86 (m, 1 H), 3.05 (s, 6 H).

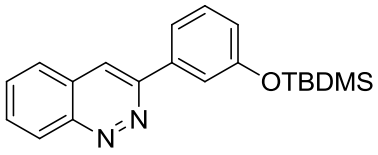
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.1, 151.2, 149.9, 137.7, 131.1, 130.1, 129.8, 129.7, 127.1, 126.6, 118.9, 115.5, 113.7, 111.6, 40.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2916, 2851, 2804, 1601, 1586, 1566, 1500, 1434, 1363, 1348, 1229, 1133, 1097, 1062, 991, 952, 913, 871, 835, 801, 794, 767, 699, 688, 684.

MS (EI, 70 eV): *m/z* (%) = 249 (100), 248 (17), 235 (22), 234 (68), 206 (23), 205 (26), 178 (39), 177 (17), 177(18), 176 (30), 165 (24), 110 (27), 102 (16), 97 (45), 77 (18), 71 (17), 69 (25), 57 (60), 56 (22), 55 (22), 44 (75), 43 (31), 43 (54), 42 (51).

HRMS (EI) for **$C_{16}H_{15}N_3$** (249.1266): 249.1256 (M^+).

Synthesis of 3-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)cinnoline (26e)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (0.77 mL, 0.77 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. A solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and *tert*-butyl(3-iodophenoxy)dimethylsilane (206 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **26e** as a yellow solid (131 mg, 63%).

m.p. (°C): 87-88.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (d, *J* = 8.6 Hz, 1 H), 8.13 (s, 1 H), 7.87 (d, *J* = 9.1 Hz, 1 H), 7.84 - 7.70 (m, 4 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 6.97 (dt, *J* = 8.6, 1.5 Hz, 1 H), 1.09 - 0.94 (m, 9 H), 0.35 - 0.19 (m, 6 H).

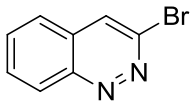
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.5, 153.4, 150.0, 138.5, 131.4, 130.4, 130.1, 129.9, 127.1, 126.7, 121.3, 120.3, 119.2, 119.0, 25.9, 18.4, -4.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3039, 2955, 2927, 2892, 2855, 1621, 1601, 1580, 1487, 1481, 1471, 1462, 1449, 1428, 1402, 1389, 1360, 1356, 1329, 1313, 1287, 1253, 1246, 1227, 1183, 1178, 1166, 1131, 1099, 1010, 1006, 999, 979, 960, 943, 895, 869, 853, 836, 825, 810, 797, 776, 741, 696, 683, 662.

MS (EI, 70 eV): *m/z* (%) = 336 (13), 281 (9), 280 (31), 279 (100), 265 (5), 176 (5), 125 (6).

HRMS (EI) for **$C_{20}H_{24}N_2OSi$** (336.1658): 336.1650 (M^+).

Synthesis of 3-bromocinnoline (26f)



According to **TP 1**, the metalation of cinnoline (**24**; 130 mg, 1.0 mmol) was completed within 5 min at -78 °C. The metalated species was then cannulated into a solution of dibromotetrachloroethane (651 mg, 2 mmol) in dry THF (2 mL), pre-cooled to -78 °C. The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **26f** as an off-white solid (116 mg, 55%).

m.p. (°C): 92.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.48 (d, *J* = 8.6 Hz, 1 H), 8.07 (s, 1 H), 7.88 - 7.81 (m, 1 H), 7.79 - 7.72 (m, 2 H).

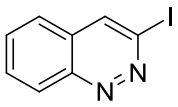
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.0, 141.2, 132.3, 131.2, 129.9, 127.8, 126.3, 125.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3033, 1568, 1554, 1529, 1471, 1418, 1295, 1178, 1137, 1100, 1045, 964, 926, 916, 854, 788, 749.

MS (EI, 70 eV): *m/z* (%) = 210 (39), 208 (38), 182 (20), 180 (19), 101 (49), 84 (16), 75 (17), 70 (13), 61 (18), 45 (15), 44 (20), 43 (100).

HRMS (EI) for **$C_8H_5BrN_2$** (207.9636): 207.9624 (M^+).

Synthesis of 3-iodocinnoline (26g)



According to **TP1**, the metalation of cinnoline (**24**; 130 mg, 1.0 mmol) was completed within 5 min at -78 °C. The metalated species was then cannulated into a solution of I_2 (518 mg, 2 mmol) in dry THF (2 mL), pre-cooled to -78 °C. The reaction mixture was allowed to warm to

25 °C overnight. Then, the reaction mixture was quenched with aq. $Na_2S_2O_3$ solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **26g** as an off-white solid (132 mg, 51%).

m.p. (°C): 109.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.47 (dd, *J* = 8.5, 1.0 Hz, 1 H), 8.30 (d, *J* = 0.9 Hz, 1 H), 7.89 - 7.83 (m, 1 H), 7.79 - 7.68 (m, 2 H).

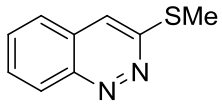
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.7, 132.6, 132.1, 131.3, 129.9, 127.5, 125.5, 116.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 1563, 1539, 1523, 1468, 1413, 1292, 1262, 1174, 1138, 1097, 1026, 959, 906, 848, 788, 748.

MS (EI, 70 eV): *m/z* (%) = 257 (14), 256 (100), 228 (23), 102 (13), 101 (91), 76 (14), 75 (37), 74 (12), 50 (11), 44 (13).

HRMS (EI) for **$C_8H_5IN_2$** (255.9497): 255.9479 (M^+).

Synthesis of 3-(methylthio)cinnoline (26h)



According to **TP1**, the metalation of cinnoline (**24**; 130 mg, 1.0 mmol) was completed within 5 min at -78 °C. The metalated species was then cannulated into a solution of $MeSO_2SMe$ (379 mg, 3 mmol) in dry THF (10 mL), pre-cooled to -78 °C. The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **26h** as brown solid (90 mg, 51%).

m.p. (°C): 81-83.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.40 - 8.33 (m, 1 H), 7.70 - 7.59 (m, 4 H), 2.78 (s, 3 H).

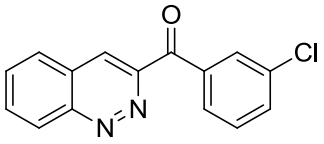
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.9, 148.9, 131.6, 129.8, 129.5, 126.3, 125.6, 119.2, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3010, 2925, 1567, 1548, 1421, 1302, 1178, 1144, 1097, 1068, 963, 918, 870, 789, 747.

MS (EI, 70 eV): *m/z* (%) = 177 (12), 176 (100), 175 (12), 148 (18), 147 (26), 89 (47).

HRMS (EI) for **$C_9H_8N_2S$** (176.0408): 176.0404 (M^+).

Synthesis of (3-chlorophenyl)(cinnolin-3-yl)methanone (26i)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (1.92 mL, 1.92 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. The reaction mixture was allowed to warm to -40 °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and 3-chlorobenzoyl chloride (135 mg, 0.77 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 (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **26i** as a yellow solid (110 mg, 53%).

m.p. (°C): 126-127.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.68 (t, *J* = 3.9 Hz, 2 H), 8.26 (t, *J* = 1.9 Hz, 1 H), 8.18 (d, *J* = 7.7 Hz, 1 H), 8.08 - 7.99 (m, 2 H), 7.89 (t, *J* = 7.6 Hz, 1 H), 7.62 (m, 1 H), 7.48 (t, *J* = 7.9 Hz, 1 H).

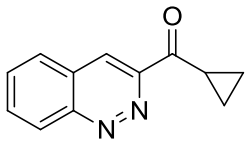
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 191.2, 151.6, 151.2, 137.9, 134.7, 133.3, 133.1, 132.2, 131.4, 130.2, 129.9, 129.7, 128.2, 126.1, 125.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2924, 1664, 1615, 1568, 1487, 1415, 1394, 1372, 1319, 1246, 1219, 1186, 1080, 954, 941, 891, 859, 805, 784, 751, 742, 737, 681, 669.

MS (EI, 70 eV): *m/z* (%) = 270 (31), 269 (32), 268 (95), 267 (59), 241 (12), 240 (24), 239 (23), 233 (36), 212 (12), 206 (17), 205 (100), 178 (11), 177 (19), 141 (14), 139 (43), 116 (13), 110 (60), 75 (33).

HRMS (EI) for **$C_{15}H_9ClN_2O$** (268.0403): 268.0400 (M^+).

Synthesis of cinnolin-3-yl(cyclopropyl)methanone (26j)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (1.92 mL, 1.92 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. The reaction mixture was allowed to warm to -40 °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and cyclopropanecarbonyl chloride (80 mg, 0.77 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 (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 9:1) to give **26j** as a yellow solid (89 mg, 58%).

m.p. (°C): 109-110.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.65 (d, *J* = 8.0 Hz, 1 H), 8.56 (s, 1 H), 8.04 - 7.94 (m, 2 H), 7.83 (t, *J* = 7.6 Hz, 1 H), 4.00 - 3.91 (m, 1 H), 1.44 - 1.37 (m, 2 H), 1.27 - 1.22 (m, 2 H).

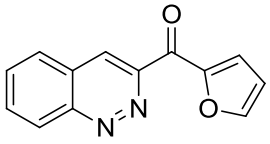
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 200.6, 151.6, 150.3, 132.7, 131.9, 130.0, 128.6, 126.0, 122.3, 17.1, 13.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3052, 3009, 2924, 2853, 1677, 1617, 1555, 1538, 1488, 1387, 1362, 1308, 1238, 1182, 1169, 1129, 1098, 1036, 964, 942, 894, 874, 796, 776, 756, 746, 717.

MS (EI, 70 eV): *m/z* (%) = 200 (11), 199 (49), 198 (38), 197 (73), 170 (30), 169 (100), 131 (38), 130 (17), 115 (17), 103 (11), 102 (12), 101 (25), 75 (16), 71 (10), 69 (10), 69 (49), 57 (15), 42 (16), 40 (49).

HRMS (EI) for **$C_{12}H_{10}N_2O$** (198.0793): 198.0810 (M^+).

Synthesis of cinnolin-3-yl(furan-2-yl)methanone (26k)



According to **TP 1**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (1.92 mL, 1.92 mmol) was added dropwise to the reaction mixture and it was stirred for 10 min at -78 °C. The reaction mixture was allowed to warm to -40 °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and furan-2-carbonyl chloride (101 mg, 0.77 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 (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **26k** as a yellow solid (92 mg, 53%).

m.p. (°C): 174-176.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.77 (s, 1 H), 8.65 (d, *J* = 8.6 Hz, 1 H), 8.39 (d, *J* = 3.6 Hz, 1 H), 8.07 - 7.98 (m, 2 H), 7.91 - 7.82 (m, 2 H), 6.71 (dd, *J* = 4.0 Hz, 2.1 Hz, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 177.6, 151.4, 151.3, 151.0, 148.5, 132.9, 132.0, 130.0, 128.3, 126.1, 125.8, 124.7, 113.0.

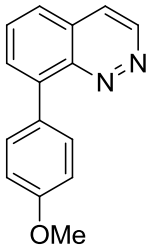
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3159, 3131, 3111, 3057, 1643, 1633, 1557, 1485, 1463, 1389, 1324, 1262, 1163, 1117, 1106, 1098, 1081, 1024, 1013, 992, 950, 935, 897, 817, 800, 782, 773, 765, 750, 657.

MS (EI, 70 eV): *m/z* (%) = 225 (10), 224 (47), 197 (15), 196 (100), 169 (12), 168 (80), 141 (13), 140 (17), 139 (43), 114 (10), 101 (11), 75 (12).

HRMS (EI) for **$C_{13}H_8N_2O_2$** (224.0586): 224.0581 (M^+).

4.3 REGIOSELECTIVE METALATION OF THE CINNOLINE SCAFFOLD IN POSITION 8

Synthesis of 8-(4-methoxyphenyl)cinnoline (27a)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and 4-iodoanisole (144 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **27a** as a brown solid (153 mg, 84%).

m.p. (°C): 121-122.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.33 (d, *J* = 5.8 Hz, 1 H), 7.92 - 7.69 (m, 6 H), 7.10 - 7.01 (m, 2 H), 3.88 (s, 3 H).

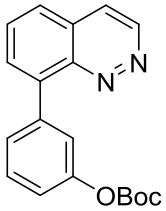
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.8, 148.9, 145.0, 141.3, 132.3, 131.2, 130.8, 130.2, 126.5, 125.7, 122.6, 113.9, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2831, 1737, 1602, 1508, 1454, 1423, 1371, 1308, 1290, 1271, 1244, 1177, 1099, 1028, 852, 832, 805, 782.

MS (EI, 70 eV): *m/z* (%) = 237 (13), 236 (68), 235 (55), 221 (32), 220 (18), 206 (17), 205 (100), 193 (10), 192 (20).

HRMS (EI) for **$C_{15}H_{12}N_2O$** (236.0950): 236.0938 (M^+).

Synthesis of *tert*-butyl (3-(cinnolin-8-yl)phenyl) carbonate (27b)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and *tert*-butyl (3-iodophenyl) carbonate (198 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **27b** as a dark oil (140 mg, 70%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.39 (d, *J* = 5.9 Hz, 1 H), 8.03 (d, *J* = 5.9 Hz, 1 H), 7.93 - 7.85 (m, 3 H), 7.65 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1 H), 7.62 - 7.59 (m, 1 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 7.31 - 7.26 (m, 1 H), 1.56 (s, 9 H).

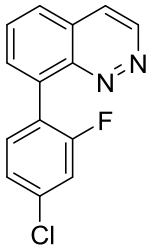
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.8, 150.9, 148.3, 143.9, 140.8, 138.6, 132.0, 132.0, 129.1, 128.5, 127.0, 126.6, 123.9, 123.7, 121.0, 83.5, 27.7 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977, 2930, 1751, 1581, 1393, 1368, 1270, 1246, 1131, 1100, 1002, 914, 853, 743, 693, 672.

MS (EI, 70 eV): *m/z* (%) = 322 (15), 221 (100), 205 (95), 192 (15), 166 (15), 139 (20).

HRMS (EI) for **$C_{19}H_{18}N_2O_3$** (322.1317): 322.1322 (M^+).

Synthesis of 8-(4-chloro-2-fluorophenyl)cinnoline (27c)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and 4-chloro-2-fluoro-1-iodobenzene (158 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **27c** as a dark solid (104 mg, 65%).

m.p. (°C): 127-129.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.39 (d, *J* = 5.9 Hz, 1 H), 8.02 (d, *J* = 5.9 Hz, 1 H), 7.98 - 7.90 (m, 1 H), 7.90 - 7.85 (m, 2 H), 7.56 - 7.47 (m, 1 H), 7.33 - 7.24 (m, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.8, 158.5, 148.5, 145.1 (d, *J* = 1 Hz), 135.1 (d, *J* = 1 Hz), 134.9 (d, *J* = 10 Hz), 133.3 (d, *J* = 4 Hz), 132.0 (d, *J* = 2 Hz), 130.8, 126.2, 124.3 (d, *J* = 16 Hz), 124.3 (d, *J* = 4 Hz), 122.5, 116.5 (d, *J* = 26 Hz).

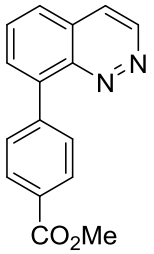
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -110.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2926, 1708, 1613, 1569, 1485, 1361, 1219, 1191, 1161, 1115, 1100, 1076, 980, 853, 823, 803, 768, 724, 706, 675.

MS (EI, 70 eV): *m/z* (%) = 257 (45), 239 (35), 223 (100), 194 (35), 169 (10).

HRMS (EI) for **$C_{14}H_8ClFN_2$** (258.0360): 258.0360 (M^+).

Synthesis of methyl 4-(cinnolin-8-yl)benzoate (27d)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and methyl 4-iodobenzoate (162 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **27d** as a brownish solid (98 mg, 60%).

m.p. (°C): 165-170.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.37 (d, *J* = 5.8 Hz, 1 H), 8.20 - 8.15 (m, 2 H), 7.94 (d, *J* = 5.8 Hz, 1 H), 7.90 - 7.82 (m, 5 H), 3.95 (s, 3 H).

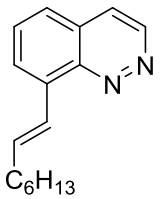
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.0, 148.4, 144.9, 142.3, 140.6, 131.4, 131.0, 129.6, 129.4, 129.4, 127.0, 126.5, 122.9, 52.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3178, 1718, 1607, 1426, 1289, 1185, 1101, 1021, 849, 778, 721, 703.

MS (EI, 70 eV): *m/z* (%) = 263 (20), 249 (22), 233 (5), 205 (100), 176 (5), 151 (5), 88 (7).

HRMS (EI) for **$C_{16}H_{12}N_2O_2$** (264.0899): 264.0898 (M^+).

Synthesis of (*E*)-8-(oct-1-en-1-yl)cinnoline (27e)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. Then, a solution of $Pd(dba)_2$ (8.9 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.2 mg, 0.03 mmol) and methyl (*E*)-1-iodooctene (148 mg, 0.62 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **27e** as a thick oil (97 mg, *E:Z* > 99:1, 65%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.31 (d, *J* = 5.8 Hz, 1 H), 8.01 - 7.92 (m, 2 H), 7.80 (d, *J* = 5.8 Hz, 1 H), 7.74 - 7.61 (m, 2 H), 6.61 (dt, *J* = 15.9 and 7.0 Hz, 1 H), 2.44 - 2.34 (m, 2 H), 1.61 - 1.52 (m, 2 H), 1.42 - 1.25 (m, 6 H), 0.93 - 0.84 (m, 3 H).

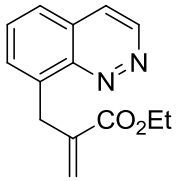
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.1, 144.8, 137.5, 135.8, 131.4, 126.2, 125.8, 124.9, 124.4, 122.6, 33.6, 31.7, 29.3, 29.0, 22.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3392, 2953, 2852, 1734, 1641, 1605, 1582, 1545, 1487, 1455, 1378, 1304, 1157, 1101, 1086, 966, 852, 808, 760, 724, 664.

MS (EI, 70 eV): *m/z* (%) = 240 (20), 211 (5), 169 (100), 155 (60), 141 (5), 128 (4), 115 (5).

HRMS (EI) for **$C_{16}H_{20}N_2$** (240.1626): 240.1622 (M^+).

Synthesis of ethyl 2-(cinnolin-8-ylmethyl)acrylate (27f)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. The reaction mixture was cooled to -40 °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and ethyl 2-(bromomethyl)acrylate (223 mg, 1.16 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 (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 7:3) to give **27f** as a brown oil (114 mg, 61%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.32 (d, *J* = 5.8 Hz, 1 H), 7.83 (d, *J* = 5.8 Hz, 1 H), 7.76 - 7.64 (m, 3 H), 5.63 - 5.59 (m, 1 H), 6.31 (s, 1 H), 4.59 (s, 2 H), 4.22- 4.14 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

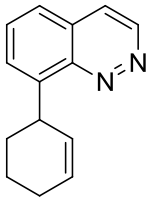
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.1, 149.3, 145.1, 139.5, 139.3, 131.3, 130.8, 127.5, 126.4, 125.5, 122.8, 60.9, 32.7, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979, 2924, 2853, 1710, 1629, 1590, 1561, 1388, 1366, 1248, 1229, 1203, 1178, 1138, 1095, 1022, 947, 852, 765, 695.

MS (EI, 70 eV): *m/z* (%) = 242 (5), 213 (12), 170 (17), 169 (100), 168 (25), 85 (14), 71 (19), 57 (27), 43 (18).

HRMS (EI) for **$C_{14}H_{14}N_2O_2$** (242.1055): 242.1056 (M^+).

Synthesis of 8-(cyclohex-2-en-1-yl)cinnoline (27g)



According to **TP 2**, the metalation of cinnoline (**24**; 100 mg, 0.77 mmol) was completed within 3 h at 50 °C. The reaction mixture was cooled to -40 °C, then a 1.0 M solution of CuCN·2LiCl (0.85 mL, 0.85 mmol) and 3-bromocyclohex-1-ene (186 mg, 1.16 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 (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 8:2) to give **27g** as a yellow oil (86 mg, 53%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.31 (d, *J* = 5.8 Hz, 1 H), 7.83 (d, *J* = 5.8 Hz, 1 H), 7.71 - 7.66 (m, 3 H), 6.08 - 6.03 (m, 1 H), 5.87 - 5.81 (m, 1 H), 5.26 - 5.20 (m, 1 H), 2.38 - 2.31 (m, 1 H), 2.16 (dq, *J* = 5.8, 2.8 Hz, 2 H), 1.78 - 1.66 (m, 3 H).

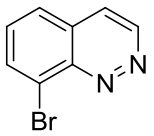
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.8, 146.2, 144.9, 131.4, 129.8, 129.5, 129.0, 126.4, 124.7, 123.0, 34.9, 31.8, 25.4, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3016, 2923, 2856, 2833, 1612, 1582, 1550, 1445, 1423, 1388, 1294, 1158, 1103, 981, 849, 762, 723, 683, 674.

MS (EI, 70 eV): *m/z* (%) = 210 (57), 209 (29), 207 (15), 195 (14), 182 (42), 181 (100), 169 (58), 168 (20), 155 (16), 154 (14), 115 (12).

HRMS (EI) for **$C_{14}H_{14}N_2$** (210.1157): 210.1141 (M^+).

Synthesis of 8-bromocinnoline (27h)



According to **TP 2**, the metalation of cinnoline (**24**; 130 mg, 1.0 mmol) was completed within 3 h at 50 °C. The reaction was allowed to cool to 25 °C, then a 1.0 M solution of $ZnCl_2$ (1.0 mL, 1.0 mmol) was added. The reaction mixture was then cooled to -78 °C, where, it was cannulated to a flask containing bromine (0.15 mL, 3.0 mmol) and dry dioxane (0.26 mL, 3.0 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL), extracted with EtOAc (3 x 15 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **27h** as an off-white solid (97 mg, 46%).

m.p. (°C): 80.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.41 (d, *J* = 6.1 Hz, 1 H), 8.15 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.85 (d, *J* = 5.8 Hz, 1 H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.62 - 7.56 (m, 1 H).

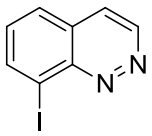
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.8, 145.9, 134.6, 131.6, 127.8, 126.8, 125.9, 122.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 3051, 1608, 1571, 1528, 1480, 1404, 1282, 1214, 1096, 978, 967, 848, 803, 778, 761, 669.

MS (EI, 70 eV): *m/z* (%) = 210 (54), 208 (65), 182 (17), 180 (17), 101 (100), 100 (18), 75 (66), 74 (39), 50 (28).

HRMS (EI) for **$C_8H_5BrN_2$** (207.9636): 207.9614 (M^+).

Synthesis of 8-iodocinnoline (27i)



According to **TP 2**, the metalation of cinnoline (**24**; 130 mg, 1.0 mmol) was completed within 3 h at 50 °C. The reaction mixture was then cooled to 0 °C and cannulated into a solution of I_2 (518 mg, 2 mmol) in dry THF (2 mL), pre-cooled to 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then at rt for 1 h. The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 x 15 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **27j** as an off-white solid (133 mg, 52%).

m.p. (°C): 82.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.38 (d, *J* = 5.9 Hz, 1 H), 8.44 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.82 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.74 (d, *J* = 5.9 Hz, 1 H), 7.44 (dd, *J* = 8.2, 7.4 Hz, 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.0, 146.0, 141.6, 132.1, 127.8, 127.3, 122.6, 103.4.

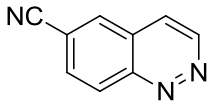
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3059, 1602, 1569, 1477, 1412, 1398, 1280, 1254, 1212, 1163, 1115, 1095, 965, 847, 800, 774, 760, 662.

MS (EI, 70 eV): *m/z* (%) = 257 (3), 256 (37), 228 (23), 102 (13), 101 (19), 58 (39), 43 (100).

HRMS (EI) for **$C_8H_5IN_2$** (255.9497): 255.9493 (M^+).

4.4 REGIOSELECTIVE SUBSEQUENT METALATION OF SUBSTITUTED CINNOLINE DERIVATIVES

Synthesis of cinnoline-6-carbonitrile (28a)



Cinnoline-6-carbonitrile (**28a**) was synthesized according to a known procedure[116b] and was obtained as a brown solid.

m.p. (°C): 129-131.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.50 (d, *J* = 5.8 Hz, 1 H), 8.69 (d, *J* = 8.9 Hz, 1 H), 8.30 (d, *J* = 1.1 Hz, 1 H), 8.01 - 7.92 (m, 2 H).

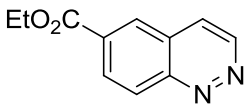
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.1, 146.4, 133.7, 131.8, 131.1, 125.2, 122.3, 117.5, 115.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 3041, 2924, 2858, 2229, 1958, 1827, 1621, 1574, 1476, 1452, 1394, 1369, 1325, 1289, 1252, 1174, 1168, 1159, 1091, 1081, 970, 912, 907, 898, 846, 777, 686, 684, 660.

MS (EI, 70 eV): *m/z* (%) = 156 (11), 155 (100), 128 (10), 127 (95), 101 (12), 100 (39), 97 (12), 76 (19), 74 (17), 71 (13), 70 (11), 69 (14), 63 (10), 61 (16), 57 (21), 55 (13), 50 (31), 45 (15), 43 (13), 43 (90).

HRMS (EI) for **$C_9H_5N_3$** (155.0483): 155.0476 (M^+).

Synthesis of ethyl cinnoline-6-carboxylate (28b)



Ethyl cinnoline-6-carboxylate (**28b**) was synthesized according to a known procedure[116b] and was obtained as a yellow solid.

m.p. (°C): 112-113.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.42 (d, *J* = 5.8 Hz, 1 H), 8.61 (dd, *J* = 5.7, 3.5 Hz, 2 H), 8.42 (dd, *J* = 9.1, 1.7 Hz, 1 H), 7.97 (d, *J* = 5.8 Hz, 1 H), 4.48 (q, *J* = 7.2 Hz, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

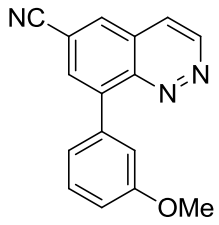
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.3, 151.5, 145.9, 132.7, 130.4, 130.1, 130.0, 125.3, 123.5, 62.1, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3039, 2986, 2952, 2923, 2905, 2875, 2852, 1961, 1827, 1719, 1485, 1454, 1443, 1373, 1366, 1302, 1281, 1267, 1250, 1229, 1166, 1146, 1120, 1091, 1022, 985, 966, 916, 869, 853, 842, 795, 779, 746, 738.

MS (EI, 70 eV): *m/z* (%) = 203 (13), 202 (100), 174 (12), 157 (28), 146 (13), 129 (51), 101 (20), 75 (20).

HRMS (EI) for **$C_{11}H_{10}N_2O_2$** (202.0742): 202.0736 (M^+).

Synthesis of 8-(3-methoxyphenyl)cinnoline-6-carbonitrile (29a)



According to **TP 2**, the metalation of cinnoline-6-carbonitrile (**28a**; 100 mg, 0.64 mmol) was completed within 1 h at 25 °C. Then, a solution of $Pd(dba)_2$ (7.4 mg, 0.01 mmol), P(*o*-furyl)$_3$ (5.9 mg, 0.03 mmol) and 1-iodo-3-methoxybenzene (120 mg, 0.51 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 7:3) to give **29a** as a yellow solid (96 mg, 72%).

m.p. (°C): 183-184.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.52 (d, *J* = 5.9 Hz, 1 H), 8.25 (d, *J* = 1.7 Hz, 1 H), 7.98 (d, *J* = 1.7 Hz, 1 H), 7.95 (d, *J* = 5.9 Hz, 1 H), 7.46 (t, *J* = 7.9 Hz, 1 H), 7.35 - 7.28 (m, 2 H), 7.06 (m, 1 H), 3.88 (s, 3 H).

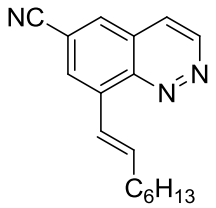
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.6, 148.3, 146.2, 143.8, 137.2, 132.6, 131.3, 129.6, 125.7, 123.5, 122.4, 117.6, 116.8, 115.1, 114.8, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3038, 2955, 2921, 2834, 2232, 1604, 1570, 1470, 1457, 1451, 1436, 1407, 1376, 1322, 1289, 1276, 1252, 1229, 1136, 1093, 1045, 1005, 928, 899, 877, 842, 812, 778, 739, 699, 674.

MS (EI, 70 eV): *m/z* (%) = 261 (42), 260 (30), 246 (10), 231 (18), 230 (100), 218 (10), 217 (13).

HRMS (EI) for **$C_{16}H_{11}N_3O$** (261.0902): 261.0897 (M^+).

Synthesis of (*E*)-8-(oct-1-en-1-yl)cinnoline-6-carbonitrile (29b)



According to **TP 2**, the metalation of cinnoline-6-carbonitrile (**28a**; 100 mg, 0.64 mmol) was completed within 1 h at 25 °C. Then, a solution of $Pd(dba)_2$ (7.4 mg, 0.01 mmol), P(*o*-furyl)$_3$ (5.9 mg, 0.03 mmol) and (*E*)-1-iodooct-1-ene (122 mg, 0.45 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 7:3) to give **29b** as a brown solid (92 mg, 68%).

m.p. (°C): 71-73.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.46 (d, *J* = 6.1 Hz, 1 H), 8.05 (d, *J* = 6.4 Hz, 2 H), 7.94 (d, *J* = 16.31 Hz, 1 H), 7.86 (d, *J* = 5.8 Hz, 1 H), 6.70 (dt, *J* = 16.0, 7.1 Hz, 1 H), 2.42 (q, *J* = 7.1 Hz, 2 H), 1.62 - 1.52 (m, 2 H), 1.44 - 1.28 (m, 6 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

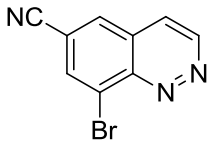
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.4, 146.2, 139.7, 138.9, 130.8, 126.0, 125.4, 123.1, 122.4, 117.8, 115.3, 33.8, 31.8, 29.2, 29.1, 22.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 3043, 2944, 2928, 2882, 2866, 2845, 2231, 1642, 1611, 1550, 1469, 1395, 1170, 1106, 977, 968, 953, 901, 887, 836, 801, 718, 659.

MS (EI, 70 eV): *m/z* (%) = 265 (27), 208 (10), 195 (31), 194 (100), 193 (19), 182 (12), 181 (19), 180 (47), 169 (12), 43 (15).

HRMS (EI) for **$C_{17}H_{19}N_3$** (265.1579): 265.1571 (M^+).

Synthesis of 8-bromocinnoline-6-carbonitrile (29c)



According to **TP 2**, the metalation of cinnoline-6-carbonitrile (**28a**; 250 mg, 1.61 mmol) was completed within 1 h at 25 °C. The reaction was then cooled to -78 °C, where, it was cannulated to a flask containing equimolar amounts of bromine (772 mg, 4.83 mmol) and dry dioxane (426 mg, 4.83 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to 25 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **29c** as a yellow solid (222 mg, 59%).

m.p. (°C): 189.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.60 (d, *J* = 5.9 Hz, 1 H), 8.30 (d, *J* = 1.5 Hz, 1 H), 8.26 (d, *J* = 1.5 Hz, 1 H), 7.93 (d, *J* = 5.9 Hz, 1 H).

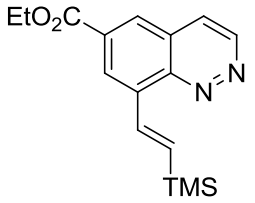
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 147.4, 147.2, 134.3, 133.2, 128.1, 126.6, 122.4, 116.3, 115.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 3043, 2920, 2848, 2234, 1611, 1461, 1413, 1392, 1366, 1284, 1224, 1168, 1140, 1092, 1075, 994, 918, 908, 887, 881, 877, 840, 798, 736.

MS (EI, 70 eV): *m/z* (%) = 235 (72), 233 (70), 207 (37), 205 (37), 127 (11), 126 (100), 125 (20), 100 (51), 99 (55), 98 (12), 76 (18), 75 (39), 74 (37), 63 (16), 62 (13), 61 (10), 50 (23), 43 (11).

HRMS (EI) for **$C_9H_4BrN_3$** (232.9589): 232.9579 (M^+).

Synthesis of (*E*)-ethyl 8-(2-(trimethylsilyl)vinyl)cinnoline-6-carboxylate (29d)



According to **TP 2**, the metalation of ethyl cinnoline-6-carboxylate (**28b**; 100 mg, 0.49 mmol) was completed within 1 h at 25 °C. Then, a solution of $Pd(dba)_2$ (5.6 mg, 0.01 mmol), P(*o*-furyl)$_3$ (4.6 mg, 0.02 mmol) and (*E*)-(2-iodovinyl)trimethylsilane (78 mg, 0.34 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane:EtOAc = 7:3) to give **29d** as a yellow solid (59 mg, 57%).

m.p. (°C): 135-137.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.43 (d, *J* = 5.9 Hz, 1 H), 8.59 (m, 1 H), 8.47 (m, 2 H), 7.93 (d, *J* = 5.9 Hz, 1 H), 7.02 (d, *J* = 19.4 Hz, 1 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 1.48 (t, *J* = 7.1 Hz, 3 H), 0.26 (s, 9 H).

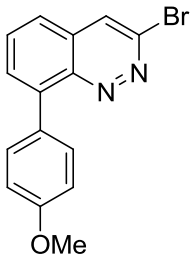
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.6, 148.5, 145.7, 138.3, 137.4, 136.8, 132.7, 128.8, 125.7, 125.5, 123.6, 62.1, 14.5, -1.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2951, 2899, 1721, 1716, 1575, 1473, 1397, 1312, 1275, 1240, 1234, 1225, 1212, 1164, 1096, 1026, 990, 862, 851, 836, 766, 760, 746, 722, 693.

MS (EI, 70 eV): *m/z* (%) = 300 (2), 272 (20), 271 (100), 199 (8), 154 (21), 73 (32).

HRMS (EI) for **$C_{16}H_{20}N_2O_2Si$** (300.1294): 300.1280 (M^+).

Synthesis of 3-bromo-8-(4-methoxyphenyl)cinnoline (29e)



According to **TP 2**, the metalation of **26f** (105 mg, 0.5 mmol) was completed within 4 h at 50 °C. Then, a solution of $Pd(dba)_2$ (8.6 mg, 0.02 mmol), P(*o*-furyl)$_3$ (7.0 mg, 0.03 mmol) and 4-iodoanisole (140 mg, 0.6 mmol) in THF (1.0 mL) was added to the reaction mixture dropwise and it was stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **29e** as a yellow solid (102 mg, 65%).

m.p. (°C): 151-153.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.10 (s, 1 H), 7.87 - 7.79 (m, 2 H), 7.76 - 7.68 (m, 3 H), 7.08 - 7.03 (m, 2 H), 3.89 (s, 3 H).

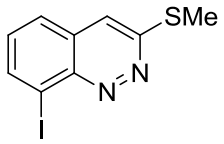
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.0, 148.1, 141.6, 141.5, 132.5, 132.4, 131.0, 129.6, 128.5, 126.2, 124.7, 113.9, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3005, 2960, 2930, 1607, 1570, 1507, 1372, 1307, 1290, 1268, 1246, 1178, 1144, 1107, 1063, 1028, 973, 887, 840, 818, 807, 783.

MS (EI, 70 eV): *m/z* (%) = 317 (11), 314 (72), 301 (26), 299 (31), 285 (100), 283 (94), 235 (10), 192 (31), 191 (15), 164 (35), 163 (38), 58 (12), 44 (29), 43 (34).

HRMS (EI) for **$C_{15}H_{11}BrN_2O$** (314.0055): 314.0044 (M^+).

Synthesis of 8-iodo-3-(methylthio)cinnoline (29f)



A dry, argon-flushed 25 mL Schlenk flask was charged with **26h** (70 mg, 0.4 mmol) and dry THF (2 mL). The solution was cooled to 0 °C, where TMPMgCl·LiCl (0.8 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and cannulated into a solution of I_2 (202 mg, 0.8 mmol) in dry THF (2 mL), pre-cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and then quenched with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 x 15 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8:2) to give **29f** as a brown oil (58 mg, 48%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.29 (d, *J* = 7.2 Hz, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 7.56 (s, 1 H), 7.33 (t, *J* = 7.7 Hz, 1 H), 2.86 (s, 3 H).

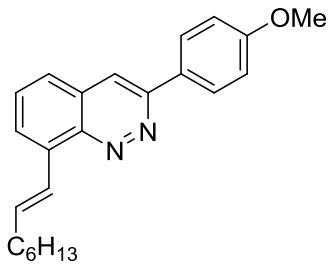
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.1, 147.1, 140.4, 132.4, 127.3, 126.6, 119.5, 103.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2988, 2921, 2894, 2852, 1718, 1711, 1597, 1558, 1510, 1493, 1444, 1411, 1384, 1365, 1358, 1291, 1281, 1269, 1240, 1182, 1179, 1104, 1066, 1020, 966, 907, 872, 861, 851, 798, 792, 772, 752, 699, 688, 684, 675, 655.

MS (EI, 70 eV): *m/z* (%) = 303 (12), 302 (100), 274 (11), 259 (16), 147 (8), 132 (40).

HRMS (EI) for **$C_9H_7IN_2S$** (301.9375): 301.9371 (M^+).

Synthesis of (*E*)-3-(4-methoxyphenyl)-8-(oct-1-en-1-yl)cinnoline (29g)



According to **TP 1**, the metalation of cinnoline (**27e**; 51 mg, 0.21 mmol) was completed within 5 min at -78 °C. Then, a 1.0 M solution of $ZnCl_2$ (0.25 mL, 0.25 mmol) was added dropwise to the reaction mixture dropwise and it was stirred for 10 min at -78 °C. A solution of $Pd(dba)_2$ (2.4 mg, 0.0042 mmol), P(*o*-furyl)$_3$ (2.4 mg, 0.0084 mmol) and 4-iodoanisole (39 mg, 0.17 mmol) in THF (0.5 mL) was added to the reaction dropwise. The reaction mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL), extracted with EtOAc (3 x 5 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **29g** as a yellowish thick oil (40 mg, *E:Z* > 99:1, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.27 - 8.22 (m, 2 H), 8.05 (s, 1 H), 7.99 (d, *J* = 16.1 Hz, 1 H), 7.87 (dd, *J* = 5.7, 2.8 Hz, 1 H), 7.67 (s, 1 H), 7.70 - 7.63 (m, 1 H), 7.11 - 7.06 (m, 2 H), 6.64 (dt, *J* = 15.9, 6.9 Hz, 1 H), 3.90 (s, 3 H), 2.40 (td, *J* = 8.6, 1.6 Hz, 2 H), 1.62 - 1.53 (m, 2 H), 1.45 - 1.37 (m, 2 H), 1.36 - 1.29 (m, 4 H), 0.93 - 0.87 (m, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.9, 152.8, 146.8, 137.4, 135.7, 131.4, 129.2, 128.4, 126.8, 125.2, 125.0, 124.4, 117.8, 114.5, 55.4, 33.7, 31.8, 29.3, 29.0, 22.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2922, 2851, 1642, 1603, 1513, 1462, 1336, 1173, 1115, 1030, 967, 891, 831, 794, 680.

MS (EI, 70 eV): *m/z* (%) = 346 (40), 275 (30), 275 (100), 133 (13), 44 (61).

HRMS (EI) for **$C_{23}H_{26}N_2O$** (346.2045): 346.2038 (M^+).

5 PREPARATION AND REGIOSELECTIVE METALATION OF BIS(TRIMETHYLSILYL)METHYL-SUBSTITUTED ARYL AND HETEROARYL DERIVATIVES

5.1 TYPICAL PROCEDURES

Typical Procedure 1 for the cross-coupling of 2 with aryl bromides (TP 1):

In a dry argon flushed Schlenk-flask the aryl bromide (1.0 equiv), $Pd(OAc)_2$ (0.02 equiv) and SPhos (0.04 equiv) were suspended in dry THF (0.3 m). Then, $(TMS)_2CHMgBr \cdot LiCl$ (1.1 equiv, 0.6 M in THF) was added and the reaction mixture was stirred at the indicated temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with NH_4Cl and using undecane as internal standard.

Typical Procedure 2 for the magnesiation of 33a with $TMP_2Mg \cdot 2LiCl$ (TP 2):

In a dry argon flushed Schlenk-flask, $TMP_2Mg \cdot 2LiCl$ (1.5 equiv, 0.6 M in THF) was placed and the ester (1.0 equiv) was added at 25 °C. The reaction mixture was stirred at this temperature for 2 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine and using undecane as internal standard.

Typical Procedure 3 for the lithiation of 5b with TMPLi (TP 3):

In a dry argon flushed Schlenk-flask, the arene (1.0 equiv) was dissolved in THF (0.5 M) and cooled to -60 °C. Then, TMPLi (2.0 equiv, 0.63 M in THF) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine and using undecane as internal standard.

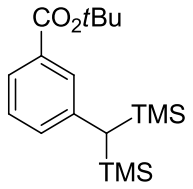
Typical Procedure 4 for the oxidation of the BTSM-substituted arenes with CAN (TP 4):

In a dry argon flushed Schlenk-flask, the arene (1.0 equiv) was dissolved in a 3:1 mixture of CH_3CN:MeOH (0.015 m) and cooled to 0 °C. Then, ceric ammonium nitrate (CAN; 5.0 equiv)

was added and the reaction mixture was stirred at this temperature for 30 min. The completion of the reaction was checked by GC analysis of reaction aliquots.

5.2 PREPARATION OF BTSM-SUBSTITUTED ARYL DERIVATIVES

Synthesis of *tert*-butyl 3-(bis(trimethylsilyl)methyl)benzoate (33a)



According to **TP 1**, the cross-coupling of *tert*-butyl 3-bromobenzoate (**32a**; 257 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 50:1) to give **33a** as colorless oil (326 mg, 97%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.66 (dt, *J* = 7.7, 1.5 Hz, 1 H), 7.59 (t, *J* = 1.6 Hz, 1 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.04 - 7.13 (m, 1 H), 1.59 (s, 9 H), 1.51 (s, 1 H), 0.03 (s, 18 H).

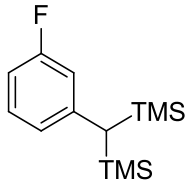
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 143.4, 132.7, 131.7, 129.5, 127.8, 124.4, 80.6, 29.5, 28.2, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2897, 2847, 1710, 1700, 1597, 1575, 1476, 1456, 1430, 1392, 1373, 1365, 1290, 1253, 1246, 1162, 1151, 1106, 1081, 1036, 999, 932, 920, 914, 866, 838, 829, 815, 775, 764, 746, 695, 692, 687, 664.

MS (EI, 70 eV): *m/z* (%) = 336 (1), 280 (23), 265 (18), 264 (20), 190 (24), 162 (14), 73 (31), 70 (11), 61 (17), 57 (14), 45 (14), 43 (100).

HRMS (EI) for **$C_{18}H_{32}O_2Si_2$** (336.1941): 336.1952 (M^+).

Synthesis of ((3-fluorophenyl)methylene)bis(trimethylsilane) (33b)



According to **TP 1**, the cross-coupling of 1-bromo-3-fluorobenzene (**32b**; 175 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 99:1) to give **33b** as a yellow oil (234 mg, 92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.13 (d, *J* = 6.4 Hz, 1 H), 6.70 (t, *J* = 7.1 Hz, 2 H), 6.63 (m, 1 H), 1.51 (s, 1 H), 0.03 (s, 18 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.0 (d, *J* = 244 Hz), 146.3 (d, *J* = 8 Hz), 129.4 (d, *J* = 9 Hz), 124.5, 115.2 (d, *J* = 22 Hz), 110.2 (d, *J* = 21 Hz), 30.1, 0.3.

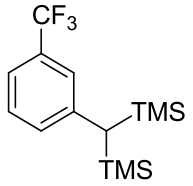
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -114.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2896, 2834, 1610, 1582, 1483, 1439, 1284, 1265, 1248, 1177, 1159, 1131, 1070, 1036, 1002, 946, 940, 888, 866, 825, 768, 737, 685.

MS (EI, 70 eV): *m/z* (%) = 254 (5), 239 (16), 166 (42), 163 (10), 162 (54), 161 (18), 147 (38), 145 (17), 135 (10), 134 (15), 73 (100), 59 (10), 45 (17).

HRMS (EI) for **$C_{13}H_{23}FSi_2$** (254.1322): 254.1313 (M^+).

Synthesis of ((3-(trifluoromethyl)phenyl)methylene)bis(trimethylsilane) (33c)



According to **TP 1**, the cross-coupling of 1-bromo-3-(trifluoromethyl)benzene (**32c**; 225 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane) to give **33c** as a colorless oil (277 mg, 91%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.29 (d, *J* = 4.7 Hz, 2 H), 7.17 (s, 1 H), 7.07 - 7.14 (m, 1 H), 1.59 (s, 1 H), 0.03 (s, 18 H).

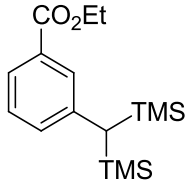
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 144.5, 131.8, 130.3 (q, *J* = 32 Hz), 128.3, 124.9 (q, *J* = 3 Hz), 124.4 (q, *J* = 272 Hz), 120.1 (q, *J* = 4 Hz), 30.0, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2898, 2836, 1607, 1591, 1487, 1456, 1442, 1325, 1315, 1251, 1200, 1158, 1123, 1090, 1073, 1035, 1000, 976, 907, 891, 864, 836, 826, 768, 743, 721, 704, 688, 671, 661.

MS (EI, 70 eV): *m/z* (%) = 304 (1), 216 (18), 130 (17), 115 (19), 91 (16), 83 (15), 77 818), 73 (100), 45 (15).

HRMS (EI) for **$C_{14}H_{23}F_3Si_2$** (304.1290): 304.1277 (M^+).

Synthesis of ethyl 3-(bis(trimethylsilyl)methyl)benzoate (33d)



According to **TP 1**, the cross-coupling of ethyl 3-bromobenzoate (**32d**; 229 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 50:1) to give **33d** as a colorless oil (281 mg, 91%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.72 (dt, *J* = 7.6, 1.5 Hz, 1 H), 7.63 (t, *J* = 1.7 Hz, 1 H), 7.25 (t, *J* = 7.7 Hz, 1 H), 7.07 - 7.16 (m, 1 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 1.58 (s, 1 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 0.03 (s, 18 H).

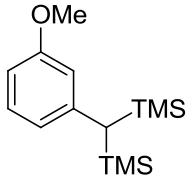
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 192.7, 167.0, 167.0, 143.7, 130.2, 128.0, 124.5, 60.7, 29.6, 14.3, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2898, 2833, 1718, 1600, 1580, 1481, 1434, 1419, 1392, 1367, 1307, 1273, 1249, 1198, 1169, 1157, 1104, 1079, 1029, 999, 924, 865, 836, 829, 827, 771, 755, 745, 695, 688, 656.

MS (EI, 70 eV): *m/z* (%) = 308 (42), 293 (22), 279 (11), 264 (11), 263 (17), 220 (13), 191 (14), 190 (62), 162 (43), 147 (29), 145 (10), 73 (100), 59 (11), 45 (14).

HRMS (EI) for **$C_{16}H_{28}O_2Si_2$** (308.1628): 308.1622 (M^+).

Synthesis of ((3-methoxyphenyl)methylene)bis(trimethylsilane) (33e)



According to **TP 1**, the cross-coupling of 1-bromo-3-methoxybenzene (**32e**; 187 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane) to give **33e** as a colorless oil (253 mg, 95%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.10 (td, *J* = 7.8 Hz, *J* = 2.6 Hz, 1 H), 6.55 (m, 3 H), 3.77 (s, 3 H), 1.47 (s, 1 H), 0.03 (s, 18 H).

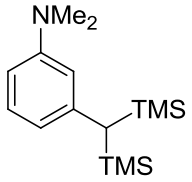
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.3, 144.8, 128.8, 121.5, 114.6, 108.3, 55.0, 29.8, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2898, 2833, 1603, 1597, 1591, 1577, 1484, 1465, 1435, 1295, 1256, 1247, 1190, 1173, 1165, 1140, 1037, 937, 930, 918, 915, 883, 863, 833, 826, 771, 769, 734, 698, 685, 667, 653.

MS (EI, 70 eV): *m/z* (%) = 266 (46), 251 (27), 179 (17), 178 (100), 73 (86), 59 (11), 45 (11).

HRMS (EI) for **$C_{14}H_{26}OSi_2$** (266.1522): 266.1522 (M^+).

Synthesis of 3-(bis(trimethylsilyl)methyl)-*N*,*N*-dimethylaniline (33f)



According to **TP 1**, the cross-coupling of 3-bromo-*N*,*N*-dimethylaniline (**32f**; 200 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed

within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 100:1) to give **33f** as a yellow oil (246 mg, 88%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.07 (t, *J* = 7.9 Hz, 1 H), 6.55 - 6.40 (m, 3 H), 2.93 (s, 6 H), 1.46 (s, 1 H), 0.04 (s, 18 H).

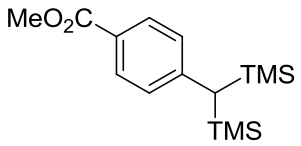
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.9, 144.0, 128.5, 119.1, 114.2, 108.7, 41.2, 29.8, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2896, 2830, 2799, 1684, 1595, 1575, 1560, 1495, 1456, 1435, 1346, 1262, 1246, 1205, 1181, 1162, 1135, 1092, 1061, 1036, 995, 975, 886, 876, 864, 832, 826, 771, 761, 743, 737, 723, 717, 698, 685, 667, 653.

MS (EI, 70 eV): *m/z* (%) = 279 (100), 278 (22), 265 (18), 264 (40), 208 (14), 207 (74), 206 (19), 205 (21), 192 (13), 191 (55), 190 (14), 178 (16), 176 (13), 73 (89), 59 (12), 45 (13).

HRMS (EI) for **$C_{15}H_{29}NSi_2$** (279.1839): 279.1813 (M^+).

Synthesis of methyl 4-(bis(trimethylsilyl)methyl)benzoate (33g)



According to **TP 1**, the cross-coupling of methyl 4-bromobenzoate (**32g**; 215 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr{\cdot}LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 50:1) to give **33g** as a colorless oil (262 mg, 89%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.87 (d, *J* = 8.6 Hz, 2 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 3.88 (s, 3 H), 1.63 (s, 1 H), 0.06 (s, 18 H).

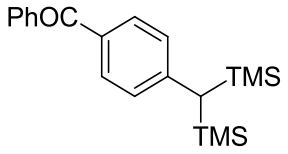
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.5, 150.1, 129.7, 128.7, 125.4, 51.9, 31.2, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2897, 2836, 1719, 1603, 1434, 1414, 1276, 1265, 1260, 1248, 1200, 1178, 1111, 1099, 1035, 1017, 970, 875, 865, 830, 771, 753, 704, 688, 669.

MS (EI, 70 eV): *m/z* (%) = 294 (27), 282 (12), 280 (11), 279 (19), 206 (22), 191 (17), 190 (88), 175 (17), 175 (60), 162 (42), 147 (20), 83 (11), 73 (100), 69 (12), 59 (12), 57 (26), 55 (13), 45 (15), 44 (12), 43 (15), 43 (17), 40 (14).

HRMS (EI) for **$C_{15}H_{26}O_2Si_2$** (294.1471): 294.1477 (M^+).

Synthesis of (4-(bis(trimethylsilyl)methyl)phenyl)(phenyl)methanone (33h)



According to **TP 1**, the cross-coupling of (4-bromophenyl)(phenyl)methanone (**32h**; 261 mg, 1.0 mmol) catalyzed by $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and SPhos (16.4 mg, 0.04 mmol) in dry THF (3.5 mL) with $(TMS)_2CHMgBr{\cdot}LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 2 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 50:1) to give **33h** as a colorless oil (245 mg, 72%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.80 - 7.75 (m, 2 H), 7.69 (d, *J* = 8.3 Hz, 2 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.50 - 7.44 (m, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 1.67 (s, 1 H), 0.06 (s, 18 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 196.5, 150.1, 149.7, 138.5, 132.8, 132.0, 130.6, 130.0, 128.3, 31.3, 0.3.

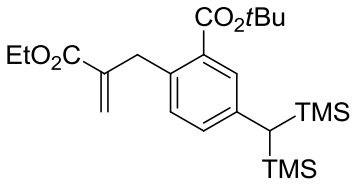
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2952, 2896, 2820, 1652, 1595, 1555, 1446, 1413, 1276, 1263, 1248, 1203, 1176, 1146, 1105, 1034, 937, 923, 864, 825, 771, 756, 740, 699, 686, 654.

MS (EI, 70 eV): *m/z* (%) = 341 (28), 340 (100), 326 (19), 325 (72), 252 (11), 73 (32).

HRMS (EI) for $\mathbf{C_{20}H_{28}OSi_2}$ (340.1679): 340.1680 (M^+).

5.3 METALATION AND TRANSFORMATION OF BTSM-SUBSTITUTED ARYL DERIVATIVES

Synthesis of *tert*-butyl 5-(bis(trimethylsilyl)methyl)-2-(2-(ethoxycarbonyl)allyl)benzoate (37a)



tert-Butyl 3-(bis(trimethylsilyl)methyl)benzoate (**33a**; 337 mg, 1.0 mmol) was metalated according to **TP 2** using $TMP_2Mg{\cdot}2LiCl$ (0.6 M in THF, 2.5 mL, 1.5 mmol). Then the reaction mixture was cooled to -40 °C and $ZnCl_2$ (1.5 mL, 1.5 mmol, 1.0 M in THF) was added. The mixture was kept at this temperature for 15 min before a 1.0 M solution of CuCN·2LiCl (1.5 mL, 1.5 mmol) and ethyl 2-(bromomethyl)acrylate (**36a**; 290 mg, 1.5 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 (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 47:3) to give **37a** as a yellow oil (415 mg, 92%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.44 (d, *J* = 1.7 Hz, 1 H), 7.04 - 6.94 (m, 2 H), 6.17 (d, *J* = 1.4 Hz, 1 H), 5.10 (d, *J* = 1.7 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 1.57 - 1.48 (m, 10 H) 3.91 (s, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 0.03 (s, 18 H).

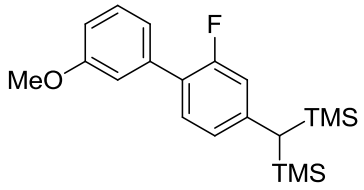
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.5, 167.4, 141.6, 141.1, 140.4, 134.0, 132.0, 131.4, 130.8, 125.3, 81.1, 60.8, 35.7, 29.1, 28.3, 14.3, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2953, 2900, 1714, 1632, 1604, 1367, 1303, 1274, 1264, 1248, 1169, 1155, 1131, 1075, 1032, 949, 919, 853, 836, 826, 772, 685.

MS (EI, 70 eV): *m/z* (%) = 448 (2), 392 (11), 302 (21), 274 (11), 273 (24), 230 (19), 229 (100), 228 (14), 214 (10), 213 (13), 155 (52), 147 (16), 75 (27), 73 (95), 57 (23).

HRMS (EI) for **$C_{24}H_{40}O_4Si_2$** (448.2465): 448.2442 (M^+).

Synthesis of ((2-fluoro-3'-methoxy-[1,1'-biphenyl]-4-yl)methylene)bis(trimethylsilane) (37i)



((3-Fluorophenyl)methylene)bis(trimethylsilane) (**33b**; 254 mg, 1.0 mmol) was metalated according to **TP 3** using TMPLi (3.17 mL, 2.0 mmol, 0.63 M in THF). Then, $ZnCl_2$ (2.1 mL, 2.1 mmol, 2.1 equiv, 1.0 M in THF) was added and the resulting solution was stirred for 15 min. $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.29 mg, 0.04 mmol) and 3-iodoanisole (187 mg, 0.8 mmol, 0.8 equiv) were added and the resulting solution was stirred for 12 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 99:1) to give **37i** as a yellow oil (274 mg, 95%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.31 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 2.0 Hz, 1 H), 7.16 - 7.12 (m, 1 H), 7.11 - 7.09 (m, 1 H), 6.90 - 6.85 (m, 1 H), 6.78 - 6.69 (m, 2 H), 3.84 (s, 3 H), 1.55 (s, 1 H), 0.05 (s, 18 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.7 (d, *J* = 247 Hz), 159.7, 145.6 (d, *J* = 8 Hz), 137.6 (d, *J* = 1 Hz), 130.1 (d, *J* = 4 Hz), 129.4, 124.9, 123.7 (d, *J* = 13 Hz), 121.5 (d, *J* = 3 Hz), 116.0 (d, *J* = 23 Hz), 114.5 (d, *J* = 3 Hz), 113.0, 55.4, 30.0 (d, *J* = 1 Hz), 0.3.

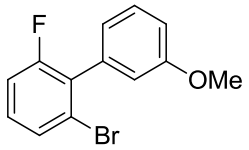
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -118.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2898, 2834, 1616, 1610, 1601, 1581, 1479, 1408, 1249, 1168, 1125, 1051, 1031, 951, 877, 866, 836, 825, 776, 732, 695, 687.

MS (EI, 70 eV): *m/z* (%) = 360 (43), 345 (20), 273 (11), 272 (46), 268 (28), 267 (45), 253 (27), 240 (11), 239 (32), 238 (13), 237 (10), 225 (11), 223 (13), 211 (13), 210 (18), 193 (14), 165 (10), 77 (11), 73 (100), 59 (12), 45 (15).

HRMS (EI) for **$C_{20}H_{29}FOSi_2$** (360.1741): 360.1743 (M^+).

Synthesis of 2-bromo-6-fluoro-3'-methoxy-1,1'-biphenyl (38a)



1-Bromo-3-fluorobenzene (**32b**; 175 mg, 1.0 mmol) was dissolved in 1 mL THF and cooled to -20 °C. Then $TMP_2Mg{\cdot}2LiCl$ (0.6 M in THF, 3.67 mL, 2.2 mmol) was added dropwise and the reaction was stirred at this temperature for 1 h. Then, a 1.0 M solution of $ZnCl_2$ (1.2 mL, 1.2 mmol) was added and the mixture was stirred for 15 min. A solution of $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.29 mg, 0.04 mmol) and 3-iodoanisole (281 mg, 1.2 mmol) in THF (1.0 mL) was added to the reaction dropwise and the reaction was stirred at 50 °C overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 99:1) to give **38a** as a yellow oil (219 mg, 78%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.50 - 7.45 (m, 1 H), 7.41 - 7.35 (m, 1 H), 7.24 - 7.16 (m, 1 H), 7.15 - 7.08 (m, 1 H), 6.99 - 6.95 (m, 1 H), 6.93 - 6.86 (m, 2 H), 3.84 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2 (d, *J* = 249 Hz), 159.4, 135.9, 130.9, 129.8 (d, *J* = 9 Hz), 129.3, 128.7 (d, *J* = 4 Hz), 124.5 (d, *J* = 3 Hz), 122.5 (d, *J* = 1 Hz), 115.8 (d, *J* = 1 Hz), 115.0 (d, *J* = 23 Hz), 114.0, 55.4.

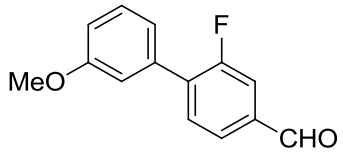
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -109.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2998, 2956, 2933, 2834, 1605, 1598, 1596, 1580, 1572, 1568, 1491, 1460, 1439, 1421, 1315, 1289, 1273, 1264, 1242, 1218, 1209, 1180, 1167, 1087, 1046, 1021, 996, 862, 848, 809, 776, 732, 720, 716, 697, 679.

MS (EI, 70 eV): *m/z* (%) = 282 (85), 280 (84), 257 (14), 239 (14), 237 (15), 186 (17), 171 (13), 170 (31), 158 (26), 157 (46), 69 (20), 57 (11), 41 (10).

HRMS (EI) for **$C_{13}H_{10}BrFO$** (279.9899): 279.9889 (M^+).

Synthesis of 2-fluoro-3'-methoxy-[1,1'-biphenyl]-4-carbaldehyde (40)



According to **TP 4**, the oxidation of **37i** (361 mg, 1.0 mmol, 1.0 equiv) with CAN (2.74 g, 5 mmol, 5 equiv) was completed within 30 min at 0 °C. CF_3COOH (5 mL) was added and the reaction mixture was stirred for further 15 min. Then, the reaction mixture was quenched with H_2O (10 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 99:1) to give **40** as a yellow oil (203 mg, 88%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.01 (d, *J* = 1.7 Hz, 1 H), 7.75 - 7.71 (m, 1 H), 7.68 - 7.64 (m, 1 H), 7.64 - 7.59 (m, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.18 - 7.14 (m, 1 H), 7.13 - 7.11 (m, 1 H), 7.00 - 6.96 (m, 1 H), 3.86 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 190.7 (d, *J* = 2 Hz), 160.1 (d, *J* = 251 Hz), 159.8, 137.3 (d, *J* = 6 Hz), 135.9 (d, *J* = 1 Hz), 135.3 (d, *J* = 14 Hz), 131.6 (d, *J* = 3 Hz), 129.8, 126.1 (d, *J* = 4 Hz), 121.6 (d, *J* = 3 Hz), 116.5 (d, *J* = 24 Hz), 114.9 (d, *J* = 3 Hz), 114.4, 55.5.

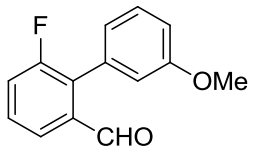
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -115.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 3004, 2936, 2834, 2733, 1693, 1607, 1600, 1590, 1582, 1567, 1509, 1480, 1464, 1436, 1412, 1386, 1297, 1272, 1252, 1233, 1205, 1172, 1143, 1121, 1112, 1049, 1021, 949, 878, 854, 845, 826, 778, 749, 733, 694, 679, 677, 654.

MS (EI, 70 eV): *m/z* (%) = 230 (100) [M^+], 229 (31), 199 (13), 170 (12), 159 (11), 158 (10), 157 (17), 133 (11).

HRMS (EI) for **$C_{14}H_{11}FO_2$** (230.0743): 230.0730 (M^+).

Synthesis of 6-fluoro-3'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (39)



2-Bromo-6-fluoro-3'-methoxy-1,1'-biphenyl (**38a**; 281 mg, 1.0 mmol) was dissolved in THF (3 mL) and cooled to -78 °C. Then *n*BuLi (2.35 M in THF, 0.55 mL, 1.3 mmol) was added and the reaction mixture was stirred at this temperature until no starting material was detected anymore (4 h). Then DMF was added (102 mg, 2.0 mmol) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 99:1) to give **39** as a yellow oil (175 mg, 76%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.83 (s, 1 H), 7.82 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.51 - 7.37 (m, 3 H), 7.03 - 6.99 (m, 1 H), 6.95 - 6.89 (m, 2 H), 3.84 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 191.2, 159.8 (d, *J* = 248 Hz), 159.6, 136.0 (d, *J* = 2 Hz), 132.9 (d, *J* = 17 Hz), 131.8 (d, *J* = 1 Hz), 129.6, 129.3 (d, *J* = 8 Hz), 123.5 (d, *J* = 1 Hz), 123.2 (d, *J* = 3 Hz), 121.0 (d, *J* = 23 Hz), 116.6 (d, *J* = 1 Hz), 114.5, 55.5.

^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -115.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 3002, 2956, 2943, 2856, 2836, 2748, 1736, 1691, 1600, 1580, 1571, 1569, 1458, 1456, 1443, 1428, 1390, 1287, 1245, 1235, 1216, 1208, 1178, 1170, 1047, 1020, 957, 866, 854, 794, 776, 740, 724, 719, 699, 680.

MS (EI, 70 eV): *m/z* (%) = 230 (47), 227 (17), 226 (10), 215 (17), 213 (30), 202 (55), 199 (19), 186 (17), 183 (30), 172 (20), 171 (20), 170 (20), 159 (23), 157 (24), 149 (12), 133 (22).

HRMS (EI) for **$C_{14}H_{11}FO_2$** (230.0743): 230.0745 (M^+).

5.4 PREPARATION OF BTSM-SUBSTITUTED HETEROARYL DERIVATIVES

Typical Procedure 1 for the cross-coupling to obtain products of type 3 (TP 1):

A dry, argon-flushed 25 mL Schlenk-flask was charged with the corresponding aryl bromide (1.0 mmol) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 5.0 mol%) which were suspended in dry toluene (1.6 mL). Then, $(TMS)_2CHMgBr \cdot LiCl$ (1.6 mL, 1.1 mmol, 0.68 M in THF) was added and the reaction mixture was stirred for the given time at 50 °C. After full conversion was detected by GC analysis, sat. aq NH_4Cl was added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the desired products.

Typical Procedure 2 for the cross-coupling to obtain products of type 6 (TP 2):

A dry, argon-flushed 25 mL Schlenk-flask was charged with the corresponding aryl bromide (1.0 mmol) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol, 5.0 mol%) which were suspended in dry toluene (3.2 mL). Then, $(TMS)_2CHZnCl \cdot MgBrCl \cdot LiCl$ (2.7 mL, 1.1 mmol, 0.41 M in THF), obtained by transmetalation of $(TMS)_2CHMgBr \cdot LiCl$ (1.6 mL, 1.1 mmol, 0.68 M in THF) with $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for the given time at 50 °C. After full conversion was detected by GC analysis, sat. aq NH_4Cl was added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the desired products.

Typical Procedure 3 for the lithiation with *n*BuLi (TP 3):

In a dry argon flushed Schlenk-flask, the arene (1.0 equiv) was dissolved in THF (0.2 M) and cooled to -30 °C. Then, *n*BuLi (1.1 equiv, 2.35 M in hexane) was added dropwise and the reaction mixture was stirred at this temperature for 30 min. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine and using undecane as internal standard.

Typical Procedure 5 for the magnesiation with TMPMgCl·LiCl (TP 4):

In a dry argon flushed Schlenk-flask, TMPMgCl·LiCl (1.5 equiv, 1.2 M in THF) was placed and the carbonyl compound (1.0 equiv) was added at 0 °C. The reaction mixture was stirred at this temperature for 75 min. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine and using undecane as internal standard.

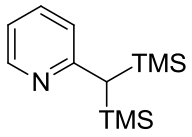
Typical Procedure 7 for the oxidation of the BTSM-substituted arenes with CAN (TP 5):

In a dry argon flushed Schlenk-flask, the BTSM-substituted compound (1.0 equiv) was dissolved in a 3:1 mixture of CH_3CN:MeOH (0.015 M) and cooled to 0 °C. Then, ceric ammonium nitrate (CAN; 5.0 equiv) was added and the reaction mixture was stirred at this temperature for 30 min. The completion of the reaction was checked by GC analysis of reaction aliquots.

Typical Procedure 8 for the Peterson olefination of the BTSM-substituted arenes (TP 6):

In a dry argon flushed Schlenk-flask, the BTSM-substituted compound (1.0 equiv) and the aldehyde (1.2 equiv) were dissolved in THF (0.0625 M) and cooled to -20 °C. Then, TBAF (tetra-*n*-butylammonium fluoride; 0.1 equiv, 1.0 M in THF) was added dropwise and the reaction mixture was stirred at this temperature for 15 min.

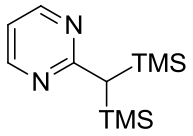
Synthesis of 2-(bis(trimethylsilyl)methyl)pyridine (44a)



According to **TP 1**, the cross-coupling of 2-bromopyridine (**43a**; 158 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry THF (1.8 mL) with $(TMS)_2CHMgBr·LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 19:1) to give **44a** as colorless oil (190 mg, 80%).

The analytical data matches the reported one in the literature.[163]

Synthesis of 2-(bis(trimethylsilyl)methyl)pyrimidine (44b)



According to **TP 1**, the cross-coupling of 2-bromopyrimidine (**43b**; 159 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry THF (1.8 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 15:1) to give **44b** as yellow oil (140 mg, 59%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.50 (d, *J* = 4.7 Hz, 2 H), 6.89 (t, *J* = 5.0 Hz, 1 H), 2.17 (s, 1 H), 0.06 - 0.03 (m, 18 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 174.2, 156.6, 116.0, 35.7, 0.2.

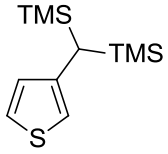
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2991, 2891, 1530, 1501, 1386, 1307, 1261, 1121, 825, 758, 751, 671.

MS (EI, 70 eV): *m/z* (%) = 238 (2), 223 (18), 129 (11), 125 (15), 113 (14), 112 (11), 111 (22), 109 (13), 95 (19), 85 (44), 84 (13), 83 (40), 71 (58).

HRMS (EI) for **$C_{11}H_{22}N_2Si_2$** (238.1322): 238.1326 (M^+).

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

Synthesis of (thiophen-3-ylmethylene)bis(trimethylsilane) (44c)



According to **TP 1**, the cross-coupling of 3-bromothiophene (**43c**; 163 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry THF (1.8 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane) to give **44c** as colorless oil (238 mg, 98%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.17 (dd, *J* = 5.0 Hz, 3.0 Hz, 1 H), 6.72 (dd, *J* = 4.7 Hz, 1.4 Hz, 1 H), 6.57 (dd, *J* = 2.8, 1.4 Hz, 1 H), 1.68 (s, 1 H), 0.07 - -0.04 (m, 18 H).

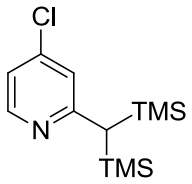
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.7, 129.6, 124.3, 117.0, 23.9, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2898, 2835, 1520, 1423, 1373, 1248, 1166, 1032, 940, 924, 827, 766, 751, 685, 639.

MS (EI, 70 eV): *m/z* (%) = 242 (34), 227 (15), 207 (20), 154 (100), 73 (61), 55 (15).

HRMS (EI) for **$C_{11}H_{22}SSi_2$** (242.0981): 242.0981 (M^+).

Synthesis of 2-(bis(trimethylsilyl)methyl)-4-chloropyridine (44d)



According to **TP 1**, the cross-coupling of 2-bromo-4-chloropyridine (**43d**; 163 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry THF (1.8 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product

was purified by flash column chromatography (*i*hexane:Et_2O = 15:1) to give **44d** as colorless oil (201 mg, 74%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.05 (d, *J* = 5.4 Hz, 1 H), 6.69 (d, *J* = 2.0 Hz, 1 H), 6.51 (dd, *J* = 5.4 Hz, 2.0 Hz, 1 H), 1.52 (s, 1 H), 0.10 - 0.07 (m, 18 H).

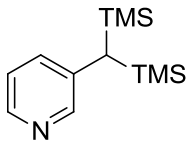
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 166.9, 150.1, 143.4, 123.1, 118.9, 33.4, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3111, 3050, 1571, 1557, 1544, 1446, 1358, 1221, 1136, 1100, 1069, 983, 863, 825, 769, 682.

MS (EI, 70 eV): *m/z* (%) = 272 (36), 271 (18), 270 (34), 260 (19), 256 (13), 254 (17), 198 (20), 196 (29), 162 (23), 139 (21), 137 (20), 73 (100).

HRMS (EI) for **$C_{12}H_{22}ClNSi_2$** (271.0979): 271.0834 (M^+).

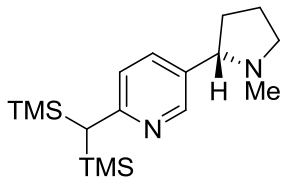
Synthesis of 3-(bis(trimethylsilyl)methyl)pyridine (44e)



According to **TP 1**, the cross-coupling of 3-bromopyridine (**43e**; 158 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry THF (1.8 mL) with $(TMS)_2CHMgBr{\cdot}LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:EtOAc = 4:1) to give **44e** as yellow oil (192 mg, 81%).

The analytical data matches the reported one in the literature.[133b]

Synthesis of (*S*)-2-(bis(trimethylsilyl)methyl)-5-(1-methylpyrrolidin-2-yl)pyridine (44f)



According to **TP 1**, the cross-coupling of (*S*)-2-bromo-5-(1-methylpyrrolidin-2-yl)pyridine (**43f**; 241 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry THF (1.8 mL) with $(TMS)_2CHMgBr \cdot LiCl$ (**30**; 1.83 mL, 1.1 mmol, 0.6 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:EtOAc:NEt_3 = 4:1:0.1) to give **44f** as orange oil (240 mg, 75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.27 (d, *J* = 2.2 Hz, 1 H), 7.46 (dd, *J* = 8.0, 2.5 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 3.27 - 3.16 (m, 1 H), 2.96 (t, *J* = 8.2 Hz, 1 H), 2.30 - 2.22 (m, 1 H), 2.19 - 2.13 (m, 1 H), 2.12 (s, 3 H), 1.97 - 1.93 (m, 1 H), 1.90 - 1.87 (m, 1 H), 1.85 - 1.73 (m, 2 H), 0.03 - 0.00 (m, 18 H).

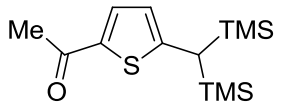
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.1, 148.9, 134.6, 132.5, 122.7, 68.8, 57.2, 40.4, 34.6, 33.0, 22.6, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2838, 2774, 1695, 1598, 1478, 1458, 1397, 1332, 1247, 1219, 1044, 868, 834.

MS (EI, 70 eV): *m/z* (%) = 321 (17), 320 (44), 319 (29), 306 (24), 305 (100), 264 (41), 263 (20), 222 (18), 135 (10), 120 (24), 92 (12), 84 (57), 73 (53).

HRMS (EI) for **$C_{17}H_{32}N_2Si_2$** (320.2104): 320.2100 (M^+).

Synthesis of 1-(5-(bis(trimethylsilyl)methyl)thiophen-2-yl)ethanone (47a)



According to **TP 2**, the cross-coupling of 1-(5-iodothiophen-2-yl)ethanone (**46a**; 252 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry toluene (3 mL) with $(TMS)_2CHZnCl{\cdot}MgBrCl{\cdot}LiCl$ (**45**; 2.7 mL, 1.1 mmol, 0.4 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 19:1) to give **47a** as brown solid (199 mg, 70%).

m.p. (°C): 93.5-95.1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48 (d, *J* = 3.9 Hz, 1 H), 6.51 (d, *J* = 3.6 Hz, 1 H), 2.46 (s, 3 H), 1.93 (s, 1 H), 0.17 - -0.02 (m, 18 H).

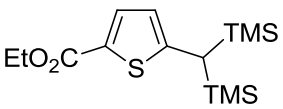
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 190.0, 158.1, 139.6, 133.7, 124.2, 26.4, 26.3, -0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2925, 1644, 1435, 1356, 1346, 1282, 1251, 1204, 1098, 1016, 925, 836, 787.

MS (EI, 70 eV): *m/z* (%) = 285 (19), 284 (73), 278 (25), 277 (58), 269 (27), 147 (39), 111 (18), 97 (22), 85 (25), 83 (19), 73 (100), 71 (29), 69.

HRMS (EI) for **$C_{13}H_{24}OSSi_2$** (284.1086): 284.1085 (M^+).

Synthesis of ethyl 5-(bis(trimethylsilyl)methyl)thiophene-2-carboxylate (47b)



According to **TP 2**, the cross-coupling of ethyl 5-iodothiophene-2-carboxylate (**46b**; 282 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry toluene (3 mL) with $(TMS)_2CHZnCl{\cdot}MgBrCl{\cdot}LiCl$ (**45**; 2.7 mL, 1.1 mmol, 0.4 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL),

extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 19:1) to give **47b** as yellow oil (217 mg, 69%).

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 7.75 (d, *J* = 3.7 Hz, 1 H), 6.28 (d, *J* = 3.7 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 1.61 (s, 1 H), 1.00 (t, *J* = 7.2 Hz, 3 H), -0.01 - -0.03 (m, 18 H).

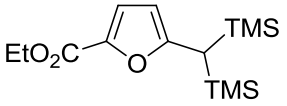
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 162.0, 154.6, 134.3, 129.3, 124.0, 60.7, 25.2, 14.4, -0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2900, 1702, 1533, 1438, 1367, 1344, 1282, 1249, 1199, 1087, 1019, 838.

MS (EI, 70 eV): *m/z* (%) = 314 (31), 299 (13), 285 (30), 257 (41), 197 (11), 196 (52), 148 (11), 147 (71), 73 (100).

HRMS (EI) for **$C_{14}H_{26}O_2SSi_2$** (314.1192): 314.1190 (M^+).

Synthesis of ethyl 5-(bis(trimethylsilyl)methyl)furan-2-carboxylate (47c)



According to **TP 2**, the cross-coupling of ethyl 5-bromofuran-2-carboxylate (**46c**; 219 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry toluene (3 mL) with $(TMS)_2CHZnCl{\cdot}MgBrCl{\cdot}LiCl$ (**45**; 2.7 mL, 1.1 mmol, 0.4 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 19:1) to give **47c** as yellow oil (257 mg, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.07 (d, *J* = 3.2 Hz, 1 H), 5.83 (d, *J* = 3.4 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.84 (s, 1 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 0.07 - 0.05 (m, 18 H).

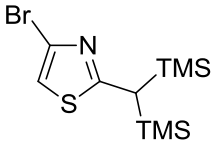
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.1, 158.9, 141.9, 120.0, 105.8, 60.4, 23.0, 14.5, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2901, 1718, 1586, 1496, 1375, 1300, 1250, 1150, 1118, 1013, 961, 827, 757.

MS (EI, 70 eV): *m/z* (%) = 298 (8), 269 (18), 180 (12), 148 (13), 147 (100), 91 (20), 83 (12), 73 (39).

HRMS (EI) for **$C_{14}H_{26}O_3Si_2$** (298.1420): 298.1421 (M^+).

Synthesis of 2-(bis(trimethylsilyl)methyl)-4-bromothiazole (47d)



According to **TP 2**, the cross-coupling of 2,4-dibromothiazole (**46d**; 243 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry toluene (3 mL) with $(TMS)_2CHZnCl{\cdot}MgBrCl{\cdot}LiCl$ (**45**; 2.7 mL, 1.1 mmol, 0.4 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:Et_2O = 19:1) to give **47d** as yellow solid (200 mg, 62%).

m.p. (°C): 76.7-78.8.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 6.32 (s, 1 H), 1.76 (s, 1 H), 0.04 (s, 18 H).

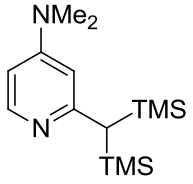
^{13}C-NMR (100 MHz, C_6D_6): δ / ppm = 173.2, 124.4, 113.1, 29.7, -0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3088, 2840, 2743, 2215, 2108, 1743, 1601, 1477, 1393, 1302, 1175, 1153, 1069, 1044, 1012, 981, 966, 875, 862, 795, 742, 721, 654.

MS (EI, 70 eV): *m/z* (%) = 321 (14), 308 (19), 242 (20), 234 (40), 232 (37), 73 (100).

HRMS (EI) for **$C_{10}H_{20}BrNSSi_2$** (321.0038): 321.0038 (M^+).

Synthesis of 2-(bis(trimethylsilyl)methyl)-*N*,*N*-dimethylpyridin-4-amine (47e)



According to **TP 2**, the cross-coupling of 2-iodo-*N*,*N*-dimethylpyridin-4-amine (**46e**; 178 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry toluene (3 mL) with $(TMS)_2CHZnCl \cdot MgBrCl \cdot LiCl$ (**45**; 2.7 mL, 1.1 mmol, 0.4 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:EtOAc:NEt_3 = 5:5:0.2) to give **47e** as orange solid (225 mg, 80%).

m.p. (°C): 150.5-158.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.00 (d, *J* = 5.8 Hz, 1 H), 6.18 (dd, *J* = 6.1, 2.5 Hz, 1 H), 6.07 (d, *J* = 2.5 Hz, 1 H), 2.90 (s, 6 H), 1.74 (s, 1 H), 0.03 - 0.00 (m, 18 H).

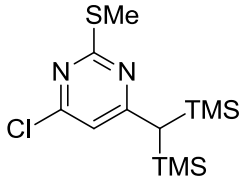
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.6, 154.3, 148.9, 105.0, 102.8, 39.1, 33.1, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2953, 2922, 2853, 1622, 1608, 1532, 1480, 1433, 1379, 1307, 1194, 1112, 1099, 1026, 998.

MS (EI, 70 eV): *m/z* (%) = 277 (100), 262 (10), 201 (22), 183 (59), 152 (19), 139 (12), 136 (10), 108 (11), 83 (10), 77 (30).

HRMS (EI) for **$C_{14}H_{28}N_2Si_2$** (280.1791): 280.1804 (M^+).

Synthesis of 4-(bis(trimethylsilyl)methyl)-6-chloro-2-(methylthio)pyrimidine (47f)



According to **TP 2**, the cross-coupling of 4-chloro-6-iodo-2-(methylthio)pyrimidine (**46f**; 287 mg, 1.0 mmol) catalyzed by $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) in dry toluene (3 mL) with $(TMS)_2CHZnCl \cdot MgBrCl \cdot LiCl$ (**45**; 2.7 mL, 1.1 mmol, 0.4 M in THF) was completed within 16 h at 50 °C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (*i*hexane:CH_2Cl_2 = 4:1) to give **47f** as white solid (271 mg, 85%).

m.p. (°C): 53.8-54.9.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 6.56 (s, 1 H), 2.53 (s, 3 H), 1.75 (s, 1 H), 0.09 - 0.07 (m, 18 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 175.8, 172.4, 160.0, 114.8, 35.0, 14.4, 0.3.

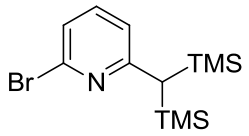
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2927, 2854, 1532, 1508, 1431, 1301, 1245, 1215, 1153, 1114, 1040, 977, 940, 861, 841, 823.

MS (EI, 70 eV): *m/z* (%) = 318 (7), 306 (13), 305 (53), 304 (37), 303 (100), 122 (10), 97 (10), 73 (47), 71 (12), 57 (13).

HRMS (EI) for **$C_{12}H_{23}ClN_2SSi_2$** (318.0809): 318.0790 (M^+).

5.5 METALATION OF BTSM-SUBSTITUTED HETEROARYL DERIVATIVES

Synthesis of 2-(bis(trimethylsilyl)methyl)-6-bromopyridine (48a)



In a dry argon flushed Schlenk-flask, pyridine **44a** (237 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) was added and the reaction mixture was stirred for 15 min. Then, $TMP_2Mg \cdot 2LiCl$ (1.8 mL, 0.6 M in THF) was added at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Then $(CBrCl_2)_2$ (652 mg, 2.0 mmol) in THF (1.0 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 20:1) to give **48a** as a yellow oil (190 mg, 60%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.31 (t, *J* = 7.7 Hz, 1 H), 7.11 (d, *J* = 6.9 Hz, 1 H), 6.81 (d, *J* = 6.9 Hz, 1 H), 1.93 (s, 1 H), 0.06 - 0.04 (m, 18 H).

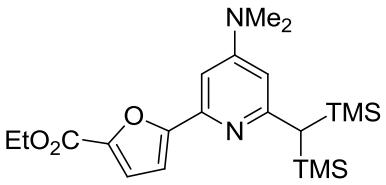
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 140.8, 138.1, 122.4, 121.5, 33.4, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944, 2888, 2842, 1551, 1541, 1421, 1398, 1273, 1251, 1221, 1156, 1107, 1096, 1078, 1032, 968, 886, 871, 829, 821, 773, 760, 753, 731, 721, 686, 672, 651.

MS (EI, 70 eV): *m/z* (%) = 315 (6), 230 (12), 228 (31), 184 (18), 73 (32), 71 (14), 69 (100).

HRMS (EI) for **$C_{12}H_{22}BrNSi_2$** (315.0474): 315.0483 (M^+).

Synthesis of ethyl 5-(6-(bis(trimethylsilyl)methyl)-4-(dimethylamino)pyridin-2-yl)furan-2-carboxylate (48b)



In a dry argon flushed Schlenk-flask, pyridine **47e** (281 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) was added and the reaction mixture was stirred for 15 min. Then, $TMP_2Mg \cdot 2LiCl$ (1.8 mL, 0.6 M in THF) was added at 0 °C and the reaction mixture was stirred at this temperature for 15 min. Then $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF) was slowly added at -20 °C and the reaction was stirred at this temperature for 15 min. Then $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), SPhos (16 mg, 0.04 mmol) and ethyl 5-bromofuran-2-carboxylate (175 mg, 0.8 mmol) were added and the reaction mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 8.5:1.5) to give **48b** as a brown solid (251 mg, 75%).

m.p. (°C): 118-121.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.22 (d, *J* = 3.7 Hz, 1 H), 7.03 (d, *J* = 3.4 Hz, 1 H), 6.87 (d, *J* = 2.5 Hz, 1 H), 6.04 (d, *J* = 2.5 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.01 (s, 6 H), 1.64 (s, 1 H), 1.38 (t, *J* = 7.1 Hz, 3 H), 0.06 (s, 18 H).

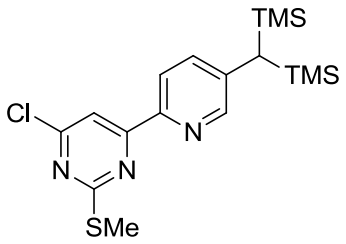
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.2, 159.3, 159.1, 155.0, 147.2, 143.7, 120.1, 109.4, 105.1, 98.6, 60.9, 39.5, 33.0, 14.5, 0.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2901, 2854, 1717, 1604, 1569, 1520, 1431, 1416, 1371, 1304, 1248, 1226, 1174, 1140, 1115, 1017, 968, 893, 852, 838, 809, 760.

MS (EI, 70 eV): *m/z* (%) = 418 (22), 405 (13), 404 (34), 403 (100), 389 (13), 375 (18), 346 (22), 345 (68), 344 (16), 331 (11), 316 (11), 374 (43), 273 (12), 245 (12), 201 (13), 73 (14).

HRMS (EI) for **$C_{21}H_{34}N_2O_3Si_2$** (418.2108): 418.2095 (M^+).

Synthesis of 4-(5-(bis(trimethylsilyl)methyl)pyridin-2-yl)-6-chloro-2-(methylthio)pyrimidine (48c)



In a dry argon flushed Schlenk-flask, pyridine **44e** (237 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) was added and the reaction mixture was stirred for 15 min. Then, $TMP_2Mg \cdot 2LiCl$ (1.8 mL, 0.6 M in THF) was added at 0 °C and the reaction mixture was stirred at this temperature for 15 min. Then $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF) was slowly added at -20 °C and the reaction was stirred at this temperature for 15 min. Then $Pd(dba)_2$ (12 mg, 0.02 mmol), tfp (9 mg, 0.04 mmol) and 4-chloro-6-iodo-2-(methylthio)pyrimidine (229 mg, 0.8 mmol) were added and the reaction mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 50:1) to give **48c** as a white solid (206 mg, 65%).

m.p. (°C): 80-82.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.34 - 8.30 (m, 1 H), 8.32 - 8.26 (m, 1 H), 8.00 (s, 1 H), 7.42 (dd, *J* = 8.2, 2.4 Hz, 1 H), 2.65 (s, 3 H), 1.65 (s, 1 H), 0.17 - -0.03 (m, 18 H).

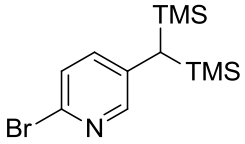
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 173.1, 164.7, 162.1, 149.8, 148.1, 143.4, 136.3, 122.0, 112.1, 27.9, 14.5, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2931, 1549, 1509, 1476, 1382, 1320, 1294, 1243, 1217, 1197, 1117, 1038, 860, 840, 811.

MS (EI, 70 eV): *m/z* (%) = 398 (12), 397 (38), 396 (25), 395 (81), 380 (17), 307 (14), 287 (10), 274 (11), 273 (20), 272 (85), 240 (13), 73 (100).

HRMS (EI) for **$C_{17}H_{26}ClN_3SSi_2$** (395.1074): 395.1071 (M^+).

Synthesis of 5-(bis(trimethylsilyl)methyl)-2-bromopyridine (48d)



In a dry argon flushed Schlenk-flask, pyridine **44e** (237 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (156 mg, 1.1 mmol) was added and the reaction mixture was stirred for 15 min. Then, $TMP_2Mg \cdot 2LiCl$ (1.8 mL, 0.6 M in THF) was added at 0 °C and the reaction mixture was stirred at this temperature for 15 min. Then $(CBrCl_2)_2$ (652 mg, 2.0 mmol) in THF (1.0 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 30:1) to give **48d** as a yellow oil (215 mg, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 2.5 Hz, 1 H), 7.30 (d, *J* = 8.3 Hz, 1 H), 7.12 (dd, *J* = 8.2, 2.6 Hz, 1 H), 1.47 (s, 1 H), 0.04 (s, 18 H).

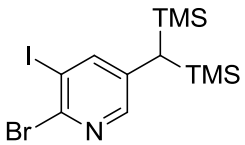
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.9, 139.0, 138.2, 136.8, 127.4, 26.0, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2898, 1551, 1453, 1440, 1370, 1250, 1207, 1128, 1088, 1032, 1017, 854, 824.

MS (EI, 70 eV): *m/z* (%) = 318 (13), 317 (43), 315 (37), 302 (10), 301 (11), 228 (14), 227 (15), 148 (14), 73 (100).

HRMS (EI) for **$C_{12}H_{22}BrNSi_2$** (315.0474): 315.0458 (M^+).

Synthesis of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-iodopyridine (48e)



In a dry argon flushed Schlenk-flask, $TMP_2Mg \cdot 2LiCl$ (2.5 mL, 0.6 M in THF) was placed and cooled to 0 °C. Pyridine **48d** (316 mg, 1.0 mmol) was added and the reaction mixture was stirred

for 2.5 h. Then the reaction mixture was cooled to -20 °C and I_2 (508 mg, 2.0 mmol) in THF (1.0 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 20:1) to give **48e** as a yellow solid (362 mg, 82%).

m.p. (°C): 85-86.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.96 (d, *J* = 2.2 Hz, 1 H), 7.70 (d, *J* = 2.5 Hz, 1 H), 1.41 (s, 1 H), 0.12 - -0.05 (m, 18 H).

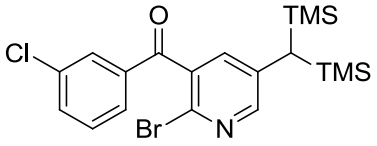
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.5, 147.8, 142.4, 140.7, 98.8, 25.9, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2923, 2852, 1550, 1401, 1376, 1246, 1194, 1122, 1033, 1020, 914, 873, 835.

MS (EI, 70 eV): *m/z* (%) = 443 (33), 441 (32), 354 (9), 352 (9), 74 (9), 73 (100).

HRMS (EI) for **$C_{12}H_{21}BrINSi_2$** (440.9441): 440.9432 (M^+).

Synthesis of (5-(bis(trimethylsilyl)methyl)-2-bromopyridin-3-yl)(3-chlorophenyl)methanone (48f)



In a dry argon flushed Schlenk-flask, $TMP_2Mg{\cdot}2LiCl$ (2.5 mL, 0.6 M in THF) was placed and cooled to 0 °C. Pyridine **48d** (316 mg, 1.0 mmol) was added and the reaction mixture was stirred for 2.5 h. Then the reaction mixture was cooled to -40 °C and $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF) was slowly added and the reaction mixture was stirred at this temperature for 15 min. Then $CuCN{\cdot}2LiCl$ (1.1 mL, 1.1 mmol, 1.0 M in THF) was slowly added followed by 3-chlorobenzoyl chloride (192 mg, 1.1 mmol) and the reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in*

vacuo. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **48f** as a yellow oil (273 mg, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 2.5 Hz, 1 H), 7.78 (s, 1 H), 7.64 - 7.59 (m, 2 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.18 (d, *J* = 2.5 Hz, 1 H), 1.56 (s, 1 H), 0.06 (s, 18 H).

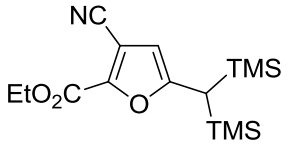
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 193.0, 151.1, 139.6, 137.5, 136.0, 135.4, 134.2, 132.9, 132.3, 130.3, 130.0, 128.3, 26.4, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2899, 1678, 1571, 1538, 1407, 1295, 1250, 1197, 1151, 1059, 1031, 919, 862, 829.

MS (EI, 70 eV): *m/z* (%) = 455 (37), 453 (26), 238 (14), 111 (9), 73 (100).

HRMS (EI) for **$C_{19}H_{25}BrClNOSi_2$** (453.0347): 453.0330 (M^+).

Synthesis of ethyl 5-(bis(trimethylsilyl)methyl)-3-cyanofuran-2-carboxylate (49a)



In a dry argon flushed Schlenk-flask, furan **47c** (237 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. Then TMPMgCl·LiCl (0.92 mL, 1.1 mmol, 1.2 M in THF) was added at 0 °C and the reaction mixture was stirred at this temperature for 15 min. Then TsCN (362 mg, 2.0 mmol) in THF (1.0 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with sat. aq NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:Et_2O = 9:1) to give **49a** as a yellow oil (281 mg, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.06 (s, 1 H), 4.40 (d, *J* = 7.1 Hz, 2 H), 1.84 (s, 1 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 0.10 - 0.07 (m, 18 H).

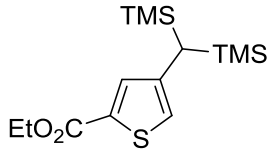
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.3, 156.6, 146.0, 112.7, 107.0, 104.5, 61.9, 23.3, 14.3, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2902, 2242, 1725, 1592, 1511, 1398, 1383, 1305, 1251, 1188, 1078, 1016, 962, 834.

MS (EI, 70 eV): *m/z* (%) = 323 (20), 205 (17), 149 (23), 147 (38), 91 (16), 73 (100).

HRMS (EI) for **$C_{15}H_{25}NO_3Si_2$** (323.1373): 323.1379 (M^+).

Synthesis of ethyl 4-(bis(trimethylsilyl)methyl)thiophene-2-carboxylate (49b)



According to **TP 3**, the lithiation of **44c** (242 mg, 1.0 mmol, 1.0 equiv) with *n*BuLi (0.47 mL, 1.1 mmol, 1.1 equiv, 2.35 M in hexane) was completed after 30 min at -30 °C. Then, ethyl chloroformate (130 mg, 1.2 mmol, 1.2 equiv) in THF (1.2 mL) was slowly added at -30 °C and the reaction mixture was allowed to warm up to room temperature. The reaction was quenched with sat. aq NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 100:1) to give **49b** as yellow oil (239 mg, 76%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.41 (d, *J* = 1.5 Hz, 1 H), 8.81 (d, *J* = 1.5 Hz, 1 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 1.64 (s, 1 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 0.03 (s, 18 H).

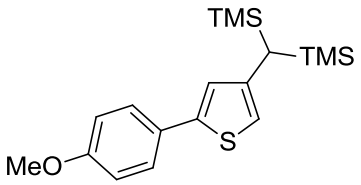
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.4, 143.0, 135.0, 132.8, 124.5, 61.0, 24.1, 14.3, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = = 2954, 2899, 2838, 1708, 1536, 1416, 1370, 1278, 1247, 1217, 1158, 1126, 1069, 1030, 953, 873, 836, 826, 761, 687.

MS (EI, 70 eV): *m/z* (%) = 314 (33), 269 (11), 257 (17), 226 (22), 196 (33), 168 (21), 153 (10), 147 (11), 137 (28), 75 (11), 73 (100), 45 (18), 43 (11).

HRMS (EI) for **$C_{14}H_{26}O_2SSi_2$** (314.1192): 314.1183 (M^+).

Synthesis of ((5-(4-methoxyphenyl)thiophen-3-yl)methylene)bis(trimethylsilane) (49c)



According to **TP3**, the lithiation of **44c** (242 mg, 1.0 mmol, 1.0 equiv) with *n*BuLi (0.47 mL, 1.1 mmol, 1.1 equiv, 2.35 M in hexane) was completed after 30 min at -30 °C. $ZnCl_2$ (1.2 mL, 1.2 mmol, 1.0 M in THF) was slowly added at -30 °C and the resulting solution was stirred for 30 min and allowed to warm up to room temperature. Then, $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), SPhos (16.4 mg, 0.04 mmol) and 4-bromoanisole (168 mg, 0.9 mmol, 0.9 equiv) were added and the reaction mixture was stirred for 12 h at 50 °C. The reaction was quenched with sat. aq NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 100:1) to give **49c** as yellow oil (285 mg, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.1 Hz, 2 H), 6.82 (s, 1 H), 6.46 (s, 1 H), 3.82 (s, 3 H), 1.62 (s, 1 H), 0.05 (s, 18 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.9, 142.5, 129.2, 127.7, 126.8, 124.6, 115.8, 114.2, 55.3, 24.1, 0.1.

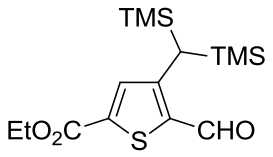
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3001, 2952, 2899, 2835, 1610, 1505, 1464, 1442, 1416, 1360, 1291, 1246, 1177, 1154, 1108, 1034, 982, 926, 859, 823, 792, 765, 722, 687, 658.

MS (EI, 70 eV): *m/z* (%) = 348 (37), 276 (10), 261 (10), 260 (38), 73 (100), 45 (14), 43 (11).

HRMS (EI) for **$C_{18}H_{28}OSSi_2$** (348.1399): 348.1392 (M^+).

5.6 TRANSFORMATION AND FUNCTIONALIZATION OF BTSM-SUBSTITUTED HETEROARYL DERIVATIVES

Synthesis of ethyl 4-(bis(trimethylsilyl)methyl)-5-formylthiophene-2-carboxylate (49k)



In a dry argon flushed Schlenk-flask, furan **51c** (393 mg, 1.0 mmol) was dissolved in THF (5.0 mL) and cooled to -20 °C. Then *i*PrMgCl·LiCl (0.85 mL, 1.1 mmol, 1.3 M in THF) was added and the reaction mixture was stirred at this temperature for 30 min. Then the reaction was cooled to -50 °C and DMF (365 mg, 5.0 mmol) in THF (10 mL) was added dropwise and the reaction mixture was kept at this temperature over night. The reaction was quenched with sat. aq NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 20:1) to give **49k** as a yellow oil (271 mg, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.95 (s, 1 H), 7.43 (s, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 2.64 (s, 1 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 0.08 - 0.06 (m, 18 H).

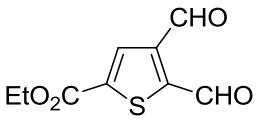
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 183.1, 161.8, 153.3, 140.3, 139.2, 134.9, 62.1, 23.9, 14.4, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2900, 1716, 1660, 1525, 1372, 1250, 1220, 1145, 1076, 1019, 975, 883, 862, 832.

MS (EI, 70 eV): *m/z* (%) = 342 (22), 313 (19), 298 (9), 209 (9), 147 (23), 73 (100), 45 (28).

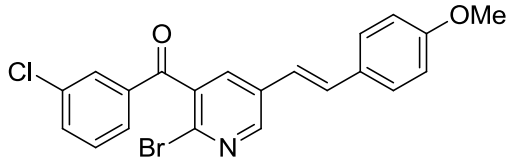
HRMS (EI) for **$C_{15}H_{26}O_3SSi_2$** (342.1141): 342.1132 (M^+).

Synthesis of ethyl 4,5-diformylthiophene-2-carboxylate (50a)



According to **TP 5**, CAN (2.74 g, 5.0 mmol, 5.0 equiv) was added in one portion to **49k** (343 mg, 1.0 mmol, 1.0 equiv) in 17 mL MeOH and 50 mL CH_3CN and the resulting mixture was stirred for 2 days. CF_3COOH (5 mL) was added to the crude reaction mixture and it was stirred for further 15 min. Then, the reaction mixture was quenched with H_2O (10 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo* to give **50a** as yellow oil (193 mg, 91%). The crude product was used without further purification.

Synthesis of (*E*)-(2-bromo-5-(4-methoxystyryl)pyridin-3-yl)(3-chlorophenyl)methanone (50b)



According to **TP 6**, (5-(bis(trimethylsilyl)methyl)-2-bromopyridin-3-yl)(3-chlorophenyl)-methanone (455 mg, 1.0 mmol, 1.0 equiv) reacted with 4-methoxybenzaldehyde (163 mg, 1.2 mmol, 1.2 equiv) catalyzed by TBAF (0.1 mL, 0.1 mmol, 0.1 equiv, 1 M in THF) at -20 °C within 15 min. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **50b** as a yellow solid (395 mg, 92%, E:Z > 99:1).

m.p. (°C): 138.9-141.9.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.57 (d, *J* = 2.2 Hz, 1 H), 7.85 (s, 1 H), 7.75 (d, *J* = 2.5 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.62 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.46 (d, *J* = 8.1 Hz, 3 H), 7.15 (d, *J* = 16.4 Hz, 1 H), 6.93 - 6.88 (m, 3 H), 3.83 (s, 3 H).

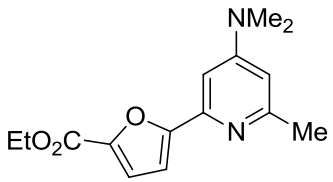
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 193.0, 160.3, 149.4, 137.3, 136.9, 135.7, 135.4, 134.3, 133.5, 133.2, 132.7, 130.3, 129.9, 128.8, 128.5, 128.4, 120.2, 114.5, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2923, 2854, 1735, 1673, 1636, 1604, 1572, 1511, 1461, 1419, 1296, 1247, 1235, 1173, 1147, 1054, 1028, 960.

MS (EI, 70 eV): *m/z* (%) = 428 (34), 427 (67), 426 (13), 313 (18), 138 (30), 111 (27).

HRMS (EI) for **$C_{21}H_{15}BrClNO_2$** (426.9975): 426.9962 (M^+).

Synthesis of ethyl 5-(4-(dimethylamino)-6-methylpyridin-2-yl)furan-2-carboxylate (50c)



In a dry argon flushed Schlenk-flask, pyridine **48b** (419 mg, 1.0 mmol) was dissolved in THF (5.0 mL) and cooled to 0 °C. Then TBAF (1.1 mL, 1.1 mmol, 1.1 equiv, 1 M in THF) was added and the reaction mixture was stirred for 15 min. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc:NEt_3 = 20:5:1) to give **50c** as a yellow oil (247 mg, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.24 (d, *J* = 3.4 Hz, 1 H), 7.13 (d, *J* = 3.2 Hz, 1 H), 6.98 (d, *J* = 2.2 Hz, 1 H), 6.32 (d, *J* = 2.2 Hz, 1 H), 4.38 (q, *J* = 7.3 Hz, 2 H), 3.06 (s, 6 H), 2.48 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

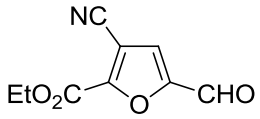
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.1, 158.7, 158.1, 155.4, 147.8, 144.1, 120.0, 109.8, 105.5, 100.6, 61.1, 39.5, 25.0, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946, 2855, 2818, 1711, 1608, 1576, 1522, 1440, 1367, 1297, 1270, 1220, 1172, 1137, 1118, 1012, 979, 880, 815. 760.

MS (EI, 70 eV): *m/z* (%) = 274 (100), 273 (22), 246 (15), 245 (29), 229 (11), 202 (18), 201 (43), 114 (25), 57 (13).

HRMS (EI) for **$C_{15}H_{18}N_2O_3$** (274.1317): 274.1309 (M^+).

Synthesis of ethyl 3-cyano-5-formylfuran-2-carboxylate (50d)



According to **TP 5**, to **49a** (324 mg, 1.0 mmol, 1.0 equiv) in 17 mL MeOH and 50 mL CH_3CN was added CAN (2.74 g, 5.0 mmol, 5.0 equiv) in one portion and the resulting mixture was stirred for 2 days. To the crude reaction mixture CF_3COOH (5 mL) was added and the reaction mixture was stirred for further 15 min. Then, the reaction mixture was quenched with H_2O (10 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (dichloromethane) to give **50d** as a yellow oil (179 mg, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.83 (s, 1 H), 7.45 (s, 1 H), 4.52 (q, *J* = 7.1 Hz, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H).

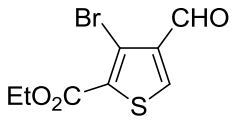
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 178.0, 155.8, 153.1, 151.0, 119.5, 110.7, 104.7, 63.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3331, 3139, 3128, 2842, 2817, 2752, 2706, 2242, 1783, 1696, 1671, 1660, 1592, 1472, 1458, 1397, 1369, 1272, 1241, 1227, 1202, 1151, 1085, 1023, 948, 934, 881, 840, 761, 763, 699.

MS (EI, 70 eV): *m/z* (%) = 193 (2), 128 (2), 120 (3), 88 (5), 85 (2), 73 (15), 45 (16), 43 (100).

HRMS (EI) for **$C_9H_7NO_4$** (193.0375): 193.0365 (M^+).

Synthesis of ethyl 3-bromo-4-formylthiophene-2-carboxylate (50e)



According to **TP 5,** CAN (2.74 g, 5.0 mmol, 5.0 equiv) was added in one portion to **49h** (392 mg, 1.0 mmol, 1.0 equiv) in 17 mL MeOH and 50 mL CH_3CN and the resulting mixture was stirred for 2 days. CF_3COOH (5 mL) was added to the crude reaction mixture and it was stirred for further 15 min. Then, the reaction mixture was quenched with H_2O (10 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane:EtOAc = 9:1) to give **50e** as a white solid (245 mg, 93%).

m.p. (°C): 97-98.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.01 (s, 1 H), 8.31 (s, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

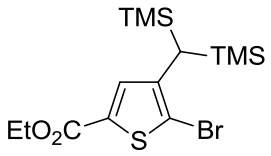
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 185.2, 160.2, 139.2, 137.6, 130.1, 117.7, 62.1, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3107, 2923, 2854, 1712, 1673, 1498, 1333, 1234, 1159, 1120, 1088, 1029, 825, 756.

MS (EI, 70 eV): *m/z* (%) = 264 (100), 262 (96), 261 (10), 236 (95), 235 (78), 234 (98), 233 (63), 221 (13), 190 (35), 189 (26), 160 (11), 137 (17), 117 (13), 82 (84), 81 (80), 77 (19).

HRMS (EI) for **$C_8H_7BrO_3S$** (261.9299): 261.9288 (M^+).

Synthesis of ethyl 4-(bis(trimethylsilyl)methyl)-5-bromothiophene-2-carboxylate (51c)



In a dry argon flushed Schlenk-flask, **49b** (315 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry DMF (2 mL) and cooled to 0 °C. Then, *N*-bromosuccinimide (178 mg, 1.0 mmol, 1.0 equiv) was added in one portion and the reaction mixture was allowed to warm up to room temperature and

stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica (*i*hexane) to give **51c** as red oil (287 mg, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 (s, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 1.84 (s, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 0.00 (s, 18 H).

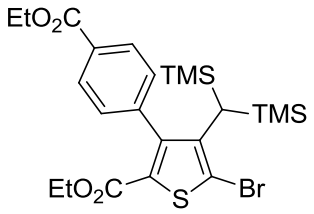
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.5, 143.2, 132.5, 132.2, 114.7, 61.2, 23.0, 14.3, -0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2900, 2852, 1712, 1541, 1408, 1348, 1278, 1248, 1204, 1161, 1070, 1035, 961, 864, 836, 826, 768, 748, 689.

MS (EI, 70 eV): *m/z* (%) = 394 (23), 392 (20), 325 (30), 313 (15), 383 (53), 276 (17), 274 (18), 225 (10), 195 (48), 167 (15), 139 (11), 111 (14), 97 (19), 95 (12), 85 (18), 83 (17), 81 (13), 73 (100), 71 (19), 69 (21), 57 (30), 55 (20), 45 (16), 43 (20).

HRMS (EI) for **$C_{14}H_{25}{}^{79}BrO_2SSi_2$** (392.0297): 392.0287($M^+$).

Synthesis of ethyl 4-(bis(trimethylsilyl)methyl)-5-bromo-3-(4-(ethoxycarbonyl)-phenyl)thiophene-2-carboxylate (53b)



According to **TP 4**, the magnesiation of **51c** (393 mg, 1.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (1.25 mL, 1.5 mmol) was completed within 75 min at 0 °C. After the addition of $ZnCl_2$ (1.6 mL, 1.6 mmol, 1.0 M in THF), the reaction mixture was stirred for 30 min at this temperature. Then, $Pd(dba)_2$ (11.5 mg, 0.02 mmol), tfp (9.29 mg, 0.04 mmol) and ethyl 4-iodobenzoate (248 mg, 0.9 mmol, 0.9 equiv) were added and the reaction mixture was stirred for 12 h at 50 °C. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was

purified by flash column chromatography on silica (*i*hexane:EtOAc = 50:1) to give **53b** as yellow crystals (366 mg, 75%).

m.p. (°C): 100 - 101.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (d, *J* = 8.1 Hz, 2 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 1.51 (s, 1 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.09 (t, *J* = 7.1 Hz, 3 H), 0.00 (s, 18 H).

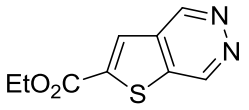
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.3, 160.9, 147.9, 144.7, 141.4, 129.9, 129.9, 129.1, 112.4, 105.2, 61.0, 61.0, 21.7, 14.3, 13.9, 1.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2955, 2898, 2852, 1715, 1611, 1427, 1366, 1341, 1271, 1248, 1214, 1152, 1100, 1086, 1023, 981, 837, 770, 763, 713, 695, 686.

MS (EI, 70 eV): *m/z* (%) = 540 (1), 481 (10), 479 (8), 469 (11), 467 (9), 462 (12), 461 (32), 423 (13), 395 (13), 393 (10), 351 (19), 349 (19), 433 (15), 343 (53), 271 (12), 73 (100), 45 (12).

HRMS (EI) for **$C_{23}H_{33}BrO_4SSi_2$** (540.0821): 540.0837 (M^+).

Synthesis of ethyl thieno[2,3-d]pyridazine-2-carboxylate (55)



According to **TP 5**, to **49k** (343 mg, 1.0 mmol, 1.0 equiv) in 17 mL MeOH and 50 mL CH_3CN was added CAN (2.74 g, 5.0 mmol, 5.0 equiv) in one portion and the resulting mixture was stirred for 2 days. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was dissolved in acetone (10 mL) and *p*TsOH·H_2O (19 mg, 0.1 mmol) was added and the reaction was stirred for 1 h. The solvents were evaporated *in vacuo*. Then the crude product was dissolved in THF (10 mL) and $N_2H_4·H_2O$ (100 mg, 2.0 mmol) was added and the reaction mixture was stirred for 1 h. Then, the reaction mixture was quenched with NH_4Cl (10 mL), extracted with EtOAc (3 x 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column

chromatography (silica, CH_2Cl_2:EtOAc:NEt_3 = 4:4:0.1) to give **55** as a brown solid (171 mg, 82%).

m.p. (°C): 117-118.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.70 (s, 1 H), 9.58 (d, *J* = 1.2 Hz, 1 H), 8.15 (s, 1 H), 4.45 (q, *J* = 7.1 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.3, 147.5, 146.7, 140.9, 140.6, 135.3, 127.6, 62.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2960, 2924, 2853, 1709, 1538, 1474, 1442, 1370, 1286, 1250, 1175, 1065, 1011, 950, 932, 798.

MS (EI, 70 eV): *m/z* (%) = 208 (100), 136 (7), 135 (17), 81 (7), 69 (6), 63 (19).

HRMS (EI) for **$C_9H_8N_2O_2S$** (208.0306): 208.0283 (M^+).

D. APPENDIX

1 LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
*n*Bu	*n*-butyl
*s*Bu	*s*-butyl
*t*Bu	*t*-butyl
calc.	calculated
CAN	ceric ammonium nitrate
conc.	concentrated
*c*Hex	cyclohexyl
δ	chemical shifts in parts per million
d	doublet
dba	*trans,trans*-dibenzylideneacetone
DMF	*N*,*N*-dimethylfomamide
DMAP	4-(dimethylamino)pyridine
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dppe	diphenylphosphinoethane
dppp	diphenylphosphinopropane
DPE-Phos	bis(2-diphenylphosphino-phenyl)ether
E	electrophile
EI	electron impact
ESI	electrospray ionization
equiv	equivalent
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
IR	infra-red
J	coupling constant (NMR)
M	Molarity
m	meta
m	multiplet
Me	methyl
Met	metal
min	minute
mmol	millimole
M.p.	melting point
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
*i*Pr	iso-propyl
q	quartet
R	organic substituent
rt	room temperature
sat.	saturated
s	singulet
S-Phos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Ts	4-toluenesulfonyl