Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

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Zincation of Heterocycles and Aryl Nonaflates.
Directed Magnesiation of Highly Substituted Anilines and
Amino-Substituted Heterocycles.
Synthesis of Heterobenzylic Zinc Compounds.
New Generation of Iminium Salts.

von

Gabriel Andrés Monzón Díaz

aus

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1) M. Mosrin, G. Monzón, T. Bresser, P. Knochel, "High Temperature Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl and Microwave irradiation", *Chem. Commun*. **2009**, *37*, 5615-5617.

2) G. Monzón, P. Knochel, "Directed *ortho*- and *meta*-Magnesiation or Zincation of Polyfunctional Aryl Nonaflates", *Synlett* **2010**, 304-308.

3) S. Wunderlich, T. Bresser, C. Dunst, G. Monzón, P. Knochel, "Efficient Preparation of Polyfunctional Organometallics via Directed *ortho*-Metalation", *Synthesis* **2010**, 2670-2678.

4) T. Bresser, M. Mosrin, G. Monzón, P. Knochel, "Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl·LiCl", *J. Org. Chem*. **2010**, *75*, 4686-4695.

5) T. Bresser, G. Monzón, M. Mosrin, P. Knochel, "Scaleable Preparation of Sensitive Functionalized Aromatics and Heteroaromatics via Directed Metalation Using TMPZnCl·LiCl" *Org. Res. Process Dev*. **2010**, *14*, 1299-1303.

6) G. Monzón, A. J. Wagner, A. Metzger, P. Knochel, "Preparation and Reactions of Heterocyclic Benzylic Zinc Reagents" *submitted for publication*.

7) G. Monzón, I. Tirotta, P. Knochel, "Room Temperature *ortho*- and *meta*-Magnesiation of Functionalized Anilines and Amino-Substituted Pyridines and Pyrazines", *Angew. Chem. Int. Ed*. **2012**, *accepted for publication.* DOI: 201205465.

A mí familia

*"Act as if everything depended on you;
trust as if everything depended on God"*

- St. Ignatius of Loyola

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A. INTRODUCTION

1. Overview

Nature has provided us with excellent organisms as organic synthetic tools for the preparation of vital compounds. These are generated in an energetic efficient manner, with benign byproducts and prepared at mild temperatures usually using water as solvent. In 1828 the origin of synthetic organic chemistry began with the synthesis of urea by *Wöhler* and of acetic acid by *Kolbe*. Ever since, the formation of C-C and C-heteroatom bonds is an indispensable tool for modern life.[1] Few years later, the work of *Frankland* with diethylzinc[2] gave birth to organometallic chemistry and it was followed by *Grignard* with the synthesis of organomagnesium compounds.[3] Since then, organometallic chemistry is a pivotal branch in organic synthesis.

Above and beyond zinc and magnesium reagents, a broad array of other metals has been investigated for the generation of organometallic reagents and transition metal-catalyzed reactions.[4] This was recognized by the 2010 Nobel Prize in Chemistry awarded to three organometallic chemists: *Heck* for the cross-coupling of organohalides with olefins catalyzed by Pd(0); *Negishi* for the catalytic cross-coupling of organozinc reagents with organohalides in the presence of a palladium catalyst; and *Suzuki* for the cross-coupling of organoboron reagents with aryl and vinyl halides promoted by palladium catalysis and a base.[5] The diversity in the chemical character and behavior of the organometallic compounds makes possible to tune them according to the needs to meet, for example lithium and magnesium reagents with their highly polar carbon-metal bond and high reactivity.[6] In contrast, zinc and boron reagents exhibit a higher stability and a broader functional group tolerance.[7] Furthermore, organometallic chemistry has found innumerous applications in organic synthesis research laboratories as well as in industry processes. For example the kilogram scale synthesis of a benzophenone-based NNRT (**1**) inhibitor of HIV-1 developed by Boehringer Ingelheim, where the arylmagnesium reagent **2** in the presence of bis[2-(*N,N*-dimethylamino)ethyl] ether couples with 3-fluoro-5-

[1] K. C. Nicolau, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed*. **2005**, *44*, 4442.

[2] a) E. Frankland, *Liebigs. Ann. Chem*. **1848-9**, *71*, 171; b) E. Frankland, *J. Chem. Soc*. **1848-9**, *2*, 263.

[3] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; b) V. Grignard, *Ann. Chim*. **1901**, *24*, 433.

[4] *Handbook of Functionalized Organometallics, Vol. 1 and 2*, (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

[5] a) The Royal Swedish Acadamy of Science, Press Release: **2010**; b) L. Croft, *Nat. Chem*. **2010**, *2*, 1009.

[6] G. Wu, M. Huang, *Chem. Rev*. **2006**, *106*, 2596.

[7] N. Miyaura, A. Suzuki, *Chem. Rev*. **1995**, *95*, 2457.

(trifluoromethyl)benzoyl chloride and affords the diaryl ketone **3** in 80% yield. This product is further reacted to obtain the NNRT (**1**) inhibitor (Scheme 1)[8]
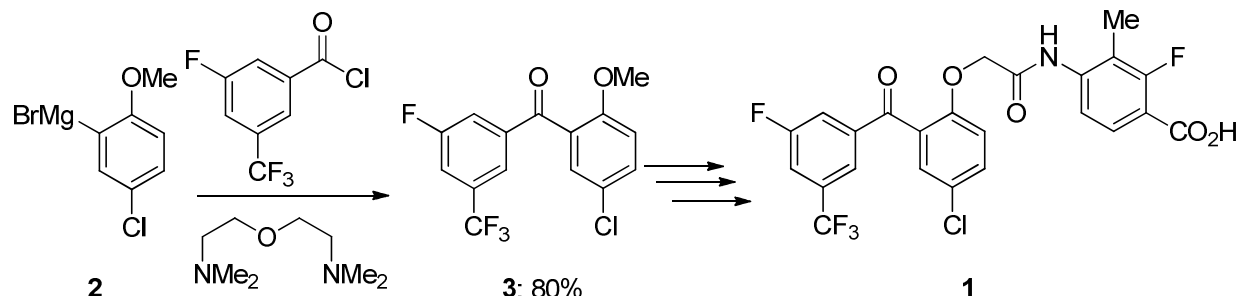
Scheme 1: Pilot plant synthesis of the NNRT (**1**) HIV-1 inhibitor from Boehringer Ingelheim.

2.   Preparation of Organometallic Reagents

2.1.   Halogen-Metal Exchange

The pioneering work developed by *Wittig*[9] and *Gilman*[10] in 1938 for the halogen-lithium exchange permitted the preparation of diverse organolithium compounds,[11] although with limited functional-group tolerance. In contrast, the halogen-magnesium exchange allowed access to new functionalized *Grignard* reagents with a broad range of applications in organic synthesis.[12] *Villiéras* demonstrated that the reaction of *i*PrMgCl (**4**) with CHBr$_3$ at –78 °C furnished the corresponding carbenoid which reacted with Me$_3$SiCl and afforded **5** in 90 % yield (Scheme 2).
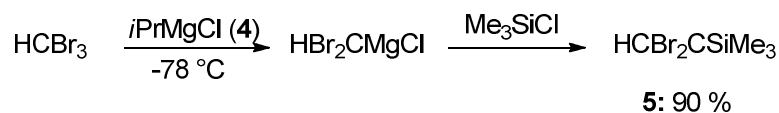
Scheme 2: *i*PrMgCl (**4**) mediated bromine-magnesium exchange.

[8] X-j. Wang, L. Zhang, X. Sun, H. Lee, D. Krishnamurthy, J. A. O´Meara, S. Landry, C. Yoakim, B. Simoneau, N. K. Yee, C. H. Senanayake, *Org. Process. Res. Dev.* **2012**, *16*, 561.
[9] G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903.
[10] a) R. G. Jones, H. Gilman, *Org. React.* **1951**, *6*, 339; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.
[11] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187; b) W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* **1975**, *40*, 2394; c) W. E. Parham, R. M. Piccirilli, *J. Org. Chem.* **1977**, *42*, 257; d) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983.
[12] a) C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, 1372; b) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, 1520; c) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, 470.

Upon the previous, *Knochel* developed an improved general method for an iodine-magnesium exchange with *i*PrMgBr, *i*PrMgCl and PhMgCl with a broad range of functional group tolerance (Scheme 3).[13]
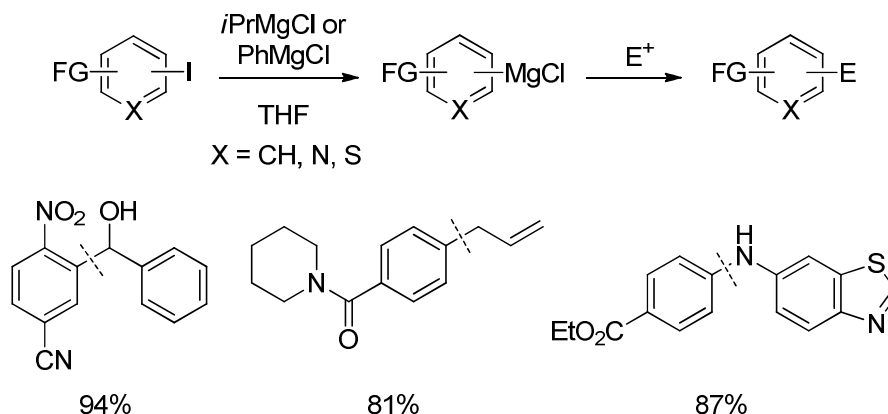
Scheme 3: Iodine-magnesium exchange of highly functionalized aryl and heteroaryl compounds.

Furthermore, the addition of LiCl (1.0 equiv) to **4** resulted in *i*PrMgCl·LiCl (**6**). The so called turbo *Grignard* showed a higher reactivity and solubility, due to the breakup of the polymeric aggregates of *i*PrMgCl and enhanced the bromine-magnesium exchange (Scheme 4).[14]
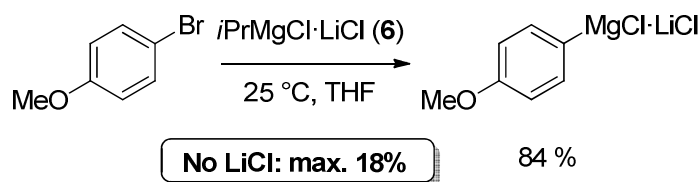
Scheme 4: Bromine-magnesium exchange accelerated by LiCl.

Recently, *Knochel* reported the first iodine-zinc exchange reaction with dialkylzinc reagents in the presence of Li(acac) as catalyst. The method exhibited an outstanding functional group tolerance towards sensitive functionalities such as ketones, isothiocyanates and aldehydes (Scheme 5).[15]

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[13] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, P. Knochel, *J. Am. Chem. Soc.* **2002**, *124*, 9390; c) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.
[14] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
[15] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
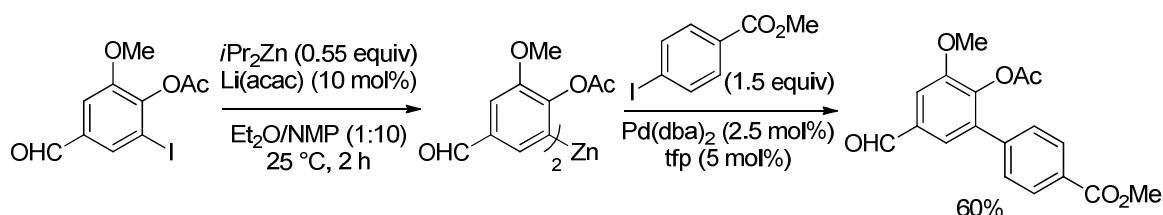
Scheme 5: Iodine-zinc exchange reaction in a functionalized aryl aldehyde.

2.2. Oxidative Insertion

The so called *Grignard* reagents constitute today one of the most versatile and widely used organometallic nucleophiles in research laboratories and in industry.[16] The most common method for their preparation is the direct magnesium-insertion into a carbon-halide bond being usually highly exothermic and presents a limited functional group tolerance. Moreover, *Rieke* showed that highly active magnesium powder (Mg*) can be prepared by the reduction of $MgCl_2$ using lithium and naphthalenide. This allowed the bromine-magnesium insertion at –78 °C with tolerance towards sensitive functional groups (Scheme 6).[17]
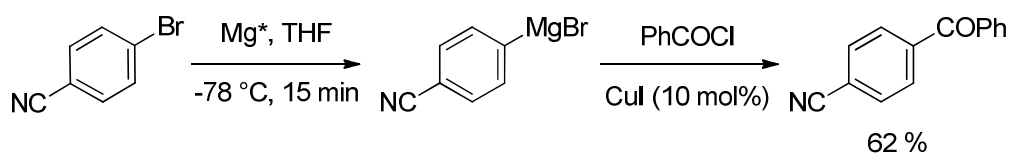
Scheme 6: Preparation of a functionalized magnesium reagent with magnesium powder (Mg*).

A new approach was developed by *Knochel,* using stoichiometric amounts of LiCl for the oxidative insertion of magnesium,[18] indium,[19] manganese[20] and aluminum[21] (Scheme 7).

[16] a) *Handbook of Grignard Reagents,* (Eds.: G. S. Silvermann, P. E. Rakita), Marcel Dekker, New York, **2000**; b) *Grignard Reagents, New Developments,* (Ed.: H. G. Richey Jr.), Wiley & Sons, New York, **2000**; c) J. Wiss, M. Länzlinger, M. Wermuth, *Org. Proc. Res. Dev.* **2005**, *9*, 365.

[17] a) R. D. Rieke, P. M. Hudnall, *J. Am. Chem. Soc.* **1972**, *94*, 7178; b) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; c) R. D. Rieke, *Science* **1989**, *246*, 1260; d) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; e) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

[18] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) F. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Comm.* **2008**, 5824.

[19] a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.

[20] Z. Peng, P. Knochel, *Org. Lett.* **2010**, *13*, 3198.
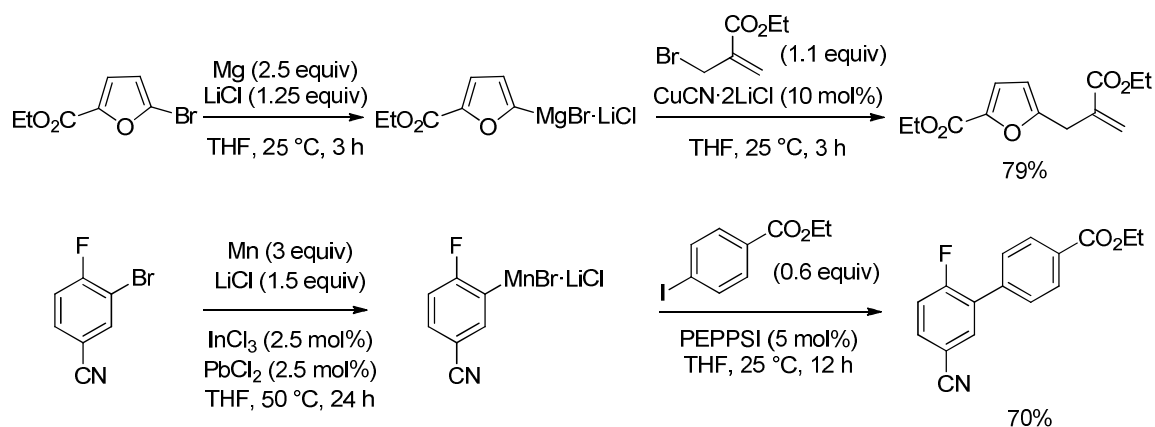
Scheme 7: Preparation of highly functionalized organomagnesium and organomaganese reagents by magnesium and manganese-insertion in the presence of LiCl.

Special interest relies on organozinc reagents due to their excellent group tolerance and extraordinary ability to transmetalate to highly reactive organocopper species[22] or palladium intermediates.[23] Thus, the zinc-insertion is possible *via* activation of the metal surface using 1,2-dibromoethane and chlorotrimethylsilane.[24] Where the zinc oxide surface is etched by elementary bromine and the zinc-oxygen bond is removed by the high oxophilicity of silicon. Moreover, *Knochel* reported the zinc insertion enhancement by LiCl into organic halides of poorly activated substrates.[25] This improvement is assumed to a higher solubility of the organozinc of type RZnX·LiCl and leads to a faster diffusion away from the metal surface, leaving the zinc readily available to react with the next organic halide, i.e. a higher turnover rate (Scheme 8).

[21] T. Blümke, Y-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313.

[22] a) P. Knochel, S. Vettel, C. Eisenberg, *Applied Organomet. Chem.* **1995**, *9,* 175; b) *Organozinc Reagents. A Practical Approach*, (Eds.: P. Knochel, P. Jones), Oxford University Press, London, **1999**; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; d) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4415.

[23] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc*. **1980**, *102*, 3298; b) M. Kobayashi, E. Negishi, *J. Org. Chem.* **1980**, *45*, 5223; c) E. Negishi, *Acc. Chem. Res*. **1982**, *15*, 340.

[24] M. Gaudemar, *Bull. Soc. Chim. Fr*. **1962**, 974.

[25] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) N. Boudet, S. Sase, P. Sinha, C-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.
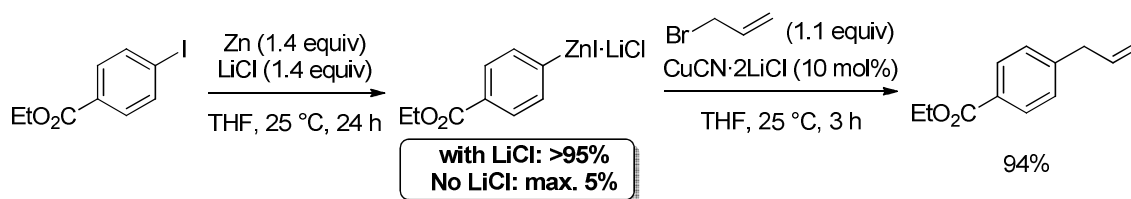
Scheme 8: Preparation of organozinc compounds *via* zinc-insertion in the presence of LiCl.

2.3. Directed Metalation

The first studies done by *Schorigin* in 1908 established the modern term "metalation" as the transfer of a metal atom from an organometallic reagent or a metal amide, in exchange for a carbon-hydrogen bond in a substrate.[26] Decades later *Beak* and *Snieckus* described the directed *ortho*-metalation, which depicts the complex-induced proximity effect for regioselective metalations with a directing group (DMG) using alkyllithium (RLi) or lithium amides (R_2NLi) bases.[27] These lithium metalations have extensively been described and found numerous synthetic applications.[28] However, they exhibit a high reactivity that may lead to undesired reactions, are difficult to handle and present limitations in the functional group tolerance. Another approach done by *Hauser* and *Eaton* led to magnesium amides of type R_2NMgCl, R_2NMgR or $(R_2N)_2Mg$.[29] Nevertheless, these bases exhibited low solubility, low kinetic basicity and the metalated intermediates showed difficulty to react with several electrophiles.[30]

In 2006, *Knochel* reported the combination of a sterically hindered (non-nucleophilic) metallic amide with LiCl for the preparation of $TMPMgCl \cdot LiCl$ (**7**) by the reaction of $i\mathrm{PrMgCl} \cdot LiCl$ (**6**)

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[26] a) P. Schorigin, *Chem. Ber.* **1908**, *41*, 2723; b) P. Schorigin, *Chem. Ber.* **1910**, *43*, 1938.

[27] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; c) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; d) E. Anctil, V. Snieckus, *The Directed ortho Metalation-Cross-Coupling Nexus. Synthetic Methodology for Aryl-Aryl and Aryl-Heteroatom-Aryl Bonds,* in *Metal-Catalyzed Cross-Coupling Reactions,* 2nd ed. (Eds.: F. Diederich, A. de Meijere) Wiley-VCH, Weinheim, **2004**, pp 761-813.

[28] a) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; b) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595; c) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; d) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827.

[29] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350; c) P. E. Eaton, C-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016; d) M-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169; e) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11375; f) Y. Kondo, A. Yoshida, T. Sakamoto. *J. Chem. Soc., Perkin Trans 1*, **1996**, 2331.

[30] R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.

with TMPH (**8**).[31] This base exhibited an elevated solubility, a high reactivity, a broad functional group tolerance and extraordinary long term stability (Scheme 9).
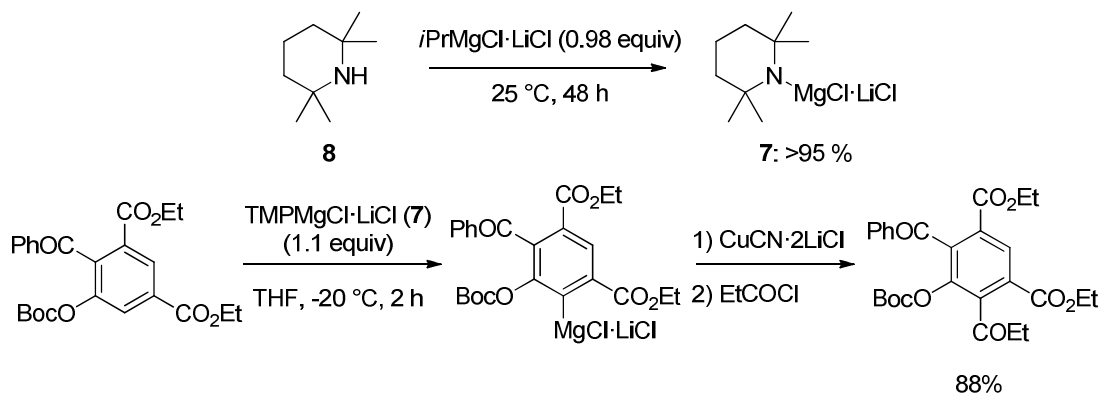
Scheme 9: Preparation of the mixed Mg/Li amide base TMPMgCl·LiCl (**7**) and a regioselective magnesiation.

However, the magnesiation using TMPMgCl·LiCl (**7**) of less activated aromatic substrates bearing electron-donor substituents or weakly electron-acceptors became difficult and led to the development of the stronger magnesium base TMP$_2$Mg·2LiCl (**9**).[32] The latter presented an improved kinetic basicity and although both Mg bases tolerate several functionalities, others are not compatible.[33] Previously, *Kondo* reported the mixed Zn/Li *t*Bu$_2$Zn(TMP)Li base used for *ortho*-metalation[34] and later *Knochel* developed the TMPZnCl·LiCl (**10**)[35] by the reaction of TMPLi[36] with ZnCl$_2$. This base tolerates sensitive functional groups as an aldehyde, nitro, methyl ketone and the zincation of electron-poor N-Heterocycles is possible, even at high temperature.[37] However, for moderately activated substrates a stronger zinc base can be used as

[31] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; c) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497; d) C. Despotopolou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.

[32] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; c) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237; d) M. Mosrin, M. Petrera, P. Knochel, *Synthesis* **2008**, 3697; e) C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984.

[33] P. Knochel, N. Millot, A. L. Rodriguey, C. E. Tucker, *Org. React.* **2001**, *58*, 417.

[34] a) Y. Kondo, H. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; b) T. Imahori, M. Uchiyama, M. Kondo, *Chem. Commun.* **2001**, 2450; c) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otami, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514.

[35] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.

[36] a) M. Cambell, V. Snieckus in *Encyclopedia of Reagents for Organic Synthesis, Vol 5* (Ed.: L. A. Paquette), Wiley, New York, **1995**; b) I. E. Kopka, Z. A. Fataftah, M. W. Rathke, *J. Org. Chem.* **1987**, *52*, 448.

[37] a) T. Bresser, M. Mosrin, G. Monzón, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686; b) M. Mosrin, G. Monzón, T. Bresser, P. Knochel, *Chem. Chommun.* **2009**, 5615.

TMP$_2$Zn·2MgCl$_2$·2LiCl (**11**)[38] which exhibits a higher kinetic basicity due to the presence of MgCl$_2$. Over the past years, new transition-metal TMP bases have been developed: TMP$_2$Mn·2MgCl$_2$·4LiCl (**12**)[39] which allows the metalation of sensitive heterocycles; TMP$_2$Fe·2MgCl$_2$·4LiCl (**13**)[40] which permits a nickel-catalyzed cross-coupling with alkyl halides; and TMP$_3$La·3MgCl$_2$·5LiCl (**14**)[41] which reacts readily with aldehydes and ketones (Scheme 10).
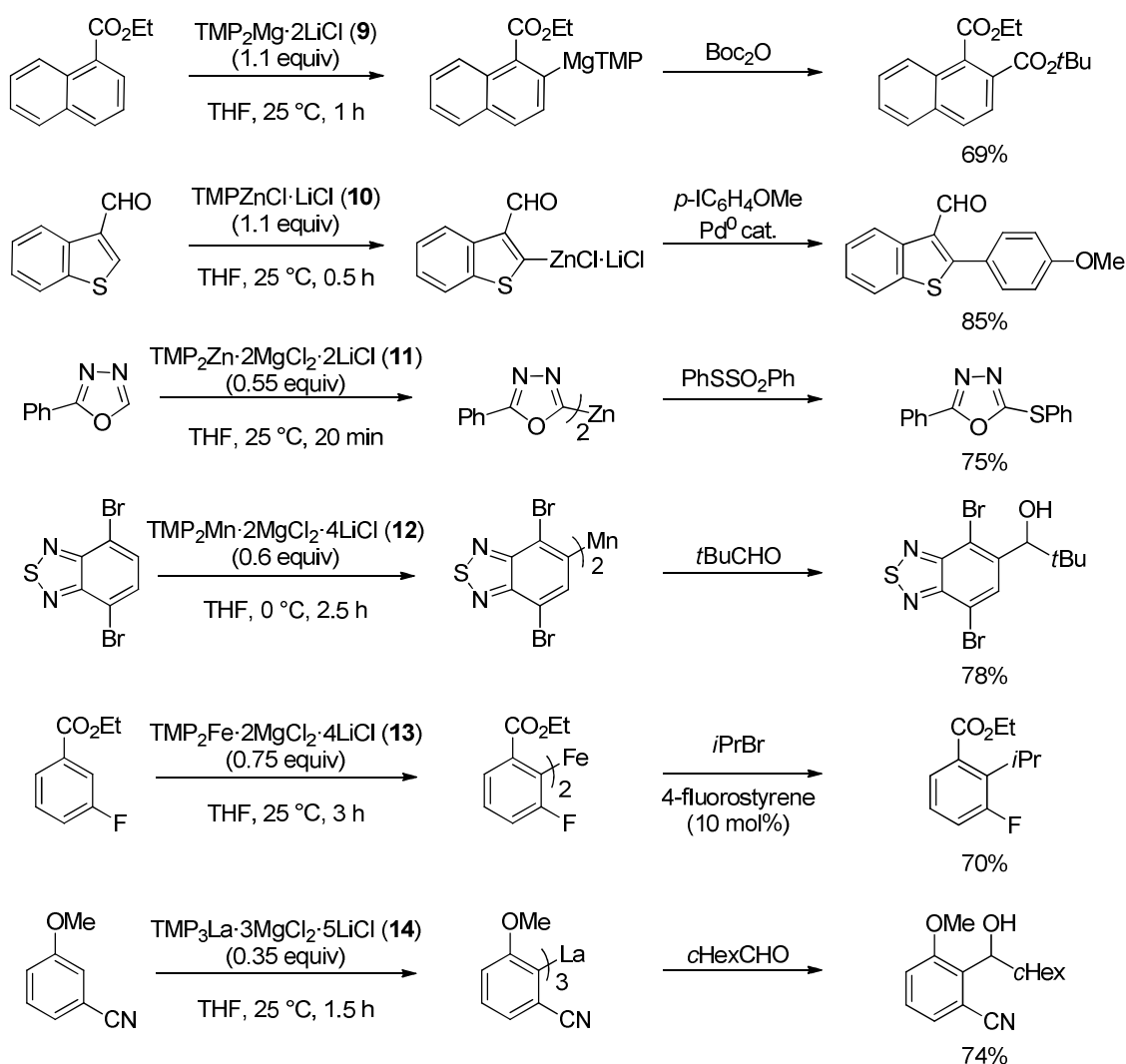
Scheme 10: Metalation of highly functionalized aromatics and heteroaromatics using different TMP bases.

[38] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.
[39] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[40] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.
[41] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.* **2010**, *16*, 3304.

Interestingly, the metalation of several N-Heterocycles is triggered by the Lewis acid $BF_3 \cdot OEt_2$. This results from the coordination between the Lewis acid, the nitrogen in the heterocycle and the TMP base, which promotes a regio-selective metalation (Scheme 11).[42]
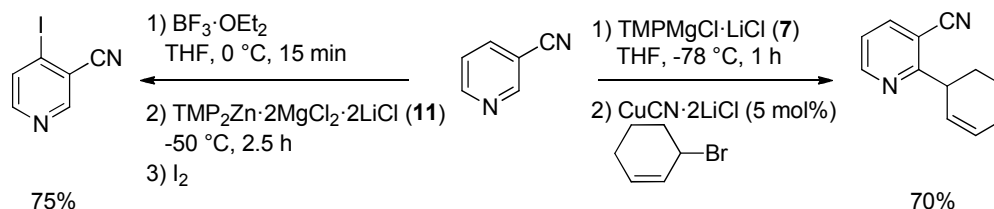
Scheme 11: Regioselective metalation with TMPMgCl·LiCl (**7**) with and without $BF_3 \cdot OEt_2$.

2.4.   Cross-Coupling Reactions of Organometallics

The first steps taken by *Wöhler*, *Liebig* and *Perkin* in transition metal-catalysis led to one of the most crucial procedures for carbon-carbon bond formation.[43] Among the transition metals employed, nickel and and palladium-catalyzed cross-couplings occupy an especial place for the synthesis of natural products, fine chemicals, pharmaceuticals and materials.[44] Usually, the cross-coupling involves an organohalide as electrophile.[45] Recently, *Reissig* demonstrated that nonafluorobutanesulfonates (ONf-) are excellent coupling reagents in Heck, Suzuki and Sonogashira reactions (Scheme 12).[46]

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[42] a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; b) B. Haag, M. Mosrin, I. Hiriyakkanavar, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[43] a) *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, (Ed.: J. Tsuji), Wiley, Chichester, **1996**; b) *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, (Ed.: J. Tsuji), Wiley, Chichester, **2004**; c) C. E. I. Knappke, A. J. von Wangelin, *Chem. Soc. Rev.* **2011**, *40*, 4948.
[44] a) *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) J.-P. Corber, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651.
[45] *Transition Metal-Catalyzed Cross Coupling Reations* in *Transition Metals for Organic Synthesis,* (Eds.: H. Geissler, M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**.
[46] a) M. Webel, H.-U. Reissig, *Synlett* **1997**, 1141; b) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2001**, 4189; c) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2002**, 1015; d) J. Högermeier, H.-U. Reissig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868.
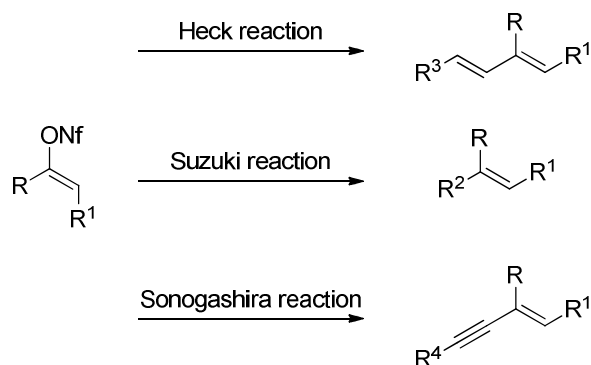
Scheme 12: Alkenyl nonaflates used for palladium-catalyzed cross-coupling reactions.

In 1972, *Kumada* and *Corriu* reported the first nickel-catalyzed cross-coupling of C(sp^2)-halides in the presence of a nickel-phosphine catalyst system.[47] Much development has been made with different applications.[48] Whereas, *Knochel* reported a nickel-catalyzed C(sp^3)-C(sp^3) cross-coupling of a benzylic zinc reagent **14** in the presence of *p*-fluorostyrene (**15**), Ni(acac)$_2$ and Bu$_4$NI (Scheme 13).[49]
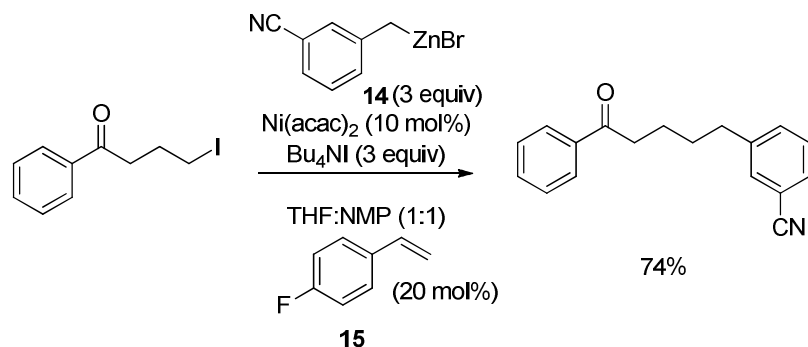
Scheme 13: Nickel-catalyzed C(sp^3)-C(sp^3) cross-coupling reaction.

2.5. Metalation of Aromatic Anilines

Aromatic and heteroaromatic amines constitute important building blocks for organic synthesis of materials, polymers[50] and pharmaceuticals.[51] For example, Lamotrigine (**16**) is an

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[47] a) T. Tamao, K. Sumitami, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374; b) R. P. Corriu, J. P. Masse, *J. Chem. Soc.* **1972**, 144.

[48] a) P. W. Manley, M. Acemoglu, W. Marterer, W. Pachinger, *Org. Res. Process. Dev.* **2003**, *7*, 436; b) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674.

[49] M. Piber, A. E. Jensen, M. Rottländer, P. Knochel, *Org. Lett.* **1999**, *1*, 1323.

[50] a) A. G. MacDiarmid, *Synth. Met.* **1997**, *84*, 27; b) N. Gospodinova, L. Terlemezyan, *Prog. Polym. Sci.* **1998**, *23*, 1443.

[51] A. W. Czarnik, *Acc. Chem. Res.* **1996**, *29*, 112 and references cited therein.

anticonvulsant drug from GlaxoSmithKline with annual sales of 325 million USD. Near in revenue are Metoclopramide (**17**) and Clonidine (**18**), just to name a few of the Top 200 generic drugs with a primary or secondary amine moiety.[52] This illustrates the need for efficient synthetic methods for the preparation of highly functionalized aromatic and heteroaromatic amines (Figure 1).

Lamotrigine (**16**)   Metoclopramide (**17**)   Clonidine (**18**)
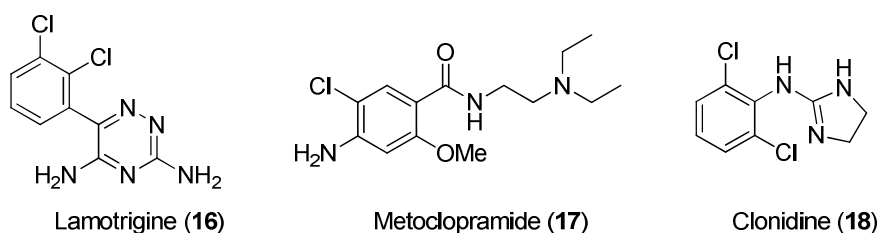
Figure 1: Aromatic and heteroaromatic amines as pharmaceuticals.

The frequent occurrence of anilines as synthetic precursors drew attention towards their *ortho*-functionalization. In this fashion, *Sugasawa* reported in 1978 the *ortho*-hydroxybenzylation and hydroxyalkylation of an unprotected aniline using anilinodichloroboranes generated *in situ*.[53] The next year, *Walborsky* performed an *α*-addition followed by *ortho*-metalation of phenyl isocyanide.[54] This was further investigated by *Fuhrer*, with an *ortho*-lithiation of *N*-pivaloylanilines with 2 equivalents of *n*BuLi in THF at 0 °C. Thus, the lithiation of the *p*-chloroaniline derivative **19** generated the dilithiated species **20**, trapped with 2-fluorobenzonitrile and due to *ortho*-interactions afforded the quinazoline **21** in 57% yield (Scheme 14).[55]

19   **20**   **21**: 57%
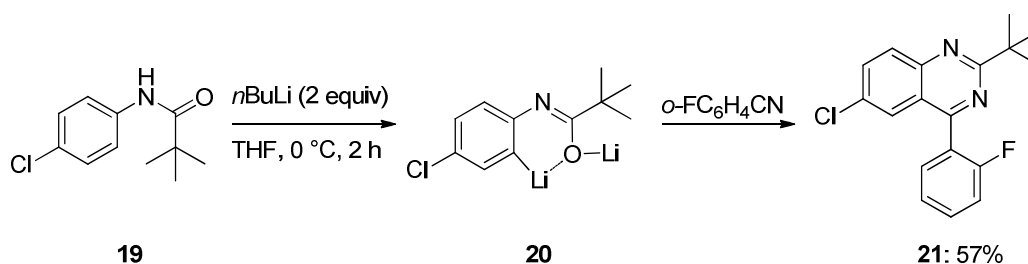
Scheme 14: *ortho*-Lithiation of *N*-(4-chlorophenyl)-2,2-dimethylpropanamide (**19**).

[52] http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252011/727239/article.pdf (accessed Jun 06, 2012).
[53] a) T. Sugasawa, T. Toyoda, M. Adachi, K. Sasakura, *J. Am. Chem. Soc.* **1978**, *100*, 4842; b) T. Sugasawa, M. Adachi, K. Sasakura, *J. Org. Chem.* **1979**, *44*, 578.
[54] H. M. Walborsky, P. Ronmam, *J. Org. Chem.* **1978**, *43*, 731.
[55] W. Fuhrer, *J. Org. Chem.* **1979**, *44*, 1133.

Additionally, *Muchowski* applied the method for the synthesis of quinolines and carried out studies in the directing effect of the trimethylacetyl-amido (*N*-Piv) and the *t*butoxycarbonyl-amido (*N*-Boc) groups.[56] *Snieckus* confirmed that the *N*-Boc moiety has a stronger directing effect for the *ortho*-lithiation of anilines and applied it for the synthesis of natural products.[57] Moreover, *Schlosser* investigated the *N*-Boc directing effect and compared it against a more electronegative, but poorly complexing substituent such as a fluorine or trifluoromethyl in *para*-position. It was shown that the lithiation of *N*-(*tert*-butoxycarbonyl)-4-trifluoromethylaniline (**22**) occurs preferentially *ortho*- to the *N*-Boc (Scheme 15).[58]
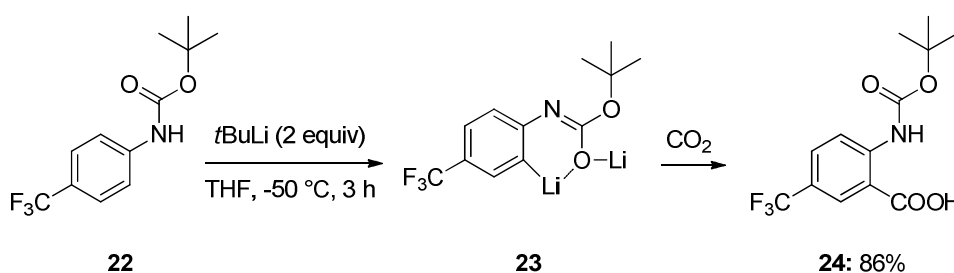
Scheme 15: *ortho*-directing effect of the *N*-Boc group compared to a trifluoromethyl group.

Finally, the *ortho*-lithiation of protected anilines has been investigated on the choice of the lithiating agent, cosolvents, functional group tolerance and electrophiles.[59] It has found applications for multikilogram pharmaceutical development[60] and natural product synthesis.[61] However, several limitations are necessary to overcome as the forcing lithiation conditions and the functional group tolerance. The task is challenging due to the existence of two active hydrogens in the free primary amine which are an obstruction towards metalation and apparently the reason for few reports on successful *ortho*-metalation of aromatic and heteroaromatic protected primary amines.

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[56] a) J. M. Muchowski, M. C. Venuti, *J. Org. Chem.* **1980**, *45*, 4798; b) I.-S. Cho, L. Gong, J. M. Muchowski, *J. Org. Chem.* **1991**, *56*, 7288.
[57] a) J. N. Reed, V. Snieckus, *Tetrahedron Lett.* **1984**, *25*, 5505; b) M. A. Siddiqui, V. Snieckus, *Tetrahedron Lett.* **1988**, *29*, 5463; c) M. A. Siddiqui, V. Snieckus, *Tetrahedron Lett.* **1990**, *31*, 1523.
[58] S. Takagishi, G. Katsoulos, M. Schlosser, *Synlett* **1991**, 360.
[59] a) P. Stanetty, H. Koller, M. Mihovilovic, *J. Org. Chem.* **1992**, *57*, 6833; b) M. G. Cabiddu, S. Cabiddu, E. Cadoni, S. De Montis, C. Fattuoni, S. Melis, *Tetrahedron* **2003**, *59*, 2893.
[60] T. A. Mulhern, M. Davis, J. J. Krikke, J. A. Thomas, *J. Org. Chem.* **1993**, *58*, 5537.
[61] H. Takihiro, Y. Uruma, Y. Tusuki, A. Miyake, H. Iio, *Tetrahedron: Asymmetry* **2006**, *17*, 2339 and references cited therein.

4.   Objectives

4.1.   Zincation of Sensitive Aromatics and Heteroaromatics

The first goal of this work is the zincation of moderately activated aromatics and heteroaromatics with the chemoselective base TMPZnCl·LiCl (**10**). The tolerance of this base towards several sensitive functional groups should be tested, as well as the thermal stability and kinetic basicity of the base at high temperatures using microwave irradiation. Upon the broad functional group tolerance of the zinc base, upscaling the zincation procedure should be tested for industrial processes interests (Scheme 16).
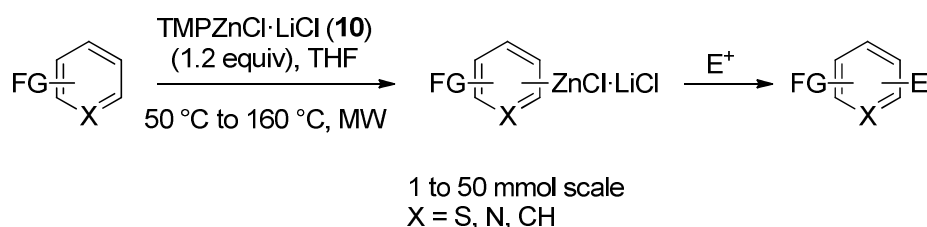
Scheme 16: Regio- and chemoselective zincation of moderately activaded aromatics and heteroaromatics with TMPZnCl·LiCl (**10**).

4.2.   Preparation of Polyfunctional Organometallics *via ortho*-Metalation

A second goal is the metalation of substituted aromatics with the TMP bases of manganese, iron and lanthanum in a multigram scale (Scheme 17).
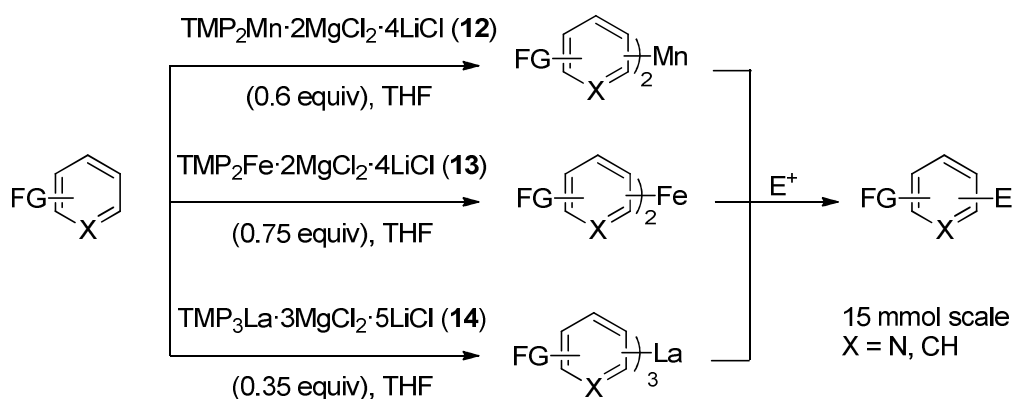
Scheme 17: Preparation of highly functionalized aromatics *via* directed *ortho*-metalation with the TMP bases of Mn, Fe and La.

4.3.   Metalation of Aryl Nonaflates

Additionally, we envisioned a protective group (PG) for functionalized phenols with the capacity to enhance the arene metalation using the TMP-magnesium and zinc bases. The group should probe to be stable towards metalation and finally be able to be further functionalized (Scheme 18).
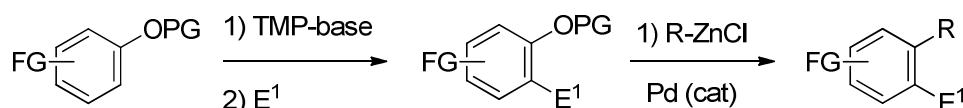
Scheme 18: Metalation of a protected phenol using TMP bases.

4.4.   Metalation of Protected Anilines and Amino N-Heterocycles

The field of *ortho*-lithiation for protected amines with lithium bases has been described, but there is no report so far for *ortho*-magnesiation of protected anilines with metal-amide bases. Thus, we envisioned the metalation of protected anilines and amino N-heterocycles with the TMP-magnesium bases. The protecting group (PG) should exhibit an *ortho*-metalation directing capacity, be stable, allow multiple selective metalations and should be easily removed (Scheme 19).
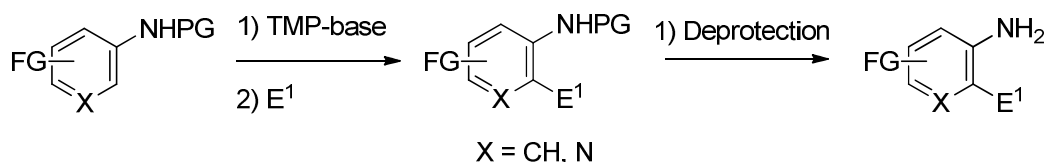
Scheme 19: Metalation of a protected anilines and Amino-substituted N-Heterocycles using TMP bases.

4.5.   Zinc Insertion in Benzylic Heterocycles

The presence of LiCl in various metal-insertion procedures facilitates the preparation of the organometallic reagents. Thus, we envisioned a general method for the synthesis of heteroaromatic benzylic zinc reagents starting from the heteroaromatic benzylic chlorides. Furthermore, the preparation of annulated heterocycles should be tested.

Scheme 20: Preparation of heterobenzylic zinc reagents.

4.6. New Generation of Iminium Salts

Interest relies on the preparation of tertiary benzyl amines in a one-pot procedure. Thus, we envisioned the reaction of the *Mannich* salt (**25**) with a metal amide to generate an unsymmetrical aminal of type **26**. The addition of an acylation agent for a second time, should generate a methylene(dialkyl)-iminium salt **27** which after the addition of an organometallic reagent should afford the addition product **28** (Scheme 21).

Scheme 21: Preparation of tertiary benzyl and phenetyl amines.

B. RESULTS AND DISCUSSION

1.   Regio- and Chemoselective Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl and Microwave Irradiation

1.1.   Introduction

The metalation of aromatics and heteroaromatics is an extraordinary tool for the synthesis of agrochemicals, pharmaceuticals and materials. Recently, several new selective bases for regio- and chemoselective metalation have been developed.[4b,62] Among these useful reagents -ate bases have received special attention.[30,34,63] Furthermore, *Knochel* reported the useful mixed magnesium/lithium amide bases TMPMgCl·LiCl (**7**)[31] and TMP$_2$Mg·2LiCl (**9**)[32] as highly active and selective bases towards the metalation of aromatics and heteroaromatics with an outstandingly toleration towards several functionalities such as a nitrile, an ester or an aryl ketone. The need of a more chemoselective base towards more sensitive functionalities such as a nitro or an aldehyde led to the development of the mixed zinc/lithium base TMP$_2$Zn·2MgCl$_2$·2LiCl (**11**)[38] and afterwards TMPZnCl·LiCl (**10**)[35] (Scheme 22).
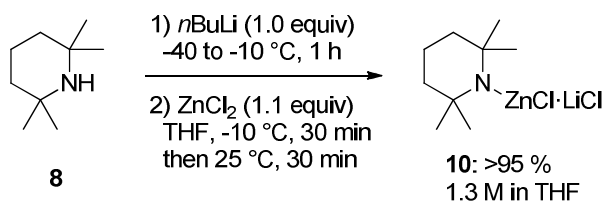
Scheme 22: Preparation of TMPZnCl·LiCl (**10**).

Moreover, TMPZnCl·LiCl (**10**) demonstrated that its higher selectivity is owed to the absence of magnesium salts (MgCl$_2$) and to the monomer stoichiometry (TMPZnX compared to TMP$_2$ZnX). Remarkably, TMPZnCl·LiCl (**10**) showed an extraordinary thermal stability under conventional heating for the zincation of poorly activated substrates with electron-donating groups or weakly electron-withdrawing substituents.[37a]

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[62] a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; b) D. M. Hodgson, S. M. Miles, *Angew. Chem. Int. Ed.* **2006**, *45*, 935.

[63] a) R. E. Mulvey, *Organometallics* **2006**, *25*, 1060; b) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatly, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921; c) W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, C. T. O´Hara, L. Russo, *Angew. Chem. Int. Ed.* **2008**, *47*, 731.

1.2. Zincation of Poorly Activated Substrates with TMPZnCl·LiCl under Microwave Irradiation

The microwave irradiation technique has been used to accelerate several organic reactions which show slow conversions under conventional heating[64] and it has been further extended to organometallic reactions.[65] Recently, it was demonstrated that microwave irradiation allows the effective zincation of various aromatics and heteroaromatics using $TMP_2Zn\cdot2MgCl_2\cdot2LiCl$ (**11**),[66] probing the high thermal stability of the RZnX reagent and a broad functional group tolerance at high temperatures.[67] Moreover, the poorly activated 3-fluoroanisole (**29**) shows a slow reaction rate when reacting it with TMPZnCl·LiCl (**10**) under heating using an oil bath at 160 °C for 2 h. However, when heating using microwave irradiation at 160 °C for 2 h resulted in > 90% yield of the zinc species **30** and turned out to be essential to achieve the full zincation. Trapping with benzoyl chloride (after transmetalation with CuCN·2LiCl)[68] furnished the new substituted aromatic **31a** in 72% yield (Scheme 23). Moreover, 1,3,5-trichlorobenzene (**32**) is zincated within 1 h at 80 °C and acylation with benzoyl chloride or allylation with ethyl 2-(bromomethyl)acrylate[69] (after addition of a catalytic amount of CuCN·2LiCl) provided the substituted arenes **31b** and **31c** in 75 and 85% yield (Scheme 23 and Table 1, entry 1).

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[64] a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldiser, L. Laberge, R. Rousell, *Tetrahedron Lett*. **1986**, *27*, 279; b) R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett*. **1986**, *27*, 4945; c) *Microwave Synthesis: Chemistry at the Speed of Light*, (Ed.: B. L. Hayes), CEM Publishing, North Carolina, **2002**; d) *Microwave-Assisted Organic Synthesis,* (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2006**; e) Mi*crowave Methods in Organic Synthesis*, (Eds.: M. Larhed, K. Olofssson), Springer, Berlin, **2006**.

[65] a) D. Dallinger, C. O Kappe, *Chem. Rev*. **2007**, *107*, 2563; b) C. O. Kappe, *Angew. Chem. Int. Ed*. **2004**, *43*, 6520; c) H. Tsukamoto, T. Matsumoto, Y. Kondo, *J. Am. Chem. Soc*. **2008**, *130*, 388; d) G. Shore, S. Morin, M. G. Organ, *Angew. Chem. Int. Ed*. **2006**, *45*, 2761; e) S. Fustero, D. Jimenez, M. Sanchez-Rosello, C. del Pozo, *J. Am. Chem. Soc*. **2007**, *129*, 6700.

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

[67] a) P. Walla, C. O. Kappe, *Chem. Commun*. **2004**, 564; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem*. **1991**, *56*, 1445.

[68] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem*. **1988**, *53*, 2390; b) P. Knochel, S. A. Rao, *J. Am. Chem. Soc*. **1990**, *112*, 6146.

[69] J. Villiéras, M. Rambaud, *Org. Synth*. **1988**, *66*, 220.
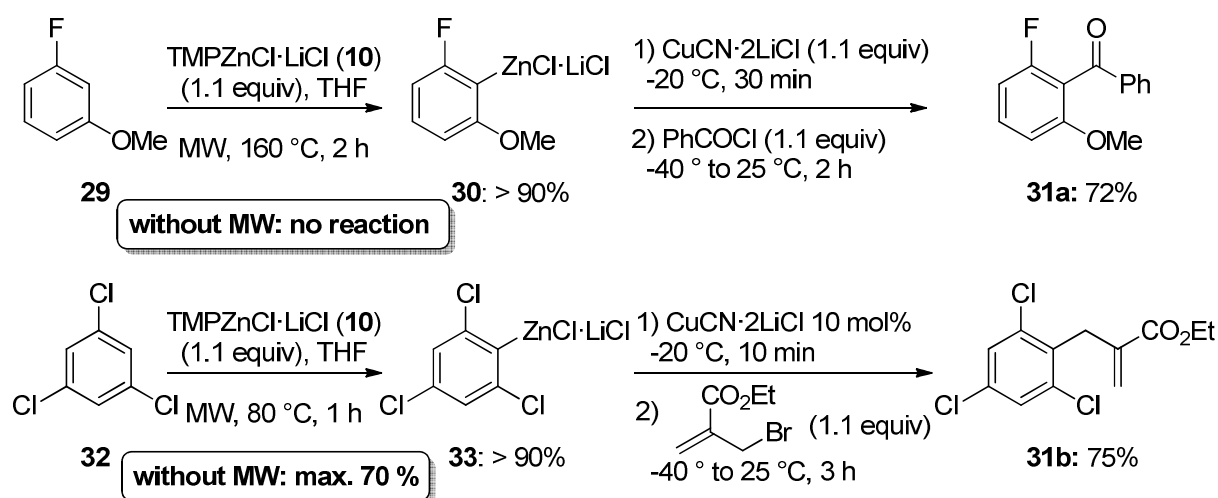
Scheme 23: Zincation of 3-fluoroanisole (**29**) and 1,3,5-trichlobenzene (**32**) using TMPZnCl·LiCl (**10**) and microwave irradiation.

This procedure could be extended to heterocyclic systems. Thus, the use of TMP$_2$Zn·2MgCl$_2$·2LiCl (**11**) for the zincation of 3-chloro-6-methoxypyridazine (**34**) leads to a mixture of regioisomers (metalation in positions 4 and 5). However, when using TMPZnCl·LiCl (**10**) (90 °C, 100 W, 1 h) **34** is regioselectively metalated in *ortho*-position to the metoxy group.[70] The resulting zinc species undergoes a Negishi Pd(0)-catalyzed cross-coupling reaction[23] and acylation reaction[71] leading to the new substituted pyridazines **31d** and **31e** in 80-89% yield (Scheme 24 and Table 1, entry 2).
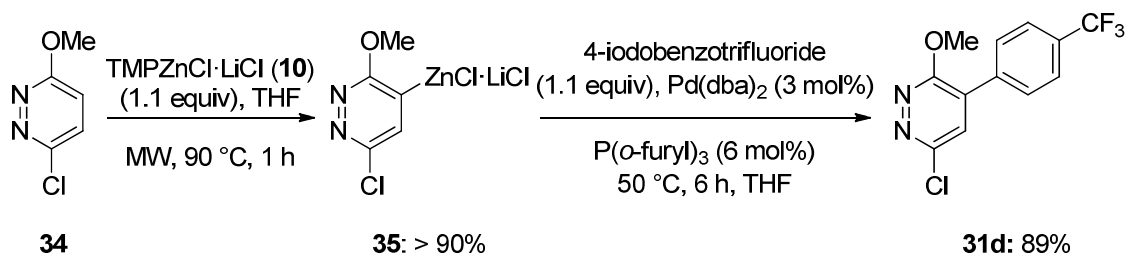
Scheme 24: Regioselective zincation of 3-chloro-6-methoxypyridazine (**34**) using TMPZnCl·LiCl (**10**) and microwave irradiation.

3-Bromobenzothiophene (**36**) was also metalated with **10** (50 °C, 100 W, 30 min) and the resulting zinc species readily underwent allylation with allyl bromide (5 mol% of CuCN·2LiCl),

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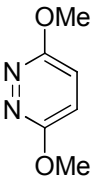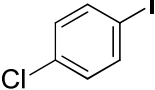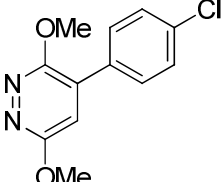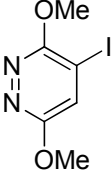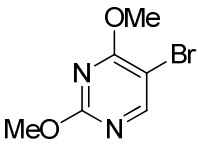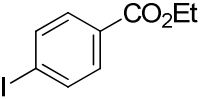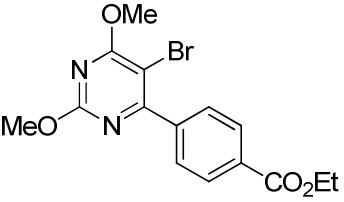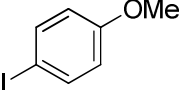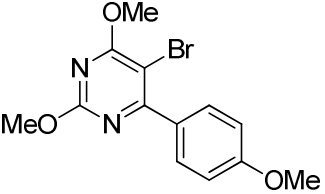
[70] The regioselectivity has been established by quenching the zinc intermediate with D$_2$O.
[71] E. Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett*. **1983**, *24*, 5181.

acylation[71] with benzoyl chloride or a Pd(0)-catalyzed cross-coupling reaction[23] leading to the new substituted heterocycles **31f-h** in 77-93% yield (entries 3-5). The zincation of 3,6-dimethoxypyridazine (**37**) with TMPZnCl·LiCl (**10**) (90 °C, 100 W, 1 h) and subsequent Neghishi cross-coupling[23] reaction or iodination afforded the desired pyridazines **31i-j** in 88-76% yield (entries 6 and 7). In addition, the sensitive heterocycle 5-bromo-2,4-dimethoxypyrimidine (**38**) is metalated at 60 °C (100 W) within 30 min to the expected zinc intermediate. Pd(0)-catalyzed cross-coupling reactions[23] lead to the new substituted pyrimidines **31k-l** in 86-92% yield (entries 8 and 9).

Table 1: Products of type **31** obtained by regio- and chemo-selective zincation using TMPZnCl·LiCl (**10**) under microwave irradiation.

Entry	Substrate	Electrophile	Product, Yield[a]
1	**32**		**31c:** 85%[b]
2	**34**		**31e:** 80%[b]
3	**36**		**31f:** 77%[c]
4	**36**		**31g:** 93%[d]
5	**36**		**31h:** 83%[b]

Entry	Substrate	Electrophile	Product, Yield[a]
6	37		31i: 88%[d]
7	37	I$_2$	31j: 76%
8	38		31k: 86%[d]
9	38		31l: 92%[d]

[a] Yield of analytically pure product; [b] 1.1 equiv CuCN·2LiCl was added; [c] 5 mol% of CuCN·2LiCl was added; [d] 3 mol% of Pd(dba)$_2$ and 6 mol% of P(*o*-furyl)$_3$ were added.

1.3. Scaleable Preparation of Sensitive Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl

Directed metalation reactions have become more significant for the functionalization of scaffolds and have provided important intermediates in organic syntheis in small scale as well as in industrial processes.[27] Therefore, we envisioned the zincations of substrates containing sensitive functional groups using TMPZnCl·LiCl (**10**) at a 2 mmol scale to be upscaled (50 mmol) in a safe and convenient manner. For the previous stated, the zinc base was prepared in a larger scale

than the previously described.[37,72] Thus, the metalation of a heteroaromatic with a sensitive functional group as a nitro is possible at a large scale. 2-Chloro-3-nitropyridine (**39**) is zincated completely within 5 h at 25 °C using TMPZnCl·LiCl (**10**). Quenching with 4-chlorobenzoyl chloride at –30 °C (after transmetalation with CuCN·2LiCl)[68] provides the ketone **40** in 77% yield (Scheme 25). Remarkably, the full zincation of caffeine (**41**) is obtained within 10 min at 25 °C. A Pd(0)-catalyzed cross-coupling reaction[23] with 4-chloro-iodobenzene using Pd(dba)$_2$ and P(o-furyl)$_3$[73] (3 and 6 mol% respectively) furnishes the new functionalized purine **42** in 79% yield. Furthermore, the metalation of 2,4-dichloropyrimidine (**43**) is achieved within 1 h at 25 °C. Trapping with 3-bromocyclohexene provides after the addition of a catalytic amount of CuCN·2LiCl[68] the allylated pyrimidine **44** in 81% yield (Scheme 25). The recovery of the valuable 2,2,6,6-tetramethylpiperidine (TMPH) from the aqueous phase after work up is also possible.[74]
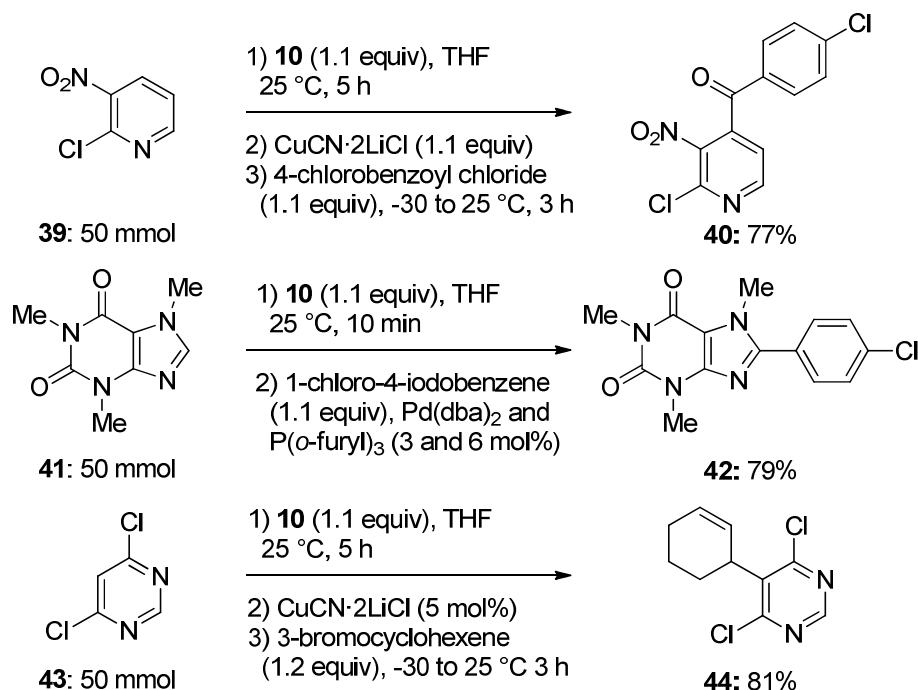
Scheme 25: Large scale zincation of sensitive functionalized aromatics and heteroaromatics using TMPZnCl·LiCl (**10**) and subsequent reactions with electrophiles.

[72] a) G. Monzón, P. Knochel, *Synlett,* **2010**, 304; b) F. Crestey, P. Knochel, *Synthesis,* **2010**, 1097.
[73] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585; b) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905; c) I. Klement, M. Rotländer, C. E. Tucker, T. N. Majid, P. Knochel, P. Venegas, G. Cahiez, *Tetrahedron,* **1996**, *52*, 7201.
[74] S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Res. Process. Dev.* **2010**, *14*, 339.

2.   Efficient Preparation of Polyfunctional Organometallics *via* Directed *ortho*-Metalation with TMP-Bases of Mn, Fe and La

2.1.   Introduction

The metalation of functionalized unsaturated substrates affords valuable intermediates in organic synthesis. The long-established lithium reagents[28] and several mixed ate-bases[28,29,30] have been developed, investigated and applied. Even though much has been achieved, there is still a need for easy to handle chemoselective bases for the metalation of organic substrates with a high functional group tolerance. Thus, the treatment of TMPMgCl·LiCl (**7**)[31] with metallic chlorides such as $ZnCl_2$,[38] $MnCl_2$·2LiCl,[39] $FeCl_2$·2LiCl[40] and $LaCl_3$·2LiCl[41] leads to ambient temperature stable and highly kinetic active amide bases. The metalations usually take place at room temperature, making them convenient for applications in industry at mild conditions. Additionally, the bases exhibit a high-atom economy since all TMP moieties can be used for the directed metalation. The spectra of electrophiles that can be reacted is broad as well as the functional groups which are tolerated. Upon this, an upscale procedure was developed and the reactions were studied in a 1-2 mmol scale and then taken to a multigram scale (ca. 4 g). The specificity of the metal in the amide base (Mn, Fe, La) was studied as the determining factor for the behavior of the corresponding organometallic reagent.

2.2.   Scaleable Preparation of Organometallics with TMP-Bases of Mn, Fe and La

The mixed amid bases were efficiently prepared by the transmetalation of TMPMgCl·LiCl (**7**) (2.0 equiv, 0 to 25 °C, 3.5 h) with the corresponding solutions of $MnCl_2$·2LiCl[39] (1.0 equiv) and $FeCl_2$·2LiCl[40] (1.0 equiv) affording **12** and **13** both in >95% yield. Due to a different stoichiometry, TMPMgCl·LiCl (**7**) (3.0 equiv, 25 °C, 12 h) was reacted with a solution of $LaCl_3$·2LiCl[41] (1.0 equiv) affording **14** in >95% yield. The three bases are stable at 25 °C for at least two months under inert gas atmosphere (Scheme 26).
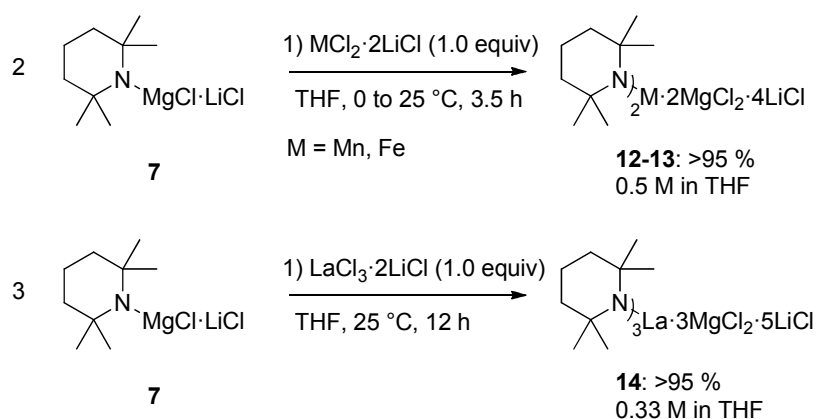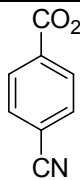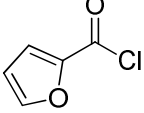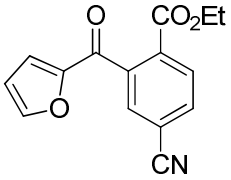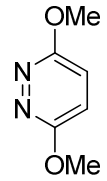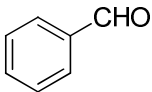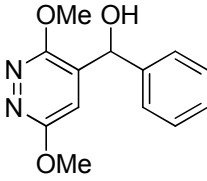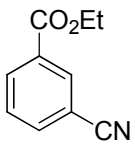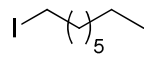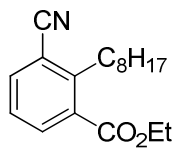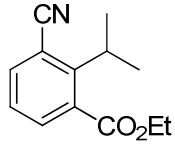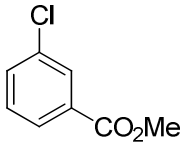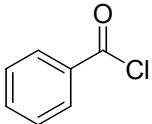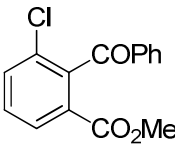
Scheme 26: Preparation of TMP-Bases of Mn, Fe and La **12-14**.

Thus, ethyl 4-cyanobenzoate (**45**) is fully manganated within 75 min at 0 °C with TMP$_2$Mn·2MgCl$_2$·4LiCl (**12**) (0.6 equiv) and the ketone **46** is obtained in 70% yield after CuCN·2LiCl mediated acylation[68] with 2-furoyl chloride (Table 2, entry 1). Similarly, the metalation of 3,6-dimethoxypyridazine (**47**) is accomplished within 30 min at 0 °C using TMP$_2$Mn·2MgCl$_2$·4LiCl (**12**) (0.6 equiv). The treatment of the metalated species with benzaldehyde afforded **48** in 94% yield (entry 2).

Furthermore, the directed ferration and subsequent cross-coupling (catalyzed by nickel impurities)[40] is feasible in larger scale. Thus the metalation of ethyl 3-cyanobenzoate (**49**) is completed within 18 h at 25 °C using TMP$_2$Fe·2LiCl·4LiCl (**13**) (0.75 equiv) and the subsequent alkylation with 1-iodooctane or the secondary 2-iodopropane in the presence of 4-fluorostyrene (10 mol%) afforded **50** and **51** both in 78% yield (entries 3 and 4).

Subsequently, the lanthanation of methyl 3-chlorobenzoate (**52**) with TMP$_3$La·3MgCl$_2$·5LiCl (**14**) (0.75 equiv) at 0 °C for 3.5 h afforded the fully lanthanated species and direct treatment with benzoyl chloride furnished **53** in 75% yield (entry 5).

Table 2: Products obtained by regio- and chemoselective metalation using TMP-Bases of Mn, Fe and La.

Entry	Substrate	Base	Electrophile	Product, Yield[a]
1	**45** (ethyl 4-cyanobenzoate, CO$_2$Et / CN)	TMP$_2$Mn (**12**)[b]	2-furoyl chloride	**46:** 70%[c]
2	**47** (3,6-dimethoxypyridazine, OMe / OMe)	TMP$_2$Mn (**12**)[b]	benzaldehyde (CHO)	**48:** 94%
3	**49** (ethyl 3-cyanobenzoate, CO$_2$Et / CN)	TMP$_2$Fe (**13**)[b]	1-iodooctane (I-(CH$_2$)$_5$-)	**50:** 78%[d]
4	**49**	TMP$_2$Fe (**13**)[b]	2-iodopropane (I)	**51:** 78%[d]
5	**52** (methyl 3-chlorobenzoate, Cl / CO$_2$Me)	TMP$_3$La (**14**)[b]	benzoyl chloride	**53:** 75%

[a] Yield of analytically pure product; [b] MgCl$_2$ and LiCl have been omitted for the sake of clarity; [c] 20 mol % of CuCN·2LiCl was added; [d] 10 mol% of 4-fluorostyrene was added.

3. Directed *ortho-* and *meta*-Magnesiation or Zincation of Polyfunctional Aryl Nonaflates

3.1. Introduction

The preparation of polyfunctional aromatics bearing various electrophilic functional groups is an important synthetic task, since these structural units are often part of biologically active molecules or new materials.[27] Especially interesting is the metalation of arenes bearing strongly electrophilic groups which may allow further reactions in the presence of an appropriate catalyst, such as nonaflates. The nonaflate moiety (NfO-) is an excellent leaving group in the presence of a transition metal catalyst (Pd, Ni) and has found many applications in organic synthesis.[46,75] It was therefore our goal to find a method for the *ortho-* and *meta*-metalation of aryl nonaflates and subsequent reaction with electrophiles.

3.2. Formal *ortho-* and *meta*-Functionalizations

The directed metalation both in *ortho-* and *meta*-positions to a nonaflate moiety is fairly unknown. We envisioned the effective metalation of functionalized aryl nonaflates using the mixed Li/Mg and Li/Zn-amide bases TMPMgCl·LiCl (**7**) and TMPZnCl·LiCl (**10**) respectively. First, we carried out the comparison of the nonaflate group against its similar triflate analogue (TfO-). Thus, 3,5-diethylester phenyl nonaflate **54** and 3,5-diethylester phenyl triflate **55** were zincated using TMPZnCl·LiCl (**10**) (1.3 equiv) at 25 °C within 3 h, leading to the corresponding zinc intermediates **56** and **57** both in 95% yield. This led to the assumption that both groups exhibit a similar directing strength towards *ortho*-metalation and showed comparable stability over time. Noticeable, the zincation occurs regioselectively at position 2, even with the presence in positions 3 and 5 of two directing ethyl ester groups,[27] although steric hindrance may also avoid the metalation in position 4. This illustrates that the SO_2CF_3 or $SO_2C_4F_9$ groups generate an electron density withdrawing effect in the arene, making the proton at position 2 the most prone

[75] a) X. Han, B. Stoltz, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 7600; b) W. Gallagher, R. J. Maleczka, *J. Org. Chem.* **2003**, *68*, 6775; c) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031; d) A. E. Jensen, W. Dohle, P. Knochel, *Tetrahedron* **2000**, *56*, 4197; e) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541.

to be abstracted. Quenching the zinc species **56** with pivaloyl chloride (after transmetalation with CuCN·2LiCl)[68] lead to the *t*butyl ketone **58a** in 72% yield. Allylation with 3-bromocyclohexene in the presence of CuCN·2LiCl[68] and Negishi cross-coupling[23] with 4-iodo-1-trifluoromethylbenzene provided the polyfunctional arenes **58a-c** in 72-85% yield (Table 3, entries 1-3).
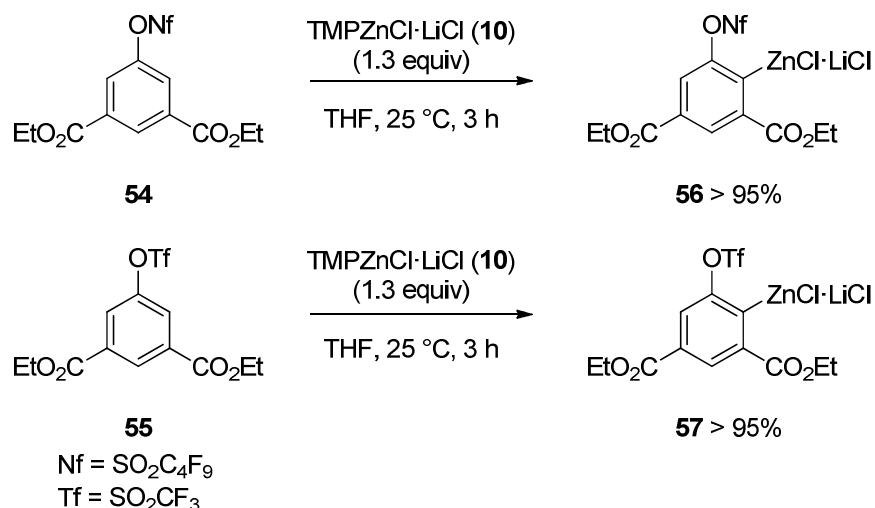
Scheme 27: Comparison of the metalation directing strength effect of (NfO-) and (TfO-).

Further experiments were carried out using the nonaflate moiety due to several advantages such as: triflating reagents such as Tf$_2$O or triflimides like Tf$_2$NPH, are more expensive than nonafluorobutanesulfonyl fluoride (NfF) which is air stable, non-toxic and presents a long storage stability. In addition, aryl nonaflates can be easily purified on silica, are stable towards decomposition over time and exhibit a slightly higher reactivity in palladium-catalyzed cross-coupling reactions when compared to aryl triflates.[46c,76]

Thus, the zincation of 3,5-dichlorophenyl nonaflate **59** occurs at 25 °C within 3 h with TMPZnCl·LiCl (**10**) (1.1 equiv). Cu(I)-mediated benzoylation[68] provides the ketone **58d** in 78% yield (Scheme 28). Negishi cross-coupling[23] with 4-trifluoromethyl- or 4-chloro-substituted iodobenzene furnished the cross-coupling products **58e** and **58f** in 76 and 83% yield, respectively (entries 4 and 5). The density electron-withdrawing effect induced by the nonaflate moiety

[76] M. Rottländer, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203.

became evident, since the zincation of 3,5-dichlorophenyl nonaflate **59** occurs at 25 °C while for 1,3,5-trichlorobenzene (**32**) high temperature and microwave irradiation is required (MW, 80 °C, 1 h).
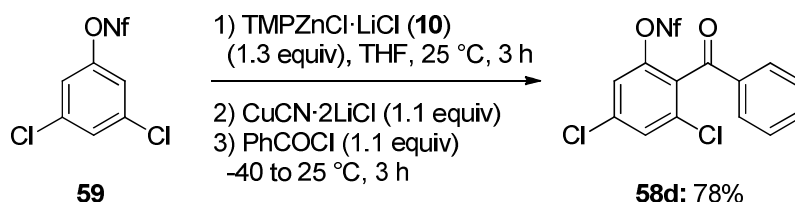
Scheme 28: Regioselective zincation of 3,5-dichloro aryl nonaflate **59** with TMPZnCl·LiCl (**10**).

Further substrates were investigated such as 3-fluorophenyl nonaflate **60** which is zincated at 25 °C within 3 h and underwent an allylation reaction with ethyl (2-bromomethyl)acrylate[77] in the presence of CuCN·2LiCl[68] providing the acrylate derivative **58g** in 72% yield or a Pd(0)-catalyzed cross-coupling[23] lead to the biphenyl derivative **58h** in 80% yield (entries 6-7).

Regrettably, attempts to perform a magnesiation in *ortho-* to the nonaflate group led to an elimination reaction (benzyne formation)[78] and to the decomposition of the organometallic intermediate. Thus, when the 3-ethylester phenyl nonaflate **61** was treated with TMPMgCl·LiCl (**7**) the magnesium intermediate **61a** immediately leads to the benzyne **61b**, even at cryogenic conditions. Quenching with furan afforded the observation of the 1,4-dihydronaphtalene **61c** (Scheme 29) and probed the good leaving group hability of the nonaflate group when a magnesium bond is formed in *ortho*-position. This has been previously reported by *Knochel* in the synthesis of polyfunctional arynes *via* 2-magnesiated diaryl sulfonates.[79]
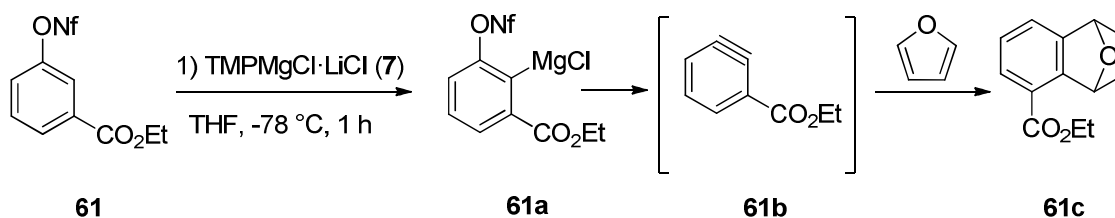
Scheme 29: Aryne formation by metalation using TMPMgCl·LiCl (**7**).

[77] J. Villiéras, M. Rambaud, *Org. Synth*. **1988**, *66*, 220.
[78] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett*. **1983**, 1211.
[79] I. Sapountzis, W. Lin, M. Fischer, P. Knochel, *Angew. Chem. Int. Ed*. **2004**, *43*, 4364.

Remarkably, we found that when using TMPZnCl·LiCl (**10**) (1.3 equiv) at 55 °C for 6 h, no elimination to the corresponding benzyne **63** was observed despite the drastic zincation conditions. A Negishi cross-coupling[23] with 3-iodo-1-trifluoromethylbenzene afforded the desired biphenyl **58i** in 65% yield (entry 8). The presence of two strong electron-withdrawing fluorine-substituents allows to zincate smoothly 2,4-difluorophenyl nonaflate **62** using TMPZnCl·LiCl (**10**) at 25 °C for 1 h. Performing a Negishi cross-coupling[23] with 4-iodo-1-trifluoromethylbenzene in the presence of a Pd-catalyst (Pd(dba)$_2$ (3 mol%), P(*o*-furyl)$_3$[73] (6 mol%), 65 °C, 6 h) provides the polyfunctional biphenyl **58j** in 89 % yield (entry 9). A magnesiation of **62** is possible in the 3-position (formally *meta*- to the nonaflate group) using TMPMgCl·LiCl (**7**) (1.1 equiv) at –20 °C for 15 min. Quenching with 4-methoxybenzaldehyde or with MeSO$_2$SMe provides the polyfunctional benzhydryl alcohol **58k** and the thioether **58l** in 94 and 81% yield, respectively (entries 10 and 11).

Thus, in the presence of a powerful directing group such as an ester group, the *para*-substituted aryl nonaflate **63** is readily magnesiated with TMPMgCl·LiCl (**7**) (1.1 equiv) at –20 °C within 3 h in *ortho*-position to the ester group. The resulting magnesium reagent is benzoylated after a transmetalation with CuCN·2LiCl[68] leading to the ketone **58m** in 65% yield (entry 12). Quenching with 4-methoxybenzaldehyde provides the lactone **58n** or the biphenyl **58o** after Negishi cross-coupling[23] in 72 and 65% yield, respectively (entries 13 and 14).

Table 3: Products of type **58** obtained by metalation of functionalized aryl nonaflates.
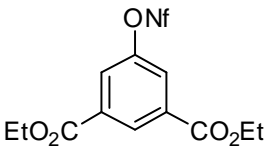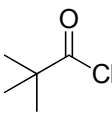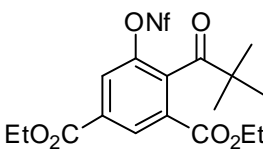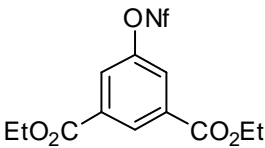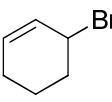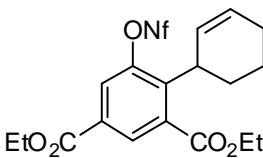
Entry	Substrate	Conditions	Electrophile	Product, Yield[a]
1	**54**	25 °C, 3 h[b]		**58a:** 72%[d]
2	**54**	25 °C, 3 h[b]		**58b:** 85%[e]

Table 3 (continued)
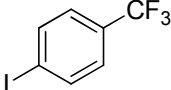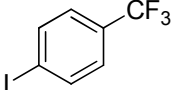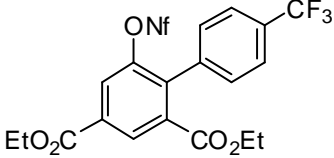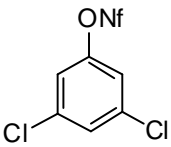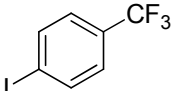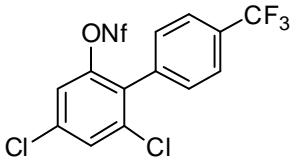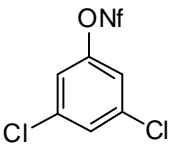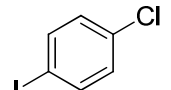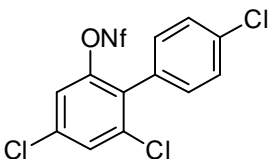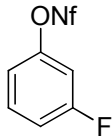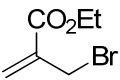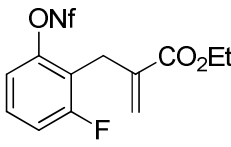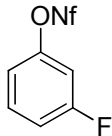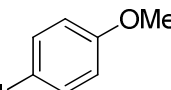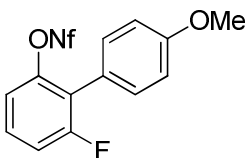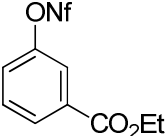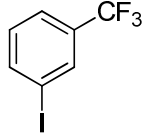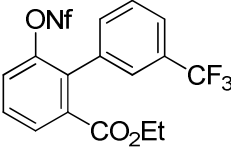
Entry	Substrate	Conditions	Electrophile	Product, Yield[a]
3	**54**	25 °C, 3 h[b]		**58c:** 83%[f]
4	**59**	25 °C, 3 h[b]		**58e:** 76%[f]
5	**59**	25 °C, 3 h[b]		**58f:** 83%[f]
6	**60**	25 °C, 3 h[b]		**58g:** 72%[e]
7	**60**	25 °C, 3 h[b]		**58h:** 80%[f]
8	**61**	55 °C, 6 h[b]		**58i:** 65%[f]

Table 3 (continued)
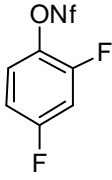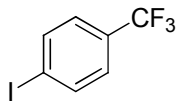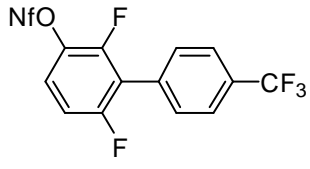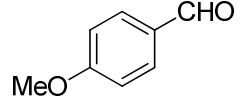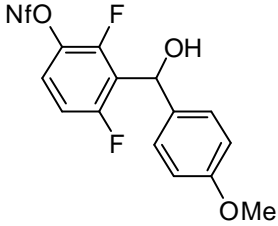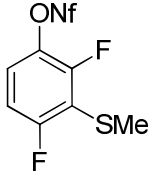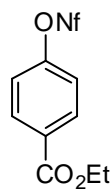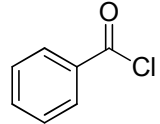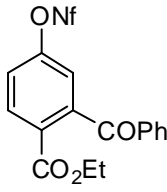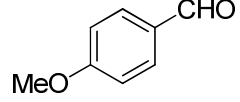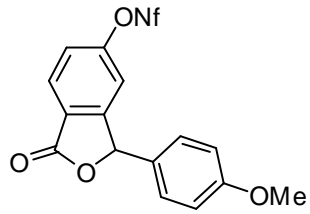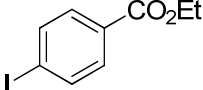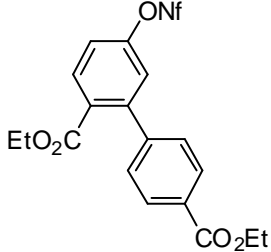
Entry	Substrate	Conditions	Electrophile	Product, Yield[a]
9	**62**	25 °C, 1 h[b]	(4-iodophenyl-CF$_3$)	**58j:** 89%[f]
10	**62**	–20 °C, 15 min[c]	(4-MeO-benzaldehyde, CHO)	**58k:** 94%
11	**62**	–20 °C, 15 min[c]	MeSO$_2$SMe	**58l:** 81%
12	**63**	–20 °C, 2 h[c]	(benzoyl chloride)	**58m:** 65%[d]
13	**63**	–20 °C, 2 h[c]	(4-MeO-benzaldehyde, CHO)	**58n:** 72%

Table 3 (continued)

Entry	Substrate	Conditions	Electrophile	Product, Yield[a]
14	**63**	–20 °C, 2 h[c]		**58o:** 65%[f]

[a] Yield of analytically pure product; [b] TMPZnCl·LiCl (1.1 equiv); [c] TMPMgCl·LiCl (1.1 equiv); [d] CuCN·2LiCl (1.1 equiv) was added; [e] 10 mol% of CuCN·2LiCl was added; [f] 3 mol% of Pd(dba)$_2$ and 6 mol% of P(o-furyl)$_3$ were added.

3.3.   Further Funtionalizations of Polyfunctional Aryl Nonaflates

Further functionalizations of the substituted polyfunctional nonaflates of type **58** have been performed. Thus, a Negishi cross-coupling[23] of the biphenyl nonaflate **58m** with 4-ethoxy-4-oxybutylzinc bromide[80] (**64**) under standard conditions (Pd(dba)$_2$ 5 mol%) and *bis*(diphenylphosphino)-ferrocene[76,81] (dppf; 5 mol%, 60 °C, 8 h) furnished the functionalized benzoate **65** in 79% yield. The cross-coupling of the 2,3,5-trisubstituted phenyl nonaflate **58c** with the benzylic zinc reagent **66**[82] in the presence of PEPPSI[83] as a catalyst (2 mol%, 25 °C, 3 h) afforded the tetrasubstituted benzene **67** in 73% yield (Scheme 30).

[80] A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228.
[81] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158.
[82] F. M. Piller, A. Metzger, A. M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[83] a) C. J. O´Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ. *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; c) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380.
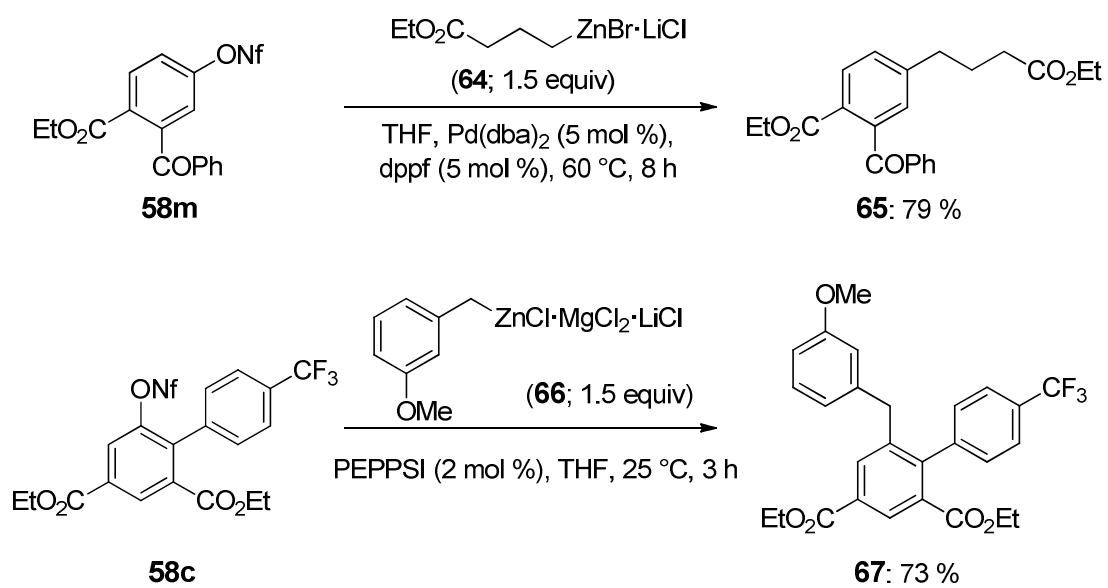
Scheme 30: Negishi cross-coupling of **58m** and **58c** with zinc reagents.

4. Directed *ortho*- and *meta*-Magnesiation of Functionalized Anilines and Amino-Substituted Pyridines and Pyrazines

4.1. Introduction

Since the synthesis of urea by *Wöhler* the formation of nitrogen-carbon bonds has been primordial in organic synthesis.[1] Special interest relies on the chemistry of amines, amides and other nitrogen-containing compounds. Their presence in Nature as building blocks as amino acids and nucleotides is fundamental[84] and they have great importance in the chemical industry, such as for the preparation of detergents, dyes, surfactants, pigment stabilizers, vulcanizing agents, and additives in the pretroleum industry.[85] Additionally, aryl and heteroaryl amines have a privileged role in pharmaceutical and agrochemical compounds[86] and different methods to prepare them, such as electrophilic alkylation, reductive alkylation, amination of aryl halides and hydroamination of olefins and alkynes have been developed.[87]

Among these aryl amines, anilines have been extensively used for the preparation of several natural products and pharmacologically active compounds. Recently, *Buchwald* reported the preparation of several dibenzodiazepines like Olanzapine (**68**) and Clozapine (**69**) by the cross-coupling of *o*-carbonyl anilines of type **70** with 1,2-dihaloarenes in the presence of catalytic quantities of palladium to afford the intermediates of type **71**. A further Pd(0)-mediated cross-coupling furnished the dibenzodiazepines derivatives **72** in 43-93% yield (Scheme 31).[88]

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[84] *Chemical Biology*, (Eds.: H. Waldmann, P. Janning), Wiley-VCH, Weinheim, Germany, **2004**.

[85] a) R. R. Egan, *J. Am. Oil Chem. Soc.* **1968**, *45*, 581; b) *Surfactant Science Series: Detergency of Specialty Surfactants*, (Eds.: S. Arif, F. Friedly), Marcel Dekker, New York, **2001**, Vol. 98; pp 71-115; c) K. S. Hayes, *Appl. Catal. A* **2001**, *221*, 187; d) *Industrial Organic Chemicals,* (Eds.: H. A. Wittcoff, B. G. Reuben, J. S. Plotkin), Wiley-Interscience, Hoboken, NJ, **2004**.

[86] a) *Pesticide Chemistry and Bioscience*, (Eds.: G. T. Brooks, T. R. Roberts), Royal Society of Chemistry, Cambridge, U.K., **1999**; b) *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application*, (Ed.: J. L. McGuire), Wiley-VCH, Weinheim, Germany, **2000**, Vols. 1-4.

[87] G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *1110*, 1611.

[88] a) D. Tsvelikhovsky, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 14228; b) R. A. Altman, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 5167.

Olanzapine (**68**)   Clozapine (**69**)
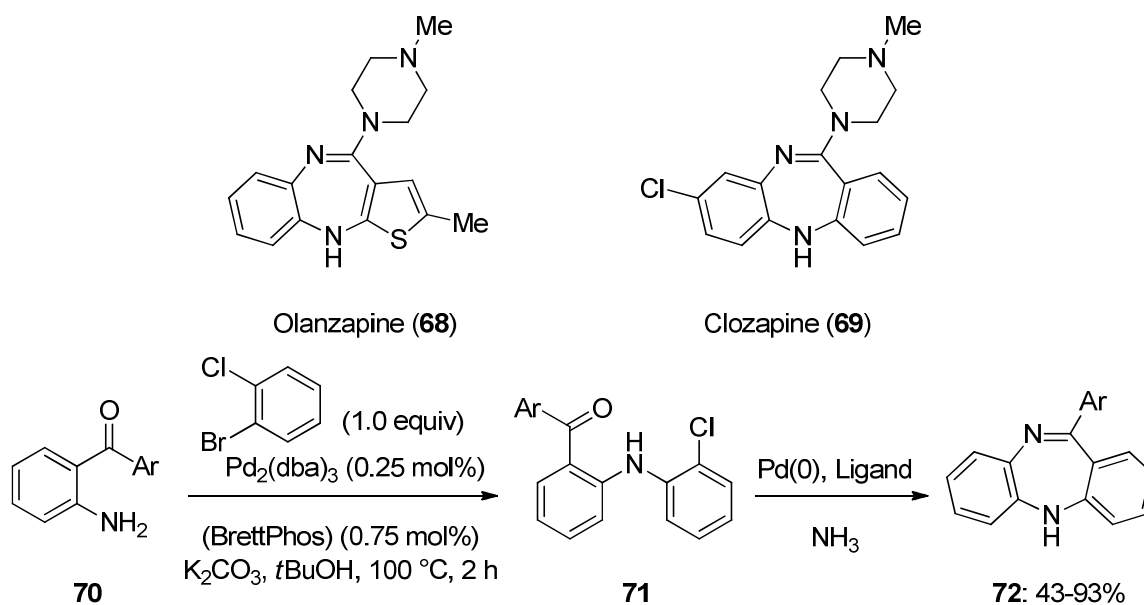
Scheme 31: Synthesis of dibenzodiazepines of type **72** from *o*-carbonyl anilines of type **70**.

Furthermore, indoles and azaindoles are prevalent structures in naturally occurring molecules and display a high biological activity. A recent approach for their synthesis involved the direct annulation of chloroanilines like 2-chloroaniline (**73**) in the presence of Pd(0) with cyclic or acyclic ketones such as tetrahydro-4*H*-pyran-4-one affording the corresponding indole **74** in 98% yield (Scheme 32).[89]
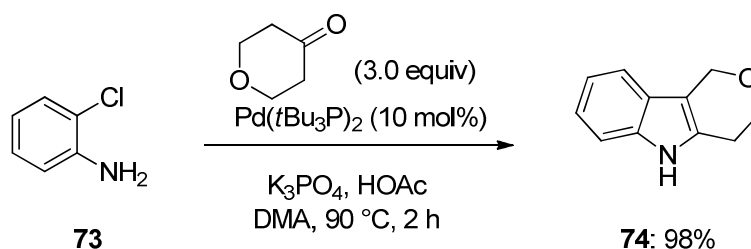
Scheme 32: Preparation of indoles from the corresponding *o*-chloroanilines.

The preparation of azaindoles is plausible through a reductive alkylation of chloroaminopyridines of type **75** to afford the alkylated products **76** in good yields. Subsequent one-pot Sonogashira

[89] M. Nazaré, C. Schneider, A. Lindenschmidt, D. W. Will, *Angew. Chem. Int. Ed.* **2004**, *43*, 4526.

cross-coupling and base-promoted indolization affords the corresponding azaindoles of type **77** (Scheme 33).[90]
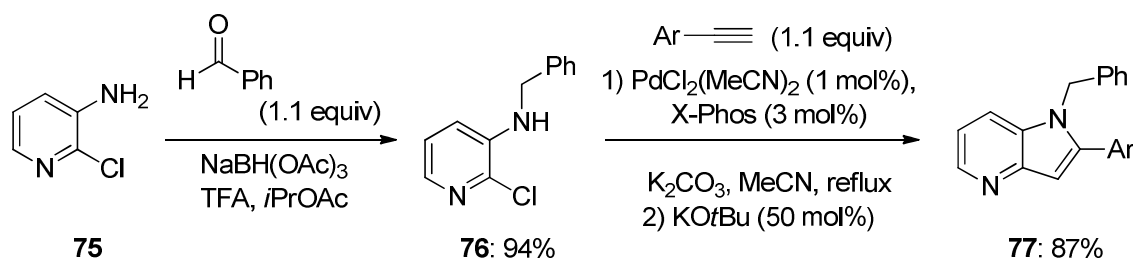
Scheme 33: Preparation of azaindoles from the corresponding chloroaminopyridines.

In special cases, the protection of the amino group in aryl and heteroaryl molecules is needed and an extensive battery of protective groups have been developed and investigated.[91] Thus, the use of the trifluoroacetyl moiety as protective group in the 2,4-dibromoaniline derivative **78**, promotes the copper-mediated synthesis of the corresponding indole **79** in 75% yield.[92] The use of a different protective group resulted insatisfactory and the –COCF$_3$ enhancement is assumed to an electron-withdrawing effect[93] in the *ortho*-substituent.[94] (Scheme 34).[95]
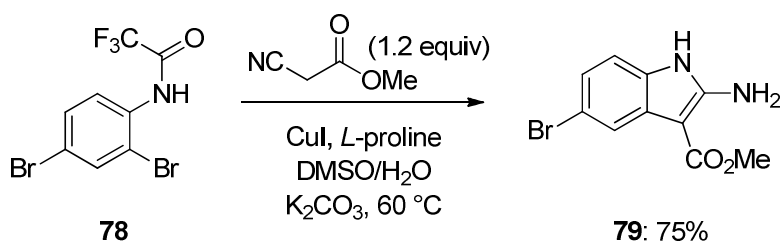
Scheme 34: Copper-catalyzed synthesis of indoles from the corresponding *N*-aromatic trifluoroacetyl amides.

[90] M. McLaughlin, M. Palucki, I. W. Davies, *Org. Lett.* **2006**, *8*, 3307.

[91] *Protective Groups in Organic Synthesis*, (Eds.: T. W. Greene, P. G. M. Wuts), John Wiley & Sons, New York, **1999**.

[92] F. Liu, D. Ma, *J. Org. Chem.* **2007**, *72*, 4844.

[93] X. Yang, H. Fu, R. Qiao, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2010**, *352*, 1033.

[94] K. C. Nicolau, C. N. C. Boddy, S. Natarajar, T.-Y. Yue, H. Li, S. Bräse, J. M. Ramanjulu, *J. Am. Chem. Soc.* **1997**, *119*, 3421.

[95] D. Li, L. Zhao, J. Zhang, *Synthesis* **2011**, 873.

Moreover, the directed lithiation of anilines[56] or aminopyridines[57] is an important method for preparing functionalized amino-substituted arenes and N-heterocycles which often have important pharmaceutical applications such as antiviral agents, [58] antibiotics,[57] etc. Although, these directed ortho-lithiations give access to various aminated aromatics, [96] the use of strong lithium bases such as *n*BuLi or *t*BuLi is incompatible with standard carbonyl functionalities such as an ester or a nitrile as well as with sensitive heterocyclic moieties (Scheme 35).
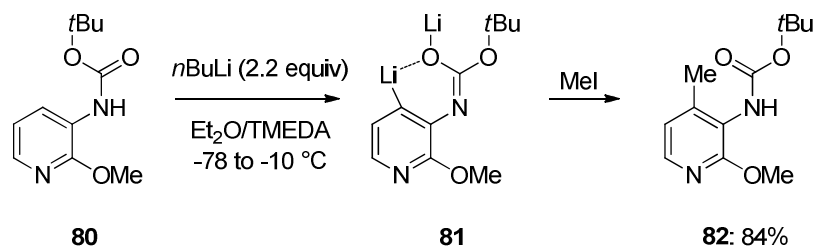
Scheme 35: *ortho*-Lithiation of Boc-amide pyridines.

The general strategy used involved the protection of the amino group with a pivaloyl, a *tert*-butoxycarbonyl or a trifluoroacetyl group leading to substrates of type ArNHCOR, which after treatment with two equivalents of base afforded an *ortho*-lithiated bimetallic intermediate. [97] Low temperatures were usually required for these lithiations.[98] Also the directed lithiation of trifluoroacetylamides protected anilines lead to extensive side products (Scheme 36).
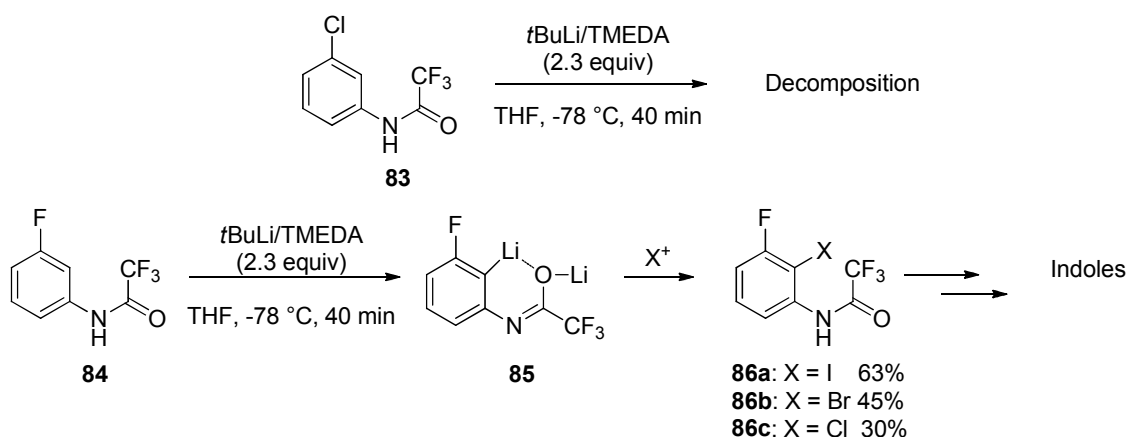
Scheme 36: Preparation of 2,3-dihalotrifluroacetanilides.

[96] T. A. Kelly, U. R. Patel, *J. Org. Chem.* **1995**, *60*, 1875.

[97] B. McKittrick, A. Failli, R. J. Steffan, R. M. Soll, P. Hughes, J. Schmid, A. A. Asselin, C. C. Shaw, R. Noureldin, G. Gavin. *J. Heterocycl. Chem.* **1990**, *27*, 2151.

[98] a) R. Sanz, V. Guilarte, N. García, *Org. Biomol. Chem.* **2010**, *8*, 3860; b) V. Guilarte, M. P. Castroviejo, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, *J. Org. Chem.* **2011**, *76*, 3416.

Recently, *Knochel* reported the preparation of fully substituted anilines for the synthesis of functionalized indoles.[99] Thus, functionalized *o*-iodo anilines were protected with 1,2-bis(chlorodimethylsilyl)ethane and subsequent Negishi cross-coupling[23] afforded the expected *o*-alkynylanilines of type **87**. Successive metalation using TMPMgCl·LiCl (**7**) (formally *meta*- to the amine) and subsequent deprotection afforded the fully functionalized anilines of type **88**, which were then transformed to the corresponding indoles of type **89** (Scheme 37).
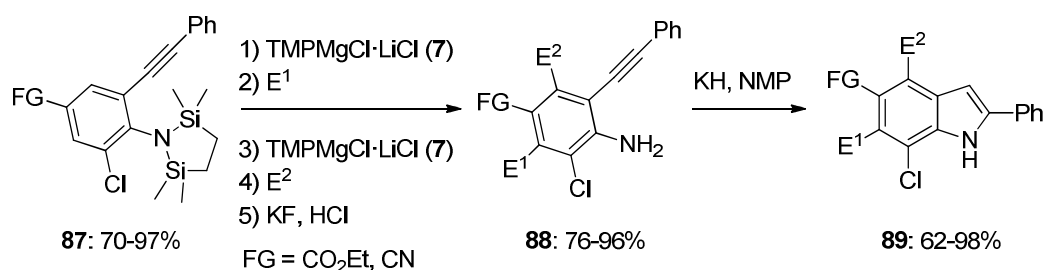
Scheme 37: Preparation of fully substituted anilines for the synthesis of functionalized indoles.

4.2.   Directed *ortho*-Metalation

The preparation of polyfunctional aromatics and heteroaromatics with a primary amine moiety is of enormous interest in organic synthesis.[100] The previous *ortho*-lithiations of anilines present several limitations towards functional group tolerance, are usually carried out at low temperatures and the range of electrophiles which can be used are limited. Thus, we envisioned a more rewarding route towards the *ortho*- and *meta*-metalation of protected aryl and heteroaryl amines. Extensive experimentation, led to the screening of aniline protective groups which would exhibit a directing effect towards metalation of the aromatic ring, be stable and easily cleaved to afford the aniline. Primarily, 3-chloroaniline (**90**) and 3,5-dichloroaniline (**91**) were chosen as the model substrates to be protected and investigated (Scheme 38).
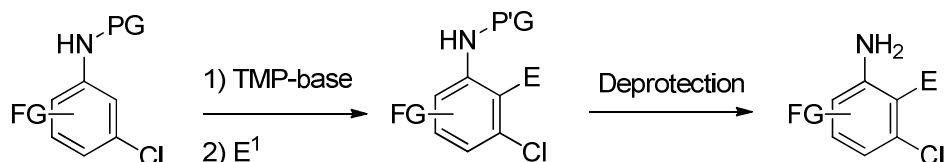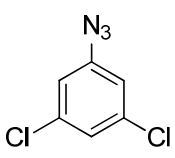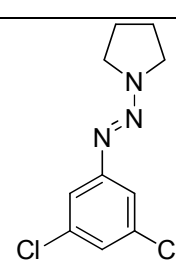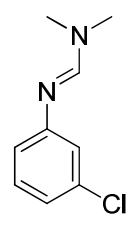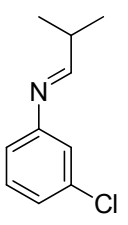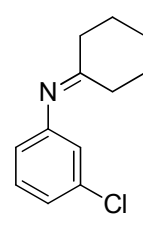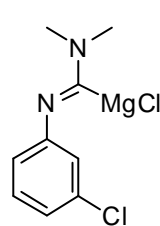
Scheme 38: Anilines protective group screening for *ortho*-magnesiation..

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[99] A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113.
[100] a) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2004**, *21*, 278; b) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73; c) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761.

Hence, the aniline synthetic analogues 1-azido-3,5-dichlorobenzene (**92**)[101] and 3,5-dichloroaryl triazene **93**[102] were subjected to several metalation conditions, but led only to decomposition of the starting material (Table 4, entries 1-2). Another approach was envisioned based on the complexation effect of the Lewis acid $BF_3 \cdot OEt_2$ with nitrogen in N-heterocycles. However, for substrates of the type **94-96**[103,104,105] resulted unsatisfactory metalation of the aromatic ring (entries 3-5). This showed that the complexation between $BF_3 \cdot OEt_2$ and a nitrogen, occurs preferentially in an aromatic ring.[42] Although, when **94** is reacted only with TMPMgCl·LiCl (**7**) (1.1 equiv) at 25 °C a magnesiated intermediate of type **97** is obtained in 55% yield[106] within 24 h (entry 3).

Table 4: Aniline protective groups screening for *ortho*-metalation.

Entry	1	2	3	4	5
Substrate	**92**	**93**	**94**	**95**	**96**
Product, Yield[a]	Dec.	Dec.	**97**: 55%[a]	Dec.	No reaction

[a] Yield determined by quenching with allyl bromide and 10% CuCN·2LiCl by Gas-Chromatography with an internal standard.

[101] S. Fantauzzi, E. Gallo, A. Caselli, C. Piangiolino, F. Ragaini, S. Cenini, *Eur. J. Org. Chem.* **2007**, 6053.
[102] C-Y. Liu, P. Knochel, *J. Org. Chem.* **2007**, *72*, 7106.
[103] J. Oszczapowicz, E. Raczynska, *Polish J. Chem.* **1983**, *57*, 419.
[104] B. Capon, Z. P. Wu, *J. Org. Chem.* **1990**, *55*, 2317.
[105] C. Caubère, P. Caubère, S. Ianelli, M. Nardelli, B. Jamart-Grégoire, *Tetrahedron*, **1994**, *50*, 11903.
[106] Determined by Gas-Chromatograpy with a CuCN·2LiCl catalyzed allylation and an internal standard.
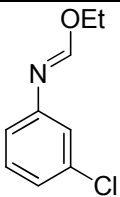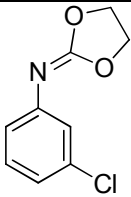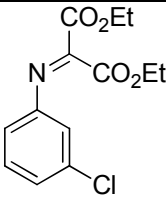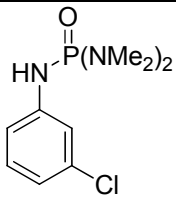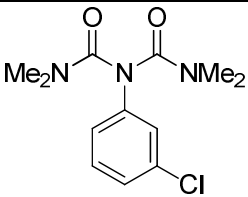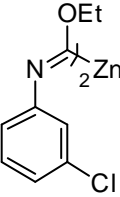
A different approach involved the installation of literature known directing metalation groups to provoke a complexation with the metallic amide base and afford the desired *ortho*-metalation of the aromatic ring. Unsatisfactorily, the directing effect by the ester **98**,[107] 1,3-dioxolane **100**,[108] diethyl ester **101**,[109] phosphorimide **102**[32,110] and *N,N*-dimethylcarbamoyl **103**[111] was not strong enough to afford the desired metalation. For instance **98** was metalated, although not in the aromatic ring, using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**11**) (0.6 equiv) at 0 °C within 2 h in 80% yield[106] (Table 5, entries 1-5).

Table 5: Aniline protective groups screening for *ortho*-metalation.

Entry	1	2	3	4	5
Substrate	**98**	**100**	**101**	**102**	**103**
Product, Yield[a]	**99:** 80%	No reaction	Dec.	No reaction	Dec.

[a] Yield determined by quenching with allyl bromide and 10% $CuCN \cdot 2LiCl$ by Gas-Chromatography with an internal standard.

Enthusiastically, a simple but efficient approach was envisioned which consisted in the removal of electron density from the aromatic ring. Thus, the installation of a bulky and electron-withdrawing fully substituted group as **105**[112] resulted unsatisfactory towards metalation. Surprisingly, pivaloyl group exhibited a directing effect for the *ortho*-metalation of 3,5-

[107] L. I. Smith, J. Nichols, Joseph, *J. Org. Chem.* **1941**, *6*, 489.
[108] S. Sakai, *Bul. Chem. Soc. Jpn.* **1977**, *50*, 3271.
[109] H. Nohira, *Bul. Chem. Soc. Jpn*, **1963**, *36*, 870.
[110] W. Gordon, *J. Med. Chem.* **1982**, *25*, 1231.
[111] W. Rauf, A. L. Thompson, J. M. Brown, *Chem. Commun.* **2009**, 3874.
[112] S. Mahapatra, *Asian J. Chem.* **2011**, *23*, 1581.

dichlorosubstituted pivaloyl amide **105**[113] when using TMPMgCl·LiCl (**7**) (1.1 equiv) at 25 °C within 6 h in a maximum of 45% yield[106] (Scheme 39).
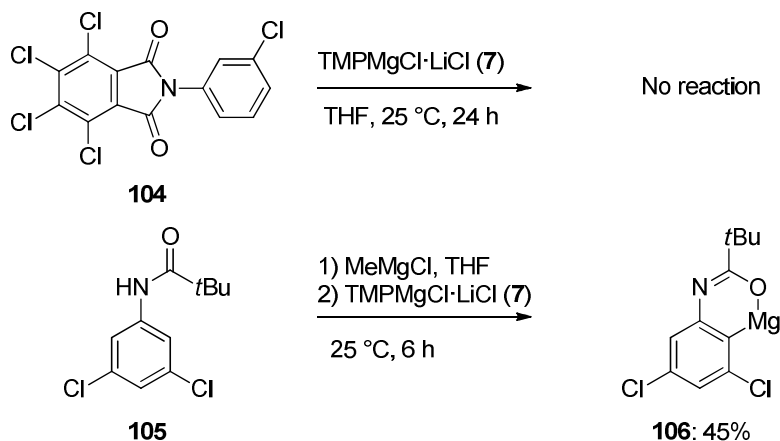
Scheme 39: *ortho*-Metalation of protected chloroanilines.

Upon the positive results obtained when using a triflate or nonaflate group for metalation of phenols reported by our group,[72a] we envisioned a similar approach for anilines. Thus, treating **107**[114] with TMP$_2$Mg·2LiCl (**9**) (1.1 equiv) at 25 °C for 5 h afforded the magnesiated species **108** in 85% yield.[106] Quenching with allyl bromide in the presence of CuCN·2LiCl (10 mol%)[68] afforded **109** in 45% yield. The discrete yield is due to the stability of the triflate group during purification (Scheme 40).
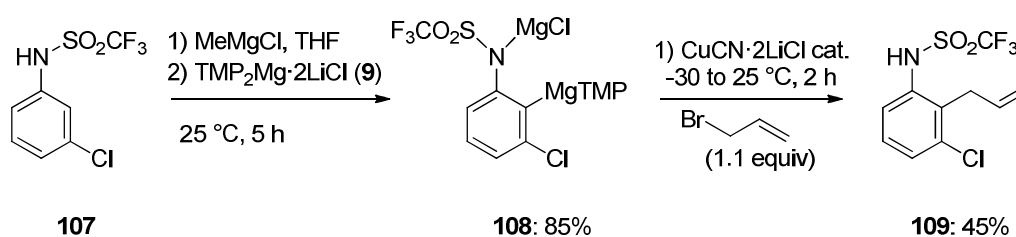
Scheme 40: *ortho*-Metalation of protected anilines with a triflate.

Further experimentation led to the protection of 3-chloroaniline (**90**) with the inexpensive, easy to handle and commercially available trifluoroacetic anhydride (**110**). The protection proceeds in

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[113] P. Stanetty, B. Krumpak, *J. Org. Chem.* **1996**, *61*, 5130.
[114] J. B. Hendrickson, R. Bergeron, *Tetrahedron Lett.* **1973**, *39*, 3839.

the presence of triethylamine (1.1 equiv) at 0 to 25 °C for 12 h and afforded the *N*-(3-chlorophenyl)-2,2,2-trifluoroacetamide **83**[115] in 91% yield (Scheme 41). This protection afforded the corresponding trifluoroacetyl amides in high yields, they are easy to handle solids and easily purified on silica or recrystallized. We tried to install a second protective group in the trifluoroacetyl amides, however it was not possible and only the starting material was recovered.
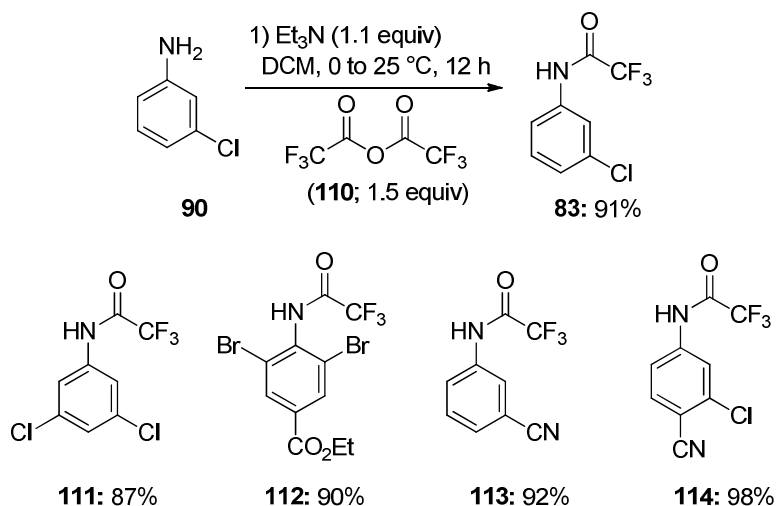
Scheme 41: Synthesis of aryl trifluoroacetyl amides.

Furthermore, **83** was treated with MeMgCl (1.1 equiv) at 0 °C to deprotonate the amide, gas evolved and the resonance structure **115** is assumed. The ring metalation was carried out using TMP$_2$Mg·2LiCl (**9**) at 25 °C for 5 h and the magnesiated species **116** was obtained in more than 90% yield.[106] Trapping with allyl bromide in the presence of catalytic CuCN·2LiCl[68] afforded the allylated product **117a** in 65% yield (Scheme 42). Fascinatingly, when **116** is transmetalated to zinc with ZnCl$_2$ a palladium-catalyzed Negishi cross-coupling[23] is possible with 4-iodotoluene and affords the corresponding biaryl product **117b** in 65% yield (Table 6, entry 1). It was found that the addition of 1.1 equivalents of MeMgCl is needed to carry out the full metalation, since the addition of 2.2 equivalents of the magnesium base lead to a lower conversion of **116**, probably due to steric hindrance. We assume a complexation of the oxygen (which presents a donor character) and kinetically activates the Mg-N bond of the base, resulting in an additional ate character of the base **9**.

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[115] J. Salazar, S. E. Lopez, O. Rebollo, *J. Fluorine Chem.* **2003**, *124*, 111.
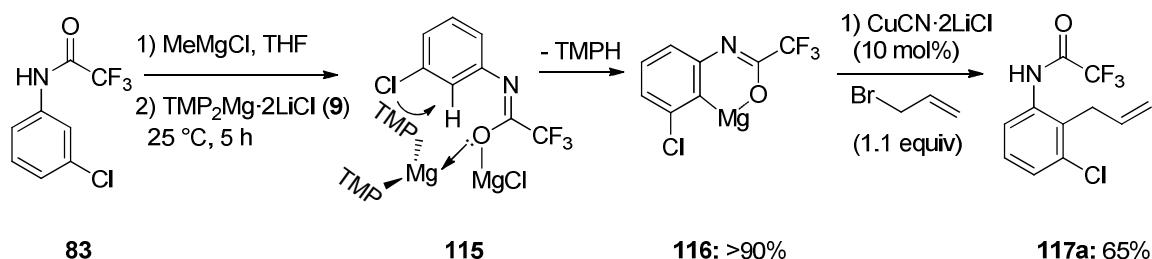
Scheme 42: Suggested mechanism for the *ortho*-metalation of the aryl trifluoroacetamide **83**.

The generality for the *ortho*-metalation was extended to other anilides with sensitive functional groups such as cyano and esters. Thus, the magnesiation of the 3,5-dichloro substituted trifluoroacetyl amide **111** goes to completion within 4 h at 25 °C using TMPMgCl·LiCl (**7**) (1.2 equiv). Quenching with iodine, a CuCN·2LiCl-mediated[68] allylation[69] or a bromine electrophile afforded the respective products **117c-e** in 68-72% yield (entries 2-4).

We have extended this approach to a double functionalization of the anilides. Thus, the magnesiation of **117e** using TMPMgCl·LiCl (**7**) (1.3 equiv) at 25 °C for 4 h and trapping with iodine afforded the tetrahalogenated anilide **117f** in 69% yield (entry 5). Furthermore, treating **111** as previously described and quenching with a sulphur electrophile afforded the thioether **117g** in 76% yield, which was further magnesiated and quenched with furoyl chloride (previous transmetalation with CuCN·2LiCl)[68] to afford the pentasubstituted aniline after workup (aq. sat. NH$_4$Cl) **117h** in 81% yield (Scheme 43).
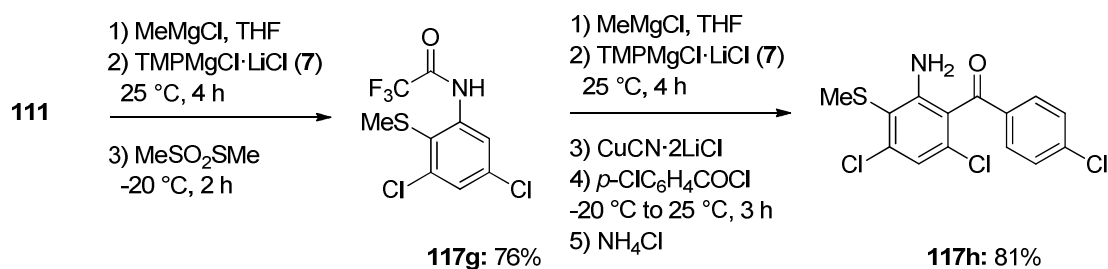
Scheme 43: Double metalation of 3,5-dichloro anilide **111** and subsequent reaction with electrophiles.

A trifluoromethyl group is perfectly tolerated and the magnesiation of 2-chloro-3-trifluoromethyl anilide **118** undergoes to completion at 25 °C within 8 h with TMP$_2$Mg·2LiCl (**9**) (1.2 equiv). Trapping with *S*-methyl methanethiosulfonate or a Cu-catalyzed allylation[68] with 3-bromocyclohexene affords the thioether **117i** or the allylated product **117j** in 75 and 66% yield, respectively (entries 6-7). Extraordinarily, the use of a magnesium base instead of a strong lithium base allows the presence of a cyano group in the starting anilide. Hence, **113** underwent efficient magnesiation with TMPMgCl·LiCl (**7**) (2.0 equiv) within 4 h. Performing an allylation[68] with 3-bromocyclohexene or Negishi cross-coupling[23] with 4-iodoanisole afforded the corresponding allylated or cross-coupled products **117k-l** in 72 and 75% yield, respectively (entries 8-9). The *ortho*-metalation occurs regioselective even when having a directing substituent in *para*-position such as for 3-chloro-4-cyanophenyl trifluoroacetamide **114**. This underwent effective magnesiation using TMPMgCl·LiCl (**7**) (1.2 equiv) at 25 °C for 3 h. Transmetalation to zinc and palladium-catalyzed cross-coupling[23] with 4-iodoethylbenzoate afforded **117m** in 63% yield. (entry 10). Remarkably, no elimination occurred (benzyne formation) at these mild conditions, as previously observed for *ortho*-lithiations of 3-halogenated trifluoroacetyl amides.[116]

Furthermore, a formal *meta*-metalation can be carried out at mild conditions. Remarkably, an ester-substituted anilide does not interfere with the metalation sequence (no addition of MeMgCl to the ester function). Thus, the 2,6-dibromo-4-methyl benzoate anilide derivative **119** is fully magnesiated at 25 °C within 4 h using TMPMgCl·LiCl (**7**) (1.3 equiv). Quenching with *p*-anisaldehyde afforded the functionalized lactone **117n** in 71% yield (Scheme 44). Analogous metalation conditions for **112** and quenching with ethyl 2-(bromomethyl)acrylate[69] (after addition of a catalytic amount of CuCN·2LiCl) afforded **117o** in 75% yield (entry 11).
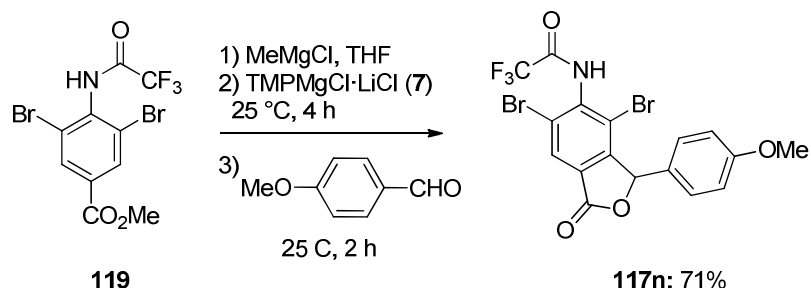
Scheme 44: Formally *meta*-metalation of a 2,4,6-trisubstituted aryl trifluoroacetylamide.

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[116] a) R. Sanz, *Org. Prep. Proced. Int.* **2008**, *40*, 215; b) R. D. Clark, J. M. Caroon, *J. Org. Chem.* **1982**, *47*, 2804.

Table 6: Products of type **117** obtained after magnesiation with TMPMgCl·LiCl (**7**) or TMP₂Mg·2LiCl (**9**) and subsequent reaction with an electrophile.
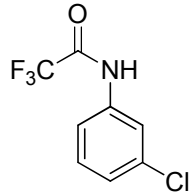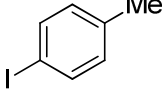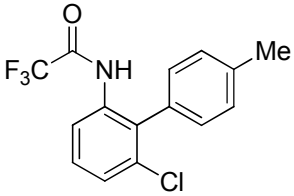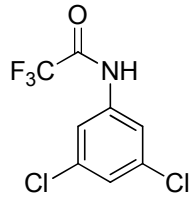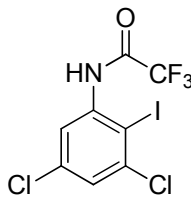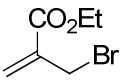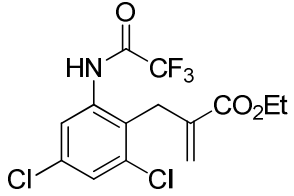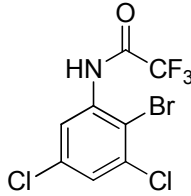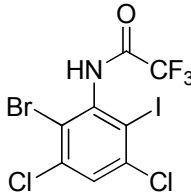
Entry	Substrate	T [°C], t[h]	Electrophile	Product, Yield[a]
1	**83**	25, 5[b]		**117b:** 65%[e]
2	**111**	25, 4[c]	I₂	**117c:** 72%
3	**111**	25, 4[c]		**117d:** 70%[f]
4	**111**	25, 4[d]	(BrCl₂C)₂	**117e:** 68%[f]
5	**117e**	25, 4[d]	I₂	**117f:** 69%

Table 6 (continued)
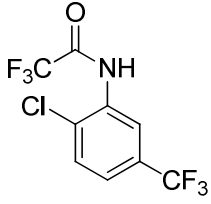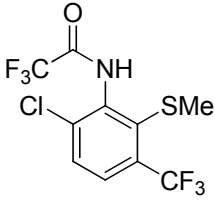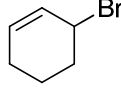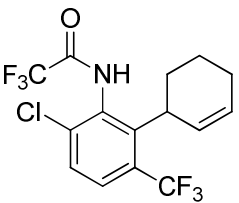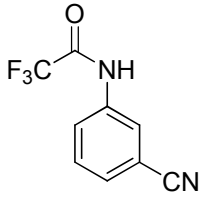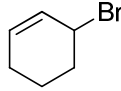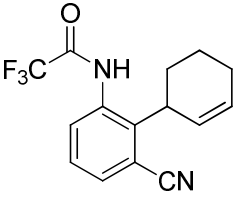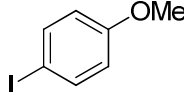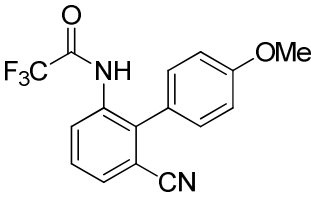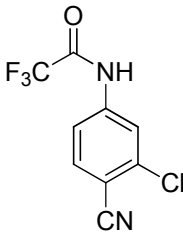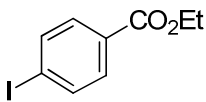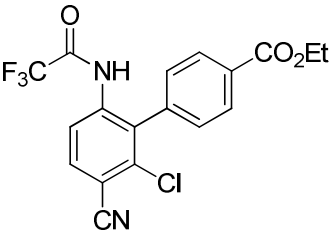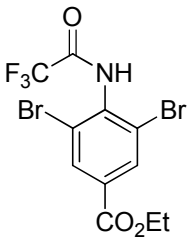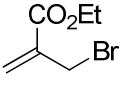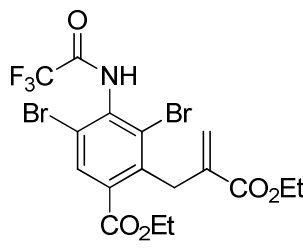
Entry	Substrate	T [°C], t[h]	Electrophile	Product, Yield[a]
6	**118**	25, 8[b]	MeSO$_2$SMe	**117i:** 75%
7	**118**	25, 8[b]		**117j:** 66%
8	**113**	25, 4[d]		**117k:** 72%[f]
9	**113**	25, 4[d]		**117l:** 75%[e]
10	**114**	25, 3[b]		**117m:** 63%[e]

Table 6 (continued)

Entry	Substrate	T [°C], t[h]	Electrophile	Product, Yield[a]
11	**112**	25, 4[b]		**117o:** 75% [c]

[a] Yield of analytically pure product; [b] TMP$_2$Mg·2LiCl (**9**) (1.2 equiv); [c] TMPMgCl·LiCl (**7**) (1.2 equiv); [d] TMPMgCl·LiCl (**7**) (2.0 equiv); [e] 3 mol% of Pd(dba)$_2$ and 6 mol% of P(o-furyl)$_3$ were added; [f] 10 mol% of CuCN·2LiCl was added.

4.3.   Directed *ortho*-Functionalizations of Heteroaryl Amines

The selective metalation of functionalized aminopyridines is of special importance due to their pharmaceutical relevance.[52,53] The *ortho*-functionalization of these heterocylces is of great interest, however very few reports are available and are limited to the use of lithium bases.[96] The newly metalation sequence developed allowed a smooth regioselective metalation of amino-pyridines and pyridazines. It was found that the regioselective metalation of the 3-amino pyridine derivative **120** is possible when using TMPMgCl·LiCl (**7**) (1.3 equiv) at 25 °C for 4 h. Quenching with 3-bromocyclohexene (after addition of a catalytic amount of CuCN·2LiCl)[68] affords the 4-allylated product **121a** in 65% yield (Scheme 45). Given the great synthetic interest, we have also performed a Negishi cross-coupling[23] after transmetalation to zinc and the appropriate palladium-catalyst system with 4-iodoethylbenzoate to afford **121b** in 65% yield (Table 7, entry 1). Remarkably, the regioselectivity of the magnesiation is possible to alter when using BF$_3$·OEt$_2$ (1.2 equiv) at –20 °C for 20 min. The subsequent addition of TMPMgCl·LiCl (**7**) (1.2 equiv) at –20 °C for 2.5 h, led to the magnesiation of the 2-position of the pyridine ring. Performing an acylation with 2,4-dichlorobenzoyl chloride (previous transmetalation with CuCN·2LiCl)[68] afforded the ketone **122** in 60% yield (Scheme 45).[117]

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[117] Experiments were done by Dr. I. Tirotta and are given here for the sake of completeness.
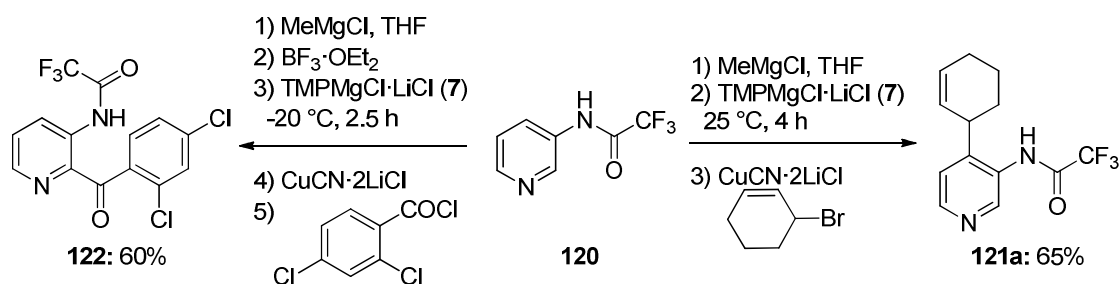
Scheme 45: *ortho*-Metalation with and without BF$_3$·OEt$_2$ of pyridyl trifluoroacetamides.

Furthermore, the 2-chloro substituted amino pyridine derivative **123** underwent efficient metalation using TMPMgCl·LiCl (**7**) (1.5 equiv) at 25 °C within 5 h. Neghishi cross-coupling[23] with 4-iodobenzotrifluoride afforded the tetrasubstituted pyridine **121c** in 80% yield (entry 3).[117]

Table 7: Products of type **121** obtained after magnesiation with TMPMgCl·LiCl (**7**) and subsequent reaction with an electrophile.

Entry	Substrate	T [°C], t[h]	Electrophile	Product, Yield[a]
1	**120**	25, 4[b]		**121b:** 65%[d]
2	**123**	25, 5[c]		**121c:** 80%[d]

[a] Yield of analytically pure product; [b] TMPMgCl·LiCl (**7**) (1.2 equiv); [c] TMPMgCl·LiCl (**7**) (1.5 equiv); [d] 3 mol% of Pd(dba)$_2$ and 6 mol% of P(o-furyl)$_3$ were added.

4.4.   Application to the Synthesis of Biologically Active Compounds

This method is of great utility for the preparation of pharmaceutically active heterocycles such as aminopyrazines. As an application, we have prepared a GSK-3 and Lck protein kinase inhibitor in two steps. This compound is useful for the treatment and prevention of diabetes, Alzheimer and transplant rejection patented by Vertex Pharmaceuticals.[118] Thus, the magnesiation of the 2-trifluoroacetylamide pyrazine **124** with TMPMgCl·LiCl (**7**) (1.2 equiv) is completed within 3 h at 0 °C. Transmetalation with $ZnCl_2$ (1.2 equiv) and palladium-catalyzed cross-coupling[23] with 2-iodoindole[119](1.1 equiv, 25 °C, 3 h) provided the substituted pyrazine **125** in 55% yield. The moderate yield is assumed to the protonolysis of the organozinc species by the unprotected indol. Smooth and standard trifluoacetyl amide deprotection with potassium carbonate (3.0 equiv)[120] in a mixture of MeOH:H_2O (1:1) at 25 °C for 12 h afforded the deprotected 3-(1*H*-indol-2-yl)pyrazin-2-amine (**126**) GSK-3 and Lck inhibitor in 83% yield (46% overall yield) (Scheme 46).
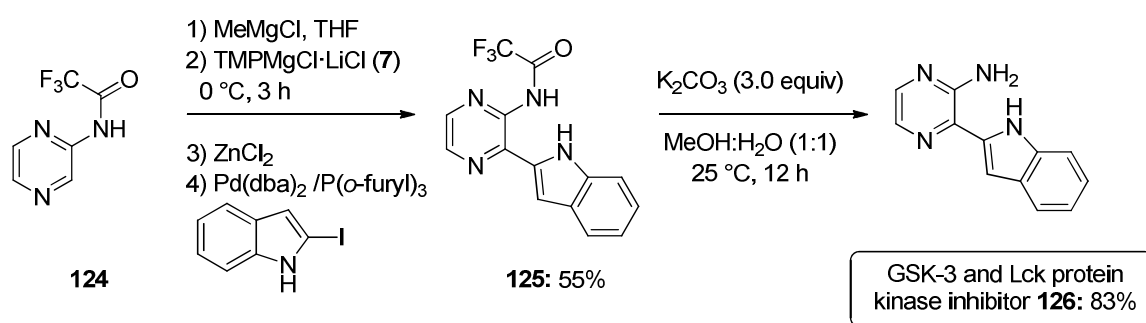
Scheme 46: Synthesis of a GSK-3 and Lck protein kinase inhibitor (**126**) by chemoselective magnesiation and subsequent deprotection.

[118] S. Harbeson, M. J. Arnost, J. Green, V. Savic, WO 03/066629, **2003**.
[119] J. Bergman, V. Lennart, *J. Org. Chem.* **1992**, *57*, 2495.
[120] Y. Chen, V. Thon, Y. Li, H. Yu, L. Ding, K. Lau, J. Qu, L. Hie, X. Chen, *Chem. Commun.* **2011**, *47*, 10815.

5.   Preparation and Reactions of Heteroaromatic Benzylicic Zinc Reagents

5.1.   Introduction

The preparation of polyfunctional organozinc reagents is an important task since these are valuable intermediates in organic synthesis.[22b,121] The broad functional group tolerance of the carbon-zinc bond allows the preparation of highly functionalized reagents and is a key feature of these type of organometallics. Thus, aryl, heteroaryl and alkyl zinc reagents are readily prepared and reacted in high yield with a broad range of electrophiles under the appropriate reaction conditions.[122] Recently, it was reported the LiCl promotes the zinc insertion into various organic halides[123] and polyfunctional aryl and benzylic zinc organometallics are accessible.[18c] Since heterocyclic scaffolds are major building blocks for pharmaceuticals, agrochemicals and materials, the preparation of the unknown heterocyclic benzylic zinc compounds from their corresponding halides was investigated. Moreover, the preparation of *N*-heterocyclic zinc reagents requires simple methods for accessing these precursors which can be of two types. First, where a stabilization of the benzylic organometallic reagent with the heterocyclic *N*-atom of the ring is possible as in **127** and **128**. These can be obtained by the mild zincation from the corresponding 2-picoline (**129**) and 4-picoline (**130**) with TMPZnCl·LiCl (**10**) (Scheme 47).[124]
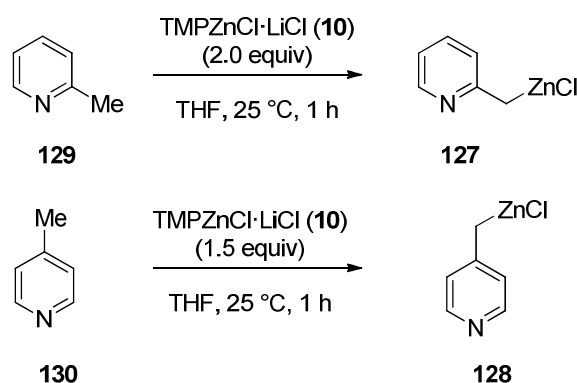
Scheme 47: Preparation of zincated 2- and 4-picolines.

[121] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.

[122] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; b) L. E. Zimmer, A. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 15633.

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

[124] S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686.

However, the generation of a zinc reagent of type **131** by deprotonation is not efficient and a benzylic chloride must be the precursor. Thus, we envisioned the preaparation of such chloromethyl derivatives starting from the metalated pyridine of type **132**, where its reaction with the *Tietze* salt[125] should provide the dimethylaminomethyl derivative **133**. This shall afford the chloromethyl derivative **134** after reaction with ethyl chloroformate (Scheme 48).
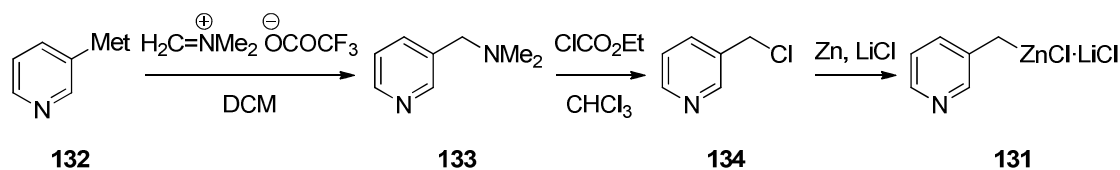
Scheme 48: Preparation of heterocyclic benzylic zinc reagents.

5.2.   Synthesis of Heterocyclic Benzylic Amines

We envisioned the use of a dimethylcarboxamide moiety as an *ortho*-directing group for metalation of the pyridine ring, followed by reaction with an electrophile and subsequent reduction of the carboxamide to the dimethylamine of type **133**. Thus, 6-chloro-*N,N*-dimethylnicotinamide (**135**) underwent full regioselective metalation using TMPMgCl·LiCl (**7**) (1.1 equiv) at –40 °C within 2 h. Quenching with *S*-methyl methanethiosulfonate afforded the functionalized nicotinamide **136** in 71% yield. Furthermore, a second metalation can be performed when **136** is magnesiated using TMPMgCl·LiCl (**7**) (1.1 equiv) at –20 °C for 1 h. Quenching with iodine afforded the trisubstituted nicotinamide **137** in 65% yield (Scheme 49).
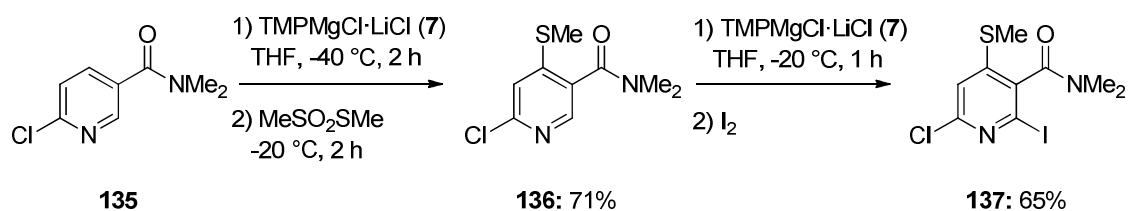
Scheme 49: Directed *ortho*-metalations of the nicotinamide **135** using TMPMgCl·LiCl (**7**).

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[125] G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 239.

Regrettably, every attempt to reduce the carboxamide moiety to its corresponding dimethylamine following literature procedures,[126] did not proceed or led to the decomposition of **135-137**.

Another route was undertaken, being this the functionalization of the dimethylamine pyridine **138**[127] by metalation. Unfortunately, it only led to low conversion of the metalated species **139** with a poor regioselectivity, even when using a Lewis acid such as $BF_3 \cdot OEt_2$ or varying the dialkylamino group (Scheme 50).
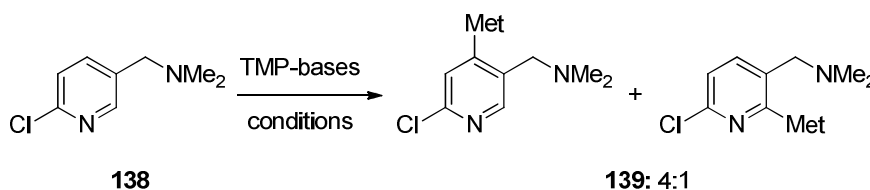
Scheme 50: Metalation of **138** using TMP-bases.

A similar approach was endeavoured for a pyrimidine scaffold using a literature-known procedure which describes the $-CNMe_2$ homologation of organometallics by employing the methylene(dimethyl)iminium ion (**140**) or so-called *Mannich´s* ion. This is normally prepared by the reaction of formaldehyde with dimethylamine in aqueous solution,[128] although it is possible to prepare it in anhydrous conditions.[129] Thus, *N,N,N´,N´*-tetramethylmethanediamine (**141**) reacts with trifluoroacetic anhydride in anhydrous DCM at 0 °C and afforded quantitatively **140** within 5 min (Scheme 51).[130]
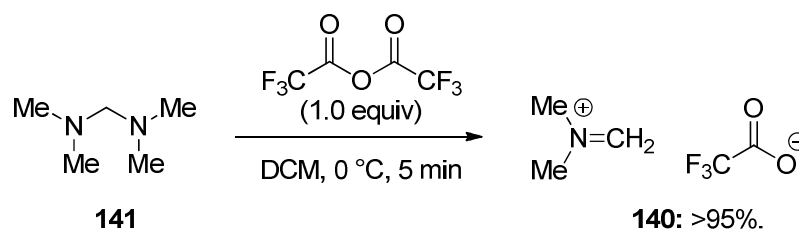
Scheme 51: Anhydrous preparation of the *Mannich*-type salt **140**.

[126] a) T. Yamakawa, M. Masaki, H. Nohira, *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2730; b) S. Itsuno, T. Wakasugi, K. Ito, A. Hirao, S. Nakahama, *Bull. Chem. Soc. Jpn*. **1985**, *58*, 1669; c) S. Das, D. Addis, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 1770 and references cited therein.

[127] A. Samadi, D. Silva, M. Chioua, M. do C. Carreiras, J. Marco-Contelles, *Synth. Commun*. **2011**, *41*, 2859.

[128] J. L. Li, *Name Reactions for Homologations*, (Ed.: E. J. Corey), John Wiley & Sons, New York, **2009.**

[129] a) A. Ahond, A. Cavé, C. Kann-Fan, H.-P. Husson, J. de Rostolan, P. Potier, *J. Am. Chem. Soc.* **1968**, *90*, 5622; b) D. Grierson, *Org. React*. **1990**, 39; c) M. Gaudry, Y. Jasor, T. B. Khac, *Org. Synth*. **1988**, *6*, 474; d) T. A. Bryson, G. H. Bonitz, C. J. Reichel, R. E. Dardis, *J. Org. Chem.* **1980**, *45*, 524.

[130] a) N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, 941; b) N. Gommermann, C. Koradin, P. Knochel, *Synthesi* **2002**, 2143.

Thus, 5-bromopyrimidine (**142**) was subjected to a bromine-lithium exchange with *n*BuLi (1.2 equiv) at –110 °C for 30 min.[131] The lithiated species was transmetalated with $ZnCl_2$ (1.3 equiv) and quenched by adding a solution of the iminium salt **140** in DCM to afford the amine **143** in 63% yield. Worth mentioning is that reacting directly the lithiated species did not afford **143** and transmetalation to zinc is necessary (Scheme 52).
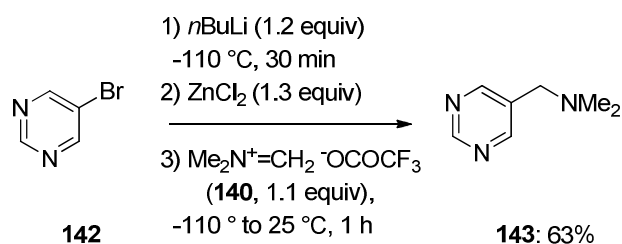
Scheme 52: Preparation of the *N,N*-dimethyl amino pyrimidine **143**.

Smoothly, the dimethyl amino pyrimidine **143** was regioselectively magnesiated using TMPMgCl·LiCl (**7**) (1.1 equiv) at –15 °C for 2 h. Quenching with a sulphur electrophile afforded the thioether **144** in 66% yield. A second regioselective metalation is possible under similar conditions at –20 °C for 1 h and subsequent quenching with 1,2-dibromotetrachloroethane resulted the trisubstituted pyrimidine **145** in 57% yield (Scheme 53).
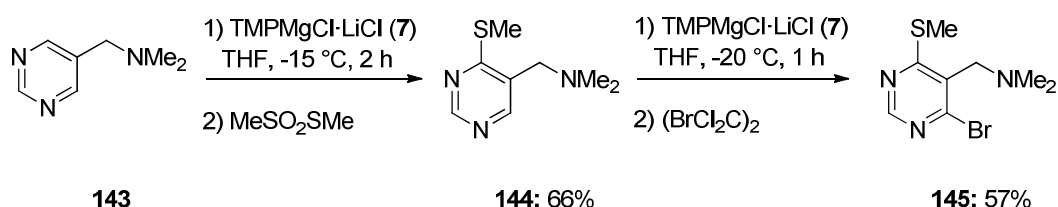
Scheme 53: Regioselective magnesiations of the pyrimidine derivative **143**.

However, any attempt to convert the dimethylamine derivatives **143-145** to the corresponding chloromethyl pyrimidine, resulted in a sluggish reaction mixture and decomposition of the starting material if the temperature was raised.

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[131] C. B. Aakeröy, J. Desper, B. Levin, J. Valdés-Martínez, *Inorg. Chim. Act*. **2006**, 1255.

5.3. Synthesis of Heterocyclic Benzylic Chlorides

Upon the previously described, a new substrate was envisioned as building block. Thus, 2-chlor-6-fluoropyridine (**146**) was fully metalated with TMPMgCl·LiCl (**7**) (1.1 equiv) at –40 °C within 5 h.[132] Trapping with iodine afforded the 6-chloro-2-iodo-3-iodopyridine (**147**) in 76% yield. Furthermore, an iodine-magnesium exchange with *i*PrMgCl·LiCl (1.1 equiv) at –30 °C for 30 min and quenching with **140** afforded the *N,N*-dimethylmethanamine pyridine derivative **148** in 79% yield. Noteworthy to mention, that a direct quenching of the metalated intermediate of **146** with **140** led to low yields of **148** due to the interference of the metalic amide. Treatment with ethyl chloroformate[133] in CHCl$_3$ afforded the 3-chloromethylpyridine **149**[134] in 60% yield (Scheme 54).
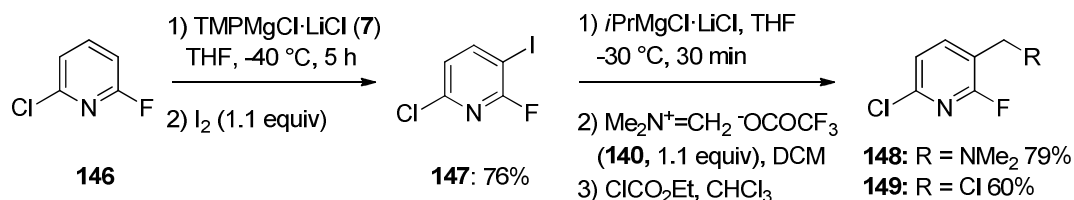
Scheme 54: Preparation of the 3-chloromethyl pyridine **149**.

A similar route was undertaken for the preparation of a pyrimidine benzylic chloride motif. Thus, the treatment of 2,4-dimethoxy-5-bromo-pyrimidine (**150**)[135] with *i*PrMgCl·LiCl (1.1 equiv) within 2 h at –20 °C led to the magnesiated intermediate which was quenched with the *Tietze´s* salt[125] and resulted **151** in 83% yield. Metalation with TMPMgCl·LiCl (**7**) (1.1 equiv) at 20 ° C for 45 min and trapping with 1,1,2-trichlorotrifluoroethane (1.1 equiv, 50 °C, 4 h) afforded **152** in 66% yield. Finally, treatment with ethyl chloroformate in CHCl$_3$ afforded the 3-chloromethylpyrimidine **153** in 72% yield (Scheme 55).

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[132] A mixture of (92:8) of regiosiomers was obtained. Regioselectivity with a milder base only led to a lower metalation conversion.

[133] D. S. Kashdan, J. A. Schwartz, H. Rapoport, *J. Org. Chem.* **1982**, *47*, 2638 and references cited therein.

[134] Z. Quan, B. B. Snider, *Org. Lett.* **2011**, *13*, 526.

[135] N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715.
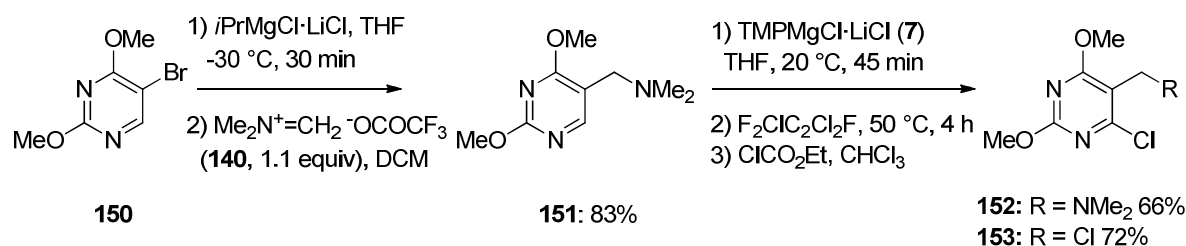
Scheme 55: Preparation of the pyrimidine benzylic chloride derivative **153**.

5.4.   Preparation and Reactions of Heterobenzylic Zinc Reagents

Previous reports described the oxidative zinc insertion into benzylic chlorides mediated by LiCl[136] and it was extended to heterobenzylic chlorides by *Wagner* and *Knochel*.[137] Thus, Zn dust was activated using 1,2-dibromoethane and chlorotrimethylsilane previous the oxidative insertion into the heterobenzylic chloride **149**. The full conversion to the heterobenzylic zinc reagent **154** was achieved within 1 h at 25 °C in 90% yield.[138] The acylation of **154** with 2,4-dichlorobenzoyl chloride (previous transmetalation with CuCN·2LiCl)[68] afforded the heterocyclic ketone **155a** in 80% yield (Scheme 56).
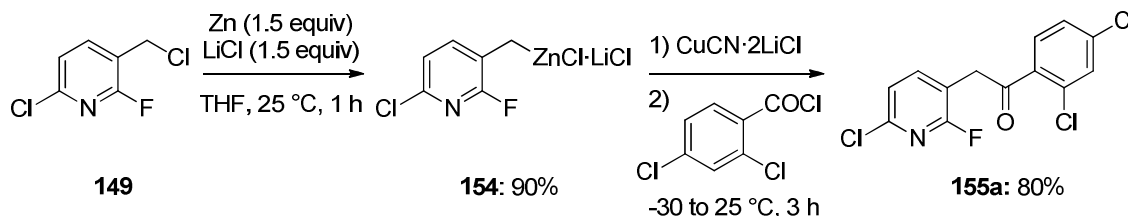
Scheme 56: Preparation of the heterobenzylic zinc reagent **154** *via* oxidative zinc-insertion and further acylation.

In that fashion, quenching **154** with acetyl chloride and 2-thiophencarbonyl chloride furnished the acylated products **155b-c** in 79-86% yield (Table 8, entries 1-2). Pd-catalyzed cross-coupling[23] with 1-bromo-2-iodobenzene afforded the pyridine **155d** in 70% yield (entry 3). Similarly, the benzylicic reagent **154** adds rapidly to aldehydes leading to the alcohols **155e-f** in 70-80% yield (entries 4-5). Quenching with a benzenesulfonamide resulted in a spontaneous cyclization into the 7-azaindoline **155g** in 63% yield (entry 6).

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[136] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.
[137] PhD thesis, Andreas J. Wagner, LMU Munich, **2011**.
[138] Determined by iodometric titration.

This reaction sequence was extended to the uracils **153**, where after zinc insertion the corresponding zinc reagent **156** was obtained in 85% yield.[138] Performing a copper-mediated acylation with CuCN·2LiCl[68] and benzoyl chloride afforded the highly functionalized uracil derivative **155h** in 88% yield (entry 7).

Table 8: Products of type **155** obtained by reaction of heterobenzylicic zinc reagents with electrophiles.
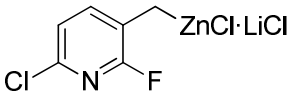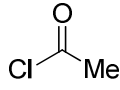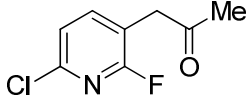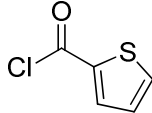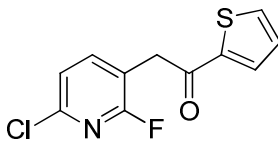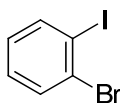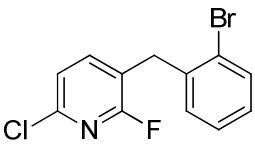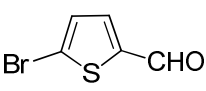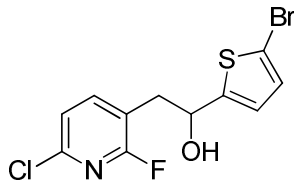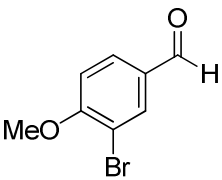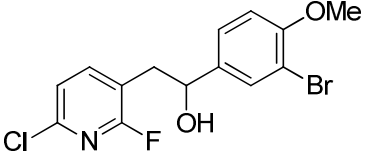
Entry	Substrate	Electrophile	Product, Yield[a]
1	**154**		**155b:** 79%[b]
2	**154**		**155c:** 86%[b]
3	**154**		**155d:** 70%[c]
4	**154**		**155e:** 70%
5	**154**		**155f:** 80%

Table 8 (continued)

Entry	Substrate	Electrophile	Product, Yield[a]
6	**154**		**155g:** 63%
7	**156**		**155h:** 88%[b]

[a] Yield of analytically pure product; [b] CuCN·2LiCl (1.1 equiv) was added; [c] Pd(dba)$_2$ and P(*o*-furyl)$_3$ in 6 mol% and 3 mol% respectively were added.

5.5. Preparation of Highly Functionalized Fused Heterocycles

The substituted N-heterocycles prepared are unique building blocks for the preparation of new annulated heteropolycycles like azaindoles[139] and furopyridines [140] with enormous interest for pharmaceutical applications. Among these, special interest relies on the furopyridines such as the CB1 and CB2 receptor (**157**)[141] and Lck and ACK-1 enyzme inhibitor (**158**).[142] Similarly, 7-azaindoles are of high-value such as the polo-like kinase (PLK) inhibitor (**159**) from Vertex or the insulin-like growth factor receptor (IGFR1) inhibitor (**160**) against cancer from Merck. [143] Additionaly, pyrido-pyridazine derivatives such as the GABA-A receptor ligand (**161**) to prevent anxiety from Merck[144] have received our attention (Figure 2).

[139] E. H. Sessions, S. Chowdhury, Y. Yin, J. R. Pocas, W. Grant, T. Schröter, L. Lin, C. Ruiz, M. D. Cameron, P. LoGrasso, T. D. Bannister, Y. Feng, *Bioorg. Med. Chem. Lett*. **2011**, *21*, 7113 and references cited therein.

[140] A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, F. Marinelli, *Org. Lett*. **2002**, *4*, 2409 and references cited therein.

[141] a) B. M. Moore, S. Gurley, S. Mustafa, WO 2011022679, **2011**; b) B. M. Moore, S. Gurley, S. Mustafa, US 20110046175, **2011**.

[142] J. J. Nunes, M. W. Martin, R. White, D. McGowan, J. E. Bemis, F. Kayser, J. Fu, J. Liu, X. Y. Jiao, US 20060046977, **2006**.

[143] J. L. Henderson, S. M. McDermott, S. L. Buchwald, *Org. Lett*. **2010**, *12*, 4438.

[144] S. C. Goodacre, D. J. Hallett, WO 2004039802, **2004**.

CB1 and CB2 Modifier (**157**)

Lck and ACK-1 Enzyme Inhibitor (**158**)

Polo-like Kinase (PLK) Inhibitor (**159**)

Insuline-like Growth Factor
Receptor (IGFR1) Inhibitor (**160**)

GABA-A Receptor Ligand (**161**)
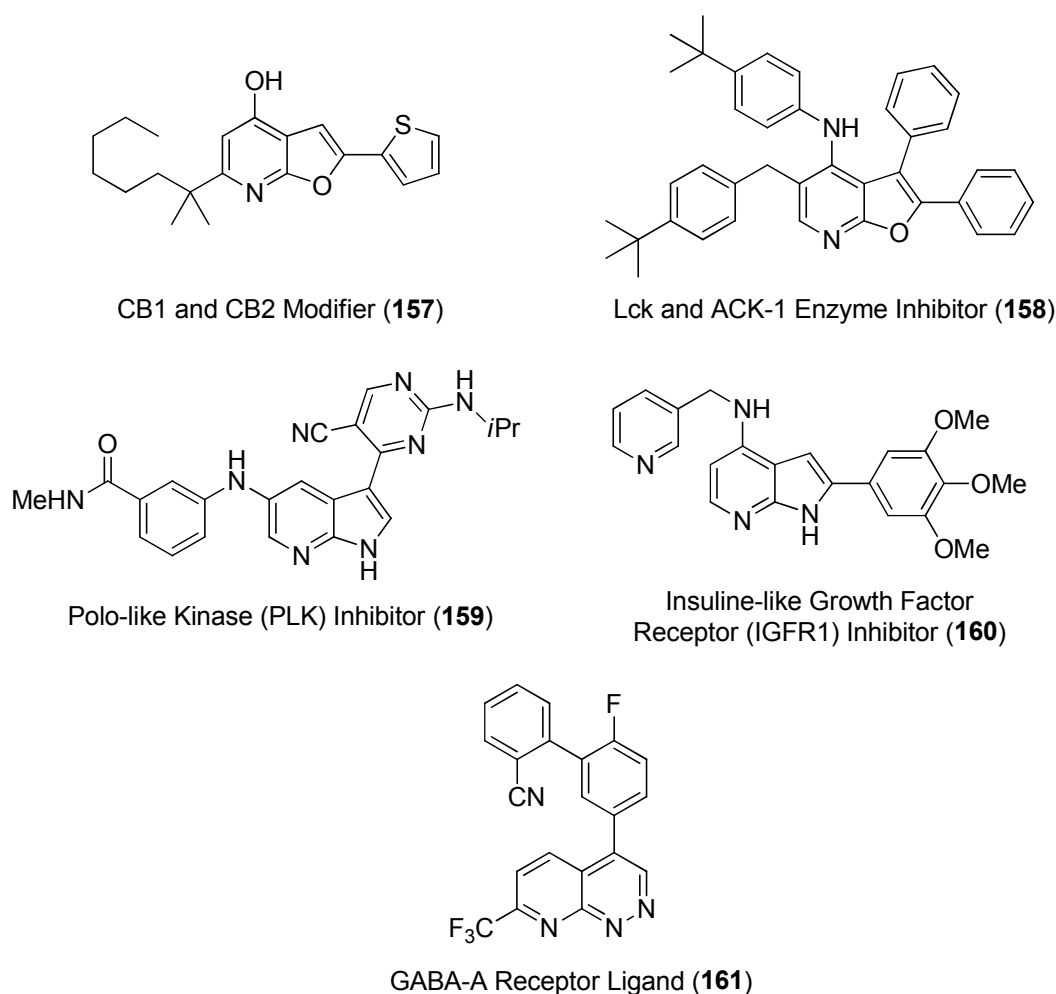
Figure 2: Functionalized annulated heteropolycycles displaying biological activity.

Having these type of heterocycles as goals, we envisioned the intramolecular fusion of the keto pyridine **155c** for the generation of the corresponding 7-azaindoline. We found that these types of transformations are not described in the literature. Thus, a reductive amination of the ketone was investigated using different sources of amines[145] and extensive experimentation was carried out. Herein, the use of a benzylic amine in combination with reducing agents was unsatisfactory,[146] the generation of an oxime[147] afforded decomposition of the starting material and finally, the use

[145] a) C. F. Lane, *Synthesis* **1975**, 135; b) R. O. Hutchins, N. R. Natale, *Org. Prep. Proc. Int.* **1979**, *11*, 201.
[146] a) B. K. Sinha, C. F. Chignell, *J. Med. Chem.* **1975**, *18*, 669; b) H. R. Morales, M. Pérez-Juárez, L. Cuéllar, L. Mendoza, H. Fernández, R. Contreras, *Synth. Commun.* **1984**, *14*, 1213; c) D. C. Remy, P. S. Anderson, M. E. Christy, B. E. Evans, *J. Org. Chem.* **1978**, *43*, 4311.
[147] B. S. Bhatti, J-P. Strachan, S. R. Breining, C. H. Miller, P. Tahiri, P. A. Crooks, N. Deo, C. S. Day, W. S. Caldwell, *J. Org. Chem.* **2008**, *73*, 3497; b) D. Pinto, J. P. Smallheer, J. M. Corte, J. R. Hu, Z. Cavallaro, C. L. Gilligan, P. J. Quan, WO 2007070826, **2007**.

of ammonia with reducing agents[148] was inadequate. Remarkably, we found that the relatively sterically hindered ketone can be reductively aminated using ammonium acetate (15.0 equiv) and sodium borohydride (1.2 equiv) in a protic solvent (EtOH) assisted by microwave irradiation[149] at 130 °C for 30 min. The annulation resulted spontaneous, due to the good leaving capability of the fluorine in the 2-positon of the pyridine, and the substituted 7-azaindoline **162a** was obtained in 68% yield. Typical oxidation procedure was performed with active manganese oxide[150] (excess) in DCM for 5 h under reflux resulting the 7-azaindole **163a** in 78% yield (Scheme 57). Similarly, the ketone **155b** was transformed to the corresponding 7-azaindoline **162b** in 60% yield and subsequent oxidation to the 7-azaindole **163b** in 92% yield (Table 9, entry 1).

155c   **162a:** 68%   **163a:** 78%
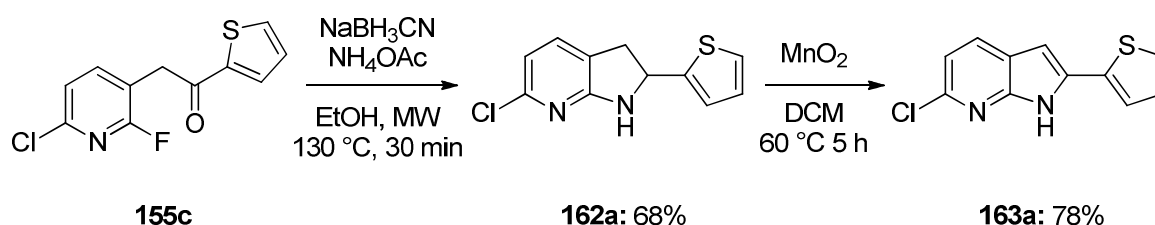
Scheme 57: Preparation of the highly functionalized 7-azaiondole **163a** from the corresponding ketone **155c** *via* reductive amination.

Inspired by the previous cyclization, we ventured promptly to the synthesis of furopyridines. Thus, the treatment of the pyridyl alcohol **155e** with sodium hydride (1.5 equiv) in THF at 25 °C for 3 h led to the corresponding alkoxide, which substitutes the fluorine in the 2-position of the pyridine affording the dihydrofuropyridine **164a** in 79% yield. Typical oxidation conditions using DDQ (2,3-dichloro-5,6-dicyanobenzo-2,4-quinone,[151] 3.0 equiv) in dioxane under reflux for 3 h provided the polyfunctional furopyridine **165a** in 60% yield (Scheme 58). Similarly, the pyridil alcohol **155f** afforded the dihydrofuropyridine **164b** and then the furopyridine **165b** in 82-86% yield, respectively (Table 9, entry 2).

[148] a) M. Vahermo, T. Suominen, A. Leinonen, J. Yli-Kauhaluoma, *Arch. Pharm. Chem. Life Sci.* **2009**, 201; b) U.-H. Dolling, A. W. Douglas, E. J. J. Grabowski, E. F. Schoenewaldt, P. Sohar, M. Sletzinger, *J. Org. Chem.* **1978**, *43*, 1634; c) K. R. Gee, P. Barmettler, M. R. Rhodes, R. N. McBurney, N. L. Reddy, L-Y. Hu, R. E. Cotter, P. N. Hamilton, E. Weber, J. F. W. Keana, *J. Med. Chem.* **1993**, *36*, 1938.

[149] L. Dong, S. Aleem, C. A. Fink, *Tetrahedron Lett.* **2010**, *51*, 5210.

[150] a) X. Zheng, M. A. Kerr, *Org. Lett.* **2006**, *8*, 3777; b) J. Lu, O. M. Khdour, J. S. Armstrong, S. M. Hecht, *Bioorg. Med. Chem.* **2010**, *18*, 7628.

[151] E. C. Taylor, J. E. Macor, J. L. Pont, *Tetrahedron* **1987**, *43*, 5145 and references cited therein.
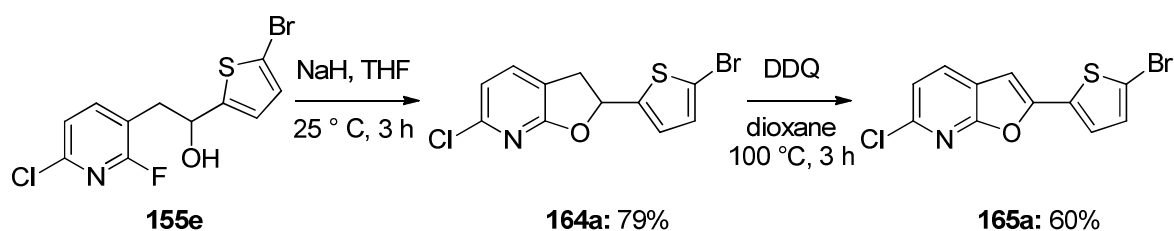
Scheme 58: Preparation of the highly functionalized furopyridine **165a** from the corresponding pyridyl alcohol **155e** *via* alkoxide substitution.

Table 9: Highly functionalized heteropolycycles.

Entry	Substrate	Product, Yield[a]	Product, Yield[a]
1	**155b**	**162b:** 60%	**163b:** 92%[b]
2	**155f**	**164b:** 86%	**165b:** 82%[b]

[a] Yield of analytically pure product. [b] Product obtained after oxidation.

Furthermore, the preparation of polyazanaphtalenes and pyrimido[4,5-*c*]pyridazines in the literature is not straightforward.[152] However, the building blocks of type **155a** and **155h** when treated with hydrazine (5.0 equiv) in DMF under reflux for 4 h provided the annulated heterocycles **166** and **167**, which upon subsequent oxidation with Pb(OAc)$_4$[153] (2.0 equiv) in THF for 4 h afforded the aromatized tri- and tetraazanaphthalenes **168** and **169** in 55-70% overall yield (Scheme 59).

---

[152] a) W. R. Mallory, R. W. Morrison, *J. Org. Chem.* **1980**, *45*, 3919; b) V. L. Styles, R. W. Morrison, *J. Org. Chem.* **1985**, *50*, 346.
[153] J. K. Kochi, *Org. React.* **1972**, *19*, 279.
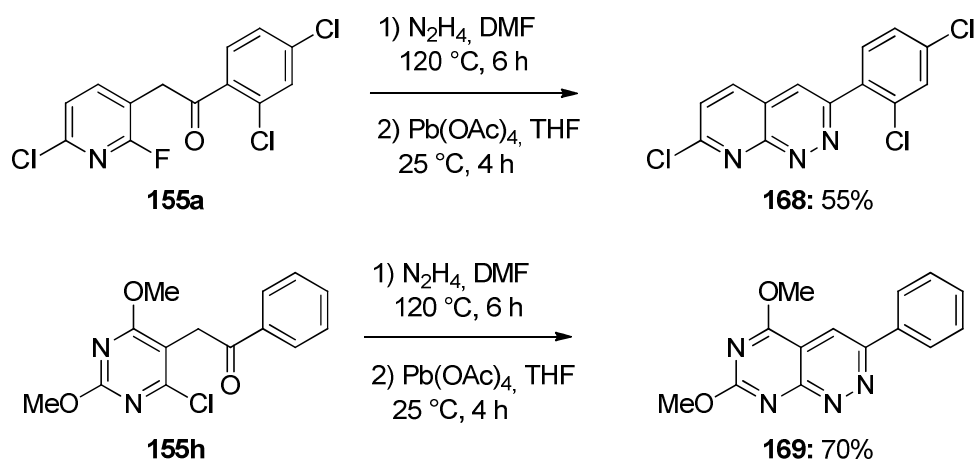
Scheme 59: Preparation of the highly functionalized polyazanaphthalenes **168** and **169** from the corresponding ketones **155a** and **155h**.

5.6. Application to the Synthesis of Biologically Active Compounds

Using this method, we envisioned the synthesis of the skeleton of a pharmaceutically important CB1 and CB2 modifier.[141] Thus, the dimethylamino pyridine **148** was selectively metalated in the 4 position with TMPMgCl·LiCl (**7**) (1.2 equiv) at –20 °C within 1 h. After transmetalation with ZnCl$_2$ quenching with bromine afforded the brominated pyridine **170** in 78% yield. Subjecting it with ethyl chloroformate afforded the benzylic chloride **171** in 80% yield. Previously described conditions for LiCl-mediated Zn insertion afforded the benzylic zinc reagent **172** in 70% yield.[138] Quenching with 2-thiophenecarboxaldehyde (0.8 equiv) and stirring at 50 °C for 2 h afforded the cyclized dihydrofuropyridine which was further oxidized with DDQ[151] in dioxane under relux for 12 h to give the furopyridine **173** in 55% overall yield. It is noteworthy to elucidate that, if no heating was applied, the addition of the zinc reagent **172** to the aldehyde was moderate and no ring closure was observed. However, when MgCl$_2$ (0.5 equiv)[154] the pyridil alcohol **174** was obtained in 50% yield. Finally, the straightforward substitution of the 4-bromo substituent of the pyridine occurs with benzylic alkoxide[155] and the protected pyridinol **175** was obtained in 75% yield (Scheme 60).

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[154] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed*. **2010**, *49*, 4665.
[155] J. M. Cid-Nunez, A. I. De Lucas Olivares, A. A. Trabanco-Suarez, G. J. Macdonald, WO 2010130423, **2010**.
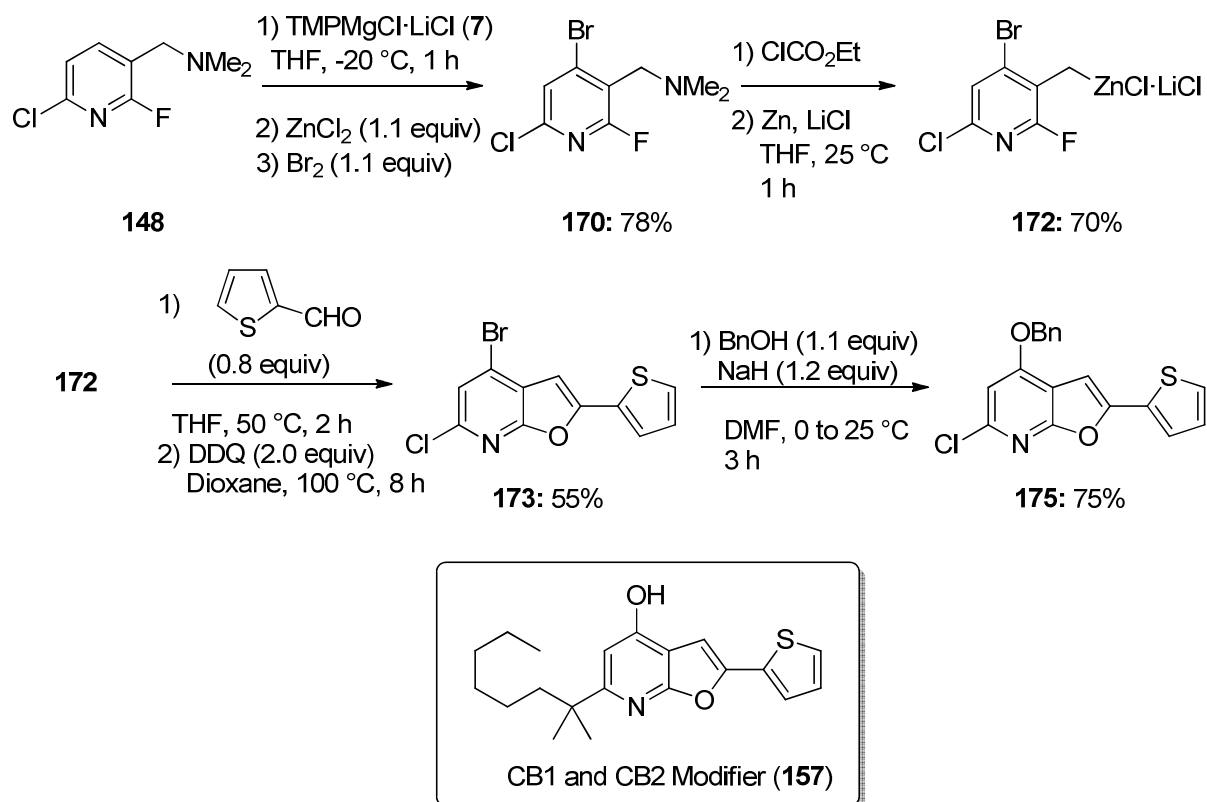
Scheme 60: Preparation of the skeleton of the CB1 and CB2 modifier (**157**).

6.   New Generation of Iminium Salts

6.1.   Introduction

Various biologically active compounds are derived from benzylamines with a high interest for the pharmaceutical industry.[156] Among these, histamine derivatives and antihistamine compounds have received special attention as Piperoxan 933F (**176**) and Neoantergan (**177**) (Figure 3).[157]

Piperoxan 933F (**176**)   Neoantergan (**177**)
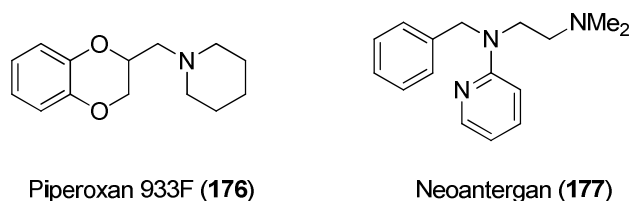
Figure 3: Histamine derivatives and antihistamine compounds.

Scarce reports related to the *Mannich* reaction for the preparation of functionalized tertiary benzylamines are available.[158] Hence, the modification of the conditions for the synthesis of heterobenzylic amines offers a one-pot procedure for the preparation of tertiary benzylamines.[137] Furthermore, the formation of an unsymmetrical aminal **178** should be possible when reacting the *Mannich*'s ion **140**[129] with a magnesiated amine **179**. Thus, the addition of a second equivalent of trifluoroacetic anhydride should acylate the less steric hindered nitrogen of **178**, i.e. the dimethylamino moiety and form the methylene(dialkyl)-iminium salt **180**. The addition of an organometallic reagent should add and afford the tertiary amine **181** (Scheme 61).

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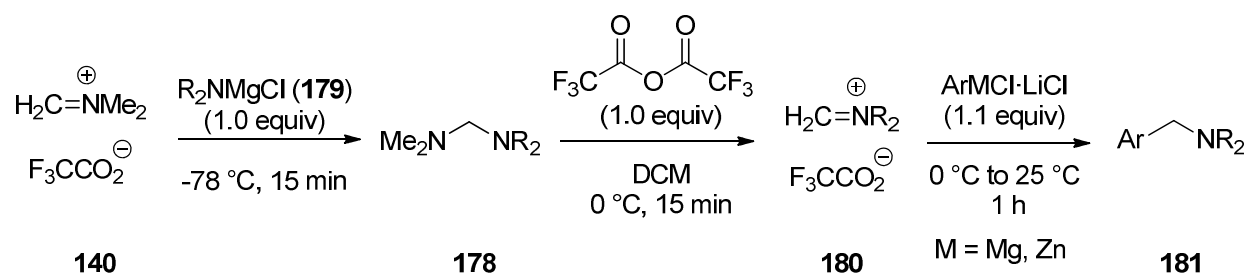
[156] (a) P. Nussbaumer, G. Dorfstaetter, M. A. Grassberger, I. Leitner, J. G. Meingassner, K. Thirring, A. Stuetz, *J. Med. Chem.* **1993**, *36*, 2115; (b) C. Altomare, L. Summo, S. Cellamare, A. V. Varlamov, L. G. Voskressensky, T. N. Borisova, A. Carotti, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 581.
[157] C. M. Marson, *Chem. Rev.* **2011**, *111*, 7121.
[158] a) G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 239; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *110*, 1044; c) J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330.

Scheme 61: Preparation of mixed aminals via *Mannich*'s cation.

6.2. Preparation of Tertiary Benzyl Amines

The *Mannich* salt **140** reacts readily with TMPMgCl·LiCl (**7**) (1.0 equiv) at –78 °C within 30 min to afford a complete conversion to the mixed aminal **182**, which could not be isolated in this form due to its aminal nature. However, the addition of trifluoroacetic anhydride (1.0 equiv) led to the formation of the 2,2,6,6-tetramethylpiperidinium cation **183**, which reacted further with 3-piridylmagnesium chloride **184** and afforded the substituted pyridine **185** in 76% yield (Scheme 62). Noteworthy, is the tolerance of the sterically demanding 2,2,6,6-tetramethylpiperidine on the aminal nitrogen.
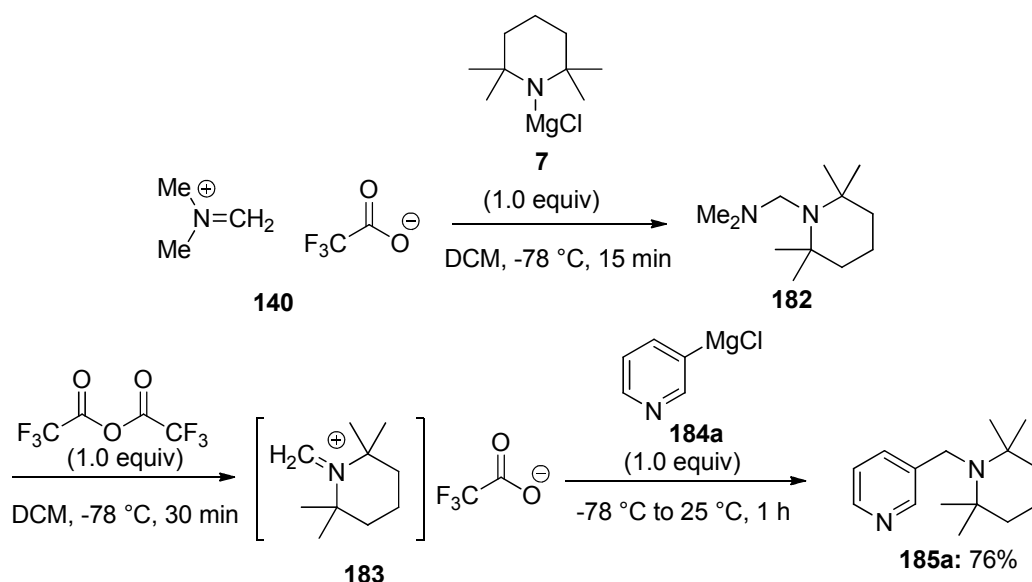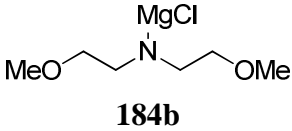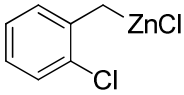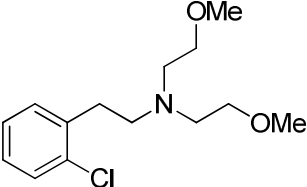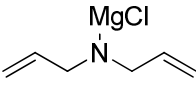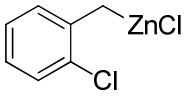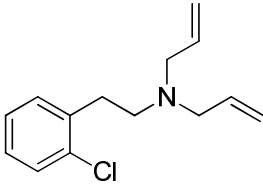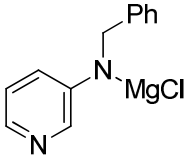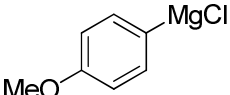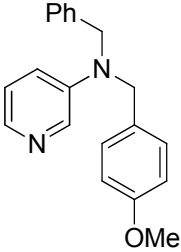
Scheme 62: Synthesis of *N*-benzyl-2,2,6,6-tetramethylpiperidine **185a**.

The metal amides were prepared by the deprotonation of the amine with MeMgCl (1.0 equiv) at 0 °C for 10 min, given that the corresponding non-metallic amines presented a lower reactivity. Moreover, the mixed aminals with an aryl or heteroaryl substituent on α-position to the aminal nitrogen diminished the reactivity. The temperature was kept at –78 °C to avoid partial decomposition of the mixed aminals. Hence, reacting various secondary amines to their corresponding aminals and a further reaction with an organomagnesium or organozinc reagent

(organolithium reagents lead to traces of product), afforded the tertiary amines **185b-d** in 45-92% yield (Table 10, entries 1-3).

Table 10: Preparation of tertiary benzyl and phenethyl amines in a one-pot procedure.

Entry	metal amide	organometallic substrate	Product, Yield[a]
1	**184b**		**185b:** 92%
2	**184c**		**185c:** 66%
3	**184d**		**185d:** 45%

[a] Yield of analytically pure product.

4.   Summary and Outlook

This work was focused on the preparation of highly functionalized organometallics through different approaches. Primarily, several aromatics, heteroaromatics, protected phenols and protected anilines were effectively metalated employing different TMP-bases. Secondarily, a general pathway for the preparation of non-conjugated heteroaromatic benzylic zinc reagents was investigated with further application for the preparation of polyheterocycles. Finally, the preparation of benzyl and phenethylamines *via* a one-pot anhydrous aminomethylation was carried out.

4.1.   Regio- and Chemoselective Zincation of Functionalized Aromatics and and Heteroaromatics using TMPZnCl·LiCl and Microwave irradiation

It was demonstrated that moderately activated aromatic and heteroaromatic substrates, bearing sensitive functionalities undergo regio- and chemoselective zincations with TMPZnCl·LiCl (**10**) at high temperatures and are stable under microwave irradiation (Scheme 63).
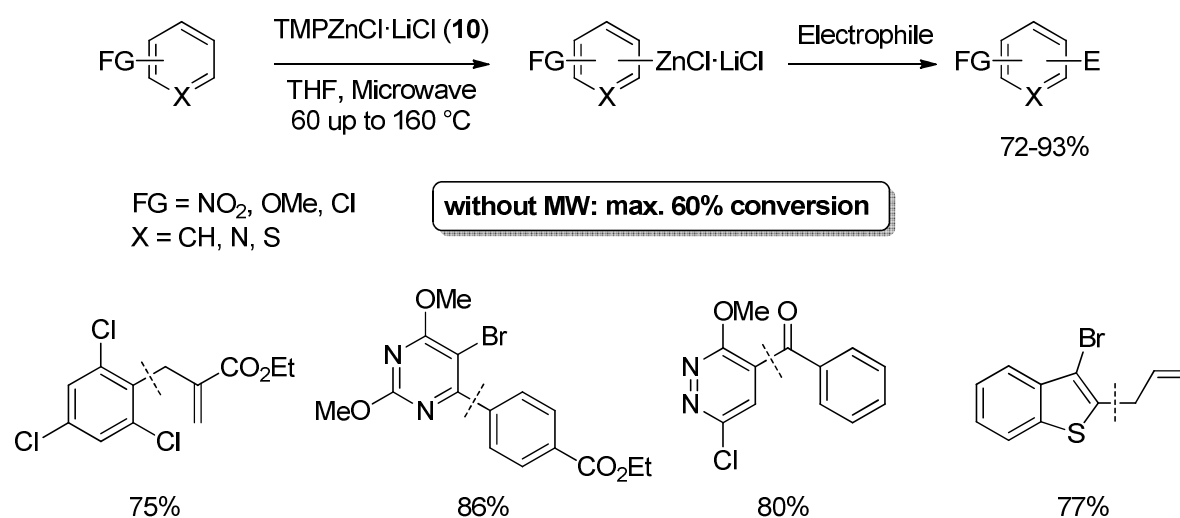
Scheme 63: Zincation of moderately activated aromatics and heteroaromatics using TMPZnCl·LiCl (**10**) and microwave irradiation.

Also, the regioselective zincations can be carried out on a multigram scale in a safely manner. The yields are comparable to the corresponding small scale and the functional group tolerance is not affected (Scheme 64).
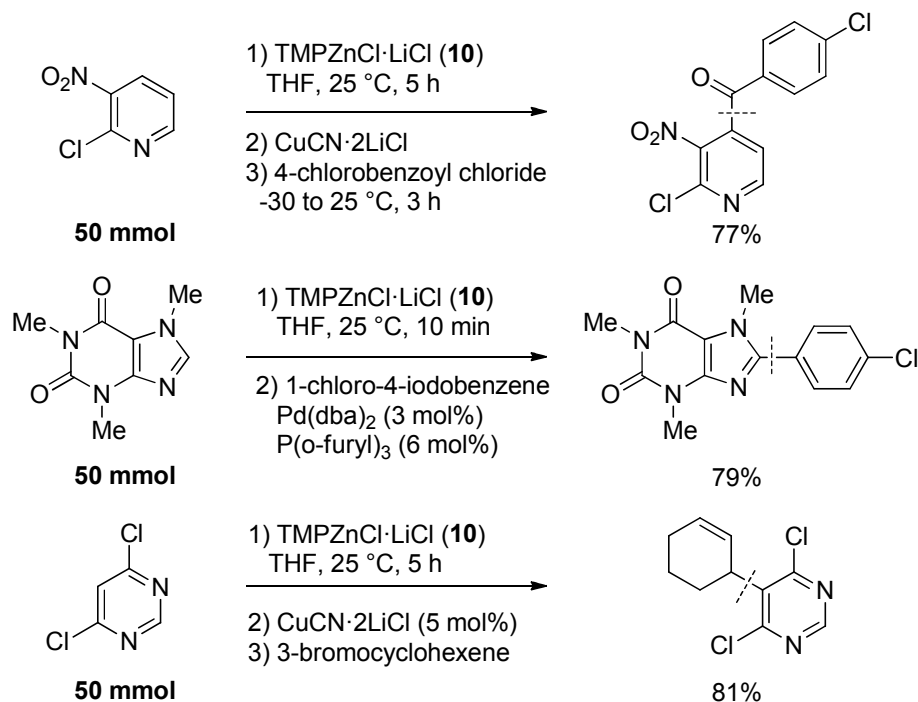
Scheme 64: Large scale zincation of sensitive functionalized aromatics and heteroaromatics using TMPZnCl·LiCl (**10**) and subsequent reactions with electrophiles.

4.2.   Efficient Preparation of Polyfunctional Organometallics *via* Directed *ortho*-Metalation with TMP-Bases of Mn, Fe and La

It was shown that the use of the bases TMP$_2$Mn·2MgCl$_2$·4LiCl (**12**), TMP$_2$Fe·2LiCl·4LiCl (**13**) and TMP$_3$La·3MgCl$_2$·5LiCl (**14**) gave access to functionalized organometallics *via* a highly efficient *ortho*-metalation. These organometallics exhibited a broad functional group tolerance, reacted with several electrophiles and an upscale was possible in good yields (Scheme 65).
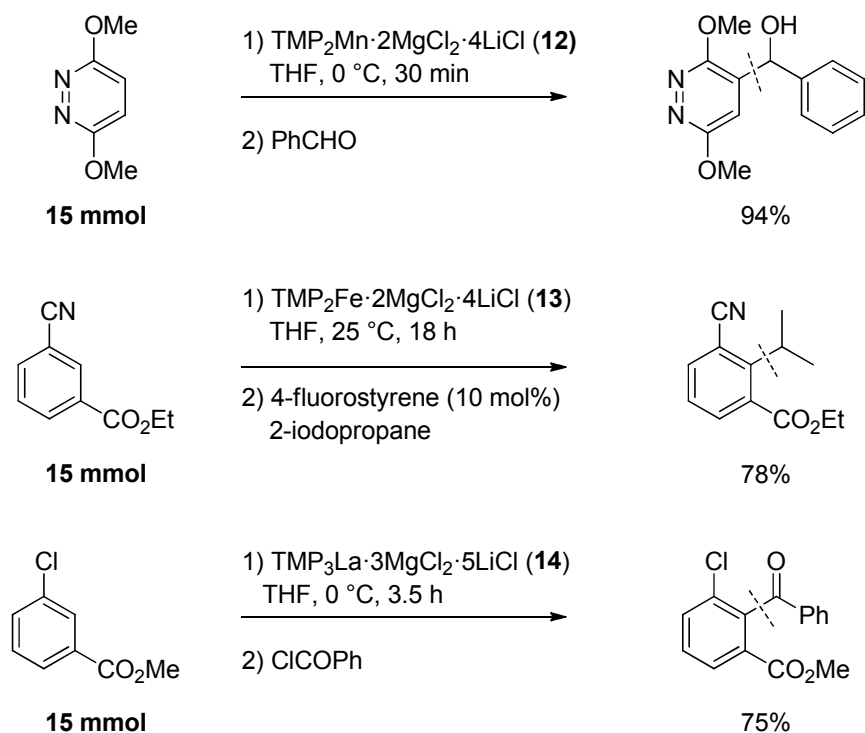
Scheme 65: Efficient preparation of organometallics *via ortho*-metalation with TMP-bases of Mn, Fe and La in a multigram scale.

4.3.   Directed *ortho*- and *meta*-Magnesiation or Zincation of Polyfunctional Aryl Nonaflates

It was demonstrated that functionalized aryl nonaflates can be magnesiated formally in *meta*-position using TMPMgCl·LiCl (**7**), but that an *ortho*-metalation is best performed with the mild and effective base TMPZnCl·LiCl (**10**). Further functionalization of the nonaflate moiety was carried out and the method could find future applications in the synthesis of natural products, pharmaceuticals and materials (Scheme 66).
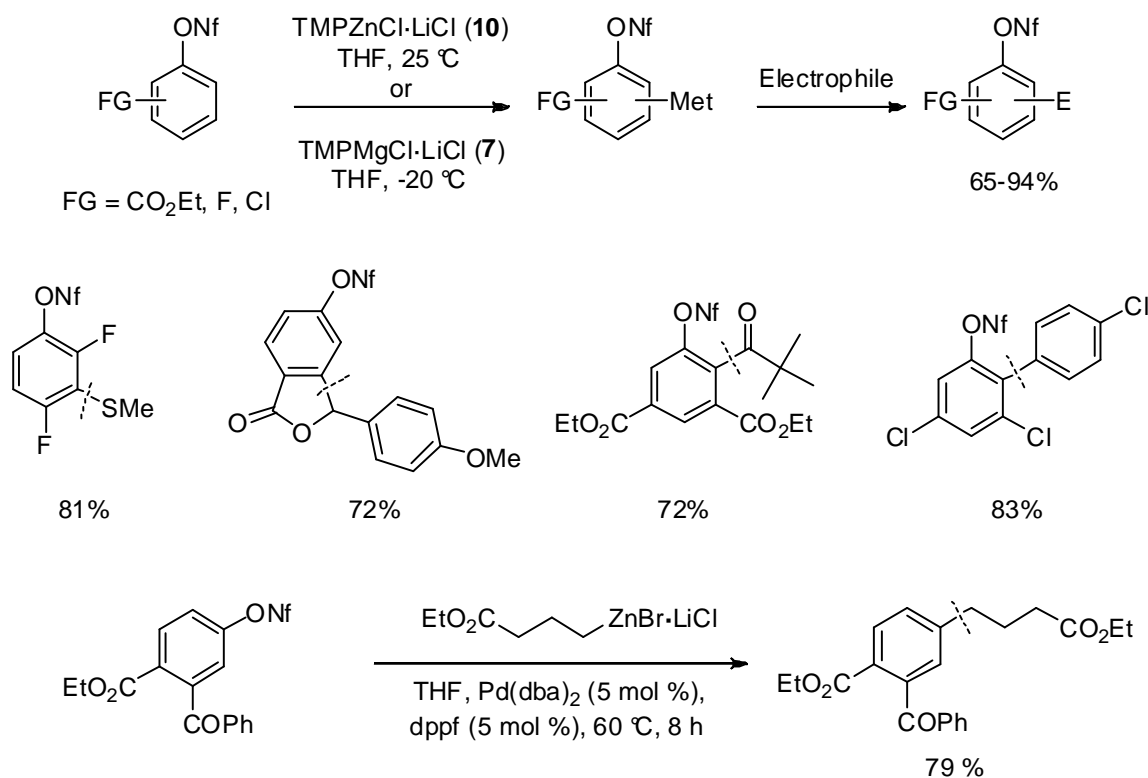
Scheme 66: Zincation or magnesiation of polyfunctional aryl nonaflates and a subsequent nonaflate moiety transformation.

4.4. Directed *ortho*- and *meta*-Magnesiation of Functionalized Anilines and Amino-Substituted Pyridines and Pyrazines

The use of an *ortho*-directing protective group for anilines and amino-substituted pyridines and pyrazines was investigated. The trifluoroacetyl group was found to be stable towards magnesiation with TMPMgCl·LiCl (**7**) and TMP$_2$Mg·2LiCl (**9**) at room temperature and allowed access for the first time to *ortho*- and *meta*-magnesiated anilides. Remarkably, these magnesiations tolerate sensitive functional groups such as a cyano or an ester and sensitive heterocycles as pyridines or pyrazine were efficiently metalated. Reaction with electrophiles led to highly substituted anilides in good yields. The trifluoroacetyl amide moiety was deprotected under mild conditions to obtain the anilines or primary amino-pyridines and pyrazines (Scheme 67).
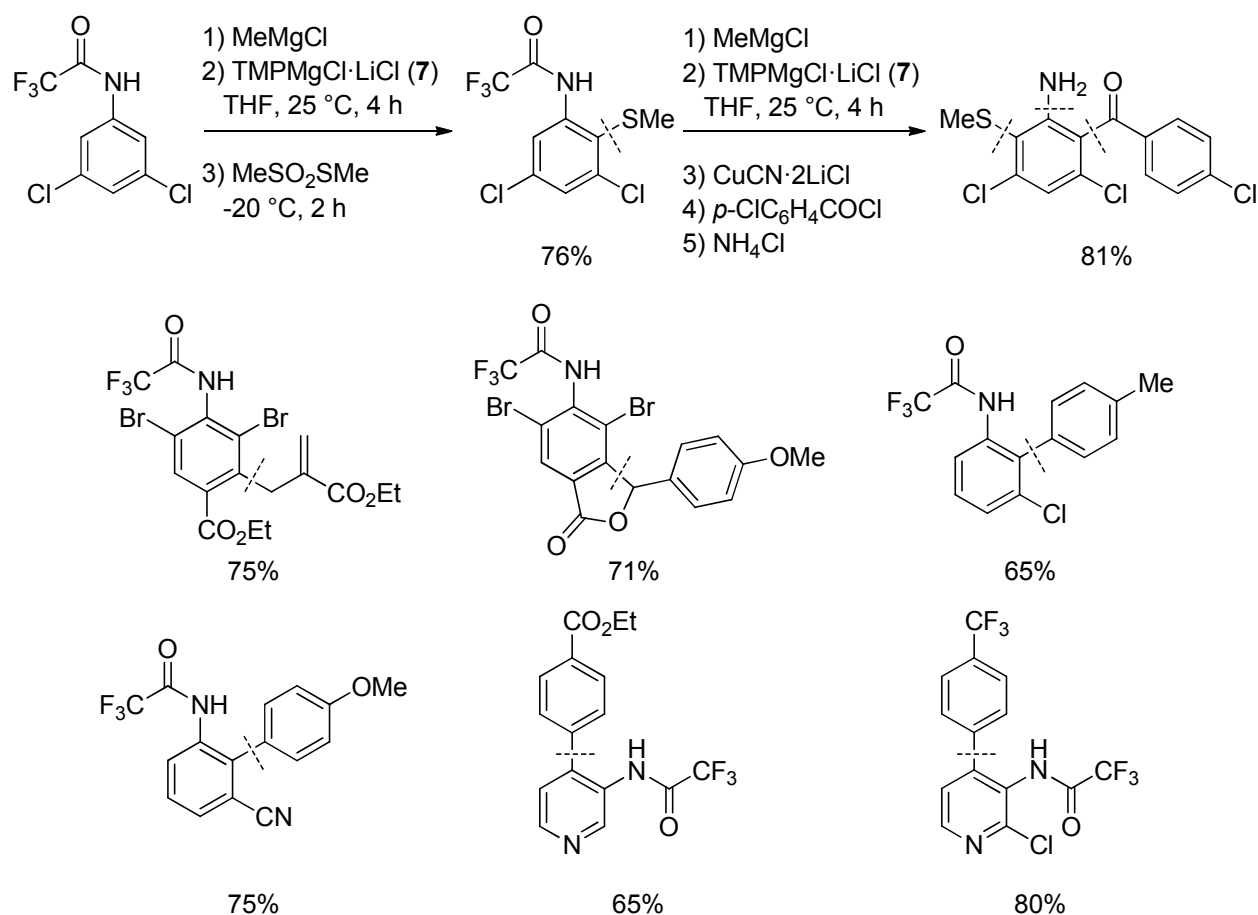
Scheme 67: Regioselective magnesiation of functionalized anilides.

This method showed a great utility for the preparation of pharmaceutically active heterocycles such as a GSK-3 and Lck protein kinase inhibitor in two steps. This compound is useful for the treatment and prevention of diabetes, Alzheimer and transplant rejection patented by Vertex Pharmaceuticals (Scheme 68).
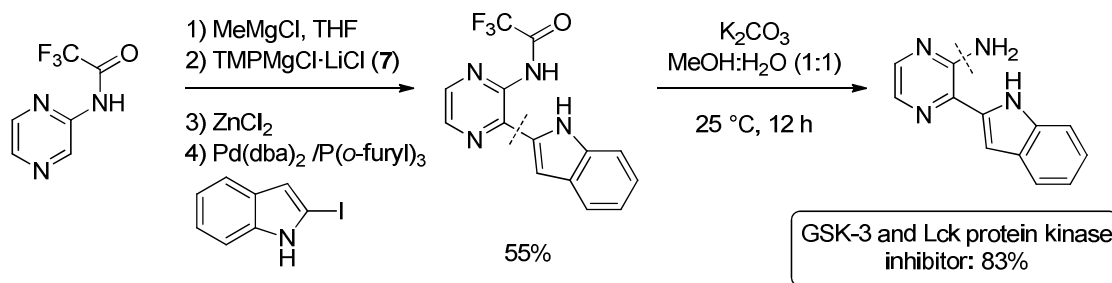
Scheme 68: Synthesis of a GSK-3 and Lck protein kinase inhibitor by chemoselective magnesiation and subsequent deprotection.

4.5.   Preparation and Reactions of Heteroaromatic Benzylic Zinc Reagents

The synthesis of non-conjugated heteroaromatic benzylic zinc reagents was carried out from the corresponding heteroaryl organometallics into the corresponding (dimethylamino)methyl compounds and a further transformation led to the heteroaromatic benzylic chlorides. The LiCl promoted oxidative zinc-insertion afforded the desired heteroaromatic benzylic zinc reagents and subsequent reaction with electrophiles afforded the corresponding products in good yields (Scheme 69).
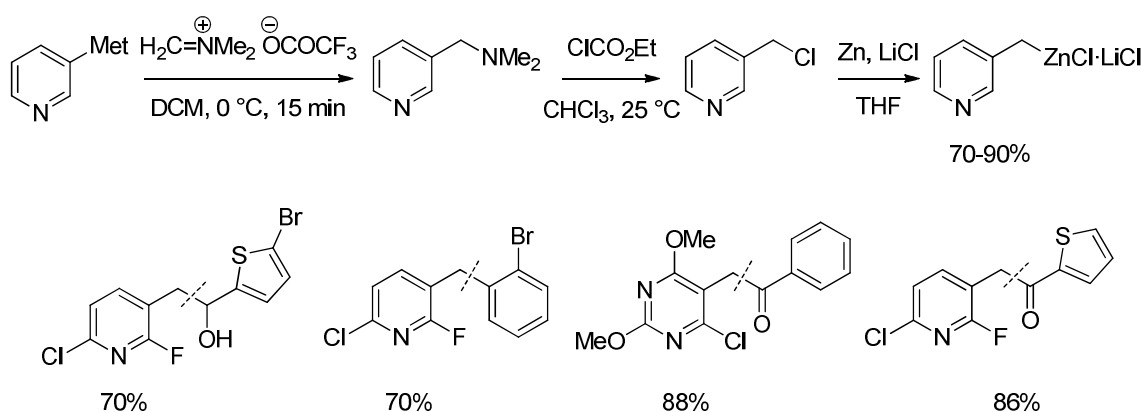
Scheme 69: Preparation of heterocyclic benzylic zinc reagents and reaction with electrophiles.

These building blocks were subjected to further transformations to obtain their corresponding annulated polyheterocycles such as 7-azaindoles, furopyridines and polyazanaphtalenes in a convenient manner (Scheme 70). The method was used for the synthesis of the skeleton of a pharmaceutically modifier CB1 and CB2 receptor (Scheme 71).
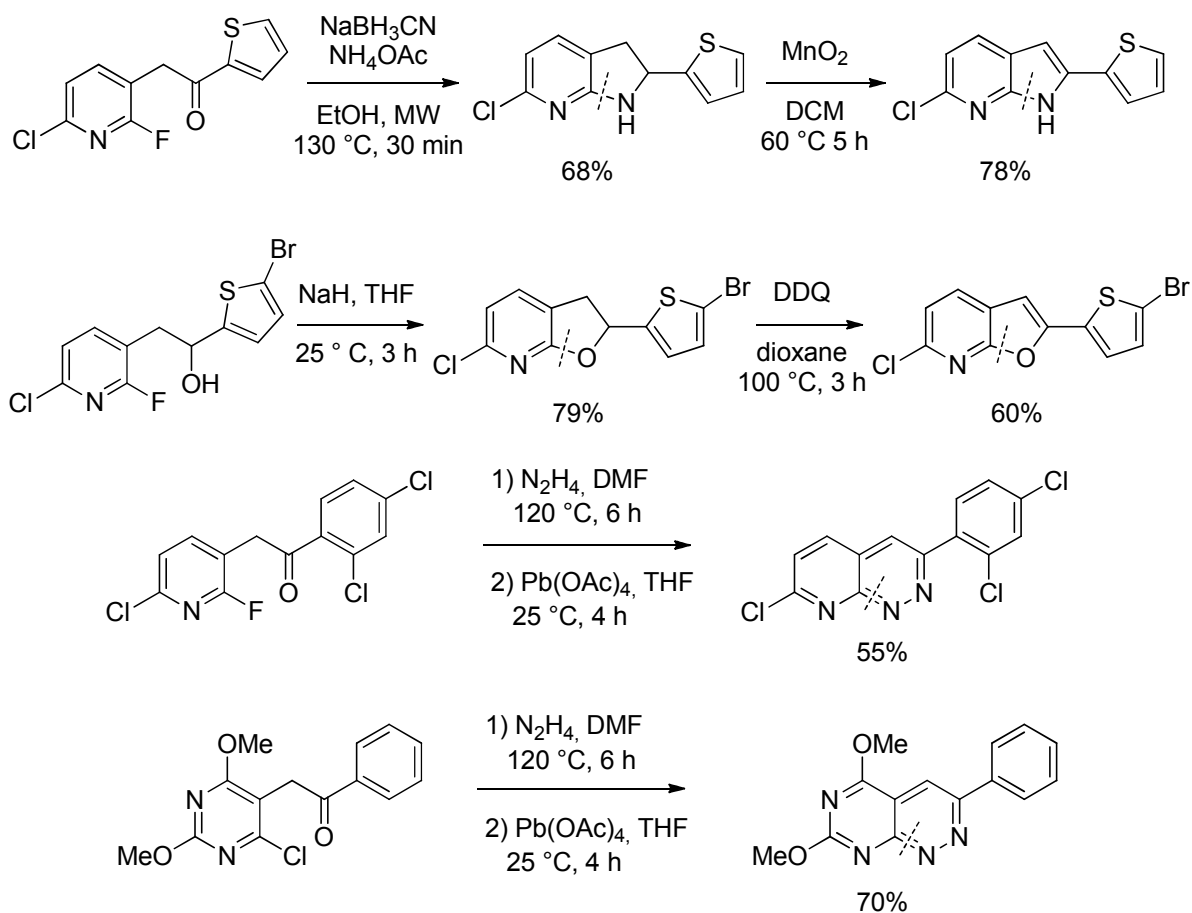
Scheme 70: Preparation of highly functionalized 7-azaiondoles, furopyridines and polyazanaphtalenes.
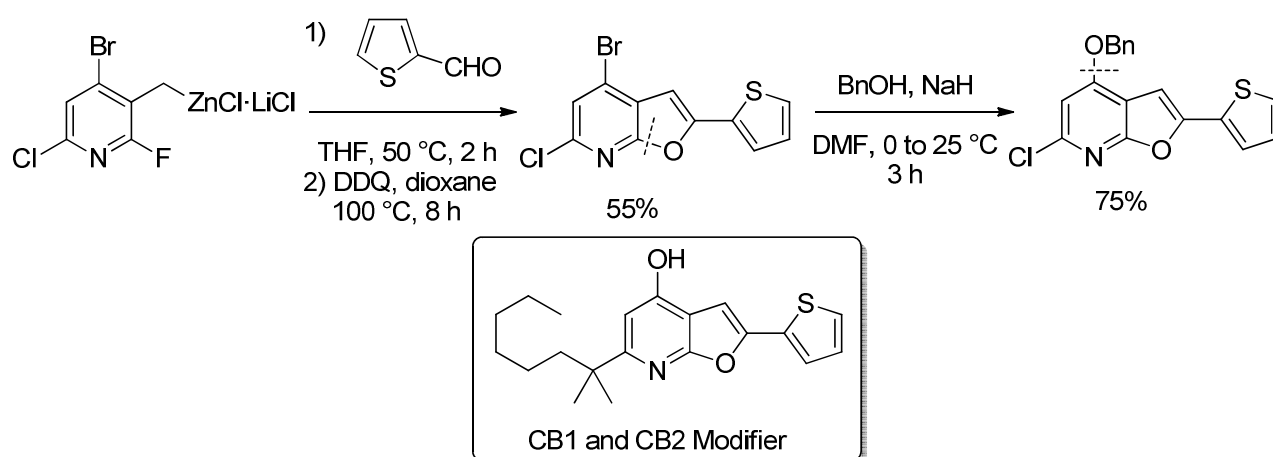
Scheme 71: Preparation of the skeleton of the CB1 and CB2 modifier.

4.6.   New Generation of Iminium Salts

It was also shown that the preparation of mixed aminals from the *Mannich*'s cation and different metal amides can be performed in a one-pot procedure using trifluroacetic anhydride as acylating agent. The reaction of the iminium ions with a range of organometallic led to tertiary benzylic amines with presence in some pharmaceutical targets (Scheme 72).
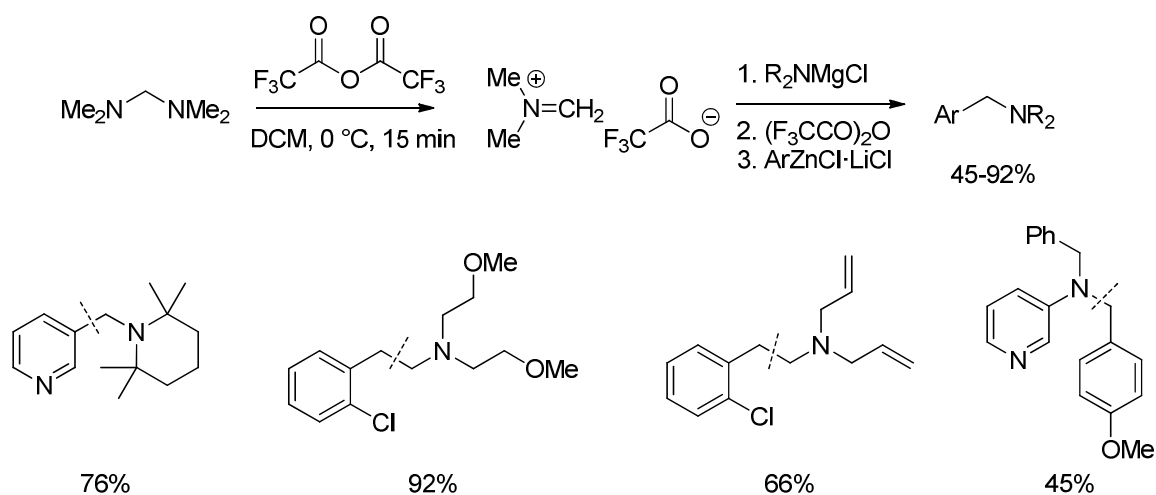
Scheme 72: Tertiary benzyl and phenethyl amine products.

C. Experimental Section

1.   General Considerations

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

1.1.   Solvents

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

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

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

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

Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

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

Pyridine was dried over KOH and distilled.

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

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

Et_3N was dried over KOH and distilled.

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

1.2. Reagents

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

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

MeMgCl solution in THF was purchased from Chemetall.

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

TMPMgCl·LiCl was prepared according to a literature procedure.[31]

TMPZnCl·LiCl was prepared according to a literature procedure.[35]

TMP$_2$Zn·2MgCl$_2$·2LiCl was prepared according to a literature procedure.[38]

TMP$_2$Mg·2LiCl was prepared according to a literature procedure.[32]

TMP$_3$La·3MgCl$_2$·5LiCl was prepared according to a literature procedure.[41]

TMP$_2$Mn·2MgCl$_2$·4LiCl was prepared according to a literature procedure.[39]

TMP$_2$Fe·2MgCl$_2$·4LiCl was prepared according to a literature procedure.[40]

CuCN·2LiCl solution (1.0 M) was prepared by drying CuCN (7.17 g, 80.0 mmol) and LiCl (6.77 g, 160.0 mmol) in a *Schlenk* flask under high vacuum at 140 °C for 5 h. After cooling to 25 °C under argon, freshly distilled THF (80 mL) was charged. Stirring was continued until the salts were dissolved.

ZnCl$_2$ solution (1.0 M) was prepared by drying ZnCl$_2$ (136.0 g, 100 mmol) in a *Schlenk* flask under high vacuum at 140 °C for 5 h. After cooling to 25 °C under argon, freshly distilled THF (100 mL) was charged and vigorous stirring was continued until the salt was dissolved.

MnCl$_2$·2LiCl solution (1.0 M) was prepared by drying LiCl (6.8 g, 160 mmol) in a *Schlenk* flask under high vacuum at 150 °C for 3 h. After cooling to 25 °C under argon, MnCl$_2$ (10.1 g, 80.0 mmol, 99% pure) was added under an inert atmosphere inside a glove-box. The *Schlenk* flask was further heated to 130 °C for 3 h under high vacuum. After cooling to 25 °C under argon, freshly distilled THF (80 mL) was charged and vigorous stirring was continued for 24 h at 25 °C.

FeCl$_2$·2LiCl solution (1.0 M) was prepared by drying LiCl (4.7 g, 110 mmol) in a *Schlenk* flask under high vacuum at 150 °C for 3 h. After cooling to 25 °C under argon, FeCl$_2$ (6.34 g, 50 mmol, 98% pure) was added under an inert atmosphere inside a glove-box. The *Schlenk* flask was further heated to 130 °C for 3 h under high vacuum. After cooling to 25 °C under argon, freshly distilled THF (50 mL) was charged. The *Schlenk* flask was wrapped in aluminium foil to protect it from light and vigorously stirred until the salt was completely dissolved (ca. 6 h).

1.3. Content determination of organometallic reagents

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

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

TMPMgCl·LiCl, **TMPZnCl·LiCl, TMP₂Zn·2MgCl₂·2LiCl, TMP₂Mg·2LiCl, TMP₃La·3MgCl₂·5LiCl, TMP₂Mn·2MgCl₂·4LiCl** and **TMP₂Fe·2MgCl₂·4LiCl** were titrated with benzoic acid against 4-(phenylazo)diphenylamine in THF.

1.4. Chromatography

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

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

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

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

1.5. Analytical data

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

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

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

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

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

2.   Typical Procedures

2.1.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMPZnCl·LiCl (TP1)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMPZnCl·LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred at 25 °C for the indicated time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.2.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMPZnCl·LiCl under conventional heating or microwave irradiation (TP2)

A dry and argon flushed 10-mL pressurized vial, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMPZnCl·LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred and heated at the corresponding temperature by using an oil bath or a Discover BenchMate Microwave system. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.3.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMP$_2$Zn·2MgCl$_2$·2LiCl (TP3)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMP$_2$Zn·2MgCl$_2$ 2LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred at the corresponding temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I$_2$ in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted three times with Et$_2$O. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.4.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMPMgCl·LiCl (TP4)

A dry and argon flushed *Schlenck* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMPMgCl·LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred at the corresponding temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of I$_2$ in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted three times with Et$_2$O. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.5.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMP$_2$Mn·2MgCl$_2$·4LiCl (TP5)

A dry and argon flushed *Schlenck* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMP$_2$Mn·2MgCl$_2$·4LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred at the corresponding temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of allyl bromide in the

presence of CuCN·2LiCl in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH₄Cl and extracted three times with Et₂O. The combined organic layers were washed with sat. aq. NaCl, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.6.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMP₂Fe·2MgCl₂·4LiCl (TP6)

A dry and argon flushed *Schlenck* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMP₂Fe·2MgCl₂·4LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred at the corresponding temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of allyl bromide in the presence of CuCN·2LiCl in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH₄Cl and extracted three times with Et₂O. The combined organic layers were washed with sat. aq. NaCl, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.7.   Typical procedure for the metalation of polyfunctional aromatics and heteroaromatics with TMP₃La·3MgCl₂·5LiCl (TP7)

A dry and argon flushed *Schlenck* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 equiv) in anhydrous THF (0.5-2.0 M). TMP₃La·3MgCl₂·5LiCl (1.1 equiv) was added dropwise and the reaction mixture was stirred at the corresponding temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with a solution of allyl bromide in the presence of CuCN·2LiCl in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH₄Cl and extracted three times with Et₂O. The combined organic layers were washed

with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.8. Typical procedure for the synthesis of aromatic and heteroaromatic trifluoroacetamides from aromatic and heteroaromatic amines (TP8)

A round bottom flask, equipped with a magnetic stirring bar and a septum was charged with the corresponding amine (1.0 equiv) in anhydrous DCM (1.0 M). After cooling to 0 °C, Et_3N (1.1 equiv) was added dropwise and stirred at 0 °C for 10 min. Trifluoroacetic anhydride (1.5 equiv) was added dropwise and the reaction mixture was allowed to warm up to 25 °C for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with DCM and one time with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.9. Typical procedure for the metalation of polyfunctional aromatic and heteroaromatic trifluoroacetamides with TMPMgCl·LiCl or TMP₂Mg·2LiCl (TP9)

A dry and argon flushed *Schlenck* flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding aromatic or heteroaromatic trifluoroacetamide (1.0 equiv) in anhydrous THF (0.5-2.0 M). After cooling to 0 °C, MeMgCl (1.1 equiv) was added dropwise and stirred at 0 °C for 10 min. TMPMgCl·LiCl (1.2 equiv) or TMP₂Mg·2LiCl (1.2 equiv) was added dropwise to the reaction mixture and stirred at the corresponding temperature and time. The completion of the reaction was checked by GC analysis of reaction aliquots quenched witha a solution of allyl bromide in the presence of CuCN·2LiCl in THF. The electrophile was added and after the completion of the reaction (checked by GC analysis of reaction aliquots) the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with EtOAc and one time with DCM. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.10. Typical procedure for Pd-catalyzed cross-cupling reactions of metalated trifluoroacetamides (TP10)

After complete metalation was achieved according to **TP9** ZnCl$_2$ (1.3 equiv) was added at 0 °C. The resulting mixture was stirred for 15 min. Then Pd(dba)$_2$ (2 mol%) and P(o-furyl)$_3$ (4 mol%) were added together with the corresponding aryl iodide and the mixture was allowed to warm to 25 °C or heated at 50 °C if required (approx. 1 to 6 h). The completion of the reaction was checked by GC analysis of reaction aliquots, then quenched with sat. aq. NH$_4$Cl and extracted three times with EtOAc and one time with DCM. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.11. Typical   procedure   for   acylation   reactions   of   metalated trifluoroacetamides (TP11)

After complete metalation was achieved according to **TP9** CuCN·2LiCl (1.1 equiv) was added at –40 °C and the mixture was stirred for 15 min. The acyl chloride was added and the reaction mixture was stirred to 0 °C or 25 °C if required (approx. 1 to 3 h). The completion of the reaction was checked by GC analysis of reaction aliquots, then quenched with sat. aq. NH$_4$Cl and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.12. Typical   procedure   for   allylation   reactions   of   metalated trifluoroacetamides (TP12)

After complete metalation was achieved according to **TP9** CuCN·2LiCl (0.1 equiv) was added at –40 °C and the mixture was stirred for 15 min. The allyl bromide was added and the reaction mixture was stirred to 0 °C or 25 °C if required (approx. 1 to 3 h). The completion of the reaction was checked by GC analysis of reaction aliquots, then quenched with sat. aq. NH$_4$Cl and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl,

dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.13. Typical procedure for the preparation of (dimethylamino)methyl heteroarenes using *N,N,N',N'*-tetramethylmethanediamine (TP13)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with *N,N,N',N'*-tetramethylmethanediamine (1.1 equiv) and anhydrous DCM (1.0 M). After cooling to 0 °C, neat trifluoroacetic anhydride (1.1 equiv) was added dropwise. After the highly exothermic reaction subsided and the smoke dissipated, the cooling was removed and the solution was allowed to warm up to 25 °C and stirring was continued for 5 min. The so prepared solution of methylene(dimethyl)iminium trifluoroacetate was then canulated dropwise to a solution of the nucleophile (organometallic reagent, 1.0 equiv) at 0 °C. The reaction was found to be complete immediately after all of the solution had been transferred. The crude mixture was quenched with sat. aq. NaHCO$_3$ and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.14. Typical procedure for the preparation of heteroaromatic benzylic chlorides from (dimethylamino)methyl heteroarenes (TP14)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with the (dimethylamino)methyl compound (1.0 equiv) and anhydrous CHCl$_3$ (1.0 M). After cooling to 0 °C, neat ethyl chloroformate (1.1 equiv) was added dropwise. The resulting solution was stirred at 0 °C for 30 min. The reaction mixture was quenched with H$_2$O and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.15. Typical procedure for the preparation of heteroaromatic benzylic zinc chlorides by LiCl-promoted direct zinc insertion (TP15)

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

2.16. Typical procedure for the preparation of diarylmethanes by the Pd-catalyzed cross-coupling of heterobenzyl zinc chlorides (TP16)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with the aryl or heteroaryl halide (0.9 equiv) in THF (1.0 M). The appropriate Pd catalyst was added and the resulting suspension was stirred for 5 min at 25 °C. After cooling at 0 °C, the heterobenzylic zinc chloride (1.0 equiv) was added dropwise. Cooling was removed and the reaction mixture was allowed to warm up to 25 °C. Stirring was continued until completion of the reaction (checked by GC analysis of reaction aliquots), then the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.17. Typical procedure for the preparation of heterophenethylic alcohols by the reaction of heterobenzyl zinc chlorides with aldehydes (TP17)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with the aldehyde (0.9 equiv) in THF (1.0 M). The heterobenzylic zinc chloride (1.0 equiv) was added dropwise at 0 °C and then allowed to warm up to 25 °C. Stirring was continued until completion of the reaction (checked by GC analysis of reaction aliquots), then the reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.18. Typical procedure for the preparation of heterobenzyl ketones by the reaction of heterobenzylic zinc chlorides with carboxylic acid chlorides (TP18)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with CuCN·2LiCl (1.1 equiv, 1 M solution in THF) followed by the dropwise addition of the heterobenzylic zinc chloride (1.0 equiv) at –20 °C. The solution was stirred at –20 °C for 10 min, after which the neat acid chloride (0.9 equiv) was added dropwise. The reaction mixture was allowed to warm up to 25 °C. Stirring was continued until completion of the reaction (checked by GC analysis of reaction aliquots), then the reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

2.19. Typical procedure for the preparation of tertiary benzyl and phenethyl amines (TP19)

A dry and argon flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum was charged with *N,N,N',N'*-tetramethylmethanediamine (1.1 equiv) and anhydrous DCM (1.0 M). After cooling to 0 °C, neat trifluoroacetic anhydride (1.1 equiv) was added dropwise and stirred to 25 °C for 5 min. The solution was cooled to –78 °C and a slurry solution was observed and the magnesium amide (1.0 equiv) in THF was added dropwise (the magnesium amide was obtained from the reaction from the secondary amine and MeMgCl at 0 °C for 10 min). Stirring was

continued at –78 °C for 15 min and then trifluoroacetic anhydride (1.0 equiv) was added dropwise and a precipitated was formed. The organomagnesium or organozinc reagent was then dropwise added. Upon complete dissolution of the precipitate, the cooling was removed and the crude mixture allowed to warm up to 25 °C for 30 min. The crude mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography.

3.   Product Synthesis and Analytical Data

3.1.   Regio- and Chemoselective Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl and Microwave Irradiation

3.1.1. Zincation of poorly activated substrates with TMPZnCl·LiCl (x) under microwave irradiation

Synthesis of (2-fluoro-6-methoxy-phenyl)-phenyl-methanone (31a)
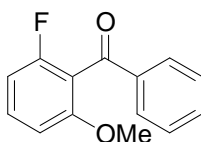
To a solution of 3-fluoroanisole (**29**) (126 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 $^{\circ}$C and the resulting mixture was heated at 160 °C (250 W) for 2 h according to **TP2**. The reaction mixture was cooled to –20 °C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoylchloride (155 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 7:3) furnished the compound **31a** (165 mg, 72%) as a pale yellow oil.

^{1}H-NMR (CDCl₃, 600 MHz) δ: 7.86 – 7.84 (m, 2 H), 7.59 – 7.56 (m, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.39 – 7.35 (m, 1 H), 6.76 – 6.78 (m, 2 H), 3.74 (s, 3 H).

¹³C-NMR (CDCl₃, 150 MHz) δ: 192.0, 159.8 (d, *J* (C – F) = 247.4 Hz), 158.1 (d, *J* (C – F) = 8.0

Hz), 137.2, 133.7, 131.3 (d, *J* (C – F) = 10.0 Hz), 129.5, 128.5, 117.3 (d, *J* (C – F) = 21.1 Hz),

108.3 (d, *J* (C – F) = 21.9 Hz), 106.9 (d, *J* (C – F) = 3.1 Hz), 56.14.

IR (ATR) $\widetilde{\nu}$ **(cm⁻¹):** 3331, 3085, 3063, 3009, 2974, 2940, 2890, 2842, 2743, 2582, 2547, 2409,

2341, 2216, 2161, 1974, 1924, 1825, 1734, 1672, 1613, 1596, 1580, 1468, 1449, 1438, 1378,

1316, 1308, 1278, 1267, 1239, 1179, 1168, 1124, 1144, 1079, 1026, 1001, 976, 947, 923, 847,

782, 755, 731, 702, 689.

MS (EI, 70 eV) m/z (%): 230 (47) [M⁺], 213 (13), 154 (11), 153 (100), 139 (38), 138 (11), 110

(11), 105 (58), 83 (10), 77 (43), 69 (11), 57 (13), 55 (11), 43 (17).

HRMS (EI) for C₁₄H₁₁FO₂ (230.0743): 230.0730.

Synthesis of 2-(2,4,6-trichloro-benzyl)-acrylic acid ethyl ester (31b)
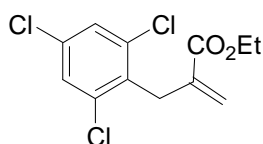
To a solution of 1,3,5-trichlorobenzene (**32**) (181 mg, 1.0 mmol) dissolved in THF (2 mL) was

added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture

was heated at 80 °C (200 W) for 1 h according to **TP2**. The reaction mixture was cooled to –20°C

and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 30 min of stirring at

the same temperature, 2-bromomethyl-acrylic acid ethyl ester (212 mg, 1.1 mmol) was added and

the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture

was quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 9:1) furnished the compound **31b** (220 mg, 75%) as a colorless oil.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.35 (s, 2 H), 6.18 (t, *J* = 1.7 Hz, 1 H), 4.96 (t, *J* = 1.9 Hz, 1 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 3.90 (t, *J* = 1.9 Hz, 2 H), 1.34 (t, *J* = 7.3 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 166.5, 136.6, 136.1, 133.6, 133.2, 128.2, 124.4, 61.1, 32.5, 14.20.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3317, 3080, 2982, 2933, 1714, 1635, 1582, 1549, 1442, 1428, 1395, 1374, 1344, 1276, 1253, 1208, 1164, 1131, 1095, 1072, 1046, 1024, 946, 856, 813, 785, 700.

MS (EI, 70 eV) m/z (%): 292 (5) [^{35}Cl-M$^+$], 259 (58), 257 (66), 249 (20), 247 (23), 231 (59), 229 (86), 185 (24), 184 (25), 149 (45), 97 (26), 83 (29), 81 (26), 71 (33), 69 (75), 57 (52), 55 (46), 44 (100), 43 (37), 41 (50).

HRMS (EI) for C$_{12}$H$_{11}$^{35}Cl$_3$O$_2$ (291.9825): 291.9809.

Synthesis of 2-benzoyl-1,3,5-trichlorobenzene (31c)

To a solution of 1,3,5-trichlorobenzene (**32**) (181 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture

was heated at 80 °C (200 W) for 1 h according to **TP2**. The reaction mixture was cooled to –20°C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoylchloride (155 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 9:1) furnished the compound **31c** (244 mg, 85%) as a pale yellow solid.

m.p.: 106.0 – 107.8 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.82 – 7.79 (m, 2 H), 7.66 – 7.61 (m, 1 H), 7.51 – 7.46 (m, 2 H), 7.41 (s, 2 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 191.7, 136.2, 135.9, 135.2, 134.5, 132.6, 129.6, 129.0, 128.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3080, 2956, 2926, 2869, 1962, 1756, 1735, 1720, 1677, 1596, 1569, 1544, 1492, 1448, 1430, 1379, 1365, 1315, 1269, 1263, 1230, 1187, 1178, 1163, 1158, 1134, 1068, 1045, 1020, 1002, 928, 869, 853, 816, 804, 758, 735, 704, 691, 683.

MS (EI, 70 eV) m/z (%): 284 (23) [^{35}Cl-M$^+$], 209 (20), 207 (21), 105 (100), 77 (25).

HRMS (EI) for C$_{13}$H$_7$^{35}Cl$_3$O (283.9562): 283.9552.

Synthesis of 6-chloro-3-methoxy-4-[4-(trifluoromethyl)phenyl]pyridazine (31d)
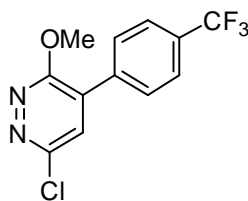
To a solution of 3-chloro-6-methoxy-pyridazine (**34**) (145 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 80 °C (100 W) for 60 min according to **TP2**. Pd(dba)$_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 1-iodo-4-trifluoromethylbenzene (300 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (dichloromethane) furnished the compound **31d** (257 mg, 89 %) as white solid.

m.p.: 139.8 – 141.2 °C

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.76 – 7.70 (m, 4 H), 7.41 (s, 1 H), 4.17 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 161.5, 151.5, 135.9, 131.8 (q, *J* (C – F) = 32.8 Hz), 131.3, 129.5, 128.9, 125.7 (q, *J* (C – F) = 3.6 Hz), 123.7 (q, *J* (C – F) = 272.4 Hz), 55.7.

IR (ATR) $\widetilde{V}$ (cm^{-1}): 3029, 2991, 2950, 2894, 2863, 2349, 2234, 1928, 1738, 1620, 1574, 1526, 1460, 1454, 1412, 1377, 1324, 1296, 1259, 1236, 1166, 1109, 1070, 1043, 1017, 961, 930, 864, 842, 778, 743, 730, 678.

MS (EI, 70 eV) m/z (%): 288 (36) [^{35}Cl-M$^+$], 287 (100), 271 (13), 217 (16), 203 (22).

HRMS (ESI) for C$_{12}$H$_8$^{35}ClF$_3$N$_2$O (288.0277): 288.0250.

Synthesis of (6-chloro-3-methoxy-pyridazin-4-yl)-phenyl-methanone (31e)

To a solution of 3-chloro-6-methoxy-pyridazine (**34**) (145 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 $^{\circ}$C and the resulting mixture was heated at 80 °C (100 W) for 60 min according to **TP2**. The reaction mixture was cooled to –20°C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoylchloride (155 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly within 2 h. The reaction mixture was quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 65:35) furnished the compound **31e** (200 mg, 80 %) as yellowish white solid.

m.p.: 97.1 – 98.8 °C

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.77 – 7.74 (m, 2 H), 7.68 – 7.63 (m, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.38 (s, 1 H), 4.07 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 190.4, 160.8, 151.3, 135.0, 134.8, 130.4, 129.7, 128,9, 128.5, 55.7.

IR (ATR) $\tilde{v}$ **(cm^{-1}):** 3080, 3026, 2955, 1810, 1668, 1595, 1579, 1530, 1489, 1458, 1449, 1371, 1327, 1308, 1287, 1268, 1192, 1173, 1161, 1124, 1096, 1078, 1023, 994, 965, 902, 832, 802, 778, 731, 709, 682, 670, 651, 623, 614.

MS (EI, 70 eV) m/z (%): 248 (21) [^{35}Cl-M$^+$], 219 (6), 183 (7), 105 (100), 91 (38), 77 (69), 51 (18).

HRMS (ESI) for C$_{12}$H$_{10}$^{35}ClN$_2$O$_2$ [M + H]$^+$ (249.0432): 249.0425.

Synthesis of 2-allyl-3-bromobenzothiophene (31f)
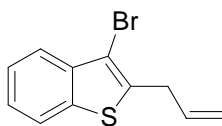
To a solution of 3-bromobenzothiophene (**36**) (213 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 ^{o}C and the resulting mixture was heated at 50 °C (120 W) for 30 min according to **TP2**. The reaction mixture was cooled to –20°C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 30 min of stirring at the same temperature, allyl bromide (133 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 95:5) furnished the compound **31f** (196 mg, 77%) as a yellow oil.

¹H-NMR (CDCl₃, 600 MHz) δ: 7.76 – 7.73 (m, 1 H), 7.44 – 7.41 (m, 1H), 7.39 – 7.31 (m, 2 H), 6.05 – 5.92 (m, 1 H), 5.19 – 5.12 (m, 2 H), 3.70 (d, J = 6.6 Hz, 2 H).

¹³C-NMR (CDCl₃, 150 MHz) δ: 138.4, 138.1, 137.4, 134.1, 124.9, 124.9, 122.7, 122.3, 117.5, 106.2, 34.2.

IR (ATR) $\tilde{\nu}$ **(cm⁻¹):** 3974, 3778, 3350, 3060, 3028, 3006, 2979, 2898, 2750, 2627, 2558, 2310, 2270, 1941, 1905, 1821, 1783, 1689, 1640, 1605, 1561, 1531, 1504, 1494, 1456, 1432, 1376, 1320, 1306, 1278, 1252, 1224, 1160, 1125, 1099, 1077, 1067, 1049, 1018, 989, 945, 915, 864, 851, 820, 748, 724, 700, 654.

MS (EI, 70 eV) m/z (%): 252 (54) [⁷⁹Br³²S-M⁺], 251 (23), 243 (20), 241 (25), 227 (29), 225 (28), 212 (15), 187 (44), 173 (89), 172 (100), 171 (51), 158 (17), 147 (29), 146 (16), 145 (20), 134 (29), 129 (48), 128 (17), 115 (28), 89 (15), 86 (21), 83 (17), 71 (17), 69 (17), 57 (27), 55 (18), 45 (24), 44 (35), 43 (20).

HRMS (EI) for C₁₁H₉⁷⁹Br³²S (251.9608): 251.9601.

Synthesis of 4-(3-bromo-benzothiophen-2-yl)-benzoic acid ethyl ester (31g)
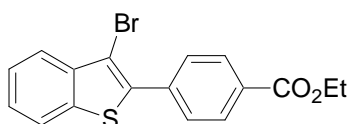
To a solution of 3-bromobenzothiophene (**36**) (213 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 50 °C (120 W) for 30 min according to **TP2**. Pd(dba)₂ (17 mg, 3 mol%) and P(o-

furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with ethyl 4-iodobenzoate (303 mg, 1.1 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 9:1) furnished the compound **31g** (336 mg, 93 %) as colorless solid.

m.p.: 98.9 – 100.2 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 8.15 – 8.14 (m, 2 H), 7.88 (d, *J* = 8.1 Hz, 1 H), 7.85 – 7.82 (m, 3 H), 7.50 – 7.41 (m, 2 H), 4.41 (q, *J* = 7.15 Hz, 2 H), 1.42 (t, *J* = 7.15 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 166.1, 139.1, 137.8, 137.4, 136.9, 130.5, 129.8, 129.5, 125.9, 125.4, 123.9, 122.2, 106.0, 61.2, 14.3.

IR (ATR) $\tilde{v}$ (cm^{-1}): 3054, 2992, 2915, 2873, 2253, 1934, 1814, 1717, 1607, 1568, 1539, 1483, 1466, 1454, 1446, 1433, 1404, 1360, 1307, 1292, 1280, 1250, 1181, 1127, 1110, 1100, 1072, 1030, 1020, 976, 933, 890, 858, 793, 762, 743, 718, 690, 697.

MS (EI, 70 eV) m/z (%): 360 (95) [^{79}Br^{32}S-M$^+$], 334 (29), 332 (23), 318 (11), 317 (47), 315 (54), 209 (13), 208 (86), 163 (14), 157 (11), 104 (31).

HRMS (EI) for C$_{17}$H$_{13}$^{79}BrO$_2$^{32}S (359.9820): 359.9815.

Synthesis of (3-bromo-benzothiophen-2-yl)-phenyl-methanone (31h)

To a solution of 3-bromobenzothiophene (**36**) (213 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 ^{o}C and the resulting mixture was heated at 50 °C (120 W) for 30 min according to **TP2**. The reaction mixture was cooled to – 20°C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoylchloride (155 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly within 2 h. The reaction mixture was quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 95:5) furnished the compound **31h** (263 mg, 83%) as a pale yellow oil.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.99 – 7.96 (m, 1 H), 7.93 – 7.89 (m, 2 H), 7.86 (q, *J* = 6.8 Hz, 1 H), 7.65 – 7.60 (m, 1 H), 7.56 – 7.52 (m, 2H), 7.51 – 7.47 (m, 2 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 189.6, 139.1, 138.3, 137.4, 135.4, 133.4, 130.0, 128.4, 127.7, 125.8, 125.0, 122.6, 111.8.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3286, 3058, 2990, 2924, 1956, 1914, 1821, 1642, 1595, 1580, 1555, 1492, 1486, 1448, 1425, 1377, 1304, 1273, 1239, 1177, 1162, 1133, 1109, 1078, 1065, 1025, 1000, 973, 951, 924, 893, 846, 816, 798, 753, 725, 706, 692, 669.

MS (EI, 70 eV) m/z (%): 316 (100) [^{79}Br^{32}S-M$^+$], 241 (72), 239 (62), 238 (20), 237 (93), 208 (21), 165 (24), 132 (37), 105 (95), 77 (58), 44 (24).

HRMS (EI) for C$_{15}$H$_9$^{79}BrO^{32}S (315.9557): 315.9557.

Synthesis of 4-(4-chloro-phenyl)-3,6-dimethoxy-pyridazine (31i)

To a solution of 3,6-dimethoxy-pyridazine (**37**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 ^{o}C and the resulting mixture was heated at 90 °C (100 W) for 1 h according to **TP2**. Pd(dba)$_2$ (17 mg, 3 mol %) and P(o-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodo-benzene (262 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (dichloromethane) furnished the compound **31i** (220 mg, 88 %) as a white solid.

m.p.: 117.1 – 118.7 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.50 (dt, J = 6.6, 2.2 Hz, 2 H), 7.38 (dt, J = 6.8, 2.2 Hz, 2 H), 6.87 (s, 1 H), 4.05 (s, 3 H), 4.04 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 162.6, 159.1, 135.6, 132.8, 131.8, 130.3, 128.7, 119.0, 54.8, 54.6.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3047, 3023, 2992, 2953, 2865, 1910, 1737, 1657, 1612, 1536, 1494, 1462, 1446, 1405, 1375, 1356, 1302, 1273, 1253, 1221, 1192, 1143, 1108, 1091, 1017, 1013, 995, 963, 909, 876, 835, 827, 821, 774, 769, 744, 718, 669, 658, 629, 612.

MS (EI, 70 eV) m/z (%): 250 (53) [^{35}Cl-M$^+$], 249 (100), 233 (11), 221 (16), 136 (21).

HRMS (EI) for C$_{12}$H$_{10}$^{35}ClN$_2$O$_2$ [M – H]$^+$ (249.0430): 249.0428.

Synthesis of 4-iodo-3,6-dimethoxypyridazine (31j)
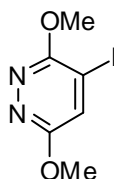
To a solution of 3,6-dimethoxy-pyridazine (**37**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 ^{o}C and the resulting mixture was heated at 90 °C (100 W) for 1 h according to **TP2**. Neat iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. Na$_2$S$_2$O$_3$ solution (10 mL) and with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 8:2) furnished the compound **31j** (201 mg, 76 %) as a white solid.

m.p.: 154.1 – 156.1 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.46 (s, 1 H), 4.01 (s, 3 H), 4.06 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 54.9, 55.9, 93.9, 130.8, 160.1, 161.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3069, 3008, 2996, 2984, 2960, 2948, 2890, 2859, 2667, 2568, 2197, 1996, 1908, 1793, 1576, 1535, 1512, 1458, 1443, 1371, 1346, 1298, 1230, 1186, 1134, 1058, 1019, 1003, 896, 856, 800, 771, 748, 667.

MS (EI, 70 eV) m/z (%): 266 (100) [M$^+$], 265 (66), 237 (29), 109 (12), 85 (14), 71 (22), 57 (25), 53 (23).

HRMS (EI) for C$_6$H$_7$IN$_2$O$_2$ (265.9552): 265.9553.

Synthesis of 4-(5-bromo-2,6-dimethoxy-pyrimidin-4-yl)-benzoic acid ethyl ester (31k)
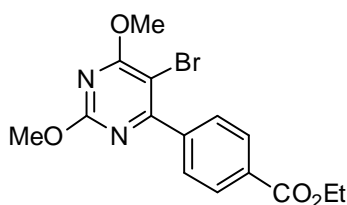
To a solution of 5-bromo-2,4-dimethoxy-pyrimidine (**38**) (219 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 ^{o}C and the resulting mixture was heated at 60 °C (100 W) for 30 min according to **TP2**. Pd(dba)$_2$ (17 mg, 3 mol %) and P(o-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL), and mixed with 4-iodo-benzoic acid ethyl ester (304 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a sat.

aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 75:25) furnished the compound **31k** (314 mg, 86 %) as a white solid.

m.p.: 128.9 – 130.7 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.12 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 4.09 (s, 3 H), 4.01 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 168.1, 166.1, 165.2, 163.5, 141.8, 131.4, 129.4, 129.1, 97.0, 61.2, 55.4, 55.3, 14.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2997, 2941, 1943, 1714, 1664, 1560, 1539, 1509, 1481, 1452, 1408, 1379, 1349, 1311, 1282, 1238, 1193, 1178, 1153, 1127, 1112, 1104, 1030, 1022, 1006, 938, 877, 865, 843, 788, 775, 732, 719, 702, 688, 688, 669, 656, 628.

MS (EI, 70 eV) m/z (%): 366 (90) [^{79}Br-M$^+$], 365 (55), 339 (29), 338 (56), 337 (32), 336 (47), 323 (36), 321 (35), 223 (16), 221 (15).

HRMS (EI) for C$_{15}$H$_{15}$^{79}BrN$_2$O$_4$: (366.0215): 366.0195.

Synthesis of 5-bromo-2,4-dimethoxy-6-(4-methoxy-phenyl)-pyrimidine (31l)
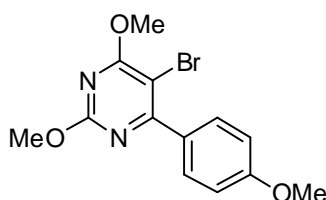
To a solution of 5-bromo-2,4-dimethoxy-pyrimidine (**38**) (219 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 ^{o}C and the resulting mixture was heated at 60 °C (100 W) for 30 min according to **TP2**. Pd(dba)$_2$ (17 mg, 3 mol %) and P(o-furyl)$_3$ (14 mg, 6 mol %) dissolved in THF (2 mL), and mixed with 1-iodo-4-methoxy-benzene (257 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 78:22) furnished the compound **31l** (300 mg, 92 %) as a white solid.

m.p.: 114.1 – 115.8 ° C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.80 (d, *J* = 8.8 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 4.07 (s, 3 H), 4.00 (s, 3 H), 3.85 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 168.1, 165.3, 163.3, 160.8, 131.2, 130.0, 113.3, 96.3, 55.4, 55.3, 55.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2989, 2940, 2836, 1615, 1583, 1565, 1543, 1519, 1482, 1447, 1416, 1380, 1352, 1309, 1300, 1258, 1201, 1194, 1188, 1177, 1150, 1109, 1030, 1019, 1008, 946, 930, 866, 836, 824, 808, 785, 740, 728, 705, 676, 660, 627.

MS (EI, 70 eV) m/z (%): 324 (100) [^{79}Br-M$^+$], 323 (47), 310 (14), 309 (15), 297 (22), 296 (39), 295 (26), 294 (36), 265 (12), 215 (38), 158 (16), 157 (12).

HRMS (EI) for C$_{13}$H$_{13}$^{79}BrN$_2$O$_3$ (324.0110): 324.0114.

3.1.2. Scaleable preparation of ssensitive functionalized aromatics and heteroaromatics using TMPZnCl·LiCl (10)

Synthesis of (2-chloro-3-nitropyridin-4-yl)(4-chlorophenyl)methanone (40)
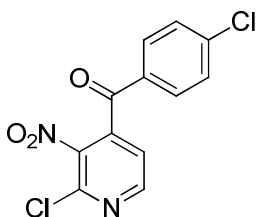
2-Chloro-3-nitropyridine (**39**) (7.91 g, 50.0 mmol, 1.0 equiv) dissolved in THF (50 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.36 M in THF, 40.5 mL, 55.0 mmol, 1.1 equiv) at 25 °C and the resulting mixture was stirred at this temperature for 5 h according to **TP1**. The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 55.0 mL, 55.0 mmol, 1.1 equiv) was added dropwise and stirred for 30 min. Then, 4-chlorobenzoylchloride (9.63 g, 55.0 mmol, 1.1 equiv) was added dropwise at –30 °C and the reaction mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (300 mL), extracted with diethyl ether (3 × 500 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/DCM = 65:35) furnished the compound **40** (11.45 g, 77%).

m.p.: 116.5 – 117.8 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.68 (d, *J* = 4.9 Hz, 2 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.38 (d, *J* = 4.9 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 188.5, 151.4, 143.8, 143.3, 43.0, 142.0, 132.3, 131.2, 129.6, 121.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 2186, 2162, 1676, 1583, 1568, 1534, 1502, 1486, 1442, 1402, 1382, 1366, 974, 858, 846, 830, 814, 800, 776, 748, 738, 716, 684, 676, 648, 634, 616.

MS (EI, 70 eV) m/z (%): 295 (8) [^{35}Cl-M$^+$], 169 (14), 141 (28), 139 (100), 129 (23), 127 (77), 111 (24).

HRMS (EI) for C$_{12}$H$_6$^{35}Cl$_2$N$_2$O$_3$ (295.9755): 295.9743.

Synthesis of 8-(4-chlorophenyl)-1,3,7-trimethyl-1*H*-purine-2,6(3H,7H) (42)
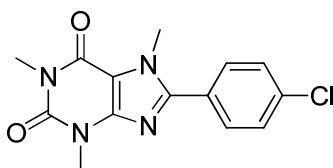
1,3,7-Trimethyl-1*H*-purine-2,6(3H,7H)-dione (**41**) (9.71 g, 50.0 mmol, 1.0 equiv) dissolved in THF (100 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.36 M in THF, 40.5 mL, 55.0 mmol) at 25 °C and the resulting mixture was stirred at this temperature for max. 10 min according to **TP1**. Pd(dba)$_2$ (850 mg, 3 mol%) and P(o-furyl)$_3$ (700 mg, 6 mol%) dissolved in THF (50 mL), and mixed with 1-chloro-4-iodobenzene (13.11 g, 55.0 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 4 h at 40 °C. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (300 mL), extracted with diethyl ether (3 × 500 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo.*. Purification by flash chromatography (DCM/Et$_2$O = 1:1) furnished compound **42** (12.09 g, 79%) as white solid.

m.p.: 198.7 – 199.5 °C.

¹H-NMR (CDCl₃, 300 MHz) δ: 7.63 (d, *J* = 8.5 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 4.02 (s, 3 H), 3.58 (s, 3 H), 3.39 (s, 3 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 155.5, 151.6, 150.8, 148.2, 136.7, 130.4, 129.2, 126.8, 108.7, 33.9, 29.8, 28.0.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2964, 1695, 1646, 1606, 1570, 1538, 1473, 1454, 1431, 1408, 1375, 1339, 1289, 1230, 1180, 1108, 1091, 1074, 1030, 1008, 978, 835, 803, 760, 749, 739, 730, 708, 685, 672, 650, 645, 639, 632, 625, 620, 614, 606. 601.

MS (EI, 70 eV) m/z (%): 304 (100) [³⁵Cl-M⁺], 303 (25), 82 (21).

HRMS (EI) for C₁₄H₁₃³⁵ClN₄O₂ (304.0727): 304.0719.

This compound is previously known: M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837.

Synthesis of 4,6-dichloro-5-(cyclohex-2-en-1-yl)pyrimidine (44)
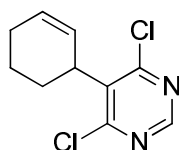
4,6-Dichloropyrimidine (**43**) (7.45 g, 50.0 mmol, 1.0 equiv) dissolved in THF (100 mL) was added to a solution of TMPZnCl·LiCl (**10**) (1.54 M in THF, 35.7 mL, 55.0 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 1 h according to **TP1**. The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 5.0 mL, 5.0 mmol) was added

and stirred at this temperature for 10 min. Then, 3-bromocyclohexene (10.47 g, 65.0 mmol) was added dropwise at –30 °C and the reaction mixture was allowed to warm up slowly to 25 °C and stirred for 3 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (300 mL), extracted with diethyl ether (3 × 500 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 95:5) furnished the compound **44** (9.23 g, 81%) as a yellow oil.

¹H-NMR (CDCl₃, 300 MHz) δ: 8.59 (s, 1 H), 5.91 – 5.84 (m, 1 H), 5.54 – 5.49 (m, 1 H), 4.21 – 4.14 (m, 1 H), 2.14 – 2.08 (m, 2 H), 1.97 – 1.67 (m, 4 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 161.7, 155.4, 135.4, 128.6, 126.2, 38.4, 25.7, 24.2, 22.5.

MS (EI, 70 eV) m/z (%): 229 (34) [^{35}Cl-M$^+$], 228 (100), 227 (28), 216 (18), 215 (32), 214 (18), 213 (53), 202 (19), 200 (33), 193 (23), 177 (32), 175 (51), 139 (25), 81 (80), 70 (16), 68 (16), 67 (47), 54 (96).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3025, 2934, 2861, 2835, 1650, 1532, 1510, 1447, 1432, 1408, 1376, 1350, 1329, 1307, 1228, 1215, 1194, 1162, 1127, 1046, 980, 934, 899, 882, 848, 808, 779, 721, 616.

HRMS (EI) for C₁₀H₁₀^{35}Cl₂N₂ (228.0221): 228.0220.

This compound is previously known: M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468.

3.2. Preparation of Polyfunctional Organometallics *via* Directed *ortho*-Metalation using TMP-Bases of Mn, Fe and La

3.2.1. Metalations with TMP₂Mn·2MgCl₂·4LiCl (12)

Synthesis of 4-cyano-2-(furan-2-carbonyl)-benzoic acid ethyl ester (46)
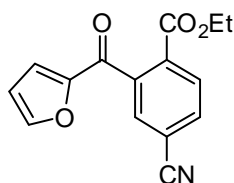
According to **TP5**, the metalation of 4-cyano-benzoic acid ethyl ester (**45**) (2.45 g, 14.0 mmol, 1.0 equiv) was completed within 75 min at 0 °C using TMP$_2$Mn·2MgCl$_2$·4LiCl (**12**) (0.48 M in THF, 17.5 mL, 8.4 mmol). The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 15.4 mL, 15.4 mmol) was added and stirred at this temperature for 10 min. Furoyl chloride (2.19 g, 16.8 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 25 °C and stirred at this temperature for 3 h. The resulting mixture was quenched with sat. aq. NH$_4$Cl (60 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether = 65:35) and afforded **46** (2.64 g, 70%) as a yellowish solid.

mp.: 115.9 – 117.4 °C.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 8.10 (d, *J* = 8.3 Hz, 1 H), 7.84 (dd, *J* = 6.6, 1.7 Hz, 1 H), 7.76 (d, *J* =1.7 Hz, 1 H), 7.60 (s, 1 H), 7.07 (d, *J* = 3.6 Hz, 1 H), 6.56 (q, *J* = 1.7 Hz, 1 H), 4.16 (q, *J* = 7.0 Hz, 2 H), 1.12 (t, *J* = 7.3 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 181.6, 164.7, 152.1, 147.6, 140.7, 133.7, 133.6, 131.6, 130.8, 119.6, 117.1, 116.0, 112.8, 62,4, 13.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3139, 3047, 2996, 2908, 2360, 2234, 2100, 1714, 1654, 1604, 1564, 1468, 1402, 1387, 1364, 1308, 1293, 1278, 1237, 1212, 1166, 1145, 1118, 1080, 1024, 1016, 982, 976, 914, 891, 882, 875, 858, 807, 777, 769, 750, 715, 697, 678, 632, 621.

MS (EI, 70 eV) m/z (%): 269 (44) [M$^+$], 241 (45), 240 (18), 224 (99), 213 (31), 212 (91),197 (18), 184 (22), 174 (41), 169 (15), 168 (17), 140 (61), 129 (20), 95 (100), 63 (15).

HRMS (EI) for C$_{15}$H$_{11}$NO$_4$ (269.0688): 269.0667.

Synthesis of (3,6-dimethoxy-pyridazin-4-yl)-phenyl-methanol (48)
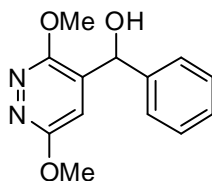
According to **TP5**, the metalation of 3,6-dimethoxy-pyridazine (**47**) (2.10 g, 15.0 mmol) was completed within 30 min at 0 °C using TMP$_2$Mn·2MgCl$_2$·4LiCl (**12**) (0.48 m in THF, 18.8 mL, 9.0 mmol). Then, benzaldehyde (1.91 g, 18.0 mmol) was added dropwise and the reaction mixture was allowed to warm up slowly to 25 °C and stirred at this temperature for 3 h. The resulting mixture was then quenched with a sat. aq. NH$_4$Cl solution (60 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether = 1:1) to give **48** (3.53 g, 94%) as a white solid.

mp.: 109.3 – 111.0 °C.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.48 – 7.44 (m, 4 H), 7.43 (d, *J* = 5.8 Hz, 1 H), 7.12 (s, 1 H), 5.99 (s, 1 H), 4.15 (s, 3 H), 4.11 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 162.7, 159.4, 140.4, 137.3, 128.6, 128.3, 126.9, 117.2, 70.2, 54.6, 54.5.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3262, 3102, 3057, 3026, 2995, 2951, 2889, 2866, 2590, 1956, 1936, 1885, 1819, 1758, 1700, 1662, 1626, 1600, 1551, 1492, 1468, 1453, 1380, 1302, 1257, 1217, 1191, 1180, 1154, 1136, 1077, 1046, 1029, 1008, 946, 912, 836, 806, 774, 765, 752, 726, 700, 683, 642, 620, 605.

MS (EI, 70 eV) m/z (%): 246 (100) [M$^+$], 245 (43), 231 (41), 155 (41), 153 (34), 105 (15).

HRMS (EI) for C$_{13}$H$_{14}$N$_2$O$_3$ (246.1004): 246.0981.

3.2.2. Metalations with TMP$_2$Fe·2MgCl$_2$·4LiCl (13)

Synthesis of 3-cyano-2-octyl-benzoic acid ethyl ester (50)
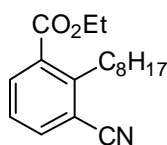
According to **TP6**, the metalation of 3-cyano-benzoic acid ethyl ester (**49**) (2.45 g, 14.0 mmol) was completed within 18 h at 25 °C using TMP$_2$Fe·2MgCl$_2$·4LiCl (**13**) (0.48 M in THF, 21.9 mL, 10.5 mmol). 1-Iodo-octane (3.70 g, 15.4 mmol) and 4-fluorostyrene (171 mg, 1.4 mmol, 0.1 equiv) were then added dropwise and the reaction mixture was allowed to stir at 25 °C overnight. The resulting mixture was then quenched with a mixture of sat. aq. NH$_4$Cl solution (60 mL) and HCl (2 M, 25 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether = 98:2) to give **50** (3.19 g, 78%) as a brown oil.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.99 (dd, J = 8.0, 1.5 Hz, 1 H), 7.70 (dd, J = 7.8, 1.5 Hz, 1 H), 7.32 (t, J = 7.8 Hz, 1 H), 4.36 (q, J = 7.0 Hz, 2 H), 3.16 – 3.11 (m, 2 H), 1.64 – 1.56 (m, 2 H), 1.43 – 1.35 (m, 6 H), 1.33 – 1.25 (m, 7 H), 0.84 (t, J = 6.6 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 166.3, 148.0, 135.9, 134.6, 131.7, 126.3, 117.6, 114.7, 61.5, 32.7, 31.8, 31.5, 29.8, 29.3, 29.2, 22.6, 14.2, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3428, 3079, 2955, 2926, 2856, 2359, 2228, 2180, 2165, 2100, 1964, 1952, 1918, 1723, 1582, 1461, 1445, 1390, 1367, 1271, 1259, 1203, 1176, 1142, 1100, 1084, 1044, 1021, 949, 910, 864, 835, 820, 761, 723, 661, 640.

MS (EI, 70 eV) m/z (%): 287 (39) [M$^+$], 242 (83), 189 (100),184 (17), 174 (64), 170 (32), 161 (55), 160 (37), 157 (30), 156 (73), 143 (32), 142 (16), 129 (19), 128 (21), 117 (22), 116 (20), 115 (25), 77 (15), 57 (39), 55 (20), 43 (50), 41 (70).

HRMS (EI) for C$_{18}$H$_{25}$NO$_2$ (287.1885): 287.1878.

Synthesis of 3-cyano-2-isopropyl-benzoic acid ethyl ester (51)
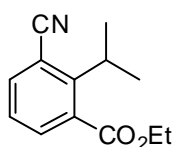
According to **TP6**, the metalation of 3-cyano-benzoic acid ethyl ester (**49**) (2.45 g, 14.0 mmol) was completed within 18 h at 25 °C using TMP$_2$Fe·2MgCl$_2$·4LiCl (**13**) (0.48 M in THF, 21.9 mL, 10.5 mmol). 2-Iodo-propane (2.62 g, 15.4 mmol) and 4-fluorostyrene (171 mg, 1.4 mmol, 0.1 equiv) were then added dropwise and the reaction mixture was allowed to stir at 25 °C overnight.

The resulting mixture was then quenched with a mixture of sat. aq. NH$_4$Cl solution (60 mL) and HCl (2 M, 25 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether = 90:10) to afford **51** (2.35 g, 78%) as a brown oil.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.72 (q, *J* = 1.5 Hz, 1 H), 7.69 (q, *J* = 1.7 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 3.65 – 3.55 (m, 1 H), 1.47 (q, *J* = 7.3 Hz, 6 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 168.0, 150.9, 136.8, 133.8, 133.1, 126.2, 118.5, 112.2, 61.8, 31.6, 21.2, 14.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3636, 3546, 3436, 3079, 2970, 2938, 2906, 2878, 2732, 2360, 2226, 2165, 2154, 2086, 2042, 1960, 1918, 1721, 1582, 1460, 1442, 1388, 1367, 1285, 1259, 1210, 1178, 1146, 1136, 1107, 1095, 1054, 1017, 962, 929, 915, 891, 864, 820, 799, 765, 728, 682, 641, 634.

MS (EI, 70 eV) m/z (%): 217 (20) [M$^+$], 189 (28), 174 (24), 172 (60), 171 (40), 170 (51), 156 (100), 154 (16), 142 (17), 130 (20), 116 (17), 115 (25), 59 (27), 44 (18), 43 (55), 43 (18), 41 (50).

HRMS (EI) for C$_{13}$H$_{15}$NO$_2$ (217.1103): 217.1109.

3.2.3. Metalations with TMP$_3$La·3MgCl$_2$·5LiCl (14)

Synthesis of 2-benzoyl-3-chloro-benzoic acid methyl ester (53)
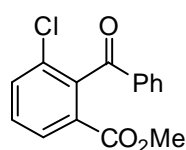
According to **TP7**, the metalation of 3-chloro-benzoic acid methyl ester (**52**) (2.39 g, 14.0 mmol) was completed within 3.5 h at 0 °C using TMP$_3$La·3MgCl$_2$·5LiCl (**14**) (0.35 M in THF, 15.0 mL, 4.9 mmol). Benzoyl chloride (2.16 g, 15.4 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 25 °C overnight. The resulting mixture was then quenched with a sat. aq. NH$_4$Cl solution (60 mL) and extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (pentane/diethyl ether = 85:15) to afford **53** (2.88 g, 75%) as a white solid.

mp.: 133.9 – 135.7 °C.

^{1}H-NMR (300 MHz, CDCl$_3$) δ: 8.03 (dd, J = 8.0, 1.2 Hz, 1 H), 7.79 – 7.76 (m, 2 H), 7.64 (dd, J = 8.0, 1.2 Hz, 1 H), 7.59 – 7.54 (m, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.47 – 7.42 (m, 2 H), 3.69 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 194.4, 165.0, 140.7, 136.6, 134.0, 133.4, 131.8, 130.3, 129.9, 128.9, 128.8, 128.7, 52.5.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3068, 3009, 2951, 1920, 1721, 1678, 1674, 1597, 1582, 1567, 1449, 1432, 1313, 1295, 1267, 1205, 1184, 1154, 1111, 1070, 1024, 1001, 996, 978, 972, 939, 927, 850, 820, 794, 766, 746, 733, 727, 717, 705, 668, 654.

MS (EI, 70 eV) m/z (%): 274 (30) [^{35}Cl-M$^+$], 242 (18), 198 (35), 197 (100), 105 (75), 77 (29).

HRMS (EI) for C$_{15}$H$_{11}$^{35}ClO$_3$ (274.0397): 274.0387.

3.3.   Directed *ortho*- and *meta*-Magnesiation or Zincation of Polyfunctional Aryl Nonaflates

Synthesis of 4-(2,2-dimethyl-propionyl)-5-(nonafluorobutane-1-sulfonyloxy)-isophthalic acid diethyl ester (58a)
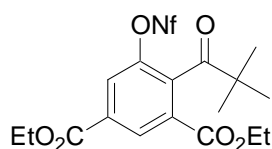
5-(Nonafluorobutane-1-sulfonyloxy)-isophthalic acid diethyl ester (**54**, 520 mg, 2.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. Then, CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added and stirred at −20 °C for 30 min. Trimethylacetyl chloride (133 mg, 1.1 mmol) was added dropwise at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction

mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 85:15) furnished the compound **58a** (434 mg, 72%) as a white solid.

m.p.: 94.7 – 96.4 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.65 (d, *J* = 1.3 Hz, 1 H), 8.18 (d, *J* = 1.5 Hz, 1 H), 4.45 (q, *J* = 7.3 Hz, 4 H), 1.45 – 1.37 (m, 6 H), 1.23 (s, 9 H).

^{13}C (75 MHz, CDCl$_3$) δ: 208.0, 163.7 (d, *J* (C – F) = 17.3 Hz), 145.4, 140.0, 133.6, 132.6, 130.9, 130.5, 126.1, 124.6, 122.8, 117.0, 108.7, 105.3, 62.6, 62.3, 45.7, 27.6, 14.2

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3097, 2987, 1720, 1702, 1615, 1563, 1482, 1466, 1430, 1412, 1396, 1371, 1352, 1311, 1291, 1239, 1209, 1194, 1137, 1095, 1026, 980, 946, 930, 917, 861, 848, 814, 788, 770, 757, 745, 732, 696, 654, 619.

HRMS (ESI$^+$) for C$_{21}$H$_{25}$F$_9$NO$_8$^{32}S [M + NH$_4$]$^+$ (622.1157): 622.1152.

Synthesis of 4-cyclohex-2-enyl-5-(nonafluorobutane-1-sulfonyloxy)-isophthalic acid diethyl ester (58b)
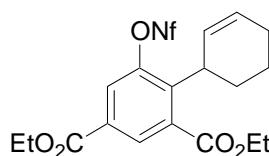
5-(Nonafluorobutane-1-sulfonyloxy)-isophthalic acid diethyl ester (**54**, 1.040 g, 2.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 1.85

mL, 2.6 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added and stirred at −20 °C for 30 min. Then, 3-bromo-cyclohexene (354 mg, 2.2 mmol) was added drop wise at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 9:1) furnished the compound **58b** (1.026 g, 85%) as a white solid.

m.p.: 48.9 – 50.7 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.11 (d, *J* = 1.5 Hz, 1 H), 8.0 (d, *J* = 1.7 Hz, 1 H), 5.88 – 5.83 (m, 1 H), 5.54 (d, *J* = 10.1 Hz, 1 H), 4.43 – 4.23 (m, 4 H), 2.15 – 1.89 (m, 5 H), 1.74 – 1.63 (m, 2 H), 1.44 – 1.35 (m, 6 H).

^{13}C (75 MHz, CDCl$_3$) δ: 167.3, 164.0, 148.5, 142.1, 136.3, 130.4, 129.4 – 124.0 (m), 61.9, 61.8, 37.2, 29.0, 24.4, 22.6, 14.1, 14.0. Observed complexity due to C–F splitting, definitive assignments have not been made.

^{19}F (282 MHz, CDCl$_3$) δ: -80.7, -109.4, -120.8, -125.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2989, 2943, 2837, 1723, 1651, 1617, 1568, 1419, 1394, 1368, 1355, 1305, 1235, 1200, 1192, 1144, 1095, 1050, 1027, 984, 962, 943, 928, 906, 881, 867, 848, 807, 785, 763, 748, 733, 698, 659, 646, 618.

HRMS (ESI$^+$) for C$_{22}$H$_{25}$F$_9$NO$_7$^{32}S [M + NH$_4$]$^+$ (618.1208): 618.1205.

Synthesis of 6-(nonafluorobutane-1-sulfonyloxy)-4'-trifluoromethyl-biphenyl-2,4-dicarboxylic acid diethyl ester (58c)
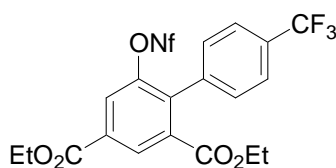
5-(Nonafluorobutane-1-sulfonyloxy)-isophthalic acid diethyl ester (**54**, 520 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. Pd(dba)$_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-iodo-4-trifluoromethyl-benzene (299 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 9:1) furnished the compound **58c** (550 mg, 83%) as a clear yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.57 (d, *J* = 1.7 Hz, 1 H), 8.17 (d, *J* = 1.5 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 4.65 (q, *J* = 7.1 Hz, 2 H), 4.07 (q, *J* = 7.3 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 0.98 (t, *J* = 7.1 Hz, 3 H).

^{13}C (75 MHz, CDCl$_3$) δ: 165.3, 163.7, 147.1, 138.7, 137.0, 132.7 (d, *J* (C − F) = 276.6 Hz), 131.7 – 131.3 (m), 130.6, 129.7, 125.2 (d, *J* (C – F) = 32.5 Hz), 62.2, 61.9, 14.2, 13.5.

^{19}F (282 MHz, CDCl$_3$) δ: -62.9, -80.7, -109.6, -120.9, -125.9.

IR (ATR) $\widetilde{\nu}$ **(cm^{-1}):** 3083, 2988, 2943, 2912, 1728, 1619, 1579, 1563, 1525, 1468, 1430, 1408, 1370, 1353, 1325, 1311, 1238, 1203, 1168, 1143, 1127, 1110, 1068, 1025, 1010, 964, 913, 844, 792, 766, 748, 736, 697, 690, 666, 654, 623.

HRMS (ESI$^+$) for C$_{23}$H$_{20}$F$_{12}$NO$_7$^{32}S [M + NH$_4$]$^+$ (682.0769): 682.0765.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2-benzoyl-3,5-dichloro-phenyl ester (58d)
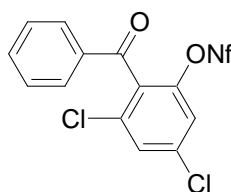
1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 3,5-dichloro-phenyl ester (**59**; 549 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. The reaction mixture was then cooled to −20 °C, CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added and stirred at −20 °C for 30 min. Then benzoyl chloride (183 mg, 1.3 mmol) was added dropwise at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether 96:4) furnished the compound **58d** (429 mg, 78%) as a white solid.

m.p.: 81.4 – 82.7 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.81 – 7.77 (m, 2 H), 7.67 – 7.62 (m, 1 H), 7.53 (d, J = 1.9 Hz, 1 H), 7.51 – 7.46 (m, 2 H), 7.44 (d, J = 1.7 Hz, 1 H).

^{13}C (75 MHz, CDCl$_3$) δ: 189.2, 146.3, 136.6, 135.3, 134.8, 133.7, 131.2, 129.7 – 129.0 (m), 128.5, 128.2, 120.8. Observed complexity due to C–F splitting, definitive assignments have not been made.

^{19}F (282 MHz, CDCl$_3$) δ: -80.7, -108.9, -120.8, -125.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3084, 2334, 1676, 1595, 1582, 1552, 1452, 1431, 1412, 1386, 1351, 1320, 1296, 1274, 1255, 1235, 1224, 1200, 1190, 1137, 1081, 1075, 1031, 1002, 950, 928, 916, 868, 827, 799, 770, 745, 730, 706, 696, 684, 654, 638, 616.

HRMS (ESI$^+$) for C$_{17}$H$_{11}$^{35}Cl$_2$F$_9$NO$_4$^{32}S [M + NH$_4$]$^+$ (565.9642): 565.9639.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4,6-dichloro-4'-trifluoromethyl-biphenyl-2-yl ester (58e)

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 3,5-dichloro-phenyl ester (**59**; 549 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. Pd(dba)$_2$ (17 mg, 3 mol%), P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-iodo-4-trifluoromethyl-benzene (299 mg, 1.1 mmol, 1.1 equiv) were then

transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 99:1) furnished the compound **58e** (441 mg, 76%) as a clear colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.38 (d, *J* = 2.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 1.9 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 2 H).

^{13}C (75 MHz, CDCl$_3$) δ: 189.4, 147.2, 134.2 (d, *J* (C − F) = 268.6 Hz), 135.3, 130.6, 129.9, 125.5 (m), 121.1.

^{19}F (282 MHz, CDCl$_3$) δ: -62.9, -80.7, -109.5, -121.0, -125.9.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 2942, 2304, 1925, 1736, 1621, 1596, 1552, 1523, 1459, 1431, 1410, 1386, 1353, 1323, 1293, 1238, 1228, 1204, 1191, 1169, 1128, 1109, 1068, 1033, 1026, 1008, 938, 862, 844, 831, 772, 747, 731 698, 686, 654, 632, 614.

HRMS (ESI$^+$) for C$_{17}$H$_6$^{35}Cl$_2$F$_{12}$O$_3$^{32}S (587.9223): 587.9217.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4,6,4'-trichloro-biphenyl-2-yl ester (58f)

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 3,5-dichloro-phenyl ester (**59**; 549 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. Pd(dba)$_2$ (17 mg, 3 mol%), P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 1-chloro-4-iodobenzene (262 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane) furnished the compound **58f** (458 mg, 83%) as a clear colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.21 (dt, *J* = 8.6, 2.0 Hz, 2 H), 7.34 (d, *J* = 2.0 Hz, 1 H), 7.45 (dt, *J* = 8.4, 2.0 Hz, 2 H), 7.56 (d, *J* = 2.06, 1 H).

^{13}C (75 MHz, CDCl$_3$) δ: 147.5, 136.2, 135.4, 134.8, 132.9, 131.5, 130.0, 129.8, 128.8, ´124.2 – 123.9 (m), 121.0. Observed complexity due to C–F splitting, definitive assignments have not been made.

^{19}F (282 MHz, CDCl$_3$) δ: -80.7, -109.5, -120.9, -125.8.

IR (ATR) $\tilde{v}$ (cm^{-1}): 3089, 2964, 2872, 2338, 2038, 1905, 1736, 1704, 1654, 1592, 1572, 1550, 1498, 1455, 1430, 1414, 1384, 1352, 1291, 1237, 1226, 1202, 1190, 1143, 1126, 1098, 1033, 1023, 1006, 935, 876, 861, 824, 782, 772, 740, 731, 697, 686, 654, 629, 614.

HRMS (ESI$^+$) for C$_{16}$H$_6$^{35}Cl$_3$F$_9$O$_3$^{32}S [M]$^+$ (553.8959): 553.8957.

Synthesis of 2-(2-(ethoxycarbonyl)allyl)-3-fluorophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (58g)
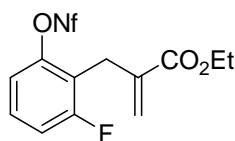
3-Fluorophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**60**; 394 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. Then, CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added and stirred at –20 °C for 30 min. Then (2-bromomethyl)acrylate (212 mg, 1.1 mmol) was added drop wise at –20 °C and stirred to 25 °C for 3. Then, it was quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 96:4) furnished the compound **58g** (361 mg, 72%) as a clear colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.35 – 7.30 (m, 1 H), 7.17 – 7.10 (m, 2 H), 6.26 (s, 1H), 5.24 (s, 1 H), 4.22 (q, J =7.1 Hz, 2 H), 3.76 (d, J =1.5 Hz, 2 H), 1.28 (t, J =7.1 Hz, 3 H).

^{13}C (150 MHz, CDCl$_3$) δ: 166.1, 161.7 (d, J (C – F) =250.8 Hz), 160.9, 148.6 (d, J (C – F) =7.3 Hz), 136.6, 128.8 (d, J (C – F) =9.8 Hz), 125.9, 120.4 (d, J (C – F) =19.9 Hz), 115.6 (d, J (C – F) =22.4 Hz), 61.0, 41.3, 25.8 (d, J (C – F) =3.1 Hz), 14.1.

^{19}F (282 MHz, CDCl$_3$) δ: -80.6, -109.4, -111.1, -120.8, -125.8.

IR (ATR) $\widetilde{V}$ (cm^{-1}): 2983, 2934, 2876, 1717, 1638, 1621, 1588, 1464, 1425, 1381, 1372, 1352, 1284, 1236, 1200, 1142, 1108, 1031, 996, 952, 903, 876, 853, 787, 733, 693, 651, 624.

HRMS (ESI$^+$) for C$_{16}$H$_{16}$F$_{10}$NO$_5$^{32}S [M + NH$_4$]$^+$ (524.0589): 524.0585.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 6-fluoro-4'-methoxy-biphenyl-2-yl ester (58h)
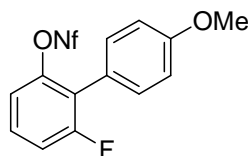
3-Fluorophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**60**; 394 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP1**. Pd(dba)$_2$ (17 mg, 3 mol%), P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 4-iodoanisole (257 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 96:4) furnished the compound **58h** (400 mg, 80%) as brown crystals.

m.p.: 39.9 – 42.3 °C

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.41 – 7.30 (m, 1 H), 7.32 (dt, *J* = 5.4, 1.3 Hz, 2 H), 7.23 – 7.17 (m, 2 H), 6.99 (dt, *J* = 6.7, 2.0 Hz), 3.85 (s, 3 H).

^{13}C (75 MHz, CDCl$_3$) δ: 160.4 (d, *J* (C − F) = 249.5 Hz), 160.0, 147.8 (d, *J* (C − F) = 5.7 Hz), 131.7 (d, *J* (C − F) = 1.5 Hz), 128.8 (d, *J* (C − F) = 9.5 Hz), 124.8, 124.6, 120.7, 117.6 (d, *J* (C − F) = 3.9 Hz), 116.1, 115.8, 113.9, 55.2.

^{19}F (282 MHz, CDCl$_3$) δ: -80.7, -109.8, -111.3, -121.0, -125.9.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3007, 2968, 2939, 2842, 2554, 2058, 1920, 1774, 1611, 1582, 1570, 1521, 1501, 1469, 1459, 1443, 1422, 1354, 1298, 1281, 1252, 1232, 1200, 1188, 1178, 1143, 1156, 1112, 1036, 1076, 1022, 1006, 974, 944, 888, 854, 831, 822, 808, 7790, 736, 726, 718, 697, 655, 636, 616.

HRMS (ESI$^+$) for C$_{17}$H$_{14}$F$_{10}$NO$_4$^{32}S [M + NH$_4$]$^+$ (518.0484): 518.0479.

Synthesis of 6-(nonafluorobutane-1-sulfonyloxy)-3'-trifluoromethyl-biphenyl-2-carboxylic acid ethyl ester (58i)
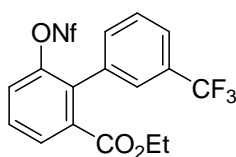
3-(Nonafluorobutane-1-sulfonyloxy)-benzoic acid ethyl ester (**61**; 448 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 55 °C and the resulting mixture was stirred at this temperature for 6 h according to **TP1**. Pd(dba)$_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 1-iodo-3-trifluoromethyl-benzene (299 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification

by flash chromatography (pentane/ether = 9:1) furnished the compound **58i** (383 mg, 65%) as a clear yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.0 – 7.9 (m, 1 H), 7.7 (d, *J* = 7.8 Hz, 1 H), 7.58 – 7.52 (m, 4 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 4.03 (q, *J* = 7.1 Hz, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

^{13}C (75 MHz, CDCl$_3$) δ: 166.0, 147.2, 134.8, 134.3, 132.8, 132.6 (d, *J* (C – F) = 265.2 Hz), 130.4, 129.9, 129.7, 128.5, 126.5 – 124.8 (m), 61.6, 13.4.

^{19}F (282 MHz, CDCl$_3$) δ: -62.9, -80.7, -109.9, -121.0, -125.9.

IR (ATR) $\tilde{V}$ (cm^{-1}): 2988, 1724, 1606, 1568, 1496, 1450, 1426, 1369, 1353, 1332, 1288, 1239, 1196, 1179, 1165, 1126, 1098, 1074, 1030, 1012, 947, 902, 856, 826, 802, 768, 746, 733, 701, 686, 661, 652, 626.

HRMS (ESI$^+$) for C$_{20}$H$_{16}$F$_{12}$NO$_5$^{32}S [M + NH$_4$]$^+$ (610.0558): 610.0553.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2,6-difluoro-3'-trifluoromethyl-biphenyl-3-yl ester (58j)

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2,4-difluoro-phenyl ester (**62**; 412 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**10**) (1.4 M in THF, 0.93 mL, 1.3 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 1 h according to **TP1**. Pd(dba)$_2$ (17 mg, 3 mol%), P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2

mL) and mixed with 1-iodo-4-trifluoromethyl-benzene (299 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 99:1) furnished the compound **58j** (492 mg, 89%) as a clear colourless oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.72 (d, J = 6.9 Hz, 2 H), 7.66 – 7.61 (m, 2 H), 7.40 – 7.36 (m, 1 H), 7.11 – 7.08 (m, 1 H).

¹³C (150 MHz, CDCl₃) δ: 158.5 (d, J (C – F) = 252.7 Hz), 158.4 (d, J (C – F) = 252.7 Hz), 151.5 (d, J (C – F) = 255.8 Hz), 151.4 (d, J (C – F) = 255.8 Hz), 133.9 (d, J (C – F) = 14.6 Hz), 133.8 – 133.5 (m), 126.0, 125.9 (d, J (C – F) = 3.7 Hz), 123.4 (d, J (C – F) = 10.4 Hz), 112.21 (m).

¹⁹F (282 MHz, CDCl₃) δ: -62.8, -80.6, -108.9, -111.7, -120.7, -125.7.

IR (ATR) $\widetilde{V}$ (cm⁻¹): 3103, 2356, 1737, 1634, 1588, 1482, 1458, 1432, 1353, 1333, 1292, 1222, 1200, 1170, 1126, 1101, 1090, 1074, 1033, 1010, 931, 924, 903, 878, 840, 816, 800, 771, 749, 740, 719, 699, 667, 652, 619.

HRMS (ESI⁺) for $C_{18}H_7F_{14}O_5{}^{32}S$ [M + CH_2O_2]⁺ (600.9791): 600.9784.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2,4-difluoro-3-[hydroxy-(4-methoxy-phenyl)-methyl]-phenyl ester (58k)

1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2,4-difluoro-phenyl ester (**62**; 412 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**7**) (1.31 M in THF, 0.85 mL, 1.1 mmol) at −20 °C and the resulting mixture was stirred at this temperature for 15 min according to **TP4**. Then, 3-methoxybenzaldehyde (150 mg, 1.1 mmol) was added at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 75:25) furnished the compound **58k** (513 mg, 94%) as a yellowish oil.

¹H NMR (300 MHz, CDCl$_3$) δ: 7.30 (d, J = 8.4 Hz, 2 H), 7.02 – 6.87 (m, 2 H), 6.88 (dd, J = 6.9, 2.2 Hz, 2 H), 6.20 (s, 1 H), 3.79 (s, 3 H).

¹³C (75 MHz, CDCl$_3$) δ: 159.5, 153.8, 133.8 (d, J (C – F) = 4.1 Hz), 133.6 (d, J (C – F) = 4.1 Hz), 132.9, 132.0, 126.9, 122.8 (d, J (C – F) = 11.1 Hz), 122.4 – 122.1 (m), 121.9, 114.3, 114.1, 112.3 (d, J (C – F) = 25.0 Hz), 112.6 (d, J (C – F) = 25.2 Hz), 67.7, 55.3.

¹⁹F (282 MHz, CDCl$_3$) δ: -80.6, -109.0, -111.6, -120.7, -125.8.

IR (ATR) $\tilde{v}$ (cm⁻¹): 3420, 3094, 3007, 2959, 2941, 2914, 2842, 1887, 1677, 1629, 1612, 1600, 1513, 1485, 1460, 1430, 1353, 1293, 1222, 1231, 1201, 1142, 1125, 1032, 1008, 980, 930, 858, 815, 796, 780, 748, 738, 715, 695, 652, 609.

HRMS (ESI⁺) for C$_{18}$H$_{15}$F$_{11}$NO$_5$^{32}S [M + NH$_4$]⁺ (566.0495): 566.0491.

Synthesis of 2,4-difluoro-3-(methylthio)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (58l)
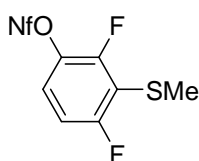
1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2,4-difluoro-phenyl ester (**62**; 412 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**7**) (1.31 M in THF, 0.85 mL, 1.1 mmol) at −20 °C and the resulting mixture was stirred at this temperature for 15 min according to **TP4**. Then, S-methyl methanethiosulfonate (139 mg, 1.1 mmol) was added at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 99:1) furnished the compound **58l** (370 mg, 81%) as a clear yellow oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.28 – 7.21 (m, 1 H), 7.00 – 6.93 (m, 1 H), 2.51 (s, 3 H).

¹³C (75 MHz, CDCl₃) δ: 161.4 (d, *J* (C – F) = 250.5 Hz), 161.3 (d, *J* (C – F) = 250.5 Hz), 154.1 (d, *J* (C – F) = 253.0 Hz), 154.0 (d, *J* (C – F) = 253.0 Hz), 133.8 – 133.6 (m), 122.4 (d, *J* (C – F) = 10.1 Hz), 119.4, 117.1 (d, *J* (C – F) = 210.9 Hz), 116.7, 116.4 (d, *J* (C – F) = 4.2 Hz), 115.1, 111.8 – 111.4 (m), 17.54.

¹⁹F (282 MHz, CDCl₃) δ: -80.6, -103.3, -109.0, -116.8, -120.7, -125.8.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3101, 2938, 2872, 1867, 1743, 1612, 1586, 1475, 1431, 1353, 1324, 1293, 1221, 1199, 1161, 1142, 1126, 1033, 1010, 977, 962, 910, 875, 862, 814, 784, 748, 739, 714, 692, 653, 606.

HRMS (ESI$^+$) for C$_{11}$H$_5$F$_{11}$O$_3$^{32}S$_2$ [M]$^+$ (457.9504): 457.9496.

Synthesis of 2-benzoyl-4-(nonafluorobutane-1-sulfonyloxy)-benzoic acid ethyl ester (58m)
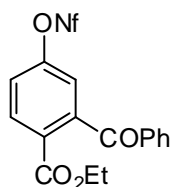
4-(Nonafluorobutane-1-sulfonyloxy)-benzoic acid ethyl ester (**63**; 553 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**7**) (1.31 M in THF, 0.85 mL, 1.1 mmol) at −20 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP4**. Then, CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added and stirred at −20 °C for 30 min. Benzoyl chloride (183 mg, 1.3 mmol) was added dropwise at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 9:1) furnished the compound **58m** (360 mg, 65 %) as a yellowish oil.

^{1}**H NMR (300 MHz, CDCl$_3$) δ:** 8.17 (d, *J* = 8.6 Hz, 1 H), 7.76 – 7.73 (m, 2 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.51 – 7.43 (m, 3 H), 7.31 (s, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 1.06 (t, *J* = 7.1 Hz, 3 H).

¹³C (75 MHz, CDCl₃) δ: 194.2, 164.4, 151.8, 144.1, 136.3, 133.7, 132.7, 129.5, 129.4, 128.8, 122.3, 120.8, 62.1, 13.6. Observed complexity due to C–F splitting, definitive assignments have not been made.

¹⁹F (282 MHz, CDCl₃) δ: -80.6, -108.4, -120.7, -125.7.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3073, 2985, 2941, 2366, 1723, 1678, 1598, 1580, 1450, 1430, 1368, 1353, 1282, 1273, 1237, 1226, 1200, 1170, 1143, 1121, 1088, 1032, 1010, 975, 883, 872, 846, 785, 768, 748, 735, 696, 686, 650, 639, 612.

HRMS (ESI⁺) for C₂₀H₁₇F₉NO₆³²S [M + NH₄]⁺ (570.0633): 570.0629.

Synthesis of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 3-(4-methoxy-phenyl)-1-oxo-1,3-dihydro-isobenzofuran-5-yl ester (58n)

4-(Nonafluorobutane-1-sulfonyloxy)-benzoic acid ethyl ester (**63**; 553 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**7**) (1.31 M in THF, 0.85 mL, 1.1 mmol) at −20 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP4**. Then, 3-methoxybenzaldehyde (150 mg, 1.1 mmol) was added at −20 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH₄Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over

anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 8:2) furnished the compound **58n** (385 mg, 72%) as a white solid.

m.p.: 72.9 – 74.9 °C

^{1}H NMR (600 MHz, CDCl$_3$) δ: 8.04 (d, *J* = 8.4 Hz, 1 H), 7.46 (dd, *J* = 6.5, 1.8 Hz, 1 H), 7.23 (d, *J* = 2.2 Hz, 1 H), 7.15 (dd, *J* = 6.7, 1.9 Hz, 2 H), 6.90 (q, *J* = 2.2 Hz, 2 H), 6.39 (s, 1 H), 3.81 (s, 3 H).

^{13}C (150 MHz, CDCl$_3$) δ: 168.4, 160.8, 153.5, 151.9, 128.8, 127.9, 126.8, 125.9, 123.0, 116.6, 114.6, 82.3, 55.4. Observed complexity due to C–F splitting, definitive assignments have not been made.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 3003, 2932, 2838, 1766, 1609, 1516, 1477, 1464, 1433, 1424, 1355, 1336, 1295, 1283, 1254, 1231, 1197, 1180, 1144, 1125, 1096, 1064, 1034, 1011, 974, 946, 900, 891, 873, 858, 830, 817, 792, 783, 763, 742, 736, 723, 702, 694, 677, 651, 612.

HRMS (ESI$^+$) for C$_{19}$H$_{15}$F$_9$NO$_6$^{32}S [M + NH$_4$]$^+$ (556.0476): 556.0473.

Synthesis of 5-(nonafluorobutane-1-sulfonyloxy)-biphenyl-2,4'-dicarboxylic acid diethyl ester (58o)
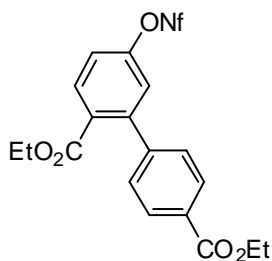
4-(Nonafluorobutane-1-sulfonyloxy)-benzoic acid ethyl ester (**63**; 553 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**7**) (1.31 M in THF, 0.85 mL, 1.1 mmol) at −20 °C and the resulting mixture was stirred at this temperature for 3 h according to **TP4**. Then, $ZnCl_2$ (1 M solution in THF, 1.1 mL, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C for 1 h. $Pd(dba)_2$ (17 mg, 3 mol%), P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) mixed with ethyl 4-iodobenzoate (304 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 6 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 87:13) furnished the compound **58o** (385 mg, 65 %) as yellowish oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.09 (dd, J = 8.2, 1.6 Hz, 2 H), 7.96 (d, J = 8.6 Hz, 1 H), 7.39 – 7.35 (m, 3H), 7.26 (d, J = 2.6 Hz, 1 H), 4.41 (q, J = 7.1 Hz, 2 H), 4.11 (q, J = 7.1 Hz, 2 H), 1.41 (t, J = 7.1 Hz, 3 H), 1.02 (t, J = 7.1, 3 H).

^{13}C (75 MHz, CDCl$_3$) δ: 166.6, 166.2, 151.0, 144.3, 132.3, 131.2, 130.2, 129.5, 128.3, 123.3, 120.5, 61.6, 61.2, 14.3, 13.7. Observed complexity due to C–F splitting, definitive assignments have not been made.

^{19}F (282 MHz, CDCl$_3$) δ: -80.6, -108.6, -120.8, -125.7.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2985, 2942, 2908, 1716, 1604, 1581, 1566, 1477, 1429, 1368, 1353, 1274, 1237, 1200, 1143, 1124, 1099, 1034, 1018, 910, 857, 776, 748, 737, 713, 697, 673, 653, 632, 612.

HRMS (ESI$^+$) for C$_{22}$H$_{21}$F$_9$NO$_7$^{32}S [M + NH$_4$]$^+$ (614.0895): 614.0891.

Synthesis of 2-benzoyl-4-(3-ethoxycarbonyl-propyl)-benzoic acid ethyl ester (65)
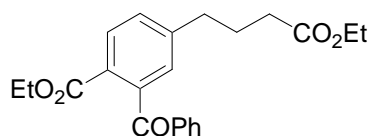
4-Nonafluorobutane-1-sulfonyloxy)-benzoic acid ethyl ester (**58m**; 276 mg, 0.5 mmol), Pd(dba)$_2$ (15 mg, 5 mol %) and dppf (14 mg, 5 mol %) dissolved in THF (2 mL) were transferred via cannula to a solution with 4-ethoxy-4-oxybutylzinc bromide (**64**) (0.67 M in THF, 1.1 mL, 0.75 mmol) and the resulting mixture was stirred at 60 °C for 8 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether = 55:45) furnished the compound **65** (145 mg, 79%) as a yellowish oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.99 (d, *J* = 8.0 Hz, 1 H), 7.76 – 7.73 (m, 2 H), 7.56 – 7.51 (m, 1 H), 7.44 – 7.36 (m, 3 H), 7.19 (s, 1 H), 4.08 (dq, *J* = 7.3, 7.1 Hz, 4 H), 2.74 (t, *J* = 7.7 Hz, 2 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 2.02 – 1.92 (m, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.02 (t, *J* = 7.1 Hz, 3 H).

^{13}C (75 MHz, CDCl$_3$) δ: 197.1, 173.1, 165.8, 146.7, 142.0, 137.3, 133.0, 130.4, 129.5, 129.3, 128.5, 127.6, 127.1, 61.3, 60.4, 35.0, 33.5, 26.0, 14.2, 13.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3631, 3449, 3332, 3061, 3028, 2981, 2938, 2907, 2872, 1716, 1673, 1603, 1598, 1580, 1512, 1476, 1449, 1415, 1390, 1368, 1314, 1277, 1206, 1176, 1138, 1085, 1048, 1024, 1002, 973, 934, 905, 852, 834, 782, 703, 688, 640, 616.

HRMS (ESI$^+$) for C$_{22}$H$_{25}$O$_5$ [M + H]$^+$ (369.1702): 369.1697.

Synthesis of 6-(3-methoxy-benzyl)-4'-trifluoromethyl-biphenyl-2,4-dicarboxylic acid diethyl ester (67)
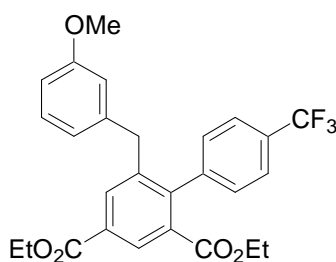
6-(Nonafluorobutane-1-sulfonyloxy)-4'-trifluoromethyl-biphenyl-2,4-dicarboxylic acid diethyl ester (**58c**, 332 mg, 0.5 mmol) and PEPPSI (6.8 mg, 2 mol %) were dissolved in THF (2 mL) and transferred via cannula to a solution with 3-methoxyphenyl-1-methylzinc chloride (**66**) (0.78 M in THF, 0.96 mL, 0.75 mmol) and the resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH$_4$Cl solution (30 mL), extracted with ether (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (DCM) furnished the compound **67** (177 mg, 73%) as a clear colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.43 (d, *J* = 1.7 Hz, 1 H), 8.11 (d, *J* = 1.9 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 7.75 (t, *J* = 7.9 Hz, 1 H), 6.68 (dd, *J* = 7.7, 2.6 Hz, 1 H), 6.38 (d, *J* = 7.5 Hz, 1 H), 6.30 (s, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 4.00 (q, *J* = 7.3 Hz, 2 H), 3.77 (s, 2 H), 3.69 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C (75 MHz, CDCl$_3$) δ: 167.1, 165.5, 159.6, 144.6, 142.8, 141.2, 140.2, 134.2, 132.6, 130.3, 129.9, 129.3, 129.1, 124.7 (d, *J* (C – F) = 3.6 Hz), 124.1 (d, *J* (C – F) = 271.9 Hz), 121.0, 119.8, 114.5, 111.5, 61.4, 61.2, 55.0, 39.4, 14.3, 13.5.

IR (ATR) $\widetilde{V}$ (cm^{-1}): 2983, 2940, 2838, 1719, 1600, 1585, 1490, 1466, 1454, 1439, 1405, 1392, 1368, 1322, 1242, 1223, 1161, 1121, 1107, 1067, 1050, 1024, 1006, 951, 923, 862, 842, 770, 724, 689, 657, 619.

HRMS (ESI$^+$) for C$_{27}$H$_{29}$F$_3$NO$_5$ [M + H]$^+$ (504.1998): 504.1991.

3.4. Directed *ortho*- and *meta*-Magnesiation of Polyfunctional *N*-Aryl and *N*-Heteroaryl Trifluoroacetylamides

3.4.1. Starting Material Synthesis

Synthesis of *N*-(3-chlorophenyl)-2,2,2-trifluoroacetamide (83)
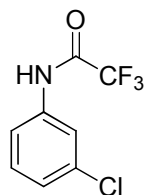
Prepared according to **TP8** from 3-chloroaniline (2.55 g, 20.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, Et$_2$O/iHex = 7:3) afforded **83** as a white solid (4.07 g, 91%). Spectral data were in full accordance with those reported in the literature: J. Salazar, S. E. López, O. Rebollo, *J. Fluorine Chem.* **2003**, *124*, 111.

Synthesis of *N*-(3,5-dichlorophenyl)-2,2,2-trifluoroacetamide (111)
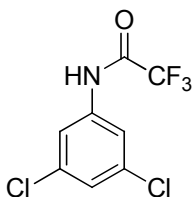
Prepared according to **TP8** from 3,5-dichloroaniline (4.86 g, 30.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, iHex/Et$_2$O = 7:3) afforded **111** as a white solid (6.76 g, 87%).

mp.: 119.5 – 121.0 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.05 (s, 1 H, NH), 7.53 (d, *J* = 1.9 Hz, 2 H), 7.23 (t, *J* = 1.9 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 155.0 (q, *J* (C – F) = 38.1 Hz), 136.7, 135.8, 126.6, 118.9, 115.4 (q, *J* (C – F) = 288.7 Hz).

IR (ATR) $\tilde{v}$ (cm^{-1}): 3293, 3202, 3144, 1706, 1617, 1590, 1555, 1419, 1342, 1298, 1257, 1154, 1116, 908, 852, 805, 742, 696, 666.

MS (EI, 70 eV) m/z (%): 257 (100), [^{35}Cl-M$^+$], 190 (46), 188 (75), 162 (32), 160 (39), 145 (28), 133 (14).

HRMS (EI) for C$_8$H$_4$^{35}Cl$_2$F$_3$NO (256.9622): 256.9632.

Synthesis of ethyl 3,5-dibromo-4-[(trifluoroacetyl)amino]benzoate (112)
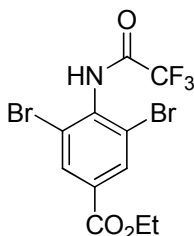
Prepared according to **TP8** from ethyl 4-amino-3,5-dibromobenzoate (12.92 g, 40.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, iHex/Et$_2$O = 6:4) afforded **112** as a white solid (14.98 g, 90%).

mp.: 144.7 – 146.4 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.20 (s, 2 H), 8.08 (s, 1 H, NH), 4.38 (q, J = 7.2 Hz, 2 H), 1.39 (t, J = 6.9 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 163.4, 154.7 (q, J (C – F) = 38.1 Hz), 135.5, 133.4, 132.8, 123.2, 115.6 (q, J (C – F) = 288.4 Hz), 62.2, 14.2.

IR (ATR) $\tilde{v}$ (cm^{-1}): 3268, 1742, 1705, 1528, 1378, 1287, 1251, 1210, 1148, 1112, 1014, 898, 865, 828, 765, 748, 691.

MS (EI, 70 eV) m/z (%): 419 (9) [^{79}Br-M$^+$], 374 (13), 343 (97), 341 (100), 315 (26), 313 (26).

HRMS (EI) for C$_{11}$H$_8$^{79}Br$_2$F$_3$NO$_3$ (416.8823): 416.8826.

Synthesis of *N*-(3-cyanophenyl)-2,2,2-trifluoroacetamide (113)
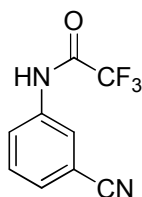
Prepared according to **TP8** from 3-aminobenzonitrile (2.36 g, 20.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 9:1) afforded **113** as a white solid (3.94 g, 92%).

mp.: 175.8 – 177.2 °C.

IR (ATR) $\tilde{V}$ **(cm^{-1}):** 3273, 3119, 2246, 1726, 1619, 1594, 1567, 1480, 1442, 1327, 1287, 1278, 1260, 1208, 1185, 1169, 1148, 1138, 1129, 1104, 996, 947, 896, 888, 799, 746, 718, 680.

MS (EI, 70 eV) m/z (%): 214 (100) [^{79}Br-M$^+$], 145 (70), 117 (32), 102 (27), 90 (15).

HRMS (EI) for C$_9$H$_5$F$_3$N$_2$O (214.0354): 214.0345.

^{1}H-NMR and ^{13}C-NMR spectral data were in full accordance with those reported in the literature: C. -Z. Tao, J. Li, Y. Fu, L. Liu, Q. -X. Guo, *Tetrahedron Lett*. **2008**, *49*, 70.

Synthesis of *N*-(3-chloro-4-cyanophenyl)-2,2,2-trifluoroacetamide (114):
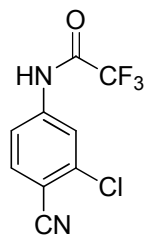
Prepared according to **TP8** from 4-amino-2-chlorobenzonitrile (6.10, 40.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 9:1) afforded **114** as a white solid (4.87 g, 98%).

m.p.: 107.0 – 109.0 °C.

^{1}**H-NMR (CDCl$_3$, 300 MHz) δ:** 8.20 (s, 1 H, NH), 7.93 (d, *J* = 2.1 Hz, 1 H), 7.71 (d, *J* = 8.6 Hz, 1 H), 7.60 (dd, *J* = 8.6, 2.1 Hz, 1 H).

^{13}**C-NMR (CD$_3$O, 100 MHz) δ:** 157.0 (q, *J* (C – F) = 38.5 Hz), 143.2, 138.3,136.0, 122.4, 120.3, 116.9 (q, *J* (C – F) = 287.5 Hz), 116.5, 110.3.

MS (EI, 70 eV) m/z (%): 248 (100) [^{35}Cl-M$^+$], 153 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3294, 2236, 1736, 1597, 1535, 1493, 1406, 1298, 1240, 1220, 1206, 1194, 1156, 1146, 1133, 1054, 930, 892, 877, 829, 710, 697, 688.

HRMS (EI) for C$_9$H$_4$ON$_2$^{35}ClF$_3$ (247.9964): 247.9969.

Synthesis of *N*-[2-chloro-5-(trifluoromethyl)phenyl]-2,2,2-trifluoroacetamide (118)
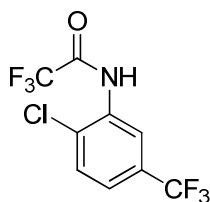
Prepared according to **TP8** from 2-chloro-5-5-(trifluoromethyl)aniline (3.91 g, 20.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 7:3) afforded **118** as a white solid (5.60 g, 96%).

m.p.: 78.8 – 80.03 °C

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.66 (d, *J* = 1.8 Hz, 1 H), 8.49 (s, 1H, NH), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.46 (dd, *J* = 8.4 Hz, 1.8, 1H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 154.8 (q, *J* (C − F) = 38.2 Hz), 132.7, 130.8 (q, *J* = 33.6 Hz), 129.97, 127.11 (d, *J* (C − F) = 1.3 Hz), 123.4 (q, *J* (C − F) = 3.8 Hz), 123.1 (q, *J* (C − F) = 272.6 Hz), 118.76 (q, *J* (C − F) = 4.0 Hz), 115.4 (q, *J* (C − F) = 288.6 Hz).

MS (EI, 70 eV) m/z (%): 292 (9) [^{35}Cl-M$^+$], 204 (23), 202 (100), 43 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3270, 1719, 1614, 1589, 1544, 1479, 1427, 1329, 1286, 1264, 1238, 1178, 1158, 1141, 1118, 1082, 1054, 954, 936, 908, 882, 822, 766, 735, 716, 697.

HRMS (EI) for C$_9$H$_4$ON$_2$^{35}ClF$_3$ [M+H]$^+$ (291.9964): 291.9955.

Synthesis of methyl 3,5-dibromo-4-[(trifluoroacetyl)amino]benzoate (119)
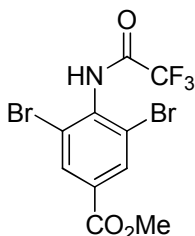
Prepared according to **TP8** from methyl 4-amino-3,5-dibromobenzoate (6.20 g, 20.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 6:4) afforded **119** as a white solid (17.45 g, 92%).

mp.: 114.8 – 116.5 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.24(s, 2 H), 7.92 (s, 1 H, NH), 3.94 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 163.4, 154.2 (q, *J* (C – F) = 38.5 Hz), 135.1, 133.1, 132.0, 122.8, 115.2 (d, *J* (C – F) = 288.4 Hz), 52.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3221, 3076, 2362, 1726, 1566, 1532, 1436, 1380, 1283, 1202, 1159, 1125, 978, 918, 898, 763, 745, 696.

MS (EI, 70 eV) m/z (%): 405 (10) [^{79}Br-M$^+$], 374 (9), 327 (10), 326 (98), 325 (10), 324 (100).

HRMS (EI) for C$_{10}$H$_6$^{79}Br$_2$F$_3$NO$_3$ (402.8667): 402.8657.

Synthesis of 2, 2, 2-trifluoro-*N*-pyridin-3-ylacetamide (120)
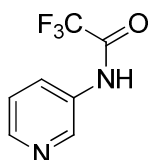
Prepared according to **TP8** from 3-aminopyridine (1.88 g, 20.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, EtOAc) afforded **120** as a white solid (3.51 g, 92%).

mp.: 128.0 – 130.6 °C.

^{1}H-NMR (DMSO-d6, 400 MHz) δ: 11.49 (s, 1 H, NH), 8.83 (s, 1 H), 8.42 (d, J = 4.7 Hz, 1 H), 8.07 (d, J = 8.4 Hz, 1 H), 7.44 (q, J = 4.7 Hz, 1 H).

^{13}C-NMR (DMSO-d6, 100 MHz) δ: 154.9 (q, J (C – F) = 37.4 Hz), 146.5, 142.5, 133.2, 128.4, 123.8, 115.6 (q, J (C – F) = 288.5 Hz).

IR (ATR) $\widetilde{v}$ (cm^{-1}): 2770, 1719, 1625, 1595, 1563, 1480, 1436, 1327, 1266, 1209, 1194, 1168, 1147, 1132, 1049, 1023, 884, 846, 813, 755, 734, 701.

MS (EI, 70 eV) m/z (%): 190 (100) [M$^+$], 121 (22), 78 (28).

HRMS (EI) for C$_7$H$_5$F$_3$N$_2$O (190.0354): 190.0334.

Synthesis of *N*-(2-chloropyridin-3-yl)-2,2,2-trifluoroacetamide (123)
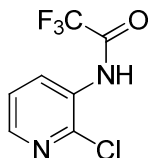
Prepared according to **TP8** from 3-amino-2-chloropyridine (3.86 g, 30.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, DCM) afforded **123** as a white solid (6.28 g, 93%).

mp.: 110.4 – 112.6 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.66 (dd, J = 8.0, 1.6 Hz, 1 H), 8.42 (s, 1 H, NH), 8.24 (d, J = 5.0 Hz, 1 H) 7.34 (q, J = 4.7 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 155.1 (q, J (C – F) = 38.1 Hz), 146.0, 140.8, 129.5, 129.4, 123.5, 115.2 (q, J (C – F) = 288.4 Hz).

IR (ATR) $\widetilde{v}$ (cm^{-1}): 3144, 2851, 1728, 1543, 1421, 1340, 1288, 1248, 1211, 1139, 1086, 912, 856, 807, 747, 726, 692.

MS (EI, 70 eV) m/z (%): 224 (39) [^{35}Cl-M$^+$], 189 (100), 119 (33), 91 (12).

HRMS (EI) for C$_7$H$_4$^{35}ClF$_3$N$_2$O (223.9964): 223.9968.

Synthesis of 2,2,2-trifluoro-*N*-pyrazin-2-ylacetamide (124)
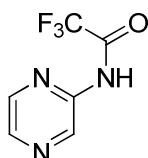
Prepared according to **TP8** from aminopyrazine (2.85 g, 30.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, DCM/EtOAc = 1:1) afforded **124** as a yellow solid (4.35 g, 76%).

mp.: 210.6 – 212.6 °C.

^{1}H-NMR (DMSO-d6, 400 MHz) δ: 12.32 (s, 1 H, NH), 9.18 (s, 1 H), 8.54 – 8.53 (m, 2 H).

^{13}C-NMR (DMSO-d6, 100 MHz) δ: 155.5 (q, *J* (C – F) = 38.4 Hz), 147.1, 143.2, 142.1, 138.1, 115.7 (q, *J* (C – F) = 288.3 Hz).

IR (ATR) $\tilde{v}$ (cm^{-1}): 3180, 3109, 2995, 2928, 1729, 1599, 1560, 1459, 1419, 1342, 1298, 1276, 1207, 1144, 1060, 1018, 893, 857, 809, 739.

MS (EI, 70 eV) m/z (%): 191 (78), [M$^+$], 122 (36), 88 (15), 79 (37), 70 (15), 61 (17), 44 (34), 43 (100).

HRMS (EI) for C$_6$H$_4$F$_3$N$_3$O (191.0306): 191.0299.

3.5.2. Metalations with TMPMgCl·LiCl (7) or TMP$_2$Mg·2LiCl (9)

Synthesis of *N*-(2-allyl-3-chlorophenyl)-2,2,2-trifluoroacetamide (117a)
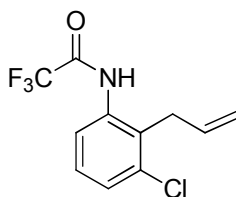
Prepared according to **TP9** from *N*-(3-chlorophenyl)-2,2,2-trifluoroacetamide **83** (224 mg, 1.0 mmol, 1.0 equiv) with TMP$_2$Mg·2LiCl (**9**) (0.76 M in THF, 1.3 mmol, 1.3 equiv) and allyl bromide (133 mg, 1.1 mmol, 1.1 equiv) according to **TP12**. Metalation conditions: 25 °C, 5 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 7:3) afforded **117a** as a yellow solid (169 mg, 64%).

mp.: 80.3 – 82.3 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.08 (s, 1 H, NH), 7.81 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.35 – 7.22 (m, 2 H), 5.99 – 5.86 (m, 1 H), 5.26 – 5.07 (m, 2 H), 3.63 (d, *J* = 6.1 Hz, 2 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 154.9 (q *J* (C – F) = 37.6 Hz), 134.9, 133.7, 128.6, 128.3, 127.9, 122.1, 117.7, 117.3, 115.8 (d *J* (C – F) = 288.7 Hz), 33.2.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3244, 1706, 1577, 1542, 1446, 1344, 1263, 1152, 992, 932, 913, 784, 745, 659.

MS (EI, 70 eV) m/z (%): 264 (14), [^{35}Cl-M$^+$], 263 (100), 196 (26), 194 (71), 168 (29), 166 (89), 164 (21), 159 (12), 153 (19), 131 (51), 130 (43), 115 (27), 103 (11), 77 (13).

HRMS (EI) for C$_{11}$H$_9$^{35}ClF$_3$NO (263.0325): 263.0319.

Synthesis of *N*-(6-chloro-4'-methylbiphenyl-2-yl)-2,2,2-trifluoroacetamide (117b)
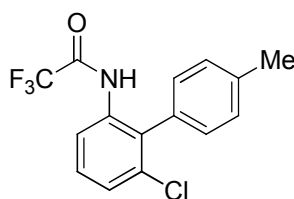
Prepared according to **TP9** from *N*-(3-chlorophenyl)-2,2,2-trifluoroacetamide **83** (448 mg, 2.0 mmol, 1.0 equiv) with TMP$_2$Mg·2LiCl (**9**) (0.76 M in THF, 2.6 mmol, 1.3 equiv) and 4-iodotoluene (480 mg, 2.2 mmol, 1.1 equiv) according to **TP10**. Metalation conditions: 25 °C, 5 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 92:8) afforded **117b** as a yellow oil (402 mg, 64%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.28 (q, *J* = 4.4 Hz, 1 H), 7.72 (s, 1 H, NH), 7.38 – 7.32 (m, 4 H), 7.16 (d, *J* = 8.3 Hz, 2 H), 2.45 (s, 3 H).

^{13}**C-NMR (CDCl$_3$, 75 MHz) δ:** 154.3 (d, *J* (C – F) = 37.4 Hz), 139.3, 134.6, 134.2, 131.5, 130.3, 130.2, 129.4, 129.3, 126.8, 115.4 (q, *J* (C – F) = 289.2 Hz), 118.8, 21.4.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3389, 1735, 1600, 1579, 1534, 1440, 1331, 1278, 1156, 1132, 1006, 910, 892, 882, 818, 785, 741, 728.

MS (EI, 70 eV) m/z (%): 314 (13), [^{35}Cl-M$^+$], 313 (100), 244 (10), 180 (11).

HRMS (EI) for C$_{15}$H$_{11}$^{35}ClF$_3$NO (313.0481): 313.0487.

Synthesis of *N*-(3,5-dichloro-2-iodophenyl)-2,2,2-trifluoroacetamide (117c)
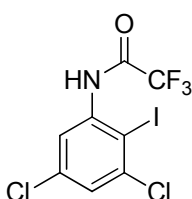
Prepared according to **TP9** from *N*-(3,5-dichlorophenyl)-2,2,2-trifluoroacetamide **111** (258 mg, 1.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 1.2 mmol, 1.2 equiv) and neat iodine (279 mg, 1.1 mmol, 1.1 equiv). Metalation conditions: 25 °C, 4 h. The reaction mixture was quenched with sat. aq. Na$_2$S$_2$O$_3$ and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 9:1) afforded **117c** as a yellow solid (275 mg, 72%).

mp.: 115.0 – 116.7 °C.

^{1}**H-NMR (CDCl$_3$, 300 MHz) δ:** 8.49 (s, 1 H, NH), 8.23 (d, *J* = 2.5 Hz, 1 H), 7.39 (d, *J* = 2.77 Hz, 1 H).

^{13}**C-NMR (CDCl$_3$, 100 MHz) δ:** 154.9 (q, *J* (C – F) = 38.4 Hz), 140.1, 138.3, 136.2, 126.5, 119.6, 115. 3 (d, *J* = 288.7 Hz), 93.0.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3260, 2361, 1713, 1562, 1531, 1402, 1388, 1332, 1260, 1192, 1156, 1018, 941, 917, 857, 810, 746.

MS (EI, 70 eV) m/z (%): 384 (<3), [^{35}Cl-M$^+$], 383 (27), 258 (57), 256 (100), 236 (20), 159 (13).

HRMS (EI) for C$_8$H$_3$^{35}Cl$_2$F$_3$INO (382.8588): 382.8588.

Synthesis of ethyl 2-{2,4-dichloro-6-[(trifluoroacetyl)amino]benzyl}acrylate (117d)
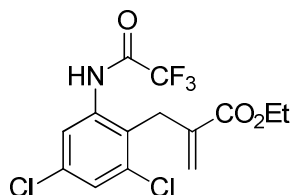
Prepared according to **TP9** from *N*-(3,5-dichlorophenyl)-2,2,2-trifluoroacetamide **111** (258 mg, 1.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 1.2 mmol, 1.2 equiv) and ethyl (2-bromomethyl)acrylate (211 mg, 1.1 mmol, 1.1 equiv) according to **TP12**. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 9:1) afforded **117d** as a white solid (256 mg, 70%).

mp.: 83.5 – 85.3 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 10.93 (s, 1 H, NH), 7.73 (d, *J* = 1.9 Hz, 1 H), 7.29 (d, *J* = 2.1 Hz, 1 H), 6.46 (s, 1 H), 6.17 (d, *J* = 1.2 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.67 (s, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 168.7, 155.9 (q, *J* (C – F) = 38.1 Hz), 136.7, 135.7, 135.2, 133.5, 131.6, 127.9, 127.5, 123.9, 115.6 (d, *J* (C – F) = 288.4 Hz), 62.1, 31.5, 13.9.

IR (ATR) $\widetilde{V}$ (cm^{-1}): 3170, 2992, 1726, 1683, 1626, 1569, 1527, 1472, 1440, 1410, 1376, 1339, 1309, 1260, 1218, 1190, 1155, 1132, 1092, 1014, 957, 925, 895, 858, 847, 821, 780, 737, 706, 653.

MS (EI, 70 eV) m/z (%): 369 (12), [^{35}Cl-M$^+$], 334 (12), 324 (19), 288 (26), 230 (15), 227 (15), 226 (100), 198 (83).

HRMS (EI) for C$_{14}$H$_{12}$^{35}Cl$_2$F$_3$NO$_3$ (369.0146): 369.0137.

Synthesis of *N*-(2-bromo-3, 5-dichlorophenyl)-2, 2, 2-trifluoroacetamide (117e)
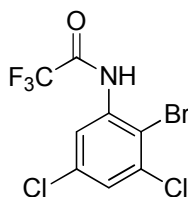
Prepared according to **TP9** from *N*-(3,5-dichlorophenyl)-2,2,2-trifluoroacetamide **111** (1.03 g, 4.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 4.8 mmol, 1.2 equiv) at 25 °C for 4 h. Neat 1, 2-dibromotetrachloroethane (1.43 g, 4.4 mmol, 1.1 equiv) was added at 0 °C, stirred for 2 h. Then, the reaction mixture was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na₂SO₄. Purification of the crude product by flash chromatography (SiO₂, *i*Hex/DCM = 9:1) afforded **117e** as a white solid (905 mg, 68%).

mp.: 97.3 – 99.6 °C.

¹H-NMR (CDCl₃, 300 MHz) δ: 8.54 (s, 1 H, NH), 8.34 (d, J = 2.5 Hz, 1 H), 7.38 (d, J = 2.5 Hz, 1 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 154.3 (d, J (C – F) = 38.1 Hz), 135.5, 134.9, 134.4, 126.8, 119.5, 113.0 (q, J (C – F) = 288.7 Hz), 112.4.

IR (ATR) $\tilde{V}$ **(cm⁻¹):** 3266, 1715, 1570, 1533, 1416, 1394, 1335, 1266, 1190, 1156, 1034, 944, 919, 859, 818, 764, 748, 689.

MS (EI, 70 eV) m/z (%): 337 (29) [³⁵Cl-M⁺], 335 (18), 260 (11), 258 (65), 256 (100), 238 (11), 236 (15), 159 (11).

HRMS (EI) for C₈H₃⁷⁹Br³⁵Cl₂F₃NO (334.8727): 334.8710.

Synthesis of *N*-(2-bromo-3,5-dichloro-6-iodophenyl)-2,2,2-trifluoroacetamide (117f)
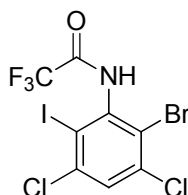
Prepared according to **TP9** from *N*-(3,5-dichlorophenyl)-2,2,2-trifluoroacetamide **117e** (1.03 g, 4.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 4.8 mmol, 1.2 equiv) at 25 °C for 4 h. Neat iodine (280 mg, 1.1 mmol, 1.1 equiv) was added at 0 °C and stirred to 25 °C for 30 min. Then, the reaction mixture was quenched with sat. aq. Na₂S₂O₃ and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na₂SO₄.

Purification of the crude product by flash chromatography (SiO$_2$, i-Hex/DCM = 1:1) afforded **117f** as a yellow solid (318 mg, 69%).

mp.: 143.6 – 145.6 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.65 (s, 1 H)

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 154.6 (d, J (C – F) = 38.7 Hz), 139.5, 137.8, 136.7, 129.9, 121.7, 113.7 (q, J (C – F) = 288.7 Hz), 102.4.

IR (ATR) $\widetilde{v}$ **(cm^{-1}):** 3203, 3052, 1725, 1554, 1527, 1388, 1364, 1338, 1197, 1163, 1053, 951, 913, 866, 842, 751, 696.

MS (EI, 70 eV) m/z (%): 463 (23) [^{35}Cl-M$^+$], 461 (13), 384 (44), 382 (68), 338 (44), 337 (12), 336 (100), 334 (58), 316 (14), 255 (14), 239 (13), 128 (13), 127 (12), 122 (10).

HRMS (EI) for C$_8$H$_2$^{79}Br^{35}Cl$_2$F$_3$NO (460.7694): 460.7693.

Synthesis of N-[3,5-dichloro-2-(methylthio)phenyl]-2,2,2-trifluoroacetamide (117g)
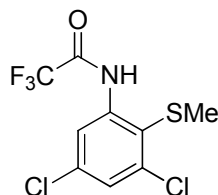
Prepared according to **TP9** from N-(3,5-dichlorophenyl)-2,2,2-trifluoroacetamide **111** (1.03 g, 4.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 4.8 mmol, 1.2 equiv) at 25 °C for 4 h. Neat S-methyl methanethiolsulfonate (245 mg, 4.4 mmol, 1.1 equiv) was addead at –20 °C and stirred for 2 h. Then, the reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, iHex/Et$_2$O = 9:1) afforded **117g** as a yellow solid (925 mg, 76%).

mp.: 73.6 – 75.4 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 9.83 (s, 1 H, NH), 8.46 (d, J = 2.1 Hz, 1 H), 7.35 (d, J = 2.1 Hz, 1 H), 2.35 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 154.8 (q, J (C – F) = 38.1 Hz), 141.1, 139.5, 136.7, 126.7, 122.5, 118.5, 115.5 (d, J (C – F) = 288.7 Hz), 18.2.

IR (ATR) $\widetilde{v}$ **(cm^{-1}):** 3309, 1714, 1564, 1531, 1398, 1326, 1262, 1148, 976, 912, 861, 854, 825, 753, 746, 714.

MS (EI, 70 eV) m/z (%): 303 (100), [^{35}Cl-M$^+$], 258 (33), 256 (58), 236 (83), 234 (72), 221 (17), 219 (25), 216 (17), 191 (15), 170 (17), 156 (14), 45 (16).

HRMS (EI) for C$_9$H$_6$^{35}Cl$_2$F$_3$NO^{32}S (302.9499): 302.9482.

Synthesis of [2-amino-4,6-dichloro-3-(methylthio)phenyl](4-chlorophenyl)methanone (117h)
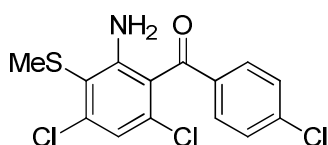
Prepared according to **TP9** from *N*-[3,5-dichloro-2-(methylthio)phenyl]-2,2,2-trifluoroacetamide **117g** (700 mg, 2.3 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 2.8 mmol, 1.2 equiv) and 4-chlorobenzoyl chloride (443 mg, 2.53 mmol, 1.1 equiv) according to **TP11**. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 9:1) afforded **117h** as a white solid (645 mg, 81%).

mp.: 177.6 – 179.4 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 9.80 (s, 1 H, NH), 8.69 (d, *J* = 2.2 Hz, 1 H), 7.87 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 2.36 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 164.1, 141.9, 140.6, 138.8, 136.6, 132.6, 129.3, 128.5, 124.8, 121.2, 118.0, 18.3.

IR (ATR) $\widetilde{v}$ **(cm^{-1}):** 3294, 1652, 1567, 1557, 1513, 1484, 1407, 1388, 1290, 1277, 1243, 1178, 1123, 1092, 1014, 978, 940, 902, 846, 818, 752, 742.

MS (EI, 70 eV) m/z (%): 347 (18) [^{35}Cl, ^{32}S-M$^+$], 345 (17), 302 (25), 301 (12), 300 (68), 299 (14), 298 (70), 139 (100), 111 (37).

HRMS (EI) for C$_{14}$H$_{10}$^{35}Cl$_3$NO^{35}S (344.9549): 344.9531.

Synthesis of *N*-[6-chloro-2-(methylthio)-3-(trifluoromethyl)phenyl]-2,2,2-trifluoroacetamide (117i)
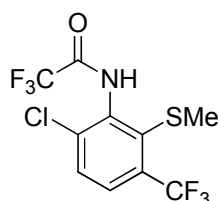
Prepared according to **TP9** from *N*-[2-chloro-5-(trifluoromethyl)phenyl]-2,2,2-trifluoroacetamide **118** (583 mg, 2.0 mmol, 1.0 equiv) with TMP$_2$Mg·2LiCl (**9**) (0.76 M in THF, 1.3 mmol, 1.3 equiv) at 25 °C for 8 h. Neat S-methyl methanethiolsulfonate (245 mg, 2.2 mmol, 1.1 equiv) was addead at –20 °C, stirred for 2h and quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 7:3) afforded **117i** as a yellow solid (505 mg, 75%).

mp.: 148.4 – 150.1 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.23 (s, 1 H, NH), 7.79 (d, J = 8.6 Hz, 1 H), 7.63 (d, J = 8.6 Hz, 1 H), 2.28 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 155.4 (q, J (C – F) = 38.1 Hz), 136.8, 134.9, 134.4, 134.0, 131.2, 127.2 (q, J (C – F) = 5.6 Hz), 122.8 (d, J (C – F) = 273.8 Hz), 115.7 (q, J (C – F) = 288.3 Hz), 19.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3196, 3053, 1711, 1575, 1535, 1401, 1320, 1241, 1153, 1126, 1100, 972, 943, 905, 833, 809, 769, 732, 667.

MS (EI, 70 eV) m/z (%): 338 (12), [^{35}Cl-M$^+$], 337 (100), 290 (44), 252 (12), 250 (16), 238 (17), 222 (14), 220 (33), 170 (14).

HRMS (EI) for C$_{10}$H$_6$^{35}ClF$_6$NO^{32}S (336.9763): 336.9731.

Synthesis   of   *N*-[6-chloro-2-cyclohex-2-en-1-yl-3-(trifluoromethyl)phenyl]-2,2,2-trifluoroacetamide (117j)
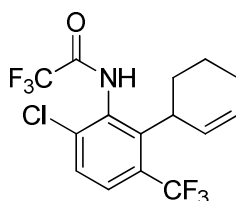
Prepared according to **TP9** from *N*-[2-chloro-5-(trifluoromethyl)phenyl]-2,2,2-trifluoroacetamide **118** (583 mg, 2.0 mmol, 1.0 equiv) with TMP$_2$Mg·2LiCl (**9**) (0.76 M in THF, 1.3 mmol, 1.3 equiv) and 3-bromocyclohexene (354 mg, 2.2 mmol, 1.1 equiv) according to **TP12**. Metalation conditions: 25 °C, 8 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 98:2) afforded **117j** as a yellow solid (490 mg, 66%).

m.p.: 199.1 – 200.6 °C.

^{1}H-NMR (CD$_3$OD, 400 MHz) δ: 7.76 (d, *J* = 8.6 Hz, 1 H), 7.64 (d, *J* = 8.6 Hz, 1 H), 5.92 – 5.42 (m, 2 H), 3.98 – 3.85 (m, 1 H), 2.17 – 1.44 (m, 6 H).

^{13}C-NMR (CD$_3$OD, 100 MHz) δ: 156.1 (d, *J* (C – F) = 250.8 Hz), 146.8 (d, *J* (C – F) = 24.5 Hz), 140.3 (*J* (C – F) = 25.2 Hz), 134.5 (d, *J* (C – F) = 12.1 Hz), 129.7 – 129.1 (m), 128.6 (d, *J* (C – F) = 6.4 Hz), 127.9, 126.7, 124.0, 121.3, 117.4 (q, *J* (C – F) = 287.2 Hz), 39.9, 30.0 (d, *J* (C – F) = 27.3 Hz), 25.3, 23.9 (d, *J* (C – F) = 17.6 Hz).

MS (EI, 70 eV) m/z (%): 371 (93) [^{35}Cl-M$^+$], 304 (30), 302 (100), 276 (24), 274 (87), 234 (20), 232 (53).

IR (ATR) $\widetilde{V}$ (cm^{-1}): 3244, 2934, 1714, 1593, 1532, 1450, 1423, 1315, 1261, 1239, 1228, 1194, 1176, 1163, 1144, 1104, 1048, 994, 935, 911, 826, 814, 769, 754, 730, 722, 703.

HRMS (EI) for C$_{15}$H$_{12}$^{35}ClF$_6$NO (371.0512): 371.0508.

Synthesis of *N*-(3-cyano-2-cyclohex-2-en-1-ylphenyl)-2,2,2-trifluoroacetamide (117k)
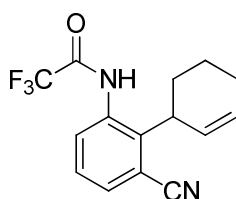
Prepared according to **TP9** from *N*-(3-cyanophenyl)-2,2,2-trifluoroacetamide **113** (427 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 4.0 mmol, 2.0 equiv) and 3-bromocyclohexene (354 mg, 2.2 mmol, 1.1 equiv) according to **TP12**. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 1:1) afforded **117k** as a yellow solid (382 mg, 65%).

mp.: 58.0 – 60.3 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 9.10 (s, 1 H, NH), 8.38 (d, *J* = 7.2 Hz, 1 H), 7.52 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 6.28 – 6.23 (m, 1 H), 5.82 (d, *J* = 9.9 Hz, 1 H), 4.21 – 4.13 (m, 1 H), 2.28 – 1.92 (m, 4 H), 1.83 – 1.53 (m, 2 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 154.7 (q, *J* (C – F) = 37.9 Hz), 137.8, 135.2, 134.0, 130.6, 128.1, 127.0, 126.9, 117.3, 115.7 (q, *J* (C – F) = 288.9 Hz), 114.1, 40.3, 28.2, 24.5, 21.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3267, 2228, 1730, 1602, 1544, 1463, 1436, 1274, 1256, 1159, 949, 900, 874, 799, 762, 737, 711, 669.

MS (EI, 70 eV) m/z (%): 294 (100) [M$^+$], 293 (19), 226 (15), 225 (83), 207 (12), 197 (38), 195 (14), 182 (13), 180 (11), 169 (15), 155 (33), 143 (11).

HRMS (EI) for C$_{15}$H$_{13}$F$_3$N$_2$O (294.0980): 294.0965.

Synthesis of *N*-(6-cyano-4'-methoxybiphenyl-2-yl)-2,2,2-trifluoroacetamide (117l)
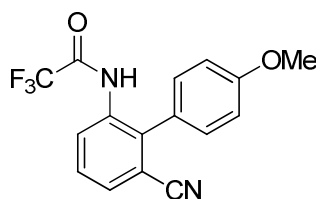
Prepared according to **TP9** from *N*-(3-cyanophenyl)-2,2,2-trifluoroacetamide **113** (427 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 4.0 mmol, 2.0 equiv) and iodoanisole (514 mg, 2.2 mmol, 1.1 equiv) according to **TP10**. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 9:1) afforded **117l** as a white solid (480 mg, 75%).

m.p.: 110.5 – 118.5 °C.

^{1}H-NMR (CD$_3$O, 400 MHz) δ: 7.80 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.78 (dd, *J* = 8.1, 1.3 Hz, 1 H),

7.57 (dd, *J* = 7.8, 8.1 Hz, 1 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.2 Hz, 2 H), 3.85 (s, 3 H).

^{13}C-NMR (CD$_3$O, 100 MHz) δ: 161.8, 157.7 (q, *J* (C – F) = 37.6 Hz), 143.5, 135.3, 133.7,

132.9, 131.7, 129.9, 127.6, 118.5, 117.2 (d, *J* (C – F) = 287.2 Hz), 115.4, 115.1, 55.8.

IR (ATR) $\widetilde{v}$ (cm^{-1}): 3260, 2242, 1724, 1605, 1547, 1516, 1464, 1440, 1274, 1251, 1209, 1181,

1162, 1147, 1117, 1039, 896, 853, 815, 799, 752, 738, 670.

MS (EI, 70 eV) m/z (%): 320 (100) [^{35}Cl-M$^+$], 251 (7), 208 (7), 179 (10).

HRMS (EI) for C$_{16}$H$_{11}$O$_2$N$_2$F$_3$ (320.0773): 320.0772.

Synthesis of ethyl 2'-chloro-3'-cyano-6'-[(trifluoroacetyl)amino]biphenyl-4-carboxylate (117m)
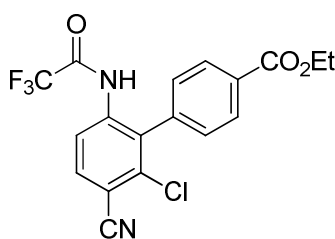
Prepared according to **TP9** from *N*-(3-chloro-4-cyanophenyl)-2,2,2-trifluoroacetamide **114** (497 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.07 M in THF, 2.4 mmol, 1.2 equiv) and ethyl 4-iodobenzoate (607 mg, 2.2 mmol, 1.1 equiv) according to **TP10**. Metalation conditions: 25 °C, 2 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 9:1) afforded **117m** as a white solid (500 mg, 63%).

m.p.: 131.7 – 133.5 °C.

^{1}H-NMR (CD$_3$OD, 400 MHz) δ: 8.13 (ddd, J = 8.1, 2.3, 1.7 Hz, 2 H), 7.95 (d, J =8.4 Hz, 1 H), 7.71 (d, J = 8.4 Hz, 1 H), 7.38 (ddd, J = 8.1, 2.3, 1.7 Hz, 2 H), 4.41 (q, J =7.1 Hz, 2 H), 1.41 (t, J = 7.1 Hz, 3 H).

^{13}C-NMR (CD$_3$OD, 100 MHz) δ: 167.4, 157.2 (q, J (C − F) = 38.2 Hz), 139.8, 139.7, 139.6, 137.5, 135.3, 132.1, 131.0, 130.6, 127.6, 117.0 (d, J (C − F) = 287.3 Hz), 116.5, 114.3, 62.4, 14.6.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3250, 2231, 1739, 1710, 1580, 1532, 1459, 1394, 1296, 1278, 1268, 1212, 1157, 1142, 1114, 1100, 1092, 1066, 1022, 901, 856, 835, 774, 752, 714, 701, 681, 667.

MS (EI, 70 eV) m/z (%): 396 (59) [^{35}Cl-M$^+$], 368 (51), 353 (33), 352 (20), 351 (100), 302 (31), 301 (17), 300 (96), 257 (17), 255 (59), 227 (14), 226 (27), 192 (58), 191 (28), 164 (14), 104 (29), 83 (18), 73 (36), 72 (13).

HRMS (EI) for C$_{18}$H$_{12}$O$_3$N$_2$^{35}ClF$_3$ (396.0489): 396.0490.

Synthesis of N-[4,6-dibromo-3-(4-methoxyphenyl)-1-oxo-1,3-dihydro-2-benzofuran-5-yl]-2,2,2-trifluoroacetamide (117n)
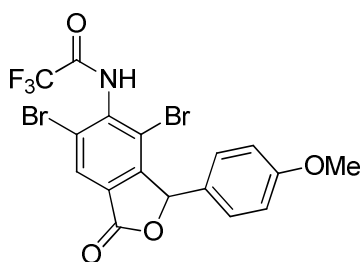
Prepared according to **TP9** from methyl 3,5-dibromo-4-[(trifluoroacetyl)amino]benzoate **119** (403 mg, 1.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 1.3 mmol, 1.3 equiv) at 25 °C for 4 h. Neat 4-methoxybenzaldehyde (177 mg, 1.3 mmol, 1.3 equiv) was added at 25 °C and stirred for 4 h. The reaction mixture was then quenched with sat. aq. NH$_4$Cl and extracted

with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, Et_2O/iHex = 3:2) afforded **117n** as a yellow solid (361 mg, 71%).

mp.: 101.5 – 103.4 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.20 (s, 1 H), 8.02 (s, 1 H, NH), 7.09 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.24 (s, 1 H), 3.81 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 166.5, 160.4, 154.3 (d, *J* (C – F) = 39.0 Hz), 148.4, 136.7, 129.5, 128.7, 128.6, 124.3, 124.3, 119.0, 115.1 (d, *J* (C – F) = 288.4 Hz), 114.0, 83.1, 54.9.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3223, 1740, 1610, 1515, 1402, 1311, 1252, 1211, 1163, 1083, 1030, 968, 914, 834, 813, 760, 726, 651.

MS (EI, 70 eV) m/z (%): 509 (100) [M$^+$], 508 (13), 507 (53), 384 (30), 376 (20), 374 (32), 372 (16), 326 (59), 324 (59), 305 (17), 290 (20), 136 (13), 135 (26), 74 (30), 73 (40), 61 (25), 59 (41), 45 (58), 43 (32).

HRMS (EI) for C$_{17}$H$_{10}$^{79}Br$_2$F$_3$NO$_4$ (506.8929): 506.8914.

Synthesis of ethyl 3,5-dibromo-2-[2-(ethoxycarbonyl)prop-2-en-1-yl]-4-[(trifluoroacetyl)amino]benzoate (117o)
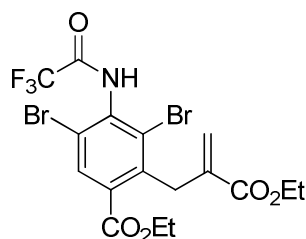
Prepared according to **TP9** from ethyl 3, 5-dibromo-4-[(trifluoroacetyl)amino]benzoate **112** (1.03 g, 4.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 4.8 mmol, 1.2 equiv) and ethyl 2-(bromomethyl)acrylate (425 mg, 2.2 mmol, 1.1 equiv) according to TP12. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO_2, Et_2O/iHex = 6:4) afforded **117o** as a white solid (797 mg, 75%).

mp.: 63.6 – 65.2 °C.

¹H-NMR (CDCl₃, 600 MHz) δ: 8.14 (s, 1 H, NH), 8.08 (s, 1 H), 6.17 (s, 1 H), 4.96 (s, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.11 (s, 2 H), 1.34–1.29 (m, 6 H).

¹³C-NMR (CDCl₃, 150 MHz) δ: 166.2, 164.8, 154.5 (d, J (C – F) = 38.4 Hz), 139.7, 136.9, 134.8, 134.2, 133.5, 128.4, 124.8, 121.0, 115.4 (q, J (C – F) = 288.3 Hz), 62.1, 60.9, 35.6, 13.9, 13.8.

IR (ATR) $\widetilde{v}$ (cm⁻¹): 3234, 2988, 1751, 1710, 1634, 1554, 1526, 1455, 1400, 1367, 1339, 1287, 1254, 1204, 1147, 1112, 1018, 958, 906, 858, 811, 790, 739, 709, 659.

MS (EI, 70 eV) m/z (%): 531 (10), [M⁺], 452 (27), 450 (25), 407 (20), 406 (87), 405 (23), 404 (100), 378 (20), 376 (19), 334 (24), 333 (15), 332 (27), 270 (14), 82 (38), 81 (16), 80 (38), 79 (19), 44 (33).

HRMS (EI) for C₁₇H₁₆⁷⁹Br₂F₃NO₅ (528.9347): 528.9343.

Synthesis of *N*-(4-cyclohex-2-en-1-ylpyridin-3-yl)-2,2,2-trifluoroacetamide (121a)
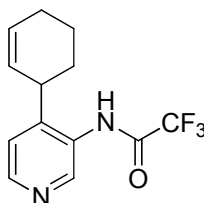
Prepared according to **TP9** from 2,2,2-trifluoro-*N*-pyridin-3-ylacetamide **120** (380 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 2.6 mmol, 1.3 equiv) and 3-bromocyclohexene (354 mg, 2.2 mmol, 1.1 equiv) according to **TP12**. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO₂, DCM/EtOAc = 4:1) afforded **121a** as a yellow oil (351 mg, 65%).

¹H-NMR (CDCl₃, 300 MHz) δ: 9.42 (s, 1 H, NH), 8.81 (s, 1 H), 8.33 (d, *J* =4.70 Hz, 1 H), 7.19 (d, *J* =4.9 Hz, 1 H), 6.08–6.09 (m, 1 H), 5.59 (d, *J* =8.4 Hz, 1 H), 3.53 – 3.48 (m, 1 H), 2.14 – 1.42 (m, 6 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 155.9 (d, *J* (C – F) = 37.8 Hz), 147.9, 145.8, 131.9, 130.2, 126.8, 124.3, 115.8 (q, *J* (C – F) = 288.6 Hz), 44.2, 38.9, 29.4, 24.5, 21.0.

IR (ATR) $\widetilde{v}$ (cm⁻¹): 3024, 2934, 1716, 1675, 1603, 1534, 1487, 1412, 1325, 1286, 1262, 1195, 1151, 1067, 1040, 987, 900, 835, 756, 726, 671.

MS (EI, 70 eV) m/z (%): 270 (72), [M$^+$], 202 (14), 201 (100), 173 (25), 171 (16), 145 (16), 131 (17).

HRMS (EI) for C$_{13}$H$_{13}$F$_3$N$_2$O (270.0980): 270.0982.

Synthesis of ethyl 4-{3-[(trifluoroacetyl)amino]pyridin-4-yl}benzoate (121b)
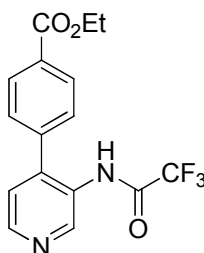
Prepared according to **TP9** from 2,2,2-trifluoro-*N*-pyridin-3-ylacetamide **120** (380 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 2.6 mmol, 1.3 equiv) and ethyl 4-iodobenzoate (607 mg, 2.2 mmol, 1.1 equiv) according to **TP10**. Metalation conditions: 25 °C, 4 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 1:1) afforded **121b** as a brown solid (450 mg, 65%).

m.p.: 93.8 – 95.5 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 9.06 (s, 1 H), 8.84 (s, 1 H, NH), 8.48 (d, *J* = 5.0 Hz, 1 H), 8.13 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 5.0 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 1.39 (t, *J* = 7.1 Hz, 3 H).

**^{13}C-NMR (CDCl$_3$, 150 MHz) δ:** 165.7, 155.5 (q, *J* (C – F) = 38.1 Hz), 147.8, 145.4, 141.9, 139.0, 131.4, 130.4, 128.8, 128.3, 124.3, 115.5 (q, *J* (C – F) = 288.5 Hz), 61.4, 14.2.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3302, 2361, 1739, 1696, 1526, 1277, 1193, 1180, 1145, 1129, 1109, 836.

MS (EI, 70 eV) m/z (%): 338 (73) [M$^+$], 310 (20), 294 (14), 293 (100).

HRMS (EI) for C$_{16}$H$_{13}$O$_3$N$_2$F$_3$ (338.0878): 338.0873.

Synthesis of *N*-[3-(2,4-dichlorobenzoyl)pyridin-2-yl]-2,2,2-trifluoroacetamide (122)
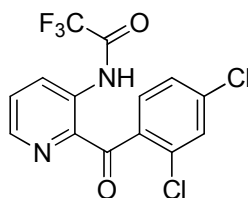
A solution of 2,2,2-trifluoro-*N*-pyridin-3-ylacetamide **120** (380 mg, 2.0 mmol, 1.0 equiv) dissolved in THF (2 mL) was cooled to 0°C and MeMgCl (2.85 M in THF, 2.2 mmol, 1.1 equiv) was added dropwise and stirred for 10 min. The reaction mixture was cooled to –20 °C and BF$_3$·OEt$_2$ (2.5 mmol, 1.25 equiv) was dropwise added and stirred for 20 min. To the mixture TMPMgCl·LiCl (**7**) (1.07 M in THF, 2.5 mmol, 1.25 equiv) was dropwise added and stirred at –20 °C for 2.5 h. CuCN·2LiCl (1 M solution in THF, 2.2 mmol, 1.1 equiv) was then added and stirred for 30 min. Then, 2,4-dichlorobenzoylchloride (461 mg, 2.2 mmol, 1.1 equiv) was added and stirred to 0 °C for 4 h. The reaction mixture was then quenched with sat. aq. NH$_4$Cl:NH$_3$ (9:1) and extracted with DCM (3 x 25 mL) and EtOAC (2 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$.After filtration, the solvent was evaporated in vacuo and purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 8:2) afforded **122** as a yellow oil (436 mg, 60%).

^{1}H-NMR (CD$_3$OD, 400 MHz) δ: 8.85 (d, *J* = 2.5 Hz, 1 H), 8.38 (dd, *J* = 8.6, 2.5 Hz, 1 H), 8.13 (d, *J* = 8.6 Hz, 1 H), 7.53 – 7.38 (m, 3 H).

^{13}C-NMR (CD$_3$OD, 100 MHz) δ: 194.1, 157.2 (q, *J* (C – F) = 38.3 Hz), 150.7, 142.2, 138.3, 138.1, 137.8, 133.7, 132.1, 130.5, 129.4, 128.1, 125.5, 117.0 (q, *J* (C – F) = 287.4 Hz).

MS (EI, 70 eV) m/z (%): 329 (29) [^{35}Cl-M$^+$], 327 (100), 173 (20).

IR (ATR) $\tilde{v}$ **(cm⁻¹):** 3296, 3068, 1734, 1718, 1676, 1581, 1546, 1481, 1470, 1390, 1376, 1310, 1291, 1263, 1229, 1206, 1143, 1103, 1058, 1021, 935, 899, 856, 844, 828, 800, 785, 739, 682, 662.

HRMS (EI) for C$_{14}$H$_7$^{35}Cl$_2$F$_3$F$_3$N$_2$O$_2$ [M-H]$^+$ (360.9837): 360.9739.

Synthesis of *N*-{2-chloro-4-[4-(trifluoromethyl)phenyl]pyridin-3-yl}-2,2,2-trifluoroacetamide (121c)
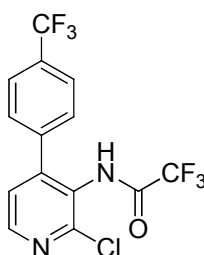
Prepared according to **TP9** from *N*-(2-chloropyridin-3-yl)-2,2,2-trifluoroacetamide **123** (448 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 3.0 mmol, 1.5 equiv) and 4-iodobenzotrifluoride (600 mg, 2.2 mmol, 1.1 equiv) according to **TP10**. Metalation conditions: 25 °C, 5 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 8:2) afforded **121c** as a brown solid (590 mg, 80%).

m.p.: 160.4 – 162.2 °C.

¹H-NMR (CDCl$_3$, 300 MHz) δ: 8.41 (d, *J* = 5.0 Hz, 1 H), 8.28 (s, 1 H, NH), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 5.0 Hz, 1 H).

¹³C-NMR (CDCl$_3$, 75 MHz) δ: 155.6 (q, *J* (C – F) = 38.6 Hz), 149.6 (d, *J* (C – F) = 36.2 Hz), 149.0, 138.9 (d, *J* (C – F) = 1.3 Hz), 131.6 (q, *J* (C – F) = 32.9 Hz), 128.1, 125.9 (q, *J* (C – F) = 3.7 Hz), 125.6, 124.2, 123.6 (q, *J* (C – F) = 272.4 Hz), 123.1 (d, *J* (C – F) = 82.6 Hz), 115.3 (q, *J* (C – F) = 288.2 Hz).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3219, 1713, 1585, 1539, 1385, 1322, 1219, 1207, 1194, 1163, 1128, 1114, 1076, 1053, 1017, 934, 848, 834, 820, 732, 653.

MS (EI, 70 eV) m/z (%): 368 (17) [^{35}Cl-M$^+$], 334 (16), 333 (100), 313 (24).

HRMS (EI) for C$_{14}$H$_7$O$_1$N$_2$^{35}ClF$_6$ (368.0151): 368.0154.

Synthesis of 2,2,2-trifluoro-*N*-[3-(1*H*-indol-2-yl)pyrazin-2-yl]acetamide (125)
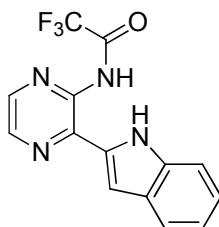
Prepared according to **TP9** from 2,2,2-trifluoro-*N*-pyrazin-2-ylacetamide **124** (382 mg, 2.0 mmol, 1.0 equiv) with TMPMgCl·LiCl (**7**) (1.10 M in THF, 2.6 mmol, 1.3 equiv) and 2-iodo-1*H*-indole (486 mg, 2.0 mmol, 1.0 equiv) according to **TP10**. Metalation conditions: 0 °C, 3 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 8:2) afforded **125** as a yellow oil (335 mg, 55%).

mp.: 232.8 – 235.0 °C.

^{1}H-NMR (DMSO-d6, 400 MHz) δ: 12.41 (s, 1 H, NH), 11.83 (s, 1 H), 9.21 (s, 1 H), 9.17 (s, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.30 (s, 1 H), 7.15 (t, *J* = 7.0 Hz, 1 H), 7.02 (t, *J* = 7.0 Hz, 1 H).

^{13}C-NMR (DMSO-d6, 100 MHz) δ: 154.9 (q, *J* (C – F) = 38.2 Hz), 144.5, 143.2, 139.6, 137.4, 136.2, 133.7, 128.0, 122.8, 120.7, 119.7, 115.3 (d, *J* (C –F) = 288.1 Hz), 111.9, 101.7.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3390, 3343, 1719, 1588, 1547, 1516, 1422, 1310, 1297, 1255, 1210, 1168, 1147, 1017, 905, 796, 750, 670.

MS (EI, 70 eV) m/z (%): 306 (100), [M$^+$], 237 (22), 167 (8).

HRMS (EI) for C$_{14}$H$_9$F$_3$N$_4$O (306.0728): 306.0731.

3.4.3. Deprotection of the trifluoroacetamide group

Synthesis of 3-(1*H*-indol-2-yl)pyrazin-2-amine (126)
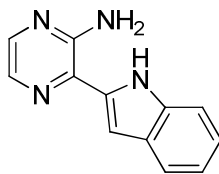
To a solution of 2,2,2-trifluoro-*N*-[3-(1*H*-indol-2-yl)pyrazin-2-yl]acetamide **125** (306 mg, 1.0 mmol, 1.0 equiv) in MeOH:H$_2$O (4 mL, 1:1) was added potassium carbonate (414 mg, 3.0 mmol, 3.0 equiv) and stirred at 25 °C for 12 h. The reaction mixture was then filtered through a pad of Na$_2$S$_2$O$_4$ and rinsed with EtOAc. The solvent was evaporated *in vacuo* and purification of the crude product by flash chromatography (SiO$_2$, EtOAc/*i*Hex = 7:3) afforded **126** as an orange solid (174 mg, 83%).

mp.: 220.6 – 222.4 °C.

^{1}H-NMR (DMSO-d6, 400 MHz) δ: 11.4 (s, 1 H, NH), 8.55 (s, 1 H), 7.94 (s, 1 H), 7.48 (q, *J* = 4.1 Hz, 1 H), 7.38 (q, *J* = 4.1 Hz, 1 H), 7.06 – 6.93 (m, 2 H), 6.86 (s, 1 H), 6.59 (s, 2 H, NH$_2$).

^{13}C-NMR (DMSO-d6, 100 MHz) δ: 154.7, 139.0, 136.7, 136.0, 134.3, 130.9, 128.7, 121.2, 119.8, 119.2, 111.4, 97.1.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3423, 1634, 1521, 1469, 1452, 1424, 1384, 1341, 1301, 1203, 1062, 1014, 897, 793, 751, 664.

MS (EI, 70 eV) m/z (%): 210 (100), [M$^+$], 183 (9), 142 (19).

HRMS (EI) for C$_{12}$H$_{10}$N$_4$ (210.0905): 210.00899.

3.5.   Preparation and Reactions of Heteroaromatic Benzylic Zinc Compunds

3.5.1. Preparation of starting materials

Synthesis of 6-chloro-*N,N*-dimethyl-4-(methylthio)nicotinamide (136)
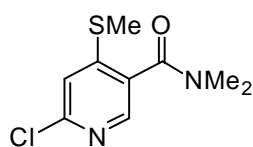
To a solution of 6-chloro-*N,N*-dimethylnicotinamide (**135**) (184 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) at –40 °C was added TMPMgCl·LiCl (**7**) (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –40 °C for 2 h. Then, neat S-methyl methanethiolsulfonate (139 mg, 1.1 mmol, 1.0 equiv) was added at once and stirred at –20 °C for 2 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over MgSO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, DCM/MeOH = 98:2) afforded **136** as a orange oil (164 mg, 71%).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.06 (s, 1 H), 7.07 (s, 1 H), 3.10 (s, 3 H), 2.88 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 166.4, 152.0, 151.2, 146.0, 129.3, 118.2, 38.3, 34.9, 14.0,

IR (ATR) $\widetilde{V}$ (cm^{-1}): 3448, 3270, 3016, 2970, 2926, 1778, 1738, 1630, 1564, 1524, 1506, 1432, 1396, 1326, 1312, 1288, 1264, 1230, 1206, 1158, 1130, 1106, 1050, 952, 934, 914, 848, 836, 816, 792, 766, 730, 698, 676.

MS (EI, 70 eV) m/z (%): 230 (14) [^{35}Cl-M$^+$], 187 (19), 186 (100), 122 (10), 45 (10).

HRMS (EI) for C$_9$H$_{11}$^{35}ClN$_2$O^{32}S (230.0281): 230.0285.

Synthesis of 6-chloro-2-iodo-*N,N*-dimethyl-4-(methylthio)nicotinamide (137)
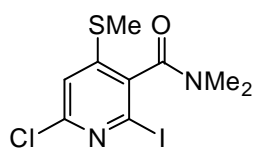
To a solution of 6-chloro-*N,N*-dimethyl-4-(methylthio)nicotinamide (**136**) (231 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) at –20 °C was added TMPMgCl·LiCl (**7**) (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –20 °C for 1 h. Then, neat iodine (280 mg, 1.1 mmol, 1.1 equiv) was added at once, cooling was removed and the resulting solution was allowed to warm up to 25 °C for 1 h. The reaction mixture was quenched with sat. aq. Na$_2$S$_2$O$_3$ and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over MgSO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, DCM/EtOAc = 7:3) afforded **137** as red solid (231 mg, 65%).

m.p.: 168.8 – 170.3 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.03 (s, 1 H), 3.15 (s, 3 H), 2.90 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 166.6, 151.6, 150.0, 135.7, 117.6, 113.6, 37.5, 34.8, 14.4,

IR (ATR) $\widetilde{V}$ **(cm^{-1}):** 2362, 1734, 1636, 1576, 1540, 1496, 1458, 1438, 1418, 1388, 1328, 1298, 1264, 1232, 1202, 1128, 1044, 912, 846, 818, 768, 750, 740, 710, 680.

MS (EI, 70 eV) m/z (%): 356 (<1) [^{35}Cl^{32}S-M$^+$], 312 (100), 311 (21), 186 (13), 157 (10), 122 (11), 46 (20), 45 (29), 44 (10), 42 (11).

HRMS (EI) for C$_9$H$_{10}$^{35}ClIN$_2$O^{32}S (355.9247): 355.9246.

Synthesis of *N,N*-dimethyl-1-pyrimidin-5-ylmethanamine (143)
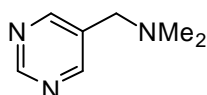
To a solution of 5-bromopyrimidine (3.2 g, 20.0 mmol, 1.0 equiv) in anhydrous THF (60 mL) at –110 °C was added *n*BuLi (10.1 mL, 24.0 mmol, 1.2 equiv) and the resulting mixture was stirred at –110 °C for 30 min. Transmetalation with ZnCl$_2$ (1.0 M in THF, 26.0 mmol, 1.3 equiv) was carried and the pyrimidin-5-ylzinc chloride was then reacted according to **TP13**. Purification of the crude product by flash chromatography (Al$_2$O$_3$, EtOAc/*i*Hex = 7:3) afforded **143** as a yellow oil (1.7 g, 63%).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 9.06 (s, 1 H), 8.62 (s, 2 H), 3.37 (s, 2 H), 2.19 (s, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 157.7, 157.3, 132.0, 58.9, 45.2.

IR (ATR) $\widetilde{V}$ **(cm^{-1}):** 3380, 3030, 2954, 2932, 2870, 2862, 2780, 2360, 2340, 1738, 1718, 1664, 1654, 1646, 1608, 1592, 1566, 1506, 1456, 1442, 1410, 1370, 1276, 1262, 1230, 1218, 1202, 1168, 1130, 1106, 1090, 1040, 930, 920, 844, 726.

MS (EI, 70 eV) m/z (%): 137 (50) [M$^+$], 136 (35), 93 (21), 66 (15), 58 (34), 58 (100), 42 (17).

HRMS (EI) for C$_7$H$_{11}$N$_3$ (137.0953): 137.0945.

Synthesis of *N,N*-dimethyl-1-[4-(methylthio)pyrimidin-5-yl]methanamine (144)
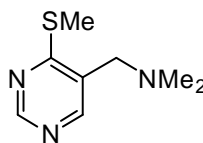
To a solution of *N,N*-dimethyl-1-pyrimidin-5-ylmethanamine **143** (823 mg, 6.0 mmol, 1.0 equiv) in anhydrous THF (6 mL) at –15 °C was added TMPMgCl·LiCl (**1**) (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –15 °C for 2 h. Then, neat S-methyl methanethiolsulfonate (833 mg, 6.6 mmol, 1.1 equiv) was added at once and stirred at –20 °C for 2 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (Al$_2$O$_3$, *i*Hex/EtOAc = 8:2) afforded **144** as a yellow oil (730 mg, 66%).

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.86 (s, 1 H), 8.28 (s, 1 H), 3.36 (s, 2 H), 2.56 (s, 3 H), 2.27 (s, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 170.0, 156.7, 153.7, 129.1, 58.3, 45.4, 12.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2942, 2928, 2818, 2772, 1564, 1526, 1456, 1420, 1382, 1354, 1316, 1298, 1256, 1192, 1174, 1130, 1114, 1098, 1026, 964, 928, 854, 840, 762, 756, 728, 704, 692.

MS (EI, 70 eV) m/z (%): 183 (51) [M$^+$], 168 (100), 139 (16), 134 (18), 125 (16), 107 (14), 93 (14), 58 (34).

HRMS (EI) for C$_8$H$_{13}$N$_3$^{32}S (183.0830): 183.0821.

Synthesis of *N,N*-dimethyl-1-[4-(methylthio)pyrimidin-5-yl]methanamine (145)
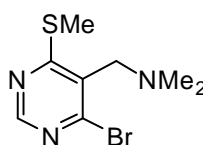
To a solution of *N,N*-dimethyl-1-[4-(methylthio)pyrimidin-5-yl]methanamine (**144**) (183 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1 mL) at –20 °C was added TMPMgCl·LiCl (**7**) (1.1 mmol, 1.1 equiv) and the resulting mixture was stirred at –20 °C for 2 h. Then, neat 1,2-dibromotetrachloroethane (358 mg, 1.1 mmol, 1.1 equiv) was added at once and stirred at –20 °C

for 2 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (Al$_2$O$_3$, *i*Hex/EtOAc = 92:8) afforded **145** as a yellow solid (149 mg, 57%).

mp.: 170.6 – 181.5 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.57 (s, 1 H), 3.61 (s, 2 H), 2.57 (s, 3 H), 2.34 (s, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 173.1, 155.6, 152.7, 129.6, 58.9, 45.4, 13.9.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2360, 2340, 1736, 1532, 1498, 1444, 1402, 1328, 1288, 1222, 1024, 960, 844, 760.

MS (EI, 70 eV) m/z (%): 261 (9) [^{79}Br^{32}S-M$^+$], 248 (20), 246 (16), 107 (29), 58 (100), 45 (13), 44 (36), 43 (11), 42 (67).

HRMS (EI) for C$_8$H$_{12}$^{79}BrN$_3$^{32}S (260.9935): 260.9943.

Synthesis of 6-chloro-2-fluoro-3-iodopyridine (147)
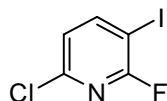
To a solution of 2-chloro-6-fluoropyridine (6.58 g, 50.0 mmol, 1.0 equiv) in anhydrous THF (25 mL) at –30 °C was added dropwise TMPMgCl·LiCl (**7**) (1.06 M in THF, 55.0 mmol, 1.1 equiv) and the resulting mixture was stirred at –30 °C for 4 h. Then, neat iodine (15.3 g, 60.0 mmol, 1.2 equiv) was added at once and stirred to 0 °C for 1 h. The reaction mixture was quenched with sat. aq. Na$_2$S$_2$O$_3$ and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 9:1) afforded **147** as a white solid (9.73 g, 76%).

mp.: 54.6 – 56.3 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.07 (t, *J* = 8.0 Hz, 1 H), 7.01 (dd, *J* = 8.0, 1.3 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$) δ: 160.9 (d, *J* (C – F) = 241.5 Hz), 151.6, 149.0 (d, *J* (C –F) = 12.6 Hz), 123.2 (d, *J* (C – F) = 5.3 Hz), 73.1 (d, *J* (C – F) = 41.5 Hz).

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2361, 2339, 1564, 1546, 1420, 1379, 1264, 1230, 1158, 1018, 914, 824, 729, 690.

MS (EI, 70 eV) m/z (%): 257 (100) [^{35}Cl-M$^+$], 130 (18), 127 (6).

HRMS (EI) for C$_5$H$_2$^{35}ClFIN (256.8904): 256.8891.

Synthesis of 1-(6-chloro-2-fluoropyridin-3-yl)-*N*,*N*-dimethylmethanamine (148)
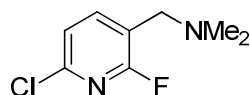
To a solution of 6-chloro-2-fluoro-3-iodopyridine **147** (15.5.g, 60.0 mmol, 1.0 equiv) in anhydrous THF (60 mL) at –30 °C was added *i*PrMgCl·LiCl (1.34 M in THF, 66.0 mmol, 1.1 equiv) and the resulting mixture was stirred at –30 °C for 30 min. The so generated solution of 6-chloro-2-fluoropyridin-3-ylmagnesium chloride was then reacted according to **TP13**. Purification of the crude product by flash chromatography (SiO$_2$, DCM/MeOH = 96:4) afforded **148** as a brown oil (8.94 g, 79%).

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.77 (t, *J* = 8.7 Hz, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 3.40 (s, 2 H), 2.21 (s, 6 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 160.3 (d, *J* (C – F) = 245.7 Hz), 146.8 (d, *J* (C – F) = 14.0 Hz), 143.7 (d, *J* (C – F)= 5.6 Hz), 121.6(d, *J* (C – F) = 5.0 Hz), 119.0 (d, *J* (C – F) = 27.5 Hz), 55.4 (d, *J* (C – F) = 2.5 Hz), 45.1.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3385, 2946, 2862, 2822, 2777, 2510, 2459, 1664, 1651, 1628, 1601, 1567, 1529, 1479, 1466, 1435, 1394, 1364, 1295, 1264, 1209, 1197, 1173, 1144, 1122, 1096, 1064, 1020, 999, 959, 928, 908, 851, 823, 803, 791, 774, 744, 739, 729, 724, 695, 686, 672, 664.

MS (EI, 70 eV) m/z (%): 189 (23) [^{35}Cl-M$^+$], 188 (68), 187 (58), 146 (26), 58 (100), 42 (10).

HRMS (EI) for C$_8$H$_{10}$^{35}ClFN$_2$ (188.0517): 188.0518.

Synthesis of 6-chloro-3-(chloromethyl)-2-fluoropyridine (149)
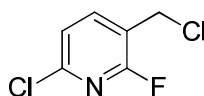
Prepared according to **TP14** from 1-(6-chloro-2-fluoropyridin-3-yl)-*N,N*-dimethylmethanamine (**148**) (5.65 g, 30.0 mmol, 1.0 equiv) and ethyl chloroformate (3.58 g, 33.0 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 85:15) afforded **149** as a white solid (3.24 g, 60%).

mp.: 83.0 – 84.0 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.83 (t, *J* = 7.9 Hz, 1 H), 7.26 (d, *J* = 7.7 Hz, 1 H), 4.57 (s, 2 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 160.0 (d, *J* (C – F) = 247.7 Hz), 149.0 (d, *J* (C – F) = 13.7 Hz), 143.4 (d, *J* (C – F) = 4.2 Hz), 122.3 (d, *J* (C – F) = 5.0 Hz), 118.4 (d, *J* (C – F) = 27.7 Hz), 38.1 (d, *J* (C – F) = 1.4 Hz).

IR (ATR) $\widetilde{V}$ (cm^{-1}): 3098, 1774, 1600, 1572, 1435, 1391, 1330, 1284, 1274, 1215, 1163, 1135, 1095, 927, 894, 841, 783, 763, 706, 686, 661.

MS (EI, 70 eV) m/z (%): 181 (22) [^{35}Cl-M$^+$], 179 (34), 146 (100), 109 (17), 108 (26).

HRMS (EI) for C$_6$H$_4$^{35}Cl$_2$FN (178.9705): 178.9705.

Spectral data were in full accordance with those reported in the literature: Z. Quan, B. B. Snider, *Org. Lett*. **2011**, *13*, 526.

Synthesis of [(2,4-dimethoxypyrimidin-5-yl)methyl]dimethylamine (151)
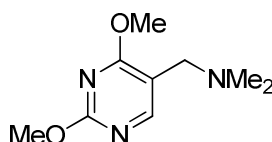
To a solution of 2,4-dimethoxy-5-bromo-pyrimidine (4.82 g, 22.0 mmol, 1 equiv.) in anhydrous THF (22 mL) *i*PrMgCl·LiCl (1.16 M in THF, 20.7 mL, 1.1 equiv) was added dropwise at –20°C and stirred for 2 h. The so obtained solution of 2,4-dimethoxypyrimidin-5-ylmagnesium chloride was then reacted according to **TP13**. Purification of the crude product by flash chromatography (Al$_2$O$_3$, Et$_2$O/*i*Hex = 4:1) afforded **xx** as a yellow oil (3.62 g, 83%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.97 (s, 1 H), 3.85 (d, *J* = 5.0 Hz, 6 H), 3.18 (s, 2 H), 2.11 (s, 6 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 169.5, 164.5, 158.5, 111.4, 54.6, 54.4, 53.8, 44.9.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2974, 2945, 2899, 2858, 2817, 2767, 1678, 1600, 1565, 1454, 1395, 1383, 1359, 1330, 1290, 1236, 1198, 1175, 1143, 1096, 1071, 1055, 1016, 959, 936, 845, 822, 790, 762, 733.

MS (EI, 70 eV): m/z (%): 197 (73) [M$^+$], 153 (60), 153 (79), 153 (100), 153 (19), 123 (19), 96 (16), 58 (20), 55 (22), 42 (31).

HRMS: for C$_9$H$_{15}$N$_3$O$_2$ (197.1164): 197.1168.

Synthesis of 1-(4-chloro-2,6-dimethoxypyrimidin-5-yl)-*N,N*-dimethylmethanamine (152)
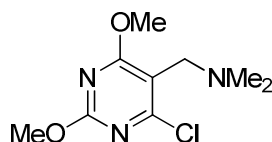
To a solution of [(2,4-dimethoxypyrimidin-5-yl)methyl]dimethylamine (**151**) (3.96 g, 20.0 mmol, 1.0 equiv) in anhydrous THF (20 mL) at 20 °C was added dropwise TMPMgCl·LiCl (**7**) (1.06 M in THF, 22.0 mmol, 1.1 equiv) and the resulting mixture was stirred at 20 °C for 45 min. Neat, 1,1,2-trichlorotrifluoroethane (4.12 g, 22.0 mmol, 1.1 equiv) was added and stirred at 50 °C for 4 h. The reaction mixture was quenched with sat. aq. NaHCO$_3$ and extracted with EtOAc (3 x 100 mL) and DCM (2 x 100 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, DCM/MeOH = 96:4) afforded **152** as an orange oil (3.06 g, 66%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 4.03 (s, 6 H), 3.40 (s, 2 H), 2.30 (s, 6 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 174.9, 165.3, 150.6, 110.4, 56.5, 53.7, 53.6, 45.1.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):**, 2945, 2899, 2858, , 2767, 1678, 1600, 1565, 1454, 1395, 1383, 1359, 1330, 1290, , 1198, 1175, 1143, , 1071, 1055, 1016, 959, 936, 790.

MS (EI, 70 eV): m/z (%): 231 (26) [^{35}Cl-M$^+$], 187 (90), 157 (12), 130 (21), 76 (11), 58 (18).

HRMS: for C$_9$H$_{14}$^{35}ClN$_3$O$_2$ (231.0775): 231.0779.

Synthesis of 4-chloro-5-(chloromethyl)-2,6-dimethoxypyrimidine (153)
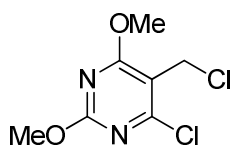
Prepared   according   to   **TP14**   from   1-(4-chloro-2,6-dimethoxypyrimidin-5-yl)-*N,N*-
dimethylmethanamine (**152**) (3.47 g, 15.0 mmol, 1.0 equiv) and ethyl chloroformate (1.79 g, 16.5
mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O =
85:15) afforded **153** as a white solid (2.41 g, 72%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 4.85 (s, 2 H), 4.13 (s, 3 H), 4.10 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 177.6, 168.6, 153.6, 105.8, 56.5, 53.6, 39.0.

IR (ATR) $\tilde{v}$ (cm^{-1}): 2785, 1656, 1600, 1530, 1400, 1310, 1190, 1110, 1085, 1071, 1055, 1016,
825, 786, 742.

MS (EI, 70 eV): m/z (%): 222 (10) [^{35}Cl-M$^+$], 187 (100), 157 (13), 130 (16), 70 (12).

HRMS: for C$_7$H$_8$^{35}Cl$_2$N$_2$O$_2$ (221.9963): 221.9971.

Synthesis of 1-(4-bromo-6-chloro-2-fluoropyridin-3-yl)-*N,N*-dimethylmethanamine (170)
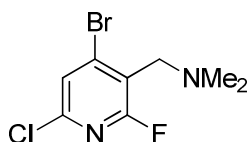
To a solution of 1-(6-chloro-2-fluoropyridin-3-yl)-*N,N*-dimethylmethanamine **148** (3.77 g, 20.0
mmol, 1.0 equiv) dissolved in anhydrous THF (20 mL) at –20 °C was added dropwise
TMPMgCl·LiCl (**7**) (1.06 M in THF, 24.0 mmol, 1.2 equiv) and the resulting mixture was stirred
at –20 °C for 1 h. Transmetalation with with anhydrous ZnCl$_2$ (1.0 M in THF, 24.0 mmol, 1.2
equiv) was carried at –20 and stirred for 30 min. Neat bromine (3.83 g, 24.0 mmol, 1.2 equiv)
was then slowly added and stirred to 0 °C for 1 h. The reaction mixture was quenched with sat.
aq. Na$_2$S$_2$O$_3$ and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed
with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash
chromatography (SiO$_2$, DCM/MeOH = 96:4) afforded **170** as a brown solid (4.17 g, 78%).

mp.: 45.5 – 47.4 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.47 (s, 1 H), 3.54 (s, 2 H), 2.30 (s, 6 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 156.3 (d, *J* (C – F) = 247.7 Hz), 147.7 (d, *J* (C – F) = 16.5 Hz), 140.4, 126.9 (d, *J* (C – F) = 5.4 Hz), 119.8 (d, *J* (C – F) = 30.2 Hz), 55.1 (d, *J* (C – F) = 3.1 Hz), 45.3.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2944, 2862, 2844, 2824, 2776, 2360, 1682, 1576, 1548, 1458, 1444, 1422, 1406, 1370, 1298, 1252, 1224, 1206, 1168, 1146, 1104, 1094, 1040, 1018, 974, 916, 836, 770, 756, 722.

MS (EI, 70 eV) m/z (%): 267 (28) [^{35}Cl-M$^+$], 266 (15), 265 (23), 253 (30), 252 (18), 251 (26), 226 (27), 224 (100), 222 (92), 108 (19), 82 (39), 81 (15), 80 (36), 58 (33), 44 (18), 43 (16).

HRMS (EI) for C$_8$H$_9$^{79}Br^{35}ClFN$_2$ (265.9622): 265.9640.

Synthesis of 4-bromo-6-chloro-3-(chloromethyl)-2-fluoropyridine (171)
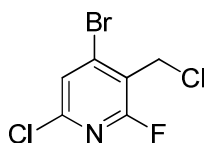
Prepared according to **TP14** from 1-(4-bromo-6-chloro-2-fluoropyridin-3-yl)-*N,N*-dimethylmethanamine **170** (2.68 g, 10.0 mmol, 1.0 equiv) and ethyl chloroformate (1.63 g, 15.0 mmol, 1.5 equiv) and stirred at 60 °C for 2 h. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 85:15) afforded **171** as a white solid (2.06 g, 80%).

mp.: 42.9 – 45.3 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.50 (s, 1 H), 4.68 (s, 2 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 159.9 (d, *J* (C – F) = 249.9 Hz), 149.3 (d, *J* (C – F) = 16.5 Hz), 139.3 (d, *J* (C – F) = 4.6 Hz), 126.1 (d, *J* (C – F) = 5.7 Hz), 119.2 (d, *J* (C – F) = 30.5 Hz), 37.4.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3100, 2362, 1740, 1576, 1546, 1440, 1420, 1378, 1278, 1234, 1218, 1206, 1198, 1168, 1100, 954, 894, 856, 820, 774, 726, 688.

MS (EI, 70 eV) m/z (%): 259 (16) [^{35}Cl-M$^+$], 257 (10), 226 (21), 224 (100), 222 (75).

HRMS (EI) for C$_6$H$_3$^{79}Br^{35}Cl$_2$FN (256.8810): 256.8805.

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

Synthesis of (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride (154)
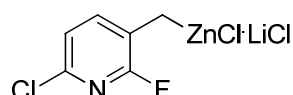
Prepared according to **TP15** from 6-chloro-3-(chloromethyl)-2-fluoropyridine **149** (540 mg, 3 mmol, 1.0 equiv), Zn dust (294 mg, 4.5 mmol, 1.5 equiv) and LiCl (191 mg, 4.5 mmol, 1.5 equiv). Reaction time: 1 h. Iodometric titration of the centrifugated solution indicated a yield of 90%.

Synthesis (4-chloro-2,6-dimethoxypyrimidin-5-yl)methylzinc chloride (156)
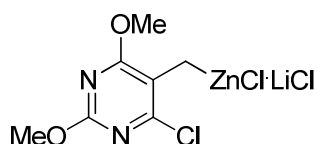
Prepared according to **TP15** from 4-chloro-5-(chloromethyl)-2,6-dimethoxypyrimidine **153** (669 mg, 3 mmol, 1.0 equiv), Zn dust (294 mg, 4.5 mmol, 1.5 equiv) and LiCl (191 mg, 4.5 mmol, 1.5 equiv). Reaction time: 1 h. Iodometric titration of the centrifugated solution indicated a yield of 85%.

Synthesis of (4-bromo-6-chloro-2-fluoropyridin-3-yl)methylzinc chloride (172)
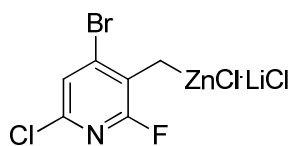
Prepared according to **TP15** from 4-bromo-6-chloro-3-(chloromethyl)-2-fluoropyridine **171** (777 mg, 3 mmol, 1.0 equiv), Zn dust (294 mg, 4.5 mmol, 1.5 equiv) and LiCl (191 mg, 4.5 mmol, 1.5 equiv). Reaction time: 1 h. Iodometric titration of the centrifugated solution indicated a yield of 70%.

3.5.3. Reactions of heterobenzylic zinc chlorides with electrophiles

Synthesis of 2-(6-chloro-2-fluoropyridin-3-yl)-1-(2,4-dichlorophenyl)ethanone (155a)
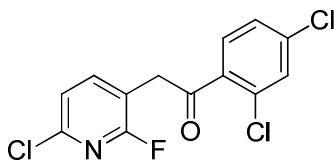
Prepared according to **TP18** from (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (5.0 mmol, 1.0 equiv) and 2,4-dichlorobenzoyl chloride (943 mg, 4.5 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO$_2$, iHex/Et$_2$O = 6:4) afforded **155a** as a white solid (1.15 g, 80%).

mp.: 85.4 – 87.0 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.68 (t, J = 7.9 Hz, 1 H), 7.52 (d, J = 8.2 Hz, 1 H), 7.47 (d, J = 1.9 Hz, 1 H), 7.35 (dd, J = 8.2, 2.1 Hz, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 4.27 (s, 2 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 196.2, 160.1 (d, J (C – F) = 245.0 Hz), 147.4 (d, J (C – F) = 14.0 Hz), 144.1 (d, J (C – F) = 5.0 Hz), 138.1, 136.0, 132.0, 130.3 (d, J (C – F) = 15.7 Hz), 127.4, 121.6 (d, J (C – F) = 5.0 Hz), 114.5, 114.3, 41.5 (d, J (C – F) = 2.2 Hz).

IR (ATR) $\tilde{v}$ **(cm^{-1}):** 1705, 1601, 1581, 1568, 1551, 1464, 1433, 1393, 1375, 1257, 1209, 1202, 1177, 1150, 1133, 1101, 1069, 995, 933, 904, 867, 849, 825, 805, 758, 673.

MS (EI, 70 eV) m/z (%): 319 (<1) [^{35}Cl-M$^+$], 174 (100), 173 (52), 146 (13), 145 (71), 111 (10).

HRMS (EI) for C$_{13}$H$_7$^{35}Cl$_3$FNO (316.9577): 316.9569.

Synthesis of 1-(6-chloro-2-fluoropyridin-3-yl)acetone (155b)
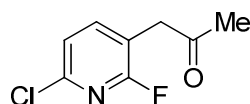
Prepared according to **TP18** from (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (2.5 mmol, 1.0 equiv) and acetyl chloride (167 mg, 2.1 mmol, 0.85 equiv). Purification of the crude product by flash chromatography (SiO$_2$, Et$_2$O/iHex = 7:3) afforded **155b** as a white solid (314 mg, 79%).

mp.: 64.9 – 66.7 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.56 (t, J = 7.7 Hz, 1 H), 7.18 (d, J = 7.7 Hz, 1 H), 3.72 (s, 2 H), 2.24 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 202.4, 159.8 (d, J (C – F) = 244.5 Hz), 146.8 (d, J (C – F) = 14.2 Hz), 143.8 (d, J (C – F) = 5.5 Hz), 121.3 (d, J (C – F) = 4.9 Hz), 114.5 (d, J (C – F) = 29.7 Hz), 41.8 (d, J (C – F) = 2.3 Hz), 29.3.

IR (ATR) $\tilde{v}$ (cm^{-1}): 3090, 2925, 1711, 1600, 1571, 1437, 1392, 1358, 1329, 1281, 1265, 1186, 1162, 1137, 1106, 1099, 1021, 915, 850, 801, 740, 678.

MS (EI, 70 eV) m/z (%): 187 (4) [^{35}Cl-M$^+$], 147 (62), 146 (20), 145 (100), 109 (37), 43 (11).

HRMS (EI) for C$_8$H$_7$^{35}ClFNO (187.0200): 187.0204.

Synthesis of 2-(6-chloro-2-fluoropyridin-3-yl)-1-(2-thienyl)ethanone (155c)
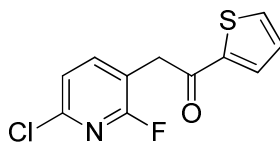
Prepared according to **TP18** from (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (2.5 mmol, 1.0 equiv) and 2-thiophenecarbonyl chloride (312 mg, 2.1 mmol, 0.85 equiv). Purification

of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 1:1) afforded **155c** as a yellow solid (467 mg, 86%).

mp.: 72.8–74.9 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.82 (dd, *J* = 3.9, 1.1 Hz, 1 H), 7.73 – 7.67 (m, 2 H), 7.21 (d, *J* = 7.7 Hz, 1 H), 7.17 – 7.14 (m, 1 H), 4.22 (s, 2 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 187.5, 160.2 (d, *J* (C – F) = 244.5 Hz), 147.3 (d, *J* (C – F) = 13.9 Hz), 144.4 (d, *J* (C – F) = 4.9 Hz), 142.9, 134.8, 132.7, 128.4, 121.8 (d, *J* (C - F) = 4.9 Hz), 114.9 (d, *J* (C – F) = 29.5 Hz), 37.8 (d, *J* (C – F) = 2.0 Hz).

IR (ATR) $\widetilde{\nu}$ **(cm^{-1}):** 3092, 2916, 1738, 1657, 1600, 1576, 1567, 1522, 1433, 1407, 1394, 1356, 1328, 1282, 1266, 1242, 1231, 1200, 1174, 1140, 1101, 1058, 978, 934, 920, 900, 855, 812, 760, 748, 725, 666.

MS (EI, 70 eV) m/z (%): 254 (<1) [^{35}Cl^{32}S-M$^+$], 111 (100).

HRMS (EI) for C$_{11}$H$_7$^{35}ClFNO^{32}S (254.9921): 254.9901.

Synthesis of 3-(2-bromobenzylic)-6-chloro-2-fluoropyridine (155d)
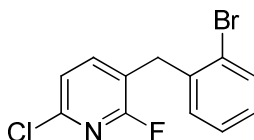
Prepared according to **TP16** from (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (2.0 mmol, 1.0 equiv) and 1-bromo-2-iodobenzene (509 mg, 1.8 mmol, 0.9 equiv). Catalyst system: Pd(dba)$_2$ (34 mg, 3 mol%) and P(o-furyl)$_3$ (28 mg, 6 mol %). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 95:5) afforded **155d** as a colorless oil (378 mg, 70%).

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.58 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 7.29 – 7.27 (m, 1 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 7.16 – 7.13 (m, 1 H), 7.11 (d *J* = 6.9 Hz, 1 H), 4.07 (s, 2 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 160.0 (d, *J* (C – F) = 245.4 Hz), 146.2 (d, *J* (C – F) = 14.0 Hz), 142.8 (d, *J* (C – F) = 5.3 Hz), 136.8, 133.0, 131.0, 128.6, 127.7, 124.5, 121.4 (d, *J* (C – F) = 5.0 Hz), 119.8 (d, *J* (C – F) = 28.9 Hz), 33.9 (d, *J* (C – F) = 1.4 Hz).

IR (ATR) $\widetilde{\nu}$ **(cm^{-1}):** 3060, 3014, 2924, 1598, 1568, 1363, 1327, 1300, 1260, 1218, 1120, 1090, 1046, 1027, 948, 926, 909, 868, 836, 817, 796, 716, 660.

MS (EI, 70 eV) m/z (%): 301 (42) [^{35}Cl-M$^+$], 299 (35), 222 (30), 221 (16), 220 (100), 185 (19), 184 (43), 97 (15), 86 (15), 85 (21), 84 (24), 83 (18), 74 (41), 71 (30), 69 (26), 59 (48), 57 (37), 55 (18), 45 (26), 43 (18).

HRMS (EI) for C$_{12}$H$_8$^{79}Br^{35}ClFN (298.9513): 298.9506.

Synthesis of 1-(5-bromo-2-thienyl)-2-(6-chloro-2-fluoropyridin-3-yl)ethanol (155e)
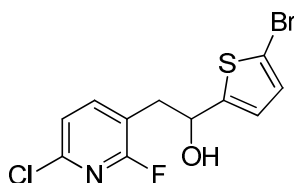
Prepared according to **TP17** from (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (2.0 mmol, 1.0 equiv) and 5-bromothiophene-2-carbaldehyde (325 mg, 1.7 mmol, 0.85 equiv). Purification of the crude product by flash chromatography (Al$_2$O$_3$, iHex/Et$_2$O = 1:1) afforded **155e** as a red solid (401 mg, 70%).

mp.: 82.6 – 85.4 °C.

^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 7.88 (t, J = 7.8 Hz, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.03 (d, J = 3.7 Hz, 1 H), 6.75 (d, J = 3.7, 1 H), 6.05 (d, J = 4.9 Hz, 1 H, OH), 5.03–4.98 (m, 1 H), 3.03–2.92 (m, 2 H).

^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 159.8 (d, J (C – F) =243.0 Hz), 151.0, 145.6 (d, J (C – F) =5.8 Hz), 144.5 (d, J (C – F) =14.2 Hz), 129.6, 123.6, 121.6 (d, J (C – F) =4.6 Hz), 118.7 (d, J (C – F) =29.0 Hz), 109.4, 67.7, 37.0 (d, J (C – F) =2.9 Hz).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3396, 3091, 1621, 1604, 1571, 1437, 1420, 1394, 1355, 1260, 1224, 1209, 1138, 1126, 1096, 1036, 991, 962, 945, 912, 844, 821, 809, 751, 736.

MS (EI, 70 eV) m/z (%): 337 (<1) [^{79}Br^{35}Cl^{32}S-M$^+$], 319 (16), 318 (12), 193 (87), 191 (100), 189 (15), 147 (26), 109 (10), 84 (37), 59 (10).

HRMS (EI) for C$_{11}$H$_8$^{79}Br^{35}ClFNO^{32}S (334.9183): 334.9158.

Synthesis of 1-(3-bromo-4-methoxyphenyl)-2-(6-chloro-2-fluoropyridin-3-yl)ethanol (155f)
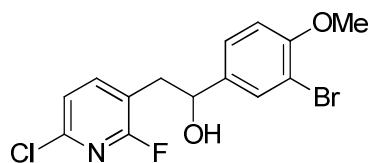
Prepared according to **TP17** from (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (2.0 mmol, 1.0 equiv) and 3-bromo-4-methoxybenzaldehyde (366 mg, 1.7 mmol, 0.85 equiv). Purification of the crude product by flash chromatography (Al$_2$O$_3$, *i*Hex/Et$_2$O = 1:1) afforded **155f** as a white solid (490 mg, 80%).

mp.: 85.9 – 87.8 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.53 – 7.48 (m, 2 H), 7.14 (dd, *J* = 8.3, 2.2 Hz, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 8.3 Hz, 1 H), 4.82 (t, *J* = 7.2 Hz, 1 H), 3.85 (s, 3 H), 2.96 (s, 1 H), 2.94 (d, *J* = 2.2 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 160.0 (d, *J* (C – F) = 245.1 Hz), 155.0, 145.9 (d, *J* (C – F) = 13.7 Hz), 144.2 (d, *J* (C – F) = 5.7 Hz), 136.3, 130.2, 125.5, 121.0 (d, *J* (C – F) = 4.8 Hz), 118.2, 117.8, 111.3 (d, *J* (C – F) = 5.1 Hz), 71.7, 55.8, 37.4 (d, *J* (C – F) = 2.6 Hz).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3351, 3276, 1739, 1602, 1566, 1500, 1459, 1432, 1405, 1394, 1282, 1265, 1196, 1168, 1131, 1100, 1049, 1013, 919, 895, 825, 801, 762, 745, 718, 676.

MS (EI, 70 eV) m/z (%): 358 (<1), [^{79}Br^{35}Cl-M$^+$], 339 (78), 326 (25), 217 (40), 216 (40), 215 (38), 214 (44), 147 (73), 146 (25), 145 (70), 144 (64), 108 (100), 78 (35), 77 (39), 65 (46).

HRMS (EI) for C$_{14}$H$_{12}$^{79}Br^{35}ClFNO$_2$ (358.9274): 358.9713.

Synthesis of 6-chloro-1-[(4-methylphenyl)sulfonyl]-2-phenyl-2, 3-dihydro-1H-pyrrolo[2, 3-b]pyridine (155g)
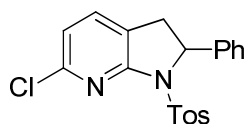
To a solution of (6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **154** (2.0 mmol, 1. 0 equiv) was added 4-methyl-*N*-[(1*E*)-phenylmethylene]benzenesulfonamide (440.8 mg, 1.7 mmol, 0.85 equiv) at 25 °C and stirred for 3 h. The reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl

and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 1:1 to 1:4) afforded **155g** as a white solid (412 mg, 63%).

mp.: 135.90 – 137.8 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.48 (d, *J* = 8.2 Hz, 2 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.23 – 7.20 (m, 3 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 7.08 – 7.07 (m, 2 H), 6.97 (d, *J* = 8.2 Hz, 1 H), 7.49 (q, *J* = 7.7 Hz, 1 H), 3.05 (q, *J* = 8.5 Hz, 1 H), 2.96 (q, *J* = 6.3 Hz, 1 H), 2.39 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 159.5, 146.9, 143.9, 143.5, 139.7, 136.8, 129.5, 128.8, 128.1, 126.8, 126.2, 121.5, 117.6, 57.9, 36.4, 21.5.

IR (ATR) $\widetilde{v}$ **(cm^{-1}):** 3256, 1598, 1569, 1494, 1450, 1433, 1396, 1322, 1304, 1263, 1148, 1093, 1061, 1024, 969, 959, 914, 819, 761, 747, 706, 699, 667.

MS (EI, 70 eV) m/z (%): 384 (9) [^{35}Cl-M$^+$], 261 (18), 260 (99), 229 (25), 155 (54), 91 (100) 65 (14), 57 (11).

HRMS (EI) for C$_{20}$H$_{17}$^{35}ClN$_2$O$_2$^{32}S (384.0699): 384.0698.

Synthesis of 2-(4-chloro-2,6-dimethoxypyrimidin-5-yl)-1-phenylethanone (155h)
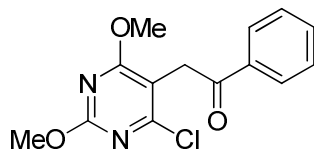
Prepared according to **TP18** from chloro[(4-chloro-2, 6-dimethoxypyrimidin-5-yl)methyl]zinc chloride **156** (3.0 mmol, 1.0 equiv) and benzoyl chloride (380.0 mg, 2.7 mmol, 0.9 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*hex/Et$_2$O = 1:1) afforded **155h** as white solid (669 mg, 88%).

mp.: 88.6 – 90.2 °C.

^{1}H-NMR (CDCl3, 300 MHz) δ: 8.03 (dt, *J* = 7.6, 2.2 Hz, 1 H), 7.60 (tt, *J* =7.4, 2.2 Hz, 2 H), 7.53 – 7.47 (m, 2 H), 4.33 (s, 2 H), 4.00 (s, 3 H), 3.94 (s, 3 H).

^{13}C-NMR (CDCl3, 75 MHz) δ: 194.6, 170.4, 163.4, 160.9, 136.4, 133.4, 128.7, 128.2, 106.9, 55.3, 54.9, 36.0.

IR (ATR) $\widetilde{v}$ **(cm^{-1}):** 2996, 2957, 2928, 1690, 1594, 1546, 1480, 1466, 1450, 1409, 1375, 1347, 1328, 1310, 1276, 1227, 1212, 1192, 1184, 1161, 1147, 1077, 1031, 1002, 987, 938, 916, 858, 840, 755, 777, 753, 688.

MS (EI, 70 eV) m/z (%): 292 (47) [^{35}Cl-M$^+$], 189 (27), 187 (100), 130 (17), 106 (23), 105 (24), 77 (57).

HRMS for C$_{14}$H$_{13}$^{35}ClN$_2$O$_3$ (292.0615): 292.0602.

Synthesis of 2-(4-bromo-6-chloro-2-fluoropyridin-3-yl)-1-(2-thienyl)ethanol (174)
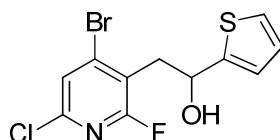
Prepared according to **TP17** from (4-bromo-6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **172** (1.0 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde (101 mg, 0.9 mmol, 0.9 equiv). A solution of MgCl$_2$ (0.5 M in THF, 0.5 mmol, 0.5 equiv) was added and stirred at 25 °C for 3 h. The reaction mixture was then quenched with sat. aq. NH$_4$Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (Al$_2$O$_3$, DCM) afforded **174** as a colorless oil (152 mg, 50%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.45 (s, 1 H), 7.29 – 7.26 (m, 1 H), 6.98 – 6.96 (m, 2 H), 5.25 (q, J = 5.0 Hz, 1 H), 3.40 – 3.19 (m, 2 H), 2.11 (s, 1 H, OH).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 160.7 (d, J (C – F) = 246.8 Hz), 147.1, 146.8, 139.4 (d, J (C – F) = 5.9 Hz), 126.8, 125.6 (d, J (C – F) = 5.3 Hz), 125.1, 123.9, 119.6 (d, J (C – F) = 31.7 Hz), 68.8, 38.0 (d, J (C – F) = 2.8 Hz).

IR (ATR) $\tilde{V}$ (cm^{-1}): 3392, 1578, 1544, 1414, 1374, 1276, 1230, 1182, 1146, 1100, 1034, 998, 946, 930, 910, 850, 834, 796, 786, 776, 728, 698.

MS (EI, 70 eV) m/z (%): 337 (<3), [^{35}Cl-M$^+$], 227 (22), 225 (100), 224 (17), 223 (73), 111 (19), 85 (42).

HRMS (EI) for C$_{11}$H$_8$Br^{35}ClFNOS (334.9183): 334.9173.

3.5.4. Preparation of highly funciontalized annulated heterocycles

Synthesis of 6-chloro-2-(2-thienyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (162a)
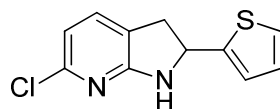
To a solution of 2-(6-chloro-2-fluoropyridin-3-yl)-1-(2-thienyl)ethanone **155c** (256 mg, 1.0 mmol, 1.0 equiv). in anhydrous EtOH (3 mL) was added ammonium acetate (1.16 g, 15.0 mmol, 15.0 equiv), sodium cyanoborohydride (76 mg, 1.2 mmol, 1.2 equiv) and stirred under microwave irradiation at 130 °C for 30 min. The reaction mixture was then quenched with sat. aq. Na_2CO_3 and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, *i*Hex/EtOAc = 7:3) afforded **162a** as a white solid (161 mg, 68%).

(Note: During the microwave irradiation, high pressure was generated and it was necessary to handle with precaution.)

mp.: 186.5–188.0 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.22 (dd, *J* = 5.0, 1.4 Hz, 1 H), 7.17 (dt, *J* = 7.5, 1.4 Hz, 1 H), 7.07 – 6.98 (m, 1 H), 6.94 (t, *J* = 3.3 Hz, 1 H), 5.32 – 5.21 (m, 2 H), 3.46 (dd, *J* = 9.4, 1.1 Hz, 1 H), 3.04 (dd, *J* = 7.0, 1.4 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 163.0, 148.2, 147.4, 133.5, 126.9, 124.7, 123.9, 119.0, 112.8, 56.6, 37.7.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3181, 1611, 1600, 1577, 1483, 1436, 1431, 1410, 1336, 1309, 1292, 1258, 1240, 1191, 1099, 1037, 992, 940, 852, 803, 788, 755, 699, 666.

MS (EI, 70 eV) m/z (%): 236 (100) [^{35}Cl-M$^+$], 235 (43), 234 (39), 205 (20), 203 (55), 200 (16), 168 (15), 144 (17), 129 (21), 127 (64), 117 (15), 91 (20).

HRMS (EI) for C$_{11}$H$_9$^{35}ClN$_2$^{32}S (236.0175): 236.0174.

Synthesis of 6-chloro-2-(2-thienyl)-1*H*-pyrrolo[2, 3-*b*]pyridine (163a)
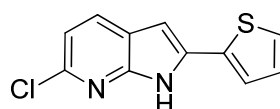
To a solution of 6-chloro-2-(2-thienyl)-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine **162a** (119 mg, 0.5 mmol, 1.0 equiv) dissolved in anhydrous toluene (5 mL) was added activated MnO_2 (435 mg, 5.0 mmol, 10.0 equiv) and stirred under reflux for 3 h. The reaction mixture was then filtered through a pad of cealite and rinsed with DCM (3 x 20 mL) and EtOAc (3 x 20 mL). The solvents were then concentrated *in vacuo* and purification of the crude product by flash chromatography (SiO_2, *i*Hex/EtOAc = 8:2) afforded **163a** as a white solid (91 mg, 78%).

mp.: 188.2 – 190.2 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 9.67 (s, 1 H, NH), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.35 – 7.34 (m, 2 H), 7.13 – 7.07 (m, 2 H), 6.65 (d, *J* = 2.2 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 148.1, 144.5, 134.3, 133.4, 130.6, 128.1, 125.7, 124.3, 120.3, 116.8, 98.2.

IR (ATR) $\tilde{V}$ (cm^{-1}): 3143, 2920, 1890, 1602, 1581, 1556, 1490, 1418, 1396, 1349, 1331, 1308, 1283, 1227, 1163, 1124, 1104, 1084, 1022, 938, 902, 847, 813, 783, 748, 692, 684.

MS (EI, 70 eV) m/z (%): 235 (16) [^{35}Cl^{32}S-M$^+$], 234 (100), 198 (9), 172 (14).

HRMS (EI) for C$_{11}$H$_7$^{35}ClN$_2$^{32}S (234.0018): 234.0009.

Synthesis of 6-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (162b)
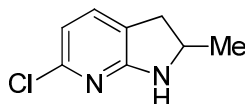
To a solution of 1-(6-chloro-2-fluoropyridin-3-yl)acetone **155b** (188 mg, 1.0 mmol, 1.0 equiv) in anhydrous EtOH (3 mL) was added ammonium acetate (1.16 g, 15.0 mmol, 15.0 equiv), sodium cyanoborohydride (76 mg, 1.2 mmol, 1.2 equiv) and stirred under microwave irradiation at 130 °C for 30 min. The reaction mixture was then quenched with sat. aq. Na_2CO_3 and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, *i*Hex/EtOAc = 7:3) afforded **162b** as a white solid (102 mg, 60%).

(Note: During the microwave irradiation, high pressure was generated and it was necessary to handle with precaution.)

mp.: 122.8 – 124.2 °C.

¹H-NMR (CDCl₃, 300 MHz) δ: 7.11 (dt, *J* = 6.1, 1.4 Hz, 1 H), 6.47 (d, *J* = 7.2 Hz, 1 H), 4.12 – 4.05 (m, 1 H), 3.14 (q, *J* = 7.7 Hz, 1 H), 2.58 (q, *J* = 5.0 Hz, 1 H), 1.29 (d, *J* = 6.4 Hz, 3 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 163.5, 147.3, 133.4, 120.2, 111.7, 52.9, 35.0, 22.7.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3221, 2973, 2960, 2920, 1614, 1575, 1494, 1441, 1419, 1409, 1383, 1373, 1349, 1329, 1308, 1257, 1245, 1216, 1192, 1127, 1096, 1082, 1046, 956, 948, 921, 902, 845, 791, 748, 719, 672.

MS (EI, 70 eV) m/z (%): 168 (32) [³⁵Cl-M⁺], 155 (29), 153 (100), 118 (15), 117 (40).

HRMS (EI) for C₈H₉³⁵ClN₂ (168.0454): 168.0455.

Synthesis of 6-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (163b)
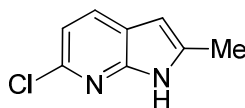
To a solution of 6-chloro-2-methyl-2,3-dihydro-1*H*-pyrrolo[2, 3-*b*]pyridine **162b** (84 mg, 0.5 mmol, 1.0 equiv) dissolved in anhydrous DCM (5 mL) was added activated MnO₂ (435 mg, 5.0 mmol, 10.0 equiv) and stirred under reflux for 3 h. The reaction mixture was then filtered through a pad of cealite and rinsed with DCM (3 x 20 mL) and EtOAc (3 x 20 mL). The solvents were concentrated *in vacuo* and purification of the crude product by flash chromatography (SiO₂, *i*Hex/EtOAc = 7:3) afforded **163b** as a white solid (77 mg, 92%).

mp.: 177.5 – 178.9 °C.

¹H-NMR (CDCl₃, 300 MHz) δ: 10.72 (s, 1 H, NH), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.16 (s, 1 H), 2.56 (s, 3 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 148.1, 142.5, 137.5, 129.7, 120.4, 115.5, 98.7, 14.3.

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3157, 3055, 1602, 1586, 1543, 1413, 1396, 1382, 1337, 1294, 1235, 1110, 974, 935, 806, 750, 705, 672, 691, 666.

MS (EI, 70 eV) m/z (%): 167 (30) [³⁵Cl-M⁺], 166 (100), 165 (88), 129 (31), 102 (13), 65 (13).

HRMS (EI) for C₈H₇³⁵ClN₂ (166.0298): 166.0294.

Synthesis of 2-(5-bromo-2-thienyl)-6-chloro-2,3-dihydrofuro[2,3-*b*]pyridine (164a)
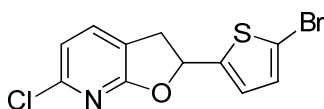
To a solution of 1-(5-bromo-2-thienyl)-2-(6-chloro-2-fluoropyridin-3-yl)ethanol **155e** (337 mg, 1.0 mmol, 1.0 equiv) in annhydrous THF (4 mL) at 0 °C was added slowly sodium hydride (60 mg, 60 % in mineral oil, 1.5 mmol, 1.5 equiv). Cooling was removed and stirred to 25 °C for 4 h, then the reaction mixture was quenched at 0 °C with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO$_2$, DCM/*i*Hex = 1:1) afforded **164a** as yellow solid (250 mg, 79 %).

mp.: 102.5–105.2 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.43 (dt, J =7.7, 1.4 Hz, 1 H), 6.93 (d, J =3.6 Hz, 1 H), 6.87–6.85 (m, 2 H), 5.96 (t, J =7.1 Hz, 1 H), 3.64 (dd, J =9.4, 1.1 Hz, 1 H), 3.28 (dd, J =6.9, 1.1 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 166.7, 149.0, 144.6, 135.5, 129.7, 125.8, 117.2, 116.8, 113.1, 78.8, 36.0.

IR (ATR) $\tilde{v}$ (cm^{-1}): 1641, 1591, 1582, 1500, 1426, 1410, 1354, 1330, 1302, 1286, 1231, 1196, 1188, 1135, 1112, 1099, 967, 940, 921, 812, 804, 792, 747, 679.

MS (EI, 70 eV) m/z (%): 317 (100), [^{79}Br^{35}Cl^{32}S-M$^+$], 316 (18), 315 (82), 235 (67), 203 (20), 201 (20), 200 (21), 174 (16), 173 (46), 172 (56), 86 (38).

HRMS (EI) for C$_{11}$H$_7$^{79}Br^{35}ClNO^{32}S (314.9120): 314.9121.

Synthesis of 2-(5-bromo-2-thienyl)-6-chlorofuro[2,3-*b*]pyridine (165a)
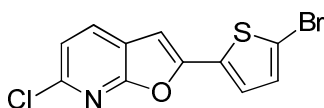
To a solution of 2-(5-bromo-2-thienyl)-6-chloro-2,3-dihydrofuro[2,3-*b*]pyridine **164a** (285 mg, 0.9 mmol, 1.0 equiv) in annhydrous 1,4-dioxane (4 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (613 mg, 2.7 mmol, 3.0 equiv) and stirred under reflux for 3 h. The reaction mixture was then quenched with sat. aq. NaHCO$_3$ and extracted with EtOAc (3 x 25 mL). The

combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, Et_2O/*i*Hex = 6:4) afforded **165a** as white solid (170 mg, 60 %).

mp.: 184.8 – 187.4 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 7.80 (d, J = 8.0 Hz, 1 H), 7.28 (d, J = 3.8 Hz, 1 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.07 (d, J = 3.8 Hz, 1 H), 6.76 (s, 1 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 160.1, 150.3, 145.5, 133.2, 131.3, 131.0, 126.0, 120.2, 119.8, 114.6, 99.7.

IR (ATR) $\tilde{v}$ (cm^{-1}): 3066, 1576, 1515, 1418, 1401, 1337, 1254, 1197, 1171, 1109, 1058, 996, 928, 886, 827, 808, 786, 757, 699.

MS (EI, 70 eV) m/z (%): 314 (100), [^{79}Br^{35}Cl^{32}S-M$^+$], 313 (70), 189 (11), 74 (17), 59 (18).

HRMS (EI) for C$_{11}$H$_5$^{79}Br^{35}ClNO^{32}S (312.8964): 312.8960.

Synthesis of 2-(3-bromo-4-methoxyphenyl)-6-chloro-2,3-dihydrofuro[2,3-*b*]pyridine (164b)
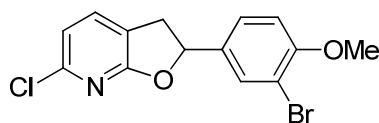
To a solution of 1-(3-bromo-4-methoxyphenyl)-2-(6-chloro-2-fluoropyridin-3-yl)ethanol **155f** (341 mg, 1.0 mmol, 1.0 equiv) in annhydrous THF (4 mL) at 0 °C was added slowly sodium hydride (60 mg, 60 % in mineral oil, 1.5 mmol, 1.5 equiv). Cooling was removed and stirred to 25 °C for 4 h, then the reaction mixture was quenched at 0 °C with H_2O and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, Et_2O/*i*Hex = 4:1) afforded **164b** as brown solid (293 mg, 86%).

mp.: 88.2 – 90.3 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.55 (d, J = 2.2 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.28 (dd, J = 8.5, 2.2 Hz, 1 H), 6.89 – 6.84 (m, 2 H), 5.78 (t, J = 7.5 Hz, 1 H), 3.88 (s, 3 H), 3.66 – 3.57 (m, 1 H), 3.14 (q, J = 7.7 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 167.4, 155.9, 148.8, 135.5, 134.2, 130.6, 125.9, 117.7, 116.5, 112.0, 111.9, 81.9, 56.4, 36.2.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2970, 2926, 2845, 1738, 1688, 1600, 1582, 1498, 1428, 1414, 1351, 1338, 1294, 1282, 1257, 1230, 1208, 1194, 1182, 1105, 1053 1017, 972, 929, 913, 878, 826, 812, 802, 745, 720, 680.

MS (EI, 70 eV) m/z (%): 341 (100) [^{79}Br^{35}Cl-M$^+$], 340 (23), 339 (77), 326 (26), 324 (18), 182 (14), 153 (14), 77 (15).

HRMS (EI) for C$_{14}$H$_{11}$^{79}Br^{35}ClNO$_2$ (338.9662): 338.9656.

Synthesis of 2-(3-bromo-4-methoxyphenyl)-6-chlorofuro[2,3-*b*]pyridine (165b)
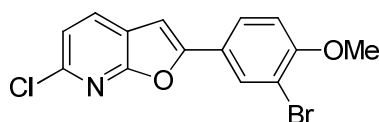
To a solution of 2-(3-bromo-4-methoxyphenyl)-6-chloro-2,3-dihydrofuro[2,3-*b*]pyridine **164b** (306 mg, 0.9 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (4 mL) was added 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (613 mg, 2.7 mmol, 3.0 equiv) and stirred under reflux for 3 h. The reaction mixture was quenched with sat. aq. NaHCO$_3$ and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 1:1) afforded **165b** as white solid (250 mg, 82%).

mp.: 181.6 – 183.2 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.01 (d, *J* = 2.2 Hz, 1 H), 7.81 – 7.75 (m, 2 H), 7.23 (d, *J* = 8.0 Hz, 1 H), 6.97 (d, *J* = 8.8 Hz, 1 H), 6.85 (s, 1 H), 3.94 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 160.4, 156.8, 154.7, 145.1, 131.2, 130.1, 125.5, 123.2, 120.1, 119.9, 112.3, 112.0, 99.0, 56.4.

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 1608, 1590, 1584, 1487, 1436, 1411, 1399, 1391, 1343, 1290, 1277, 1267, 1263, 1183, 1153, 1129, 1112, 1053, 1017, 933, 910, 830, 825, 762, 684.

MS (EI, 70 eV) m/z (%): 339 (72) [^{79}Br^{35}Cl-M$^+$], 326 (28), 324 (23), 182 (11), 77 (11).

HRMS (EI) for C$_{14}$H$_9$^{79}Br^{35}ClNO$_2$ (336.9505): 336.9665.

Synthesis of 7-chloro-3-(2,4-dichlorophenyl)pyrido[2,3-*c*]pyridazine (168)
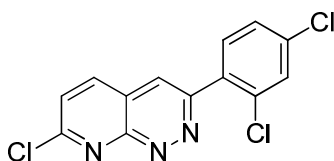
To a solution of 2-(6-chloro-2-fluoropyridin-3-yl)-1-(2,4-dichlorophenyl)ethanone **155a** (318 mg, 1.0 mmol, 1.0 equiv) in dimethyl formamide (2 mL) was added hydrazine (1.0 M in THF, 5.0 mmol, 5.0 equiv) and refluxed for 6 h. The reaction mixture was then quenched with sat. aq. Na_2CO_3 and extracted with EtOAc (3 x 50 mL) and DCM (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. The crude product was filtered through a short pad of SiO_2 and rinsed with DCM and EtOAc. The solvents were removed *in vacuo* and the resulting product was dissolved in anhydrous THF (4 mL) and $Pb(OAc)_4$ (887 mg, 2.0 mmol, 2.0 equiv) was added and stirred for 4 h. The reaction mixture was then quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, DCM/EtOAC = 97:3) afforded **168** as a yellow solid (170 mg, 55%).

mp.: 251.5 – 253.6 °C.

^{1}H-NMR (CDCl$_3$, 600 MHz) δ: 8.33 (s, 1 H), 8.26 (d, J = 8.5 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 1 H), 7.73 (d, J = 8.5 Hz, 1 H), 7.60 (d, J = 1.9 Hz, 1 H), 7.48 (dd, J = 8.5, 2.0 Hz, 1 H).

^{13}C-NMR (CDCl$_3$, 150 MHz) δ: 156.4, 155.9, 153.9, 138.9, 136.4, 133.8, 133.3, 133.2, 130.2, 128.8, 128.0, 124.2, 119.5.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3083, 1593, 1553, 1523, 1481, 1384, 1358, 1244, 1144, 1112, 1108, 1066, 1027, 909, 859, 840, 817, 804, 727, 706, 664.

MS (EI, 70 eV) m/z (%): 311 (76) [^{35}Cl-M$^+$], 310 (15), 309 (74), 285 (32), 284 (14), 283 (88), 282 (17), 281 (100), 249 (13), 246 (99), 245 (20), 213 (31), 212 (21), 211 (95), 210 (18), 176 (24), 175 (31), 170 (12), 141 (11), 140 (10), 123 (23), 106 (12), 99 (11), 92 (11), 75 (13), 74 (16).

HRMS for C$_{13}$H$_6$^{35}Cl$_3$N$_3$ (308.9627): 308.9619.

Synthesis of 5,7-dimethoxy-3-phenylpyrimido[4,5-*c*]pyridazine (169)
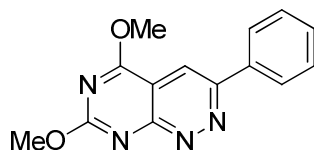
To a solution of 2-(4-chloro-2,6-dimethoxypyrimidin-5-yl)-1-phenylethanone **155h** (293 mg, 1.0 mmol, 1.0 equiv) in dimethyl formamide (2 mL) was added hydrazine (1.0 M in THF, 5.0 mmol, 5.0 equiv) and refluxed for 6 h. The reaction mixture was then quenched with sat. aq. Na_2CO_3 and extracted with EtOAc (3 x 50 mL) and DCM (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. The crude product was filtered through a short pad of SiO_2 and rinsed with DCM and EtOAc. The solvents were removed *in vacuo* and the resulting product was dissolved in anhydrous THF (4 mL) and Pb(OAc)$_4$ (887 mg, 2.0 mmol, 2.0 equiv) was added and stirred for 4 h. The reaction mixture was then quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na_2SO_4. Purification of the crude product by flash chromatography (SiO_2, DCM) afforded **169** as a yellow solid (188 mg, 70%).

mp.: 177.8 – 179.5 °C.

^{1}H-NMR (CDCl$_3$, 400 MHz) δ: 8.35 (s, 1 H), 8.19 – 8.16 (m, 2 H), 7.56 – 7.49 (m, 3 H), 4.27 (d, $J = 1.2$ Hz, 6 H).

^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 169.7, 164.4, 159.7, 155.3, 135.6, 129.6, 128.8, 126.8, 116.2, 108.8, 55.8, 55.6.

IR (ATR) $\tilde{v}$ (cm^{-1}): 1615, 1575, 1544, 1495, 1460, 1421, 1381, 1322, 1295, 1269, 1242, 1193, 1120, 1062, 1041, 973, 956, 911, 815, 779, 756, 725, 698.

MS (EI, 70 eV) m/z (%): 268 (100) [M$^+$], 240 (41), 197 (25), 140 (45).

HRMS for C$_{14}$H$_{12}$N$_4$O$_2$ (268.0960): 268.0952.

Synthesis of 2-(4-bromo-6-chloro-2-fluoropyridin-3-yl)-1-(2-thienyl)ethanol (174)
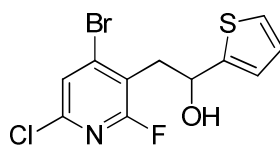
Prepared according to **TP17** from [(4-bromo-6-chloro-2-fluoropyridin-3-yl)methyl]zinc chloride **172** (1.0 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde (101 mg, 0.9 mmol, 0.9 equiv). A solution of anhydrous MgCl$_2$ (0.5 mmol, 0.5 M in THF, 0.5 equiv) was added and further stirred at 25 °C for 3 h. Purification of the crude product by flash chromatography (Al$_2$O$_3$, DCM) afforded **174** as a colorless oil (152 mg, 50%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.45 (s, 1 H), 7.29 – 7.26 (m, 1 H), 6.98 – 6.96 (m, 2 H), 5.25 (q, J = 5.0 Hz, 1 H), 3.40 – 3.19 (m, 2 H), 2.11 (s, 1 H, OH).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 160.7 (d, J (C – F) = 246.8 Hz), 147.1, 146.8, 139.4 (d, J (C – F) = 5.9 Hz), 126.8, 125.6 (d, J (C – F) = 5.3 Hz), 125.1, 123.9, 119.6 (d, J (C – F) = 31.7 Hz), 68.8, 38.0 (d, J (C – F) = 2.8 Hz).

IR (ATR) $\tilde{V}$ (cm^{-1}): 3392, 1578, 1544, 1414, 1374, 1276, 1230, 1182, 1146, 1100, 1034, 998, 946, 930, 910, 850, 834, 796, 786, 776, 728, 698.

MS (EI, 70 eV) m/z (%): 337 (<3), [^{79}Br^{35}Cl^{32}S-M$^+$], 227 (22), 225 (100), 224 (17), 223 (73), 111 (19), 85 (42).

HRMS (EI) for C$_{11}$H$_8$^{79}Br^{35}ClFNO^{32}S (334.9183): 334.9173.

Synthesis of 4-bromo-6-chloro-2-(2-thienyl)furo[2,3-*b*]pyridine (173)
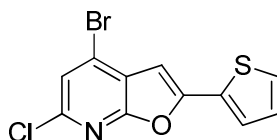
Prepared according to **TP17** from (4-bromo-6-chloro-2-fluoropyridin-3-yl)methylzinc chloride **172** (10.0 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde (897 mg, 8.0 mmol, 0.8 equiv) were stirred at 50 °C for 2 h. Purification of the crude product by a short pad of SiO$_2$ and rinsed with EtOAc (3 x 100 mL). The solvent was removed *in vacuo* and the resulting product was dissolved in anhydrous 1,4-dioxane (10 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.99 g, 22.0 mmol, 2.2 equiv) was added and stirred under reflux for 12 h. The reaction mixture was quenched with sat. aq. NaHCO$_3$ and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na$_2$SO$_4$. Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/DCM = 7:3) afforded **173** as a white solid (1.38 g, 55%).

mp.: 128.1 – 129.8 °C.

¹H-NMR (CDCl₃, 300 MHz) δ: 7.57 (dd, J = 3.7, 1.1 Hz, 1 H), 7.45 – 7.43 (m, 2 H), 7.12 (t, J = 3.7 Hz, 1 H), 6.81 (s, 1 H).

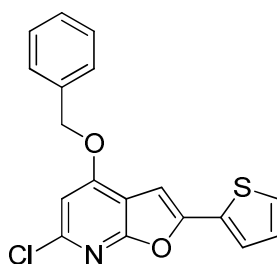**¹³C-NMR (CDCl₃, 75 MHz)** δ: 159.2, 152.0, 145.1, 131.3, 128.3, 127.8, 126.6, 125.6, 122.8, 122.4, 99.2.

IR (ATR) $\widetilde{\nu}$ (cm⁻¹): 2360, 2340, 1738, 1582, 1560, 1418, 1354, 1330, 1268, 1202, 1100, 1052, 994, 960, 896, 854, 844, 838, 794, 752, 712.

MS (EI, 70 eV) m/z (%): 315 (100), [^{79}Br^{35}Cl^{32}S-M⁺], 314 (15), 313 (71), 170 (14).

HRMS (EI) for C₁₁H₅^{79}Br^{35}ClNO^{32}S (312.8964): 312.8960.

Synthesis of 4-(benzylicoxy)-6-chloro-2-(2-thienyl)furo[2,3-*b*]pyridine (175)

To a solution of sodium hydride (144 mg, 3.6 mmol, 1.2 equiv) dissolved in DMF (9 mL) at 0 °C was added benzylic alcohol (357 mg, 3.3 mmol, 1.1 equiv) and stirred for 10 min. Then, 4-bromo-6-chloro-2-(2-thienyl)furo[2,3-*b*]pyridine **173** (944 mg, 3.0 mmol, 1.0 equiv) was added slowly at 0 °C and stirred to 25 °C for 2 h. The reaction mixture was then quenched at 0 °C with sat. aq. NH₄Cl and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl and dried over Na₂SO₄. Purification of the crude product by flash chromatography (SiO₂, *i*Hex/DCM = 7:3) afforded **175** as a yellow solid (765 mg, 75%).

mp.: 162.9 – 164.6 °C.

¹H-NMR (CDCl₃, 300 MHz) δ: 7.49 – 7.33 (m, 7 H), 7.08 (t, J = 3.7 Hz, 1 H), 6.88 (s, 1 H), 6.79 (s, 1 H), 5.24 (s, 2 H).

¹³C-NMR (CDCl₃, 75 MHz) δ: 161.5, 160.2, 149.5, 146.7, 134.9, 132.1, 128.8, 128.7, 128.0, 127.7, 126.5, 125.4, 110.3, 103.5, 97.5, 71.1.
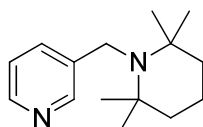
IR (ATR) $\widetilde{\nu}$ (cm⁻¹): 1581, 1460, 1450, 1346, 1321, 1316, 1212, 1156, 1096, 998, 953, 922, 846, 826, 799, 758, 707, 700.

MS (EI, 70 eV) m/z (%): 342 (7), [^{35}Cl^{32}S-M$^+$], 341 (38), 111 (7), 92 (6), 91 (100).

HRMS (EI) for C$_{18}$H$_{12}$^{35}ClNO$_2$^{32}S (341.8114): 341.0273.

3.6. New Generation of Iminium Salts

Synthesis of 3-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]pyridine (185a)

Prepared according to **TP19** from pyridin-3-ylmagnesium chloride (1.0 mmol, 1.0 equiv) and TMPMgCl·LiCl (**7**) (1.10 M, 2.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 1:1) afforded **185a** as a white solid (300 mg, 76%).

mp.: 82.5 – 83.9 °C.

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.63 (s, 1 H), 8.36 (d, *J* = 6.4 Hz, 1 H), 7.76 (d, J = 8.6 Hz, 1 H), 7.17 (dd, J = 8.6, 4.7 Hz, 1 H), 3.80 (s, 2 H), 1.65 – 1.49 (m, 5 H), 0.98 (s, 12 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 148.9, 147.0, 141.0, 134.5, 122.8, 54.9, 45.7, 41.2, 27.6, 17.8.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2966, 2925, 1469, 1429, 1261, 1240, 1174, 1132, 1103, 1025, 900, 849, 788, 715, 694.

MS (EI, 70 eV) m/z (%): 232 (<2), [M$^+$], 218 (14), 217 (100), 161 (23), 92 (33), 69 (10), 65 (10), 40 (10).

HRMS (EI) for C$_{15}$H$_{24}$N$_2$ (232.1939): 232.1936.

Synthesis of 2-(2-chlorophenyl)-*N,N*-bis(2-methoxyethyl)ethanamine (185b)
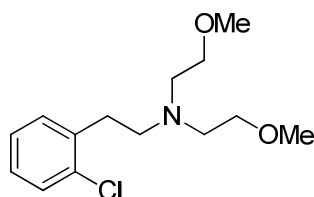
Prepared according to **TP19** from 2-chlorobenzylzinc chloride (1.0 mmol, 1.0 equiv) and magnesium chloride bis(2-methoxyethyl)amide (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/Et$_2$O = 1:1) afforded **185b** as a yellow oil (500 mg, 92%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.31 – 7.28 (m, 1 H), 7.21 – 7.07 (m, 3 H), 3.46 (t, *J* = 6.1 Hz, 4 H), 3.32 (s, 6 H), 2.91 – 2.85 (m, 2 H), 2.81 – 2.77 (m, 6 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 138.1, 134.0, 131.0, 129.4, 127.4, 126.8, 71.2, 58.9, 55.0, 53.9, 31.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 2952, 2835, 1706, 1611, 1584, 1558, 1510, 1451, 1404, 1363, 1301, 1244, 1172, 1120, 1105, 1061, 1030, 952, 822, 736, 698, 678.

MS (EI, 70 eV) m/z (%): 270 (<1), [^{35}Cl-M$^+$], 228 (19), 226 (73), 146 (100), 139 (29), 59 (11).

HRMS (EI) for C$_{14}$H$_{22}$^{35}ClNO$_2$ [M-H$^+$] (270.1253): 270.1253.

Synthesis of diallyl[2-(2-chlorophenyl)ethyl]amine (185c)
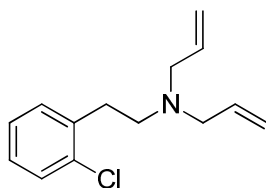
Prepared according to **TP19** from 2-chlorobenzylzinc chloride (1.0 mmol, 1.0 equiv) and magnesium chloride *N,N*-diallylamide (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 98:2) afforded **185c** as a colorless oil (282 mg, 66 %).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 7.33 – 7.30 (m, 1 H), 7.22 – 7.09 (m, 3 H), 5.94 – 5.80 (m, 2 H), 5.23 – 5.11 (m, 4 H), 3.18 (dt, J = 6.4, 1.4 Hz, 4 H), 2.92 – 2.87 (m, 2 H), 2.72 – 2.76 (m, 2 H).
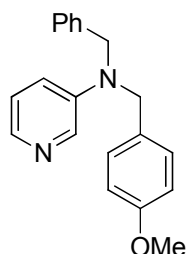
^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 138.2, 135.7, 134.0, 130.9, 129.4, 127.4, 126.7, 117.4, 56.8, 53.1, 31.1.

IR (ATR) $\widetilde{\nu}$ (cm^{-1}): 3073, 2929, 2804, 1643, 1475, 1443, 1418, 1354, 1259, 1100, 1052, 1045, 994, 916, 748, 682.

MS (EI, 70 eV) m/z (%): 235 (<1), [^{35}Cl-M$^+$], 139 (10), 111 (29), 110 (41), 103 (17), 81 (19), 77 (13), 68 (18).

HRMS (EI) for C$_{14}$H$_{18}$^{35}ClN (235.1128): 235.1113.

Synthesis of *N*-benzyl-2-chloro-*N*-(4-methoxybenzyl)pyridin-3-amine (185d)

Prepared according to **TP19** from 4-methoxyphenylzinc chloride (1.0 mmol, 1.0 equiv) and magnesium chloride *N*-benzyl-2-chloropyridin-3-amide (1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO$_2$, *i*Hex/EtOAc = 7:3) afforded **185d** as a yellow oil (122 mg, 45%).

^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 8.04 (dd, *J* = 4.7, 1.7 Hz, 1 H), 7.33 – 7.30 (m, 4 H), 7.26 – 7.17 (m, 4 H), 7.05 (dd, *J* = 7.8, 4.6 Hz, 1 H), 6.87 – 6.82 (m, 2 H), 4.26 (s, 2 H), 4.22 (s, 2 H), 3.80 (s, 3 H).

^{13}C-NMR (CDCl$_3$, 75 MHz) δ: 158.9, 147.6, 144.3, 143.0, 137.3, 131.8, 129.7, 129.2, 128.9, 128.4, 127.3, 122.4, 116.2, 114.8, 113.8, 55.6.

IR (ATR) $\tilde{v}$ (cm^{-1}): 3062, 3029, 2835, 1706, 1611, 1584, 1558, 1510, 1451, 1404, 1363, 1301, 1244, 1193, 1172, 1120, 1061, 1030, 952, 822, 736, 698, 678.

MS (EI, 70 eV) m/z (%): 339 (<1), [^{35}Cl-M$^+$], 121 (100).

HRMS (EI) for C$_{20}$H$_{19}$^{35}ClN$_2$O (338.1186): 338.1178.

D. APPENDIX

List of Abbreviations

Ac	acetyl
acac	pentane-1,3-dionato (acetylacetonato)
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
br	broad (NMR)
Bu	butyl
conc.	concentrated
d	doublet (NMR)
dba	*trans,trans*-dibenzylideneacetone
dist.	distilled
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
equiv	equivalent
E	electrophile
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
LDA	lithium *N,N*-diisopropylamide
M	mol/L

m	*meta*
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidin-2-one
o	*ortho*
p	*para*
PEPPSI-*i*Pr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	phenyl
ppm	parts per million
R	organic substituent
rpm	revolutions per minute
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*t*Bu	*tert*-butyl
t	reaction time
TFAO$^-$	trifluoroacetate
TLC	thin layer chromatography
THF	tetrahydrofuran
tfp	tris(2-furyl)phosphine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Tol	tolyl
Ts	4-toluenesulfonyl
TP	typical procedure

Curriculum Vitae

Gabriel Andrés Monzón Díaz

Date of Birth: 02 March 1985

Place of Birth: Guatemala City, Guatemala

Citizenship: Guatemalan

Educational Background

1990 – 2002   Colegio Liceo Javier, Guatemala.

2003 – 2007   Studies of chemistry (licenciate) at Universidad del Valle de Guatemala.

05/2007 – 10/2007   Licenciate thesis under the supervision of Prof. Dr. Bruce Lipshutz at the
                         University of California Santa Barbara.
                         "Heck-Cross Coupling of Bromoarenes in Aqueous Medium"

01/2009 – 06/2012   PhD studies in the research group of Prof. Dr. Paul Knochel at the
                         Ludwig-Maximilians-Universität München.

Language Proficiency

Spanish   mother tongue

English   fluent

German   fluent

Italian   basic proficiency

Publications

1. M. Mosrin, G. Monzón, T. Bresser, P. Knochel, "High Temperature Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl and Microwave irradiation", *Chem. Commun.* **2009**, *37*, 5615-5617.

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<u>G. Monzón</u>, P. Knochel, "High Temperature Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl", Poster presentation at the *16th European Symposium of Organic Chemistry*, July 12th to 16th 2009, Prague, Czech Republic.