Dissertation zur Erlangung des Doktorgrades

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PREPARATION AND DIRECT CROSS-COUPLING OF ORGANOALUMINUM REAGENTS, STUDIES ON SF_5-SUBSTITUTED ORGANOMETALLICS AND REGIOSELECTIVE METALATIONS OF SILYLATED N-HETEROAROMATICS

von

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

München, 18. April 2013

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Klaus Groll

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Parts of this PhD thesis have been published

Communications

1.) Tobias D. Blümke, Klaus Groll, Konstantin Karaghiosoff, Paul Knochel: „*New Preparation of Benzylic Aluminum and Zinc Organometallics by Direct Insertion of Aluminum Powder*"
Org. Lett. **2011**, *13*, 6440-6443.

2.) Klaus Groll, Tobias D. Blümke, Andreas Unsinn, Diana Haas, Paul Knochel: „*Direct Pd-Catalyzed Cross-Coupling of Functionalized Organoaluminum Reagents*
[Direkte Pd-katalysierte Kreuzkupplung von funktionalisierten Organo-aluminiumreagentien]"
Angew. Chem. Int. Ed. **2012**, *51*, 11157-11161; *Angew. Chem.* **2012**, *124*, 11319-11323.

3.) Annette Frischmuth, Andreas Unsinn, Klaus Groll, Heinz Stadtmüller, Paul Knochel: „*Preparations and Reactions of SF_5-Substituted Aryl and Heteroaryl Derivatives via Mg and Zn Organometallics*"
Chem. Eur. J. **2012**, *18*, 10234-10238.

4.) Klaus Groll, Sophia M. Manolikakes, Xavier Mollat du Jourdin, Milica Jaric, Aleksei Bredihhin, Konstantin Karaghiosoff, Thomas Carell, Paul Knochel: „*Regioselective Metalations of Pyrimidines and Pyrazines by Using Frustrated Lewis Pairs of $BF_3{\cdot}OEt_2$ and Hindered Magnesium- and Zinc-Amide Bases*
[Regioselektive Metallierungen von Pyrimidinen und Pyrazinen mit frustrierten Lewis-Paaren aus $BF_3{\cdot}OEt_2$ und sterisch gehinderten Mg- und Zn-Amidbasen]"
Angew. Chem. Int Ed. **2013**, *52*, 6776-6780; *Angew. Chem.* **2013**, *125*, 6909-6913.

Reviews

1.) Paul Knochel, Tobias D. Blümke, Klaus Groll, Yi-Hung Chen: "*Preparation of Organoalanes for Organic Synthesis*" in *Topics in Organometallic Chemistry, Vol. 41: Modern Organoaluminum Reagents,* (Eds. S. Woodward, S. Dagorne), Springer Berlin/Heidelberg, 2012; Ch. 36 (DOI: 10.1007/3418_2012_36).

"Walking with a friend in the dark is better than walking alone in the light."

Helen Keller (1880-1968)

Für Tina
und meine Familie

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
Alk	alkyl
aq	aqueous
Ar	aryl
BTM	bis(trimethylsilyl)methyl
Bu	butyl
calc.	calculated
CAN	ceric ammonium nitrate
conc.	concentrated
Cy	cyclohexyl
dba	*trans*,*trans*-dibenzylideneacetone
DBE	1,2-dibromoethane
dist.	distilled
DMAc	dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetra-hydropyrimidine-2(*1H*)-one
DMSO	dimethyl sulfoxide
δ	chemical shifts in ppm
E	electrophile
EDG	electron-donating group
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
*i*hexane	*iso*-hexane
HRMS	high resolution mass spectrometry
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
M	molarity
m	meta
m.p.	melting point
Me	methyl
Met	metal
min	minute
mmol	millimole
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NEP	*N*-ethyl-2-pyrrolidine
Nf	nonaflate
NMP	*N*-methyl-2-pyrrolidine
NMR	nuclear magnetic resonance
o	*ortho*
Oct	octyl
p	*para*
PEPPSI-*i*Pr	[1,3-bis(2,6-di(isopropyl)-phenyl)imidazol-2-ylidene] (3-chloropyridyl)-palladium(II) dichloride
Ph	phenyl
ppm	parts per million
R	organic substituent
RuPhos	2-dicyclohexylphosphino-2',6'-di(isopropoxy)-biphenyl
sat.	saturated
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
*s*Bu	*sec*-butyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsiliconate
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBTMPA	*N*-(*tert*-butyl)-2,2,4-trimethylpentan-3-amide
*t*Bu	*tert*-butyl
TMEDA	*N,N,N',N'*-tetramethylene-diamine
Tf	triflate
tfp	tris-(2-furyl)phosphine
THF	tetrahydrofuran

TIPS	tri(isopropylsilyl)	TMS	trimethylsilyl
TLC	thin layer chromatography	Ts	4-toluenesulfonyl
TMP	2,2,6,6-tetramethyl-piperidyl	X	halide or pseudohalide
tmpp	tris(2,4,6-trimethoxy-phenyl)phosphine	XantPhos	4,5-bis(diphenylphosphino)-9,9'-dimethylxanthene

A. INTRODUCTION

1. ORGANOMETALLIC CHEMISTRY

The great impact of organometallic reagents in the broad field of chemistry was once more honored in 2010 "for palladium-catalyzed cross-couplings" with the Nobel Prize in Chemistry.[1] The use of transition metal-assisted reactions for the formation of new C-C bonds, especially with nucleophiles bearing a carbon-metal bond, gives access to a wide variety of new transformations of chemical structures in the areas of total synthesis, material science or industrial applications.[2] Even though the organometallic chemistry was pioneered already over 150 years and was honored with a Nobel Prize for the first time a century ago, the recent award to *R. F. Heck*, *E. Negishi* and *A. Suzuki* proves the still high demand for the development of new organometallic methods. Certainly, the future of organic chemistry is directed to green chemistry which uses only a minimum of substances, particularly hazardous ones, to obtain a maximum of desired product.[3] However, as this prospective era of chemistry which is rather based on metal-free C-H-activation[4] and organocatalyzed couplings[5] is not yet able to solve a broad range of the sophisticated problems of organic synthesis in an applicable manner, the chemistry of organometallic reagents remains a major division to solve such tasks. Nevertheless, the so far developed methods in organometallic chemistry need further investigations and development of new strategies for realizing the ambitious challenges of a continuously growing world population with a limited feedstock of resources.[6]

A major advantage of the organometallic chemistry is the broad scope of developed methods for transformations of chemical structures which is mostly based on the variety of applied metal in the organometallic reagent.[7] The difference in reactivity of the respective organometallic is caused by the distinct electronegativity of the metal and moreover by its nature as main-group or transition metal. Thus, carbon-metal bonds show a higher reactivity the more electropositive the specific metal is, as the bond between them shows a stronger polarized character and is less covalent. In the case of transition metals, their d-orbitals can interact in the bonding to the carbon and in the reaction itself, which allows them to undergo special transformations that are not possible with main-group metals. The most-common organometallic reagents bear Li, Mg, Al, Zn or B as metallic part which in principle decrease in reactivity in the mentioned order but on the other hand show an increasing functional group tolerance. This allows a detailed strategy planning by using the appropriate metal for the desired reaction of the given molecule.

An example for an application of different organometallic species even on a pilot plant scale was shown by Novartis for the synthesis of PDE472 (**1**) which is a drug target for the treatment of

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1 *The Nobel Prize in Chemistry 2010*, Nobelprize.org, 13.03.2013, www.nobelprize.org/nobel_prizes/chemistry/laureates/2010.

2 a) *Metal-Catalyzed Cross-Coupling Reactions, 2nd Ed.* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.

3 a) B. M. Trost, *Science* **1991**, *254*, 1471; b) C. J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13197.

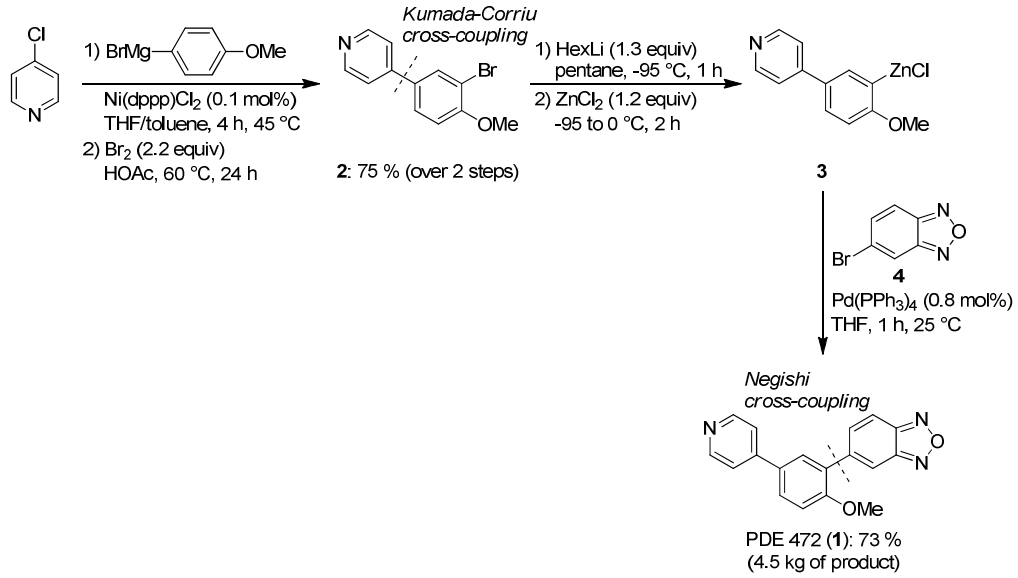
4 a) D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

5 F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev.* **2012**, *41*, 2406.

6 a) C. Okkerse, H. van Bekkum, *Green Chem.* **1999**, *1*, 107; b) T. Collins, *Science* **2001**, *291*, 48.

7 a) E. Negishi, *Organometallics in Organic Synthesis*, Wiley, New York, **1980**; b) *Handbook of Functionalized Organometallics* (Ed. P. Knochel), Wiley-VCH, Weinheim, **2005**.

asthma as it is a selective inhibitor of the phosphodiesterase PDE4D isoenzyme (Scheme 1).[8] Here, first a *Kumada-Corriu*[9] cross-coupling with a *p*-anisyl *Grignard* reagent was applied to obtain after bromination the biphenyl **2**. The thereof derived aromatic zinc reagent **3** was subsequently reacted in a *Negishi* coupling with bromide **4**. This scaled up reaction gives the desired PDE472 in 4.5 kg and a yield of 73 %.



Scheme 1: Synthesis of PDE 472 (**1**) of Novartis using different cross-coupling reactions.

[8] P. W. Manley, M. Acemoglu, W. Marterer, W. Pachinger, *Org. Process Res. Dev.* **2003**, *7*, 436.

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

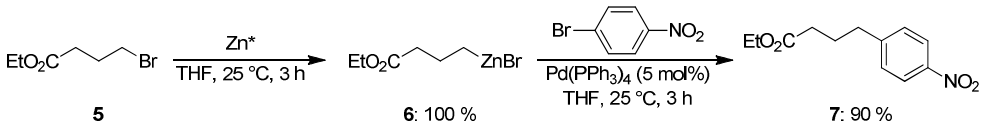
2. Preparation of Organometallic Reagents

In the over 150 year old history of organometallic chemistry a variety of methods for the synthesis of organometallic compounds has evolved. Beneath them the direct insertion using elemental metal sources, the halogen-metal exchange starting from another metal reagent and the metalation with organometallic bases which transforms a C-H bond into the corresponding carbon-metal functionality are the most common ones. In the following these three methods are explained separately. Thereby, the descriptions are focused on the metals Mg, Zn and Al, as these are mainly used in the subsequent parts. Additional information of other metal reagents is only given in cases where it is necessary in the context. More complete coverage of the only briefly mentioned organometallic reagents can be found in the further literature.[7]

2.1. Direct Insertion

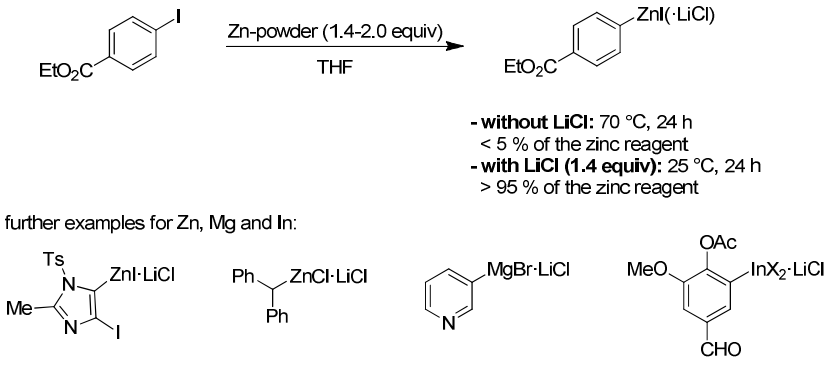
The oxidative addition of elemental metal into a carbon-halogen bond displays the pioneering method for the synthesis of organometallic reagents. Historically, it was first reported for zinc in 1849 by *Frankland*,[10] for aluminum in 1859 by *Hallwachs* and *Schafarik*[11] and for magnesium in 1900 by *Grignard*.[12] Since then the insertion of a zerovalent metal into an organic halide which results in an organometallic where the metal atom exhibits a higher oxidation state was subjected to several revolutions. Therefore, it was possible to avoid the formerly harsh reaction conditions to arrive at an insertion using ambient temperatures in typical organic media.
A particular milestone in this development was achieved by *Rieke* and co-workers at the end of the last century.[13] They were able to realize the oxidative addition reactions by using highly active metal powders. These were obtained by the reduction of corresponding metal salts with alkali metals and in most cases with an electron carrier like naphthalene. Using those highly reactive metals enables to perform the insertion reaction at ambient conditions and therefore the tolerance of selected functional groups like esters and nitriles. Thus, ethyl 4-bromo-butanoate (**5**) could be converted at room temperature within 3 h into the corresponding zinc reagent **6** in quantitative yield using the so-called *Rieke* zinc (Zn*) which was obtained from $ZnCl_2$ and lithium naphthalenide (Scheme 2).[13d] After a *Negishi* cross-coupling with 1-bromo-4-nitrobenzene in the presence of $Pd(PPh_3)_4$ the desired ethyl 4-(4-nitrophenyl)butanoate (**7**) was isolated. This method to prepare highly active metal powders for the direct insertion which have to be stored under inert atmosphere was seemingly well applied for magnesium (Mg*)[12b] and aluminum (Al*).[12d]

[10] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171 and 213.
[11] A. Hallwachs, W. Schafarik, *Liebigs Ann. Chem.* **1859**, *109*, 206.
[12] V. Grignard, *Compt. Rend. Acad. Sc. Paris* **1900**, *130*, 1322.
[13] a) R. D. Rieke, *Aldrichim. Acta* **2000**, *33*, 52; b) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301; c) R. D. Rieke, L.-C. Chao, *Syn. React. Inorg. Metal-Org. Chem.* **1974**, *4*, 101; d) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.



Scheme 2: Oxidative addition using *Rieke* zinc (Zn*) and subsequent trapping.

Recently, *Knochel* and co-workers showed that also the use of commercial available metal turnings or powder is possible for an oxidative addition into highly functionalized halides at mild conditions when LiCl was used as additive for the insertion of zinc,[14] magnesium[15] or indium[16] (Scheme 3). This allowed a very broad scope for the used organic halides like aromatic, heteroaromatic and benzylic as well as the presence of a lot of functional groups like esters, nitriles and aldehydes, naturally also dependent on the applied metal. The role of this salt has been elucidated by means of experimental, computational and analytical studies.[17, 18] Thus, LiCl allows a fast and efficient insertion reaction as it lowers the energy of the transition state for the insertion[17] and the formed organometallic reagents R-MetX·LiCl are usually present as ate-species of the type $Li^+R\text{-}MetXCl^-$ as was verified by ESI-measurements.[18] Another positive effect of LiCl is the increased solubility of the organometallic reagent in THF solution[19] and thus in the insertion reaction a free metal surface is believed to be regenerated which allows a further reaction with the starting halide.[14a]



Scheme 3: Examples of LiCl-mediated metal insertion into functionalized halides.

2.2. Halogen-Metal Exchange

A further, very convenient approach to organometallic reagents starting from halides is an exchange reaction using an organometallic precursor as source for the metal. The driving force

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

[15] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.

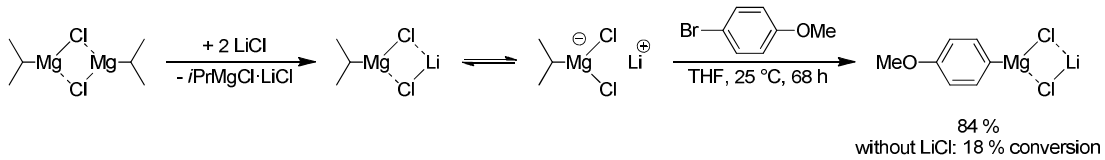
[16] a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648; b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236.

[17] C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780.

[18] a) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; b) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.

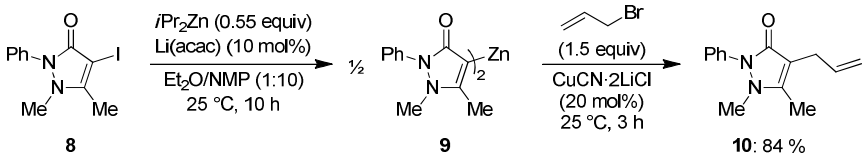
[19] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

of this exchange is the formation of the more stable organometallic reagent.[20] Pioneered was this type of reaction by *Prévost* in 1931, who started with EtMgBr and formed allylic magnesium reagents.[21] A very common variation of this exchange reaction is the formation of lithium compounds by using e.g. *n*BuLi, *t*BuLi or PhLi, which was found by *Wittig* and *Gilman*.[22]
Over 50 years, later the *Knochel* group reported the preparation of aromatic *Grignard* reagents by treating the corresponding aryl iodide with *i*PrMgBr or PhMgCl.[23] A major improvement of this method was achieved by using the LiCl-complexed, monomeric so-called "Turbo-*Grignard*" reagent *i*PrMgCl·LiCl. Due to an ate-character of this species it shows an improved reactivity and allows performing exchange reactions also with electron-rich aryl bromides (Scheme 4).[24]



Scheme 4: Br-Mg-exchange reaction by using Turbo-*Grignard* possessing an ate character.

For the transformation of aromatic and heteroaromatic iodides to the corresponding diorganozinc reagents 0.55 equiv of iPr$_2$Zn and catalytic amounts of Li(acac) as promoter for an intermediate ate-complex formation were needed.[25] Thus, the iodophenazone **8** underwent an exchange reaction smoothly to give the corresponding zinc reagent **9** which could be allylated in the presence of catalytic amounts of CuCN·2LiCl (Scheme 5).[26] Recently, also a chlorine-zinc-exchange was reported by using a zincate exchange reagent in the presence of Co(II) or Fe(III) salts as catalyst.[27]



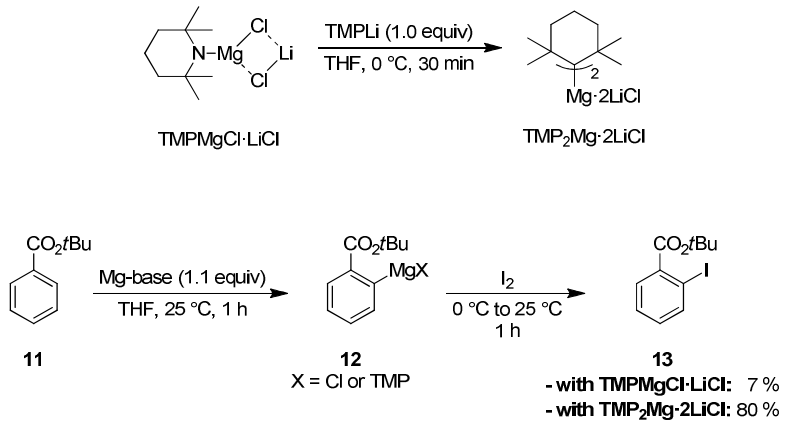
Scheme 5: I-Zn-exchange reaction using catalytic amounts of Li(acac).

2.3. METALATION

A pathway to organometallic reagents which is not limited by the availability of the corresponding halide precursors is the directed metalation. Here, a C-H bond is converted to a

[20] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.
[21] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[22] a) G. Wittig, U. Poeckels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106; c) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1.
[23] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.
[24] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[25] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[26] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.
[27] L. Melzig, C. R. Diene, C. J. Rohbogner, P. Knochel, *Org. Lett.* **2011**, *13*, 3174.

carbon-metal bond by the use of metal bases. Historically, this task was achieved the first time with *n*BuLi as base.[28] Later on non-nucleophilic, sterically hindered lithium amide bases have been established, e.g. LDA or TMPLi.[29] For the preparation of organomagnesium reagents which display a much higher functional group tolerance *Hauser* and co-workers developed magnesium amide bases of the type R_2NMgX and $(R_2N)_2Mg$.[30] However, major drawbacks of those bases were a very low solubility (0.2-0.7 M) and therefore an excess of the base (> 2 equiv) was needed for high conversions and reaction rates.[31] The presence of LiCl leads analogous as for organometallic reagents to a monomeric structure of the metal amide bases[32] and allows thus a higher solubility and reactivity in the metalation reactions.[33] The first example for one of these LiCl-activated TMP bases was TMPMgCl·LiCl which is prepared from TMP-H and *i*PrMgCl·LiCl and can be obtained as a 1.2 M solution in THF.[34] An even higher kinetic basicity shows $TMP_2Mg·2LiCl$ which is obtained from TMPMgCl·LiCl by addition of TMPLi and allows an efficient metalation of *tert*-butyl benzoate (**11**) at ambient conditions (Scheme 6).[35] The resulting magnesium reagent **12** affords after iodolysis the *o*-iodobenzoate **13**.

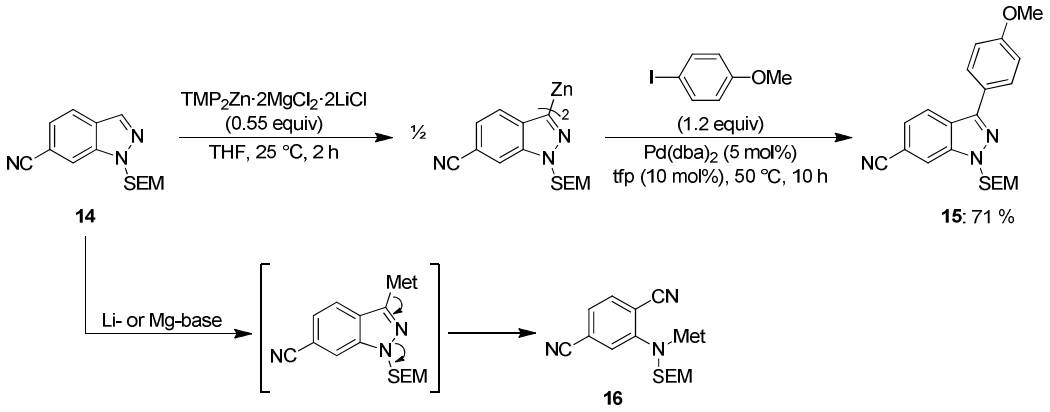


Scheme 6: Magnesiation of ester **11** with the highly active $TMP_2Mg·2LiCl$.

This method of mixed Li/metal amide bases was also extended to further metals like Zn, Al, Mn, Fe, Zr and La.[33] The use of TMP-zinc bases allows moreover the functionalization of electron-poor N-heteroaromatics or such substrates that bear e.g. a nitro-, aldehyde- or methyl ketone-

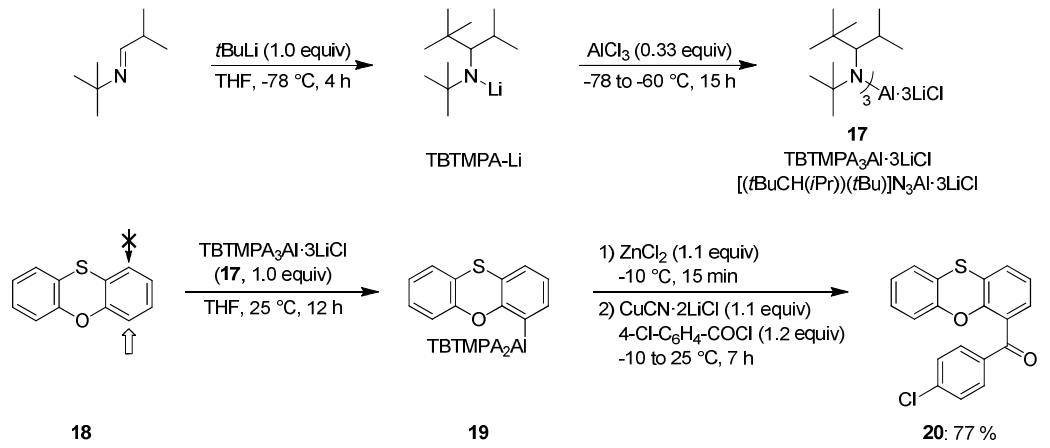
[28] a) H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109; b) G. Wittig, G. Fuhrmann, *Chem. Ber.* **1940**, *73*, 1197.
[29] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[30] C. R. Hauser, H. W. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295.
[31] a) P. E. Eaton, C.-H. Lee, Y. Xiong, R. Gilardi, *J. Am. Chem. Soc.* **1989**, *111*, 8016; b) W. Schlecker, A. Huth, E, Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[32] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Wheaterstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[33] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[34] 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) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113; d) N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525; e) N. Boudet, S. R. Dubbaka, P. Knochel, *Org. Lett.* **2008**, *10*, 1715; f) M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497.
[35] 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.

group.[36] A very recent example for the application of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ is the metalation of indazoles of type **14** which undergo fragmentation when Li- or Mg-bases are used (Scheme 7).[36d] Thus, after zincation and subsequent cross-coupling the 3-arylated indazole **15** is formed. In the case of lithium or magnesium reagents the aminonitriles such as **16** are produced quantitatively.



Scheme 7: Zincation of indazole **14** which potentially fragments while metalated.

Besides the aluminate base $(i\text{Bu})_3\text{Al(TMP)Li}$[37] also the LiCl-activated aluminum base $TMP_3Al{\cdot}3LiCl$ is known.[38] An even more sterically hindered amide like *N*-(*tert*-butyl)-2,2,4-trimethylpentan-3-amide (TBTMPA) produces the base $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})]N_3Al{\cdot}3LiCl$ ($TBTMPA_3Al{\cdot}3LiCl$, **17**) which showed the highest activity in the metalation of electron-rich substrates. The alumination using this base allows unusual regioselectivities as is shown in the case of phenoxathiine (**18,** Scheme 8). Due to the oxophilicity of aluminum the metalation occurs selectively *alpha* to the oxygen and the aluminated species **19** can undergo a subsequent acylation to give ketone **20**.



Scheme 8: Regioselective alumination of phenoxathiine (**18**) using the very active base **17**.

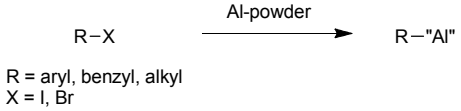
[36] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; c) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; d) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.

[37] H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921.

[38] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 1501.

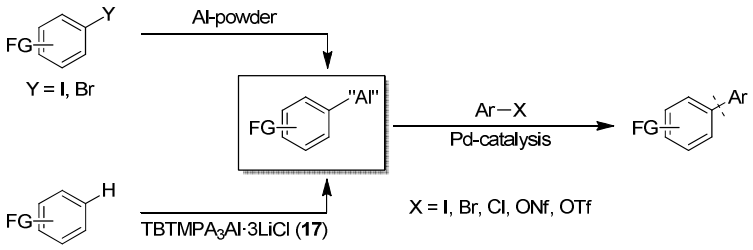
3. OBJECTIVES

One aim of this thesis was the preparation of new organoaluminum reagents by an insertion into various functionalized organic halides using commercial Al-powder (Scheme 9). Especially the synthesis of benzyl- and alkylaluminum compounds was in the focus. The use of aluminum as metal component should lead to several advantages compared to the developed methods using magnesium or zinc, for example the very low price, the relatively low toxicity and the possibility of an almost quantitatively recycling.[39] Even though a few methods for an Al-insertion are known these reactions need special activated Al-sources and often harsh conditions which goes along with a low functional group tolerance.



Scheme 9: Preparation of organoaluminum reagents by using commercial Al-powder.

A drawback in most of the reported applications of organoaluminum reagents is their need for a prior transmetalation, mostly to zinc, to perform an efficient cross-coupling.[40] As this strategy clearly contradicts the concept of atom economy,[3] a direct Pd-catalyzed cross-coupling of the aluminum reagents derived from an oxidative addition would be highly desired (Scheme 10). Possible electrophiles for such a direct cross-coupling would be aryl halides and pseudohalides. Furthermore, also the recently reported organoaluminum amides prepared by alumination of arenes and heteroarenes using the sterically hindered base **17** required a transmetalation with zinc salts to afford the corresponding cross-coupling products.[38] Also, for these nucleophiles a direct arylation in the presence of a Pd-catalyst was objected.



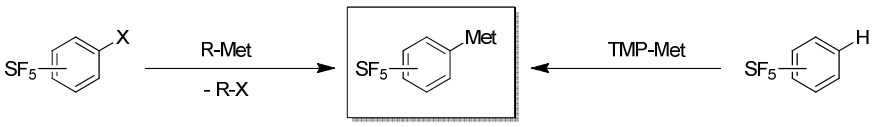
Scheme 10: Direct cross-coupling of organoaluminum reagents.

As fluorinated molecules gain a high attention in pharmaceutical and agrochemical research as well as material science continuously, growing interest is focused on the synthesis of such compounds. Furthermore, also analogs for the very common CF_3-function are studied. A very similar but more bulky substitute is the SF_5-group. Organometallics bearing this substituent are only barely known and tolerate this function only at low temperatures. Despite the reported lithium reagents, SF_5-substituted organomagnesium or -zinc compounds should display an

[39] a) *Mineral commodity summaries 2013*, U.S. Geological Survey, 13.03.2013, http://minerals.usgs.gov/minerals/pubs/mcs. b) H. W. Roesky, *Inorg. Chem.* **2004**, *43*, 7284; c) M. E. Schlesinger in *Aluminum Recycling*, CRC-Press, Boca-Raton, **2006**; d) A. F. Hollemann, E. Wiberg, N. Wiberg, in *Lehrbuch der anorganischen Chemie*, de Gruyter, Berlin, **1995**, 1061.

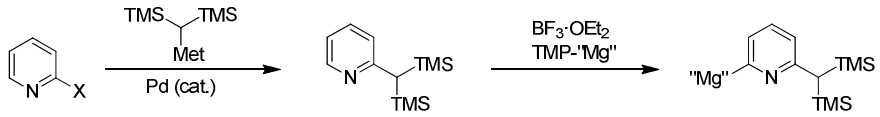
[40] a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; b) E. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738.

increased stability and compatibility with this fluorinated group. To access these organometallics, different pathways were chosen. On the one hand, a halide-metal exchange was studied starting from a SF_5-substituted organic halide with an exchange reagent R-Met (Scheme 11). On the other hand, also a directed metalation of substrates bearing this group was desired by applying sterically hindered TMP-metal bases (TMP-Met). Besides arene substrates, especially the preparation of heterocyclic organometallics bearing a SF_5-function was objected.



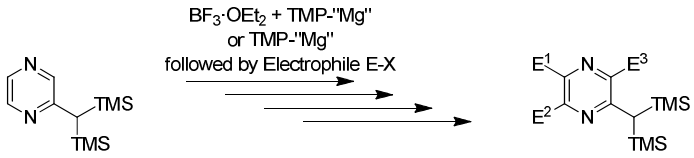
Scheme 11: Preparation of SF_5-substituted organometallics.

Finally, a regioselective metalation of N-heteroaromatics substituted by a bulky bissilylated methyl-group was aimed. For this task, the use of a combination of TMP-metal bases with the strong *Lewis* acid $BF_3{\cdot}OEt_2$ was studied. An advantage of silylated-substituents such as bis(trimethylsilyl)methyl is that it equals a masked methyl-group. Thus, due to steric effects not the more acidic benzylic position is deprotonated but the heteroaromatic core. A potential substrate for this strategy would be the pyridine scaffold. The introduction of the bulky silylated group was objected by a Pd-catalyzed cross-coupling of the corresponding metal reagent and a heteroaromatic halide (Scheme 12).



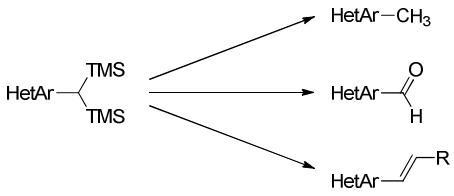
Scheme 12: Regioselective metalation of bis(trimethylsilyl)methyl-substituted pyridine.

Even more importantly would be a regioselective metalation of a diazine such as pyrazine substituted by bis(trimethylsilyl)methyl. Here, the bulky group should allow a differentiation of the three remaining positions of the heteroaromatic core. Thus, a regioselective full functionalization of this important diazine scaffold should be possible (Scheme 13).



Scheme 13: Regioselective full functionalization of pyrazine derivatives.

A further significant feature of the bissilylated methyl-substituent would be the various possible subsequent modifications. First of all, a deprotection to the corresponding methyl-substituted derivative can be achieved easily (Scheme 14). Moreover, also an oxidation of this function to an aldehyde is known and should be studied after metalation of the heteroaromatic core. In the presence of carbonyl-groups the bis(trimethylsilyl)methyl-substituent is also transformed to the corresponding alkene.



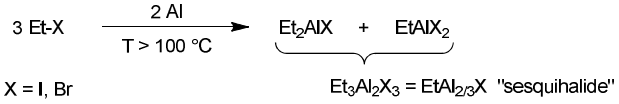
Scheme 14: Transformations of the bis(trimethylsilyl)methyl-group.

B. RESULTS & DISCUSSION

1. Preparation of Functionalized Organoaluminum Sesquihalides

1.1. Introduction

As mentioned in chapter A.2.1, in 1859 *Hallwachs* and *Schafarik* successfully prepared organoaluminum reagents for the first time.[11] They observed the reaction of ethyl iodide with aluminum turnings at 100 °C without the presence of a solvent (Scheme 15). The formed product of the formula $Et_3Al_2I_3$ could be separated by fractional distillation in a 1:1-mixture of diethylaluminum iodide (Et_2AlI) and ethylaluminum diiodide ($EtAlI_2$).[41] Such a mixture which results from the oxidative addition of aluminum into organic halides is usually termed as sesquihalide and abbreviated as $RAl_{2/3}X$.[42] An alternative description would be $R_{2-n}AlX_{n+1}$ with n = 0 or 1.



Scheme 15: First reported synthesis of an organoaluminum sesquihalide.

This method could only be applied to short aliphatic chains like methyl or ethyl and allylic halides.[42] For higher alkyl halides this insertion reaction was mostly inefficient. Remarkably, also the preparation of arylaluminum sesquiiodides was possible, however only for phenyl and tolyl substrates and again at high temperatures.[43] Further studies on the neat reaction of aromatic halides with aluminum powder concerned mostly on the activation of the passivated metal surface. Thus, small amounts of $AlCl_3$ or gallium showed to be beneficial for an activated aluminum surface which was applicable in an insertion reaction into phenyl and naphthyl iodide, bromide or even chloride.[44] However, the oxidative addition still needed harsh conditions like temperatures of 120-130 °C and neat mixing of the reagents.

Standard protocols for the preparation of organoaluminum reagents use so far mostly a transmetalation reaction of a different organometallic reagent with an aluminum salt or a diorganoaluminum halide.[45] Though, this indirect pathway is limited due to the stability and functional group tolerance of the precursory organolithium or organomagnesium reagent. A more straightforward approach to organoaluminum compounds displays the direct aluminum insertion into functionalized aryl halides which was reported recently by the *Knochel* group.[46] Here, as already was shown for insertion reactions of Zn or Mg (see chapter A.2.1) addition of the salt LiCl was valuable. In contrast to the before mentioned metal insertion methods a

[41] A. Cahours, *Liebigs Ann. Chem.* **1860**, *114*, 227.

[42] T. Mole, E. A. Jeffery, *Organoaluminium Compounds*, Elsevier, Amsterdam, **1972**.

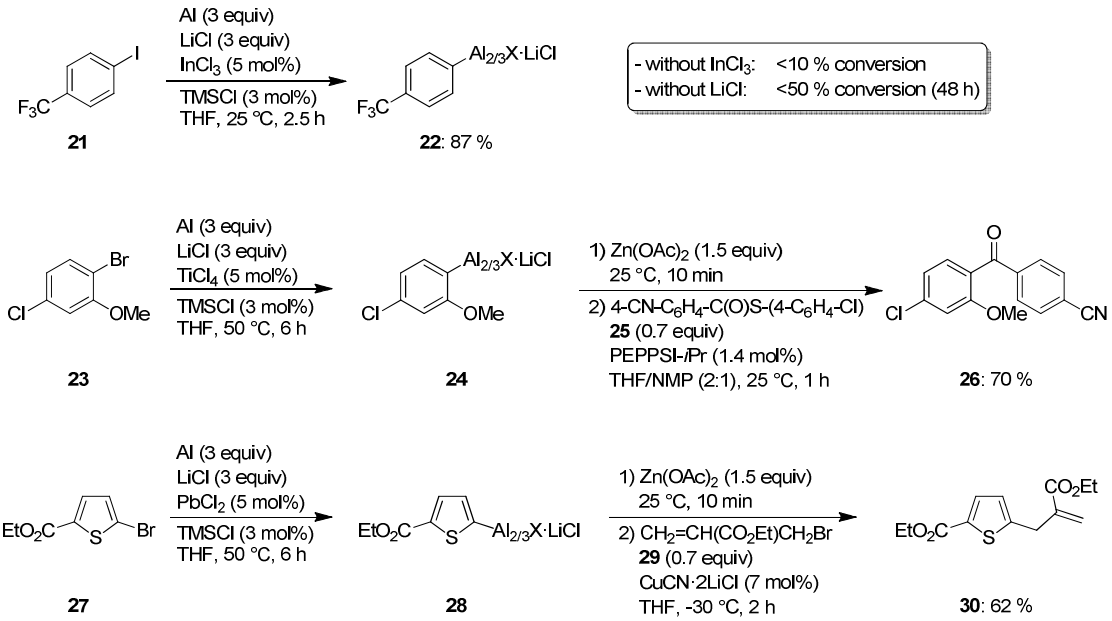
[43] a) J. F. Spencer, M. L. Wallace, *J. Chem. Soc., Trans.* **1908**, *93*, 1827; b) A. V. Grosse, J. M. Mavity, *J. Org. Chem.* **1940**, *5*, 106.

[44] a) H. Adkins, C. Scanley, *J. Am. Chem. Soc.* **1951**, *73*, 2854; b) D. Wittenberg, *Liebigs Ann. Chem.* **1962**, *654*, 23; c) X. Tang, D. Rawson, S. Woodward, *Synlett* **2010**, 636.

[45] a) G. Wittig, D. Wittenberg, *Liebigs Ann. Chem.* **1957**, *606*, 1; b) W. Seidel, *Z. Anorg. Allg. Chem.* **1985**, *524*, 101; c) C. Hawner, K. Li, V. Cirriez, A. Alexakis, *Angew. Chem. Int. Ed.* **2008**, *47*, 8211; d) S. Zhou, D.-W. Chuang, S.-J. Chang, H.-M. Gau, *Tetrahedron: Asymmetry* **2009**, *20*, 1407; e) H. Gao, P. Knochel, *Synlett* **2009**, 1321.

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

catalyst was needed to trigger the oxidative addition, even though the mechanistic effect of this metallic chlorides has not been established yet. The most efficient catalysts for the insertion in THF that were found are $InCl_3$, $BiCl_3$, $TiCl_4$ and $PbCl_2$ (Scheme 16). The activation of the aluminum surface was achieved by addition of catalytic amounts of TMSCl.[47]



Scheme 16: Catalyzed Al-insertion into functionalized aromatic halides.

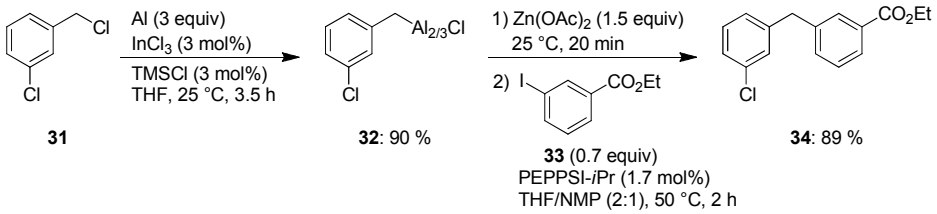
Thereby, the choice of used catalyst depends on the structure of the substrate. For most aromatic iodides of the type **21** $InCl_3$ and $BiCl_3$ gave the highest yields for the aluminum insertion at 25-50 °C in 2-24 h (Scheme 16). In the absence of either $InCl_3$ or the additive LiCl, the insertion did not reach completion. When the insertion was performed with bromides such as **23**, $TiCl_4$ showed a higher activity and allowed the formation of organoaluminum sesquihalides **24** in good yields. These chlorides however were not able to catalyze the insertion of aluminum into carbonyl-functionalized halides of the type **27**. For these substrates, $PbCl_2$ was a suitable catalyst which could be applied to aromatic and heteroaromatic halides bearing an ester- or an amide-substituent. The thus prepared arylaluminum compounds like **24** and **28** could be functionalized subsequently after a transmetalation with $Zn(OAc)_2$ e.g. by a *Liebeskind-Srogl*-acylation[48] using thioester **25** and PEPPSI-*i*Pr[49] as catalyst to give ketone **26** or by a Cu-catalyzed allylation affording thiophene **30**. So far, this method was only applied on aromatic halides. Thus, an extension to functionalized benzyl or alkyl halides would be of high interest.

1.2. Preparation of Benzylaluminum Sesquichlorides

The above mentioned method for the preparation of arylaluminum reagents was investigated for an extension to benzylic substrates. For the optimization of this reaction 3-chlorobenzyl

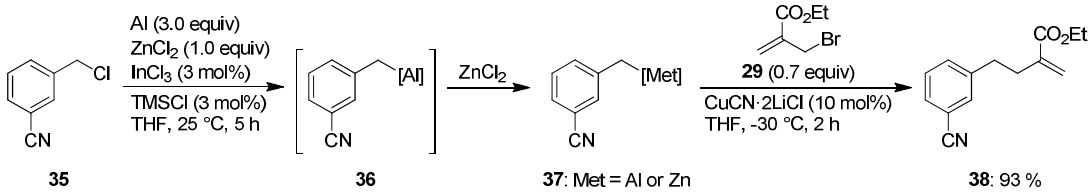
[47] K. Takai, T. Ueda, T. Hayashi, T. Moriwake, *Tetrahedron Lett.* **1996**, *37*, 7049.
[48] J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376.
[49] M. Organ, S. Avola, I. Dubovyk, N. Hadei, E. Assen B. Kantchev, C. J. O'Brien, *Chem. Eur. J.* **2006**, *12*, 4749.

chloride (**31**) was used as starting material. Several experiments on the oxidative addition of aluminum powder (3.0 equiv) into **31** with the established catalysts $PbCl_2$, $TiCl_4$ and $InCl_3$ as well as in the presence and absence of LiCl revealed the optimum conditions. The most active and also most efficient catalyst was $InCl_3$ (3 mol%) without the addition of LiCl as it provided the benzylaluminum sesquichloride **32** in 90 % yield after 3.5 h at 25 °C (Scheme 17). After a transmetalation with $Zn(OAc)_2$ (1.5 equiv) and a Pd-catalyzed cross-coupling the diarylmethane **34** was obtained in 89 % yield[50] which represents a class of molecules that shows a high pharmacological potential.[51]



Scheme 17: Optimized conditions for the Al-insertion into benzyl chloride **31**.

For ester- or nitrile-functionalized benzyl chlorides however, these conditions did not afford the corresponding benzylaluminum reagents in a satisfying yield. Nevertheless, an optimization of this insertion method into substrates such as **35** was achieved by an *in situ*-trapping of the intermediate organometallic reagent with $ZnCl_2$.[52] Thus, the benzylmetal reagent of the type **37** was obtained in good yield when a solution of $ZnCl_2$ (1.0 equiv) in THF was added to the insertion mixture of Al powder (3.0 equiv) and $InCl_3$ (3 mol%) before the substrate was adjoined (Scheme 18). The nature of this organometallic was verified by ^{1}H-, ^{13}C- and ^{27}Al-NMR spectroscopy and identified as a mixture of a benzylzinc and benzylaluminum reagent. Furthermore, an allylation reaction in the presence of CuCN·2LiCl with ethyl (2-bromomethyl)acrylate[53] (**29**, 0.7 equiv) afforded the expected product **38** in a very good yield.[50] This variation of the Al-insertion was also suitable for secondary benzyl chlorides.



Scheme 18: Al-insertion and *in situ*-trapping with $ZnCl_2$ for the preparation of the mixed benzylzinc and benzylaluminum reagent of type **37**.

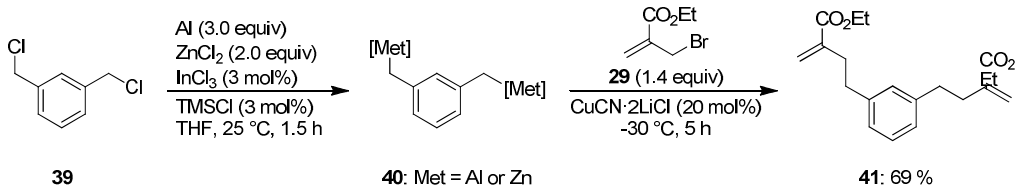
[50] These experiments were performed by Dr. Tobias D. Blümke and are given for the sake of completeness. For further information, see: T. D. Blümke, *PhD Thesis*, Ludwig-Maximilians-Universität, Munich, **2012**.

[51] a) P. D. Leeson, J. C. Emmett, V. P. Shah, G. A. Showell, R. Novelli, H. D. Prain, M. G. Benson, D. Ellis, N. J. Pearce, A. H. Underwood, *J. Med. Chem.* **1989**, *32*, 320; b) N. Kaila, K. Janz, A. Huang, A. Moretto, S. DeBernardo, P. W. Bedard, S. Tam, J. Clerin, J. C. Keith, D. H. H. Tsao, N. Sushkova, G. D. Shaw, R. T. Camphausen, R. G. Schraub, Q. Wang, *J. Med. Chem.* **2007**, *50*, 40.

[52] a) F. M. Piller, A. Metzger, M. A. Schade, B. H. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; b) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082.

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

Moreover, this *in situ*-trapping also allowed the preparation of benzylic bimetallic reagents. So far, only a few preparation methods for such compounds are known.[54] Usually, high dilution (< 0.1 M) and dropwise addition of the benzylic substrate are needed and therefore not very practicable. In contrast, when 1,3-bis(chloromethyl)benzene (**39**) was subjected to an insertion reaction using Al-powder (3.0 equiv), $InCl_3$ (3 mol%) and $ZnCl_2$ (2.0 equiv) in THF at a concentration of 0.5 M the 1,3-benzylic bimetallic **40** was obtained in good yield (Scheme 19). Subsequent trapping of this reagent by a Cu-catalyzed allylation reaction afforded the bis-functionalized benzene derivative **41** in 69 % isolated yield.



Scheme 19: Preparation and subsequent trapping of the 1,3-benzylic bimetallic **40**.

1.3. Preparation of Alkylaluminum Sesquihalides

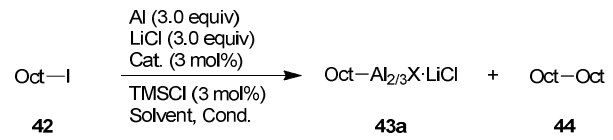
Even though the oxidative addition of aluminum into ethyl iodide was already reported over a century ago,[11] this method has not been established as a standard protocol in organic synthesis. The absence of a solvent and the harsh conditions of this reaction hampers its preparative use. Therefore, a variation of the above mentioned method for the preparation of alkylaluminum sesquihalides by a catalyzed direct insertion into alkyl halides in THF at ambient temperatures would be desirable. The well-established catalysts for the insertion reaction into aromatic halides were thus tested in the presence of LiCl by using octyl iodide (**42**) as reference substrate (Table 1). Furthermore, the possible use of various solvents was investigated, especially non-coordinating ones but also very polar solvents.

The comparison of the catalysts $InCl_3$, $BiCl_3$, $TiCl_4$ and $PbCl_3$ (3 mol%) in the insertion reaction using Al-powder (3.0 equiv), LiCl (3.0 equiv) in THF at 25 °C for 16 h reveals a full conversion of the aliphatic iodide, except for $PbCl_2$ where only 88 % of 1-iodooctane (**42**) has reacted (Table 1, entries 1-4). However, the more active catalysts $InCl_3$, $BiCl_3$ and $TiCl_4$ show a less selective reaction as they form predominately the homodimer of the starting material, hexadecane (**44**). The desired octylaluminum sesquihalide **43a** was produced only in yields of 20-40 %, when those catalysts were used (entries 1-3). In contrast, the less reactive $PbCl_2$ showed a selective formation of the desired organoaluminum reagent **43a** (entry 4). For reaching full conversion with $PbCl_2$ in THF the insertion reaction had to be performed at 50 °C and after 2.5 h the starting iodide **42** was converted to the octylaluminum sesquihalide **43a** in 90 % (entry 5).

[54] a) M. F. Lappert, T. R. Martin, *J. Chem. Soc., Dalton Trans.* **1982**, 1959; b) B. Jousseaume, J. G. Duboudin, *J. Organomet. Chem.* **1982**, *238*, 171; c) L. M. Engelhardt, R. I. Papasergio, C. L. Raston, A. H. White, *J. Chem. Soc., Dalton Trans.* **1984**, 311; d) C. L. Raston, G. Salem, *J. Chem. Soc., Dalton Trans.* **1984**, 1702; e) W. P. Leung, C. L. Raston, B. W. Skelton, A. H. White, *J. Chem. Soc., Dalton Trans.* **1984**, 1801; f) H. Yoshida, S. Nakano, Y. Yamaryo, J. Ohshita, A. Kunai, *Org. Lett.* **2006**, *8*, 4157.

After the ideal catalyst was found for the Al-insertion also a variety of solvents were tested for this reaction (Table 1). Dimethoxyethane (DME) was found to be a suitable solvent for an oxidative addition of aluminum into 1-iodooctane (**42**) as 70 % of the desired organoaluminum reagent were detected (entry 6). However, the rate of the insertion was slightly lower than in THF, because after 17 h at 25 °C a conversion of 80 % was observed. In the case of DMF, already after 1 h at 25 °C the complete starting material was consumed (entry 7). Though, only 1-chlorooctane was observed as product, which was formed by a nucleophilic substitution of the iodide analogous to a *Finkelstein* reaction.[55] This intermediate could then finally react to the desired octylaluminum reagent **43a**, when the reaction mixture was heated to 80 °C for 4 d, but only in an unsatisfying yield. The use of non-coordinating solvents for organoaluminum chemistry is of high interest due to the increased Lewis acidity the Al-center shows when its empty orbital is not complexed by a Lewis basic solvent like an ether.[56] To our delight, the catalyzed Al-insertion into 1-iodooctane (**42**) proceeded seemingly well in hydrocarbon solvents like benzene and toluene, however only after heating the reaction mixture to 80 °C (entries 8 and 9). The yield of octylaluminum reagent **43a** was in both solvents comparable (75-78 %). As LiCl is not soluble in hydrocarbon solvents, a reference experiment for an Al-insertion in toluene using $PbCl_2$ as catalyst in the absence of LiCl was conducted and an even higher yield of the organometallic **43a** was observed (83 %, entry 9, footnote f).

Table 1: Screening of catalysts and solvents for the Al-insertion into octyl iodide (**42**).



42 **43a** **44**

Entry	Cat.	Solvent	Cond.	Conversion[a]	Yield of **43a**[b]	Yield of **44**[a]
1	$InCl_3$	THF	25 °C, 16 h	96 %	35 %	50 %
2	$BiCl_3$	THF	25 °C, 16 h	93 %	40 %	30 %
3	$TiCl_4$	THF	25 °C, 16 h	97 %	20 %	50 %
4	$PbCl_2$	THF	25 °C, 16 h	88 %	60 %	-[c]
5	$PbCl_2$	THF	50 °C, 2.5 h	95 %	90 %	-[c]
6	$PbCl_2$	DME	25 °C, 40 h	89 %	70 %	-[c]
7	$PbCl_2$	DMF	80 °C, 96 h	98 %[d]	40 %[e]	-[c]
8	$PbCl_2$	Benzene	80 °C, 4.5 h	95 %	78 %	-[c]
9	$PbCl_2$	Toluene	80 °C, 4.5 h	91 %	75 %[f]	-[c]

[a] Determined by GC analysis using tetradecane as internal standard. [b] Determined by GC analysis of an iodolyzed aliquot using tetradecane as internal standard. [c] Not observed. [d] After 1 h at 25 °C, a quantitative conversion to octyl chloride was observed, which reacted in an Al-insertion only after heating to 80 °C. [e] Accompanied by 15 % Oct-Cl. [f] When the insertion was carried out in the absence of LiCl, 83 % of octylaluminum sesquihalide **43a** was detected.

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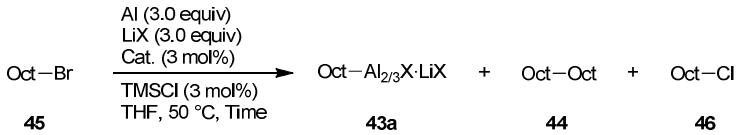
As bromo-derivatives are in general cheaper than their iodo-analogues, an oxidative addition using aluminum powder into bromides would be also highly desirable. Thus, also a catalyzed Al-insertion into octyl bromide (**45**) was investigated (Table 2).

Table 2: Screening of catalysts and additives for the Al-insertion into octyl bromide (**45**).

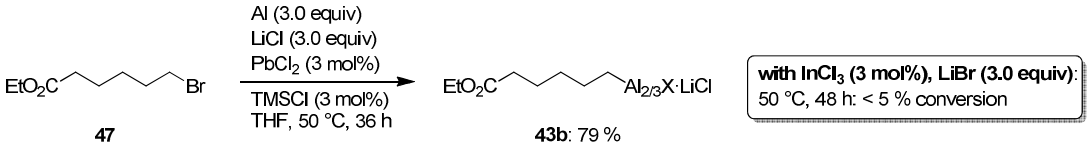


Entry	Cat.	LiX	Time	Conversion[a]	Yield of **43a**[b]	Yield of **44**[a]	Yield of **46**[a]
1	$PbCl_2$	LiCl	70 h	95 %	80 %	-[c]	-[c]
2	$PbCl_2$	LiCl[d]	24 h	69 %	< 5 %[e]	-[c]	46 %
3	$TiCl_4$	LiCl	18 h	96 %	44 %[f]	17 %	-[c]
4	$BiCl_3$	LiCl	18 h	83 %	58 %	-[c]	-[c]
5	$InCl_3$	LiCl	18 h	97 %	54 %	-[c]	30 %
6	$InCl_3$	LiBr	8 h	95 %	88 %	-[c]	-[c]

[a] Determined by GC analysis using tetradecane as internal standard. [b] Determined by GC analysis of an iodolyzed aliquot using tetradecane as internal standard. [c] Not observed. [d] An extra amount of 0.5 equiv LiI were added to the reaction mixture. [e] The formation of 25 % of Oct-I (**42**) was observed. [f] Octane was produced in 30 %.

Even though $PbCl_2$ showed the best result in the case of 1-iodooctane (**42**) the oxidative addition of Al-powder (3.0 equiv) in the presence of LiCl (3.0 equiv) into octyl bromide (**45**) using this catalyst (3 mol%) proceeded only very slowly at 50 °C (Table 2, entry 1). After 18 h only a conversion of 37 % was observed. Full conversion was detected after 70 h and remarkably the yield of octylaluminum sesquihalide **43a** after this prolonged reaction time was indeed very high. An attempt to increase the kinetics of the insertion by addition of 0.5 equiv LiI to perform a partial halide substitution of octyl bromide (**45**) to the iodide **42** which should undergo the insertion faster (entry 2). However, this was not successful and surprisingly, no active species at all was produced. This mixture of chloride and iodide salt resulted in the formation of octyl chloride (**46**) and octyl iodide (**42**) which apparently did not react in an oxidative addition. The highly active catalyst $TiCl_4$ produced the desired organoaluminum compound **43a** in 44 % after 18 h at 50 °C which was accompanied by the homodimer hexadecane (**44**) and a significant amount of octane which corresponds to the hydrolysis of the active species (entry 3). The use of $BiCl_3$ as catalyst led to an incomplete reaction after 18 h at 50 °C and afforded 54 % of octylaluminum sesquihalide **43a** (entry 4). A comparable amount of the desired aluminum reagent was formed with catalytic amounts of $InCl_3$ and LiCl (3.0 equiv) as additive (entry 5). However, a substitution of the bromide in the starting material by a chloride was observed and 30 % of 1-chlorooctane (**46**) were formed. This problem could be overcome by using LiBr (3.0 equiv) instead and an efficient insertion could be performed (entry 6). Using this modified procedure 88 % of the desired octylaluminum sesquihalide **43a** was produced after 8 h at 50 °C.
In contrast, when the alkyl halide was functionalized with a carbonyl group, as it is the case for ethyl 6-bromohexanoate (**47**), $InCl_3$ does not show any catalytic activity (Scheme 20). In

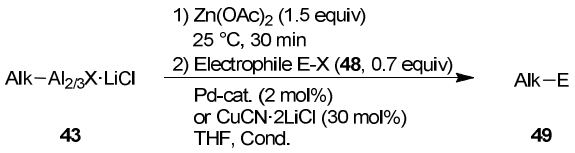
accordance with the catalyzed Al-insertion into aromatic halides, $PbCl_2$ is needed as catalyst for carbonyl-functionalized substrates. Thus, by using Al-powder (3.0 equiv), LiCl (3.0 equiv) and catalytic amounts of $PbCl_2$ (3 mol%) the desired alkylaluminum reagent **43b** is produced in a good yield of 79 % after 36 h at 50 °C (Scheme 20).

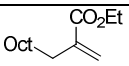
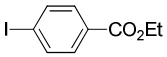
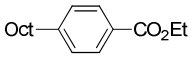
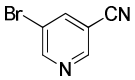
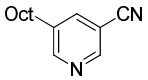
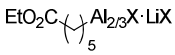
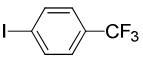
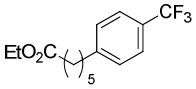
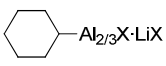
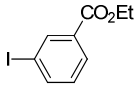
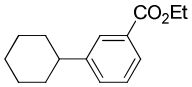


Scheme 20: Al-insertion into ethyl 6-bromohexanoate (**47**).

The thus prepared alkylaluminum sesquihalides could be used for different trapping reactions. Like for aryl and benzyl reagents a transmetalation of the aluminum compounds was conducted with Zn(OAc) (1.5 equiv, 25 °C, 30 min) and a subsequent allylation or a Pd-catalyzed cross-coupling gave good yields (Table 3).

Table 3: Functionalizations of alkylaluminum reagents **43** after transmetalation with $Zn(OAc)_2$.



Entry	Nucleophile	Electrophile, Cond.	Product Yield[a]
	Oct−$Al_{2/3}X·LiX$		
1	**43a**	**48a**, -30 to 25 °C, 12 h	**49a**: 78 %[b]
			
2	**43a**	**48b**, 25 °C, 30 min	**49b**: 75 %[c] (70 %[d])
			
3	**43a**	**48c**, 50 °C, 4 h	**49c**: 60 %[c]
			
4	**43b**	**48d**, 50 °C, 3 h	**49d**: 85 %[c]
			
5	**43c**	**48e**, 50 °C, 4 h	**49e**: 62 %[c]

[a] Yield of isolated, analytically pure product. [b] CuCN·2LiCl (30 mol%) was added. [c] $Pd(OAc)_2$ (2 mol%) and S-Phos (4 mol%) were added. [d] Cross-coupling conditions: PEPPSI-*i*Pr (2 mol%), THF/NMP (2:1), 25 °C, 16 h.

Using octylaluminum sesquihalide **43a** which was either obtained starting from octyl iodide or bromide afforded the allylated product **49a** in a yield of 78 % when CuCN·2LiCl (30 mol%) was added to the transmetalated nucleophile and ethyl (2-bromomethyl)acrylate (**48a**, Table 3,

entry 1). The cross-coupling of this aluminum reagent with ethyl 4-iodobenzoate (**48b**) in the presence of catalytic amounts of $Pd(OAc)_2$ (2 mol%) and S-Phos[57] (4 mol%) in THF gave the desired ethyl benzoate **49b** in a yield of 75 % after 30 min at 25 °C (entry 2). This catalyst system proved to be more efficient for alkylaluminum sesquihalides than the conditions that were applied for aromatic and benzylic reagents after transmetalation (PEPPSI-*i*Pr (2 mol%), THF/NMP (2:1)) as it afforded the cross-coupling product in a higher yield (75 % compared to 70 %) and in a shorter reaction time (30 min compared to 16 h). Furthermore, also heteroaromatic bromides such as **48c** could be used as electrophile in cross-couplings using $Pd(OAc)_2$ (2 mol%) and S-Phos (4 mol%) to afford the desired pyridine derivative **49c** in 60 % yield after 4 h at 50 °C (entry 3). Also, the ester-functionalized alkylaluminum reagent **43b** underwent a smooth cross-coupling with this catalyst system and gives the desired product **49d** in an isolated yield of 85 % (entry 4). The above mentioned catalyzed Al-insertion method for alkyl bromides can also be applied for secondary alkyl substrates. Thus, cyclohexylaluminum sesquihalide **43c** is obtained from cyclohexyl bromide with Al-powder (3.0 equiv), LiBr (3.0 equiv) and $InCl_3$ (3 mol%) in THF after 18 h at 50 °C. This aluminum reagent was then cross-coupled with ethyl 3-iodobenzoate (**48e**) to give the desired product **49e** in 62 % yield after 4 h at 50 °C (entry 5).

Using alkylaluminum sesquihalides in a direct cross-coupling without prior transmetalation to Zn was also achieved, but will be discussed in the following part (see page 31). All attempts to use the alkylaluminum reagents that were prepared in non-coordinating solvents like toluene or benzene in carboalumination reactions following the procedures of *Negishi* or *Wipf*[58] with either Cp_2ZrCl_2 or Cp_2TiCl_2 did not produce any satisfying results.

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2. Direct Cross-Coupling of Organoaluminum Reagents

2.1. Introduction

Even though organoaluminum reagents were the first non-*Grignard* compounds that underwent a Pd- or Ni-catalyzed cross-coupling,[59] these organometallic reagents have not been used widely for such C-C bond formations in contrast to B,[60] Zn,[61] Sn[62] or Mg.[63] In general, the cross-coupling of aluminum compounds was restricted to triorganoalanes such as $AlPh_3$[64] or $AlEt_3$,[65] in which case only one organic rest was transferred. However, the coupling of mixed organoalanes like $RAlEt_2$ or $RAl(i\text{Bu})_2$ (R = Ar, alkenyl or alkynyl)[66] as well as organoaluminates e.g. $RAl(i\text{Bu})_3Li$[37] have been reported recently. In these reactions, the unsaturated R group was always transferred selectively. The cross-coupling of alkyl, vinyl and allyl groups is also possible by using appropriate amino and oxygen-containing ligands.[67] Alternatively, the organoalanes needed transmetalation with zinc salts for an efficient cross-coupling.[40, 68] This was also the case for the functionalized organoaluminum sesquihalides that were obtained by the above mentioned catalyzed Al-insertion.[46] However, to promote possible applications of these organoaluminum sesquihalides in organic synthesis a practical, direct cross-coupling would be highly desirable.

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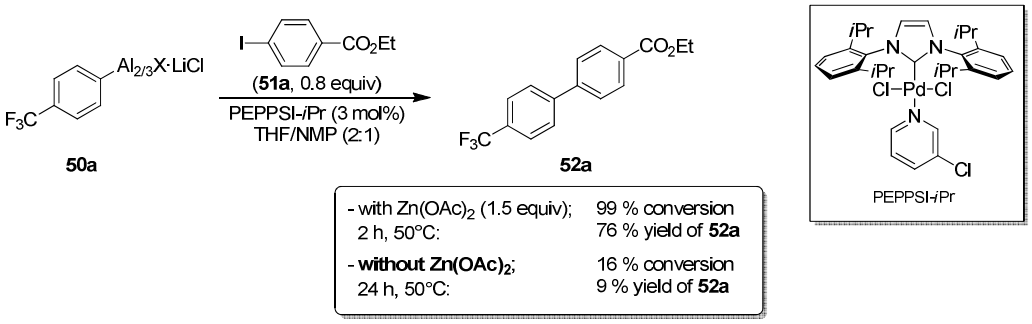
2.2. Development of the Conditions for a Direct Cross-Coupling

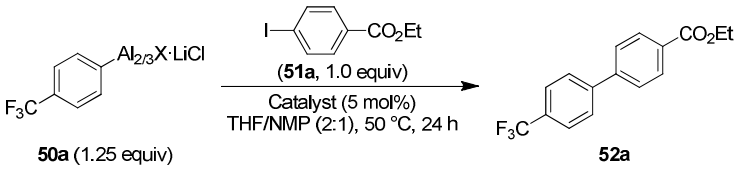
As already shown in chapter B.1, aryl-, benzyl- and alkylaluminum sesquihalides undergo a very efficient cross-coupling in the presence of PEPPSI-*i*Pr after a prior transmetalation of the organoaluminum compound with Zn salts. Thus, the cross-coupling product **52a** is obtained in a yield of 76 % with catalytic amounts of PEPPSI-*i*Pr (3 mol%) in THF/NMP (2:1) after 2 h at 50 °C, when the corresponding arylaluminum sesquihalide **50a** was transmetalated previously with $Zn(OAc)_2$ (1.5 equiv, Scheme 21). If a cross-coupling is attempted without a previous addition of $Zn(OAc)_2$ the conversion of the electrophile **51a** is very low even after a prolonged reaction time of 24 h at 50 °C. Here, only 9 % of the desired biphenyl **52a** were detected.



Scheme 21: Cross-coupling of organoaluminum reagent **50a** in the presence of PEPPSI-*i*Pr with and without prior transmetalation to Zn.

As only traces of the desired product **52a** were produced with catalytic amounts of PEPPSI-*i*Pr, various other catalyst systems were tested for a direct cross-coupling of the arylaluminum sesquihalide **50a** with ethyl 4-iodobenzoate (**51a**) in THF/NMP (2:1) at 50 °C for 24 h (Table 4).

Table 4: Screening of catalysts for a direct cross-coupling of organoaluminum reagent **50a**.



Entry	Catalyst	Conversion of **51a**[a]	Yield of **52a**[a]
1	$Pd(OAc)_2$ + PCy_3	12 %	10 %
2	$Pd(PPh_3)_4$	25 %	21 %
3	$Pd(PPh_3)_2Cl_2$	11 %	8 %
4	$PdCl_2$ + dppf	12 %	10 %
5	$Pd(OAc)_2$ + P(*p*-tolyl)$_3$	14 %	6 %
6	$Pd(OAc)_2$ + S-Phos	49 %	10 %
7	$Pd(dba)_2$ + RuPhos	72 %	48 %
8	$PdCl_2$ + *i*Pr·HCl	99 %	25 %
9	$Pd(PhCN)_2Cl_2$	99 %	20 %
10	$Pd(tmpp)_2Cl_2$	99 %[b]	69 %

[a] Determined by GC analysis using tetradecane as internal standard. [b] After 6 h at 50 °C, a conversion > 95 % of **51a** was achieved.

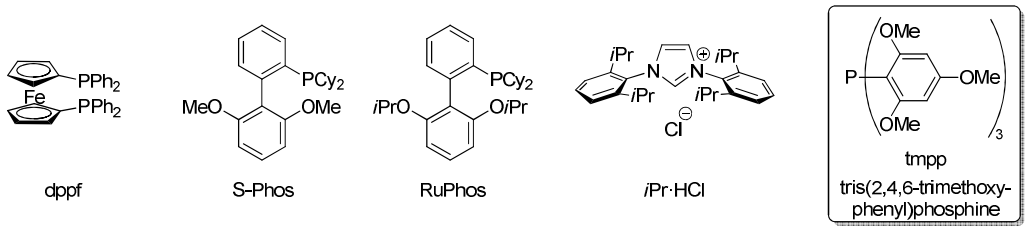


Figure 1: Applied ligands in the screening of catalyst systems in Table 4.

The recently described cross-coupling of $ArAlEt_2(THF)$ with various electrophiles is performed by using the catalyst system of $Pd(OAc)_2$ and PCy_3.[66d] However, this combination did not lead to satisfying results for a direct cross-coupling of arylaluminum sesquihalide **50a** as only a conversion of 12 % of the electrophile **51a** was detected after 24 h at 50 °C (Table 4, entry 1). Similarly, the preformed Pd catalysts $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$, which were widely used before for transferring one phenyl substituent of $AlPh_3$,[64] afforded only 21 % or 8 %, respectively of the desired biphenyl **52a** (entries 2 and 3). Further catalyst systems of $PdCl_2$ or $Pd(OAc)_2$ with common phosphine ligands like dppf, P(*p*-tolyl)$_3$ or S-Phos (Figure 1) likewise only produced the desired product in 10 % or less (entry 4-6). Another powerful phosphine ligand developed by *Buchwald*, RuPhos,[69] gave in combination with $Pd(dba)_2$ at least 48 % of biphenyl **52a** (entry 7). However, the rate of the cross-coupling reaction decreased dramatically after a few hours and did not reach full conversion after 24 h at 50 °C. Interestingly, in the case of the NHC-ligand *i*Pr·HCl[70] a conversion > 95 % was achieved within this reaction time (entry 8). Though, only an unsatisfying yield of 25 % was detected for the desired product **52a** with this catalyst system. Also, the quite simple complex $Pd(PhCN)_2Cl_2$ achieved a full conversion of the electrophile **51a** after 24 h at 50 °C, but again with a low yield of 20 % for the biphenyl **52a** (entry 9). On the contrary, the preformed complex $Pd(tmpp)_2Cl_2$[71] bearing the very electron-rich ligand tmpp affords a yield of 69 % of the desired product **52a** (entry 10). Here, full conversion was already achieved after 6 h at 50 °C.

As this electron-rich tmpp-ligand showed such a high activity various Pd-sources were tested in this direct cross-coupling, to improve the yield of the product **52a** (Table 5). Additionally, more transition metal-salts were examined to test a possible Ni- or Fe-catalyzed cross-coupling using this ligand.

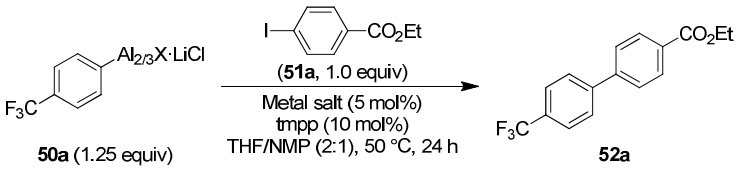
For comparison with the preformed complex $Pd(tmpp)_2Cl_2$ also mixing $PdCl_2$ (5 mol%) together with tmpp (10 mol%) as ligand in the reaction mixture was tested (Table 5, entry 1). This combination afforded the desired biphenyl **52a** in a comparable yield of 67 %, however, the conversion was significantly lower as only 6 % of **51a** reacted after 2 h at 50 °C. The use of other Pd-salts such as $Pd(OAc)_2$ or $Pd(dba)_2$ in the catalyst system gave the product in considerably lower yields (entries 2 and 3). Moreover, trying different salts of Ni or Fe as cheaper substitutes for Pd for a possible direct cross-coupling of organoaluminum sesquihalides did not lead to any conversion at all and were therefore not investigated further (entries 4-7).

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

[70] a) A. J. Arduengo, III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523; b) L. Jafarpour, E. D. Stevens, S. P. Nolan, *J. Organomet. Chem.* **2000**, *606*, 49.

[71] a) K. R. Dunbar, J.-S. Sun, *J. Chem. Soc., Chem. Commun.* **1994**, 2387; b) K. Dunbar, S. C. Haefner, *Polyhedron* **1994**, *13*, 727.

Table 5: Screening of various transition metal salts in combination with tmpp as ligand.

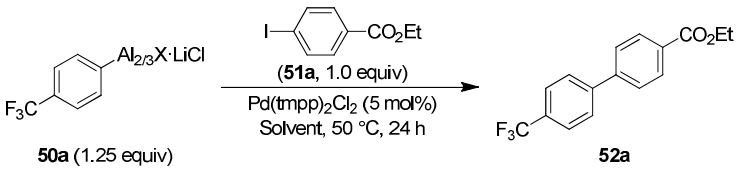


Entry	Metal salt	Conversion of **51a**[a]	Yield of **52a**[a]
1	$PdCl_2$	99 %	67 %
2	$Pd(OAc)_2$	99 %	43 %
3	$Pd(dba)_2$	99 %	45 %
4	$NiCl_2$	-[b]	-
5	$Ni(acac)_2$	-[b]	-
6	$FeCl_3$	-[b]	-
7	$Fe(acac)_3$	-[b]	-

[a] Determined by GC analysis using tetradecane as internal standard. [b] No conversion (< 5 %) of **51a** was observed.

After the preformed complex of $Pd(tmpp)_2Cl_2$ was found as ideal catalyst for the direct cross-coupling of arylaluminum sesquihalide **50a** with ethyl 4-iodobenzoate **51a**, the influence of the solvent system was studied further (Table 6).

Table 6: Screening of the solvent system for the direct cross-coupling using $Pd(tmpp)_2Cl_2$.



Entry	Solvent		Conversion of **51a**[a]	Yield of **52a**[a]
1	THF/NMP	(1:1)	99 %	71 %
2	THF/NMP	(1:2)	99 %	79 %
3	THF/NEP	(1:2)	64 %	61 %
4	THF/DMPU	(1:2)	81 %	73 %
5	THF/DMAc	(1:2)	11 %	6 %
6	THF/DMF	(1:2)	99 %	89 % (83 %[b])

[a] Determined by GC analysis using tetradecane as internal standard. [b] Isolated yield of **52a** after 2 h at 50 °C.

Increasing the percentage of polar solvent, i.e. NMP, from 33 % (THF/NMP (2:1), Table 4, entry 10) over 50 % (THF/NMP (1:1), Table 6, entry 1) to 66 % (THF/NMP (1:2), entry 2) improved constantly the yield of the cross-coupling product **52a** from 69 % over 71 % to 79 %. Therefore, further polar co-solvents were tested in a ratio of 2:1 with THF. Interestingly, the very similar NEP did not achieve full conversion and a decreased yield of 61 % was observed (entry 3). Also DMPU gave a lower yield of the biphenyl **52a** (73 %, entry 4) compared to NMP. The use of DMAc as polar component of the solvent system did lead to almost no product formation and also a very low conversion (entry 5). In contrast, when a mixture of THF/DMF (1:2) was applied

in the cross-coupling, the yield of the desired product was improved to 89 % as was detected by GC analysis (entry 6). Moreover, already after a reaction time of 2 h at 50 °C the biphenyl **52a** could be isolated in a yield of 83 %. Hence, the preformed complex of $Pd(tmpp)_2Cl_2$ in a solvent system of THF/DMF (2:1) allows an efficient direct cross-coupling of arylaluminum sesquihalides at 50 °C without the need for a prior transmetalation to Zn.

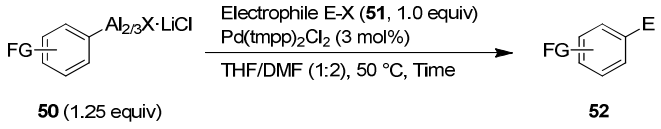
2.3. Direct Cross-Coupling of Arylaluminum Sesquihalides

After the ideal conditions were found for the direct cross-coupling of organoaluminum sesquihalides, the scope of this method was estimated by using various electrophiles of the type **51** for a reaction with different arylaluminum reagents. First, halogenated arylaluminum compounds of the type **50** (1.25 equiv) were tested in the cross-coupling with several aryl halides and pseudohalides in the presence of $Pd(tmpp)_2Cl_2$ (3 mol%) in THF/DMF (1:2) at 50 °C (Table 7). Thus, the 4-(trifluoromethyl)phenylaluminum sesquihalide **50a** undergoes not only a direct cross-coupling with an aryl iodide as shown in the previous part but also with an heteroaromatic bromide such as **51b** in an excellent yield of 96 % (entry 1). Remarkably, also a chloride is a possible electrophile, especially when it is a very active one like **51c** (entry 2). After 5 h at 50 °C, the corresponding pyridine derivative **52c** is isolated in a yield of 70 %. Besides iodides, bromides and chlorides also pseudohalides like nonaflates and triflates can be used as electrophiles in the cross-coupling. Comparing the coupling of arylaluminum reagent **50a** using either nonaflate **51d** or triflate **51d'** shows that both reactions gave a full conversion after 4 h (entry 3). However, the yield of the cross-coupling with the nonaflate shows a higher yield for the desired product **52d** (93 % compared to 84 %). Furthermore, the *meta*-substituted (trifluoromethyl)phenylaluminum sesquihalide **50b** (1.25 equiv), prepared by a $TiCl_4$-catalyzed (3 mol%), Al-insertion in the presence of LiCl, underwent a cross-coupling with the sensitive aryl iodide **51e** bearing a relative acidic acetyl group, affording the expected product **52e** in 86 % yield (entry 4). When the even more sensitive 4-bromobenzaldehyde (**51f**) was used as electrophile the yield of the desired biphenyl **52f** was 59 % after 18 h at 50 °C (entry 5). This aryl bromide could also be used in a cross-coupling with *m*-fluorophenylaluminum reagent **50c** (1.43 equiv) to afford the aldehyde **52g** in an isolated yield of 62 % (entry 6). Using an aryl iodide such as **51g** improved the yield of the cross-coupling dramatically and the ethyl benzoate **52h** was isolated in 92 % (entry 7). Also, an *ortho*-substituent is possible in the nucleophile. Thus, the aluminum reagent **50d** undergoes an efficient cross-coupling with the nitro-functionalized electrophile **51h** to give **52i** in 91 % yield (entry 8). In contrast, a cross-coupling with 4-iodonitrobenzene (**51h**) using *p*-chlorophenylaluminum compound **50e** (1.43 equiv) afforded the desired biphenyl in only a yield of 53 % (entry 9).

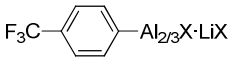
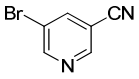
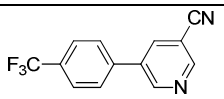
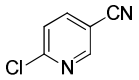
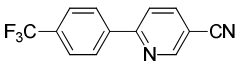
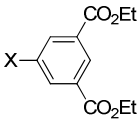
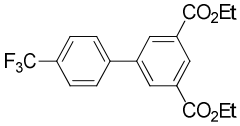
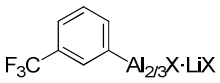
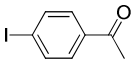
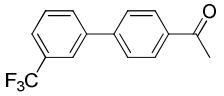
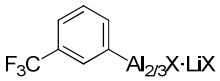
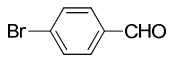
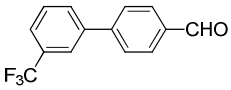
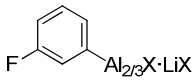
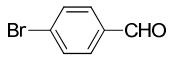
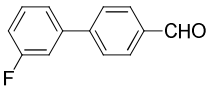
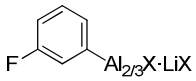
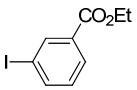
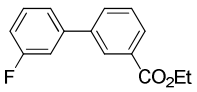
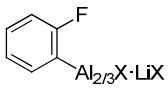
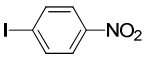
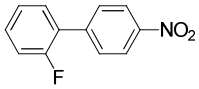
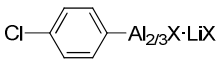
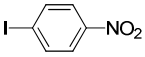
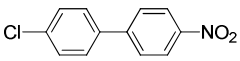
Besides aryl (pseudo)halides this direct cross-coupling of arylaluminum sesquihalides could also be extended to an alkenyl nonaflate like **53**[72] (Scheme 22). The coupling of the arylaluminum reagent **50a** with this electrophile afforded the styrene derivative **54** in a yield of 76 %.

[72] a) I. M. Lyapkalo, M. Webel, H.-U. Reißig, *Eur. J. Org. Chem.* **2002**, 1015; b) J. Hörgermeier, H.-U. Reißig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868.

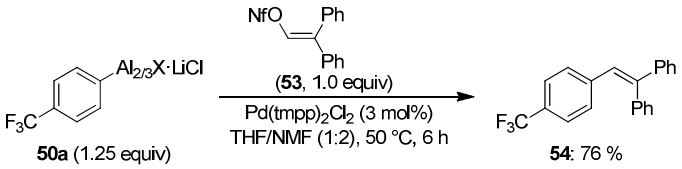
Table 7: Direct cross-coupling of halogenated arylaluminum sesquihalides of type **50**.



50 (1.25 equiv) **52**

Entry	Nucleophile	Electrophile, Time	Product Yield[a]
			
1	**50a**	**51b**, 6 h	**52b**: 96 %
			
2	**50a**	**51c**, 5 h	**52c**: 70 %
			
3	**50a**	**51d** (X = ONf), **51d'** (X = OTf), 4 h	**52d**: 93 % (X = ONf) 84 % (X = OTf)
			
4	**50b**	**51e**, 2 h	**52e**: 86 %
			
5	**50b**	**51f**, 18 h	**52f**: 59 %
			
6	**50c**	**51f**, 3 h	**52g**: 62 %[b]
			
7	**50c**	**51g**, 3 h	**52h**: 92 %
			
8	**50d**	**51h**, 3 h	**52i**: 91 %
			
9	**50e**	**51h**, 6 h	**52j**: 53 %[b]

[a] Yield of isolated, analytically pure product. [b] 1.43 equiv of nucleophile was used.

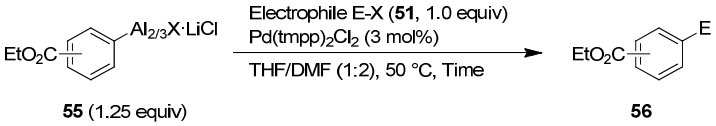


50a (1.25 equiv) **54**: 76 %

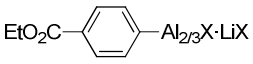
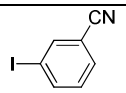
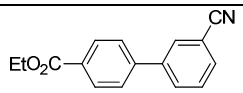
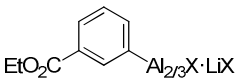
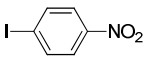
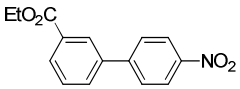
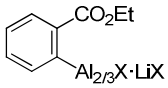
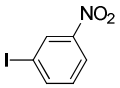
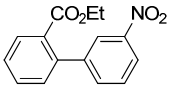
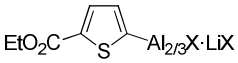
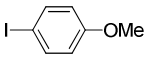
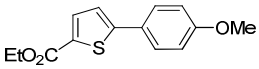
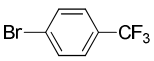
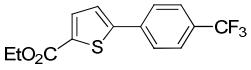
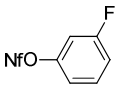
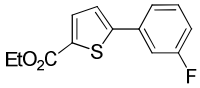
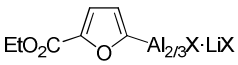
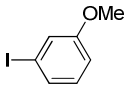
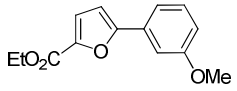
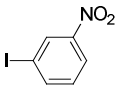
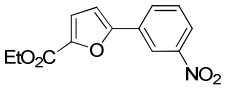
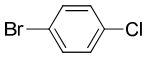
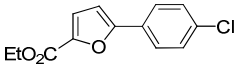
Scheme 22: Direct cross-coupling of the arylaluminum reagent **50a** with alkenyl nonaflate **53**.

The high functional group-tolerance of this direct cross-coupling method is especially shown, when ester-substituted nucleophiles of the type **55** were applied (Table 8). Thus, aryl and heteroarylaluminum reagents bearing an ethyl ester-group, readily prepared by Al-insertion in the presence of LiCl using $PbCl_2$ (3 mol%), reacted smoothly with various aryl iodides, bromides and nonaflates **51**. Comparing the cross-coupling of *para*-, *meta*- and *ortho*-substituted ethyl benzoatealuminum reagents **55a-c** with aryl iodides **51h-j** shows the formation of the desired

Table 8: Direct cross-coupling of ester-functionalized arylaluminum sesquihalides of type **55**.



55 (1.25 equiv) **56**

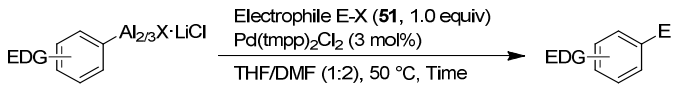
Entry	Nucleophile	Electrophile, Time	Product Yield[a]
			
1	**55a**	**51i**, 2 h	**56a**: 96 %
			
2	**55b**	**51h**, 2 h	**56b**: 73 %
			
3	**55c**	**51j**, 48 h	**56c**: 38 %[b]
			
4	**55d**	**51k**, 2 h	**56d**: 96 %
			
5	**55d**	**51l**, 6 h	**56e**: 89 %
			
6	**55d**	**51m**, 6 h	**56f**: 86 %
			
7	**55e**	**51n**, 2 h	**56g**: 91 %
			
8	**55e**	**51j**, 1 h	**56h**: 62 % (76 %[c])
			
9	**55e**	**51o**, 5 h	**56i**: 65 %

[a] Yield of isolated, analytically pure product. [b] After 48 h at 50 °C, the conversion of electrophile **51** was 59 %. [c] 1.43 equiv of nucleophile was used.

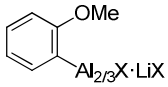
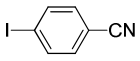
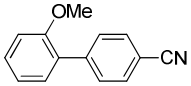
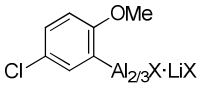
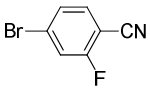
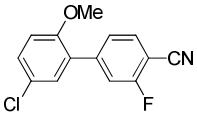
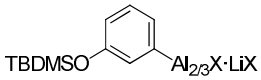
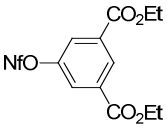
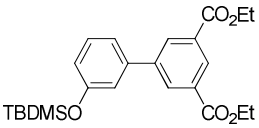
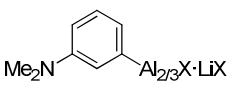
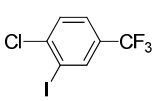
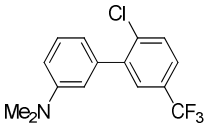
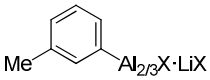
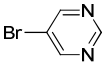
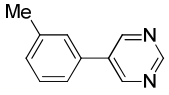
products **56a-c** in yields of 38-96 % (entries 1-3). Here, the *para*-functionalized nucleophile gives an excellent yield of 96 % (entry 1). On the other hand, when the nucleophile has the coordinating ester-function in position 2 only a conversion of 59 % was observed and the 2-ethyl ester-substituted biphenyl **56c** could be isolated in a low yield of 38 % (entry 3). On the contrary, the thiophene-derived nucleophile **55d** undergoes very high yielding cross-couplings regardless if the electrophile is an aryl iodide, bromide or nonaflate (entries 4-6). Also, the organoaluminum reagent **55e**, obtained by an Al-insertion into ethyl 5-bromofuran-2-carboxylate, affords the desired cross-coupling product **56g** in a very good yield of 91 % with the rather electron-rich electrophile **51n** (entry 7). Interestingly, the electron-poor iodide **51j** which should be a better electrophile gives the corresponding product **56h** in a lower yield (entry 8). This heteroaromatic aluminum reagent **55e** undergoes as well a direct cross-coupling with 1-bromo-4-chlorobenzene (**51o**) in the presence of $Pd(tmpp)_2Cl_2$ to give **56i** in an isolated yield of 65 % (entry 9).

In addition to the so far described electron-poor nucleophiles of the type **50** and **55**, arylaluminum sesquihalides bearing an electron-donating group (EDG) undergo seemingly well a direct cross-coupling with various electrophiles (Table 9).

Table 9: Direct cross-coupling of electron-rich arylaluminum sesquihalides of type **57**.



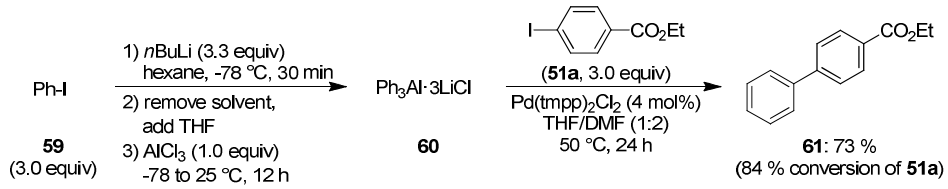
57 (1.25 equiv) **58**

Entry	Nucleophile	Electrophile, Time	Product Yield[a]
1	 **57a**	 **51p**, 1 h	 **58a**: 78 %
2	 **57b**	 **51q**, 8 h	 **58b**: 74 %
3	 **57c**	 **51d**, 4 h	 **58c**: 40 %
4	 **57d**	 **51r**, 6 h	 **58d**: 63 %
5	 **57e**	 **51s**, 2 h	 **58e**: 98 %

[a] Yield of isolated, analytically pure product.

Thus, the *o*-anisylaluminum reagent **57a** formes with 4-iodobenzonitrile (**51p**) the cross-coupling product **58a** in a yield of 78 % after 1 h at 50 °C (Table 9, entry 1). Also, the disubstituted arylaluminum reagent **57b** undergoes a smooth cross-coupling with electrophile **51q** to give the highly functionalized biphenyl **58b** in 74 % yield (entry 2). However, the direct cross-coupling with the silyl-protected phenol derivative **57c** was less efficient and only 40 % of the corresponding product **58c** was isolated (entry 3). Remarkably, also amino-groups on the nucleophile can be tolerated in a direct cross-coupling reaction as the *N*,*N*-dimethylamino-substituted biphenyl **58d** is formed by a reaction of aluminum reagent **57d** with electrophile **51r** in 63 % (entry 4). Finally, the *m*-tolylaluminum sesquihalide **57e** proofs to be an excellent nucleophile for a cross-coupling as it forms the pyrimidine derivative **58e** in an almost quantitative yield of 98 % (entry 5).

To show the high potential of the found catalyst system a cross-coupling of a triorganoaluminum compound with 3.0 equiv of electrophile was attempted. For all reported cross-coupling reactions with triarylalanes the transfer of only one aryl group was possible and the remaining two substituents were wasted.[64, 65] Remarkably, when $Pd(tmpp)_2Cl_2$ (4 mol%) was used as catalyst for a cross-coupling of $Ph_3Al{\cdot}3LiCl$ (**60**, 1.0 equiv) with ethyl 4-iodobenzoate (**51a**, 3.0 equiv) more than one phenyl group was transferred (Scheme 23). The conversion of the electrophile **51a** reached 84 % after 24 h at 50 °C and the cross-coupling product **61** was isolated in 73 %. Thus, all three groups of $Ph_3Al{\cdot}3LiCl$ which was prepared from iodobenzene **59** (3.0 equiv) by an iodine-lithium exchange with *n*BuLi (3.3 equiv) followed by transmetalation with $AlCl_3$ (1.0 equiv) are taking part in the direct cross-coupling by using $Pd(tmpp)_2Cl_2$ as catalyst.

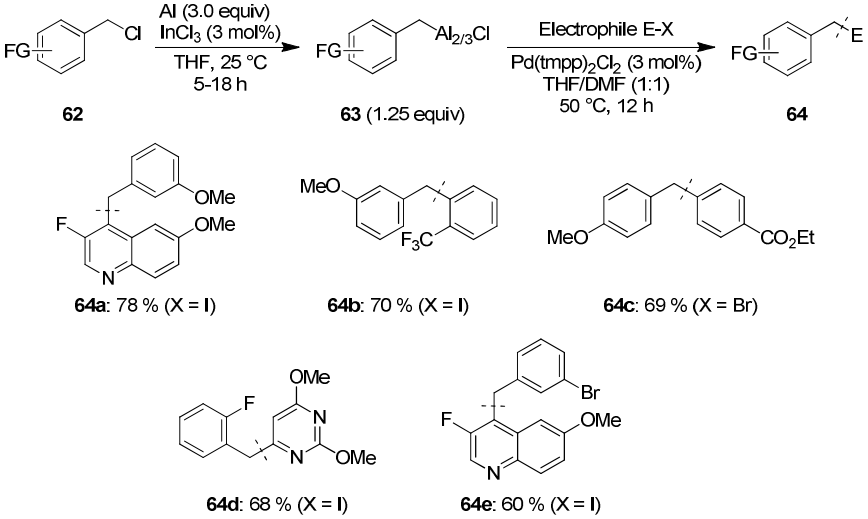


Scheme 23: Transfer of all three phenyl groups of $AlPh_3{\cdot}3LiCl$ (**60**) by using $Pd(tmpp)_2Cl_2$.

2.4. Direct Cross-Coupling of Benzyl- and Alkylaluminum Sesquihalides

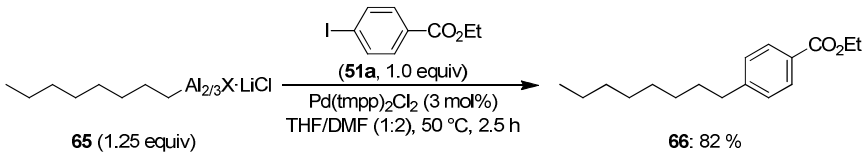
In a precedent part of this thesis it was already shown that benzyl- and alkylaluminum reagents undergo efficient cross-coupling reactions after a prior transmetalation with zinc salts. However, a direct version analogous to the one described for arylaluminum compounds would be of high interest. Thus, the cross-coupling conditions that were developed for aromatic systems were tested on benzylic substrates and proved to be quite general (Scheme 24). Even though the sesquichlorides **63** are not complexed by LiCl, as the $InCl_3$-catalyzed Al-insertion are performed in the absence of this salt, these aluminum reagents undergo smooth direct cross-coupling reactions with catalytic amounts of $Pd(tmpp)_2Cl_2$ (3 mol%). Due to the fact that the benzylaluminum reagents are prepared as a 0.5 M solution in THF, the subsequent cross-coupling was conducted in THF/DMF (1:1) to prevent a further dilution of the reaction

mixture.[73] Thus, the methoxy-substituted diarylmethanes **64a-c** were obtained in yields of 69-78 % from the corresponding benzylaluminum reagents **63** and aryl iodides or bromides as electrophiles (Scheme 24). Moreover, also halogenated benzylaluminum reagents can be applied in a direct cross-coupling with heteroaromatic iodides to afford the pharmacologically interesting structures **64d-e** in yields of 60-68 %. Remarkably, an iodo-electrophile was coupled selectively to give quinoline derivative **64e** and a bromo-substituent in the nucleophile was tolerated.



Scheme 24: Direct cross-coupling of benzylaluminum sesquichlorides of the type **63.**

Additionally, the octylaluminum sesquihalide **65** undergoes a smooth cross-coupling with ethyl 4-iodobenzoate (**51a**) by using the optimized conditions for aromatic nucleophiles (Scheme 25). Noteworthy, the ethyl 4-octylbenzoate **66** was isolated in a higher yield (82 %) than in the cross-coupling reactions after a prior transmetalation to Zn with either PEPPSI-*i*Pr or the combination of $Pd(OAc)_2$ and S-Phos (70-75 %, Table 3, entry 2). However, all attempts to use further alkylaluminum reagents in a direct cross-coupling in the presence of $Pd(tmpp)_2Cl_2$ have been unsatisfying and afforded the desired alkylated benzenes in yields of less than 50 %.



Scheme 25: Direct cross-coupling of octylaluminum reagent **65**.

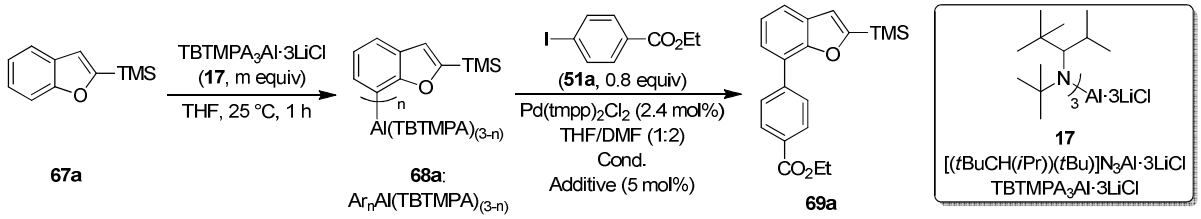
2.5. Direct Cross-Coupling of Organoaluminum Amides from Alumination

As described in chapter A.2.3, a different approach for the preparation of organoaluminum reagents is a directed alumination of arenes and heteroarenes with a sterically hindered Al-

[73] The direct cross-coupling reactions of benzylaluminum reagents were performed by Dr. Tobias D. Blümke and are given for the sake of completeness. For further information, see: T. D. Blümke, *PhD Thesis*, Ludwig-Maximilians-Universität, Munich, **2012**.

bases such as $TBTMPA_3Al{\cdot}3LiCl$ (**17**, Scheme 8). The thus obtained organoaluminum amides were reluctant to undergo a direct C-C bond formation and a transmetalation to the corresponding zinc species was always required for cross-coupling.[38] As $Pd(tmpp)_2Cl_2$ showed a high generality for the direct cross-coupling of organoaluminum sesquihalides, prepared by Al-insertion into the corresponding organic halides, this catalyst was also investigated for a functionalization of the organoaluminum amides **68** obtained *via* metalation (Table 10).

Table 10: Optimization of the direct cross-coupling of organoaluminum amide **68a**.



Entry	equiv **17** (m)	Cond.	n	Additive	Conversion of **51a**[a]	Yield of **69a**[a]
1	1.0	50 °C, 12 h	1	-	19 %	-[b]
2	1.0	80 °C, 6 h	1	-	76 %	50 %
3	1.0	80 °C, 6 h	1	4-fluorostyrene	97 %	61 %
4	0.5	80 °C, 6 h	2	4-fluorostyrene	98 %	79 % (73 %[c])

[a] Determined by GC analysis using tetradecane as internal standard. [b] Not determined. [c] Isolated yield of analytically pure product **69a**.

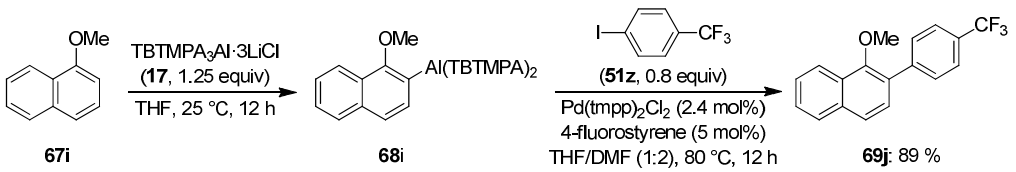
Preliminary experiments showed that a direct cross-coupling of organoaluminum amides of type **68a** at 50 °C did lead only to a low conversion of 19 % after 12 h (Table 10, entry 1), in contrast to arylaluminum sesquihalides which reached usually full conversion after 1-6 h at this temperature. However, increasing the temperature to 80 °C afforded after 6 h 50 % of the desired product **69a** at a conversion of 76 % (entry 2). Full conversion could be achieved after 12 h at this temperature. The rate of the direct cross-coupling could be improved by addition of catalytic amounts of 4-fluorostyrene (5 mol%) which is known to promote the reductive elimination of cross-couplings.[74] Thus, using this co-catalyst already after 6 h at 80 °C a full conversion was detected and the yield of the desired product **69a** was increased to 61 % (entry 3). Besides the investigations on the direct cross-coupling, we also studied possible improvements of the alumination reaction. Here, the atom economy of this step was improved as already 0.5 equiv of the Al-base **17** proved to be sufficient to fully metalate the corresponding substrate. To our delight, the thus obtained bisorganoaluminum monoamides of the type $Ar_2Al(TBTMPA)$ **68a** (n = 2) seemed to be more efficient in the direct cross-coupling in the presence of $Pd(tmpp)_2Cl_2$ (2.4 mol%) and the co-catalyst 4-fluorostyrene (5 mol%) as after 6 h at 80 °C the arylated benzofuran derivative **69a** could be isolated in a yield of 73 % (entry 4). Further studies on the solvent system, different additives like *i*PrI, *i*PrOH or $AlCl_3$ as well as the amount of 4-fluorostyrene did not improve the yield further.

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

The optimum conditions for the direct cross-coupling of aluminated substrates proved to be in the presence of $Pd(tmpp)_2Cl_2$ (2.4 mol%) and 4-fluorostyrene (5 mol%) in THF/DMF (1:2) at 80 °C and were applied efficiently to various compounds **67** to afford the desired cross-coupling products **69** (Table 11).

Moreover, the silylated benzofuran **67a** underwent after alumination a smooth cross-coupling with nonaflate **51t** to give the 6-arylated benzofuran **69b** in 71 % yield (Table 11, entry 1). Remarkably, a free NH_2-group is readily tolerated in these cross-couplings. Alumination of 2-methoxypyridine (**67b**) using base **17** (0.5 equiv, 25 °C, 0.5 h) followed by cross-coupling with the unprotected iodoaniline **51u** (0.8 equiv) provides the biphenyl **69c** in 73 % yield (entry 2). The alumination of 2-methoxynaphthalene (**67c**) with amide **17** is selective in position 3 and the 2,3-disubstituted naphthalene **69d** is obtained after direct cross-coupling with 4-iodobenzonitrile (**51p**) in 88 % yield (entry 3). Other anisole derivatives such as 1,4-dimethoxybenzene (**67d**) or 4-chloroanisole (**67e**) are rapidly metalated and subsequent cross-coupling with iodide **51v** or bromide **51w** gave the products **69e-f** in 74-86 % yield, respectively (entries 4-5). Alumination of phenoxathiine (**67f**) with the Al-base **17** (0.5 equiv) occurs *ortho* to oxygen and after cross-coupling the heterocycle **69g** was obtained in 76 % yield (entry 6). Furthermore, dibenzofuran (**67g**) and -thiophene (**67h**) were used after alumination in the direct cross-coupling with iodides **51x** and **51y** leading to the arenes **69h-i** in 63-72 % yield (entries 7-8).

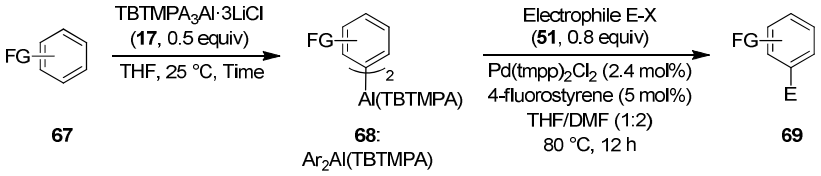
So far, no useful, regioselective metalation of 1-methoxynaphthalene (**67i**) in position 2 was reported,[37, 75] however, by using the Al amide **17** (1.25 equiv, 25 °C, 12 h) a smooth alumination occurs selectively at this position (Scheme 26). Here, the use of less equivalents of sterically hindered Al-amide **17** did not lead to a full conversion of the naphthalene **67i**. Thus, by using 1.25 equiv of the base the monoorganoaluminum reagent **68i** was obtained. The subsequent cross-coupling with aryl iodide **51z** gave the naphthalene **69j** in 89 % yield.

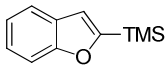
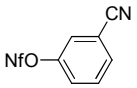
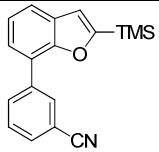
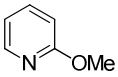
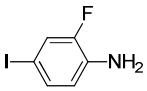
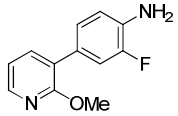
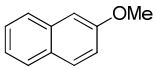
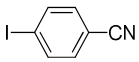
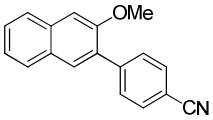
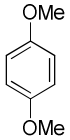
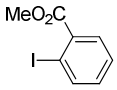
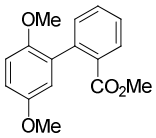
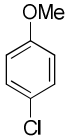
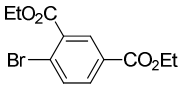
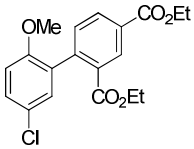
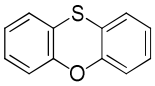
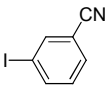
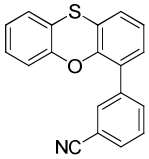
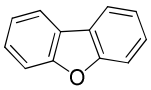
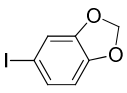
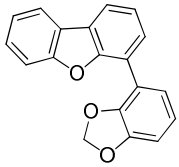
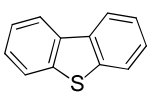
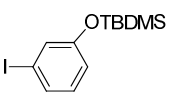
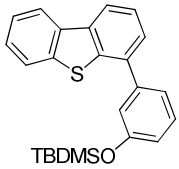


Scheme 26: Direct cross-coupling of aluminated 1-methoxynaphthalene (**68i**).

[75] a) M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975; b) J. Betz, W. Bauer, *J. Am. Chem. Soc.* **2002**, *124*, 8699.

Table 11: Direct cross-coupling of bisorganoaluminum amides of type **68**.



Entry	Substrate, Metalation Time	Electrophile	Product Yield[a]
1	 **67a**, 1 h	 **51t**	 **69b**: 71 %
2	 **67b**, 0.5 h	 **51u**	 **69c**: 73 %
3	 **67c**, 1 h	 **51p**	 **69d**: 88 %
4	 **67d**, 1 h	 **51v**	 **69e**: 74 %
5	 **67e**, 1 h	 **51w**	 **69f**: 86 %
6	 **67f**, 1 h	 **51i**	 **69g**: 76 %
7	 **67g**, 1 h	 **51x**	 **69h**: 72 %
8	 **67h**, 2 h	 **51y**	 **69i**: 63 %

[a] Yield of isolated, analytically pure product.

3. Preparations and Reactions of SF_5-substituted Organometallics

3.1. Introduction

The physico-chemical and pharmacological properties of organic molecules are often significantly modified by the incorporation of fluorine atoms.[76] The preparation of fluoro- or trifluoromethyl-substituted aromatics and heteroaromatics has become an active research field.[77] Recently, it has been shown that the replacement of CF_3-groups with SF_5-substituents may increase the biological activity of pharmacologically active substances.[78] Also, due to its specific physico-chemical properties[79] and to the increased availability of SF_5-substituted starting materials,[80] this fluorous group is beginning to find many applications in material sciences.[78, 81] However, synthetic methods leading to SF_5-substituted aryl and heteroaryl derivatives are rare.

The SF_5-group is sensitive to polar organometallic species such as organolithiums, for example 1-bromo-4-(pentafluorosulfanyl)-benzene with *n*-butyllithium in THF even at -78 °C. In contrast, the reaction with *t*BuLi in diethyl ether at -78 °C produced the desired lithium intermediate without side reactions.[82] Additionally, halogen-lithium exchange reactions require low temperatures and are not compatible with several important functional groups, such as ketones, aldehydes or esters. In contrast as shown above, the halogen-magnesium exchange has been found to be the method of choice for preparing new functionalized organomagnesium reagents of considerable synthetic utility. As organomagnesium and -zinc reagents show a higher functional group compatibility, the preparation of such reagents bearing a SF_5-substituent was investigated. For the synthesis of these organometallics the in A.2 mentioned methods were studied such as halogen-magnesium exchange using *i*PrMgCl·LiCl[24] or directed metalations with highly active TMP-metal bases.[33-36]

[76] a) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303; b) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013; c) J.-P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992.

[77] a) A. M. Sipyagin, C. P. Bateman, Y.-T. Tan, J. S. Thrasher, *J. Fluorine Chem.* **2001**, *112*, 287; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5432; c) A. T. Parsons, S. L. Buchwald, *Nature* **2011**, *480*, 184; d) X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo, G. Liu, *J. Am. Chem. Soc.* **2011**, *134*, 878; e) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 536; f) T. L. Liu, X. Shao, Y. Wu, Q. Shen, *Angew. Chem. Int. Ed.* **2012**, *51*, 540.

[78] a) J. T. Welch, D. S. Lim, *Bioorg. Med. Chem.* **2007**, *15*, 6659; b) P. Wipf, T. Mo, S. Geib, D. Caridha, G. Dow, L. Gerena, N. Roncal, E. Milner, *Org. Biomol. Chem*. **2009**, 4163; c) B. Stump, C. Eberle, W. B. Schweizer, M. Kaiser, R. Brun, R. L. Kraut-Siegel, D. Lentz, F. Diederich, *ChemBioChem* **2009**, *10*, 79; for a review see: d) S. Altomonte, M. Zanda, *J. Fluorine Chem.* **2012**, *143*, 57.

[79] P. Kirsch, *Modern Fluoroorganic Chemistry. Synthesis, Reactivity and Applications,* Wiley-VCH, Weinheim, **2004**.

[80] a) W. A. Sheppard, *J. Am. Chem. Soc.* **1960,** *82*, 4751; b) J. R. Case, N. H. Ray, H. L. Roberts, *J. Chem. Soc.* **1961**, 2066; c) W. A. Sheppard, *J. Am. Chem. Soc.* **1962,** *84*, 3072; d) R. D. Bowden, P. J. Comina, M. P. Greenhall, B. M. Kariuki, A. Loveday, D. Philp, *Tetrahedron* **2000**, *56*, 3399; e) A. M. Sipyagin, C. P. Bateman, Y.-T. Tan, J. S. Thrasher, *J. Fluorine Chem.* **2001**, *112*, 287; f) S. Ait-Mohand, W. R. Dolbier, Jr., *Org. Lett.* **2002**, *4*, 3013; g) R. W. Winter, G. L. Gard, *J. Fluorine Chem.* **2004**, *125*, 549; h) T. A. Sergeeva, W. R. Dolbier, Jr., *Org. Lett.* **2004**, *6,* 2417; i) V. K. Brel, *J. Fluorine Chem.* **2007**, *128*, 862.

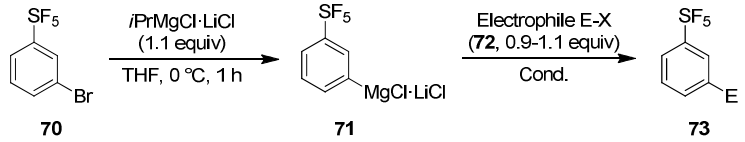
[81] a) P. Kirsch, M. Bremer, *Angew. Chem. Int. Ed.* **2000**, *39*, 4216; b) V. K. Brel, *J. Fluorine Chem.* **2007**, *128*, 862; d) D. S. Lim, J. S. Choi, C. S. Pak, J. T. Welch, *J. Pestic. Sci.* **2007**, *32*, 255.

[82] P. Kirsch, M. Bremer, M. Heckmeier, K. Tarumi, *Angew. Chem. Int. Ed.* **1999**, *38*, 1989.

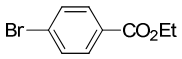
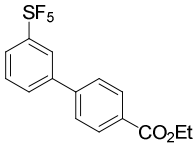
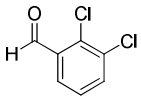
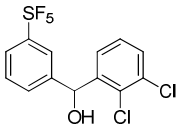
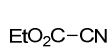
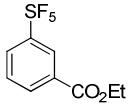
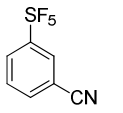
3.2. Preparation using Halogen-Magnesium Exchange

First, a bromide-magnesium exchange with the commercially available 1-bromo-3-(pentafluorosulfanyl)benzene (**70**) using *i*PrMgCl·LiCl (1.1 equiv) was studied (Table 12). After 1 h at 0 °C the corresponding *Grignard* reagent **71** bearing a SF_5-group in position 3 was afforded. This organometallic could be functionalized subsequently in various ways. Thus, after transmetalation of the SF_5-substituted arylmagnesium reagent **71** with $ZnCl_2$ (1.1 equiv, 0 °C. 30 min) the corresponding cross-coupling product **73a** was obtained in a yield of 84 % (entry 1) by using electrophile **72a** and catalytic amounts of PEPPSI-*i*Pr (2 mol%). Furthermore, *Grignard* reagent **71** adds to aldehydes such as **72b** (1.1 equiv, 0 to 25 °C, 5 min) to give the SF_5-functionalized alcohol **73b** in an isolated yield of 81 % (entry 2). Introduction of an ethyl ester-group was achieved by trapping the organometallic **71** with ethyl cyanoformate (**72c**, 1.0 equiv). The desired ethyl benzoate **73c** bearing a SF_5-group in *meta*-position was obtained after 30 min at -30 °C in 71 % yield (entry 3). Moreover, also a cyano-function could be attached by using tosyl cyanide (**72d**, 1.0 equiv, -30 °C, 30 min) for trapping the organomagnesium reagent **71**. The desired 3-(pentafluorosulfanyl)benzonitrile (**73d**) could be isolated in a yield of 55 % (entry 4).

Table 12: Preparation of SF_5-substituted *Grignard* reagent **71** *via* Br-Mg exchange.



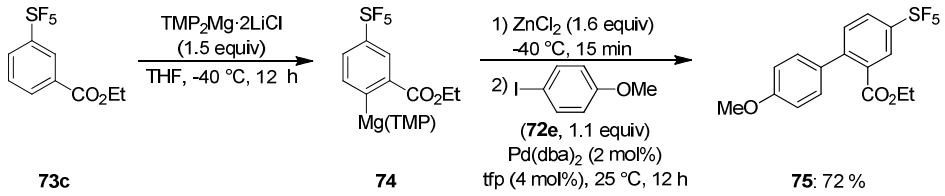
70 **71** **73**

Entry	Electrophile	Cond.	Product Yield[a]
		25 °C, 2 h[b]	
1	**72a**		**73a**: 84 %
		0 to 25 °C, 5 min	
2	**72b**		**73b**: 81 %
		-30 °C, 30 min	
3	**72c**		**73c**: 71 %
		-30 °C, 30 min	
4	**72d**		**73d**: 55 %

[a] Yield of isolated, analytically pure product. [b] After transmetalation with $ZnCl_2$ (1.1 equiv, 0 °C, 30 min), PEPPSI-*i*Pr (2 mol%) and electrophile **72a** were added.

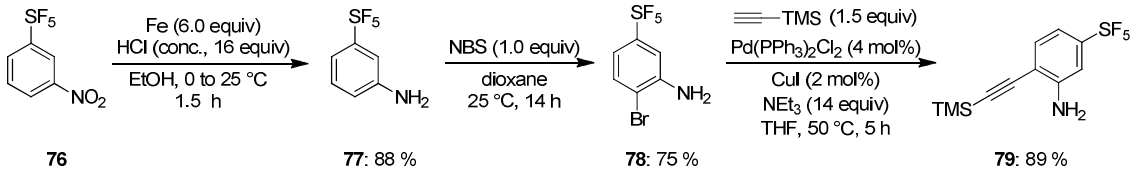
3.3. PREPARATION USING DIRECTED METALATION

After it was shown that the SF_5-group is compatible in a Br-Mg exchange reaction at 0 °C, an extension to metalations using TMP-magnesium amides was desired. Ethyl 3-(pentafluorosulfanyl)benzoate (**73c**) which was prepared as described above proved to be the most favorable substrate for such magnesiations due to the directing nature of the ethyl ester-function. Indeed, this substrate was metalated using $TMP_2Mg{\cdot}2LiCl$ (1.5 equiv) at -40 °C in 12 h (Scheme 27). The metalation occurs regioselectively in *para*-position to the SF_5-group due to steric hindrance of this bulky substituent with the TMP-metal base. The obtained magnesium reagent **74** underwent after transmetalation to Zn a smooth Pd-catalyzed cross-coupling with 4-iodoanisole (**72e**) to give the SF_5-substituted biphenyl **75** in a yield of 72 %.



Scheme 27: Directed metalation of ethyl benzoate **73c** and subsequent functionalization.

Besides SF_5-functionalized arenes, especially heteroaromatic substrates bearing this group gain high attention.[78] Thus, the preparation of a SF_5-substituted indole was desired and even more its subsequent metalation. Starting from commercial 1-nitro-3-(pentafluorosulfanyl)benzene (**76**) first acetylene derivative **79** was prepared over 3 steps (Scheme 28). After reduction of the nitro-group of **76**[78a] the obtained aniline **77** was brominated using NBS (1.0 equiv, 25 °C, 14 h) to give the bromo-derivative **78** in 75 %. This bromoaniline was then used in a *Sonogashira* cross-coupling[83] with (trimethylsilyl)acetylene (1.5 equiv, 50 °C, 5 h) providing SF_5-substituted 2-((trimethylsilyl)ethynyl)aniline **79** in 89 % yield.



Scheme 28: Preparation of the precursor **79** for a SF_5-substituted indole.

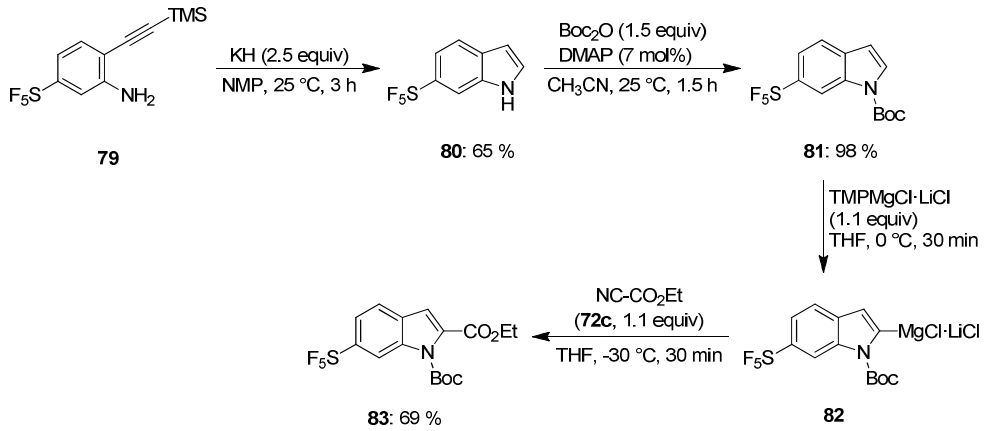
The thus obtained precursor **79** was then directly used in a cyclization reaction with KH (2.5 equiv) in NMP (Scheme 29).[84] After 3 h at 25 °C the desired 6-(pentafluorosulfanyl)-1*H*-indole (**80**) was isolated in a yield of 65 %. For a subsequent metalation of this substrate the free nitrogen was protected with Boc_2O (1.5 equiv, 25 °C, 1.5 h) using catalytic amounts of DMAP (7 mol%)[85] in an almost quantitative yield. This SF_5-substituted indole derivative **81** could be readily metalated with TMPMgCl·LiCl (1.1 equiv) at 0 °C for 30 min. Trapping the 2-magnesiated

[83] a) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627; b) T. Sakamoto, M. Shiraiwa, Y. Kondo, H. Yamanaka, *Synthesis* **1983**, 312.

[84] a) A. L. Rodriguez, W. Dohle, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 2488; b) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571; c) A. H. Stoll, P. Knochel, *Org. Lett.* **2007**, *10*, 113.

[85] L. F. Silva, Jr., M. V. Craveiro, M. T. P. Gambardella, *Synthesis* **2007**, 3851.

indole **82** with ethyl cyanoformate (**72c**, 1.1 equiv, -30 °C, 30 min) afforded the ethyl ester functionalized heteroaromatic **83** in a yield of 69 % together with 27 % starting material **81**.

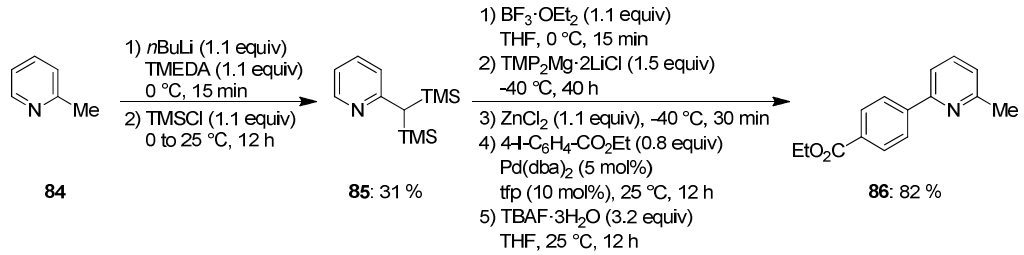


Scheme 29: Cyclization to the SF_5-substituted indole **80** and subsequent metalation.

4. Regioselective Metalations of BTM-substituted N-Heteroaromatics

4.1. Introduction

The functionalization of N-heteroaromatics is of great importance, since these structures are present in numerous natural products, pharmaceuticals and agrochemicals.[86] They also find interesting applications in material science as well as polymer chemistry.[87] A very promising pathway for such functionalizations of these scaffolds is, as was already mentioned in A.2.3, the directed metalation using sterically hindered metal amides. The use of LiCl-activated TMP-magnesium and -zinc bases has already proven to be very efficient for several heterocyclic structures.[33] However, non-activated pyridines were only metalated in low yields when these bases were applied. These drawback could be overcome by an activation of the azabenzene by a strong *Lewis* acid such as $BF_3{\cdot}OEt_2$.[88] For lithiations this strategy was pioneered by *Kessar* and co-workers.[89] The combination of $BF_3{\cdot}OEt_2$ with TMP-Mg bases was successfully applied for regioselective metalations of pyridine, quinoline, quinine and nicotine derivatives as well as for methylthiopyrazine.[88] Though, the use of this concept on methyl-substituted pyridines did not lead to a desired functionalization of the pyridine core, but the benzylic position was metalated as these protons show a higher acidity. In contrast, 2-methylpyridine (**84**) was selectively metalated in position 6, when previously two TMS-groups were attached to the benzylic position (Scheme 30).[90]



Scheme 30: Functionalization of 2-picoline (**84**) after protection of the benzylic position.

The protection of the methyl-group of 2-picoline (**84**) by two silyl groups can be performed *via* lithiation.[91] The thus obtained pyridine derivative **85** bearing a BTM-group (BTM = bis(trimethylsilyl)methyl) is then metalated selectively at the heteroaromatic core (Scheme 30).[90] The remaining benzylic proton is tolerated due to steric hindrance of the two silyl groups with the TMP-Mg base. The same effect was already observed in lithiations with *s*BuLi and

[86] T. Eicher, S. Hauptmann, A. Speicher, *The Chemistry of Heterocycles*, *2nd Ed.*, Wiley-VCH, Weinheim, **2003**.

[87] a) K.-T. Wong, T. S. Hung, Y. Lin, C.-C. Wu, G.-H. Lee, S.-M. Peng, C. H. Chou, Y. O. Su, *Org. Lett.* **2002**, *4*, 513; b) N. Hebbar, C. Foil-Petit, Y. Ramondenc, G. Plé, N. Plé, *Tetrahedron* **2011**, *67*, 2287; c) P. Kar, R. Haldar, C. J. Gómez-García, A. Ghosh, *Inorg. Chem.* **2012**, *51*, 4265.

[88] a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451; b) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306; c) S. M. Manolikakes, M. Jaric, K. Karaghiosoff, P. Knochel, *Chem. Commun.* **2013**, *49*, 2124.

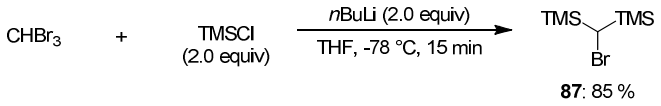
[89] a) S. V. Kessar, P. Singh, R. Vohra, N. Kaur, K. Singh, *J. Chem. Soc., Chem. Commun.* **1991**, 568; b) S. V. Kessar, P. Singh, *Chem. Rev.* **1997**, *97*, 721; c) S. V. Kessar, P. Singh, K. N. Singh, P. V. Bharatam, A. K. Sharma, S. Lata, A. Kaur, *Angew. Chem. Int. Ed.* **2008**, *47*, 4703.

[90] M. Jaric, *PhD Thesis*, Ludwig-Maximilians-Universität, Munich, **2011**.

[91] K. Hassall, C. H. Schiesser, J. M. White, *Organometallics* **2007**, *26*, 3094.

TMEDA by *Snieckus* and co-workers.[92] On the contrary, when primary alkyl lithium reagents are used for the metalation, the benzylic position is deprotonated.[93] After magnesiation of pyridine derivative **85** using a combination of $BF_3{\cdot}OEt_2$ and $TMP_2Mg{\cdot}2LiCl$ and subsequent transmetalation to Zn, a *Negishi* cross-coupling can be performed. The silylated intermediate is easily deprotected by using $TBAF{\cdot}3H_2O$[94] without prior purification and the desired 2-methyl-6-aryl pyridine **86** was obtained in 82 % yield over two steps.[90]

The above mentioned preparation of 2-BTM-pyridine (**85**) starting from 2-picoline (**84**) *via* lithiation with 1.1 equiv *n*BuLi and trapping with 1.1 equiv trimethylsilyl chloride (Scheme 30) is possible because the intermediate mono-silylated picoline is preferentially lithiated a second time due to the higher acidity of its benzylic protons.[91] However, only a yield of 31 % was reported for this synthesis. A different approach to such BTM-substituted heteroaromatics would be the use of a cross-coupling reaction of a BTM-metal reagent[95] with the corresponding heterocyclic halide. The desired precursor for these organometallics is e.g. BTM bromide (**87**) which is easily obtained from the common chemicals bromoform, TMSCl and *n*BuLi in 85 % yield (Scheme 31).[96] This strategy for the synthesis of BTM-substituted heteroaromatics should consist of a high generality and allow a potential tolerance of several functional groups in contrast to the use of lithium bases. Recently, the BTM-group attracts a lot of attention, e.g. in *Wittig* rearrangements or *Prins* cyclizations.[97]



Scheme 31: Synthesis of BTM bromide (**87**).

Besides the fact that the BTM-group is a masked methyl-group, it moreover has a very high steric demand. Thus, regioselective metalations of selected BTM-substituted heteroaromatics should be possible by mainly using steric effects of the bulky BTM-group and the TMP-metal base. Furthermore, the silylated substituent can also undergo additional transformations to useful functional groups.[98] Thus, *Palomo et al.* showed the oxidation of the nitrogen-bond BTM-group of **88** to an aldehyde by using CAN ($(NH_4)_2Ce(NO_3)_6$) in yields of 82-88 % (Scheme 32).[98a]

[92] a) R. J. Mills, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1565; b) R. J. Mills, N. J. Taylor, V. Snieckus, *J. Org. Chem.* **1989**, *54*, 4372.

[93] a) R. I. Papasergio, C. L. Raston, A. H. White, *J. Chem. Soc., Dalton Trans.* **1987**, 3085; b) B. W. Skelton, V.-A. Tolhurst, A. H. White, A. M. Williams, A. J. Wilson, *J. Organomet. Chem.* **2003**, *674*, 38; c) A. Molter, F. Mohr, *Z. Anorg. Allg. Chem.* **2009**, *635*, 134.

[94] a) M. Reiffen, R. W. Hoffmann, *Tetrahedron Lett.* **1978**, *19*, 1107; b) A. Couture, H. Cornet, E. Deniau, P. Grandclaudon, S. Lebrun, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 469.

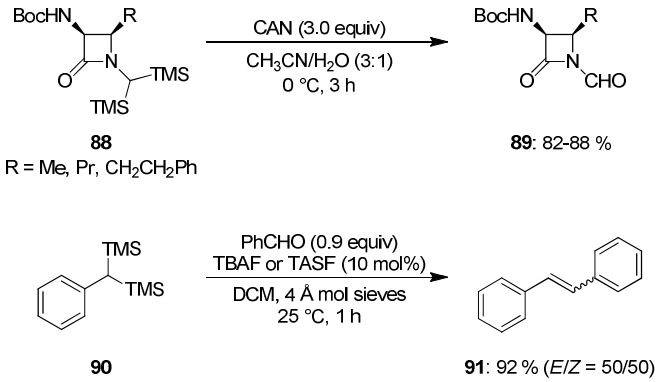
[95] a) P. J. Davidson, D. H. Harris, M. F. Lappert, *J. Chem. Soc., Dalton Trans.* **1976**, 2268; b) H. J. Breunig, W. Kanig, A. Soltani-Neshan, *Polyhedron* **1983**, *2*, 291; c) D. R. Williams, Á. I. Morales-Ramos, C. M. Williams, *Org. Lett.* **2006**, *8*, 4393; d) M. Westerhausen, B. Rademacher, *J. Organomet. Chem.* **1991**, *421*, 175.

[96] N. Wiberg, G. Wagner, G. Müller, J. Rieden, *J. Organomet. Chem.* **1984**, *271*, 381.

[97] a) X. Sun, J. Lei, C. Sun, Z. Song, L. Yan, *Org. Lett.* **2012**, *14*, 1094; b) J. Lu, Z. Song, Y. Zhang, Z. Gan, H. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 5367.

[98] a) C. Palomo, J. M. Aizpurua, M. Legido, A. Mielgo, R. Galarza, *Chem. Eur. J.* **1997**, *3*, 1432; b) J. Lasarte, C. Palomo, J. P. Picard, K. Dunogues, J. M. Aizpurua, *J. Chem. Soc., Chem. Commun.* **1989**, 72; c) C. Palomo, J. M. Aizpurua, J. M. García, I. Ganoba, F. P. Cossio, B. Lecea, C. López, *J. Org. Chem.* **1990**, *55*, 2498; d) A. R. Bassindale, R. J. Ellis, J. C.-Y. Lau, P. G. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1986**, 593.

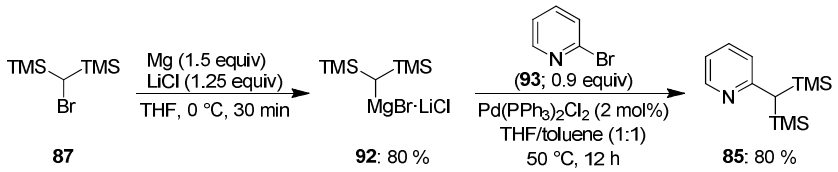
This bissilylated substituent also performs a *Peterson* olefination[99] in the presence of carbonyl compounds and catalytic amounts of fluoride. For example, α,α-bis(trimethylsilyl)toluene (**90**) is converted to a 1:1-mixture of *E*- and *Z*-stilbene (**91**) in 92 % yield when it is reacted with benzaldehyde and TBAF or TASF (10 mol%) in 1 h at 20 °C (Scheme 32).[98c]



Scheme 32: Oxidation and *Peterson* olefination of the BTM-group.

4.2. Regioselective Metalation of 2-BTM-pyridine

Starting from BTM bromide (**87**) the corresponding LiCl-complexed organomagnesium and -zinc reagents were prepared by an insertion reaction. In the following cross-coupling with 2-bromopyridine (**93**) the *Grignard* reagent **92** proved to be more efficient and produced the desired 2-BTM-pyridine (**85**) by a *Kumada-Corriu* coupling[9] in the presence of $Pd(PPh_3)_2Cl_2$ (2 mol%) in a yield of 80 % (Scheme 33).



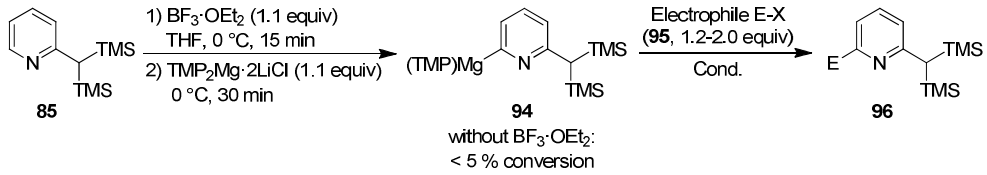
Scheme 33: Preparation of 2-BTM-pyridine (**85**) *via Kumada-Corriu* cross-coupling.

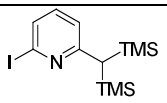
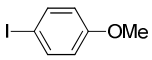
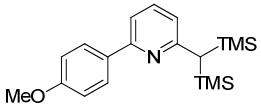
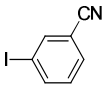
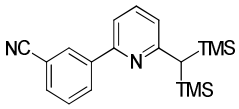
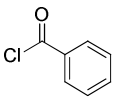
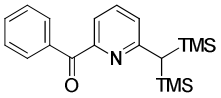
The thus obtained masked 2-methylpyridine **85** was then metalated by using a combination of $BF_3{\cdot}OEt_2$ (1.1 equiv) and $TMP_2Mg{\cdot}2LiCl$ (1.1 equiv) at 0 °C (Table 13). In the absence of the *Lewis* acid no metalation was detected. After 30 min at 0 °C the magnesiated pyridine **94** was obtained which could be functionalized in various ways. The iodo-derivative **96a** was isolated in 71 % yield after trapping the organometallic **94** with iodine (entry 1). Furthermore, the metalated pyridine **94** underwent smooth *Negishi* cross-coupling after a transmetalation to Zn with electron-rich as well as electron-deficient electrophiles of the type **95a-b** to give the desired 6-arylated derivatives **96b-c** in yields of 77 or 71 %, respectively (entries 2 and 3). Seemingly well, a Cu-mediated acylation reaction was realized. Here, the 6-magnesiated pyridine **94** reacted

[99] a) D. J. Peterson, *J. Org. Chem.* **1968**, *33*, 780; b) L. F. van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195.

after a transmetalation using $ZnCl_2$ with benzoyl chloride (**95c**) in the presence of CuCN·2LiCl to afford the ketone **96d** in an isolated yield of 70 % (entry 4).

Table 13: Regioselective metalation of 2-BTM-pyridine (**85**) and subsequent trapping.

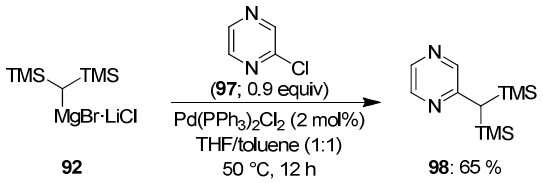


Entry	Electrophile	Cond.	Product Yield[a]
1	I_2	-78 to 25 °C, 12 h	 **96a**: 71 %
2	 **95a**	25 °C, 12 h[b]	 **96b**: 77 %
3	 **95b**	50 °C, 12 h[b]	 **96c**: 71 %
4	 **95c**	-40 to 25 °C, 12 h[c]	 **96d**: 70 %

[a] Yield of isolated, analytically pure product. [b] After transmetalation with $ZnCl_2$ (1.2 equiv, 0 °C, 15 min), $Pd(dba)_2$ (2 mol%), tfp (4 mol%) and electrophile **95** were added. [c] After transmetalation with $ZnCl_2$ (2.5 equiv, 0 °C, 15 min), CuCN·2LiCl (1.1 equiv) and electrophile **95** were added.

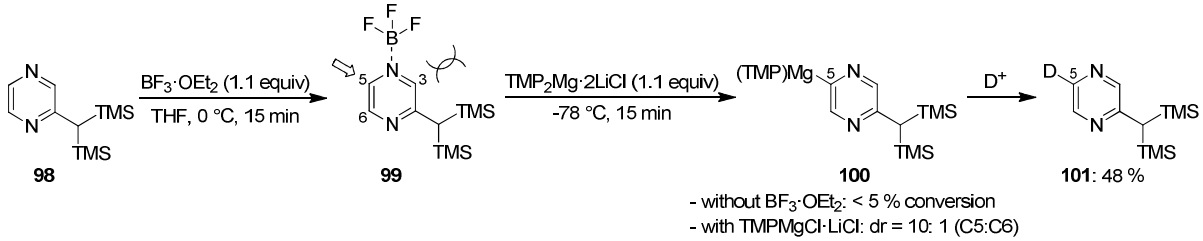
4.3. Regioselective Metalation of 2-BTM-pyrazine

Besides its protecting function of the benzylic position, a further feature of the BTM-group attached to heteroaromatics is the bulky nature of this substituent. Hence, a shielding function of the *ortho*-position might be applicable for substrates such as pyrazine. The introduction of the BTM-substituent to this diazine works in the same way as for the pyridine substrate *via* a *Kumada-Corriu* cross-coupling of the BTM-*Grignard* reagent **92** with the commercially available 2-chloropyrazine (**97**). Thus, 2-BTM-pyrazine (**98**) is obtained in a yield of 65 % (Scheme 34).
In the case of pyrazine derivative **98** two possible complexation sites for BF_3·OEt_2 are present. However, due to the bulky BTM-substituent the *Lewis* acid is selectively complexed at the least hindered nitrogen (Scheme 35). This fact was verified by NMR-spectroscopy of the reaction mixture at -20 °C (see page 135). The ^{13}C NMR spectrum of the complex **99** showed two quartets for the carbons 3 and 5 due to a ^3J-coupling with the fluorine of the complexed BF_3. Thus, those



Scheme 34: Preparation of 2-BTM-pyrazine (**98**) *via Kumada-Corriu* cross-coupling.

two positions should be more activated by the *Lewis* acid in a subsequent metalation than position 6 (inductive effect). Additionally, position 3 is sterically hindered by the BTM-group in *ortho*-position. Consequential, the BF_3-complexed pyrazine **99** is selectively metalated in position 5 using $TMP_2Mg{\cdot}2LiCl$ (1.1 equiv) as it bears the most accessible activated proton. This regioselectivity of the magnesiation was confirmed by deuterolysis which afforded exclusively the 5-deuterated 2-BTM-pyrazine (**101**) in an isolated yield of 48 % (Scheme 35). No deuterium incorporation was detected in the benzylic position. In the absence of the *Lewis* acid $BF_3{\cdot}OEt_2$, no metalation using $TMP_2Mg{\cdot}2LiCl$ was observed which shows the need for an activation of the diazine **98** for an efficient deprotonation. When TMPMgCl·LiCl was used for a magnesiation of the complex **99**, the selectivity was decreased significantly and a 10:1-mixture of 5- and 6-magnesiated 2-BTM-pyrazine was obtained.

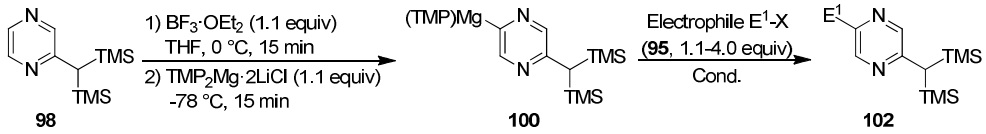


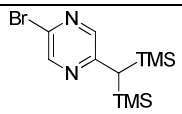
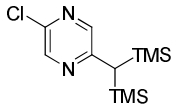
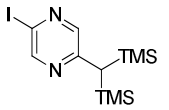
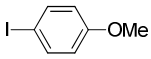
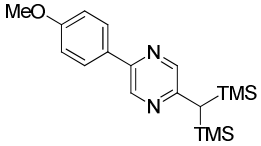
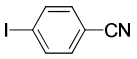
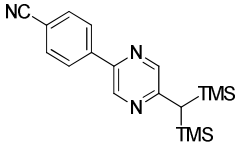
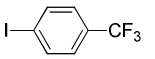
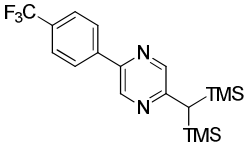
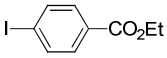
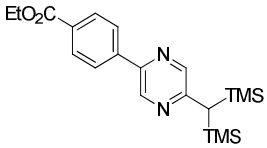
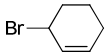
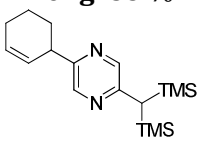
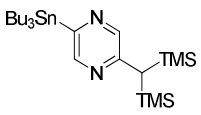
Scheme 35: Selective formation of complex **99** and subsequent metalation in position 5.

Using this procedure of *Lewis* acid-activated metalation allowed the introduction of various functional groups to 2-BTM-pyrazine selectively in position 5 (Table 14). Thus, the 5-halogenated 2-BTM-pyrazines **102a-c** were obtained in yields of 61-89 % when 2-BTM-pyrazine (**98**) was metalated by $TMP_2Mg{\cdot}2LiCl$ (1.1 equiv) after prior addition of $BF_3{\cdot}OEt_2$ (1.1 equiv) and subsequently trapped with either $(BrCl_2C)_2$, $PhSO_2Cl$[100] or I_2 (entries 1-3). Furthermore, the organomagnesium compound **100** undergoes a smooth Pd-catalyzed cross-coupling with several aryl iodides after previous transmetalation to Zn. Interestingly, the electron-rich electrophile **95a** shows the highest yield for this coupling and affords the 5-arylated pyrazine **102d** in 81 % (entry 4). The electron-deficient aryl iodides **95d-f** are coupled in lower yields of 53-74 % (entries 5-7). A Cu-catalyzed allylation in position 5 subsequent to a transmetalation to Zn of the magnesium reagent **100** was even less efficient and afforded the desired product **102h** in a yield of 47 % (entry 8). To compare the selective magnesiation of the pyrazine core in position 5 with benzylic lithiations of 2-BTM-pyridine (**85**) using *n*BuLi and TMEDA a stannylation was performed as this trapping reaction affords quantitatively the benzylic tin reagent of 2-BTM-pyridine (**85**).[93c] In contrast to the results in the literature, by using the

[100] a) I. Creton, I. Marek, J. F. Normant, *Synthesis* **1996**, 1499; b) H. Rezaei, S. Yamanoi, F. Chemla, J. F. Normant, *Org. Lett.* **2000**, *2*, 419.

Table 14: Regioselective metalation of 2-BTM-pyrazine (**98**) and subsequent trapping.



Entry	Electrophile	Cond.	Product Yield[a]
1	$(BrCl_2C)_2$	-78 to 25 °C, 12 h	 **102a**: 89 %
2	$PhSO_2Cl$	-78 to 25 °C, 12 h	 **102b**: 61 %
3	I_2	-78 to 25 °C, 12 h	 **102c**: 65 %
4	 **95a**	-78 to 25 °C, 12 h[b]	 **102d**: 81 %
5	 **95d**	-78 to 25 °C, 12 h[b]	 **102e**: 74 %
6	 **95e**	-78 to 25 °C, 12 h[b]	 **102f**: 66 %
7	 **95f**	-78 to 25 °C, 12 h[b]	 **102g**: 53 %
8	 **95g**	-78 to 25 °C, 12 h[c]	 **102h**: 47 %
9	Bu_3SnCl **95h**	-78 to 25 °C, 12 h	 **102i**: 55 %

[a] Yield of isolated, analytically pure product. [b] After transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min), $Pd(dba)_2$ (2 mol%), tfp (4 mol%) and electrophile **95** were added. [c] After transmetalation with $ZnCl_2$ (1.2 equiv, -78 °C, 15 min), CuCN·2LiCl (20 mol%) and electrophile **95** were added.

sterically hindered $TMP_2Mg{\cdot}2LiCl$ as base and quenching subsequently with tributyltin chloride (**95h**) afforded selectively the 5-stannylated pyrazine derivative **102i** in an isolated yield of 55 % (entry 9).

To verify the regioselectivity of the magnesiation of 2-BTM-pyrazine (**98**) by using a combination of $BF_3{\cdot}OEt_2$ and $TMP_2Mg{\cdot}2LiCl$ a x-ray structure analysis of a single crystal of 2-BTM-5-bromopyrazine (**102a**) was conducted. The resulting molecular structure confirms the *para*-substitution of the bulky BTM-group and the bromide (Figure 2). Thus, 5-substituted 2-BTM-pyrazine derivatives **102** are obtained selectively by magnesiation of 2-BTM-pyrazine (**98**) with $BF_3{\cdot}OEt_2$ and $TMP_2Mg{\cdot}2LiCl$.

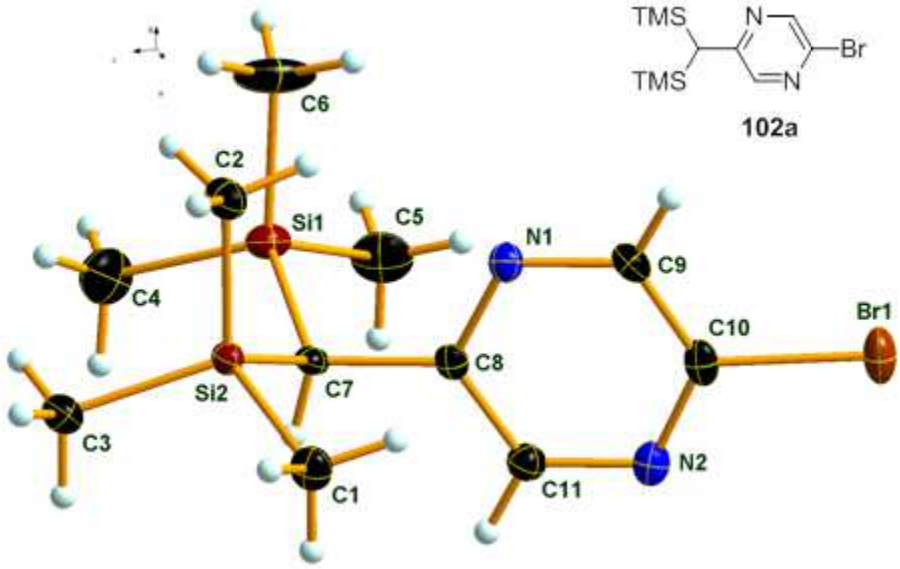
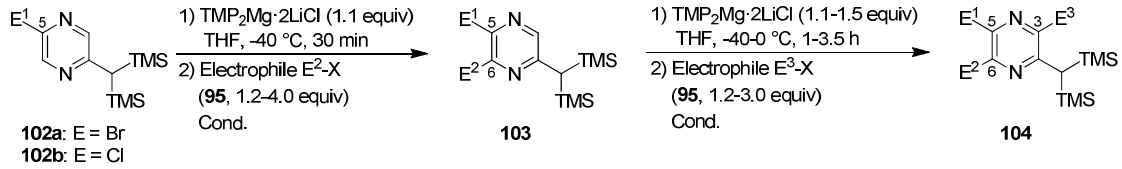


Figure 2: Molecular structure of 2-BTM-5-bromopyrazine (**102a**) from x-ray analysis.

4.4. Regioselective Full Functionalization of 2-BTM-pyrazine

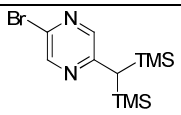
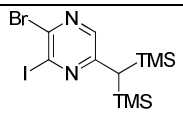
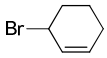
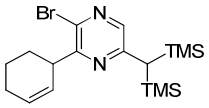
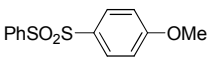
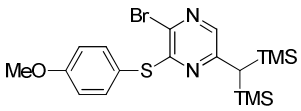
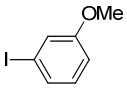
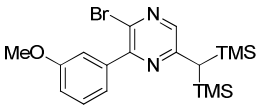
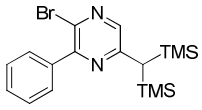
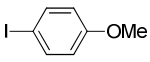
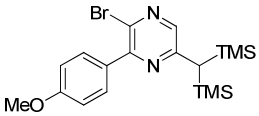
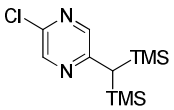
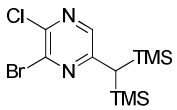
The obtained 5-substituted 2-BTM-pyrazine derivatives **102** can potentially undergo further regioselective metalations as the remaining C-H bond differ in the accessibility. More precisely, position 6 is less sterically hindered than position 3 which is *ortho* to the bulky BTM-substituent and should therefore undergo a selective metalation. Indeed, the 5-bromo and 5-chloro derivatives **102a-b** were magnesiated exclusively in position 6 by $TMP_2Mg{\cdot}2LiCl$ after 30 min at -40 °C (Scheme 36). For the second metalation of the 2-BTM-pyrazine core of **102a-b** no activation by the *Lewis* acid $BF_3{\cdot}OEt_2$ was needed as these halogenated heteroaromatics are more activated. In contrast, the presence of $BF_3{\cdot}OEt_2$ in the reaction mixture prevented a metalation completely.

After magnesiation of the 5-halogenated pyrazines **102a-b** several quenching reactions were possible to afford the trisubstituted derivatives **103** (Table 15). Thus, 2-BTM-5-bromopyrazine (**102a**) is magnesiated by $TMP_2Mg{\cdot}2LiCl$ (1.1 equiv, -40 °C, 30 min) and subsequently iodolyzed to give the iodo derivative **103a** in a yield of 86 % (entry 1). Also, a Cu-mediated allylation with 3-bromocyclohexene (**95g**) affords the desired product **103b** in a very good yield of 88 %



Scheme 36: Regioselective full functionalization of BTM-substituted pyrazines **102a-b**.

Table 15: Preparation of 5,6-functionalized 2-BTM-pyrazines **103** according to Scheme 36.

Entry	Substrate	Electrophile E^2-X	Cond.	Product Yield[a]
		I_2	-78 to 25 °C, 12 h	
1	**102a**			**103a**: 86 %
			-40 to 25 °C, 12 h[b]	
2	**102a**	**95g**		**103b**: 88 %
			-40 to 25 °C, 12 h	
3	**102a**	**95i**		**103c**: 70 %
			40 °C, 12 h[c]	
4	**102a**	**95j**		**103d**: 74 %
			40 °C, 12 h[c]	
5	**102a**	**95k**		**103e**: 70 %
			40 °C, 48 h[c]	
6	**102a**	**95a**		**103f**: 47 %
		$(BrCl_2C)_2$	-78 to 25 °C, 12 h	
7	**102b**			**103g**: 93 %

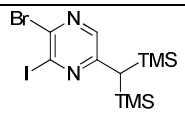
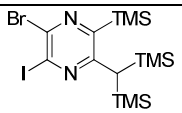
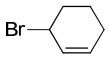
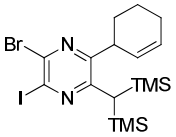
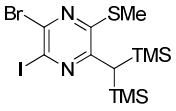
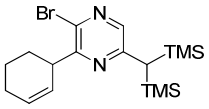
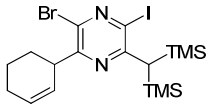
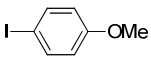
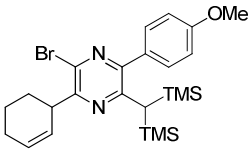
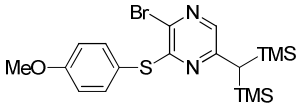
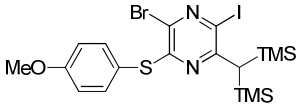
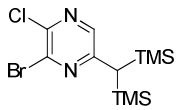
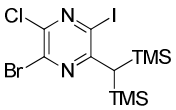
[a] Yield of isolated, analytically pure product. [b] After transmetalation with $ZnCl_2$ (2.5 equiv, -40 °C, 15 min), CuCN·2LiCl (1.0 equiv) and electrophile **95** were added. [c] After transmetalation with $ZnCl_2$ (1.2 equiv, -40 °C, 15 min), $Pd(dba)_2$ (2-3 mol%), tfp (4-6 mol%) and electrophile **95** were added.

(entry 2). By using *S*-(4-methoxyphenyl) benzenesulfonothioate (**95i**) as trapping reagent a thioether-function can be introduced and the expected product **103c** is obtained in a yield of 70 % (entry 3). After a transmetalation to Zn of the 6-magnesiated derivative of **102a**, a *Negishi* cross-coupling can be performed with aryl iodides **95j-k** by using $Pd(dba)_2$ (2-3 mol%) and tfp

(4-6 mol%) as catalyst system (entries 4 and 5). The desired cross-coupling products **103d-e** are formed in yields of 70-74 %. Interestingly, when 4-iodoanisole (**95a**) is used as electrophile instead of the *meta*-substituted isomer **95j** the yield is significantly lower (47 %, entry 6). Furthermore, 2-BTM-5-chloro-pyrazine (**103b**) is metalated seemingly well by using $TMP_2Mg{\cdot}2LiCl$ (1.1 equiv) in 30 min at -40 °C. Quenching the resulting organometallic with $(BrCl_2C)_2$ affords the brominated derivative **103g** in a yield of 93 % (entry 7).

Finally, also the remaining position of the pyrazine core of the trisubstituted diazines **103** is functionalized by treatment with $TMP_2Mg{\cdot}2LiCl$ to give the fully functionalized pyrazines **104** (Scheme 36). In some cases, the reaction temperature has to be increased to -20 to 0 °C as well as a higher excess of $TMP_2Mg{\cdot}2LiCl$ was needed. Nevertheless, the bromo-iodopyrazine **103a** was magnesiated by using 1.1 equiv $TMP_2Mg{\cdot}2LiCl$ at -40 °C after 3.5 h. Subsequent trapping with trimethylsilyl cyanide afforded the 3-silylated pyrazine **104a** in 72 % yield (entry 1). After a transmetalation to Zn the magnesiated compound reacted also with 3-bromocyclohexene (**95g**) in the presence of catalytic amounts of $CuCN{\cdot}2LiCl$ to give the allylated pyrazine **104b** in 59 % (entry 2). However, the introduction of a thiomethyl-function was less efficient and the fully functionalized derivative **104c** was only obtained in 36 % (entry 3). For the metalation of the allylated bromopyrazine **103b** 1.3 equiv of the sterically hindered base $TMP_2Mg{\cdot}2LiCl$ were needed and a full conversion was observed after 1 h at 0 °C. A subsequent trapping with iodine gave the expected product **104d** in 78 % yield (entry 4). Furthermore, the magnesium reagent derived from **103b** underwent after transmetalation to Zn a Pd-catalyzed cross-coupling with 4-iodoanisole (**59a**) to give the 3-arylated fully functionalized pyrazine **104e** in 59 % yield (entry 5). Here, the amount of catalyst had to be increased to 5 mol% and a prolonged reaction time of 24 h at 40 °C was needed, possibly due to the steric hindrance of the *ortho*-BTM-substituent. For the *S*-*p*-anisyl-substituted pyrazine **103c** an even higher excess of TMP-base was needed for an efficient metalation (entry 6). Thus, with 1.5 equiv of $TMP_2Mg{\cdot}2LiCl$ the trisubstituted derivative **103c** was selectively magnesiated at the remaining position of the pyrazine core after 3.5 h at -20 °C. Subsequent iodolysis afforded the desired product **104f** in a yield of 72 %. Finally, also the trihalogenated BTM-pyrazine **104g** is accessible by using this strategy for the subsequent regioselective full functionalization of 2-BTM-pyrazine (**98**). After a chlorine and a bromine have been introduced by the first or second metalation reaction, respectively to give the pyrazine **103g**, this substrate is then magnesiated one more time with $TMP_2Mg{\cdot}2LiCl$ (1.1 equiv) at -40 °C for 2 h and quenched with iodine (entry 7). Thus, 2-BTM-6-bromo-5-chloro-3-iodopyrazine (**104g**) is obtained in 83 % yield.

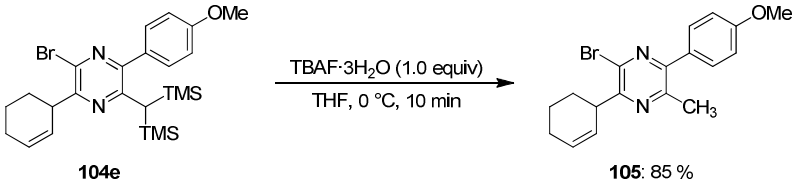
Table 16: Preparation of fully functionalized pyrazines **104** according to Scheme 36.

Entry	Substrate (Metalation Cond.)	Electrophile E^3-X	Cond.	Product Yield[a]
1	 **103a** (1.1 equiv $TMP_2Mg{\cdot}2LiCl$, -40 °C, 3.5 h)	TMS-CN	-78 to 25 °C, 12 h	 **104a**: 72 %
2	**103a** (1.1 equiv $TMP_2Mg{\cdot}2LiCl$, -40 °C, 3.5 h)	 **95g**	-40 to 25 °C, 12 h[b]	 **104b**: 59 %
3	**103a** (1.1 equiv $TMP_2Mg{\cdot}2LiCl$, -40 °C, 3.5 h)	$MeSSO_2Me$ **95l**	-78 to 25 °C, 12 h	 **104c**: 36 %
4	 **103b** (1.3 equiv $TMP_2Mg{\cdot}2LiCl$, 0 °C, 1 h)	I_2	-78 to 25 °C, 12 h	 **104d**: 78 %
5	**103b** (1.3 equiv $TMP_2Mg{\cdot}2LiCl$, 0 °C, 1 h)	 **95a**	40 °C, 24 h[c]	 **104e**: 59 %
6	 **103c** (1.5 equiv $TMP_2Mg{\cdot}2LiCl$, -20 °C, 3.5 h)	I_2	-78 to 25 °C, 12 h	 **104f**: 72 %
7	 **103g** (1.1 equiv $TMP_2Mg{\cdot}2LiCl$, -40 °C, 2 h)	I_2	-78 to 25 °C, 12 h	 **104g**: 83 %

[a] Yield of isolated, analytically pure product. [b] After transmetalation with $ZnCl_2$ (2.5 equiv, -40 °C, 15 min), $CuCN{\cdot}2LiCl$ (20 mol%) and electrophile **95** were added. [c] After transmetalation with $ZnCl_2$ (1.3 equiv, 0 °C, 15 min), $Pd(dba)_2$ (5 mol%), tfp (10 mol%) and electrophile **95** were added.

4.5. Subsequent Transformations of BTM-substituted Pyrazines

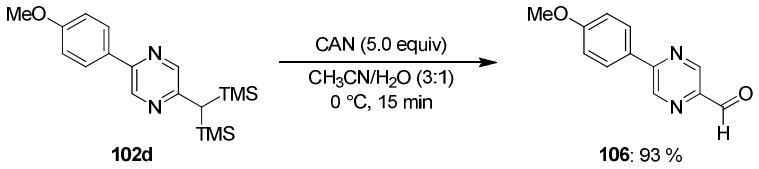
A major advantage of the BTM-substituent is besides its sterical demand, which allows a full differentiation of the positions in metalations, the fact that it can be transformed into several functionalities afterwards. First of all, a deprotection of the BTM-group to a methyl-substituent is easily achieved by addition of 1.0 equiv TBAF·3H_2O to the tetrasubstituted pyrazine **104e** in THF at 0 °C for 10 min (Scheme 37). Thus, the fully functionalized methylpyrazine **105** is obtained in 85 % yield.



104e **105**: 85 %

Scheme 37: Deprotection of the BTM-group to afford the methylpyrazine derivative **105**.

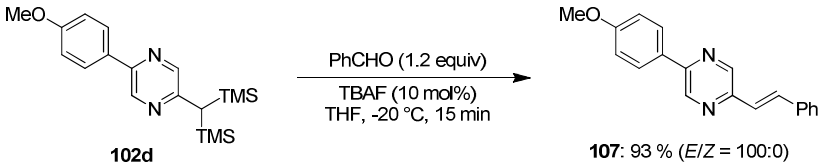
As it was already shown for *N*-bound BTM-groups,[98a] this substituent undergoes also an oxidation to an aldehyde when it is attached to a pyrazine ring. Treating the 5-arylated 2-BTM-pyrazine **102d** with ceric ammonium nitrate (CAN) in a mixture of acetonitrile and water (3:1) the desired aldehyde **106** is formed immediately in a very high yield of 93 % (Scheme 38). Hence, by first introducing the BTM-group *via* a *Kumada-Corriu* cross-coupling and subsequent regioselective metalation, an aldehyde function can be introduced indirectly by means of a subsequent oxidation of this bissilylated substituent.



102d **106**: 93 %

Scheme 38: Oxidation of the BTM-group of **102d** to give aldehyde **106**.

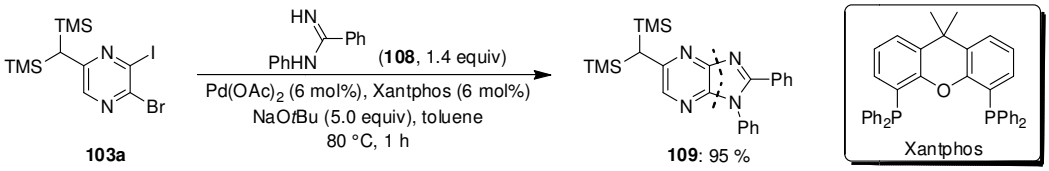
In the presence of a carbonyl-function the BTM-group furthermore undergoes a *Peterson* olefination using fluoride as catalyst (see Scheme 32).[98c] This method is also applicable in the case of pyrazine **102d** which bears a BTM-group in position 2 (Scheme 39). Mixing the bissilylated substrate **102d** with benzaldehyde in THF at -20 °C the corresponding styrene derivative **107** is obtained in 93 % yield after addition of catalytic amounts of dry TBAF (10 mol%). In contrast to the literature procedure, no molecular sieve was added to the reaction mixture and even more importantly the *E*-styrene derivative was formed diastereoselectively.



102d **107**: 93 % (*E*/*Z* = 100:0)

Scheme 39: *Peterson* olefination of the BTM-substituted pyrazine **102d**.

Remarkably, even though a *Peterson* olefination of BTM-functionalized substrates can also be induced by a strong base such as alkali alkoxides,[98d] this group is compatible in a Pd-catalyzed diamination using NaO*t*Bu. This method was first reported by *You* and co-workers for the synthesis of (hetero)aryl fused imidazoles as potential fluorescent scaffolds.[101] However, harsh conditions like 24 h at 140 °C in toluene and the addition of molecular sieves are needed for the twofold amination of 2,3-dichloropyrazine. In contrast, starting from the regioselectively obtained *ortho*-bromo-iodopyrazine **103a** bearing a BTM-substituent an annulation reaction with *N*-phenyl-benzamidine (**108**) was performed in the presence of $Pd(OAc)_2$ (6 mol%) and Xantphos[102] (6 mol%) in 1 h at 80 °C (Scheme 40). Here, the addition of molecular sieves was not needed to obtain the desired BTM-substituted imidazo[4,5-*b*]pyrazine **109** in an excellent yield of 95 %.



Scheme 40: Regioselective annulation to afford imidazo[4,5-*b*]pyrazine derivative **109**.

Due to the regioselective introduction of the halide-functions on the pyrazine core of **103a** the regiospecific annulation affords the 1,2-disubstituted pyrazine fused imidazole **109** seemingly regioselectively. The *anti*-conformation of the bulky BTM-substituent and the *N*-bound phenyl-group was confirmed by crystal structure analysis of **109** (Figure 3).

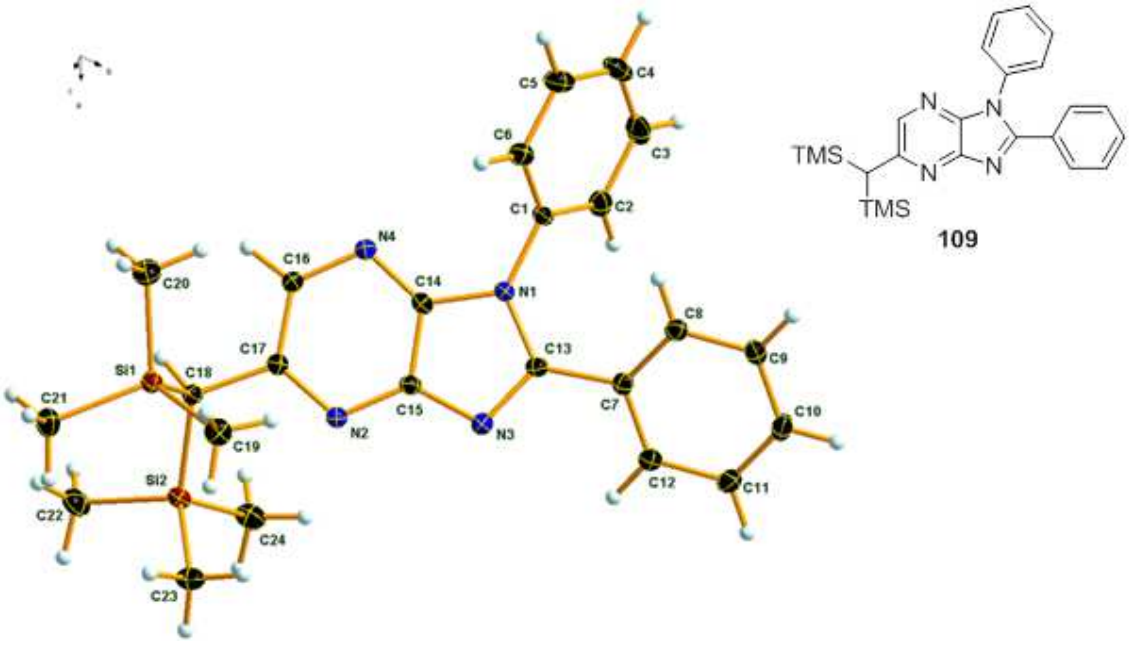


Figure 3: Molecular structure of BTM-substituted imidazo[4,5-*b*]pyrazine **109**.

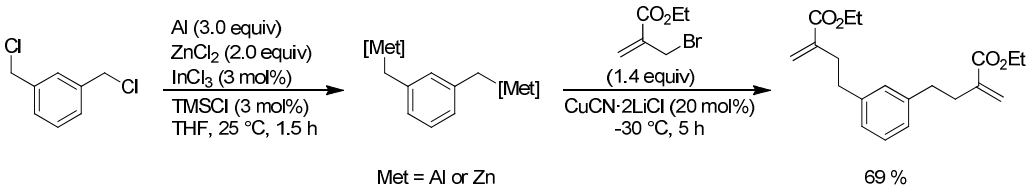
[101] D. Zhao, J. Hu, N. Wu, X. Huang, X. Qin, J. Lan, J. You, *Org. Lett.* **2011**, *13*, 6516.

[102] a) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081; b) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741.

5. SUMMARY

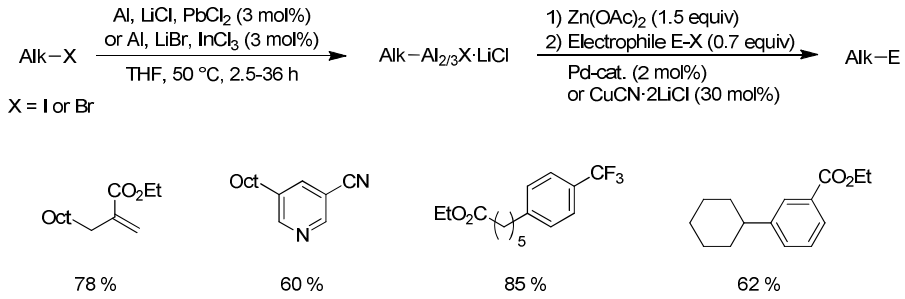
5.1. PREPARATION OF BENZYL- AND ALKYLALUMINUM SESQUIHALIDES

In this work the catalyzed Al-insertion into aryl halides was extended to functionalized benzyl and alkyl substrates. Using commercial aluminum powder together with $InCl_3$ as catalyst allowed the oxidative addition to give benzylaluminum sesquichlorides without LiCl as additive. In some cases, an *in situ*-trapping by $ZnCl_2$ of the intermediate aluminum reagent was needed. This procedure enabled also access to benzylic bimetallic reagents which undergo a smooth Cu-catalyzed allylation (Scheme 41).



Scheme 41: Preparation of a benzylic bimetallic and subsequent Cu-catalyzed allylation.

Furthermore, also alkylaluminum sesquihalides could be prepared by this method. Nevertheless, the choice of catalyst is dependent on the structure of the alkyl halide. Thus, $PbCl_2$ proved to be most efficient for the oxidative addition into aliphatic iodides such as 1-iodooctane in the presence of LiCl. However, for the corresponding bromide $InCl_3$ showed a higher activity in the formation of the desired aluminum reagent, but needed LiBr as additive. On the contrary, when ester-functionalized substrates are used, $PbCl_2$ is needed as catalyst and also a prolonged reaction time. After a transmetalation of the alkylaluminum sesquihalides to Zn, they underwent an allylation in the presence of CuCN·2LiCl or Pd-catalyzed cross-couplings with aromatic and heteroaromatic electrophiles (Scheme 42). Additionally, it was shown that these insertion reactions are possible not only in THF but also in non-coordinating solvents such as benzene or toluene.

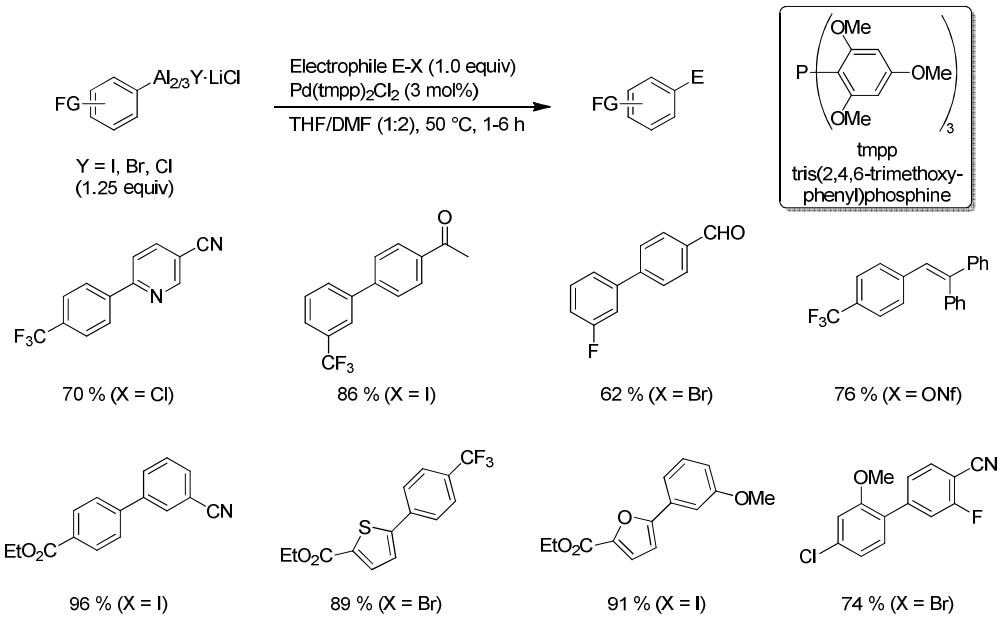


Scheme 42: Al-insertion into alkyl halides and subsequent trapping after transmetalation to Zn.

5.2. DIRECT CROSS-COUPLING OF ORGANOALUMINUM REAGENTS

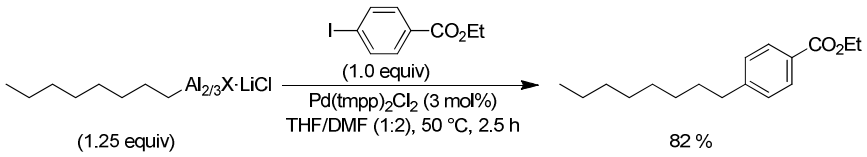
As the organoaluminum sesquihalides derived from Al-insertion were reluctant to undergo a cross-coupling with most of the commonly used Pd-catalysts without prior transmetalation to

Zn, this work was focused on the development of reaction conditions for a direct cross-coupling of organoaluminum reagents. Extensive studies revealed $Pd(tmpp)_2Cl_2$ (3 mol%) as ideal catalyst in THF/DMF (1:2) to conduct direct C-C bond formations of aryl- and heteroarylaluminum compounds with various aryl iodides, bromides and nonaflates as well as in special cases also chlorides and triflates. Due to the mild conditions of 1-6 h at 50 °C several functional groups can be tolerated such as an ester, a cyano, a nitro-group as well as a methyl-ketone or an aldehyde (Scheme 43).



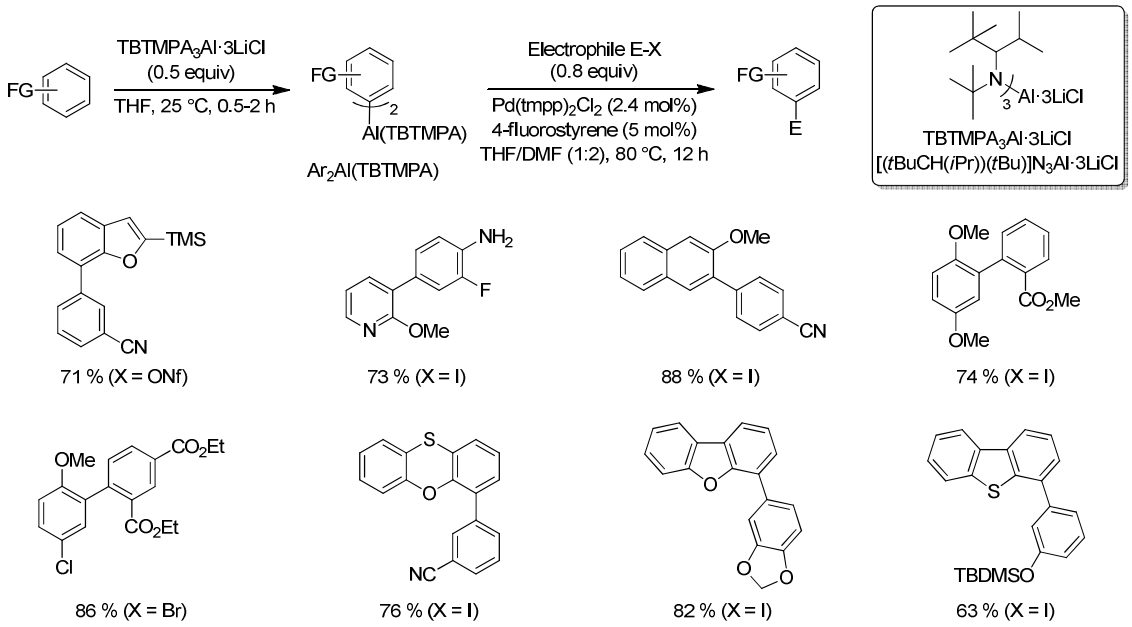
Scheme 43: Direct cross-coupling of arylaluminum sesquihalides.

Moreover, also octylaluminum sesquihalide underwent a smooth cross-coupling when these conditions were used. Thus, the desired ethyl 4-octylbenzoate was obtained in 82 % after 2.5 h at 50 °C (Scheme 44).



Scheme 44: Direct cross-coupling of octylaluminum sesquihalide with ethyl 4-iodobenzoate.

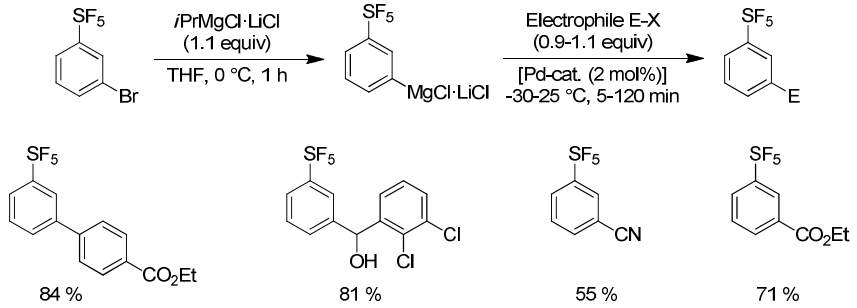
Additionally, organoaluminum amides derived from alumination using the sterically hindered base $TBTMPA_3Al·3LiCl$ undergo a direct cross-coupling using $Pd(tmpp)_2Cl_2$ as catalyst. Here, the atom economy of the metalation reaction could be improved as already 0.5 equiv were sufficient for an efficient alumination. The thus obtained bisorganoaluminum amides $Ar_2Al(TBTMPA)$ showed interestingly a higher activity in the direct cross-couplings which where performed at 80 °C for 12 h with 4-fluorostyrene as promoter of the reductive elimination. This method allowed the cross-coupling of several interesting arenes and heteroarenes with various electrophiles and displays a very high functional group tolerance (Scheme 45).



Scheme 45: Direct cross-coupling after alumination using $TBTMPA_3Al·3LiCl$.

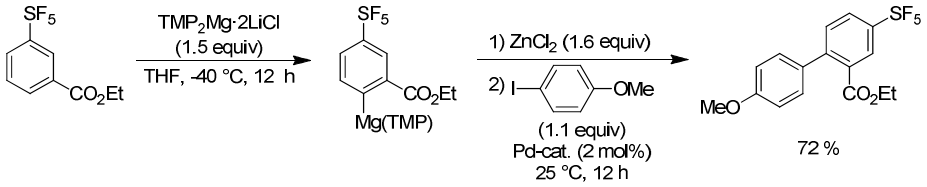
5.3. Preparations and Reactions of SF_5-substituted Organometallics

Due to the high demand for fluorinated compounds, especially in pharmaceutical and agrochemical research, the synthesis and reactivity of organometallic reagents bearing a SF_5-group was investigated. So far, only lithium compounds with this CF_3-analog were known. For the preparation of SF_5-substituted *Grignard* reagents a Br-Mg exchange was performed starting from the commercial 1-bromo-3-(pentafluorosulfanyl)benzene. After addition of *i*PrMgCl·LiCl the desired organomagnesium compound with a SF_5-substituent in *meta*-position was obtained after 1 h at 0 °C. The resulting organometallic was used in several subsequent functionalizations such as Pd-catalyzed cross-couplings or addition to aldehydes. Furthermore, SF_5-substituted benzonitrile or ethyl benzoate were prepared (Scheme 46).



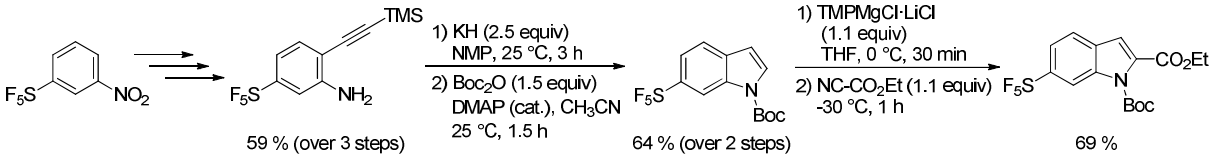
Scheme 46: Preparation of a SF_5-substituted *Grignard* reagent *via* Br-Mg exchange.

The thus prepared *meta*-SF_5-substituted ethyl benzoate was an excellent precursor for a directed metalation using $TMP_2Mg·2LiCl$. Due to steric hindrance the metalation occurs *para* to the bulky SF_5-group. After transmetalation of the obtained magnesium reagent a *Negishi* cross-coupling afforded the corresponding SF_5-functionalized biphenyl (Scheme 47).



Scheme 47: Metalation of SF_5-substituted ethyl benzoate and subsequent cross-coupling.

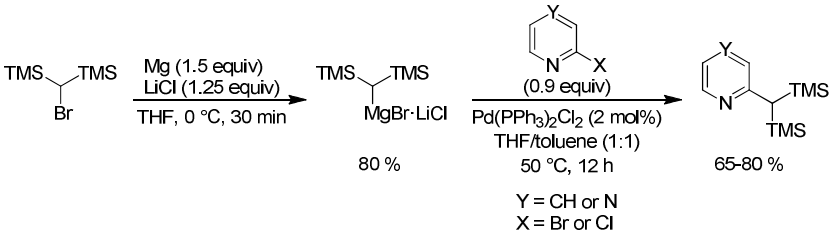
For the preparation of a SF_5-substituted heteroaromatic the commercially available 1-nitro-3-(pentafluorosulfanyl)benzene was reacted to a *ortho*-acetylene-substituted aniline. This derivative underwent a cyclization with KH to give a SF_5-functionalized indole. After Boc-protection, the indole scaffold was magnesiated with TMPMgCl·LiCl and an ester-group was introduced to afford the desired indole derivative bearing a SF_5-substituent in 69 % yield (Scheme 48).



Scheme 48: Preparation of a SF_5-functionalized indole derivative and subsequent metalation.

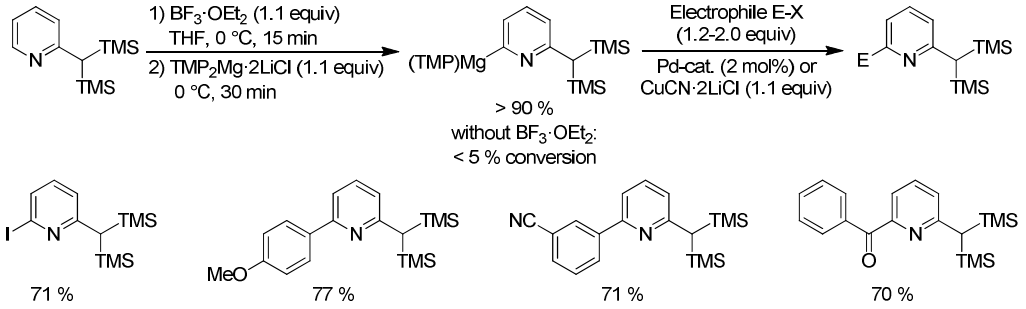
5.4. Regioselective Metalations of BTM-substituted N-Heteroaromatics

The final part of this work was the regioselective metalation of N-heteroaromatics bearing a BTM-group (BTM = bis(trimethylsilyl)methyl). This bulky group can be modified into various functions such as methyl, aldehyde or an olefin. The introduction of this bissilylated substituent was achieved by a *Kumada-Corriu* cross-coupling of the corresponding *Grignard* reagent with heteroaromatic halides such as 2-bromopyridine or 2-chloropyrazine (Scheme 49).



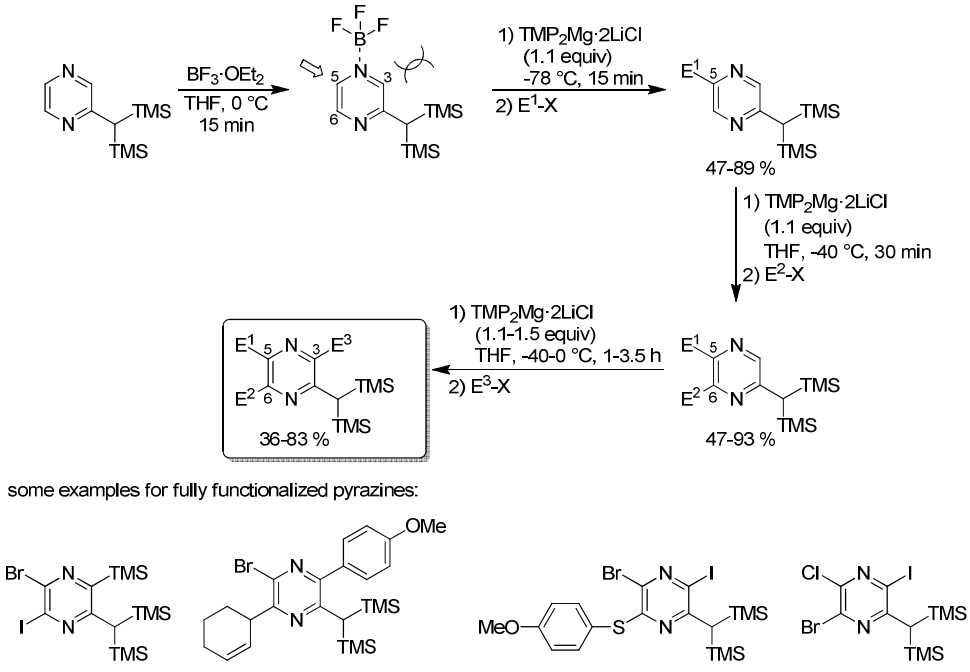
Scheme 49: Preparation of BTM-substituted heteroaromatics *via Kumada-Corriu* cross-coupling.

The thus prepared 2-BTM-pyridine was metalated by a combination of $BF_3{\cdot}OEt_2$ and $TMP_2Mg{\cdot}2LiCl$ selectively at position 6 of the pyridine core. The benzylic position was protected by the two TMS-groups due to steric hindrance. In the absence of the *Lewis* acid, no metalation occurred. The resulting magnesiated pyridine derivative underwent several trapping reactions such as an iodolysis, Pd-catalyzed cross-couplings or a Cu-mediated acylation (Scheme 50).



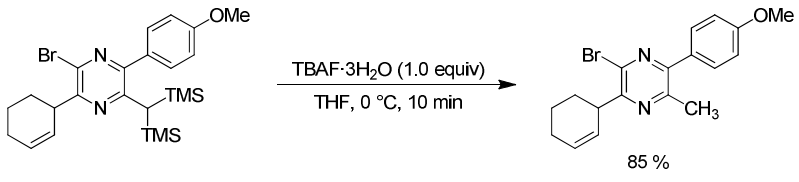
Scheme 50: Regioselective metalation of 2-BTM-pyridine using BF_3-assisted magnesiation.

For 2-BTM-pyrazine, the bulky bissilylated substituent allowed a differentiation of the three remaining positions of the pyrazine core. Thus, a regioselective full functionalization of this diazine scaffold was achieved. First, a BF_3-assisted magnesiation using $TMP_2Mg{\cdot}2LiCl$ resulted in a selective metalation of position 5 due to a selective complexation of the *Lewis* acid at the least hindered nitrogen. The formation of this complex was verified by NMR-spectroscopy. Furthermore, positions 6 and 3 can be functionalized subsequently by a magnesiation with $TMPMg_2{\cdot}2LiCl$ to afford fully functionalized pyrazine derivatives (Scheme 51).



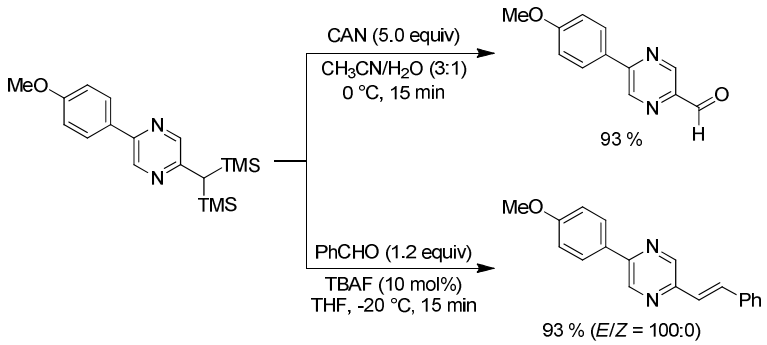
Scheme 51: Regioselective full functionalizations of 2-BTM-pyrazine.

After the metalation of the heteroaromatic core, the BTM-substituent was transformed into various functional groups. Thus, deprotection of the bissilylated group afforded e.g. a fully functionalized methylpyrazine derivative (Scheme 52).



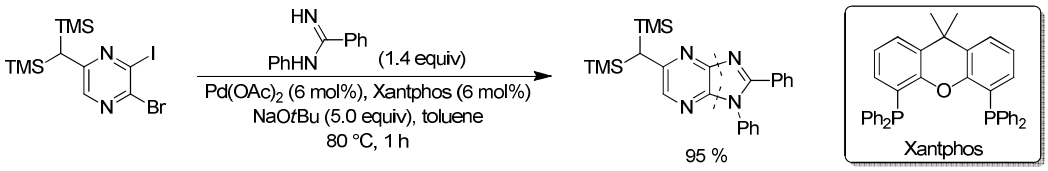
Scheme 52: Deprotection of the BTM-group to afford a fully functionalized methylpyrazine.

Furthermore, the BTM-function was converted into an aldehyde by oxidation with CAN. The desired pyrazine-carbaldehyde was produced in an excellent yield of 93 % (Scheme 53). Seemingly well, a *Peterson* olefination was performed with a 5-arylated 2-BTM-pyrazine derivative by using benzaldehyde and catalytic amounts of TBAF. The expected *E*-styrene compound was formed diastereoselectively (Scheme 53).



Scheme 53: Oxidation and *Peterson* olefination of the BTM-substituent.

Moreover, the *ortho*-bromo-iodopyrazine derivative which was obtained by the above mentioned method was used in a Pd-catalyzed diamination with an amidine. Thus, the BTM-functionalized imidazo[4,5-*b*]pyrazine is formed regiospecific in an excellent yield of 95 % (Scheme 54). Remarkably, the BTM-substituent is tolerated by the strong base NaO*t*Bu. The regiochemistry of this product was confirmed by x-ray analysis.



Scheme 54: Regioselective annulation to afford a BTM-substituted imidazo[4,5-*b*]pyrazine.

C. EXPERIMENTAL SECTION

1. General Considerations

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

1.1. Solvents

Solvents needed for moisture sensitive reactions were dried according to the following standard procedures via distillation over drying agents and stored under an inert gas atmosphere:

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

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

DME (1,2-dimethoxyethane) was predried over $CaCl_2$ and distilled from Na/benzophenone ketyl under argon.

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

DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) was predried over CaH_2 (4 h) and distilled off.

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

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

NEP (*N*-ethylpyrrolidinone) was refluxed over CaH_2 and distilled from CaH_2.

NMP (*N*-methylpyrrolidinone) was refluxed over CaH_2 and distilled from CaH_2.

Pyridine was dried over KOH and distilled.

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

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

Triethylamine was dried over KOH and distilled.

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

1.2. REAGENTS

Commercially available reagents were used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use. Aluminum powder was purchased from Aldrich (200 mesh, 99 %) or ChemPur (100 mesh, 99.8 %). $PbCl_2$ (99.999 %) and $InCl_3$ (anhydrous, 99.99 %) were purchased from ChemPur. $TiCl_4$ was purchased from Acros, distilled and used as a 1 M solution in toluene. The nonaflates were prepared according to literature known procedures.[103]

BF_3·OEt_2 was distilled under Ar prior to use.

Bis(trimethylsilyl)methyl bromide ($(TMS)_2CHBr$, **87**) was prepared according a literature procedure,[96] besides that *n*BuLi (2.0 equiv) was slowly added with a syringe pump (0.3 mL/min) to the cooled mixture of $CHBr_3$ (1.0 equiv) and TMSCl (2.1 equiv).

***S*-(4-Methoxyphenyl) benzenesulfonothioate ($PhSO_2S$(*p*-MeO-C_6H_4, 95i)** was prepared according to a literature procedure.[104]

***N*-Phenyl-benzamidine (108)** was prepared according to a literature procedure.[105]

$PhSO_2Cl$ was stirred with 3 mol% $AlCl_3$ and 3 mol% toluene overnight and then distilled off.

TBAF solution in THF was prepared by drying TBAF·$3H_2O$ (1.58 g, 5.0 mmol) in a *Schlenk*-flask under high vacuum for 48 h at 50 °C. After cooling to 25 °C, dry THF (5.0 mL) was added and stirred until a clear solution was obtained.[98c]

TMPH was distilled under Ar prior to use.

CuCN·2LiCl solution was prepared by drying CuCN (8.96 g, 100 mmol) and LiCl (8.48 g, 200 mmol) in a *Schlenk*-flask under high vacuum for 5 h at 140 °C. After cooling to 25 °C, dry THF (100 mL) was added and the mixture was stirred for 24 h.

$ZnCl_2$ solution was prepared by drying $ZnCl_2$ (68.2 g, 500 mmol) in a *Schlenk*-flask under high vacuum for 6 h at 140 °C. After cooling to 25 °C, dry THF (500 mL) was added and the mixture was stirred until all salts were dissolved.

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

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

TMPMgCl·LiCl[34a] and **TMP_2Mg·2LiCl**[35a] were prepared as reported in the literature.

[103] J. Hörgermeier, H.-U. Reißig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868.
[104] K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, *3*, 343.
[105] Y. Wang, H. Wang, J. Peng, Q. Zhu, *Org. Lett.* **2011**, *13*, 4604.

The content of organometallic reagent was determined either by the method of *Paquette* using *i*PrOH and 1,10-phenanthroline as indicator (organolithium reagents)[106] or the method of *Knochel* using I_2 (organomagnesium or -zinc reagents)[107] prior to use. Organoaluminum reagents were titrated as described below.

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

1.3. ANALYTICAL DATA

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

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

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

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

NMR spectra were recorded on *Varian* Mercury 200, *Bruker* AC 300, WH 400, or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak, i.e. chloroform-d (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR), acetone-d6 (δ 2.05 ppm for ^{1}H NMR and δ 206.3 ppm for ^{13}C NMR) or benzene-d6 (δ 7.16 ppm for ^{1}H NMR and δ 128.1 ppm for ^{13}C NMR). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dddq (doublet of doublet of doublet of quartet), dt (doublet of triplet), m (multiplet), q (quartet), quint (quintet), sxt (sextet), oct (octet), as well as br (broad).

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

1.4. CHROMATOGRAPHY

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

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

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

2. Preparation and Reaction of Functionalized Organoaluminum Reagents

2.1. Typical Procedures

2.1.1. Typical Procedure for Aluminum Insertion with $InCl_3$ or $PbCl_2$ (TP 1)

LiCl (763 mg, 18.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 450 °C (heat gun) on high vacuum (10^{-1} mbar). Catalyst ($InCl_3$ or $PbCl_2$, respectively, 0.18 mmol) was added and dried for 5 min at 450 °C on high vacuum. After addition of aluminum powder (486 mg, 18.0 mmol) the flask was evacuated again and refilled with argon. THF (6.0 mL) was added and after addition of chlorotrimethylsilane (20 mg, 0.02 mL, 0.18 mmol), the suspension was heated until ebullition occurred. Then the organic halide (6.0 mmol) was added and the reaction mixture was stirred at the given temperature, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask. The content of active aluminum species was either determined by GC analysis of a reaction aliquot treated with iodine (3-4 balls) in dry THF (0.7 mL) under argon for 5 min and washed with sat. aq $Na_2S_2O_3$ solution or by titration as described below.

2.1.2. Typical Procedure for Aluminum Insertion with $TiCl_4$ (TP 2)

LiCl (763 mg, 18.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 450 °C (heat gun) on high vacuum (10^{-1} mbar). Aluminum powder (486 mg, 18.0 mmol) was added and the flask was evacuated and refilled with argon. After addition of THF (6.0 mL), $TiCl_4$ (0.18 mmol, 0.18 mL, 1 M solution in toluene) and chlorotrimethylsilane (20 mg, 0.02 mL, 0.18 mmol), the suspension was heated until ebullition occurred. Then, the aryl bromide (6.0 mmol) was added and the reaction mixture was stirred at the given temperature, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask. The amount of active aluminum species was either determined by GC analysis of a reaction aliquot treated with iodine (3-4 balls) in dry THF (0.7 mL) under argon for 5 min and washed with sat. aq $Na_2S_2O_3$ solution or by titration as described below.

2.1.3. Titration of Organoaluminum Sesquihalides $RAl_{2/3}X$[108]

Iodine (200 mg) was placed in a dry flask and dissolved in THF (3.0 mL). After addition of the organoaluminum solution (0.5 mL), the mixture was stirred for 30 min at 25 °C. The non-reacted iodine was titrated with a stock solution of $Na_2S_2O_3$ (0.1 M) and the concentration c of the organoaluminum solution was calculated as follows: $c = \left(n(I_2) - \frac{V(Na_2S_2O_3) \times 0.1\ M}{2}\right) \div 0.5\ mL$

2.1.4. Typical Procedure for Direct Cross-Coupling of Organoaluminum Reagents (TP 3)

In a dry and argon flushed flask $Pd(tmpp)_2Cl_2$ (30 mg, 0.02 mmol) and the electrophile (0.8 mmol) were dissolved in DMF. Then, the organoaluminum reagent (1.0 mmol) in THF was added and the mixture was stirred at 50 °C for the given time. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (7.5 mL) and water (2.5 mL) were added and the aqueous layer was extracted with Et_2O or EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

2.1.5. Typical Procedure for Alumination and Subsequent Direct Cross-Coupling (TP 4)

First, *N*-*tert*-butyl(2-methylpropylidene)amine was prepared following a known procedure[109] and distilled twice at atmospheric pressure prior usage. In a dry and argon flushed 50 mL *Schlenk*-tube, equipped with a magnetic stirring bar, *N*-*tert*-butyl(2-methylpropylidene)amine (191 mg, 1.5 mmol) was dissolved in THF (1.5 mL). This solution was cooled to -78 °C and *t*BuLi (1.5 M in pentane, 1.0 mL, 1.5 mmol) was added dropwise and stirred at this temperature for 1 h, then slowly warmed to 0 °C within 4 h. In a further dry and argon flushed 10 mL *Schlenk*-flask, THF (1.5 mL) was cooled to -78 °C and dry $AlCl_3$ (67 mg, 0.5 mmol) was added in small portions over a period of 20 min. The resulting mixture was stirred at -78 °C for 1 h and then slowly warmed to 0 °C within 4 h. This freshly prepared solution was added to the lithium amide at -60 °C and the mixture was stirred for 2 h.

The fresh aluminum *tris*-(*tert*-butyl-(1-isopropyl-2,2-dimethyl-propyl)-amide) *tris*(lithium chloride) ([(*t*BuCH(*i*Pr))(*t*Bu)]$N_3Al{\cdot}3LiCl$, **17**) solution (0.5 mmol) was concentrated *in vacuo* to a final volume of approximately 1.5 mL and used without titration. The corresponding arene (1.0 mmol) was added neat and the mixture was stirred at 25 °C for the indicated time. Complete

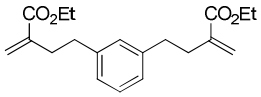
[108] T. R. Crompton, *Chemical Analysis of Organometallic Compounds*, *Vol. 5*, Academic Press, London, **1977**, p. 311.
[109] G. Stork, S. R. Dowd, *Org. Synth*. **1974**, *54*, 46.

metalation was detected by GC analysis of reaction aliquots, quenched with iodine or allyl bromide in the presence of CuCN·2LiCl using tetradecane as internal standard.

The thus prepared organoaluminum reagent (1.0 mmol) was added to a solution of $Pd(tmpp)_2Cl_2$ (30 mg, 0.02 mmol) and the electrophile (0.8 mmol) in DMF (2.0 mL). Afterwards, 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) was added and the mixture was stirred at 80 °C for 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (7.5 mL) and water (2.5 mL) were added and the aqueous layer was extracted with Et_2O or EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

2.2. Reactions of Organoaluminum Reagents after Prior Transmetalation to Zn

Diethyl 4,4'-(1,3-phenylene)bis(2-methylenebutanoate) (41)



$InCl_3$ (13 mg, 0.06 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 450 °C (heat gun) on high vacuum (10^{-1} mbar). After addition of aluminum powder (162 mg, 6.0 mmol) the flask was evacuated again and refilled with argon. $ZnCl_2$ (4.0 mL, 4.0 mmol, 1.0 M in THF) was added and after addition of chlorotrimethylsilane (7 mg, 0.01 mL, 0.06 mmol), the suspension was heated until ebullition occurred. Then 1,3-bis(chloromethyl)benzene (**39**, 350 mg, 2.0 mmol) was added and the reaction mixture was stirred at 25 °C for 1.5 h, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask. The reaction mixture was cooled to -30 °C and CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.0 M in THF) was added followed by ethyl (2-bromomethyl)acrylate (**29**, 540 mg, 2.8 mmol). The reaction mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, 2 M HCl (2 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, pentane / Et_2O = 10:1) afforded the desired product **41** (319 mg, 69 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.11 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 6.95 (dd, *J* = 7.3 Hz, 1.7 Hz, 2H), 6.17 (d, *J* = 1.5 Hz, 2H), 5.21 (q, *J* = 1.3 Hz, 2H), 4.00 (q, *J* = 7.1 Hz, 4H), 2.75 - 2.71 (m, 4H), 2.65 - 2.61 (m, 4H), 0.97 (t, *J* = 7.1 Hz, 6H).

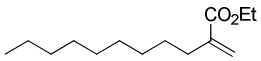
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 141.5, 140.4, 128.7, 128.3, 126.1, 124.3, 60.1, 34.9, 34.1, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2931, 1711, 1630, 1445, 1408, 1369, 1302, 1270, 1251, 1182, 1136, 1092, 1028, 942, 860, 817, 791, 703.

MS (EI, 70 eV): m/z (%) = 284 (26), 256 (26), 239 (53), 238 (44), 217 (17), 211 (24), 210 (40), 193 (20), 183 (32), 182 (15), 173 (72), 171 (54), 170 (32), 157 (33), 155 (19), 145 (70), 144 (16), 143 (100), 142 (21), 141 (28), 141 (28), 130 (17), 129 (42), 128 (56), 127 (11), 117 (17), 115 (21), 105 (48), 104 (31), 103 (21), 91 (19), 85 (12), 78 (16), 71 (16), 69 (11), 57 (25), 55 (13), 42 (21), 41 (15).

HRMS ($C_{20}H_{26}O_4$): calc.: 330.1831; found: 330.1820 (M^+).

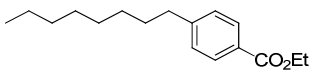
Ethyl 2-methyleneundecanoate (49a)



LiCl (254 mg, 6.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 450 °C (heat gun) on high vacuum (10^{-1} mbar). $PbCl_2$ (17 mg, 0.06 mmol) was added and dried for 5 min at 450 °C on high vacuum. After addition of aluminum powder (162 mg, 6.0 mmol) the flask was evacuated again and refilled with argon. THF (2.0 mL) was added and after addition of chlorotrimethylsilane (7 mg, 0.01 mL, 0.06 mmol), the suspension was heated until ebullition occurred. Then 1-iodooctane (**42**, 480 mg, 0.36 mL, 2.0 mmol) was added and the reaction mixture was stirred at 50 °C for 2.5 h, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask containing anhydrous $Zn(OAc)_2$ (550 mg, 3.0 mmol). The resulting suspension was stirred for 30 min at 25 °C. The reaction mixture was cooled to -30 °C and CuCN·2LiCl (0.60 mL, 0.60 mmol, 1.0 M in THF) was added followed by ethyl (2-bromomethyl)acrylate (**48a**, 270 mg, 1.4 mmol). The reaction mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, a mixture sat. aq NH_4Cl / NH_3 (25 % in H_2O) = 4:1 (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, pentane / Et_2O = 9:1) afforded the desired product **49a** (246 mg, 78 %) as yellowish oil.

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

Ethyl 4-octylbenzoate (49b)

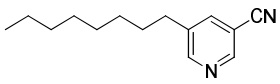


[110] S. Vettel, A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 7473.

LiBr (261 mg, 3.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 300 °C (heat gun) on high vacuum (10^{-1} mbar). $InCl_3$ (7 mg, 0.03 mmol) was added and dried for 5 min at 450 °C on high vacuum. After addition of aluminum powder (81 mg, 3.0 mmol) the flask was evacuated again and refilled with argon. THF (1.0 mL) was added and after addition of chlorotrimethylsilane (4 mg, 0.01 mL, 0.03 mmol), the suspension was heated until ebullition occurred. Then 1-bromooctane (**45**, 193 mg, 0.17 mL, 1.0 mmol) was added and the reaction mixture was stirred at 50 °C for 8 h, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask containing anhydrous $Zn(OAc)_2$ (275 mg, 1.5 mmol). The resulting suspension was stirred for 30 min at 25 °C. Then, $Pd(OAc)_2$ (4 mg, 0.02 mmol), S-Phos (16 mg, 0.04 mmol) and ethyl 4-iodobenzoate (**48b**, 193 mg, 0.12 mL, 0.7 mmol) in THF (1.5 mL) were added and the reaction mixture was stirred for 30 min at 25 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **49b** (138 mg, 75 %) as colorless oil.

The analytical data matches the reported one in the literature.[111]

5-Octylnicotinonitrile (49c)



LiBr (521 mg, 6.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 300 °C (heat gun) on high vacuum (10^{-1} mbar). $InCl_3$ (13 mg, 0.06 mmol) was added and dried for 5 min at 450 °C on high vacuum. After addition of aluminum powder (162 mg, 6.0 mmol) the flask was evacuated again and refilled with argon. THF (2.0 mL) was added and after addition of chlorotrimethylsilane (7 mg, 0.01 mL, 0.06 mmol), the suspension was heated until ebullition occurred. Then 1-bromooctane (**45**, 386 mg, 0.35 mL, 2.0 mmol) was added and the reaction mixture was stirred at 50 °C for 8 h, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask containing anhydrous $Zn(OAc)_2$ (550 mg, 3.0 mmol). The resulting suspension was stirred for 30 min at 25 °C. Then, $Pd(OAc)_2$ (8 mg, 0.04 mmol), S-Phos (32 mg, 0.08 mmol) and 5-bromonicotinonitrile (**48c**, 256 mg, 1.4 mmol) in THF (1.5 mL) were added and the reaction mixture was stirred for 4 h at 25 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and

[111] O. Vechorkin, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 9756.

purification by flash column chromatography (silica gel, pentane / Et_2O = 9:1) afforded the desired product **49c** (182 mg, 60 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.71 (s, 1H), 8.63 (s, 1H), 7.75 (s, 1H), 2.66 (t, *J* = 7.74 Hz, 2H), 1.68 - 1.56 (m, 2H), 1.36 - 1.21 (m, 10H), 0.87 (t, *J* = 6.63 Hz, 3H).

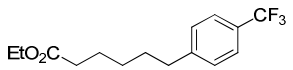
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.3, 149.7, 138.6, 138.5, 116.7, 109.6, 32.6, 31.7, 30.7, 29.2, 29.1, 29.0, 22.6, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3041, 2953, 2923, 2854, 2233, 1592, 1565, 1465, 1457, 1447, 1423, 1378, 1325, 1255, 1153, 1026, 960, 937, 894, 808, 766, 716, 702.

MS (EI, 70 eV): m/z (%) = 216 (9), 215 (9), 187 (15), 173 (11), 145 (17), 132 (16), 131 (100), 119 (13), 118 (83), 117 (27), 90 (16), 63 (10), 57 (42), 43 (34), 41 (44).

HRMS ($C_{14}H_{20}N_2$): calc.: 216.1626; found: 216.1508 (M^+).

Ethyl 6-(4-(trifluoromethyl)phenyl)hexanoate (49d)



LiCl (254 mg, 6.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 450 °C (heat gun) on high vacuum (10^{-1} mbar). $PbCl_2$ (17 mg, 0.06 mmol) was added and dried for 5 min at 450 °C on high vacuum. After addition of aluminum powder (162 mg, 6.0 mmol) the flask was evacuated again and refilled with argon. THF (2.0 mL) was added and after addition of chlorotrimethylsilane (7 mg, 0.01 mL, 0.06 mmol), the suspension was heated until ebullition occurred. Then ethyl 6-bromohexanoate (**47**, 446 mg, 0.36 mL, 2.0 mmol) was added and the reaction mixture was stirred at 50 °C for 36 h, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask containing anhydrous $Zn(OAc)_2$ (550 mg, 3.0 mmol). The resulting suspension was stirred for 30 min at 25 °C. Then, $Pd(OAc)_2$ (8 mg, 0.04 mmol), S-Phos (32 mg, 0.08 mmol) and 1-iodo-4-(trifluoromethyl)benzene (**48d**, 381 mg, 0.21 mL, 1.4 mmol) in THF (1.5 mL) were added and the reaction mixture was stirred for 3 h at 50 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, pentane / Et_2O = 9:1) afforded the desired product **49d** (343 mg, 85 %) as colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.52 (d, *J* = 8.04 Hz, 2H), 7.27 (d, *J* = 8.04 Hz, 2H), 4.12 (q, *J* = 7.11 Hz, 2H), 2.67 (t, *J* = 7.67 Hz, 2H), 2.29 (t, *J* = 7.48 Hz, 2H), 1.69 - 1.62 (m, 4H), 1.36 (quint, *J* = 7.71 Hz, 2H), 1.24 (t, *J* = 7.11 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 173.7, 146.6, 128.6, 128.1 (q, ^2J(C,F) = 32 Hz), 125.2 (q, ^3J(C,F) = 4 Hz), 124.4 (q, ^1J(C,F) = 272 Hz), 60.2, 35.5, 34.2, 30.8, 28.6, 24.7, 14.2.

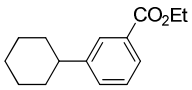
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2936, 2860, 1732, 1618, 1465, 1447, 1418, 1373, 1322, 1246, 1160, 1118, 1110, 1066, 1033, 1018, 939, 843, 820, 777, 757, 734.

MS (EI, 70 eV): m/z (%) = 288 (4), 269 (17), 268 (45), 243 (25), 222 (29), 198 (23), 173 (13), 172 (18), 159 (95), 153 (14), 140 (46), 133 (11), 129 (17), 127 (12), 109 (40), 101 (50), 91 (15), 88 (100), 83 (15), 73 (49), 70 (24), 61 (28), 60 (61), 59 (15), 55 (51).

HRMS ($C_{15}H_{19}F_3O_2$): calc.: 288.1337; found: 288.1344 (M^+).

Ethyl 3-cyclohexylbenzoate (49e)



LiBr (521 mg, 6.0 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 300 °C (heat gun) on high vacuum (10^{-1} mbar). $InCl_3$ (13 mg, 0.06 mmol) was added and dried for 5 min at 450 °C on high vacuum. After addition of aluminum powder (162 mg, 6.0 mmol) the flask was evacuated again and refilled with argon. THF (2.0 mL) was added and after addition of chlorotrimethylsilane (7 mg, 0.01 mL, 0.06 mmol), the suspension was heated until ebullition occurred. Then cyclohexyl bromide (326 mg, 0.25 mL, 2.0 mmol) was added and the reaction mixture was stirred at 50 °C for 18 h, until GC analysis of a hydrolyzed reaction aliquot showed full conversion. Remaining aluminum was separated by centrifugation (2000 rpm, 40 min) and the supernatant solution was carefully cannulated to a new dry and argon-flushed *Schlenk*-flask containing anhydrous $Zn(OAc)_2$ (550 mg, 3.0 mmol). The resulting suspension was stirred for 30 min at 25 °C. Then, $Pd(OAc)_2$ (8 mg, 0.04 mmol), S-Phos (32 mg, 0.08 mmol) and ethyl 3-iodobenzoate (**48e**, 386 mg, 0.25 mL, 1.4 mmol) in THF (1.5 mL) were added and the reaction mixture was stirred for 4 h at 50 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **49e** (200 mg, 62 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89 (s, 1H), 7.86 (ddd, *J* = 7.33, 1.52, 1.38 Hz, 1H), 7.30 - 7.42 (m, 2H), 4.38 (q, *J* = 7.00 Hz, 2H), 2.63 - 2.50 (m, 1H), 1.93 - 1.72 (m, 5H), 1.50 - 1.21 (m, 8H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.9, 148.3, 131.4, 130.5, 128.2, 128.0, 127.0, 60.8, 44.4, 34.3, 26.8, 26.1, 14.4.

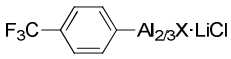
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2923, 2850, 1715, 1604, 1586, 1477, 1463, 1447, 1391, 1366, 1286, 1274, 1263, 1227, 1191, 1133, 1104, 1080, 1024, 998, 925, 884, 865, 851, 816, 750, 695, 677.

MS (EI, 70 eV): m/z (%) = 232 (100), 204 (24), 203 (41), 187 (68), 176 (67), 163 (17), 161 (17), 159 (45), 149 (15), 148 (60), 135 (37), 131 (38), 129 (18), 119 (15), 117 (81), 115 (46), 103 (32), 91 (81), 89 (15), 81 (17), 79 (19), 77 (35), 65 (15), 55 (25).

HRMS ($C_{15}H_{20}O_2$): calc.: 232.1463; found: 232.1445 (M^+).

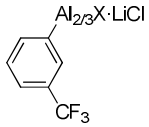
2.3. Preparation of Arylaluminum Sesquihalides

Preparation of Organoaluminum Reagent 50a



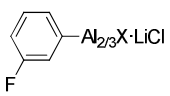
According to **TP 1** using $InCl_3$ (40 mg, 0.18 mmol), the reaction mixture was stirred for 2.5 h at 25 °C after addition of 1-iodo-4-(trifluoromethyl)benzene (1.632 g, 0.88 mL, 6.0 mmol). The concentration of the organoaluminum reagent **50a** was determined as 0.72 M by the described titration method.

Preparation of Organoaluminum Reagent 50b



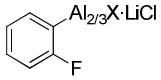
According to **TP 2**, the reaction mixture was stirred for 4 h at 50 °C after addition of 1-bromo-3-(trifluoromethyl)benzene (1.350 g, 0.84 mL, 6.0 mmol). The concentration of the organoaluminum reagent **50b** was determined as 0.61 M by the described titration method.

Preparation of Organoaluminum Reagent 50c



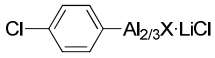
According to **TP 2**, the reaction mixture was stirred for 20 h at 50 °C after addition of 3-bromofluorobenzene (0.875 g, 5.0 mmol). The concentration of the organoaluminum reagent **50c** was determined as 0.64 M by the described titration method.

Preparation of Organoaluminum Reagent 50d



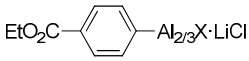
According to **TP 2**, the reaction mixture was stirred for 3.5 h at 30 °C after addition of 2-bromofluorobenzene (0.875 g, 0.55 mL, 5.0 mmol). The concentration of the organoaluminum reagent **50d** was determined as 0.78 M by the described titration method.

Preparation of Organoaluminum Reagent 50e



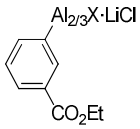
According to **TP 2**, the reaction mixture was stirred for 16 h at 50 °C after addition of 1-bromo-4-chlorobenzene (0.766 g, 4.0 mmol). The concentration of the organoaluminum reagent **50e** was determined as 0.48 M by the described titration method.

Preparation of Organoaluminum Reagent 55a



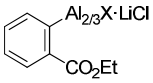
According to **TP 1** using $PbCl_2$ (50 mg, 0.18 mmol), the reaction mixture was stirred for 24 h at 50 °C after addition of ethyl 4-iodobenzoate (1.656 g, 1.00 mL, 6.0 mmol). The concentration of the organoaluminum reagent **55a** was determined as 0.52 M by the described titration method.

Preparation of Organoaluminum Reagent 55b



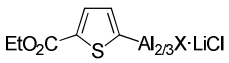
According to **TP 1** using $PbCl_2$ (42 mg, 0.15 mmol), the reaction mixture was stirred for 24 h at 50 °C after addition of ethyl 3-iodobenzoate (1.380 g, 0.83 mL, 5.0 mmol). The concentration of the organoaluminum reagent **55b** was determined as 0.57 M by the described titration method.

Preparation of Organoaluminum Reagent 55c



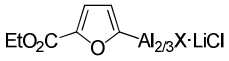
According to **TP 1** using $PbCl_2$ (42 mg, 0.15 mmol), the reaction mixture was stirred for 3 h at 50 °C after addition of ethyl 2-iodobenzoate (1.380 g, 0.84 mL, 5.0 mmol). The concentration of the organoaluminum reagent **55c** was determined as 0.59 M by the described titration method.

Preparation of Organoaluminum Reagent 55d



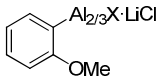
According to **TP 1** using $PbCl_2$ (42 mg, 0.15 mmol), the reaction mixture was stirred for 24 h at 50 °C after addition of ethyl 5-bromothiophene-2-carboxylate (1.176 g, 5.0 mmol). The concentration of the organoaluminum reagent **55d** was determined as 0.80 M by the described titration method.

Preparation of Organoaluminum Reagent 55e



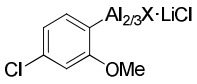
According to **TP 1** using $PbCl_2$ (42 mg, 0.15 mmol), the reaction mixture was stirred for 24 h at 50 °C after addition of ethyl 5-bromofuran-2-carboxylate (1.095 g, 5.0 mmol). The amount of active species of the organoaluminum reagent **55e** was determined as 60 % by GC analysis of an iodolyzed reaction aliquot as titration failed due to the black color of the solution of **55e** in THF.

Preparation of Organoaluminum Reagent 57a



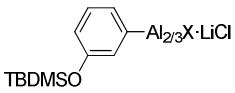
According to **TP 2**, the reaction mixture was stirred for 20 h at 50 °C after addition of 1-bromo-2-methoxybenzene (0.935 g, 0.62 mL, 5.0 mmol). The concentration of the organoaluminum reagent **57a** was determined as 0.70 M by the described titration method.

Preparation of Organoaluminum Reagent 57b



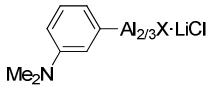
According to **TP 2**, the reaction mixture was stirred for 20 h at 50 °C after addition of 1-bromo-4-chloro-2-methoxybenzene (0.886 g, 4.0 mmol). The concentration of the organoaluminum reagent **57b** was determined as 0.60 M by the described titration method.

Preparation of Organoaluminum Reagent 57c



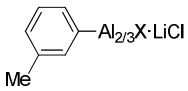
According to **TP 1** using $InCl_3$ (27 mg, 0.12 mmol), the reaction mixture was stirred for 15 h at 50 °C after addition of *tert*-butyl(3-iodophenoxy)dimethylsilane (1.337 g, 4.0 mmol). The concentration of the organoaluminum reagent **57c** was determined as 0.89 M by the described titration method.

Preparation of Organoaluminum Reagent 57d



According to **TP 1** using $InCl_3$ (27 mg, 0.12 mmol), the reaction mixture was stirred for 12 h at 50 °C after addition of 3-iodo-*N,N*-dimethylaniline (0.988 g, 4.0 mmol). The concentration of the organoaluminum reagent **57d** was determined as 0.73 M by the described titration method.

Preparation of Organoaluminum Reagent 57e



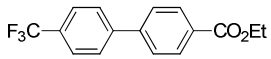
According to **TP 1** using $InCl_3$ (33 mg, 0.15 mmol), the reaction mixture was stirred for 6 h at 50 °C after addition of 1-iodo-3-methylbenzene (1.090 g, 5.0 mmol). The concentration of the organoaluminum reagent **57e** was determined as 0.81 M by the described titration method.

2.4. Direct Cross-Coupling of Aryl- and Alkylaluminum Sesquihalides

Preparation of $Pd(tmpp)_2Cl_2$

$PdCl_2$ (748 mg, 4.22 mmol) and NaCl (493 mg, 8.43 mmol) were dissolved in MeOH (40 mL) at 25 °C (1-3 h) and a solution of tmpp (4.940 g, 9.28 mmol) in dry DCM (20 mL) was added. After stirring for 1 h at 25 °C, the solution turned dark red and the solvent was removed *in vacuo* to give a dark red crystalline solid. *n*-Hexane (10 mL) and acetone (120 mL) were added and the solution was heated to reflux. The colorless, crystalline precipitate was filtered off and the red solution was evaporated to dryness *in vacuo* to give $Pd(tmpp)_2Cl_2$ (5.085 g, 4.09 mmol, 97 %) as dark red crystals.

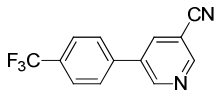
Ethyl 4'-(trifluoromethyl)biphenyl-4-carboxylate (52a)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (60 mg, 0.048 mmol) and ethyl 4-iodobenzoate (**51a**; 442 mg, 0.27 mL, 1.6 mmol) were dissolved in dry DMF (5.6 mL). Organoaluminum reagent **50a** (2.8 mL, 2.0 mmol, 0.72 M in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 20:1) afforded the biphenyl **52a** (391 mg, 83 %) as colorless crystals.

The analytical data matches the reported one in the literature.[112]

5-[4-(Trifluoromethyl)phenyl]pyridine-3-carbonitrile (52b)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (25 mg, 0.020 mmol) and 5-bromopyridine-3-carbonitrile (**51b**; 128 mg, 0.70 mmol) were dissolved in dry DMF (2.4 mL). Organoaluminum reagent **50a** (1.2 mL, 0.88 mmol, 0.72 M in THF) was added and the mixture was stirred for 6 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / EtOAc = 5:1) afforded the desired product **52b** (167 mg, 96 %) as colorless solid.

M.p. (°C): 137-138.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.06 (s, 1H), 8.93 (s, 1H), 8.18 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.5, 151.4, 139.0, 137.4, 135.6, 131.4 (q, ^2J(C,F) = 33 Hz), 127.6, 126.4 (q, ^3J(C,F) = 4 Hz), 123.8 (q, ^1J(C,F) = 272 Hz), 116.2, 110.3.

[112] M. Amatore, C. Gosmini, *Angew. Chem. Int. Ed.* **2008**, *47*, 2089.

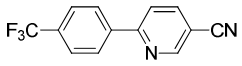
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3045, 2361, 2336, 2232, 1734, 1618, 1585, 1560, 1429, 1399, 1360, 1319, 1287, 1224, 1202, 1177, 1152, 1111, 1072 , 1050, 1024, 1015, 982, 962, 934, 907, 869, 850, 834, 773, 701.

MS (EI, 70 eV): m/z (%) = 248 (29), 99 (12), 97 (19), 85 (51), 83 (23), 71 (71), 70 (13), 69 (27), 57 (100), 56 (16), 55 (31), 43 (71), 41 (19).

HRMS ($C_{13}H_7N_2F_3$): calc.: 248.0561; found: 248.0560 (M^+).

6-[4-(Trifluoromethyl)phenyl]pyridine-3-carbonitrile (52c)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (25 mg, 0.020 mmol) and 6-chloropyridine-3-carbonitrile (**51c**; 97 mg, 0.70 mmol) were dissolved in dry DMF (2.4 mL). Organoaluminum reagent **50a** (1.2 mL, 0.88 mmol, 0.72 M in THF) was added and the mixture was stirred for 5 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / EtOAc = 7:1) afforded the desired product **52c** (121 mg, 70 %) as colorless solid.

M.p. (°C): 128-129.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.99 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 2H), 8.07 (dd, *J* = 8.2 Hz, *J* = 1.7 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H).

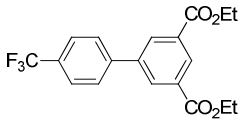
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.8, 152.5, 140.5, 140.2, 132.3 (q, ^2J(C,F) = 33 Hz), 127.7, 126.0 (q, ^3J(C,F) = 4 Hz), 123.9 (q, ^1J(C,F) = 272 Hz), 120.3, 116.6, 108.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2953, 2919, 2850, 2359, 2337, 2235, 2156, 1975, 1716, 1618, 1591, 1556, 1551, 1474, 1414, 1380, 1322, 1312, 1277, 1229, 1206, 1190, 1167, 1148, 1122, 1111, 1066, 1033, 1022, 1012, 966, 940, 868, 835, 766, 732, 695.

MS (EI, 70 eV): m/z (%) = 248 (100), 179 (29), 97 (24), 85 (24), 83 (26), 81 (13), 71 (45), 70 (12), 69 (33), 57 (67), 56 (13), 55 (37), 43 (52), 41 (21).

HRMS ($C_{13}H_7N_2F_3$): calc.: 248.0561; found: 248.0558 (M^+).

Diethyl 4'-(trifluoromethyl)biphenyl-3,5-dicarboxylate (52d)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (25 mg, 0.020 mmol) and diethyl 5-{[(nonafluorobutyl)-sulfonyl]oxy}benzene-1,3-dicarboxylate (**51d**; 364 mg, 0.70 mmol) or diethyl 5-{[(trifluoro-methyl)sulfonyl]oxy}benzene-1,3-dicarboxylate (**51d'**; 259 mg, 0.70 mmol), respectively were dissolved in dry DMF (2.4 mL). Organoaluminum reagent **50a** (1.2 mL, 0.88 mmol, 0.72 M in THF) was added and the mixture was stirred for 4 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the biphenyl **4d** (238 mg, 93 % for the nonaflate **52d**; 215 mg, 84 % for the triflate **52d'**) as colorless crystals.

M.p. (°C): 105-107.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.71 (s, 1H), 8.45 (d, *J* = 1.3 Hz, 2H), 7.79-7.72 (m, 4H), 4.45 (q, *J* = 7.1 Hz, 4H), 1.44 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.5, 142.7, 140.3, 132.2, 131.8, 130.2 (q, ^2J(C,F) = 33 Hz), 130.0, 127.5, 125.9 (q, ^3J(C,F) = 4 Hz), 124.1 (q, ^1J(C,F) = 272 Hz), 61.6, 14.3.

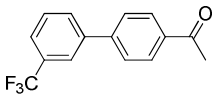
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2930, 2851, 2360, 1708, 1654, 1636, 1617, 1479, 1447, 1395, 1373, 1335, 1321, 1236, 1195, 1144, 1120, 1108, 1060, 1025, 1014, 984, 956, 942, 932, 918, 884, 866, 854, 833, 759, 743, 723, 686.

MS (EI, 70 eV): m/z (%) = 367 (13), 366 (61), 322 (18), 321 (100), 293 (23), 265 (14), 220 (14), 209 (13).

HRMS ($C_{19}H_{17}O_4F_3$): calc.: 366.1079; found: 366.1072 (M^+).

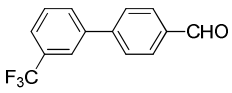
1-[3'-(Trifluoromethyl)biphenyl-4-yl]ethanone (52e)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-(4-iodophenyl)ethanone (**51e**; 197 mg, 0.80 mmol) were dissolved in dry DMF (3.3 mL). Organoaluminum reagent **50b** (1.6 mL, 1.0 mmol, 0.61 M in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2OAc = 9:1) afforded the desired product **52e** (182 mg, 86 %) as yellow oil.

The analytical data matches the reported one in the literature.[46]

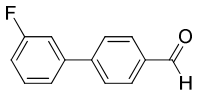
1-[3'-(Trifluoromethyl)biphenyl-4-yl]ethanone (52f)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-bromobenzaldehyde (**51f**; 259 mg, 1.40 mmol) were dissolved in dry DMF (4.0 mL). Organoaluminum reagent **50b** (2.9 mL, 1.8 mmol, 0.61 M in THF) was added and the mixture was stirred for 18 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2OAc = 5:1) afforded the desired product **52f** (207 mg, 59 %) as yellow oil.

The analytical data matches the reported one in the literature.[113]

3'-Fluorobiphenyl-4-carbaldehyde (52g)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-bromobenzaldehyde (**51f**; 130 mg, 0.70 mmol) were dissolved in dry DMF (3.1 mL). Organoaluminum reagent **50c** (1.6 mL, 1.0 mmol, 0.64 M in THF) was added and the mixture was stirred for 3 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **52g** (87 mg, 62 %) as colorless needles.

M.p. (°C): 68-69.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 10.10 (s, 1H), 8.08 - 7.88 (m, 4H), 7.66 - 7.46 (m, 3H), 7.28 - 7.13 (m, 1H).

^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 193.1, 164.7 (d, ^1J(C,F) = 245 Hz), 146.5 (d, ^4J(C,F) = 2 Hz), 143.5 (d, ^3J(C,F) = 8 Hz), 137.6, 132.4 (d, ^3J(C,F) = 9 Hz), 131.5, 129.1, 124.7 (d, ^4J(C,F) = 3 Hz), 116.5 (d, ^2J(C,F) = 22 Hz), 115.4 (d, ^2J(C,F) = 23 Hz).

^{19}F-NMR (376 MHz, acetone-d6): δ / ppm = -114.2.

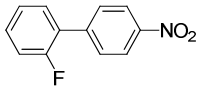
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2826, 2818, 2740, 1937, 1690, 1603, 1594, 1565, 1515, 1486, 1472, 1445, 1408, 1391, 1371, 1315, 1294, 1262, 1212, 1186, 1177, 1171, 1154, 1110, 1080, 1002, 882, 875, 845, 827, 781, 768, 728, 708, 687.

MS (EI, 70 eV): m/z (%) = 201 (10), 200 (98), 199 (100), 172 (19), 171 (53), 170 (79), 169 (10), 151 (12).

HRMS ($C_{13}H_9OF$): calc.: 200.0637; found: 200.0640 (M^+).

[113] a) B. H. Lipshutz, J. A. Sclafani, P. A. Blomgren, *Tetrahedron* **2000**, *56*, 2139; b) M. Kosugi, T. Ishikawa, T. Nogami, T. Migita, *Nippon Kagaku Kaishi* **1985**, 520.

2-Fluoro-4'-nitrobiphenyl (52i)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (50 mg, 0.040 mmol) and 1-iodo-4-nitrobenzene (**51h**; 349 mg, 1.4 mmol) were dissolved in dry DMF (4.4 mL). Organoaluminum reagent **50d** (2.2 mL, 1.8 mmol, 0.78 M in THF) was added and the mixture was stirred for 3 h at 50 °C. Purification by flash column chromatography (silica gel, pentane / Et_2O = 49:1) afforded the desired product **52i** (278 mg, 91 %) as yellow solid.

M.p. (°C): 86-88.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.30 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.50 - 7.37 (m, 2H), 7.15 - 7.32 (m, 2H).

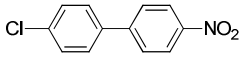
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.7 (d, ^1J(C,F) = 250 Hz), 147.2, 142.4 (d, ^3J(C,F) = 1 Hz), 130.6 (d, ^3J(C,F) = 8 Hz), 130.5 (d, ^3J(C,F) = 3 Hz), 129.8 (d, ^4J(C,F) = 3 Hz), 126.8 (d, ^2J(C,F) = 13 Hz), 124.8 (d, ^4J(C,F) = 4 Hz), 123.7, 116.5 (d, ^2J(C,F) = 22 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2848, 2360, 2336, 2156, 1615, 1598, 1512, 1504, 1476, 1452, 1402, 1339, 1318, 1303, 1250, 1209, 1189, 1106, 1099, 868, 855, 849, 820, 766, 752, 734, 721, 693.

MS (EI, 70 eV): m/z (%) = 218 (21), 217 (100), 187 (33), 171 (44), 170 (86), 169 (16), 159 (34), 151 (23), 150 (13), 85 (13).

HRMS ($C_{12}H_8FNO_2$): calc.: 217.0539; found: 217.0527 (M^+).

4-Chloro-4'-nitrobiphenyl (52j)

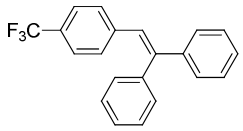


According to **TP 3,** $Pd(tmpp)_2Cl_2$ (50 mg, 0.040 mmol) and 1-iodo-4-nitrobenzene (**51h**; 299 mg, 1.2 mmol) were dissolved in dry DMF (4.0 mL). Organoaluminum reagent **50e** (3.6 mL, 1.7 mmol, 0.48 M in THF) was added and the mixture was stirred for 6 h at 50 °C. Purification by flash column chromatography (silica gel, pentane / Et_2O = 15:1) afforded the desired product **52j** (149 mg, 53 %) as yellow solid.

The analytical data matches the reported one in the literature.[114]

[114] M. Dai, B. Liang, C. Wang, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 221.

1-(2,2-Diphenylethenyl)-4-(trifluoromethyl)benzene (54)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (25 mg, 0.020 mmol) and 2,2-diphenylethenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**53**; 311 mg, 0.65 mmol) were dissolved in dry DMF (2.2 mL). Organoaluminum reagent **50a** (1.1 mL, 0.81 mmol, 0.72 M in THF) was added and the mixture was stirred for 6 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane) afforded the desired product **54** (160 mg, 76 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.43 - 7.30 (m, 10H), 7.25 - 7.19 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.00 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 145.1, 142.9, 141.0, 139.7, 130.3, 129.6, 128.8, 128.4 (q, ^2J(C,F) = 32 Hz), 128.3, 128.1, 127.9, 127.7, 126.6, 124.9 (q, ^3J(C,F) = 4 Hz), 124.2 (q, ^1J(C,F) = 272 Hz).

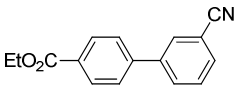
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 2863, 1614, 1492, 1445, 1412, 1382, 1350, 1323, 1165, 1118, 1111, 1067, 1016, 944, 880, 829, 767, 756, 697.

MS (EI, 70 eV): m/z (%) = 325 (20), 324 (100), 323 (10), 255 (18), 254 (10), 253 (13), 252 (11), 246 (14), 178 (12).

HRMS ($C_{21}H_{15}F_3$): calc.: 324.1126; found: 324.1116 (M^+).

Ethyl 3'-cyanobiphenyl-4-carboxylate (56a)

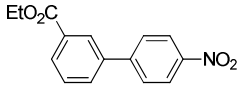


According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 3-iodobenzonitrile (**51i**; 183 mg, 0.80 mmol) were dissolved in dry DMF (3.8 mL). Organoaluminum reagent **55a** (1.9 mL, 1.0 mmol, 0.52 M in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the desired product **56a** (192 mg, 96 %) as colorless solid.

The analytical data matches the reported one in the literature.[115]

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

Ethyl 4'-nitrobiphenyl-3-carboxylate (56b)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-iodo-4-nitrobenzene (**51h**; 199 mg, 0.80 mmol) were dissolved in dry DMF (3.5 mL). Organoaluminum reagent **55b** (1.8 mL, 1.0 mmol, 0.57 M in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / DCM = 1:1) afforded the desired product **56b** (159 mg, 73 %) as colorless solid.

M.p. (°C): 87-90.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.36 - 8.28 (m, 3H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.84 - 7.74 (m, 3H), 7.58 (t, *J* = 7.7 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).

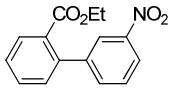
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.1, 147.4, 146.5, 139.0, 131.51, 131.50, 129.8, 129.2, 128.4, 127.9, 124.2, 61.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3119, 2986, 2910, 1728, 1596, 1588, 1514 , 1475, 1464, 1438, 1395, 1364, 1345, 1326, 1307, 1280, 1247, 1193, 1172, 1124, 1108, 1084, 1044, 1017, 1000, 920, 889, 865, 850, 816, 770, 762, 738, 698, 686.

MS (EI, 70 eV): m/z (%) = 271 (41), 241 (23), 227 (15), 226 (71), 213 (15), 153 (11), 152 (47), 151 (31), 59 (100), 45 (67), 44 (19), 43 (23), 41 (12).

HRMS ($C_{15}H_{13}NO_4$): calc.: 271.0845; found: 271.0837 (M^+).

Ethyl 3'-nitrobiphenyl-2-carboxylate (56c)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-iodo-3-nitrobenzene (**51j**; 199 mg, 0.80 mmol) were dissolved in dry DMF (3.5 mL). Organoaluminum reagent **55c** (1.7 mL, 1.0 mmol, 0.59 M in THF) was added and the mixture was stirred for 48 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / DCM = 1:1) afforded the desired product **56c** (82 mg, 38 %) as colorless solid.

M.p. (°C): 81-82.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.26 - 8.17 (m, 2H), 7.97 (dd, *J* = 7.67, 1.31 Hz, 1H), 7.67 - 7.46 (m, 4H), 7.35 (dd, *J* = 7.57, 1.03 Hz, 1H), 4.14 (q, *J* = 7.11 Hz, 2H), 1.08 (t, *J* = 7.11 Hz, 3H).

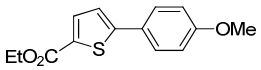
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.4, 147.9, 143.3, 140.3, 134.6, 134.1, 131.7, 130.7, 130.5, 128.7, 128.3, 123.5, 122.0, 61.1, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 2987, 2904, 1721, 1681, 1595, 1578, 1569, 1522, 1489, 1478, 1468, 1450, 1446, 1389, 1364, 1346, 1308, 1284, 1277, 1247, 1160, 1136, 1115, 1102, 1089, 1084, 1055, 1022, 1001, 989, 967, 931, 914, 885, 872, 853, 812, 803, 770, 763, 737, 707, 688, 681, 658.

MS (EI, 70 eV): m/z (%) = 272 (10), 271 (52), 243 (25), 227 (19), 226 (100), 210 (26), 208 (14), 196 (34), 181 (18), 180 (52), 179 (27), 168 (14), 153 (12), 152 (49), 151 (53), 150 (15), 141 (13), 139 (14), 76 (17).

HRMS ($C_{15}H_{13}NO_4$): calc.: 271.0845; found: 271.0838 (M^+).

Ethyl 5-[4-(methoxy)phenyl]thiophene-2-carboxylate (56d)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-iodo-4-methoxybenzene (**51k**; 187 mg, 0.80 mmol) were dissolved in dry DMF (2.6 mL). Organoaluminum reagent **55d** (1.3 mL, 1.0 mmol, 0.75 M in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **56d** (202 mg, 96 %) as colorless solid.

M.p. (°C): 77-79.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.73 (d, *J* = 3.74 Hz, 1H), 7.57 (d, *J* = 8.79 Hz, 2H), 7.17 (d, *J* = 3.93 Hz, 1H), 6.93 (d, *J* = 8.79 Hz, 2H), 4.36 (q, *J* = 7.11 Hz, 2H), 3.84 (s, 3H), 1.39 (t, *J* = 7.11 Hz, 3H).

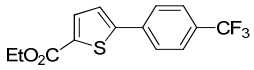
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.3, 160.1, 151.2, 134.3, 131.4, 127.5, 126.3, 122.5, 114.4, 61.0, 55.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3015, 2988, 2917, 2359, 2336, 2156, 2017, 2004, 1974, 1698, 1604, 1571, 1534, 1508, 1446, 1432, 1364, 1276, 1254, 1247, 1178, 1098, 1051, 1023, 1012, 864, 826, 818, 799, 748, 682.

MS (EI, 70 eV): m/z (%) = 263 (10), 262 (100), 234 (39), 219 (42), 217 (58), 191 (20), 190 (16), 145 (44), 89 (10).

HRMS ($C_{14}H_{14}O_3S$): calc.: 262.0664; found: 262.0659 (M^+).

Ethyl 5-[4-(trifluoromethyl)phenyl]thiophene-2-carboxylate (56e)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-bromo-4-(trifluoromethyl)benzene (**51l**; 180 mg, 0.80 mmol) were dissolved in dry DMF (2.6 mL). Organoaluminum reagent **55d** (1.3 mL, 1.0 mmol, 0.75 M in THF) was added and the mixture was stirred for 6 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **56e** (213 mg, 89 %) as colorless solid.

M.p. (°C): 96-98.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.78 (d, *J* = 3.9 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 3.7 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.0, 148.8, 136.8, 134.2, 134.0, 130,4 (q, ^2J(C,F) = 33 Hz), 126.3, 126.1 (q, ^3J(C,F) = 4 Hz), 124.8, 123.9 (q, ^1J(C,F) = 272 Hz), 61.4, 14.3.

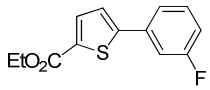
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2985, 2359, 2337, 2156, 1973, 1701, 1684, 1612, 1450, 1412, 1368, 1319, 1284, 1272, 1252, 1163, 1123, 1114, 1100, 1067, 1048, 1009, 959, 838, 813, 748, 736.

MS (EI, 70 eV): m/z (%) = 301 (10), 300 (46), 272 (42), 256 (16), 228 (16), 183 (51), 44 (100).

HRMS ($C_{14}H_{11}F_3O_2S$): calc.: 300.0432; found: 300.0435 (M^+).

Ethyl 5-(3-fluorophenyl)thiophene-2-carboxylate (56f)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 3-fluorophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**51m**; 315 mg, 0.80 mmol) were dissolved in dry DMF (2.6 mL). Organoaluminum reagent **55d** (1.3 mL, 1.0 mmol, 0.75 M in THF) was added and the mixture was stirred for 6 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **56f** (172 mg, 86 %) as colorless solid.

M.p. (°C): 56-57.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.75 (d, *J* = 3.9 Hz, 1H), 7.44 - 7.27 (m, 4H), 7.09 - 7.00 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.1 (d, ^1J(C,F) = 247 Hz), 162.1, 149.3 (d, ^4J(C,F) = 3 Hz), 135.5 (d, ^3J(C,F) = 8 Hz), 134.1, 133.3, 130.6 (d, ^3J(C,F) = 9 Hz), 124.2, 121.9 (d, ^4J(C,F) = 3 Hz), 115.5 (d, ^3J(C,F) = 21 Hz), 113.1 (d, ^3J(C,F) = 23 Hz), 61.3, 14.3.

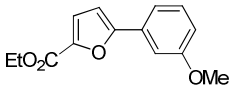
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -112.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3100, 3066, 2989, 2961, 2904, 1697, 1660, 1610, 1582, 1538, 1475, 1438, 1364, 1347, 1272, 1247, 1172, 1161, 1123, 1100, 1081, 1021, 998, 888, 875, 835, 819, 773, 746, 677.

MS (EI, 70 eV): m/z (%) = 250 (54), 222 (37), 206 (14), 205 (100), 178 (16), 133 (62).

HRMS ($C_{13}H_{11}FO_2S$): calc.: 250.0464; found: 250.0466 (M^+).

Ethyl 5-(3-methoxyphenyl)furan-2-carboxylate (56g)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-iodo-3-methoxybenzene (**51n**; 187 mg, 0.10 mL, 0.80 mmol) were dissolved in dry DMF (3.4 mL). Organoaluminum reagent **55e** (1.7 mL, 1.0 mmol, 60 % in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / DCM = 1:1) afforded the desired product **56g** (179 mg, 91 %) as yellow solid.

M.p. (°C): 47-49.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.39 - 7.29 (m, 3H), 7.23 (d, *J* = 3.6 Hz, 1H), 6.92 - 6.86 (m, 1H), 6.72 (d, *J* = 3.7 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

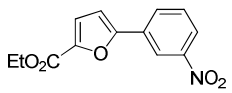
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.9, 158.8, 157.3, 143.9, 130.8, 129.9, 119.7, 117.4, 114.8, 110.0, 107.1, 60.9, 55.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3116, 3072, 2986, 2972, 2927, 2905, 2870, 2844, 1704, 1596, 1528, 1517, 1474, 1464, 1448, 1433, 1372, 1320, 1300, 1280, 1225, 1217, 1192, 1160, 1136, 1114, 1085, 1070, 1039, 1022, 994, 959, 946, 863, 834, 815, 782, 761, 692, 677.

MS (EI, 70 eV): m/z (%) = 247 (13), 246 (100), 218 (60), 201 (32), 174 (49), 115 (38), 102 (26).

HRMS ($C_{14}H_{14}O_4$): calc.: 246.0892; found: 246.0882 (M^+).

Ethyl 5-(3-methoxyphenyl)furan-2-carboxylate (56h)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-iodo-3-nitrobenzene (**51j**; 199 mg, 0.80 mmol or 174 mg, 0.70 mmol) were dissolved in dry DMF (3.4 mL). Organoaluminum reagent **55e** (1.7 mL, 1.0 mmol, 60 % in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / DCM = 1:1) afforded the desired product **56h** (131 mg, 62 % or 138 mg, 76 %) as yellow solid.

M.p. (°C): 133-134.

^{1}H-NMR (400 MHz, acetone-d6): δ / ppm = 8.60 (t, *J* = 1.86 Hz, 1H), 8.26 (d, *J* = 1.96 Hz, 1H), 8.24 (d, *J* = 1.76 Hz, 1H), 7.80 (t, *J* = 8.02 Hz, 1H), 7.36 (d, *J* = 3.52 Hz, 1H), 7.33 (d, *J* = 3.72 Hz, 1H), 4.38 (q, *J* = 7.24 Hz, 2H), 1.37 (t, *J* = 7.14 Hz, 3H).

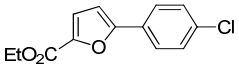
^{13}C-NMR (100 MHz, acetone-d6): δ / ppm = 158.8, 155.5, 149.9, 146.0, 132.1, 131.6, 131.3, 124.1, 120.6, 119.9, 110.5, 61.7, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1712, 1536, 1527, 1515, 1462, 1375, 1348, 1302, 1282, 1272, 1220, 1152, 1137, 1113, 1092, 1021, 863, 803, 762, 741, 731, 680.

MS (EI, 70 eV): m/z (%) = 262 (15), 261 (84), 233 (52), 231 (18), 217 (17), 216 (45), 203 (10), 189 (35), 170 (21), 131 (14), 115 (16), 114 (34), 113 (12), 77 (10), 74 (68), 59 (100), 45 (77), 44 (32), 43 (25), 41 (16).

HRMS ($C_{13}H_{11}NO_5$): calc.: 261.0637; found: 261.0631 (M^+).

Ethyl 5-(4-chlorophenyl)furan-2-carboxylate (56i)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-bromo-4-chlorobenzene (**51o**; 153 mg, 0.80 mmol) were dissolved in dry DMF (3.4 mL). Organoaluminum reagent **55e** (1.7 mL, 1.0 mmol, 60 % in THF) was added and the mixture was stirred for 5 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 8:1) afforded the desired product **56i** (130 mg, 65 %) as colorless needles.

M.p. (°C): 68-70.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.70 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H).

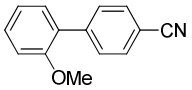
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.7, 156.2, 144.1, 134.7, 129.0, 128.0, 126.0, 119.7, 107.1, 60.9, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2956, 2923, 2853, 1723, 1584, 1565, 1521, 1477, 1470, 1410, 1369, 1295, 1277, 1268, 1214, 1144, 1108, 1094, 1061, 1018, 1010, 962, 922, 864, 837, 829, 813, 801, 762, 734, 715, 672.

MS (EI, 70 eV): m/z (%) = 252 (30), 250 (100), 224 (18), 222 (68), 206 (15), 180 (17), 178 (58), 151 (30), 149 (89), 131 (35), 115 (22), 114 (44), 113 (27), 75 (17).

HRMS ($C_{13}H_{11}O_3Cl$): calc.: 250.0397; found: 250.0396 (M^+).

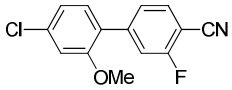
2'-Methoxybiphenyl-4-carbonitrile (58a)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (50 mg, 0.040 mmol) and 4-iodobenzonitrile (**51p**; 321 mg, 1.4 mmol) were dissolved in dry DMF (5.0 mL). Organoaluminum reagent **57a** (2.5 mL, 1.8 mmol, 0.70 M in THF) was added and the mixture was stirred for 1 h at 50 °C. Purification by flash column chromatography (silica gel, pentane / Et_2O = 9:1) afforded the desired product **58a** (229 mg, 78 %) as colorless needles.

The analytical data matches the reported one in the literature.[116]

4'-Chloro-3-fluoro-2'-methoxybiphenyl-4-carbonitrile (58b)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (25 mg, 0.020 mmol) and 4-bromo-2-fluorobenzonitrile (**51q**; 173 mg, 0.80 mmol) were dissolved in dry DMF (3.3 mL). Organoaluminum reagent **57b** (1.7 mL, 1.0 mmol, 0.60 M in THF) was added and the mixture was stirred for 8 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / DCM = 2:1) afforded the desired product **58b** (156 mg, 74 %) as colorless solid.

M.p. (°C): 157-158.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.67 - 7.59 (m, 1H), 7.42 - 7.34 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.08 - 6.98 (m, 2H), 3.84 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.8 (d, ^1J(C,F) = 258 Hz), 156.8, 145.0 (d, ^3J(C,F) = 8 Hz), 136.0, 132.9, 131.1, 126.0 (d, ^4J(C,F) = 2 Hz), 125.7 (d, ^3J(C,F) = 3 Hz), 121.3, 117.4 (d, ^2J(C,F) = 20 Hz), 114.1, 112.2, 99.7 (d, ^2J(C,F) = 16 Hz), 55.9.

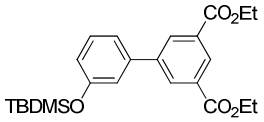
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2949, 2918, 2850, 2359, 2337, 2233, 2156, 2024, 2004, 1973, 1616, 1593, 1575, 1558, 1506, 1483, 1468, 1446, 1429, 1392, 1318, 1273, 1253, 1207, 1185, 1181, 1120, 1103, 1017, 904, 880, 853, 835, 795, 741.

MS (EI, 70 eV): m/z (%) = 263 (38), 262 (17), 261 (100), 211 (72), 183 (9), 182 (37).

HRMS ($C_{14}H_9ClFNO$): calc.: 261.0357; found: 261.0347 (M^+).

[116] N. Alam, C. Amatore, C. Combellas, J. Pinson, J.-M. Savéant, A. Thiébault, J.-N. Verpeaux, *J. Org. Chem.* **1988**, *53*, 1496.

Diethyl 3'-((tert-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-3,5-dicarboxylate (58c)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and diethyl 5-{[(nonafluorobutyl)-sulfonyl]oxy}benzene-1,3-dicarboxylate (**51d**; 676 mg, 1.3 mmol) were dissolved in dry DMF (4.0 mL). Organoaluminum reagent **57c** (1.9 mL, 1.6 mmol, 0.89 M in THF) was added and the mixture was stirred for 4 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **58c** (223 mg, 40 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.67 (t, *J* = 1.6 Hz, 1H), 8.44 (s, 1H), 8.44 (s, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.26 (dt, *J* = 6.3, 1.5 Hz, 1H), 7.14 (t, *J* = 1.9 Hz, 1H), 6.91 (dt, *J* = 6.3, 1.4 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 4H), 1.46 (t, *J* = 7.1 Hz, 6H), 1.04 (s, 9H), 0.26 (s, 6H).

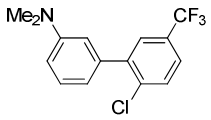
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.8, 156.3, 141.7, 140.7, 132.2, 131.4, 130.0, 129.3, 120.3, 119.8, 119.1, 61.4, 25.7, 18.3, 14.4, -4.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 2932, 2860, 1725, 1599, 1580, 1489, 1472, 1458, 1444, 1410, 1371, 1335, 1300, 1235, 1206, 1118, 1070, 1027, 1002, 969, 877, 839, 828, 782, 757.

MS (EI, 70 eV): m/z (%) = 429 (9), 383 (5), 373 (8), 372 (31), 371 (100), 298 (3), 267 (4), 75 (4).

HRMS ($C_{24}H_{32}O_5Si$): calc.: 428.2019; found: 428.2005 (M^+).

2'-Chloro-*N,N*-dimethyl-5'-(trifluoromethyl)biphenyl-3-amine (58d)



According to **TP 3,** $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 1-chloro-2-iodo-4-(trifluoromethyl)benzene (**51r**; 245 mg, 0.80 mmol) were dissolved in dry DMF (2.8 mL). Organoaluminum reagent **57d** (1.4 mL, 1.0 mmol, 0.73 M in THF) was added and the mixture was stirred for 6 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **58d** (150 mg, 63 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.64 (sd, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 6.82 – 6.75 (m, 3H), 3.00 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.3, 142.2, 138.9, 136.4, 130.3, 129.1 (q, ^2J(C,F) = 33 Hz), 129.0, 128.1 (q, ^3J(C,F) = 4 Hz), 124.9 (q, ^3J(C,F) = 4 Hz), 123.8 (q, ^1J(C,F) = 272 Hz), 117.4, 113.3, 112.3, 40.6.

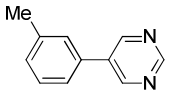
^{19}F-NMR (376 MHz, acetone-d6): δ / ppm = -62.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2920, 2888, 2852, 2806, 1689, 1680, 1601, 1578, 1500, 1484, 1436, 1406, 1353, 1329, 1283, 1257, 1245, 1166, 1121, 1087, 1069, 1035, 992, 961, 906, 863, 850, 825, 778, 735, 716, 698, 661.

MS (EI, 70 eV): m/z (%) = 301 (32), 300 (46), 299 (100), 298 (98), 285 (15), 284 (12), 220 (16), 149 (12).

HRMS ($C_{15}H_{13}ClF_3N$): calc.: 299.0689; found: 299.0686 (M^+).

5-(*m*-Tolyl)pyrimidine (58e)



According to **TP 3,** Pd(tmpp)$_2$Cl$_2$ (30 mg, 0.024 mmol) and 5-bromopyrimidine (**51s**; 127 mg, 0.80 mmol) were dissolved in dry DMF (2.5 mL). Organoaluminum reagent **57e** (1.2 mL, 1.0 mmol, 0.81 M in THF) was added and the mixture was stirred for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et$_2$O = 1:1) afforded the desired product **58e** (133 mg, 98 %) as colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ / ppm = 9.20 (s, 1H), 8.94 (s, 2H), 7.46 - 7.34 (m, 3H), 7.28 (d, *J* = 6.63 Hz, 1H), 2.45 (s, 3H).

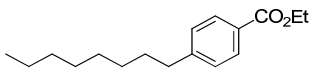
^{13}C-NMR (75 MHz, CDCl$_3$): δ / ppm = 157.2, 154.9, 139.2, 134.5, 134.1, 129.8, 129.3, 127.7, 124.1, 21.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3034, 2919, 2861, 1738, 1607, 1588, 1577, 1554, 1434, 1413, 1400, 1346, 1308, 1186, 1167, 1125, 1099, 1032, 1000, 987, 901, 879, 861, 784, 724, 698.

MS (EI, 70 eV): m/z (%) = 170 (100), 169 (17), 155 (8), 116 (29), 115 (44), 89 (8), 59 (8).

HRMS ($C_{11}H_{10}N_2$): calc.: 170.0844; found: 170.0838 (M^+).

Ethyl 4-octylbenzoate (66)



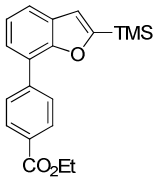
The organoaluminum reagent of 1-iodooctane (2.401 g, 1.81 mL, 10.0 mmol) was prepared according to **TP 1** with LiCl (1.272 g, 30.0 mmol) and PbCl$_2$ (83 mg, 0.30 mmol) in 2.5 h at 50 °C. The concentration of the organoaluminum reagent **65** was determined as 0.69 M (81 %) by the described titration method.

The following cross-coupling with ethyl 4-iodobenzoate (**51a**; 221 mg, 0.13 mL, 0.8 mmol) and the organoaluminum reagent (1.4 mL, 1.0 mmol) was conducted according to **TP 3** with $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and dry DMF (2.8 mL) for 2 h at 50 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **66** (172 mg, 82 %) as colorless oil.

The analytical data matches the reported one in the literature.[111]

2.5. Direct Cross-Coupling after Alumination

Ethyl 4-(2-(trimethylsilyl)benzofuran-7-yl)benzoate (69a)



Benzofuran-2-yltrimethylsilane (**67a**; 381 mg, 2.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 1.0 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with ethyl 4-iodobenzoate (**51a**; 442 mg, 1.6 mmol), $Pd(tmpp)_2Cl_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (1.0 mL, 0.10 mmol, 0.1 M in DMF) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **69a** (396 mg, 73 %) as colorless solid.

M.p. (°C): 83-85.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.14 (m, *J* = 8.60 Hz, 2H), 7.97 (m, *J* = 8.42 Hz, 2H), 7.55 (dd, *J* = 7.67, 0.94 Hz, 1H), 7.46 (dd, *J* = 7.48, 0.94 Hz, 1H), 7.30 - 7.20 (m, 1H), 7.00 (s, 1H), 4.39 (q, *J* = 7.11 Hz, 2H), 1.39 (t, *J* = 7.11 Hz, 3H), 0.33 (s, 9 H).

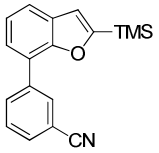
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.6, 163.9, 155.3, 141.4, 129.7, 129.2, 129.1, 128.4, 124.1, 123.8, 123.0, 121.1, 116.1, 60.9, 14.4, -1.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2958, 2906, 1706, 1666, 1610, 1539, 1478, 1474, 1440, 1394, 1367, 1316, 1284, 1268, 1252, 1246, 1217, 1190, 1181, 1156, 1128, 1111, 1100, 1065, 1056, 1025, 969, 962, 937, 905, 880, 841, 795, 762, 745, 714, 696.

MS (EI, 70 eV): m/z (%) = 339 (26), 338 (100), 323 (18), 293 (10), 251 (15), 235 (28).

HRMS ($C_{20}H_{22}O_3Si$): calc.: 338.1338; found: 338.1329 (M^+).

3-(2-(Trimethylsilyl)benzofuran-7-yl)benzonitrile (69b)



Benzofuran-2-yltrimethylsilane (**67a**; 381 mg, 2.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 1.0 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with 3-cyanophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**51t**; 642 mg, 1.6 mmol), $Pd(tmpp)_2Cl_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (1.0 mL, 0.10 mmol, 0.1 M in DMF) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **69b** (329 mg, 71 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.23 (s, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 0.38 (s, 9H).

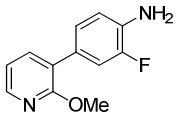
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.1, 155.0, 138.1, 132.6, 132.0, 130.7, 129.3, 129.2, 123.5, 123.1, 122.7, 121.4, 118.9, 116.2, 112.7, -1.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3067, 2959, 2900, 2230, 1598, 1577, 1536, 1488, 1468, 1429, 1394, 1320, 1288, 1269, 1250, 1227, 1168, 1158, 1109, 1064, 964, 913, 838, 800, 779, 757, 744, 689.

MS (EI, 70 eV): m/z (%) = 292 (13), 291 (55), 277 (19), 276 (100), 260 (18).

HRMS ($C_{18}H_{17}NOSi$): calc.: 291.1079; found: 291.1074 (M^+).

2-Fluoro-4-(2-methoxypyridin-3-yl)aniline (69c)



2-Methoxypyridine (**67b**; 381 mg, 2.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 1.0 mmol) according to **TP 4** with stirring for 30 min at 25 °C. The subsequent cross-coupling with 2-fluoro-4-iodoaniline (**51u**; 380 mg, 1.6 mmol), $Pd(tmpp)_2Cl_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (1.0 mL, 0.10 mmol, 0.1 M in DMF) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / EtOAc = 5:1) afforded the desired product **69c** (256 mg, 73 %) as colorless solid.

M.p. (°C): 71-73.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.11 (d, *J* = 3.2 Hz, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.93 (t, *J* = 6.0 Hz, 1H), 6.81 (t, *J* = 8.7 Hz, 1H), 3.98 (s, 3H), 3.82 (br s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.7, 151.1 (d, ^1J(C,F) = 238 Hz), 145.1, 137.8, 134.0 (d, ^2J(C,F) = 13 Hz), 127.1 (d, ^3J(C,F) = 7 Hz), 125.1 (d, ^4J(C,F) = 3 Hz), 123.6 (d, ^4J(C,F) = 2 Hz), 117.1, 116.4 (d, ^3J(C,F) = 4 Hz), 116.0 (d, ^2J(C,F) = 20 Hz), 53.5.

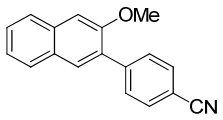
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -135.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3483, 3359, 3227, 1646, 1582, 1526, 1464, 1451, 1396, 1332, 1312, 1301, 1244, 1224, 1180, 1167, 1147, 1110, 1071, 1024, 1016, 904, 870, 824, 807, 790, 776, 770, 714, 700, 668, 658.

MS (EI, 70 eV): m/z (%) = 219 (14), 218 (100), 201 (11), 189 (14), 175 (12), 148 (12).

HRMS ($C_{12}H_{11}FN_2O$): calc.: 218.0855; found: 218.0849 (M^+).

4-(3-Methoxynaphthalen-2-yl)benzonitrile (69d)



2-Methoxynaphthalene (**67c**; 158 mg, 1.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 0.50 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with 4-iodobenzonitrile (**51p**; 183 mg, 0.8 mmol), Pd(tmpp)$_2$Cl$_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) in DMF (2.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **69d** (183 mg, 88 %) as colorless solid.

M.p. (°C): 125-127.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.80 (dd, *J* = 7.9, 4.6 Hz, 2H), 7.75 (s, 1H), 7.72 (s, 4H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.26 (s, 1H), 3.94 (s, 3H).

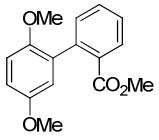
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.6, 143.2, 134.4, 131.7, 130.4, 130.3, 130.2, 128.6, 127.8, 127.0, 126.4, 124.3, 119.1, 110.7, 106.0, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 3011, 2226, 1629, 1605, 1512, 1497, 1469, 1446, 1429, 1407, 1360, 1334, 1309, 1271, 1252, 1197, 1172, 1125, 1037, 1023, 949, 896, 863, 855, 839, 827, 815, 741, 716, 702.

MS (EI, 70 eV): m/z (%) = 260 (21), 259 (100), 244 (14), 243 (10), 216 (20), 214 (15), 190 (10).

HRMS ($C_{18}H_{13}NO$): calc.: 259.0997; found: 259.0990 (M^+).

Methyl 2',5'-dimethoxybiphenyl-2-carboxylate (69e)



1,4-Dimethoxybenzene (**67d**; 138 mg, 1.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 0.50 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with methyl 2-iodobenzoate (**51v**; 210 mg, 0.8 mmol), $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) in DMF (2.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the desired product **69e** (161 mg, 74 %) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.87 (dd, *J* = 6.7, 0.9 Hz, 1H), 7.55 (td, *J* = 7.7, 1.1 Hz, 1H), 7.44 - 7.31 (m, 2H), 6.91 - 6.78 (m, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H).

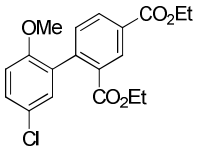
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.5, 153.6, 150.3, 138.5, 131.6, 131.5, 131.4, 131.2, 129.3, 127.2, 116.1, 113.0, 111.2, 55.8, 55.7, 51.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3027, 3010, 2955, 2932, 2905, 2834, 1723, 1584, 1572, 1501, 1487, 1462, 1443, 1435, 1415, 1308, 1291, 1279, 1267, 1248, 1226, 1207, 1178, 1162, 1149, 1128, 1088, 1048, 1023, 964, 957, 920, 876, 806, 800, 776, 744, 734, 720, 711, 666.

MS (EI, 70 eV): m/z (%) = 273 (13), 272 (100), 241 (39), 226 (12), 198 (25), 183 (14).

HRMS ($C_{16}H_{16}O_4$): calc.: 272.1049; found: 272.1048 (M^+).

Diethyl 5'-chloro-2'-methoxybiphenyl-2,4-dicarboxylate (69f)



1-Chloro-4-methoxybenzene (**67e**; 285 mg, 2.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 1.0 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with diethyl 4-bromobenzene-1,3-dicarboxylate (**51w**; 482 mg, 1.6 mmol), $Pd(tmpp)_2Cl_2$ (60 mg, 0.048 mmol) and 4-fluorostyrene (1.0 mL, 0.10 mmol, 0.1 M in DMF) in DMF (4.0 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 2:1) afforded the desired product **69f** (501 mg, 86 %) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (d, *J* = 1.7 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H),

4.42 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

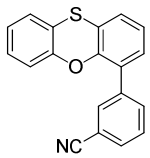
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.0, 165.6, 154.7, 141.7, 132.3, 132.1, 131.5, 131.3, 130.7, 129.9, 129.5, 128.8, 125.6, 111.4, 61.3, 61.0, 55.5, 14.3, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2939, 2905, 2842, 1716, 1610, 1563, 1501, 1481, 1464, 1443, 1410, 1393, 1366, 1302, 1227, 1175, 1139, 1109, 1100, 1082, 1024, 928, 886, 856, 833, 808, 790, 772, 739, 710, 687, 657.

MS (EI, 70 eV): m/z (%) = 364 (34), 363 (22), 362 (100), 333 (14), 331 (34), 319 (11), 317 (30), 305 (28), 304 (15), 303 (75), 289 (13), 275 (17), 274 (11), 230 (12), 208 (11).

HRMS ($C_{19}H_{19}ClO_5$): calc.: 362.0921; found: 362.0909 (M^+).

3-Phenoxathiin-4-ylbenzonitrile (69g)



Phenoxathiin (**69g**; 200 mg, 1.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 0.50 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with 3-iodobenzonitrile (**51i**; 183 mg, 0.8 mmol), $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) in DMF (2.0 mL) was conducted at 80 °C for 12 h, after addition of a further portion of $Pd(tmpp)_2Cl_2$ (15 mg, 0.012 mmol) full conversion was achieved after further 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / EtOAc = 49:1) afforded the desired product **69g** (184 mg, 76 %) as colorless solid.

M.p. (°C): 168-171.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.85 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.71 - 7.65 (m, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.21 - 7.01 (m, 6H), 6.86 (d, *J* = 8.2 Hz, 1H).

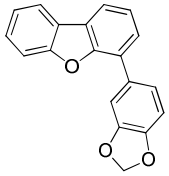
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 152.1, 149.1, 138.4, 133.9, 133.1, 130.9, 129.2, 129.0, 128.8, 127.9, 127.2, 126.9, 125.0, 124.6, 122.1, 120.7, 118.8, 117.5, 112.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3038, 2960, 2923, 2854, 2227, 1601, 1578, 1508, 1488, 1471, 1458, 1438, 1398, 1263, 1222, 1216, 1199, 1080, 1070, 1052, 1027, 923, 891, 864, 819, 806, 784, 744, 713, 693, 685.

MS (EI, 70 eV): m/z (%) = 302 (19), 301 (100), 300 (9), 272 (6), 269 (7).

HRMS ($C_{19}H_{11}NOS$): calc.: 301.0561; found: 301.0550 (M^+).

4-(1,3-Benzodioxol-5-yl)dibenzo[*b*,*d*]furan (69h)



Dibenzo[*b*,*d*]furan (**67g**; 168 mg, 1.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 0.50 mmol) according to **TP 4** with stirring for 1 h at 25 °C. The subsequent cross-coupling with 5-iodo-1,3-benzodioxole (**51x**; 198 mg, 0.8 mmol), Pd(tmpp)$_2$$Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) in DMF (2.0 mL) showed full conversion after further 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **69h** (167 mg, 72 %) as colorless solid.

M.p. (°C): 79-81.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 7.7 Hz, 1H), 7.91 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.44 - 7.33 (m, 3H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.1, 153.2, 147.9, 147.3, 130.4, 127.2, 126.5, 125.6, 124.9, 124.2, 123.2, 122.7, 122.5, 120.6, 119.3, 111.8, 109.3, 108.6, 101.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2360, 2338, 1506, 1481, 1453, 1409, 1351, 1338, 1257, 1230, 1193, 1178, 1170, 1092, 1039, 932, 913, 882, 852, 841, 815, 790, 745, 737, 720, 713, 694, 668.

MS (EI, 70 eV): m/z (%) = 289 (23), 288 (100), 287 (13), 229 (15), 202 (8), 200 (7), 144 (6).

HRMS ($C_{19}H_{12}O_3$): calc.: 288.0786; found: 288.0778 (M^+).

***tert*-Butyl(3-(dibenzo[*b*,*d*]thiophen-4-yl)phenoxy)dimethylsilane (69i)**

Dibenzo[*b*,*d*]thiophene (**67h**; 184 mg, 1.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 0.50 mmol) according to **TP 4** with stirring for 2 h at 25 °C. The subsequent cross-coupling with *tert*-butyl(3-iodophenoxy)dimethylsilane (**51y**; 267 mg, 0.8 mmol), Pd(tmpp)$_2$$Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) in DMF (2.0 mL) showed full conversion after further 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **69i** (195 mg, 63 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.21 – 8.15 (m, 2H), 7.87 – 7.84 (m, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.51 – 7.46 (m, 3H), 7.42 – 7.33 (m, 2H), 7.26 (s, 1H), 6.95 (d, *J* = 6.9 Hz, 1H), 1.05 (s, 9H), 0.30 (s, 6H).

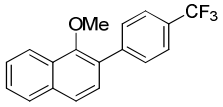
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.0, 142.0, 139.6, 138.5, 136.9, 136.2, 135.8, 129.8, 126.8, 126.7, 125.0, 124.3, 122.6, 121.7, 121.3, 120.4, 119.9, 119.8, 25.7, 18.2, -4.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2954, 2928, 2885, 2856, 1598, 1582, 1574, 1492, 1473, 1462, 1442, 1427, 1380, 1361, 1329, 1298, 1259, 1250, 1220, 1176, 1160, 1116, 1102, 1082, 1050, 1030, 1017, 1000, 945, 880, 836, 801, 780, 747, 726, 716, 698, 670.

MS (EI, 70 eV): m/z (%) = 391 (16), 390 (48), 335 (14), 334 (37), 333 (100), 317 (27), 258 (15), 167 (11).

HRMS ($C_{24}H_{26}OSSi$): calc.: 390.1474; found: 390.1460 (M^+).

1-Methoxy-2-(4-(trifluoromethyl)phenyl)naphthalene (69j)



1-Methoxynaphthalene (**67i**; 158 mg, 1.0 mmol) was metalated using [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al·3LiCl (**17**; 1.25 mmol) according to **TP 4** with stirring for 12 h at 25 °C. The subsequent cross-coupling with 1-iodo-4-(trifluoromethyl)benzene (**51z**; 218 mg, 0.8 mmol), $Pd(tmpp)_2Cl_2$ (30 mg, 0.024 mmol) and 4-fluorostyrene (0.5 mL, 0.05 mmol, 0.1 M in DMF) in DMF (4.5 mL) showed full conversion after 12 h at 80 °C. Purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **69j** (216 mg, 89 %) as colorless crystals.

M.p. (°C): 91-95.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.27 (d, *J* = 7.5 Hz, 1H), 7.91 – 7.70 (m, 6H), 7.61 – 7.48 (m, 3H), 3.61 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 155.3, 142.4, 134.7, 129.7, 129.2 (q, ^2J(C,F) = 32 Hz), 128.4, 128.2, 127.94 (q, ^1J(C,F) = 272 Hz), 127.91, 127.86, 126.7, 126.5, 125.3 (q, ^3J(C,F) = 4 Hz), 124.3, 122.6, 61.4.

^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = -62.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 3014, 2960, 2935, 2845, 1616, 1597, 1578, 1501, 1464, 1448, 1407, 1365, 1344, 1321, 1289, 1249, 1210, 1156, 1119, 1108, 1100, 1070, 1053, 1018, 982, 958, 871, 859, 844, 814, 797, 755, 744, 718, 696, 689.

MS (EI, 70 eV): m/z (%) = 303 (22), 302 (100), 287 (35), 286 (10), 219 (10), 218 (51), 189 (19).

HRMS ($C_{18}H_{13}F_3O$): calc.: 302.0918; found: 302.0912 (M^+).

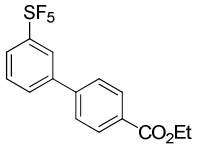
3. Preparations and Reactions of SF_5-substituted Organometallics

3.1. Preparation using Halogen-Magnesium Exchange

Typical Procedure for the Br-Mg Exchange using *i*PrMg·LiCl (TP 5)

A dry argon flushed *Schlenk*-flask was charged with the starting aryl bromide in THF (approx. 1.0 M solution) and cooled to the indicated temperature. Then *i*PrMgCl·LiCl (1.1 equiv) was added and the reaction mixture was stirred at the given temperature, until GC analysis of a hydrolyzed reaction aliquot showed full conversion.

Ethyl 3'-(pentafluorosulfanyl)biphenyl-4-carboxylate (73a)



According to **TP 5,** 1-bromo-3-(pentafluorosulfanyl)benzene (**70**; 283 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with *i*PrMgCl·LiCl (0.86 mL, 1.1 mmol, 1.28 M in THF) in 1 h at 0 °C. Then, $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of ethyl 4-bromobenzoate (**72a**; 206 mg, 0.15 mL, 0.9 mmol) and PEPPSI-*i*Pr (12 mg, 0.02 mmol, 2 mol%), the mixture was stirred for 2 h at 25 °C. After a full conversion was detected by GC analysis, sat. aq NaCl (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 95:5) afforded the desired product **73a** (267 mg, 84 %) as colorless solid.

M.p. (°C): 70-71.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 8.42 Hz, 2H), 7.98 (s, 1H), 7.77 (t, *J* = 8.23 Hz, 2H), 7.64 (d, *J* = 8.42 Hz, 2H), 7.57 (t, *J* = 7.95 Hz, 1H), 4.42 (q, *J* = 7.11 Hz, 2H), 1.43 (t, *J* = 7.11 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 154.3 (quint, ^2J(C,F) = 17 Hz), 143.5, 141.2, 130.31, 130.28, 129.29, 129.28, 127.2, 125.4 (quint, ^3J(C,F) = 5 Hz), 124.9 (quint, ^3J(C,F) = 5 Hz), 61.2, 14.3

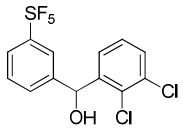
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 84.1 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 62.7 (d, ^2J(F,F) = 149 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3073, 3001, 2986, 1703, 1664, 1609, 1603, 1564, 1477, 1458, 1446, 1434, 1398, 1368, 1310, 1297, 1271, 1188, 1180, 1160, 1119, 1106, 1020, 1014, 977, 927, 860, 834, 809, 802, 763, 705, 694, 656.

MS (EI, 70 eV): m/z (%) = 352 (39), 324 (39), 308 (17), 307 (100), 170 (10), 152 (55), 151 (13).

HRMS ($C_{15}H_{13}F_5O_2S$): calc.: 352.0556; found: 352.0549 (M^+).

(2,3-Dichlorophenyl)[3-(pentafluorosulfanyl)phenyl]methanol (73b)



According to **TP 5,** 1-bromo-3-(pentafluorosulfanyl)benzene (**70**; 283 mg, 1.0 mmol) in dry THF (1.0 mL) reacted with *i*PrMgCl·LiCl (0.86 mL, 1.1 mmol, 1.28 M in THF) in 1 h at 0 °C. Then, 2,3-dichlorobenzaldehyde (**72b**; 193 mg, 1.1 mmol) was added at 0 °C and the reaction mixture was stirred for further 5 min at 25 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 3:1) afforded the desired product **73b** (308 mg, 81 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89 (t, *J* = 1.9 Hz, 1H), 7.72 - 7.60 (m, 1H), 7.54 – 7.34 (m, 4H), 7.28 (t, *J* = 7.9 Hz, 1H), 6.27 (s, 1H), 2.55 (s br, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.1 (quint, ^2J(C,F) = 17 Hz), 153.9, 142.9, 142.4, 133.5, 130.7, 130.1, 128.9, 127.9, 126.0, 125.5 (quint, ^3J(C,F) = 5 Hz), 124.5 (quint, ^3J(C,F) = 5 Hz), 72.4.

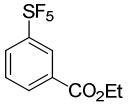
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 84.2 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 62.8 (d, ^2J(F,F) = 149 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3272, 2964, 2924, 1706, 1604, 1584, 1565, 1482, 1451, 1438, 1421, 1326, 1288, 1241, 1195, 1180, 1159, 1112, 1099, 1061, 1038, 976, 913, 896, 836, 817, 793, 781, 743, 726, 690, 643, 625, 615, 594, 572, 559.

MS (EI, 70 eV): m/z (%) = 378 (3), 74 (63), 59 (100), 45 (73), 44 (22).

HRMS ($C_{13}H_9Cl_2F_5OS$): calc.: 377.9671; found: 377.9669 (M^+).

3-(Pentafluorosulfanyl)benzoic acid ethyl ester (73c)



According to **TP 5,** 1-bromo-3-(pentafluorosulfanyl)benzene (**70**; 1.132 g, 4.0 mmol) in dry THF (4.0 mL) reacted with *i*PrMgCl·LiCl (3.5 mL, 4.4 mmol, 1.27 M in THF) in 1 h at 0 °C. Then, ethyl cyanoformate (**72c**; 396 mg, 0.40 mL, 4.0 mmol) was added at -30 °C and the reaction mixture

was stirred for further 30 min at this temperature. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (20 mL) was added and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **73c** (782 mg, 71 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.48 - 8.43 (m, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 8.00 - 7.92 (m, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.8, 153.9 (quint, ^2J(C,F) = 17 Hz), 132.5, 131.5, 130.0 (quint, ^3J(C,F) = 4 Hz), 128.9, 127.2 (quint, ^3J(C,F) = 5 Hz), 61.8, 14.3.

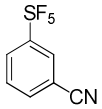
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 83.2 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 62.6 (d, ^2J(F,F) = 149 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 1724, 1438, 1370, 1301, 1268, 1177, 1129, 1102, 1022, 896, 823, 751, 712, 683, 665, 644.

MS (EI, 70 eV): m/z (%) = 276 (12), 248 (27), 231 (100), 152 (14), 95 (18), 89 (13), 76 (18), 75 (19).

HRMS ($C_9H_9F_5O_2S$): calc.: 276.0243; found: 276.0225 (M^+).

3-(Pentafluorosulfanyl)benzonitrile (73d)



According to **TP 5,** 1-bromo-3-(pentafluorosulfanyl)benzene (**70**; 283 mg, 1.0 mmol) in dry THF (4.0 mL) reacted with *i*PrMgCl·LiCl (0.87 mL, 1.1 mmol, 1.27 M in THF) in 1 h at 0 °C. Then, tosyl cyanide (**72d**; 181 mg, 1.0 mmol) was added at -30 °C and the reaction mixture was stirred for further 30 min at this temperature. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **73d** (126 mg, 55 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06 - 8.04 (m, 1H), 8.01 - 7.99 (m, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.1 (quint, ^2J(C,F) = 17 Hz), 135.0, 130.2 (quint, ^3J(C,F) = 4 Hz), 129.91, 129.87 (quint, ^3J(C,F) = 5 Hz), 116.9, 113.6.

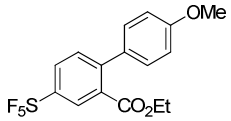
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3016, 2996, 2960, 2928, 2922, 2870, 2856, 2820, 2810, 1738, 1464, 1426, 1408, 1400, 1376, 1366, 1338, 1332, 1324, 1316, 1260, 1216, 1202, 1186, 1172, 1160, 1136, 1096, 1066, 1058, 1030, 1022, 988, 974, 886, 854, 834, 804.

MS (EI, 70 eV): m/z (%) = 229 (100), 210 (5), 121 (100), 102 (22), 95 (13), 89 (15), 76 (10), 75 (21).

HRMS ($C_7H_4F_5NS$): calc.: 228.9985; found: 228.9978 (M^+).

3.2. Preparation using Directed Metalation

4'-Methoxy-4-(pentafluorosulfanyl)biphenyl-2-carboxylic acid ethyl-ester (75)



A dry argon flushed *Schlenk*-flask was charged with a solution of 3-(pentafluorosulfanyl)benzoic acid ethyl ester (**73c**; 276 mg, 1.0 mmol) in dry THF (1.0 mL). After cooling to -40 °C, $TMP_2Mg{\cdot}2LiCl$ (1.9 mL, 1.5 mmol, 0.80 M in THF) was added dropwise and the reaction mixture was stirred for 12 h at this temperature. Then, $ZnCl_2$ (1.6 mL, 1.6 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of 4-iodoanisole (**72e**; 257 g, 1.1 mmol), $Pd(dba)_2$ (12 mg, 0.02 mmol, 2 mol%) and tfp (9 mg, 0.04 mmol, 4 mol%), the reaction mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **75** (275 mg, 72 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 2.2 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.30 - 7.24 (m, 2H), 7.02 - 6.95 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.2, 159.7, 152.1 (quint, ^2J(C,F) = 18 Hz), 145.3, 131.8, 131.7, 131.0, 129.5, 128.1 (quint, ^3J(C,F) = 4 Hz), 127.4 (quint, ^3J(C,F) = 5 Hz), 113.8, 61.6, 55.3, 13.7.

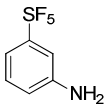
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 83.6 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 63.1 (d, ^2J(F,F) = 150 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3027, 2970, 2943, 2907, 2842, 1728, 1605, 1576, 1518, 1478, 1464, 1440, 1421, 1405, 1388, 1364, 1311, 1285, 1254, 1239, 1176, 1152, 1107, 1036, 1019, 1001, 911, 902, 856, 824, 814, 801, 783, 749, 734, 663.

MS (EI, 70 eV): m/z (%) = 382 (100), 354 (17), 337 (42), 210 (14), 139 (11).

HRMS ($C_{16}H_{15}F_5O_3S$): calc.: 382.0662; found: 382.0647 (M^+).

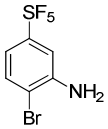
3-(Pentafluorosulfanyl)aniline (77)



Hydrochloric acid (37 %, 15 mL, 0.49 mol) was added dropwise to a suspension of 1-nitro-3-(pentafluorosulfanyl)benzene (**76**; 7.53 g, 30.2 mmol) and iron powder (10.13 g, 181.4 mmol) in ethanol (300 mL) while stirring at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 1.5 h. The remaining iron powder was removed by decantation and ammonia (150 mL) was added to the resulting solution until pH 10 was adjusted. The solution was extracted with dichloromethane (3 × 250 mL) and the combined organic extracts were washed with H_2O (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was further purified by flash column chromatography (silica gel, *i*hexane / EtOAc = 2:1) to afford the desired product **77** (5.86 g, 88 %) as orange crystals.

The analytical data matches the reported one in the literature.[78a]

2-Bromo-5-(pentafluorosulfanyl)aniline (78)



N-Bromosuccinimide (2.67 g, 15.0 mmol) in 1,4-dioxane (15 mL) was added to a solution of 3-(pentafluorosulfanyl)-aniline (**77**; 3.15 g, 15.0 mmol) in 1,4-dioxane (60 mL). The resulting mixture was stirred for 14 h at 25 °C. The solution then was extracted with EtOAc (3 × 50 mL) and the combined extracts were washed with sat. aq NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, pentane / DCM = 1:1, 2 % NEt_3) to afford the desired product **78** (3.36 g, 75 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.50 – 7.43 (m, 1H), 7.12 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.27 (s br, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.7 (quint, ^2J(C,F) = 18 Hz), 144.2, 132.5, 116.2 (quint, ^3J(C,F) = 5 Hz), 112.6 (quint, ^3J(C,F) = 5 Hz), 111.9.

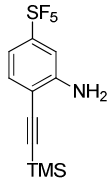
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 84.3 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 62.8 (d, ^2J(F,F) = 150 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 3317, 3205, 1621, 1589, 1481, 1422, 1312, 1300, 1256, 1160, 1110, 1026, 919, 866, 830, 800, 785, 658.

MS (EI, 70 eV): m/z (%) = 299 (100), 297 (99), 191 (15), 189 (15), 172 (13), 170 (13), 110 (13), 90 (100) 63 (17), 52 (12).

HRMS ($C_6H_5F_5NSBr$): calc.: 296.9246; found: 296.9257 (M^+).

5-(Pentafluorosulfanyl)-2-((trimethylsilyl)ethynyl)aniline (79)



2-Bromo-5-(pentafluorosulfanyl)aniline (**78**; 3.28 g, 11.0 mmol), $Pd(PPh_3)_2Cl_2$ (309 mg, 0.44 mmol, 4 mol%) and CuI (42 mg, 0.22 mmol, 2 mol%) were placed in an argon-filled *Schlenk*-flask. After addition of NEt_3 (35 mL, 0.15 mol) and THF (35 mL), (trimethylsilyl)acetylene (1.62 g, 16.5 mmol) was added. The mixture was stirred at 50 °C for 5 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, *i*hexane / DCM = 85:15, 1 % NEt_3) to give the desired product **79** (3.05 g, 89 %) as yellow crystals.

M.p. (°C): 54-56.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.35 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 2.2 Hz, 1H), 7.06 - 7.00 (m, 1H), 4.46 (s br, 2H), 0.31 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.3 (quint, ^2J(C,F) = 17 Hz), 148.0, 132.1, 114.8 (quint, ^3J(C,F) = 5 Hz), 111.4 (quint, ^3J(C,F) = 5 Hz), 110.8, 102.8, 99.6, -0.1.

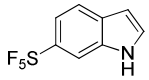
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 84.6 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 62.3 (d, ^2J(F,F) = 150 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3493, 3390, 2965, 2906, 2153, 1739, 1612, 1560, 1491, 1430, 1315, 1298, 1253, 1232, 1212, 1149, 1107, 1056, 933, 834, 804, 763, 703.

MS (EI, 70 eV): m/z (%) = 316 (12), 315 (73), 301 (18), 300 (100), 192 (11), 191 (11), 188 (21), 177 (28), 172 (13), 158 (18), 150 (32), 139 (16), 130 (68), 96 (21), 89 (24), 77 (66), 73 (21).

HRMS ($C_{11}H_{14}F_5NSSi$): calc.: 315.0536; found: 315.0542 (M^+).

6-(Pentafluorosulfanyl)-*1H*-indole (80)



Potassium hydride (KH, 30% suspension in mineral oil) was transferred to a *Schlenk*-flask, evaporated and filled with argon. After the addition of dry hexane, the suspension was stirred for a short time before the solvent was removed again with a syringe. This process was repeated four times to give after evaporation *in vacuo* and refilling with argon, a white powder of KH. KH (303 mg, 7.56 mmol) was suspended under argon in NMP (10 mL). A solution of 5-(pentafluorosulfanyl)-2-((trimethylsilyl)ethynyl)aniline (**79**; 952 mg, 3.02 mmol) dissolved in NMP (10 mL) was added dropwise at 25 °C and the reaction mixture was stirred for 3 h. The reaction was quenched with H_2O (15 mL) at 0 °C, and sat. aq NH_4Cl (30 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography (silica gel, *i*hexane / EtOAc = 5:1) to afford the desired product **80** (0.47 g, 65 %) as yellow crystals.

M.p. (°C): 97-99.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.38 (s br, 1H), 7.90 - 7.84 (m, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.40 (dd, *J* = 6.3, 3.2 Hz, 1H), 6.64 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.8 (quint, ^2J(C,F) = 17 Hz), 133.9, 129.7, 128.0, 120.1, 117.3 (quint, ^3J(C,F) = 4 Hz), 109.8 (quint, ^3J(C,F) = 5 Hz), 102.9.

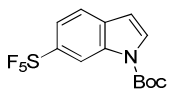
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 87.3 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 65.7 (d, ^2J(F,F) = 150 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2916, 2850, 1688, 1588, 1454, 1416, 1380, 1144, 1072, 1038, 1000, 916, 834, 806, 782, 710, 660, 638.

MS (EI, 70 eV): m/z (%) = 243 (97), 135 (50), 116 (44), 108 (21), 107 (11), 89 (20), 74 (66), 73 (12), 59 (100), 45 (73), 44 (40), 43 (33), 41 (21).

HRMS ($C_8H_6F_5NS$): calc.: 243.0141; found: 243.0145 (M^+).

6-(Pentafluorosulfanyl)-1*H*-indole-1-carboxylic acid *tert*-butyl ester (81)



A solution of 6-(pentafluorosulfanyl)-*1H*-indole (**80**; 304 mg, 1.3 mmol), di-*tert*-butyl dicarbonate (409 mg, 1.9 mmol) and 4-dimethylaminopyridine (11 mg, 0.09 mmol) in acetonitrile (4 mL) was stirred at 25 °C for 1.5 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3 × 15 mL). The extract was washed with sat. aq $NaHCO_3$

(20 mL) and NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the desired product **81** (421 mg, 98%) as colorless solid.

M.p. (°C): 89-90.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.66 (s, 1H), 7.76 (d, *J* = 3.5 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.60 (s, 1H), 6.61 (dd, *J* = 3.8, 0.7 Hz, 1H), 1.69 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.4 (quint, ^2J(C,F) = 17 Hz), 149.1, 133.6, 132.5, 129.3, 120.3, 120.1 (quint, ^3J(C,F) = 5 Hz), 114.0 (quint, ^3J(C,F) = 5 Hz), 106.7, 84.9, 28.1.

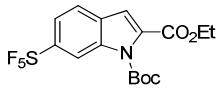
^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 86.1 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 64.9 (d, ^2J(F,F) = 150 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1740, 1469, 1444, 1396, 1374, 1365, 1350, 1270, 1256, 1216, 1184, 1162, 1137, 1099, 1071, 1041, 1028, 913, 892, 866, 842, 835, 808, 782, 764, 756, 726, 655, 633, 586, 568.

MS (EI, 70 eV): m/z (%) = 343 (28), 287 (33), 270 (22), 135 (15), 134 (18), 83 (15), 57 (51).

HRMS ($C_{13}H_{14}F_5NO_2S$): calc.: 343.0665; found: 343.0661 (M^+).

6-(Pentafluorosulfanyl)-1*H*-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-ethyl ester (83)



A dry argon flushed *Schlenk*-flask was charged with a solution of 6-(pentafluorosulfanyl)-1*H*-indole-1-carboxylic acid *tert*-butyl ester (**81**; 172 mg, 0.50 mmol) in dry THF (1.0 mL). After cooling to 0 °C, TMPMgCl·LiCl (0.50 mL, 0.55 mmol, 1.1 M in THF) was added dropwise and the reaction mixture was stirred for 30 min at this temperature. Then, ethyl cyanoformate (**72c**; 54 mg, 0.05 mL, 0.55 mmol) was added at -30 °C and the reaction mixture was stirred for further 30 min at this temperature. Afterwards, sat. aq NH_4Cl (10 mL) was added at -30 °C and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / EtOAc = 19:1) afforded the desired product **83** (144 mg, 69 %) as colorless solid along with starting material **81** (47 mg, 27 %).

M.p. (°C): 53-54.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.59 (d, *J* = 1.0 Hz, 1H), 7.67 - 7.59 (m, 2H), 7.05 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.64 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.2, 152.0 (quint, ^2J(C,F) = 18 Hz), 148.4, 135.7, 134.1, 129.5, 121.6, 120.7 (quint, ^3J(C,F) = 4 Hz), 113.8 (quint, ^3J(C,F) = 5 Hz), 112.7, 85.7, 61.8, 27.7, 14.0.

^{19}F-NMR (282 MHz, $CDCl_3$): δ / ppm = 85.2 (quint, ^2J(F,F) = 149 Hz, 1F, SF_{ax}), 64.5 (d, ^2J(F,F) = 150 Hz, 4F, SF_{eq}).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2361, 2339, 1745, 1730, 1554, 1469, 1433, 1394, 1370, 1316, 1294, 1236, 1201, 1156, 1135, 1084, 1060, 1135, 970, 956, 926, 893, 856, 846, 833, 808, 766, 755, 743, 667, 645, 636, 621.

MS (EI, 70 eV): m/z (%) = 415 (4), 315 (83), 269 (44), 57 (100).

HRMS ($C_{16}H_{18}F_5NO_4S$): calc.: 415.0877; found: 415.0869 (M^+).

4. Regioselective Metalations of BTM-substituted N-Heteroaromatics

4.1. Typical Procedures

4.1.1. Typical Procedure for BF_3-assisted Metalations (TP 6)

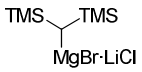
A dry argon flushed *Schlenk*-flask was charged with a solution of the N-heterocycle (1.0 equiv) in dry THF. After cooling to 0 °C, $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the mixture was stirred for 15 min at this temperature. Then, the reaction mixture was cooled to the given temperature followed by dropwise addition of a THF-solution of the indicated metal TMP-amide base and stirred for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF.

4.1.2. Typical Procedure for Metalations with TMP-Metal bases (TP 7)

A dry argon flushed *Schlenk*-flask was charged with a solution of the N-heterocycle (1.0 equiv) in dry THF. After cooling to the given temperature, a THF-solution of the indicated metal TMP-amide base was added dropwise and the reaction mixture was stirred for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF.

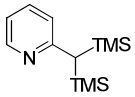
4.2. Regioselective Metalation of 2-BTM-pyridine

Preparation of Grignard Reagent $(TMS)_2CHMgBr \cdot LiCl$ (92)



LiCl (1.590 g, 37.5 mmol) was placed in a dry argon flushed *Schlenk*-flask and dried for 10 min at 450 °C (heat gun) on high vacuum (10^{-1} mbar). Mg turnings (1.094 g, 45.0 mmol) were added and the flask was evacuated again and refilled with argon. Then, THF (30.0 mL) was added and after addition of chlorotrimethylsilane (33 mg, 0.04 mL, 0.30 mmol) and 1,2-dibromoethane (56 mg, 0.03 mL, 0.30 mmol), the suspension was heated until ebullition occurred. The flask was cooled to 0 °C and bis(trimethylsilyl)methylbromide (**87**; 7.178 g, 30.0 mmol) was added dropwise. After stirring for 30 min at 0 °C, the solids were allowed to settle and the supernatant solution was carefully cannulated to a new dry and argon flushed *Schlenk*-flask. Titration of the organomagnesium reagent **92** against iodine in THF gave a concentration of 0.68 M (80 %).

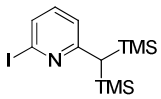
2-(Bis(trimethylsilyl)methyl)pyridine (85)



In a dry argon flushed *Schlenk*-flask 2-bromopyridine (**93**; 1.58 g, 10.0 mmol, 0.96 mL) and $Pd(PPh_3)_2Cl_2$ (180 mg, 0.25 mmol, 2.5 mol%) were suspended in dry toluene (16.2 mL). Then, $(TMS)_2CHMgBr{\cdot}LiCl$ (**92**; 16.2 mL, 11.0 mmol, 0.68 M in THF) was added and the reaction mixture was stirred for 12 h at 50 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (15 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **85** (1.90 g, 80 %) as colorless oil.

The analytical data matches the reported one in the literature.[91]

2-(Bis(trimethylsilyl)methyl)-6-iodopyridine (96a)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyridine (**85**; 237 mg, 1.0 mmol) in dry THF (5.0 mL) and $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.64 mL, 1.1 mmol, 0.67 M in THF) in 30 min at 0 °C. Then, the reaction mixture was cannulated to a solution of iodine (508 g, 2.0 mmol) in THF (5.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq $Na_2S_2O_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **96a** (258 mg, 71 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.33 (d, *J* = 7.67 Hz, 1H), 7.06 (t, *J* = 7.67 Hz, 1H), 6.80 (d, *J* = 7.67 Hz, 1H), 1.80 (s, 1H), 0.04 (s, 18H).

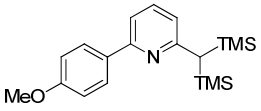
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.4, 136.9, 129.1, 121.7, 117.0, 33.3, -0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2896, 2855, 1564, 1536, 1418, 1390, 1269, 1246, 1223, 1166, 1103, 1093, 1074, 1031, 978, 888, 873, 835, 824, 775, 764, 757, 733, 724, 689, 678, 655.

MS (EI, 70 eV): m/z (%) = 362 (2), 349 (24), 348 (100), 340 (14), 316 (13), 301 (21), 275 (11), 237 (26), 236 (79), 177 (18), 164 (14), 161 (19), 149 (15), 148 (12), 105 (11), 99 (10), 97 (16), 95 (10), 85 (29), 83 (21), 78 (12), 73 (74), 71 (42), 70 (12), 69 (19), 57 (65), 56 (23), 55 (29).

HRMS ($C_{12}H_{21}IN_2Si_2$): calc.: 362.0252; found: 362.0249 ($[M-H]^+$).

2-(Bis(trimethylsilyl)methyl)-6-(4-methoxyphenyl)pyridine (96b)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyridine (**85**; 475 mg, 2.0 mmol) in dry THF (10.0 mL) and BF_3·OEt_2 (312 mg, 0.27 mL, 2.2 mmol) reacted with TMP_2Mg·2LiCl (3.00 mL, 2.2 mmol, 0.74 M in THF) in 30 min at 0 °C. Then, $ZnCl_2$ (2.4 mL, 2.4 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 1-iodo-4-methoxybenzene (**95a**; 562 mg, 2.4 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol, 2 mol%) and tfp (19 mg, 0.08 mmol, 4 mol%) in THF (3.0 mL), the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (15 mL) was added and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **96b** (528 mg, 77 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.01 (d, *J* = 9.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 1.84 (s, 1H), 0.05 (s, 18H).

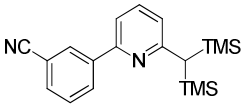
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.9, 160.1, 156.6, 136.8, 136.1, 127.9, 120.9, 116.8, 114.0, 55.3, 33.1, 1.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2899, 2837, 1609, 1585, 1562, 1513, 1488, 1455, 1438, 1303, 1244, 1176, 1110, 1033, 988, 901, 854, 834, 789, 778, 757, 739, 685.

MS (EI, 70 eV): m/z (%) = 344 (21), 343 (57), 342 (43), 330 (12), 329 (38), 328 (100), 256 (26), 255 (18), 178 (21), 73 (28).

HRMS ($C_{19}H_{29}NOSi_2$): calc.: 343.1788; found: 343.1778 (M^+).

3-(6-(Bis(trimethylsilyl)methyl)pyridin-2-yl)benzonitrile (96c)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyridine (**85**; 711 mg, 3.0 mmol) in dry THF (6.0 mL) and BF_3·OEt_2 (468 mg, 0.41 mL, 3.3 mmol) reacted with TMP_2Mg·2LiCl (5.41 mL, 3.3 mmol, 0.61 M in THF) in 30 min at 0 °C. Then, $ZnCl_2$ (3.6 mL, 3.6 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 3-iodobenzonitrile (**95b**; 824 g, 3.6 mmol), $Pd(dba)_2$ (35 mg, 0.06 mmol, 2 mol%) and tfp (28 mg, 0.12 mmol, 4 mol%) in THF (4.0 mL), the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq

NH_4Cl (20 mL) was added and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **96c** (716 mg, 71 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.32 (s, 1H), 8.27 (d, *J* = 8.04 Hz, 1H), 7.65 (d, *J* = 7.67 Hz, 1H), 7.55 (td, *J* = 7.71, 2.15 Hz, 2H), 7.40 (d, *J* = 7.48 Hz, 1H), 6.88 (d, *J* = 7.67 Hz, 1H), 1.89 (s, 1H), 0.07 (s, 18H).

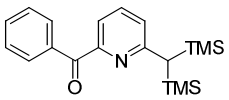
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.8, 153.2, 141.0, 136.6, 131.7, 130.8, 130.3, 129.4, 122.7, 119.0, 114.7, 112.7, 33.4, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 3057, 2951, 2896, 2232, 2227, 1602, 1576, 1562, 1482, 1450, 1424, 1396, 1305, 1278, 1264, 1254, 1242, 1181, 1172, 1148, 1097, 1087, 1078, 1063, 1051, 989, 986, 927, 915, 909, 896, 855, 837, 824, 803, 777, 757, 743, 705, 684, 658.

MS (EI, 70 eV): m/z (%) = 339 (10), 338 (31), 337 (20), 325 (11), 324 (30), 323 (100), 251 (18), 250 (32), 149 (21), 97 (10), 85 (14), 83 (14), 73 (68), 71 (20), 69 (15), 58 (23), 57 (32), 55 (19).

HRMS ($C_{19}H_{26}N_2Si_2$): calc.: 338.1635; found: 338.1632 (M^+).

(6-(Bis(trimethylsilyl)methyl)pyridin-2-yl)(phenyl)methanone (96d)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyridine (**85**; 949 mg, 4.0 mmol) in dry THF (16.0 mL) and $BF_3{\cdot}OEt_2$ (624 mg, 0.54 mL, 4.4 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (6.70 mL, 4.4 mmol, 0.66 M in THF) in 30 min at 0 °C. Then, $ZnCl_2$ (10.0 mL, 10.0 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. Subsequently, CuCN·2LiCl (4.4 mL, 4.4 mmol, 1.0 M in THF) and benzoyl chloride (**95c**; 675 mg, 0.56 mL, 4.8 mmol) were added at -40 °C, then the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, a mixture sat. aq NH_4Cl / NH_3 (25 % in H_2O) = 4:1 (20 mL) was added and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **96d** (956 mg, 70 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8. 13 - 8.01 (m, 2H), 7.72 - 7.61 (m, 2H), 7.55 (t, *J* = 7.29 Hz, 1H), 7.43 (t, *J* = 7.57 Hz, 2H), 7.05 (dd, *J* = 7.29, 1.31 Hz, 1H), 1.92 (s, 1H), 0.00 (s, 18H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 194.8, 163.7, 154.7, 136.8, 136.4, 132.3, 130.9, 127.8, 125.7, 119.3, 33.4, 0.18.

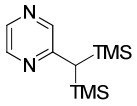
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2952, 2897, 2849, 1662, 1595, 1575, 1441, 1405, 1319, 1300, 1271, 1247, 1232, 1170, 1154, 1082, 1033, 989, 975, 952, 881, 856, 835, 825, 777, 761, 739, 705, 688, 661.

MS (EI, 70 eV): m/z (%) = 342 (54), 341 (53), 340 (10), 328 (11), 327 (27), 326 (85), 254 (12), 252 (22), 238 (13), 236 (10), 196 (11), 169 (21), 168 (17), 105 (34), 97 (12), 83 (14), 77 (38), 75 (12), 73 (100), 71 (14), 69 (19), 57 (29), 55 (22).

HRMS ($C_{19}H_{27}NOSi_2$): calc.: 341.1631; found: 341.1616 (M^+).

4.3. Regioselective Metalation of 2-BTM-pyrazine

2-(Bis(trimethylsilyl)methyl)pyrazine (98)



In a dry argon flushed *Schlenk*-flask 2-chloropyrazine (**97**; 2.863 g, 25.0 mmol, 2.2 ml) and $Pd(PPh_3)_2Cl_2$ (438 mg, 0.625 mmol, 2.5 mol%) were suspended in dry toluene (40.0 mL). Then, $(TMS)_2CHMgBr{\cdot}LiCl$ (**92**; 40.0 mL, 27.5 mmol, 0.68 M in THF) was added and the reaction mixture was stirred for 12 h at 50 °C. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (50 mL) was added and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **98** (3.875 g, 65 %) as colorless needles.

M.p. (°C): 67-68.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.30 (s, 1 H), 8.17 - 8.07 (m, 2 H), 1.79 (s, 1 H), -0.01 (s, 18 H).

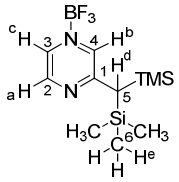
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.8, 144.3, 143.4, 139.0, 30.1, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3042, 2958, 1570, 1512, 1471, 1393, 1320, 1245, 1191, 1176, 1102, 1058, 1030, 1010, 940, 863, 825, 778, 754, 724, 692, 676.

MS (EI, 70 eV): m/z (%) = 239 (17), 238 (65), 237 (28), 224 (20), 223 (100), 165 (11), 150 (22), 73 (52), 61 (15), 45 (10), 44 (17), 43 (30).

HRMS ($C_{11}H_{22}N_2Si_2$): calc.: 238.1322; found: 238.1319 (M^+).

BF_3-complex of 2-(Bis(trimethylsilyl)methyl)pyrazine (99)



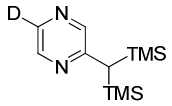
A dry argon flushed *Schlenk*-flask was charged with a solution of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 30 mg, 0.13 mmol) in dry THF-d8 (0.65 mL). After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (20 mg, 0.02 mL, 0.14 mmol) was added dropwise and the mixture was stirred for 15 min at this temperature. Then, the reaction mixture was cannulated to a dried NMR-tube and stored under argon. This tube was submitted to NMR spectroscopy at -20 °C (see page 135).

^{1}H-NMR (400 MHz, THF-d8, -20 °C): δ / ppm = 9.04 (d, ^3J = 3.2 Hz, 1H, H-a), 8.40 (s, 1H, H-b), 8.39 (d, ^3J = 3.2 Hz, 1H, H-c), 2.47 (s, 1H, H-d), 0.07 (s, 18H, H-e).

^{13}C-NMR (100 MHz, THF-d8, -20 °C): δ / ppm = 166.7, 148.3, 134.9 (q, ^3J(C,F) = 2 Hz), 130.5 (q, ^3J(C,F) = 2 Hz), 30.9, -0.8.

^{13}C-NMR (100 MHz, ^{1}H-coupled, THF-d8, -20 °C): δ / ppm = 166.7 (dt, ^2J(C,H) = 10 Hz, ^3J(C,H) = 6 Hz, C-1), 148.3 (dd, ^1J(C,H) = 109 Hz, ^2J(C,H) = 7 Hz, C-2), 134.9 (dddq, ^1J(C,H) = 190 Hz, other couplings not resolved, C-3), 130.5 (dddq, ^1J(C,H) = 193 Hz, ^3J(C,H) = 12 Hz, 6 Hz, ^3J(C,F) = 2 Hz, C-4), 30.9 (d, br., ^1J(C,H) = 112 Hz, C-5), -0.9 (q, oct, ^1J(C,H) = 119 Hz, ^3J(C,H) = 2 Hz, C-6).

2-(Bis(trimethylsilyl)methyl)-5-deuteropyrazine (101)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 119 mg, 0.50 mmol) in dry THF (2.50 mL) and $BF_3{\cdot}OEt_2$ (78 mg, 0.07 mL, 0.55 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.18 mL, 0.55 mmol, 0.55 M in THF) in 15 min at -78 °C. Then, deuterated acetic acid (D_3C-CO_2D; 2.0 mL) was added dropwise and the mixture was stirred for further 15 min at this temperature. After addition of sat. aq $NaHCO_3$ (5 mL) the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired 2-(bis(trimethylsilyl)methyl)-5-deuteropyrazine (**101**; 57 mg, 48 %) as colorless needles. NMR spectroscopy revealed an exclusive incorporation of deuterium at position 5. The ratio of ^{2}H:^{1}H at this position was determined as 79:21.

M.p. (°C): 68-70.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.36 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 1.5 Hz, 1H), 1.85 (s, 1H), 0.04 (s, 18H).

^{2}H-NMR (61 MHz, CH_2Cl_2): δ / ppm = 8.15.

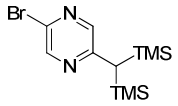
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.0, 144.34, 143.4, 138.7 (t, ^{1}J(C,D) = 27 Hz), 30.3, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2957, 2900, 2862, 2267, 1560, 1506, 1463, 1451, 1393, 1326, 1243, 1187, 1116, 1102, 1055, 1030, 1010, 929, 895, 867, 847, 826, 778, 759, 724, 692, 674, 657.

MS (EI, 70 eV): m/z (%) = 239 (12), 238 (11), 224 (30), 167 (14), 150 (11), 149 (100), 127 (16), 111 (10), 97 (15), 85 (22), 83 (19), 73 (25), 71 (40), 70 (14), 69 (28), 57 (41).

HRMS ($C_{11}H_{21}{}^{2}HN_2Si_2$): calc.: 239.1384; found: 239.1374 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromopyrazine (102a)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 2.385 g, 10.0 mmol) in dry THF (50.0 mL) and BF_3·OEt_2 (1.561 g, 1.36 mL, 11.0 mmol) reacted with TMP_2Mg·2LiCl (16.9 mL, 11.0 mmol, 0.65 M in THF) in 15 min at -78 °C. Then, the reaction mixture was cannulated to a solution of 1,2-dibromotetrachloroethane ($(BrCl_2C)_2$; 6.513 g, 20.0 mmol) in THF (100 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NH_4Cl (25 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **102a** (2.808 g, 89 %) as colorless needles.

M.p. (°C): 65-66.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.47 (d, *J* = 1.3 Hz, 1H), 7.94 (d, *J* = 1.3 Hz, 1H), 1.82 (s, 1H), 0.04 (s, 18H).

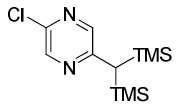
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.5, 145.9, 143.8, 134.9, 29.5, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2953, 2897, 2867, 1547, 1460, 1442, 1404, 1319, 1302, 1260, 1247, 1239, 1182, 1115, 1106, 1029, 1011, 912, 868, 834, 825, 778, 763, 753, 723, 689, 682.

MS (EI, 70 eV): m/z (%) = 318 (16), 317 (12), 316 (16), 303 (34), 301 (36), 237 (24), 230 (17), 73 (100), 45 (11).

HRMS ($C_{11}H_{21}BrN_2Si_2$): calc.: 316.0427; found: 316.0419 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-chloropyrazine (102b)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 715 mg, 3.0 mmol) in dry THF (9.0 mL) and $BF_3{\cdot}OEt_2$ (468 mg, 0.41 mL, 3.3 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (4.9 mL, 3.3 mmol, 0.68 M in THF) in 15 min at -78 °C. Then, the reaction mixture was cannulated to a solution of benzenesulfonyl chloride ($PhSO_2Cl$; 2.119 g, 1.50 mL, 12.0 mmol) in THF (40.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **102b** (499 mg, 61 %) as colorless needles.

M.p. (°C): 70-72.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.38 (d, *J* = 1.5 Hz, 1H), 7.94 (d, *J* = 1.5 Hz, 1H), 1.84 (s, 1H), 0.04 (s, 18H).

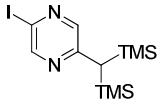
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.2, 143.9, 143.1, 142.8, 29.5, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 2952, 2899, 2851, 1551, 1500, 1466, 1445, 1406, 1319, 1307, 1249, 1242, 1187, 1170, 1126, 1111, 1028, 1018, 917, 869, 835, 823, 767, 754, 722, 685.

MS (EI, 70 eV): m/z (%) = 272 (26), 271 (12), 259 (23), 258 (11), 257 (55), 137 (13), 186 (10), 184 (26), 73 (100), 57 (16).

HRMS ($C_{11}H_{21}ClN_2Si_2$): calc.: 272.0932; found: 272.0929 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-iodopyrazine (102c)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 238 mg, 1.0 mmol) in dry THF (5.0 mL) and $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.64 mL, 1.1 mmol, 0.67 M in THF) in 15 min at -78 °C. Then, the reaction mixture was cannulated to a solution of iodine (508 g, 2.0 mmol) in THF (5.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq $Na_2S_2O_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **102c** (238 mg, 65 %) as colorless needles.

M.p. (°C): 69-70.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.61 (d, *J* = 1.4 Hz, 1H), 7.98 (d, *J* = 1.4 Hz, 1H), 1.77 (s, 1H), 0.04 (s, 18H).

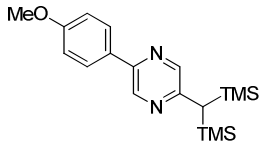
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.8, 151.3, 145.3, 110.7, 29.5, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3049, 2956, 2896, 2868, 1537, 1456, 1439, 1406, 1326, 1314, 1299, 1259, 1254, 1245, 1240, 1179, 1112, 1089, 1027, 1008, 911, 868, 835, 825, 779, 763, 752, 723, 696, 688, 680.

MS (EI, 70 eV): m/z (%) = 364 (32), 363 (11), 350 (11), 349 (54), 340 (11), 276 (20), 237 (32), 177 (21), 161 (15), 97 (15), 85 (26), 83 (14), 73 (100), 71 (32), 69 (17), 57 (50), 55 (23).

HRMS ($C_{11}H_{21}IN_2Si_2$): calc.: 364.0288; found: 364.0281 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-(4-methoxyphenyl)pyrazine (102d)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 1.908 g, 8.0 mmol) in dry THF (16.0 mL) and BF_3·OEt_2 (1.249 g, 1.09 mL, 8.8 mmol) reacted with TMP_2Mg·2LiCl (15.4 mL, 8.8 mmol, 0.57 M in THF) in 15 min at -78 °C. Then, $ZnCl_2$ (9.6 mL, 9.6 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 1-iodo-4-methoxybenzene (**95a**; 2.247 g, 9.6 mmol), $Pd(dba)_2$ (92 mg, 0.16 mmol, 2 mol%) and tfp (74 mg, 0.32 mmol, 4 mol%) in THF (4.0 mL), the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (30 mL) was added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **102d** (2.223 g, 81 %) as colorless solid.

M.p. (°C): 106-107.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.80 (d, *J* = 1.4 Hz, 1H), 8.20 (d, *J* = 1.4 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 1.90 (s, 1H), 0.08 (s, 18H).

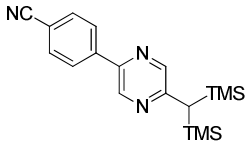
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.4, 157.9, 146.7, 143.1, 140.0, 129.4, 127.5, 114.3, 55.3, 29.8, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3002, 2953, 2896, 2831, 1607, 1583, 1569, 1518, 1501, 1469, 1456, 1437, 1414, 1340, 1317, 1296, 1270, 1247, 1235, 1182, 1175, 1115, 1102, 1051, 1029, 1018, 1006, 920, 869, 836, 827, 806, 779, 765, 743, 727, 712, 689, 666, 656.

MS (EI, 70 eV): m/z (%) = 344 (100), 343 (67), 330 (24), 329 (79), 271 (13), 257 (11), 256 (26), 241 (14), 230 (32), 73 (57).

HRMS ($C_{18}H_{28}N_2OSi_2$): calc.: 344.1740; found: 344.1738 (M^+).

4-(5-(Bis(trimethylsilyl)methyl)pyrazin-2-yl)benzonitrile (102e)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 238 mg, 1.0 mmol) in dry THF (5.0 mL) and $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.70 mL, 1.1 mmol, 0.65 M in THF) in 15 min at -78 °C. Then, $ZnCl_2$ (1.2 mL, 1.2 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 4-iodobenzonitrile (**95d**; 275 mg, 1.2 mmol), $Pd(dba)_2$ (12 mg, 0.02 mmol, 2 mol%) and tfp (9 mg, 0.04 mmol, 4 mol%) in THF (1.5 mL), the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **102e** (251 mg, 74 %) as yellow solid.

M.p. (°C): 89-91.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.90 (d, *J* = 1.4 Hz, 1H), 8.27 (d, *J* = 1.4 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 1.97 (s, 1H), 0.08 (s, 18H).

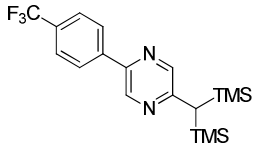
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.9, 144.6, 143.8, 141.1, 140.8, 132.7, 126.6, 118.7, 112.3, 30.7, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2958, 2896, 2228, 1608, 1576, 1559, 1517, 1501, 1467, 1405, 1339, 1313, 1269, 1259, 1246, 1195, 1181, 1107, 1049, 1030, 1021, 1012, 924, 913, 873, 853, 839, 827, 808, 778, 763, 734, 727, 721, 716, 708, 687.

MS (EI, 70 eV): m/z (%) = 340 (27), 339 (49), 338 (28), 325 (15), 324 (50), 251 (25), 177 (18), 149 (49), 127 (20), 111 (23), 109 (16), 99 (19), 97 (39), 96 (19), 95 (23), 85 (55), 83 (42), 81 (26), 73 (64), 71 (71), 70 (19), 69 (45), 67 (16), 57 (100), 55 (51).

HRMS ($C_{18}H_{25}N_3Si_2$): calc.: 339.1587; found: 339.1564 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-(4-(trifluoromethyl)phenyl)pyrazine (102f)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 238 mg, 1.0 mmol) in dry THF (5.0 mL) and $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.70 mL, 1.1 mmol, 0.65 M in THF) in 15 min at -78 °C. Then, $ZnCl_2$ (1.2 mL, 1.2 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 1-iodo-4-(trifluoromethyl)benzene (**95e**; 326 mg, 0.18 mL, 1.2 mmol), $Pd(dba)_2$ (12 mg, 0.02 mmol, 2 mol%) and tfp (9 mg, 0.04 mmol, 4 mol%) in THF (1.5 mL), the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **102f** (251 mg, 66 %) as colorless solid.

M.p. (°C): 95-96.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.89 (s, 1H), 8.27 (s, 1H), 8.10 (d, *J* = 6.0 Hz, 2H), 7.72 (d, *J* = 6.0 Hz, 2H), 1.95 (s, 1H), 0.09 (s, 18H).

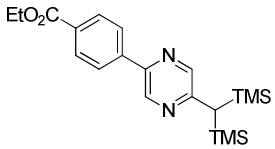
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.3, 145.3, 143.6, 140.7, 140.2, 130.8 (q, ^2J(C,F) = 32 Hz), 126.4, 125.8 (q, ^3J(C,F) = 4.0 Hz), 124.1 (q, ^1J(C,F) = 272 Hz), 30.4, 0.13.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 1735, 1617, 1569, 1524, 1505, 1472, 1412, 1323, 1276, 1246, 1187, 1165, 1135, 1117, 1104, 1072, 1030, 1012, 926, 871, 835, 777, 762, 740, 726, 689.

MS (EI, 70 eV): m/z (%) = 384 (10), 383 (31), 382 (100), 381 (50), 368 (23), 367 (85), 295 (11), 294 (38), 290 (20), 268 (11), 96 (12), 73 (86).

HRMS ($C_{18}H_{25}F_3N_2Si_2$): calc.: 382.1508; found: 382.1503 (M^+).

Ethyl 4-(5-(bis(trimethylsilyl)methyl)pyrazin-2-yl)benzoate (102g)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 477 mg, 2.0 mmol) in dry THF (4.0 mL) and $BF_3{\cdot}OEt_2$ (312 mg, 0.27 mL, 2.2 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (3.20 mL, 2.2 mmol, 0.70 M in THF) in 15 min at -78 °C. Then, $ZnCl_2$ (2.4 mL, 2.4 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature.

After addition of a solution of ethyl 1-iodobenzoate (**95f**; 718 mg, 0.44 mL, 2.4 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol, 2 mol%) and tfp (19 mg, 0.08 mmol, 4 mol%) in THF (1.5 mL), the mixture was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **102g** (410 mg, 53 %) as colorless solid.

M.p. (°C): 126-127.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.91 (d, *J* = 1.31 Hz, 1H), 8.27 (d, *J* = 1.31 Hz, 1H), 8.15 (d, *J* = 8.42 Hz, 2H), 8.06 (d, *J* = 8.60 Hz, 2H), 4.40 (q, *J* = 7.11 Hz, 2H), 1.95 (s, 1H), 1.42 (t, *J* = 7.11 Hz, 3H), 0.08 (s, 18H).

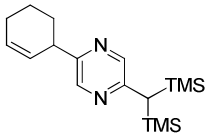
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 160.1, 145.6, 143.6, 140.90, 140.89, 130.7, 130.1, 126.0, 61.1, 30.4, 14.4, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2898, 2857, 1715, 1611, 1567, 1517, 1469, 1448, 1410, 1367, 1338, 1301, 1277, 1272, 1260, 1248, 1243, 1185, 1176, 1109, 1097, 1048, 1032, 1022, 1013, 922, 869, 862, 834, 776, 757, 735, 726, 698, 692, 675.

MS (EI, 70 eV): m/z (%) = 387 (36), 386 (100), 385 (77), 372 (28), 371 (79), 357 (17), 313 (10), 299 (10), 298 (28), 272 (17), 240 (34), 225 (10), 96 (14), 73 (70).

HRMS ($C_{20}H_{30}N_2O_2Si_2$): calc.: 386.1846; found: 386.1838 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-(cyclohex-2-en-1-yl)pyrazine (102h)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 2.39 g, 10.0 mmol) in dry THF (20.0 mL) and $BF_3{\cdot}OEt_2$ (1.56 g, 1.36 mL, 11.0 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (17.6 mL, 11.0 mmol, 0.63 M in THF) in 15 min at -78 °C. Then, $ZnCl_2$ (15.0 mL, 15.0 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of CuCN·2LiCl (2.0 mL, 2.0 mmol, 1.0 M in THF, 20 mol%) and 3-bromocyclohexene (**95g**; 2.42 mg, 1.75 mL, 15.0 mmol), the reaction was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, a mixture sat. aq NH_4Cl / NH_3 (25 % in H_2O) = 4:1 (30 mL) was added and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **102h** (1.49 g, 47 %) as colorless solid.

M.p. (°C): 64-66.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.28 (d, *J* = 1.12 Hz, 1H), 8.12 (d, *J* = 1.31 Hz, 1H), 5.91 - 6.00 (m, *J* = 10.00, 3.37, 3.04, 3.04 Hz, 1H), 5.79 (dd, *J* = 10.10, 2.06 Hz, 1H), 3.48 - 3.57 (m, 1H), 1.99 - 2.16 (m, 3H), 1.82 (s, 1H), 1.62 - 1.80 (m, 3H), 0.04 (s, 18H).

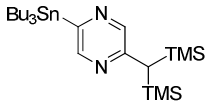
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.7, 154.2, 143.2, 142.3, 129.3, 128.0, 41.0, 30.3, 29.5, 24.9, 21.0, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3024, 2953, 2919, 2857, 2836, 1726, 1691, 1674, 1652, 1507, 1470, 1444, 1404, 1337, 1296, 1261, 1247, 1217, 1182, 1106, 1031, 985, 922, 898, 885, 868, 832, 826, 779, 768, 752, 724, 684, 655.

MS (EI, 70 eV): m/z (%) = 319 (22), 318 (73), 317 (22), 304 (23), 303 (88), 290 (10), 289 (19), 275 (17), 245 (12), 237 (16), 202 (13), 83 (18), 74 (22), 73 (100), 71 (11), 69 (14), 59 (32), 57 (25), 55 (20).

HRMS ($C_{17}H_{30}N_2Si_2$): calc.: 318.1948; found: 318.1939 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-(tributylstannyl)pyrazine (102i)



According to **TP 6,** a mixture of 2-(bis(trimethylsilyl)methyl)pyrazine (**98**; 238 mg, 1.0 mmol) in dry THF (5.0 mL) and $BF_3{\cdot}OEt_2$ (156 mg, 0.14 mL, 1.1 mmol) reacted with $TMP_2Mg{\cdot}2LiCl$ (2.36 mL, 1.1 mmol, 0.47 M in THF) in 15 min at -78 °C. Then, the reaction mixture was cannulated to a solution of tri-*n*-butyltin chloride (Bu_3SnCl, **95h**; 358 mg, 0.30 mL, 1.1 mmol) in THF (5.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (10 mL), sat. aq NaCl (10 mL) and then dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1, 1 % NEt_3) afforded the desired product **102i** (288 mg, 55 %) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.35 (d, *J* = 1.5 Hz, 1H), 8.33 (d, *J* = 1.6 Hz, 1H), 1.76 (s, 1H), 1.65 - 1.47 (m, 6H), 1.31 (sxt, *J* = 7.2 Hz, 6H), 1.13 (t, *J* = 8.0 Hz, 6H), 0.86 (t, *J* = 7.3 Hz, 9H), 0.05 (s, 18H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.4, 158.6, 149.9, 146.4, 30.0, 29.0 (^3J(C,^{119}Sn) = 21 Hz, ^3J(C,^{117}Sn) = 20 Hz), 27.2 (^2J(C,^{119}Sn) = 57 Hz, ^2J(C,^{117}Sn) = 54 Hz), 13.6, 9.8 (^1J(C,^{119}Sn) = 342 Hz, ^1J(C,^{117}Sn) = 327 Hz), 0.2.

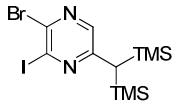
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2871, 2851, 1542, 1488, 1464, 1456, 1438, 1419, 1376, 1313, 1278, 1261, 1248, 1234, 1171, 1124, 1080, 1031, 1022, 960, 906, 870, 837, 827, 775, 761, 691, 683, 664.

MS (EI, 70 eV): m/z (%) = 527 (5), 471 (21), 469 (18), 361 (14), 359 (45), 358 (24), 357 (75), 356 (35), 355 (53), 354 (18), 353 (24), 238 (13), 237 (20), 224 (13), 223 (53), 165 (13), 97 (18), 75 (15), 73 (100), 57 (28), 56 (20), 55 (15).

HRMS ($C_{23}H_{47}N_2Si_2Sn$): calc.: 527.2294; found: 527.2301 ($[M-H]^+$).

4.4. Regioselective Full Functionalization of 2-BTM-pyrazine

5-(Bis(trimethylsilyl)methyl)-2-bromo-3-iodopyrazine (103a)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-bromopyrazine (**102a**; 1.269 g, 4.0 mmol) in dry THF (16.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (6.60 mL, 4.4 mmol, 0.67 M in THF) in 30 min at -40 °C. Then, the reaction mixture was cannulated to a solution of iodine (3.046 g, 12.0 mmol) in THF (12.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NaS_2O_3 (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **102a** (1.520 g, 86 %) as colorless needles.

M.p. (°C): 55-57.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84 (s, 1H), 1.78 (s, 1H), 0.06 (s, 18H).

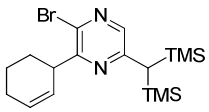
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.2, 141.2, 141.1, 121.1, 29.5, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2949, 2893, 1518, 1507, 1476, 1386, 1365, 1322, 1299, 1263, 1249, 1242, 1185, 1154, 1112, 1032, 1014, 910, 887, 862, 836, 825, 778, 767, 746, 726, 686.

MS (EI, 70 eV): m/z (%) = 442 (4), 429 (13), 427 (13), 293 (13), 167 (18), 150 (11), 149 (100), 127 (11), 85 (22), 83 (12), 73 (66), 71 (39), 70 (15), 69 (22), 57 (43), 56 (13), 55 (27).

HRMS ($C_{11}H_{20}BrIN_2Si_2$): calc.: 441.9393; found: 441.9390 (M^+).

5-(Bis(trimethylsilyl)methyl)-2-bromo-3-(cyclohex-2-en-1-yl)pyrazine (103b)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-bromopyrazine (**15a**; 1.269 g, 4.0 mmol) in dry THF (16.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (6.70 mL, 4.4 mmol, 0.66 M in THF)

in 30 min at -40 °C. Then, $ZnCl_2$ (10.0 mL, 10.0 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of CuCN·2LiCl (4.0 mL, 4.0 mmol, 1.0 M in THF) and 3-bromocyclohexene (**95g**; 773 mg, 0.56 mL, 4.8 mmol), the reaction was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, a mixture sat. aq NH_4Cl / NH_3 (25 % in H_2O) = 4:1 (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **103b** (1.399 g, 88 %) as colorless solid.

M.p. (°C): 85-86.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.75 (s, 1H), 5.90 - 5.82 (m, 1H), 5.67 - 5.60 (m, 1H), 4.00 - 3.91 (m, 1H), 2.12 - 1.80 (m, 4H), 1.75 (s, 1H), 1.73 - 1.62 (m, 2H), 0.03 (s, 18H).

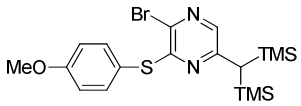
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.0, 158.3, 140.9, 135.3, 128.1, 127.8, 41.2, 28.9, 28.3, 24.8, 21.5, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2949, 2938, 2909, 2895, 2861, 1534, 1512, 1452, 1447, 1409, 1395, 1386, 1362, 1342, 1299, 1277, 1260, 1247, 1197, 1165, 1115, 1049, 1042, 1027, 1020, 909, 871, 864, 840, 827, 777, 771, 754, 739, 719, 698, 685.

MS (EI, 70 eV): m/z (%) = 398 (30), 396 (32), 383 (33), 381 (28), 301 (17), 243 (13), 229 (19), 216 (14), 215 (34), 177 (21), 164 (11), 85 (20), 83 (11), 81 (18), 73 (100), 71 (30), 69 (16), 57 (49), 55 (20).

HRMS ($C_{17}H_{29}BrN_2Si_2$): calc.: 396.1053; found: 396.1042 (M^+).

5-(Bis(trimethylsilyl)methyl)-2-bromo-3-((4-methoxyphenyl)thio)pyrazine (103c)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-bromopyrazine (**102a**; 952 mg, 3.0 mmol) in dry THF (12.0 mL) reacted with TMP_2Mg·2LiCl (5.42 mL, 3.3 mmol, 0.61 M in THF) in 30 min at -40 °C. Then, the reaction mixture was cannulated to a solution of *S*-(4-methoxyphenyl) benzenesulfonothioate ($PhSO_2S$(*p*-MeO-C_6H_4), **95i**; 2.523 g, 9.0 mmol) in THF (9.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NH_4Cl (10 mL) and sat. aq $NaHCO_3$ (10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 49:1) afforded the desired product **103c** (957 mg, 70 %) as colorless crystals.

M.p. (°C): 96-97.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H), 1.58 (s, 1H), -0.20 (s, 18H).

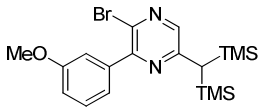
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.1, 159.3, 157.0, 138.6, 138.2, 131.2, 119.3, 115.1, 55.4, 29.1, -0.2

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 3000, 2956, 2895, 2861, 2836, 1884, 1587, 1570, 1519, 1491, 1485, 1462, 1438, 1404, 1390, 1301, 1288, 1268, 1255, 1241, 1177, 1170, 1159, 1122, 1101, 1096, 1023, 1007, 937, 924, 893, 862, 842, 824, 808, 796, 775, 767, 749, 739, 730, 712, 686, 666, 656.

MS (EI, 70 eV): m/z (%) = 456 (46), 455 (15), 454 (45), 441 (30), 439 (26), 350 (10), 349 (57), 348 (13), 347 (54), 300 (48), 287 (37), 165 (27), 139 (23), 138 (12), 137 (10), 73 (100).

HRMS ($C_{18}H_{27}BrN_2OSSi_2$): calc.: 454.0566; found: 454.0563 (M^+).

5-(Bis(trimethylsilyl)methyl)-2-bromo-3-(3-methoxyphenyl)pyrazine (103d)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-bromopyrazine (**102a**; 317 mg, 1.0 mmol) in dry THF (4.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.69 mL, 1.1 mmol, 0.65 M in THF) in 30 min at -40 °C. Then, $ZnCl_2$ (1.2 mL, 1.2 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 1-iodo-3-methoxybenzene (**95j**; 281 g, 0.14 mL, 1.2 mmol), $Pd(dba)_2$ (12 mg, 0.02 mmol, 2 mol%) and tfp (9 mg, 0.04 mmol, 4 mol%) in THF (0.75 mL), the mixture was heated to 40 °C for 24 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **103d** (313 mg, 74 %) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.91 (s, 1H), 7.42 - 7.31 (m, 3H), 7.04 - 6.96 (m, 1H), 3.86 (s, 3H), 1.90 (s, 1H), 0.07 (s, 18H).

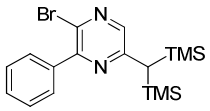
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.1, 158.8, 152.7, 141.6, 138.9, 133.4, 129.0, 121.9, 115.2, 114.8, 55.3, 29.3, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3001, 2953, 2898, 2835, 1742, 1700, 1600, 1582, 1544, 1530, 1511, 1489, 1463, 1452, 1429, 1386, 1366, 1322, 1317, 1286, 1244, 1198, 1179, 1154, 1105, 1087, 1079, 1029, 995, 938, 861, 840, 827, 787, 768, 739, 696, 669, 658.

MS (EI, 70 eV): m/z (%) = 424 (30), 423 (15), 422 (28), 410 (12), 409 (43), 408 (12), 407 (35), 343 (15), 336 (14), 334 (16), 269 (11), 206 (27), 137 (29), 122 (11), 73 (100), 57 (12).

HRMS ($C_{18}H_{27}BrN_2OSi_2$): calc.: 422.0845; found: 422.0830 (M^+).

5-(Bis(trimethylsilyl)methyl)-2-bromo-3-phenylpyrazine (103e)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-bromopyrazine (**102a**; 317 mg, 1.0 mmol) in dry THF (4.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.93 mL, 1.1 mmol, 0.57 M in THF) in 30 min at -40 °C. Then, $ZnCl_2$ (1.2 mL, 1.2 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of iodobenzene (**95k**; 245 g, 0.13 mL, 1.2 mmol), $Pd(dba)_2$ (18 mg, 0.03 mmol, 3 mol%) and tfp (14 mg, 0.06 mmol, 6 mol%) in THF (0.75 mL), the mixture was heated to 40 °C for 24 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **103e** (276 mg, 70 %) as yellow solid.

M.p. (°C): 47-50.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.91 (s, 1H), 7.81 - 7.75 (m, 2H), 7.52 - 7.42 (m, 3H), 1.91 (s, 1H), 0.07 (s, 18H).

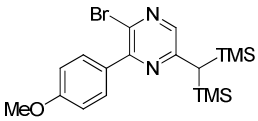
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.8, 153.0, 141.6, 137.7, 133.5, 129.4, 129.1, 127.9, 29.3, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2949, 2895, 1820, 1531, 1508, 1490, 1448, 1381, 1367, 1294, 1281, 1260, 1249, 1242, 1203, 1194, 1181, 1156, 1117, 1105, 1075, 1047, 1030, 1023, 966, 921, 911, 837, 823, 781, 772, 749, 722, 693, 669.

MS (EI, 70 eV): m/z (%) = 394 (25), 393 (11), 392 (24), 380 (13), 379 (43), 378 (13), 377 (40), 313 (16), 306 (16), 301 (11), 299 (10), 222 (17), 175 (28), 149 (10), 136 (27), 122 (13), 85 (16), 73 (100), 71 (21), 69 (10), 57 (31), 55 (13).

HRMS ($C_{17}H_{25}BrN_2Si_2$): calc.: 392.0740; found: 392.0734 (M^+).

5-(Bis(trimethylsilyl)methyl)-2-bromo-3-(4-methoxyphenyl)pyrazine (103f)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-bromopyrazine (**102a**; 317 mg, 1.0 mmol) in dry THF (4.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.69 mL, 1.1 mmol, 0.65 M in THF)

in 30 min at -40 °C. Then, $ZnCl_2$ (1.2 mL, 1.2 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 1-iodo-4-methoxybenzene (**95a**; 281 g, 1.2 mmol), $Pd(dba)_2$ (12 mg, 0.02 mmol, 2 mol%) and tfp (9 mg, 0.04 mmol, 4 mol%) in THF (0.75 mL), the mixture was heated to 40 °C for 48 h. Then, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **103f** (201 mg, 47 %) as yellow crystals.

M.p. (°C): 52-56.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.85 (s, 1H), 7.79 (d, *J* = 8.79 Hz, 2H), 6.99 (d, *J* = 8.98 Hz, 2H), 3.87 (s, 3H), 1.88 (s, 1H), 0.07 (s, 18H).

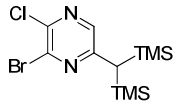
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.4, 158.6, 152.5, 141.0, 133.3, 131.0, 130.1, 113.4, 55.3, 29.3, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3122, 3071, 3012, 2952, 2896, 2840, 1700, 1668, 1608, 1575, 1533, 1504, 1463, 1451, 1441, 1420, 1370, 1307, 1302, 1279, 1247, 1204, 1175, 1153, 1114, 1106, 1030, 1024, 1010, 916, 908, 896, 865, 840, 829, 810, 797, 793, 780, 767, 741, 726, 700, 686, 670.

MS (EI, 70 eV): m/z (%) = 424 (33), 423 (16), 422 (30), 410 (14), 409 (44), 408 (13), 407 (40), 344 (20), 343 (25), 336 (16), 334 (16), 329 (22), 301 (11), 270 (10), 269 (10), 255 (14), 206 (34), 178 (14), 177 (16), 161 (12), 137 (36), 134 (19), 133 (19), 122 (11), 85 (18), 73 (100), 71 (23), 57 (33), 56 (10), 55 (13).

HRMS ($C_{18}H_{27}BrN_2OSi_2$): calc.: 422.0845; found: 422.0847 (M^+).

5-(Bis(trimethylsilyl)methyl)-3-bromo-2-chloropyrazine (103g)



According to **TP 7,** a mixture of 2-(bis(trimethylsilyl)methyl)-5-chloropyrazine (**102b**; 355 mg, 1.3 mmol) in dry THF (5.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (2.34 mL, 1.4 mmol, 0.61 M in THF) in 30 min at -40 °C. Then, the reaction mixture was cannulated to a solution of 1,2-dibromotetrachloroethane ($(BrCl_2C)_2$; 847 mg, 2.6 mmol) in THF (9.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **103g** (425 mg, 93 %) as colorless needles.

M.p. (°C): 67-68.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.89 (s, 1H), 1.85 (s, 1H), 0.07 (s, 18H).

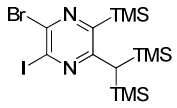
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.9, 143.8, 140.7, 138.2, 29.7, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2965, 2952, 2897, 1528, 1486, 1401, 1374, 1310, 1268, 1252, 1244, 1214, 1187, 1174, 1118, 1030, 910, 903, 863, 837, 825, 772, 748, 730, 717, 688, 660.

MS (EI, 70 eV): m/z (%) = 352 (11), 350 (9), 335 (14), 264 (21), 262 (17), 74 (9), 73 (100).

HRMS ($C_{11}H_{20}BrClN_2Si_2$): calc.: 350.0037; found: 350.0030 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromo-6-iodo-3-(trimethylsilyl)pyrazine (104a)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-iodopyrazine (**103a**; 222 mg, 0.50 mmol) in dry THF (1.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (0.86 mL, 0.55 mmol, 0.64 M in THF) in 3.5 h at -40 °C. Then, the reaction mixture was cannulated to a solution of trimethylsilyl cyanide (TMS-CN; 149 mg, 0.20 mL, 1.5 mmol) in THF (1.50 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane) afforded the desired product **104a** (186 mg, 72 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 2.55 (s, 1H), 0.41 (s, 9H), 0.06 (s, 18H).

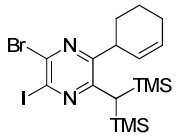
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.4, 160.2, 137.8, 120.8, 31.9, 0.3, -1.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2897, 1473, 1455, 1407, 1307, 1293, 1247, 1202, 1164, 1096, 1037, 932, 824, 768, 727, 715, 685.

MS (EI, 70 eV): m/z (%) = 515 (1), 501 (12), 389 (16), 387 (15), 263 (24), 172 (15), 73 (100).

HRMS ($C_{14}H_{28}BrIN_2Si_3$): calc.: 513.9788; found: 513.9800 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromo-3-(cyclohex-2-en-1-yl)-6-iodopyrazine (104b)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-iodopyrazine (**103a**; 443 mg, 1.0 mmol) in dry THF (2.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.67 mL, 1.1 mmol, 0.66 M in THF) in 3.5 h at -40 °C. Then, $ZnCl_2$ (2.50 mL, 2.5 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of CuCN·2LiCl (0.20 mL, 0.20 mmol, 1.0 M in THF) and 3-bromocyclohexene (**95g**; 193 mg, 0.14 mL, 1.2 mmol), the reaction was allowed to warm to 25 °C over 12 h. After a full conversion was detected by GC analysis, a mixture sat. aq NH_4Cl / NH_3 (25 % in H_2O) = 4:1 (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane) afforded the desired product **104b** (308 mg, 59 %) as colorless solid.

M.p. (°C): 41-43.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 5.93 - 5.81 (m, 1H), 5.60 (dd, *J* = 10.1, 1.2 Hz, 1H), 3.97 - 3.83 (m, 1H), 2.47 (s, 1H), 2.14 - 1.76 (m, 4H), 1.75 - 1.60 (m, 2H), 0.05 (s, 18H).

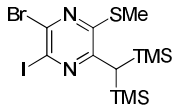
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.4, 157.2, 132.2, 128.4, 127.4, 116.2, 40.5, 31.8, 28.3, 24.7, 21.4, 0.28.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2949, 2929, 2904, 2857, 2833, 1487, 1444, 1434, 1392, 1348, 1334, 1295, 1278, 1257, 1247, 1190, 1175, 1134, 1112, 1053, 1042, 1025, 896, 834, 824, 773, 764, 738, 723, 683, 666, 656.

MS (EI, 70 eV): m/z (%) = 524 (19), 522 (16), 509 (24), 507 (21), 436 (14), 434 (14), 397 (13), 395 (12), 243 (18), 185 (10), 149 (41), 81 (14), 73 (100), 71 (14), 57 (12).

HRMS ($C_{17}H_{28}BrIN_2Si_2$): calc.: 522.0019; found: 522.0017 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromo-6-iodo-3-(methylthio)pyrazine (104c)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-iodopyrazine (**103a**; 443 mg, 1.0 mmol) in dry THF (2.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.72 mL, 1.1 mmol, 0.64 M in THF) in 3.5 h at -40 °C. Then, a solution of *S*-methyl methanethiolsulfonate ($MeSSO_2Me$, **95l**; 379 mg, 0.31 mL, 3.0 mmol) in THF (3.0 mL) was cannulated to the reaction mixture at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NH_4Cl (15 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane) afforded the desired product **104c** (176 mg, 36 %) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 2.52 (s, 1H), 2.50 (s, 3H), 0.09 (s, 18H).

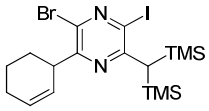
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.1, 156.0, 129.8, 111.8, 32.3, 14.3, 0.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2927, 2896, 1469, 1423, 1390, 1371, 1329, 1311, 1286, 1258, 1247, 1227, 1167, 1116, 1038, 961, 906, 837, 824, 771, 744, 728, 685.

MS (EI, 70 eV): m/z (%) = 490 (13), 488 (12), 475 (29), 473 (26), 402 (16), 400 (15), 363 (16), 361 (13), 73 (100).

HRMS ($C_{12}H_{22}BrIN_2SSi_2$): calc.: 487.9270; found: 487.9261 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromo-6-(cyclohex-2-en-1-yl)-3-iodopyrazine (104d)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-(cyclohex-2-en-1-yl)pyrazine (**103b**; 795 mg, 2.0 mmol) in dry THF (4.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (3.70 mL, 2.5 mmol, 0.68 M in THF) in 1 h at 0 °C. Then, the reaction mixture was cannulated to a solution of iodine (1.015 g, 4.0 mmol) in THF (4.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NaS_2O_3 (15 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane) afforded the desired product **104d** (820 mg, 78 %) as colorless solid.

M.p. (°C): 44-45.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 5.91 - 5.83 (m, 1H), 5.60 (dd, *J* = 10.0, 1.1 Hz, 1H), 3.94 - 3.85 (m, 1H), 2.48 (s, 1H), 2.12 - 1.63 (m, 6H), 0.05 (s, 18H).

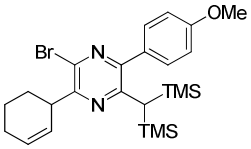
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.4, 157.2, 132.2, 128.4, 127.4, 116.3, 40.6, 31.9, 28.3, 24.7, 21.5, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2949, 2929, 2905, 2888, 2856, 2833, 1487, 1443, 1434, 1393, 1348, 1334, 1295, 1278, 1257, 1247, 1191, 1175, 1134, 1112, 1074, 1053, 1042, 1025, 1004, 895, 845, 835, 825, 773, 764, 737, 723, 683, 666.

MS (EI, 70 eV): m/z (%) = 524 (21), 522 (21), 509 (28), 507 (22), 436 (15), 434 (15), 397 (15), 395 (12), 341 (14), 243 (24), 185 (10), 73 (100).

HRMS ($C_{17}H_{28}BrIN_2Si_2$): calc.: 522.0019; found: 522.0017 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromo-6-(cyclohex-2-en-1-yl)-3-(4-methoxyphenyl)-pyrazine (104e)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-(cyclohex-2-en-1-yl)pyrazine (**103b**; 398 mg, 1.0 mmol) in dry THF (2.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (2.12 mL, 1.3 mmol, 0.59 M in THF) in 1 h at 0 °C. Then, $ZnCl_2$ (1.3 mL, 1.3 mmol, 1.0 M in THF) was added and the reaction mixture was stirred for further 15 min at this temperature. After addition of a solution of 1-iodo-4-methoxybenzene (**95a**; 351 g, 1.5 mmol), $Pd(dba)_2$ (29 mg, 0.05 mmol, 5 mol%) and tfp (23 mg, 0.10 mmol, 10 mol%) in THF (1.50 mL), the mixture was heated to 40 °C for 24 h. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 99:1) afforded the desired product **104e** (297 mg, 59 %) as yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.37 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 5.93 - 5.83 (m, 1H), 5.69 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.06 - 3.95 (m, 1H), 3.86 (s, 3H), 2.30 (s, 1H), 2.18 - 1.67 (m, 6H), -0.02 (s, 18H).

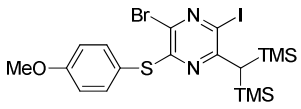
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.6, 157.0, 156.1, 150.5, 133.9, 130.7, 130.5, 128.1, 128.0, 113.8, 55.3, 41.0, 28.4, 27.0, 24.8, 21.6, 0.51.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2949, 2898, 2858, 2835, 1607, 1577, 1514, 1456, 1445, 1398, 1350, 1337, 1326, 1302, 1246, 1174, 1151, 1133, 1107, 1040, 1025, 1006, 909, 855, 838, 826, 807, 772, 732, 722, 683.

MS (EI, 70 eV): m/z (%) = 505 (20), 504 (53), 503 (20), 502 (45), 493 (10), 490 (23), 489 (68), 488 (25), 487 (66), 424 (10), 416 (20), 414 (16), 350 (17), 349 (24), 335 (15), 321 (11), 277 (13), 243 (31), 200 (10), 149 (19), 145 (12), 144 (100), 81 (13), 73 (98).

HRMS ($C_{24}H_{35}BrN_2OSi_2$): calc.: 502.1471; found: 502.1466 (M^+).

2-(Bis(trimethylsilyl)methyl)-5-bromo-3-iodo-6-((4-methoxyphenyl)thio)pyrazine (104f)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-2-bromo-3-((4-methoxyphenyl)thio)pyrazine (**103c**; 228 mg, 0.50 mmol) in dry THF (2.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (1.17 mL, 0.75 mmol, 0.64 M in THF) in 3.5 h at -20 °C. Then, the reaction mixture was cannulated to a solution of iodine (254 g, 1.0 mmol) in THF (4.0 mL) at -78 °C. The reaction

mixture was allowed to warm to 25 °C over 12 h, sat. aq NaS_2O_3 (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 19:1) afforded the desired product **104f** (209 mg, 72 %) as colorless crystals.

M.p. (°C): 109-111.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.43 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H), 2.38 (s, 1H), -0.18 (s, 18H).

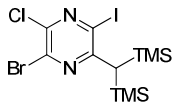
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.5, 161.2, 156.6, 138.1, 128.4, 118.7, 115.3, 113.0, 55.5, 21.1, 0.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2996, 2952, 2894, 2833, 1591, 1574, 1492, 1475, 1465, 1437, 1405, 1322, 1289, 1244, 1221, 1185, 1170, 1110, 1094, 1030, 1012, 933, 908, 841, 821, 798, 770, 742, 735, 727, 686.

MS (EI, 70 eV): m/z (%) = 582 (36), 580 (28), 567 (22), 565 (26), 475 (20), 473 (13), 456 (13), 453 (10), 427 (16), 189 (26), 139 (15), 127 (21), 72 (11), 73 (100), 55 (12).

HRMS ($C_{18}H_{26}BrIN_2OSSi_2$): calc.: 579.9532; found: 579.9520 (M^+).

2-(Bis(trimethylsilyl)methyl)-6-bromo-5-chloro-3-iodopyrazine (104g)



According to **TP 7,** a mixture of 5-(bis(trimethylsilyl)methyl)-3-bromo-2-chloropyrazine (**103g**; 176 mg, 0.50 mmol) in dry THF (1.0 mL) reacted with $TMP_2Mg{\cdot}2LiCl$ (0.86 mL, 0.55 mmol, 0.64 M in THF) in 2 h at -40 °C. Then, the reaction mixture was cannulated to a solution of iodine (254 g, 1.0 mmol) in THF (4.0 mL) at -78 °C. The reaction mixture was allowed to warm to 25 °C over 12 h, sat. aq NaS_2O_3 (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane) afforded the desired product **104g** (198 mg, 83 %) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 2.50 (s, 1H), 0.09 (s, 18H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.5, 141.7, 137.0, 116.4, 32.6, 0.0.

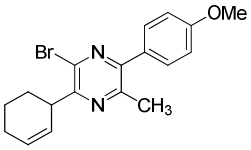
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2897, 1499, 1460, 1403, 1332, 1290, 1249, 1218, 1186, 1106, 1043, 1026, 914, 838, 823, 776, 743, 725, 686, 659.

MS (EI, 70 eV): m/z (%) = 478 (3), 476 (2), 463 (14), 461 (11), 390 (29), 388 (22), 73 (100).

HRMS ($C_{11}H_{19}BrClIN_2Si_2$): calc.: 475.9003; found: 475.8960 (M^+).

4.5. Subsequent Transformations of BTM-substituted Pyrazines

2-Bromo-3-(cyclohex-2-en-1-yl)-6-(4-methoxyphenyl)-5-methylpyrazine (105)



A *Schlenk*-flask was charged with 2-(bis(trimethylsilyl)methyl)-5-bromo-6-(cyclohex-2-en-1-yl)-3-(4-methoxyphenyl)-pyrazine (**104e**; 257 mg, 0.51 mmol) in THF (1.0 mL) and cooled to 0 °C. Then, TBAF·$3H_2O$ (161 mg, 0.51 mmol) was added and the reaction mixture was stirred for 10 min at this temperature. After a full conversion was detected by GC analysis, sat. aq NaCl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *i*hexane / Et_2O = 9:1) afforded the desired product **105** (155 mg, 85 %) as colorless solid.

M.p. (°C): 77-79.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.55 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.97 - 5.90 (m, 1H), 5.76 (d, *J* = 10.2 Hz, 1H), 4.10 - 3.99 (m, 1H), 3.86 (s, 3H), 2.59 (s, 3H), 2.21 - 1.69 (m, 6H).

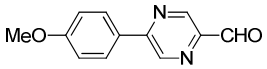
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 160.1, 156.2, 151.0, 149.2, 137.5, 130.5, 129.7, 128.6, 127.6, 113.8, 55.3, 41.1, 28.2, 24.7, 22.7, 21.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2925, 2856, 2838, 1724, 1607, 1579, 1537, 1516, 1501, 1458, 1441, 1433, 1398, 1376, 1353, 1338, 1331, 1303, 1292, 1245, 1200, 1187, 1175, 1156, 1142, 1127, 1108, 1081, 1051, 1033, 1022, 1010, 987, 958, 932, 911, 895, 872, 826, 810, 801, 790, 784, 768, 762, 733, 724, 689, 679, 673.

MS (EI, 70 eV): m/z (%) = 361 (22), 360 (100), 359 (36), 358 (99), 345 (45), 343 (39), 332 (18), 331 (40), 330 (18), 329 (38), 317 (23), 295 (17), 294 (88), 293 (31), 292 (81), 291 (21), 280 (24), 279 (79), 251 (19), 149 (19), 103 (21), 77 (38).

HRMS ($C_{18}H_{19}BrN_2O$): calc.: 358.0681; found: 358.0669 (M^+).

5-(4-Methoxyphenyl)pyrazine-2-carbaldehyde (106)



A round-bottom flask was charged with 2-(bis(trimethylsilyl)methyl)-5-(4-methoxy-phenyl)pyrazine (**102d**; 172 mg, 0.50 mmol) in a mixture of CH_3CN (24.0 mL) and H_2O (8.0 mL) and cooled to 0 °C. Then, CAN ($(NH_4)_2Ce(NO_3)_6$; 1.371 g, 2.50 mmol) was added and the reaction mixture was stirred for 15 min at this temperature. After a full conversion was detected by GC analysis, sat. aq $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). The crude mixture was after evaporation of the solvents *in vacuo* filtered over a pad of silica and washed with EtOAc to afford the desired product **106** (100 mg, 93 %) as colorless solid.

M.p. (°C): 137-139.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 10.14 (s, 1H), 9.11 (d, *J* = 8.1 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 9.1 Hz, 2H), 3.89 (s, 3H).

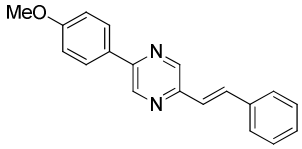
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 192.1, 162.3, 155.5, 144.4, 143.1, 141.0, 129.2, 127.6, 114.7, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2955, 2922, 2846, 1702, 1652, 1602, 1580, 1564, 1517, 1508, 1477, 1467, 1458, 1444, 1424, 1314, 1297, 1250, 1231, 1196, 1182, 1170, 1154, 1111, 1024, 1018, 1005, 974, 958, 940, 924, 850, 832, 826, 799, 772, 740, 722, 711.

MS (EI, 70 eV): m/z (%) = 215 (15), 214 (100), 186 (14), 177 (14), 161 (10), 158 (17), 133 (30), 132 (21), 85 (10), 71 (14), 57 (20), 55 (10).

HRMS ($C_{12}H_{10}N_2O_2$): calc.: 214.0742; found: 214.0733 (M^+).

(*E*)-2-(4-Methoxyphenyl)-5-styrylpyrazine (107)



A *Schlenk*-flask was charged with 2-(bis(trimethylsilyl)methyl)-5-(4-methoxy-phenyl)pyrazine (**102d**; 172 mg, 0.50 mmol) in dry THF (8.0 mL) and cooled to -20 °C. Then, benzaldehyde (64 mg, 0.06 mL, 0.60 mmol) and TBAF (0.05 mL, 0.05 mmol, 1.0 M in THF) were added and the reaction mixture was stirred for 15 min at this temperature. After a full conversion was detected by GC analysis, sat. aq NH_4Cl (10 mL), sat. aq $NaHCO_3$ (5 mL) and H_2O (10 mL) were added and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, DCM) afforded the desired product **107** (134 mg, 93 %) as colorless solid.

M.p. (°C): 181-183.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.95 (s, 1H), 8.63 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.44 - 7.29 (m, 3H), 7.20 (d, *J* = 16.0 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 3H).

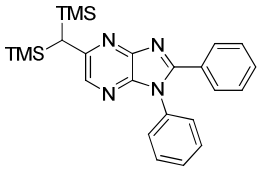
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.1, 150.3, 148.4, 142.8, 140.9, 136.4, 134.0, 128.9, 128.8, 128.7, 128.1, 127.2, 124.1, 114.5, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 3060, 3030, 3002, 2959, 2933, 2923, 2914, 2852, 2835, 1630, 1603, 1580, 1574, 1518, 1481, 1463, 1449, 1438, 1414, 1362, 1350, 1300, 1264, 1244, 1216, 1199, 1177, 1155, 1149, 1107, 1074, 1053, 1028, 1019, 1007, 992, 987, 971, 960, 951, 941, 929, 915, 886, 876, 850, 843, 836, 823, 800, 782, 743, 726, 690, 652.

MS (EI, 70 eV): m/z (%) = 289 (12), 288 (63), 287 (100), 244 (12), 128 (11), 85 (11), 71 (16), 69 (11), 57 (22), 55 (12).

HRMS ($C_{19}H_{15}N_2O$): calc.: 287.1179; found: 287.1183 ($[M-H]^+$).

5-(Bis(trimethylsilyl)methyl)-1,2-diphenyl-*1H*-imidazo[4,5-*b*]pyrazine (109)



A *Schlenk*-flask was charged with 5-(bis(trimethylsilyl)methyl)-2-bromo-3-iodopyrazine (**103a**; 93 mg, 0.21 mmol) in dry toluene (2.0 mL). Then, *N*-phenyl-benzamidine (**108**; 59 mg, 0.30 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol, 6 mol%), Xantphos (7 mg, 0.013 mmol, 6 mol%) and NaO*t*Bu (96 mg, 1.0 mmol) were added subsequently and the reaction mixture was heated to 80 °C for 1 h. After a full conversion was detected by GC analysis, sat. aq NaCl (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, ihexane / Et_2O = 7:1) afforded the desired product **109** (86 mg, 95 %) as colorless solid.

M.p. (°C): 119-123.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.95 (s, 1H), 7.70 - 7.64 (m, 2H), 7.55 - 7.45 (m, 3H), 7.42 - 7.28 (m, 5H), 2.02 (s, 1H), 0.11 (s, 18H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.2, 154.6, 148.1, 138.9, 138.5, 135.1, 130.3, 129.74, 129.69, 129.2, 128.8, 128.3, 127.4, 29.8, 0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 3058, 2953, 2897, 2858, 1597, 1576, 1550, 1500, 1496, 1482, 1465, 1453, 1443, 1405, 1380, 1357, 1336, 1312, 1282, 1269, 1259, 1250, 1245,

1238, 1218, 1181, 1175, 1160, 1155, 1125, 1118, 1079, 1022, 1002, 995, 979, 974, 927, 918, 885, 864, 834, 827, 811, 777, 759, 753, 740, 719, 705, 696, 684, 670, 654.

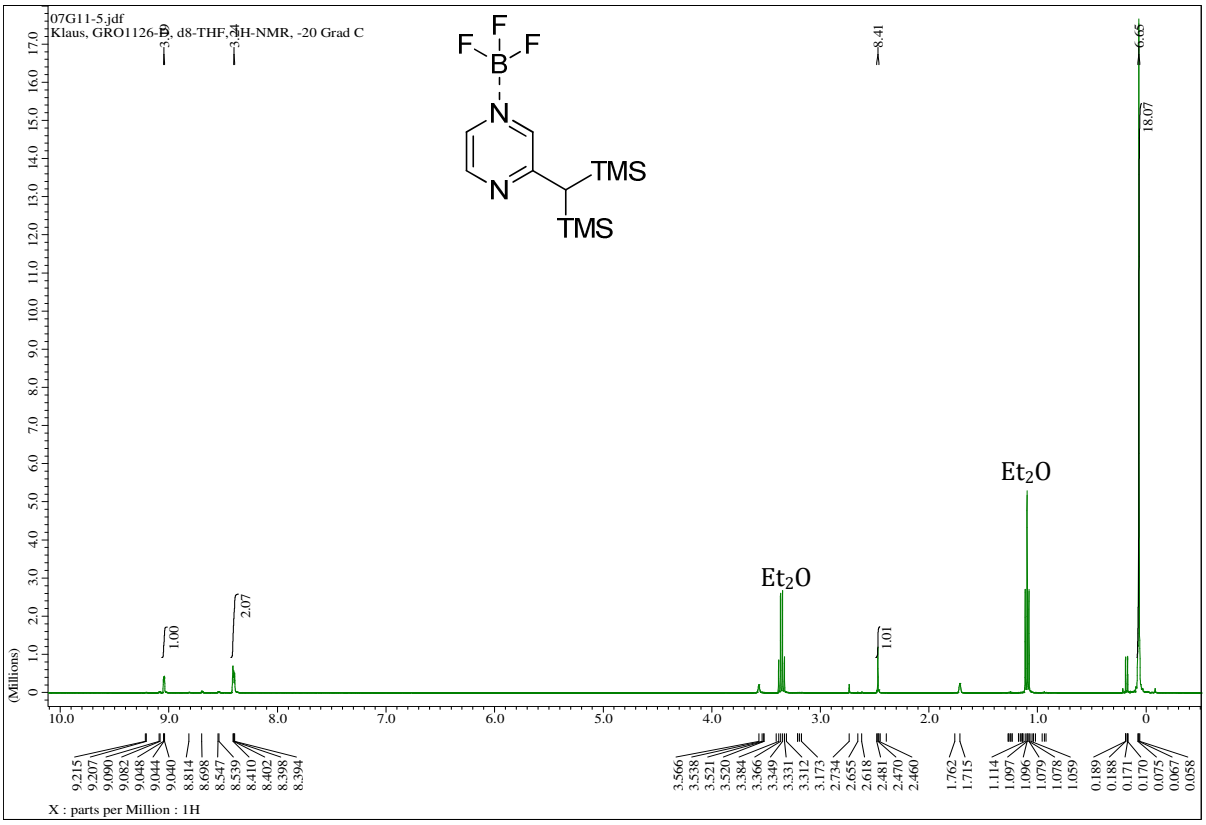
MS (EI, 70 eV): m/z (%) = 431 (38), 430 (100), 429 (78), 416 (27), 415 (65), 357 (22), 343 (15), 342 (29), 286 (13), 285 (13), 97 (25), 93 (12), 91 (13), 85 (27), 83 (48), 81 (13), 79 (12), 77 (24), 73 (45), 69 (13), 68 (14), 67 (18).

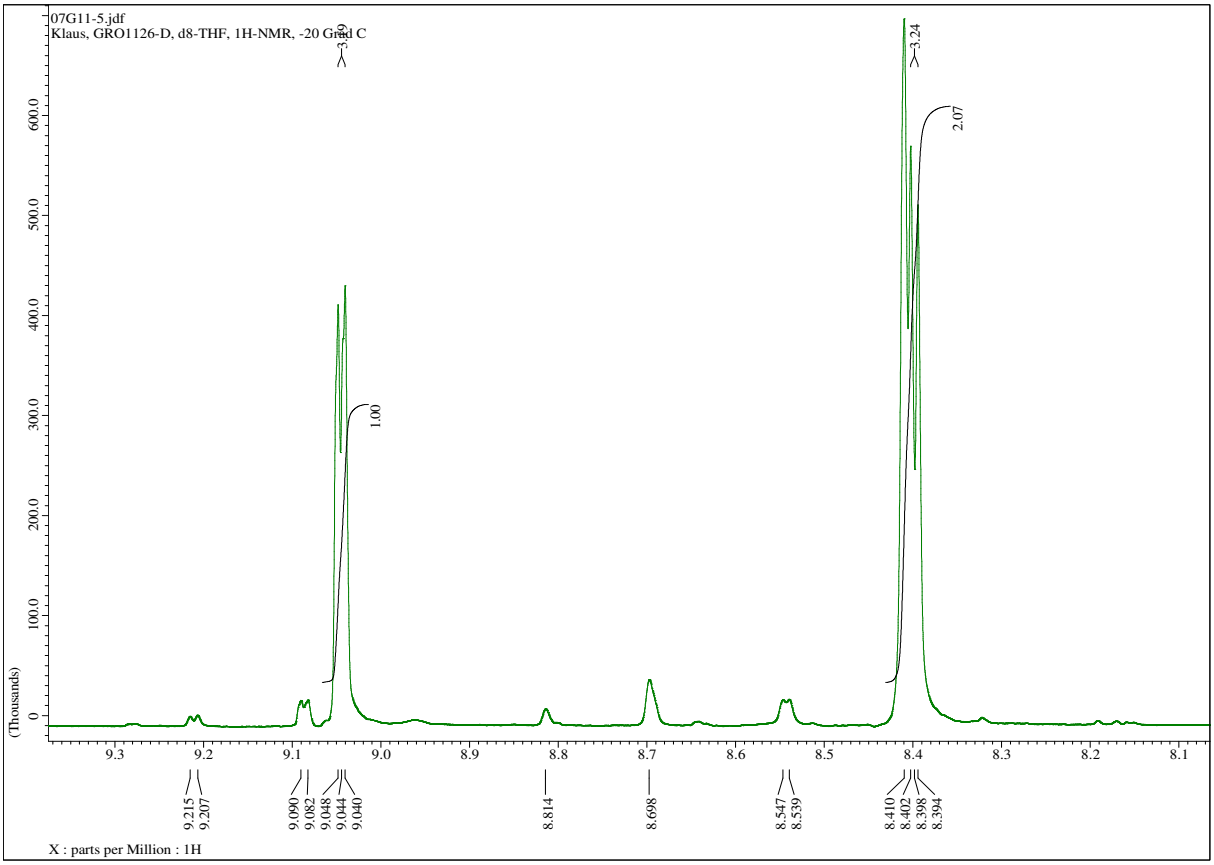
HRMS ($C_{24}H_{30}N_4Si_2$): calc.: 430.2009; found: 430.2004 (M^+).

D. APPENDIX

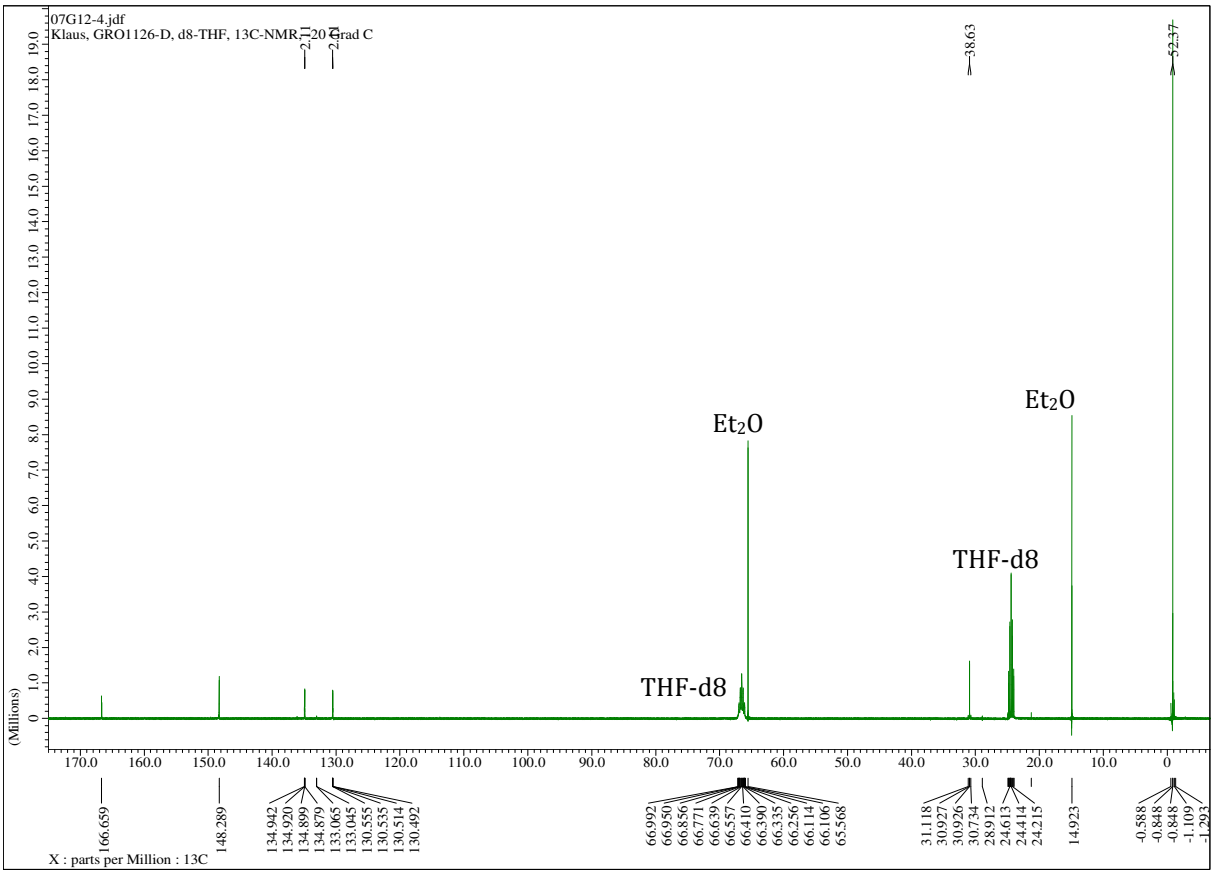
1. NMR-Spectra of the Lewis Adduct **99**

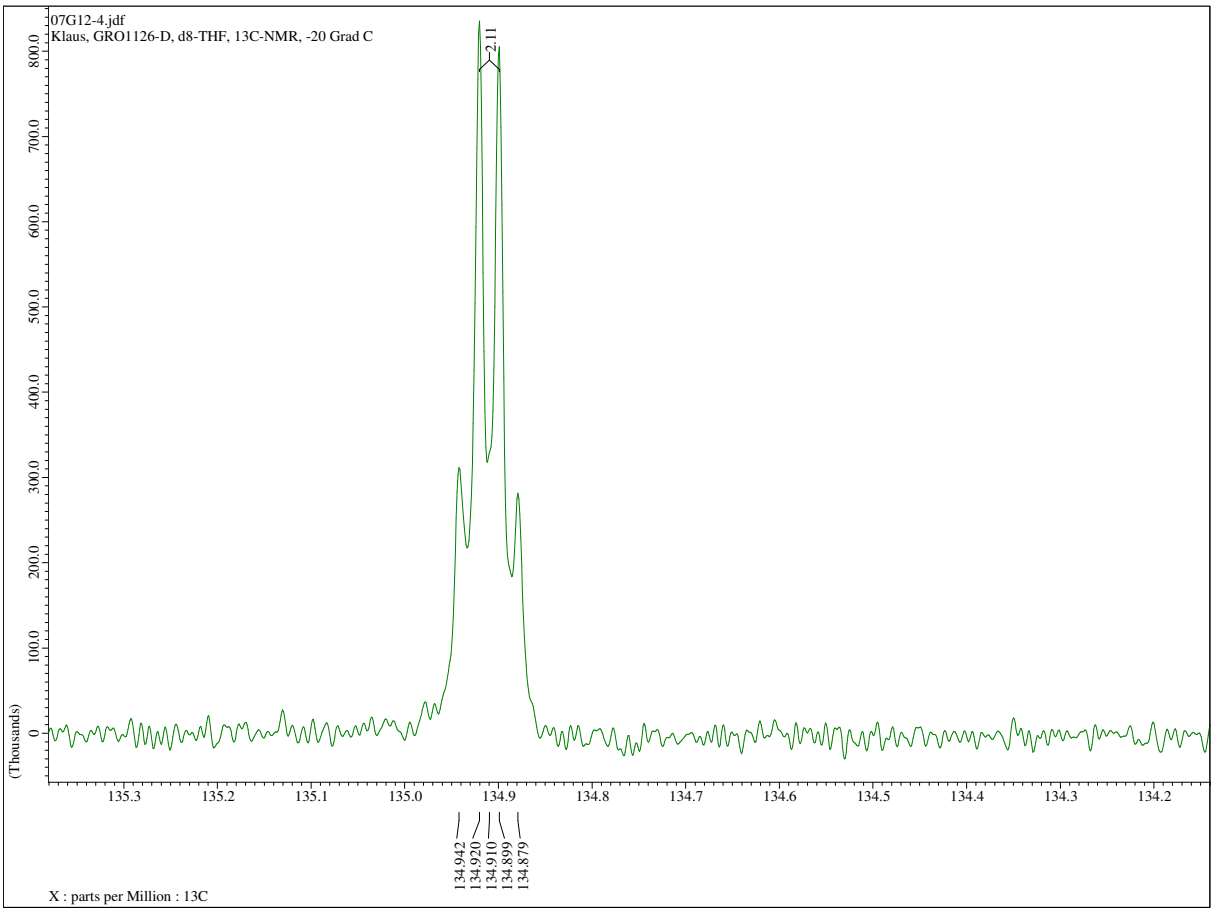
1.1. ^{1}H NMR, -20 °C, THF-D8

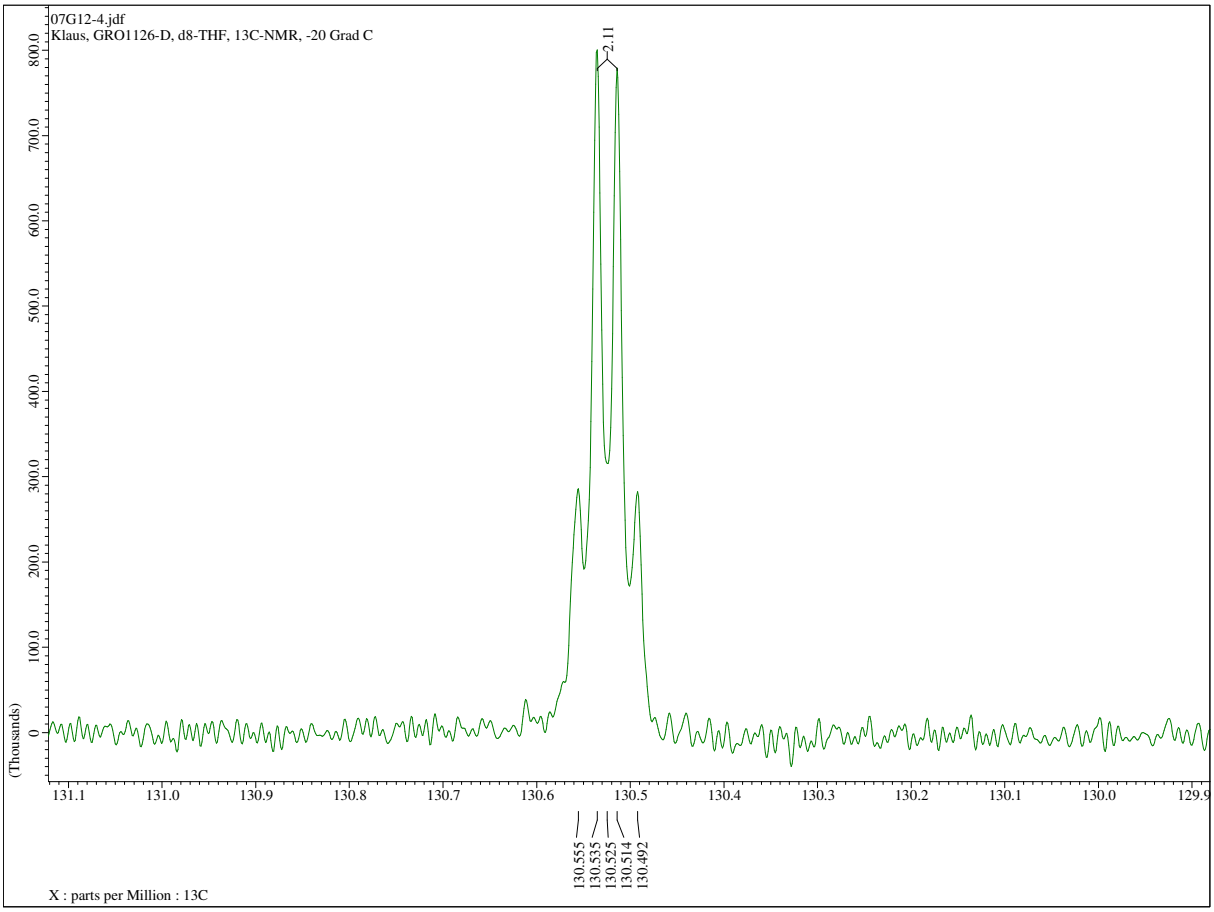




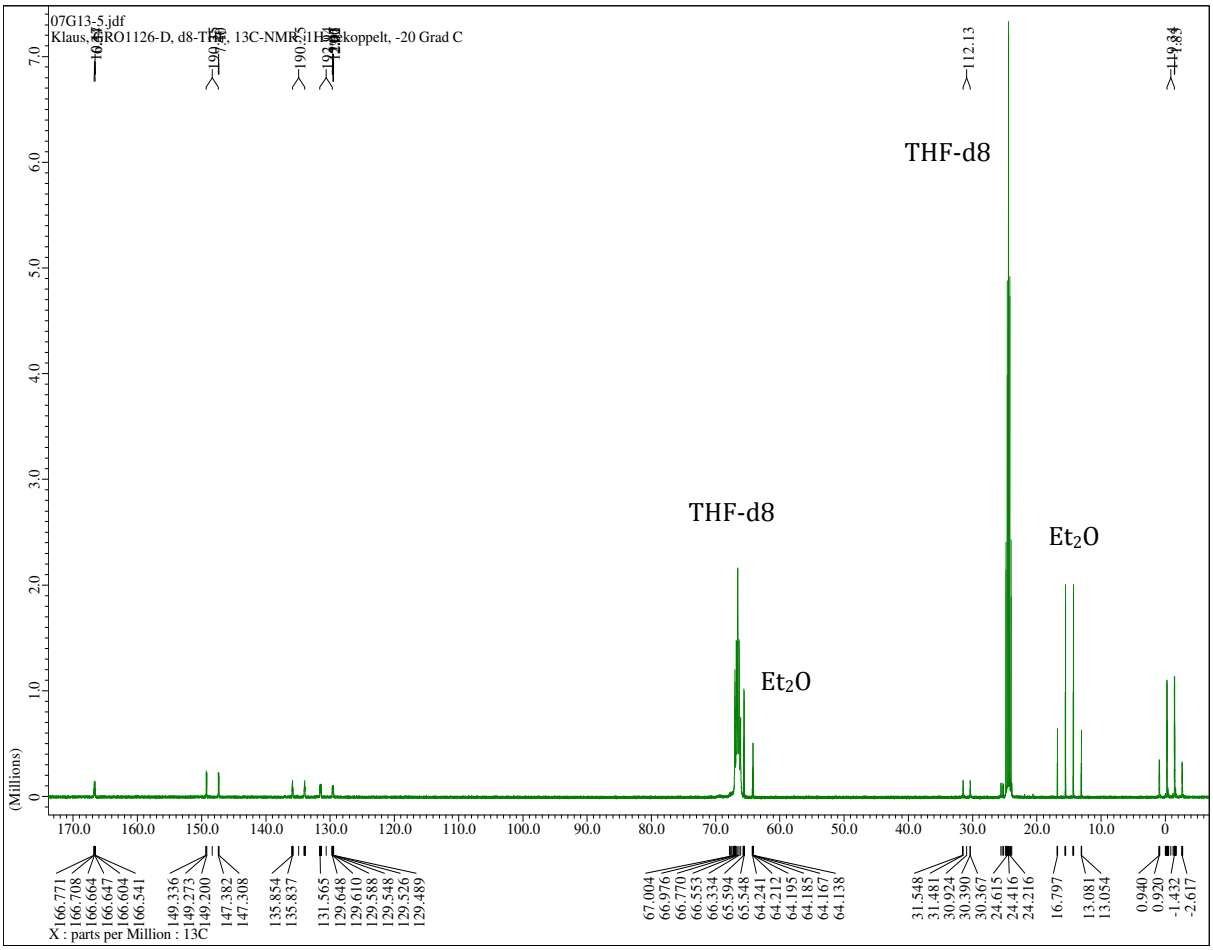
1.2. ^{13}C NMR, -20 °C, THF-D8

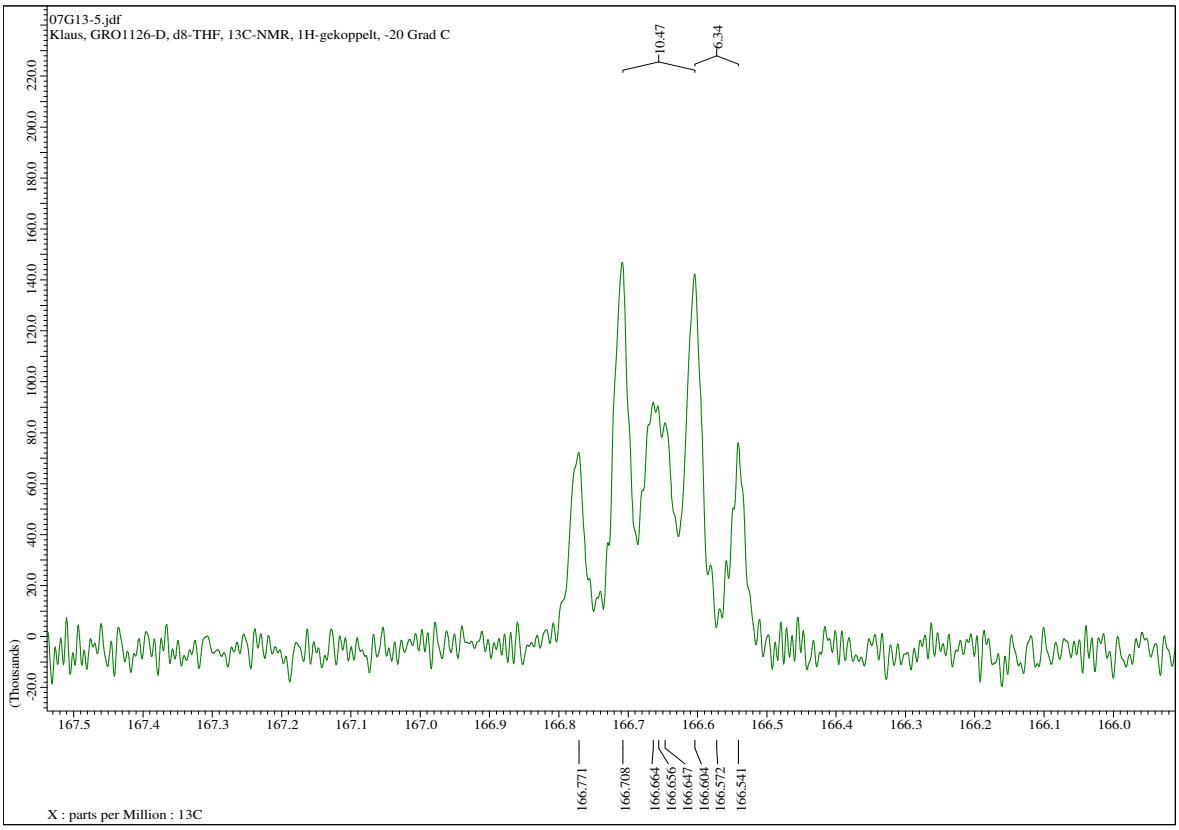


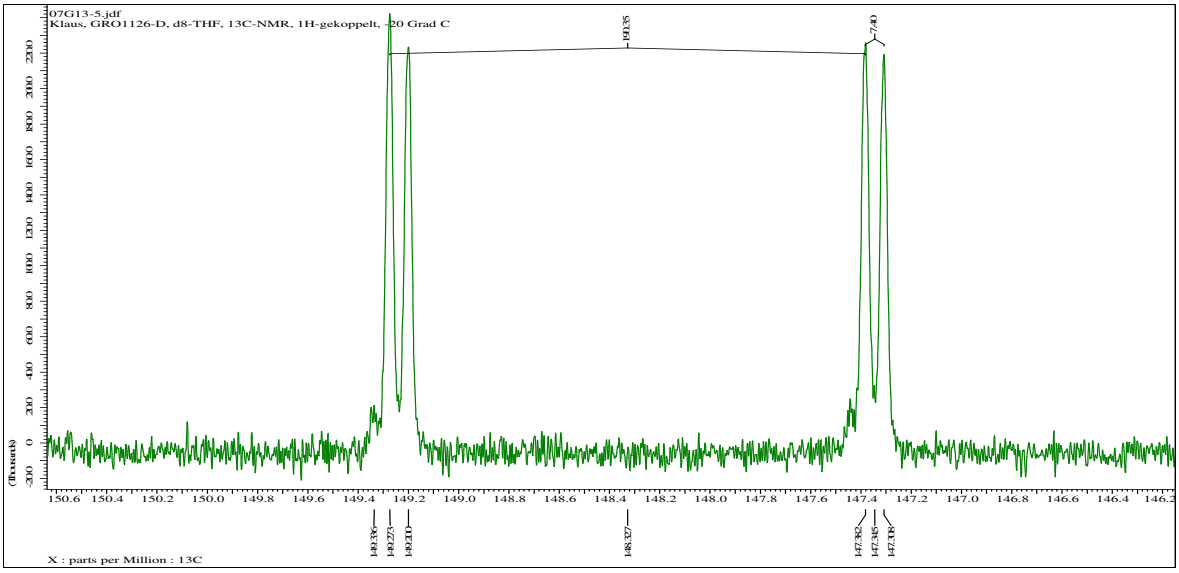


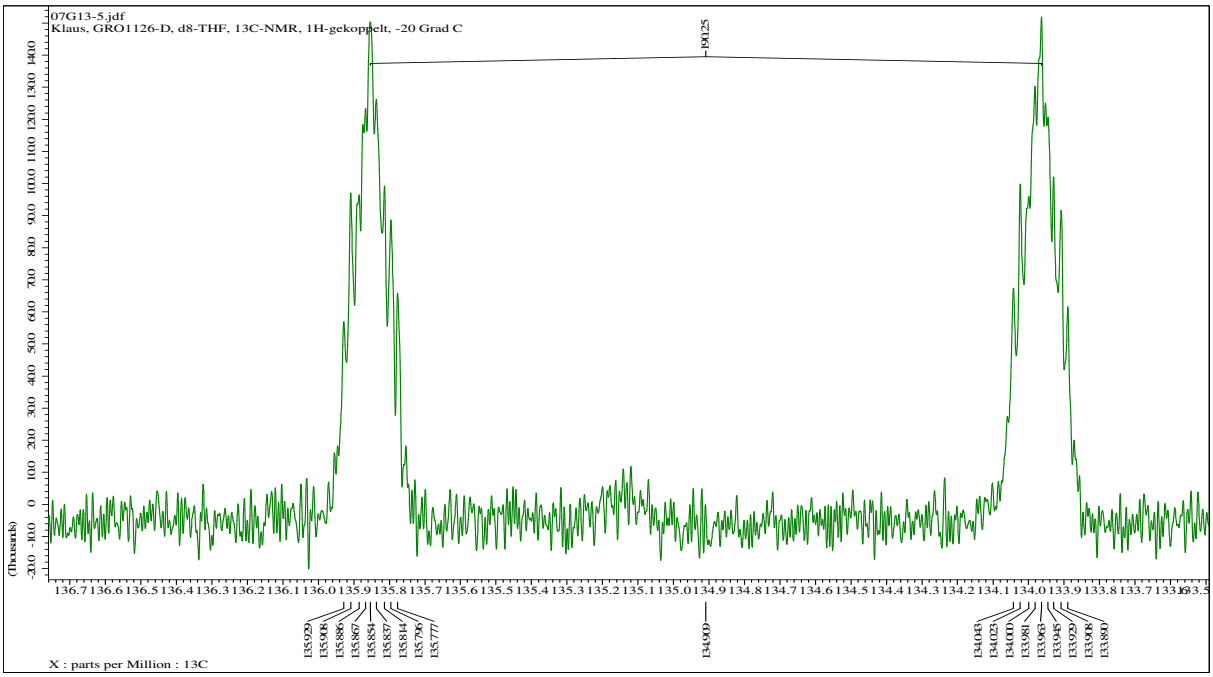

07G12-4.jdf
Klaus, GRO1126-D, d8-THF, 13C-NMR, -20 Grad C
2.11
800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0
(Thousands)
131.1
131.0
130.9
130.8
130.7
130.6
130.5
130.4
130.3
130.2
130.1
130.0
129.9
130.555
130.535
130.525
130.514
130.492
X : parts per Million : 13C

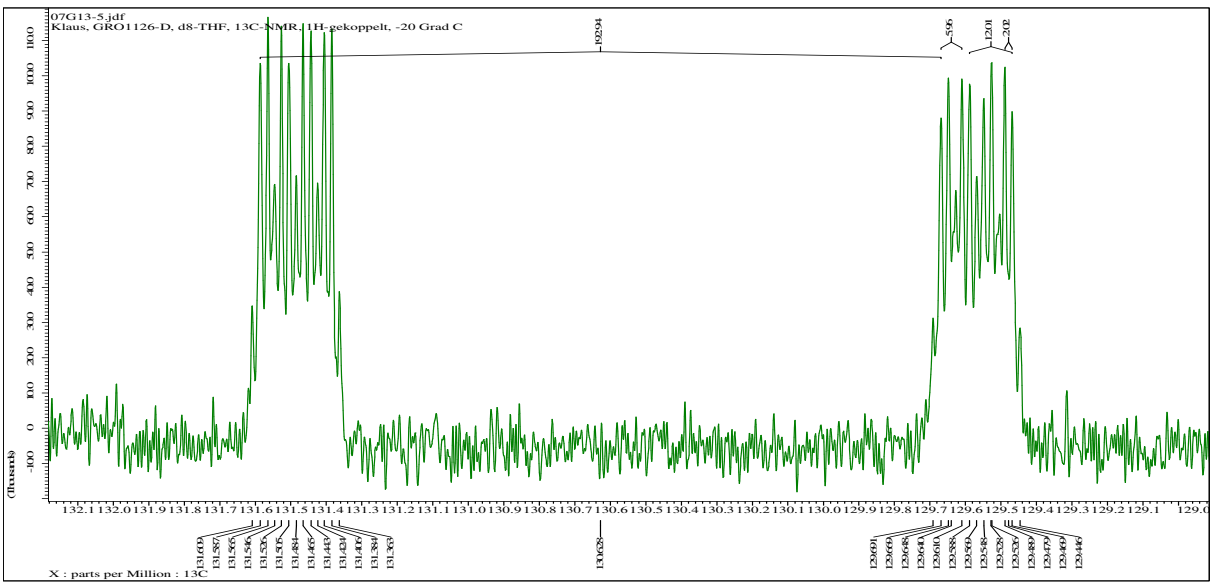
1.3. ^{13}C-NMR, -20 °C, THF-D8, 1H-COUPLED

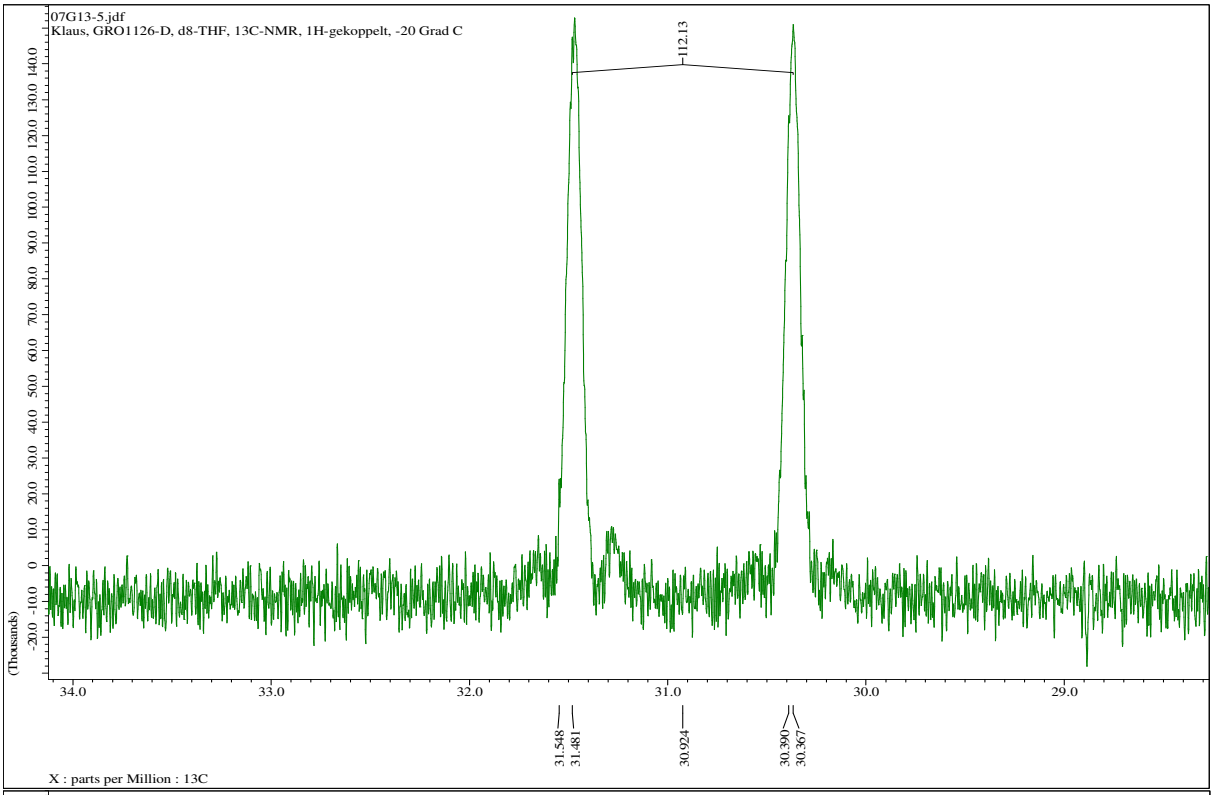


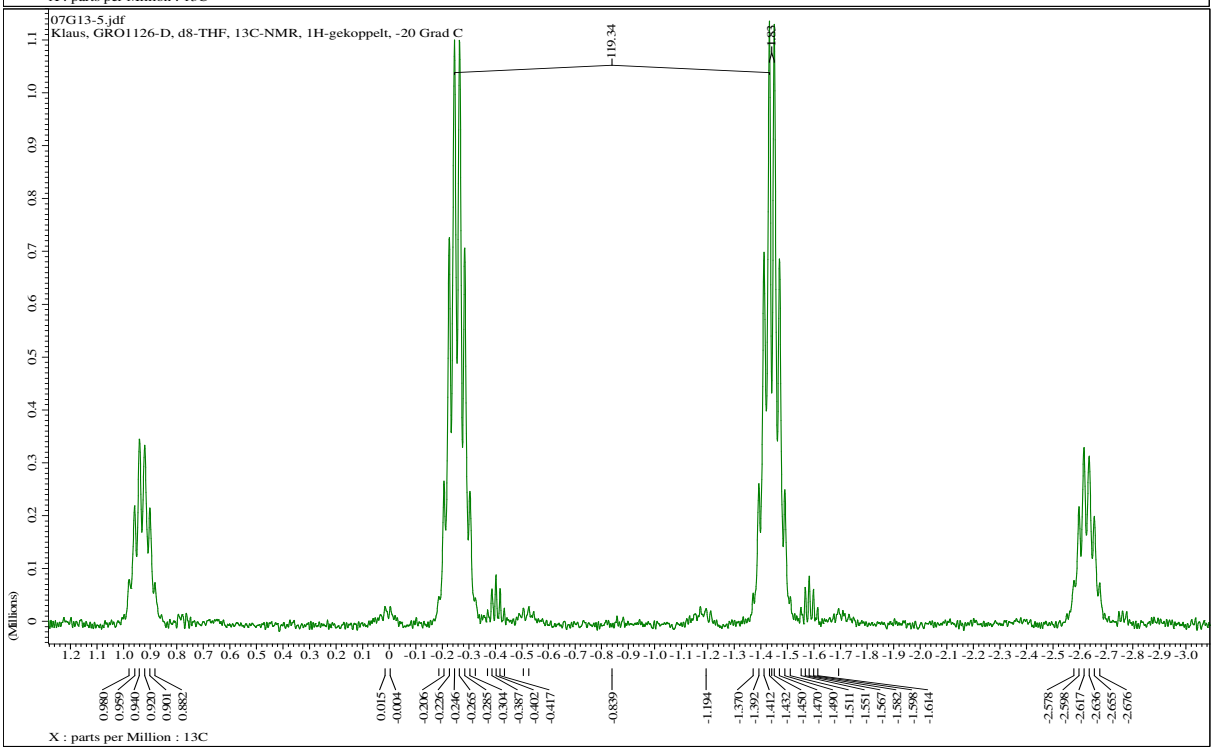



07G13-5.jdf
Klaus, GRO1126-D, d8-THF, 13C-NMR, 1H-gekoppelt, -20 Grad C
19.35
7.40
(Thousands)
X : parts per Million : 13C


07G13-5.jdf
Klaus, GRO1126-D, d8-THF, 13C-NMR, 1H-gekoppelt, -20 Grad C
19.25
(Thousands)
X : parts per Million : 13C


07G13-5.jdf
Klaus, GRO1126-D, d8-THF, 13C-NMR, 1H-gekoppelt, -20 Grad C
19.29
5.96
12.01
3.05
(Thousands)
X : parts per Million : 13C


07G13-5.jdf
Klaus, GRO1126-D, d8-THF, 13C-NMR, 1H-gekoppelt, -20 Grad C
112.13
(Thousands)
34.0
33.0
32.0
31.0
30.0
29.0
31.548
31.481
30.924
30.390
30.367
X : parts per Million : 13C


07G13-5.jdf
Klaus, GRO1126-D, d8-THF, 13C-NMR, 1H-gekoppelt, -20 Grad C
119.34
119.23
(Millions)
0.980
0.959
0.940
0.920
0.901
0.882
0.015
-0.004
-0.206
-0.226
-0.246
-0.265
-0.285
-0.304
-0.387
-0.400
-0.417
-0.839
-1.194
-1.370
-1.392
-1.412
-1.432
-1.450
-1.470
-1.490
-1.511
-1.551
-1.567
-1.582
-1.598
-1.614
-2.578
-2.598
-2.617
-2.636
-2.655
-2.676
X : parts per Million : 13C

2. X-RAY DATA FOR **102A** AND **109**

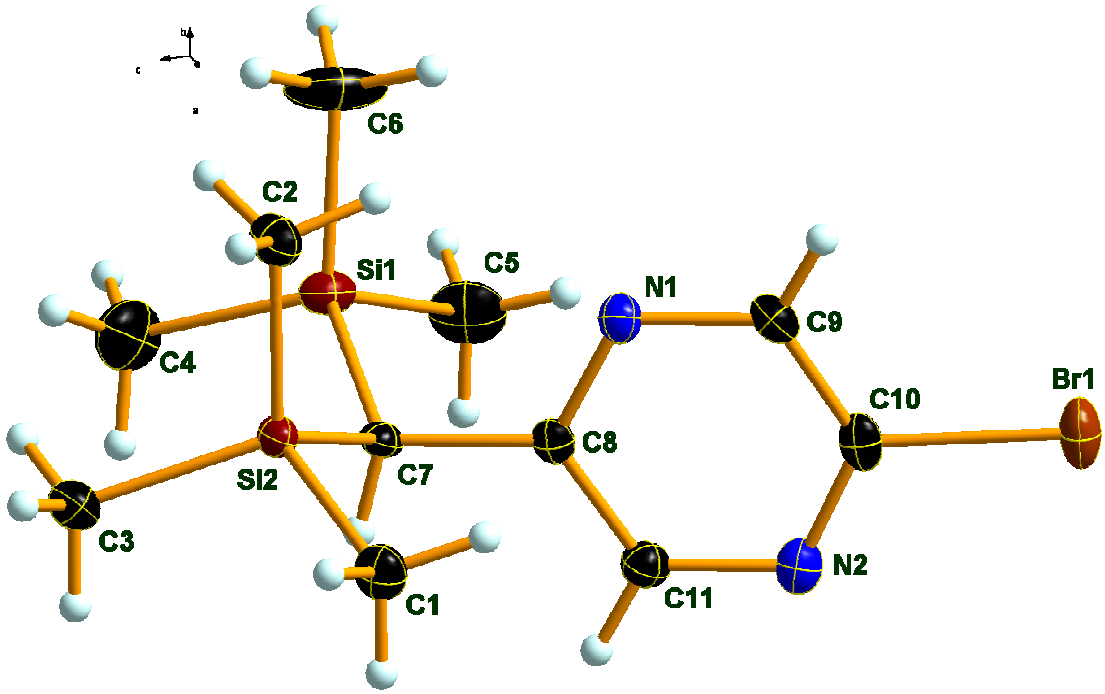


Figure 4: DIAMOND view of the molecular structure of compound **102a** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 17: structure of compound **102a** in the crystal; selected atom distances (in Å).

Br1 – C10	1.903(2)	Si2 – C7	1.907(2)
Si1 – C4	1.869(3)	N1 – C8	1.348(3)
Si1 – C5	1.861(3)	N1 – C9	1.341(3)
Si1 – C6	1.864(3)	N2 – C10	1.325(4)
Si1 – C7	1.905(2)	N2 – C11	1.336(3)
Si2 – C1	1.870(2)	C7 – C8	1.498(3)
Si2 – C2	1.870(3)	C8 – C11	1.400(3)
Si2 – C3	1.870(2)	C9 – C10	1.386(4)

Table 18: Molecular structure of compound **102a** in the crystal; selected bond angles (in °).

C4 – Si1 – C5	109.3(1)	C10 – N2 – C11	115.2(2)
C4 – Si1 – C6	109.4(2)	Si1 – C7 – Si2	119.6(1)
C4 – Si1 – C7	109.2(1)	Si1 – C7 – C8	109.8(1)
C5 – Si1 – C6	108.3(1)	Si2 – C7 – C8	110.9(1)
C5 – Si1 – C7	107.9(1)	N1 – C8 – C7	118.3(2)
C6 – Si1 – C7	112.8(1)	N1 – C8 – C11	119.7(2)
C1 – Si2 – C2	108.3(1)	C7 – C8 – C11	122.1(2)
C1 – Si2 – C3	109.1(1)	N1 – C9 – C10	120.4(2)
C1 – Si2 – C7	108.0(1)	Br1 – C10 – N2	117.3(2)
C2 – Si2 – C3	109.3(1)	Br1 – C10 – C9	119.0(2)
C2 – Si2 – C7	112.9(1)	N2 – C10 – C9	123.7(2)
C3 – Si2 – C7	109.2(1)	N2 – C11 – C8	123.3(2)
C8 – N1 – C9	117.7(2)		

Table 19: Molecular structure of compound **102a** in the crystal; selected torsion angles (in °).

C4 – Si1 – C7 – Si2	-68.5(2)	C9 – N1 – C8 – C11	1.6(3)
C4 – Si1 – C7 – C8	161.6(2)	C8 – N1 – C9 – C10	0.5(4)
C5 – Si1 – C7 – Si2	172.8 (1)	C11 – N2 – C10 – Br1	-177.4(2)
C5 – Si1 – C7 – C8	42.9(2)	C11 – N2 – C10 – C9	1.5(3)
C6 – Si1 – C7 – Si2	53.3(2)	C10 – N2 – C11 – C8	0.8(4)
C6 – Si1 – C7 – C8	-76.6(2)	Si1 – C7 – C8 – N1	71.4(2)
C1 – Si2 – C7 – Si1	-170.8(1)	Si1 – C7 – C8 – C11	-108.1(2)
C1 – Si2 – C7 – C8	-41.3(2)	Si2 – C7 – C8 – N1	-63.1(2)
C2 – Si2 – C7 – Si1	-51.1(2)	Si2 – C7 – C8 – C11	117.4(2)
C2 – Si2 – C7 – C8	78.3(2)	N1 – C8 – C11 – N2	-2.4(4)
C3 – Si2 – C7 – Si1	70.8(1)	C7 – C8 – C11 – N2	177.1(2)
C3 – Si2 – C7 – C8	-159.8(2)	N1 – C9 – C10 – Br1	176.6(2)
C9 – N1 – C8 – C7	-177.9(2)	N1 – C9 – C10 – N2	-2.2(4)

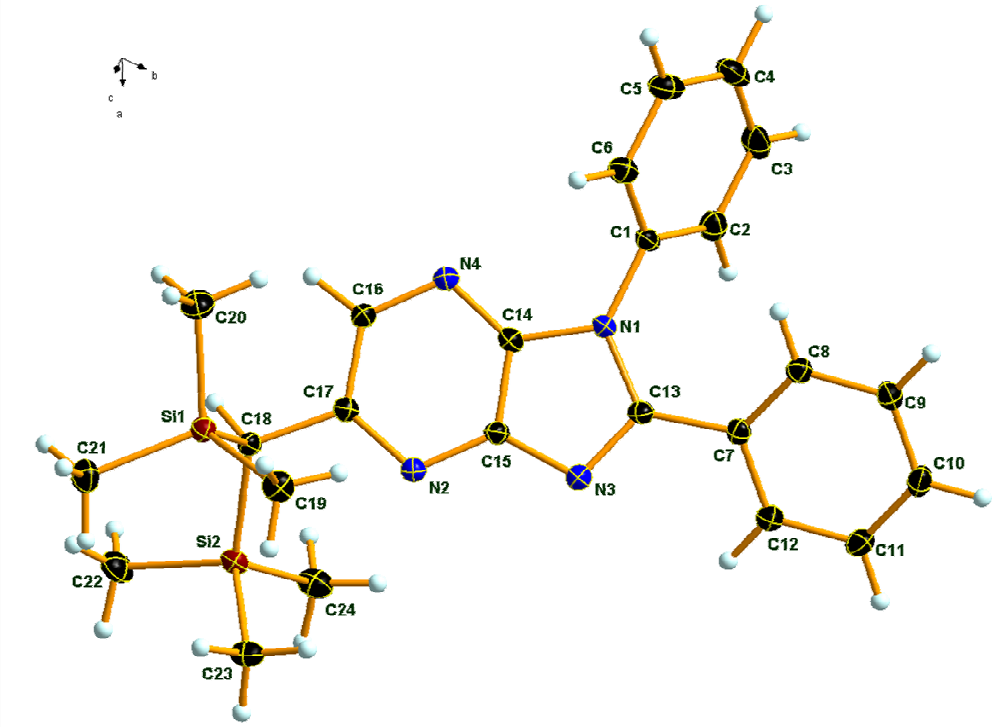


Figure 5: DIAMOND view of the molecular structure of compound **109** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Table 20: Molecular structure of compound **109** in the crystal; selected atom distances (in Å).

Si1 – C18	1.904(2)	C1 – C2	1.387(2)
Si1 – C19	1.871(2)	C1 – C6	1.392(2)
Si1 – C20	1.876(2)	C2 – C3	1.391(2)
Si1 – C21	1.877(2)	C3 – C4	1.389(3)
Si2 – C18	1.898(2)	C4 – C5	1.390(3)
Si2 – C22	1.880(2)	C5 – C6	1.390(2)
Si2 – C23	1.871(2)	C7 – C8	1.400(2)
Si2 – C24	1.864(2)	C7 – C12	1.404(2)
N1 – C1	1.438(2)	C7 – C13	1.476(2)
N1 – C13	1.394(2)	C8 – C9	1.393(3)
N1 – C14	1.386(2)	C9 – C10	1.392(2)
N2 – C15	1.345(2)	C10 – C11	1.396(2)
N2 – C17	1.352(2)	C11 – C12	1.387(3)
N3 – C13	1.327(2)	C14 – C15	1.402(2)
N3 – C15	1.380(2)	C16 – C17	1.420(2)
N4 – C14	1.328(2)	C17 – C18	1.508(2)
N4 – C16	1.341(2)		

Table 21: Molecular structure of compound **109** in the crystal; selected bond angles (in °).

C18 – Si1 – C19	110.6(1)	C14 – N4 – C16	112.2(1)	N1 – C13 – N3	113.1(2)
C18 – Si1 – C20	108.4(1)	N1 – C1 – C2	120.6(1)	N1 – C13 – C7	125.0(1)
C18 – Si1 – C21	111.7(1)	N1 – C1 – C6	118.3(1)	N3 – C13 – C7	121.9(1)
C19 – Si1 – C20	109.1(1)	C2 – C1 – C6	121.1(2)	N1 – C14 – N4	128.3(1)
C19 – Si1 – C21	109.3(1)	C1 – C2 – C3	119.3(2)	N1 – C14 – C15	106.1(1)
C20 – Si1 – C21	107.6(1)	C2 – C3 – C4	120.2(2)	N4 – C14 – C15	125.5(2)
C18 – Si2 – C22	107.5(1)	C3 – C4 – C5	120.0(2)	N2 – C15 – N3	127.5(1)
C18 – Si2 – C23	112.4(1)	C4 – C5 – C6	120.4(2)	N2 – C15 – C14	122.0(2)
C18 – Si2 – C24	112.2(1)	C1 – C6 – C5	119.0(2)	N3 – C15 – C14	110.5(1)
C22 – Si2 – C23	109.1(1)	C8 – C7 – C12	119.3(2)	N4 – C16 – C17	124.2(2)
C22 – Si2 – C24	106.9(1)	C8 – C7 – C13	123.0(1)	N2 – C17 – C16	121.8(2)
C23 – Si2 – C24	108.5(1)	C12 – C7 – C13	117.6(1)	N2 – C17 – C18	118.0(1)
C1 – N1 – C13	130.2(1)	C7 – C8 – C9	119.8(2)	C16 – C17 – C18	120.2(2)
C1 – N1 – C14	124.5(1)	C8 – C9 – C10	120.5(2)	Si1 – C18 – Si2	115.3(1)
C13 – N1 – C14	105.4(1)	C9 – C10 – C11	120.0(2)	Si1 – C18 – C17	109.0(1)
C15 – N2 – C17	114.2(1)	C10 – C11 – C12	119.7(2)	Si2 – C18 – C17	114.1(1)
C13 – N3 – C15	104.8(1)	C7 – C12 – C11	120.7(2)		

Table 22: Molecular structure of compound **109** in the crystal; selected torsion angles (in °).

C19 – Si1 – C18 – Si2	74.6(1)	C16 – N4 – C14 – C15	0.4(2)
C19 – Si1 – C18 – C17	-55.2(1)	C14 – N4 – C16 – C17	0.9(2)
C20 – Si1 – C18 – Si2	-165.8(1)	N1 – C1 – C2 – C3	-177.9(2)
C20 – Si1 – C18 – C17	64.4(1)	C6 – C1 – C2 – C3	2.0(3)
C21 – Si1 – C18 – Si2	-47.5(1)	N1 – C1 – C6 – C5	178.4(2)
C21 – Si1 – C18 – C17	-177.2(1)	C2 – C1 – C6 – C5	-1.4(3)
C22 – Si2 – C18 – Si1	83.6(1)	C1 – C2 – C3 – C4	-1.0(3)

C22 – Si2 – C18 – C17	-149.2(1)	C2 – C3 – C4 – C5	-0.4(3)
C23 – Si2 – C18 – Si1	-36.4(1)	C3 – C4 – C5 – C6	0.9(3)
C23 – Si2 – C18 – C17	90.8(1)	C4 – C5 – C6 – C1	0.0(3)
C24 – Si2 – C18 – Si1	-159.1(1)	C12 – C7 – C8 – C9	0.3(2)
C24 – Si2 – C18 – C17	-31.9(2)	C13 – C7 – C8 – C9	176.0(2)
C13 – N1 – C1 – C2	57.5(2)	C8 – C7 – C12 – C11	-0.2(2)
C13 – N1 – C1 – C6	-122.4(2)	C13 – C7 – C12 – C11	-176.1(2)
C14 – N1 – C1 – C2	-124.3(2)	C8 – C7 – C13 – N1	33.2(2)
C14 – N1 – C1 – C6	55.8(2)	C8 – C7 – C13 – N3	-145.3(2)
C1 – N1 – C13 – N3	178.8(1)	C12 – C7 – C13 – N1	-151.1(2)
C1 – N1 – C13 – C7	0.1(3)	C12 – C7 – C13 – N3	30.4(2)
C14 – N1 – C13 – N3	0.3(2)	C7 – C8 – C9 – C10	-0.2(2)
C14 – N1 – C13 – C7	-178.3(1)	C8 – C9 – C10 – C11	0.0(2)
C1 – N1 – C14 – N4	2.9(3)	C9 – C10 – C11 – C12	0.1(2)
C1 – N1 – C14 – C15	-178.5(1)	C10 – C11 – C12 – C7	0.0(2)
C13 – N1 – C14 – N4	-178.6(2)	N1 – C14 – C15 – N2	179.5(1)
C13 – N1 – C14 – C15	0.1(2)	N1 – C14 – C15 – N3	-0.5(2)
C17 – N2 – C15 – N3	-178.4(2)	N4 – C14 – C15 – N2	-1.8(3)
C17 – N2 – C15 – C14	1.7(2)	N4 – C14 – C15 – N3	178.3(2)
C15 – N2 – C17 – C16	-0.5(2)	N4 – C16 – C17 – N2	-0.9(2)
C15 – N2 – C17 – C18	-179.2(1)	N4 – C16 – C17 – C18	177.8(1)
C15 – N3 – C13 – N1	-0.6(2)	N2 – C17 – C18 – Si1	92.7(1)
C15 – N3 – C13 – C7	178.1(1)	N2 – C17 – C18 – Si2	-37.7(2)
C13 – N3 – C15 – N2	-179.3(2)	C16 – C17 – C18 – Si1	-86.0(2)
C13 – N3 – C15 – C14	0.6(2)	C16 – C17 – C18 – Si2	143.6(1)
C16 – N4 – C14 – N1	178.9(2)		

Single crystals of compounds **102a** and **109**, suitable for X-ray diffraction, were obtained by slow evaporation of pentane solutions at ambient temperature. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å). Data collection was performed with the CrysAlis CCD software;[117] CrysAlis RED software[118] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[119] was applied. The structures were solved with SHELXS-97,[120] refined with SHELXL-97[121] and finally checked using PLATON.[122] Details for data collection and structure refinement are summarized in Table 23.

CCDC-926466 (for **102a**) and CCDC-926467 (for **109**) contain supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[117] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

[118] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

[119] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., **2005**.

[120] G. M. Sheldrick, SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany, **1997**.

[121] G. M. Sheldrick, SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, **1997**.

[122] A. L. Spek, PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, The Netherlands, **1999**.

Table 23: Details for X-ray data collection and structure refinement for compounds **102a** and **109**.

	102a	**109**
Empirical formula	$C_{11}H_{21}BrN_2Si_2$	$C_{24}H_{30}N_4Si_2$
Formula mass	317.39	430.70
T [K]	173(2)	100(2)
Crystal size [mm]	0.427 × 0.187 × 0.161	0.537 × 0.528 × 0.187
Crystal description	colorless block	colorless block
Crystal system	monoclinic	triclinic
Space group	*P*21	*P*-1
a [Å]	9.9897(3)	9.2004(4)
b [Å]	6.1601(2)	11.9272(9)
c [Å]	12.6532(4)	12.5249(9)
α [°]	90.0	63.504(6)
β [°]	93.282(3)	87.843(5)
γ [°]	90.0	81.973(5)
V [Å^3]	777.37(4)	1217.54(14)
Z	2	2
$\rho_{calcd.}$ [g cm^{-3}]	1.356	1.175
μ [mm^{-1}]	2.778	0.163
F(000)	328	460
Θ range [°]	4.16 – 28.28	4.22 – 28.28
Index ranges	-13 ≤ h ≤ 13	-12 ≤ h ≤ 12
	-8 ≤ k ≤ 8	-15 ≤ k ≤ 15
	-16 ≤ l ≤ 16	-16 ≤ l ≤ 16
Reflns. collected	9322	14555
Reflns. obsd.	3544	4717
Reflns. unique	3844	6002
	(R_{int} = 0.0340)	(R_{int} = 0.0336)
R_1, wR_2 (2σ data)	0.0276, 0.0548	0.0408, 0.0958
R_1, wR_2 (all data)	0.0327, 0.0570	0.0572, 0.1065
GOOF on F^2	1.013	1.022
Peak/hole [e Å^{-3}]	0.349 / -0.285	0.414 / -0.260