Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Lewis Acid Triggered Regioselective Metalation and Deprotection of Uracils, Uridines and Cytidines, Preparation of Pyrrolo[2,3-*d*]pyrimidines *via* an Intramolecular Copper-mediated Carbomagnesation of Ynamides and Regioselective Preparation of Tetrasubstituted Fluorobenzenes

von

Johannes Nickel

aus Brandenburg a. d. Havel, Deutschland

2016

Erklärung

Diese Dissertation wurde im Sinne von §7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Paul Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

Berlin, 25. Oktober 2016

.....

Johannes Nickel

Dissertation eingereicht am	13.9.2016
1. Gutachter	Prof. Dr. Paul Knochel
2. Gutachter	Prof. Dr. Konstantin Karaghiosoff
Mündliche Prüfung am	20.10.2016

This work was carried out from September 2013 to August 2016 under the guidance of Prof. Dr. Paul Knochel at the Faculty of Chemistry and Pharmacy of the Ludwig-Maximilians Universität, Munich. First of all, I would like to thank Prof. Dr. Paul Knochel, for giving me the opportunity of doing my Ph.D. in his group, and for his invaluable support and guidance in the course of my scientific research.

I am also very grateful to Prof. Dr. Konstantin Karaghiosoff for agreeing to be second reviewer of this thesis and I thank all members of my defense committee: Prof. Dr. Manfred Heuschmann, Prof. Dr. Klaus T. Wanner, Prof. Dr. Heinz Langhals and Dr. Thomas Magauer for their interest in this manuscript by accepting to be referees.

Further I would like to thank Dr. Daniela Sustac, Mario Ellwart, Dorothée Ziegler, Andrew Kononov and Dr. Anna Chentsova who have been carefully proofreading this manuscript.

I would like to thank my students, Juri Skotnitzki, Johannes Raab, Evgeniya Shlaen, Genrich Ebel, Susanna Held, Konstantin Mallon und Tomas Saiegh for the contribution to this thesis.

I want to extend my gratitude to many past and present co-workers I have met in our research group for the great and helpful atmosphere in our group and in particular to my labmates in F2.012: Dr. Sarah Fernandez, Dr. Diana Haas, Moritz Balkenhohl, Max Hofmayer, Alexander John, Ferdinand Lutter, Alicia Castello-Mico, Denise Cibu, Dr. Olesya Kuzmina, Dr. Maitane Fernández and Dr. Dorian Didier. Thank you for your support and all the fun hours we shared together.

Special thanks to all the members of the cooking team: Mario Ellwart, Dr. Simon Herbert, Dr. Thomas Klatt, Robert Greiner, Carl-Phillip Tüllmann, Gabriel Kiesl, Michael Eisolt und Andreas Baumann for always having a great lunch and sheering up my day.

For their help in organizing everyday live in the lab, I would like to thank Dr. Vladimir Malakhov, Peter Dowling, Yulia Tsvik, Sophie Hansen and Renate Schröder.

Zum Ende möchte ich noch einen ganz besonderen Dank an meine gesamte Familie für ihre riesige Unterstützung während meines Studiums und meiner Promotion aussprechen. Кро́ме того́, моя люби́мая Аннушка большо́е спаси́бо тебе. Без твоей помощи я бы не смог этого сделать.

Parts of this PhD thesis have been published

Communications

1) Lydia Klier, Eider Aranzamendi, Dorothée Ziegler, **Johannes Nickel**, Konstantin Karaghiosoff, Thomas Carell, Paul Knochel: Lewis Acid Triggered Regioselective Magnesiation and Zincation of Uracils, Uridines, and Cytidines, *Org. Lett.* **2016**, *18*, 1068.
2) **Johannes Nickel**, Tomas Saiegh, Simon A. Herbert, Paul Knochel: Regioselective Functionalizations of Fluoroaromatics using a Remote *Para*-Lithiation, *Org. Lett.* **2016**, *in manuscript*.

Full paper

3) **Johannes Nickel**, Maitane Fernández, Lydia Klier, Paul Knochel: Synthesis of Pyrrolo[2,3-*d*]pyrimidines via Copper-Mediated Carbomagnesiations of *N*-sulfonyl ynamides. Application to the preparation of Rigidin A and a 7-Azaserotonin Derivative, *Chem. Eur. J.* **2016**, 22, 14397.

"If you want to build a ship, don't drum up people to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea.”

Antoine de Saint-Exupery

Meiner Familie und Anna

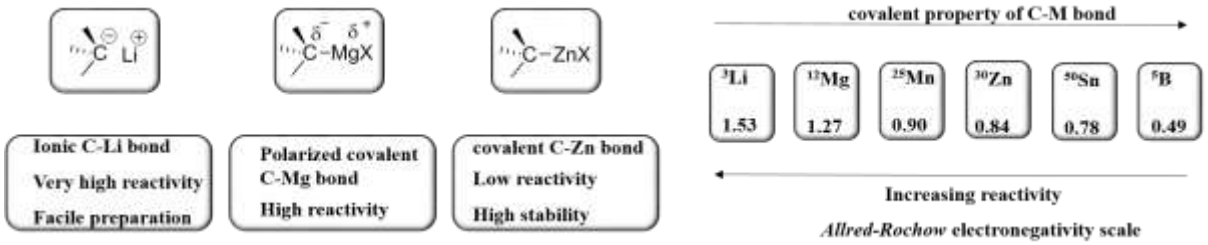
TABLE OF CONTENTS

A. INTRODUCTION

1. OVERVIEW

Achieving selectivity in chemical reactivity and controlling the outcome of a reaction will always be important goals in synthetic organic chemistry. Considering the advances of modern synthetic methods, organometallic chemistry has been established as one of the most significant disciplines that offers a broad toolset to perform selective transformatins of chemical molecules.[1] The first organometallic compound ever synthesized[2] is considered to be "*Cadet´s fuming liquid*", a mixture of Me_4As_2 (cacodyl) and Me_4As_2O (cacodyl oxide), prepared by *Cadet* in 1760.[3] Since the first report of a carbon-zinc bond, based on *Frankland*'s finding of diethylzinc in the 19th century,[4] organometallic species have become increasingly valuable intermediates. Another milestone was set by *Grignard*'s achievements on organomagnesium reagents at the beginning of the 20th century.[5] Aside from zinc and magnesium, several other metals have been examined and a considerable number of organometallic reagents have enabled access to new synthetic methods for efficient and selective reactions.

In general the nature of the carbon-metal bond exceedingly influences the reactivity of the organometallic reagent. Thus, the reactivity of an organometallic species is proportional to the ionic nature of the metal-carbon bond and therefore increases with the difference in electronegativity between metal and carbon atom (Scheme 1).[6]



Scheme 1: Comparision of metals in organometallic species with respect to their electronegativity difference between the metal and carbon atom (according to *Allred-Rochow* electronegativity scale).

[1] For general review, see: a) P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. Kneisel in *Handbook of Functionalized Organometallics*, (Eds.: P. Knochel), Wiley-VCH, Weinheim **2005**, p. 251. b) P. Knochel, P. Millot, A. L. Rodriguez, C. E. Tucker in *Organic reactions*, (Eds.: L. E. Overman), Wiley & Sons Inc., New York, **2001**, p. 1.
[2] C. Eschenbroich, *Organometallchemie*, Wiley-VCH, Weinheim, **2008**, p. 1.
[3] a) J.J. Berzelius. *Jahresber*. **1839**, *18*, 487. b) J. H. Burns, J. Waser, *J. Am. Chem. Soc.* **1957**, *79*, 859. c) D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[4] a) E. Frankland, *Liebigs Ann. Chem*. **1848**, *71*, 171. b) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[5] V. *Grignard*, *C. R. Acad. Sci.* **1900**, *130*, 1322.
[6] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414.

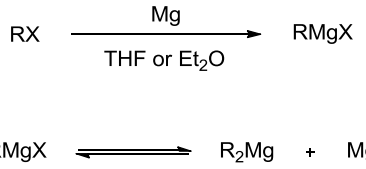
As a consequence the polar lithium-carbon species displays high reactivity along with low functional group tolerance and requires low reaction temperatures.[7] Metals such as zinc, tin and boron form bonds with increasing covalent character with carbon atoms, which on one hand exhibit lower reactivity and often require the use of transition metal catalysts, but on the other hand tolerate many functional moieties.[8]

Today numerous protocols exists for the synthesis of scaffolds comprising carbon-heteroatom bonds *via* the use of organometallic intermediates. However, the growing demand from the chemical industry for novel agrochemicals and pharmaceutical substances[9] as well as the importance of sustainable chemistry with limited resources and decreasing environmental pollution will always be a driving force for science. Therefore the need to discover more efficient organometallic methods and reagents in synthetic chemistry still exists and represents an exciting challenge.

1.1. Preparation of Organometallic Reagents

1.1.1. Oxidative Insertion

The most common preparation of organometallic reagents consists of the direct oxidative addition of magnesium metal (powder or turnings) to organic halides in an aprotic solvent like tetrahydrofuran (THF) or diethyl ether under inert atmosphere due to the sensitivity of *Grignard* reagents to air and moisture (Scheme 2).



Scheme 2: Preparation of *Grignard* reagents by oxidative addition and *Schlenk* equilibrium.

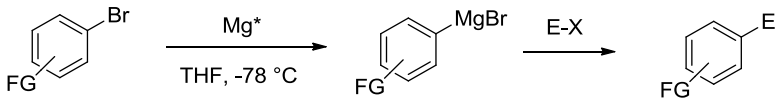
An oxidative insertion was first observed by *Frankland* in 1848, when he prepared dialkylzinc reagents by reacting zinc metal with alkyl halides.[4] A few decades later *Grignard* discovered

[7] G. Wu, M. Huang, *Chem. Rev*. **2006**, *106*, 2596.
[8] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117. b) P. Knochel, S. Vettel, C. Eisenberg, *Appl. Organomet. Chem.* **1995**, *9*, 175. c) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[9] a) T. Collins, *Science* **2001**, *291*, 48. b) C. Okkerse, H. van Bekkum, *Green Chem.* **1999**, *1*, 107.

in 1900 a convenient preparation of organomagnesium compounds by performing a reaction of elemental magnesium and organic halides in diethyl ether.[5]

The detailed mechanism of this reaction is not yet fully clarified, but a radical pathway is generally accepted.[10] In solution, a *Grignard* reagent (RMgX) is in a so called *Schlenk* equilibrium with R_2Mg and MgX_2, depending on the solvent, temperature and the anion X^-.[11]

The *Grignard* reagents became one of the most widely used C-C bond forming tools as they display several advantages. Firstly, it is an atom economical reaction and, secondly magnesium is an inexpensive metal, which exhibits low toxicity. However, for the synthesis of functionalized *Grignard* reagents bearing sensitive functional groups such as ester, keto, cyano or nitro groups some modifications are nessesary. *Rieke* developed highly activated metal powders, which also enabled the aforementioned halides bearing functional groups to be transformed into *Grignard* reagents. These *Rieke* metals can be prepared *via* reduction of an anhydrous metal chloride by an alkali metal such as lithium, sodium or potassium in THF (Scheme 3).[12] Another option is the direct trapping of *Grignard* reagents with an electrophile (*Barbier*-conditions) to overcome the stability problems.[13]



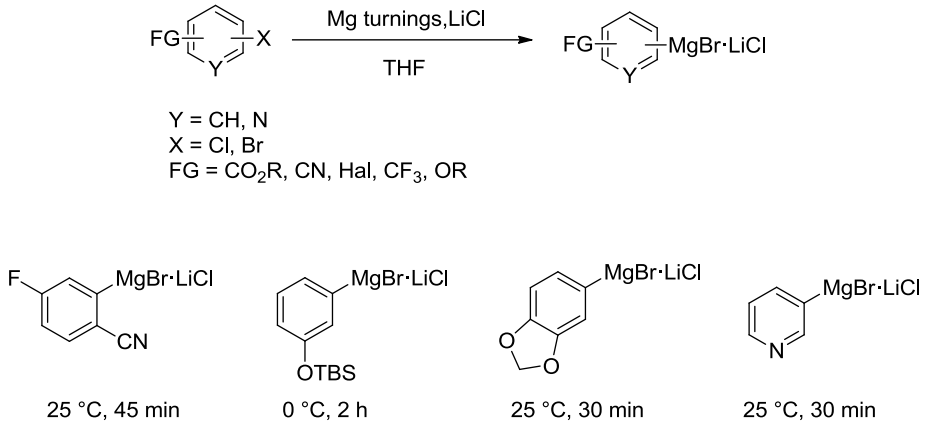
FG = CO_2tBu, OCO*t*Bu, CN, etc.
E-X = PhCHO, PhCOCl, allyl bromide

Scheme 3: Preparation of functionalized *Grignard* reagents using "*Rieke* magnesium".

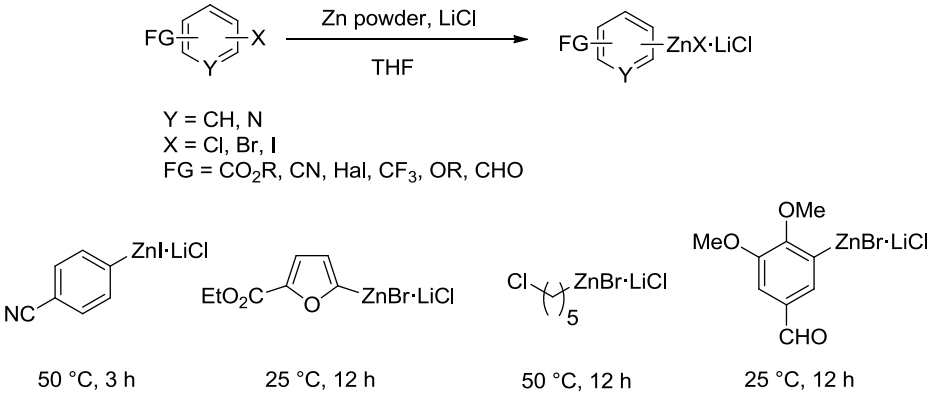
Recently, *Knochel* and coworkers reported a convenient methodology for the generation of aryl and heteroaryl magnesium and zinc organometallics from aryl and heteroaryl halides by a direct metal insertion in the presence of LiCl (Scheme 4, Scheme 5).[14]

[10] a) H. M. Walborksy, *Acc. Chem. Res.* **1990**, *23*, 286. b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95. c) J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004**, *248*, 623.
[11] W. Schlenk, W. Jr. Schlenk, *Chem. Ber.* **1929**, *62*, 920.
[12] a) R. D. Rieke, L.-C. Chao, *Syn. React. Inorg. Metal-Org. Chem.* **1974**, *4*, 101. b) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301. c) R. D. Rieke, *Science* **1989**, *246*, 1260. d) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445. e) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925. f) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R.Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.
[13] C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springer, Berlin, Heidelberg, New York, **1993**, p. 1.
[14] Zn reagents: 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. Mg reagents: d) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. e) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

This salt plays an important role in improving reaction kinetics. Firstly, it solubilizes the resulting organomagnesium compound and thus facilitates the formation of a clean metal surface. Secondly, the highly ionic character of LiCl solutions facilitates charge separation and accelerates the metal insertion.[15] This new approach allows more for selective reactions which proceeds under mild conditions.



Scheme 4: Selected examples of LiCl promoted Mg insertion.



Scheme 5: Selected examples of LiCl promoted Zn insertion.

1.1.2. Halogen-Metal Exchange Reactions

The direct oxidative addition of magnesium is a common procedure for the preparation of organomagnesium compounds. However, this approach possesses several drawbacks: metal reactivity can lead to the reduction of electrophilic functional groups and can cause exothermic reactions. These limitations can be considerably reduced by using a halogen-metal exchange reaction.

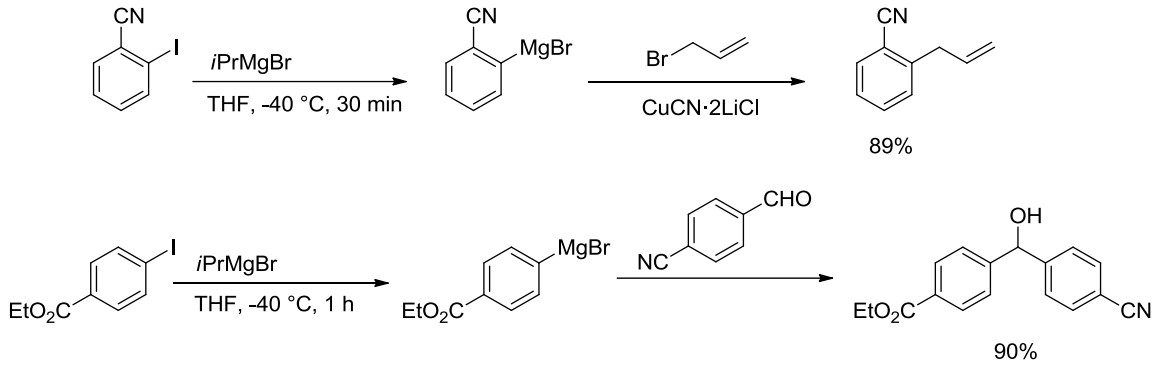
[15] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, **2003**, p. 46.

The first examples of this approach were briefly reported by *Prévost*[16] in 1931 and *Urion*[17] in 1934. The driving force for the halogen-metal exchange reaction is the formation of the more stable organometallic species (sp > sp^2(alkenyl) > sp^2(aryl) > sp^3(prim) > sp^3(sec)). In 1971, *Tamborski* demonstrated the essential role of the electronic properties of both the halogen atom and the organic molecule in the formation rate of the new Grignard reagent.[18] The reactivity order (I > Br > Cl >> F) is also influenced by the halogen-carbon bond strength, by the electronegativity and polarizability of the halide.

The halogen-lithium exchange reaction discovered by *Wittig*[19] and *Gilman*[20] allows the preparation of a broad range of organolithium derivatives and has become of great importance for the preparation of aromatic and heteroaromatic compounds, using commercially available alkyllithium reagents and corresponding organic halides, mainly bromides and iodides.[21]

Although the reaction proceeded very fast, the main drawbacks of the use of lithium reagents are the very low temperature required and the moderate functional groups tolerance. In contrast, the halogen-magnesium exchange turns out to be a very efficient method for the preparation of new functionalized reagents of great synthetic utility.[22]

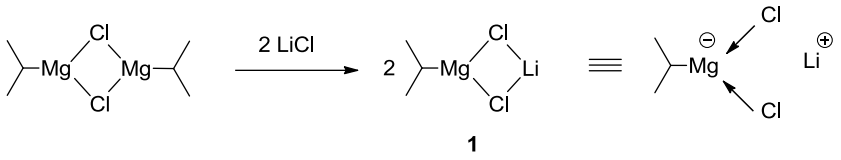
In 1998, *Knochel* reported remarkable examples of iodine-magnesium exchange reactions at low temperatures with excellent functional group tolerance to prepare various functionalized aromatic *Grignard* reagents (Scheme 6).[23]



Scheme 6: Preparation of polyfunctional *Grignard* reagents starting from aryl iodides.

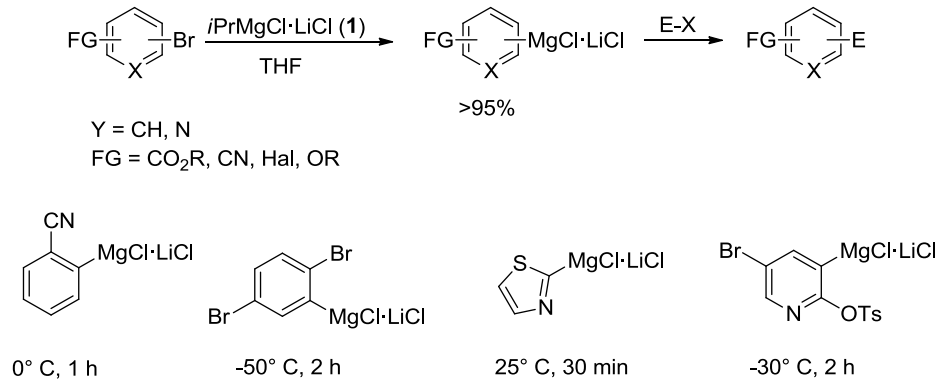
[16] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[17] E. Urion, *Comp. Rend. Acad. Sci. Paris* **1934**, *198*, 1244.
[18] C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153.
[19] G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903.
[20] a) R. G. Jones, H. Gilman, *Org. Reactions* **1951**, *6*, 339.
[21] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187. b) W. E. Parham, L. D. Jones, Y. Sayed, *J. Org. Chem.* **1975**, *40*, 2394. c) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704. d) W. E. Parham, D. W. Boykin, *J. Org. Chem.* **1977**, *42*, 260. e) W. E. Parham, D. W. Boykin, *J. Org. Chem.* **1977**, *42*, 257. f) C. E. Tucker,T. N. Majid, P. Knochel, *J. Am. Chem. Soc*. **1992**, *114*, 3983.
[22] For a review on functionalized organomagnesium reagents see: P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed*. **2003**, *42*, 4302.
[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.

However, several unactivated, electron rich aryl bromides show low conversion at ambient temperature. To overcome this problem, *Knochel* developed the reagent *i*PrMgCl·LiCl (**1**) to improve the bromine-magnesium exchange by adding a stochiometric amount of LiCl, which dramatically enhances the reactivity of the Grignard reagent by the formation of magnesium-lithium ate complexes (Scheme 7). [24]



Scheme 7: Effect of LiCl on *Grignard* reagent *i*PrMgCl.

A tremendous variety of aromatic and heteroaromatic bromides were converted into the corresponding organo magnesium reagents and can subsequently be quenched by electrophiles (Scheme 8).[25]



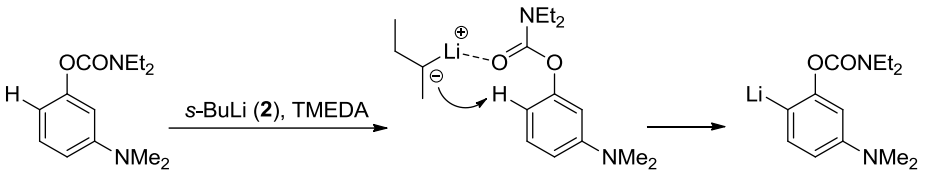
Scheme 8: LiCl-mediated bromine-magnesium exchange of various aryl and heteroaryl bromides.

1.1.3. Directed Metalation

The third major way to generate organometallic compounds is the directed metalation of a C-H bond using alkyl metals or metal amide bases. In contrast to insertion and exchange reactions, in this method there is no need for a halogen-carbon bond. The first deprotonation reaction with an organometallic involved the reaction between fluorene and EtLi reported by

[24] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[25] a) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159. b) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726. c) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543. d) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

Schlenk in 1928.[26] A few years later, *Gilman* and *Bebb*[27] and *Wittig* and *Fuhrmann*[28] discovered the example of anisole *ortho* deprotonation by *n*-BuLi. This concept of directed *ortho*-metalation (D*o*M), which describes the regioselective functionalization of aromatic systems in the presence of a directing metalation group (DMG), developed quickly into a new conceptual framework in synthetic aromatic chemistry. The most valuable work to expand the scope, introduce new DMG´s and characterize their reactivity was done by the groups of *Hauser*,[29] as well as by *Snieckus*.[30] The DMG is typically a Lewis basic moiety that interacts with the Lewis acidic metal cation allowing deprotonation in *ortho*-position to the directing group (Scheme 9). For instance, amides, carbamides, sulfonamides, esters, cyanide, sulfoxides and sulfones are considered to be efficient directing groups in contrast to ethers or amines, which are poor directing groups.



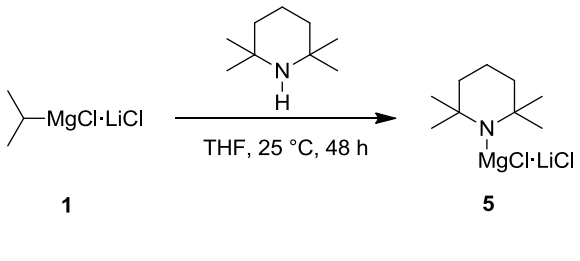
Scheme 9: Regioselective lithiation *ortho* to a carbamate.

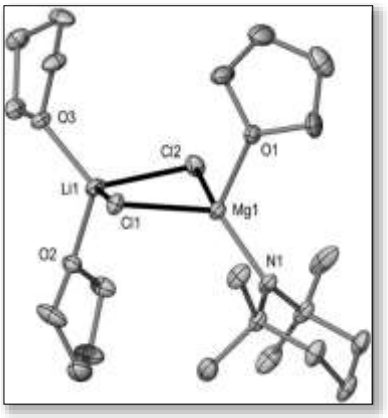
Traditionally, strong bases such as alkyllithium reagents like *s*-BuLi (**2**) or PhLi have been extensively used for these kinds of metalations. Additionally, non-nucleophilic, sterically hindered lithium bases (R_2NLi) such as lithium diisopropylamide (**3**: LDA) or TMPLi (**4**: TMP = 2,2,6,6-tetramethylpiperidyl) found broad applications. However, such bases can cause complications since they often lead to undesired side reactions due to their high reactivity, strong nucleophilicity (e.g. *Chichibabin* addition[31]) and low functional group tolerance. Therefore such deprotonation reactions have to be carried out at very low temperatures (-100 °C to -78 °C).

[26] W. Schlenk, E. Bergmann, *Ann. Chem.* **1928**, *463*, 98.
[27] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109.
[28] G. Wittig, G. Fuhrmann, *Chem. Ber.* **1940**, *73*, 1197.
[29] a) W. H. Puterbaugh, C.R. Hauser, *J. Org. Chem.* **1964**, *29*, 853. b) D. W. Slocum, D. I. Sugarman, *Adv. Chem. Ser.* **1974**, *130*, 227.
[30] a) V. Snieckus, *Pure & Appl. Chem.* **1990**, *62*, 2047. b) T. K. Macklin, J. Panteleev, V. Snieckus, *Angew. Chem. Int. Ed.* **2008**, *47*, 2097.
[31] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Burlington, **2005**, p. 80.

Alternatively, the use of milder magnesium amide bases is generally preferred when dealing with more sensitive functional groups. Based on *Meunier*'s original discoveries,[32] *Hauser*[33] reported the use of diethyl- and diisopropylaminomagnesium bromide, whereas *Eaton* and later *Mulzer* used the more sterically demanding bases TMPMgX and TMP_2Mg.[34] However, these magnesium amides suffer from low solubility and low kinetic basicity due to the aggregation and a large excesses of both base and electrophile is needed to overcome these limitations.[35]

A significant improvement for this approach was achieved by the findings of the *Knochel* group, showing that the addition of stoichomeric amounts of LiCl, deaggregates the amide bases to create bimetallic species with the general formula $R_2NMgCl{\cdot}LiCl$.[36] These reagents and especially TMPMgCl·LiCl (**5**) show high solubility in THF, increased reactivity and additionally, offer long term stability under inert atmosophere at room temperature. An explanation for this behaviour was proposed by studies from *Mulvey* in which TMPMgCl·LiCl (**5**) was crystalized as a monomeric species (Scheme 10).[37] Although the reacting structure may be different from the crystal and the structure in solution.[38]

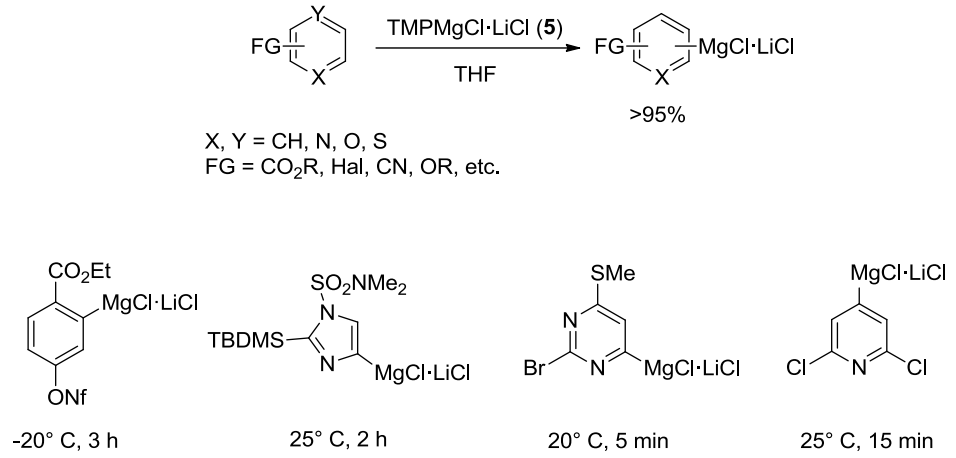




Scheme 10: Preparation and crystal structure of TMPMgCl·LiCl (**5**).

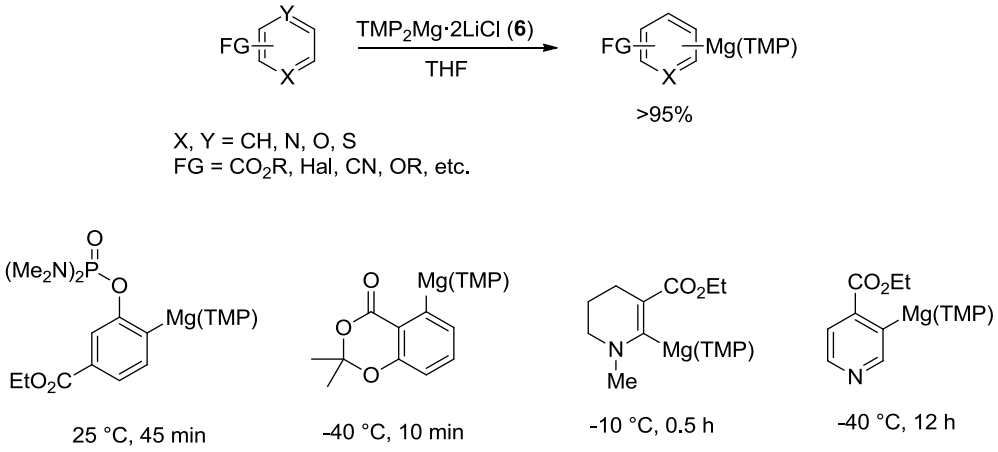
[32] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[33] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295. b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[34] a) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016. b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[35] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.
[36] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[37] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[38] R. Neufeld, D. Stalke, *Chem. Eur. J.* **2016**, *22*, DOI: 10.1002/chem.201601494.

The excellent kinetic basicity and broad functional group tolerance makes TMPMgCl·LiCl (**5**) suitable for deprotonation of various activated aromatics, heterocyclic and aliphatic coumpounds in a highly regio- and chemoselective manner (Scheme 11).[39]



Scheme 11: Magnesiation of various aromatic and hetero-aromatic substrates by using TMPMgCl·LiCl (**5**).

The concept was expanded by the development of magnesium bis amide bases, such as $TMP_2Mg·2LiCl$ (**6**) in order to deprotonate moderately activated aromatic and heteroaromatic compounds (Scheme 12).[40]

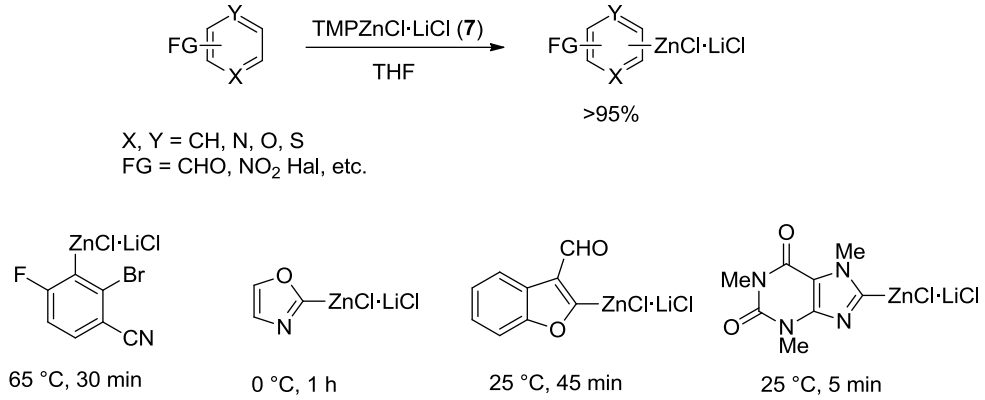


Scheme 12: Magnesiation of various aromatic, hetero-aromatic and non-aromatic substrates by using $TMP_2Mg·2LiCl$ (**6**).

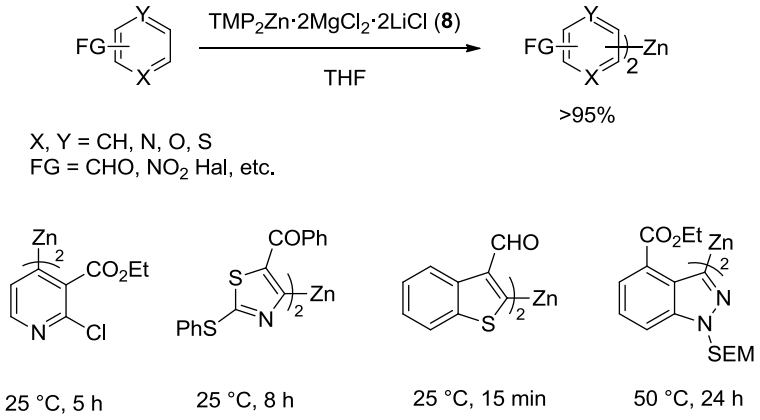
Despite the excellent reactivity of these magnesium bases and their high tolerance toward nitriles, esters, and aryl ketones, there are still numerous functional groups, that are not compatible with TMPMgCl·LiCl (**5**) or $TMP_2Mg·2LiCl$ (**6**).

[39] For a review see: T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem*. **2014**, *79*, 4253.
[40] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503. c) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374.

For example, molecules bearing an aldehyde or nitro group, as well as very electron poor heterocycles do not undergo directed magnesiations due to degradation. By transmetalation of TMPLi (**4**) or TMPMgCl·LiCl (**5**) with $ZnCl_2$, the milder zinc amides TMPZnCl·LiCl[41] (**7**) and $TMP_2Zn·2MgCl_2·2LiCl$[42] (**8**), respectively, can be readily prepared. These bases can be used for the mild zincation of a variety of sensitive substrates (Scheme 13, Scheme 14).



Scheme 13: Zincation of various functionalized aromatic compounds using TMPZnCl·LiCl (**7**).



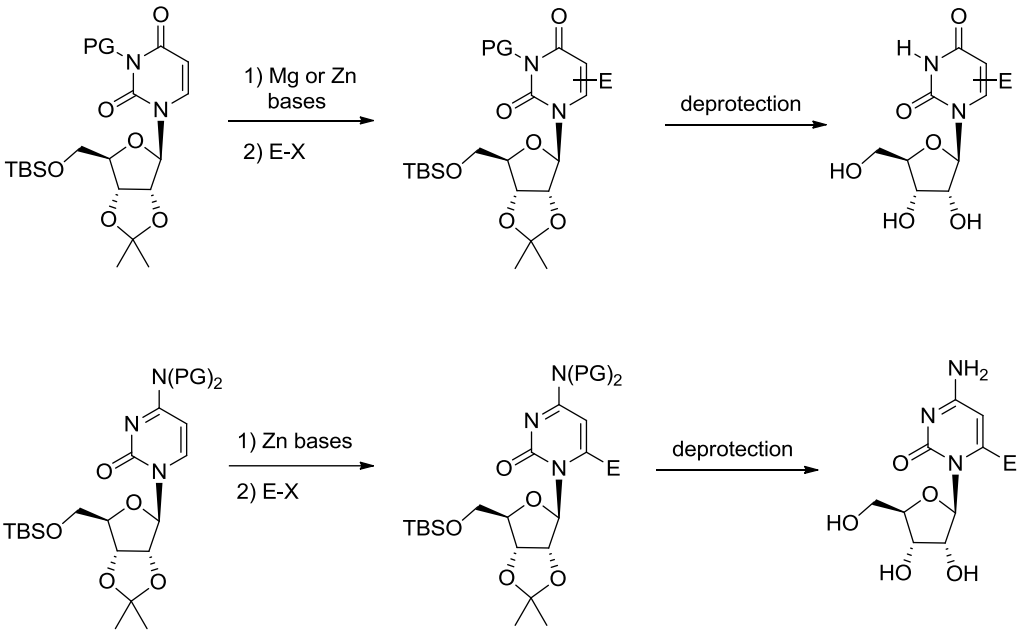
Scheme 14: Zincation of various sensitive heterocycles using $TMP_2Zn·2MgCl_2·2LiCl$ (**8**).

[41] a) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584. b) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914. c) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. d) D. Haas, M. Mosrin, P. Knochel, *Org. Lett.* **2013**, *15*, 6162.

[42] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705. b) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468. c) M. Kienle, C. Dunst, P. Knochel, *Org. Lett.* **2009**, *11*, 5158. d) A. Unsinn, P. Knochel, *Chem. Commun.* **2012**, *48*, 2680.

1.2. Objectives

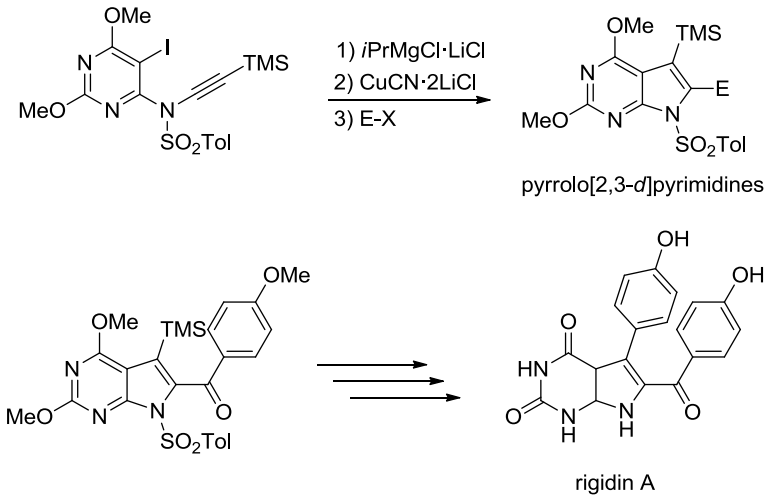
The aim of the first project was the development of a regioselective metalation of uracil, uridine and cytidine in positions C(5) and C(6) by Mg- and Zn-organometallics. The addition of Lewis acids as additives should trigger either kinetic or thermodynamic deprotonation. Subsequent quenching with various electrophiles and removal of the attached protecting groups should enable the acces to several functionalized heterocycles (Scheme 15).



Scheme 15: Regioselective functionalization of uridine and cytidine.

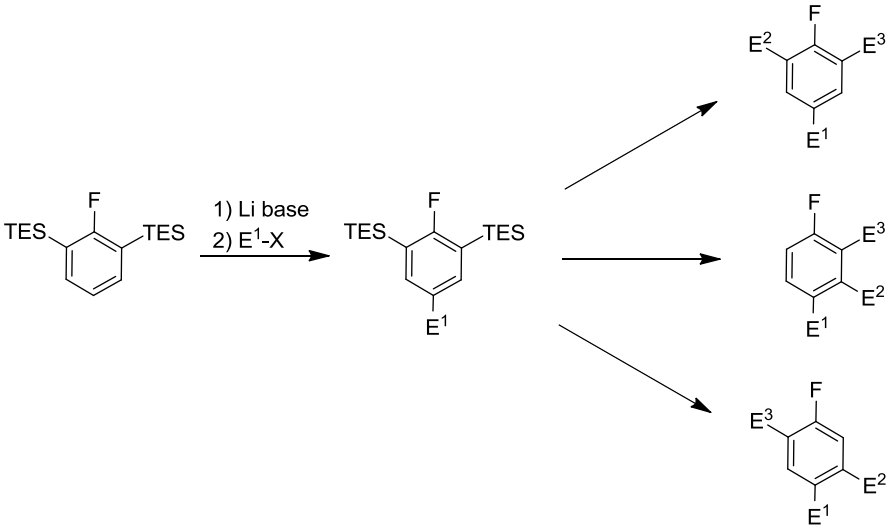
In a second project, the synthetic method for the preparation of functionalized highly diversified indoles as well as azaindoles[43] developed by *Frischmuth* and *Knochel*, will be applied for the preparation of pyrrolo[2,3-*d*]pyrimidines in order to create a novel synthetic route to the marine alkaloid rigidin A.[44] Starting from functionalized iodo-ynamides an iodine-magnesium exchange reaction is proposed to be carried out, followed by a copper-mediated ring closing reaction. Subsequent allylation or acylation reactions will allow to explore the scope of the methodology affording highly functionalized pyrrolo[2,3-*d*]pyrimidines and provide a fast access to the desired natural product (Scheme ***16***).

[43] A. Frischmuth, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10084.
[44] a) R. Scott, A. Kornienko, *ChemMedChem* **2014**, *9*, 1428. b) R. A. Davis, L. V. Christensen, A. D. Richardson, R. M. da Rocha, C. M. Ireland, *Mar. Drugs* **2003**, *1*, 27. c) M. Tsuda, K. Nozawa, K. Shimbo, J. Kobayashi, *J. Nat. Prod.* **2003**, *66*, 292.



Scheme 16: Preparation pyrrolo[2,3-*d*]pyrimidines *via* copper-mediated carbomagnesiation of ynamides leads to natural product rigidin A.

Furthermore, a new synthetic protocol for regioselective metalations of fluorobenzenes that bear sterically hindered, but removable silyl groups was developed to furnish unusual *para*-substituted aromatic compounds. Subsequent desilylation and regioselective functionalization with common organometallics should afford various tetrasubstituted fuorobenzene derivatives (Scheme 17).



Scheme 17: Metalation of fluorobenzenes in *para*-position and further desilylation and functionalization.

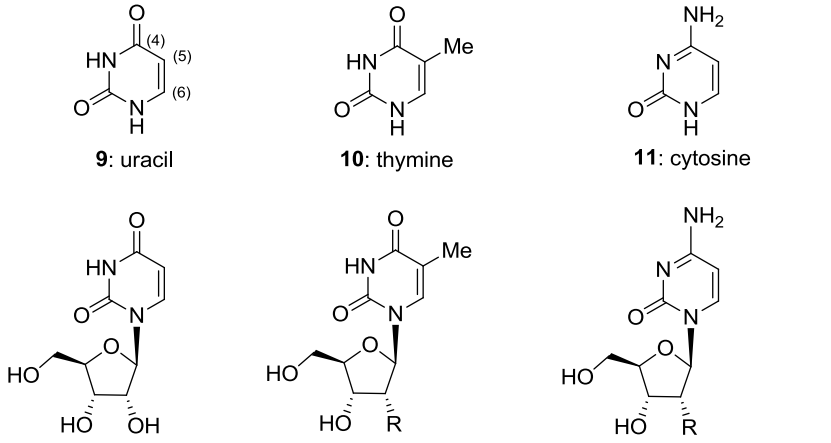
B. RESULTS & DISCUSSION

1. METALATION AND DEPROTECTION OF URACILS, URIDINES AND CYTIDINES

1.1. General Introduction

1.1.1. DNA Bases and Natural Products

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are two of the most crucial molecules in nature and occurs in every cell of the human body and as well as almost all other organisms.[45] DNA carries the genetic information and is essential for the growth, development, functioning and reproduction of cells. DNA is structured in two strands called polynucleotides, each consisting of a chain of simpler units (nucleotides). Each nucleotide is composed of a nucleoside and a phosphate moiety. A nucleoside simply consists of a nucleobase and a five-carbon sugar (either ribose or deoxyribose). Some pyrimidine nucleobases that are relevant for this current work (uracil (**9**), thymine (**10**), cytosine (**11**)) and the corresponding nucleosides (uridine (**12**), thymidine (**13b**), cytidine (**14b**)) are displayed in Scheme 18.

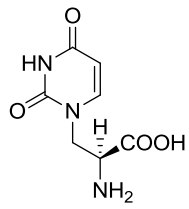


Scheme 18: Pyrimidine nucleobases uracil, thymine, cytosine and their nucleosides uridine, desoxythymidine, desoxycytidine and cytidine.

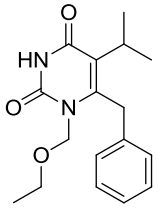
[45] L. Stryer in *Biochemie*, (Eds.: J. M. Berg, J. L. Tymoczko, L. Stryer), Springer Spektrum, Berlin, Heidelberg, **2013**, p. 110.

Furthermore, the pyrimidine scaffold can be found in numerous natural products.[46] The uracilylalanine willardiine is an example of a non-proteogenic amino acid and was first isolated from seeds of *Acacia willardiana* by *Gmelin* in 1959 (Scheme 19).[47]

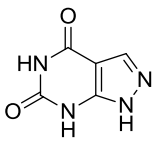
In recent years, several pathways for the synthesis of analogues of emivirine were developed. It belongs to the non-nucleoside reverse transcriptase inhibitors (NNRTIs)[48] and targets the retrovirus HIV-1. The xanthine oxidase inhibitor oxypurinol[49] is an active metabolite of the drug allopurinol and can be used for the treatment of hyperuricemia and gout. Moreover, the scaffold is present in larger biomolecules such as the peptide family penilumamide,[50] isolated from *Penicillum* in 2010.



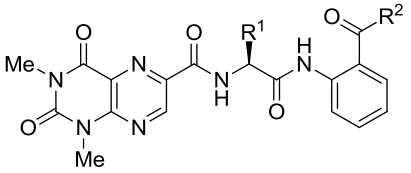
willardiine



emivirine



oxypurinol



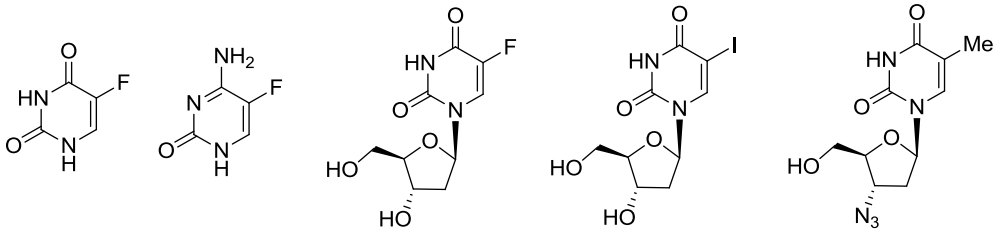
	R^1	R^2
penilumamide:	C_2H_4SOMe	OMe
penilumamide B:	C_2H_4SMe	OMe
penilumamide C:	$C_2H_4SO_2Me$	OMe
penilumamide D:	Me	NH_2

Scheme 19: Natural products containing the uracil scaffold.

Moreover, pyrimidine nucleobases represent important molecules in pharmaceutical applications[51] as they display antibiotic, antifungal, anticancer and antiviral activity.[52] To briefly mention, 5-fluorocytosine (flucytosine) has antimycotic activity, while 5-fluorouracil (adrucil) and 5-fluorodesoxyuridine (floxuridine) are clinically established anticancer drugs (Scheme 20).

[46] I. M. Lagoja, *Chem. Biodiversity* **2005**, *2*, 1.
[47] a) I. Virtanen, R. Gmelin, *Acta. Chem. Scand.* **1959**, *13*, 1244. b) T. S. Ashworth, E. G. Brown, F. M. Roberts, *Biochem. J.* **1972**, *129*, 897.
[48] a) H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, N. Inouye, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq, T. Miyasaka, *J. Med. Chem*. **1995**, *38*, 2860. b) O. S. Pedersen, E. B. Pedersen, *Antiviral Chem. Chemother*. **1999**, *10*, 2860.
[49] T. Nagamatsu, T. Fujita, K. Endo, *J. Chem. Soc., Perkin Trans. 1*. **2000**, 33.
[50] a) S. W. Meyer, T. F. Mordhorst, C. Lee, P. R. Jensen, W. Fenical, M. Köck, *Org. Biomol. Chem.* **2010**, *8*, 2158. b) M. Chen, C. L. Shao, X. M. Fu, C. J. Kong, Z. G. She, C. Y. Wang. *J. Nat. Prod.* **2014**, *77*, 1601.
[51] *Science of Synthesis, Six-Membered Hetarenes with Two Identical Heteroatoms* (Ed. Y. Yammamoto), Georg Thieme Verlag, **2004**, p. 379.
[52] *Heterocyclic Chemistry, Vol. 5* (Eds.: J. A. Joule, K. Mills), John Wiley & Sons, West Sussex, **2010**, p. 645.

Furthermore, various antiviral agents are based on functionalized nucleosides including both modifications at the sugar moiety or heterocyclic system. For example, idoxuridine displays activity against hepatitis or zidovudine (AZT) acts as an anti-HIV protease inhibitor.[52]



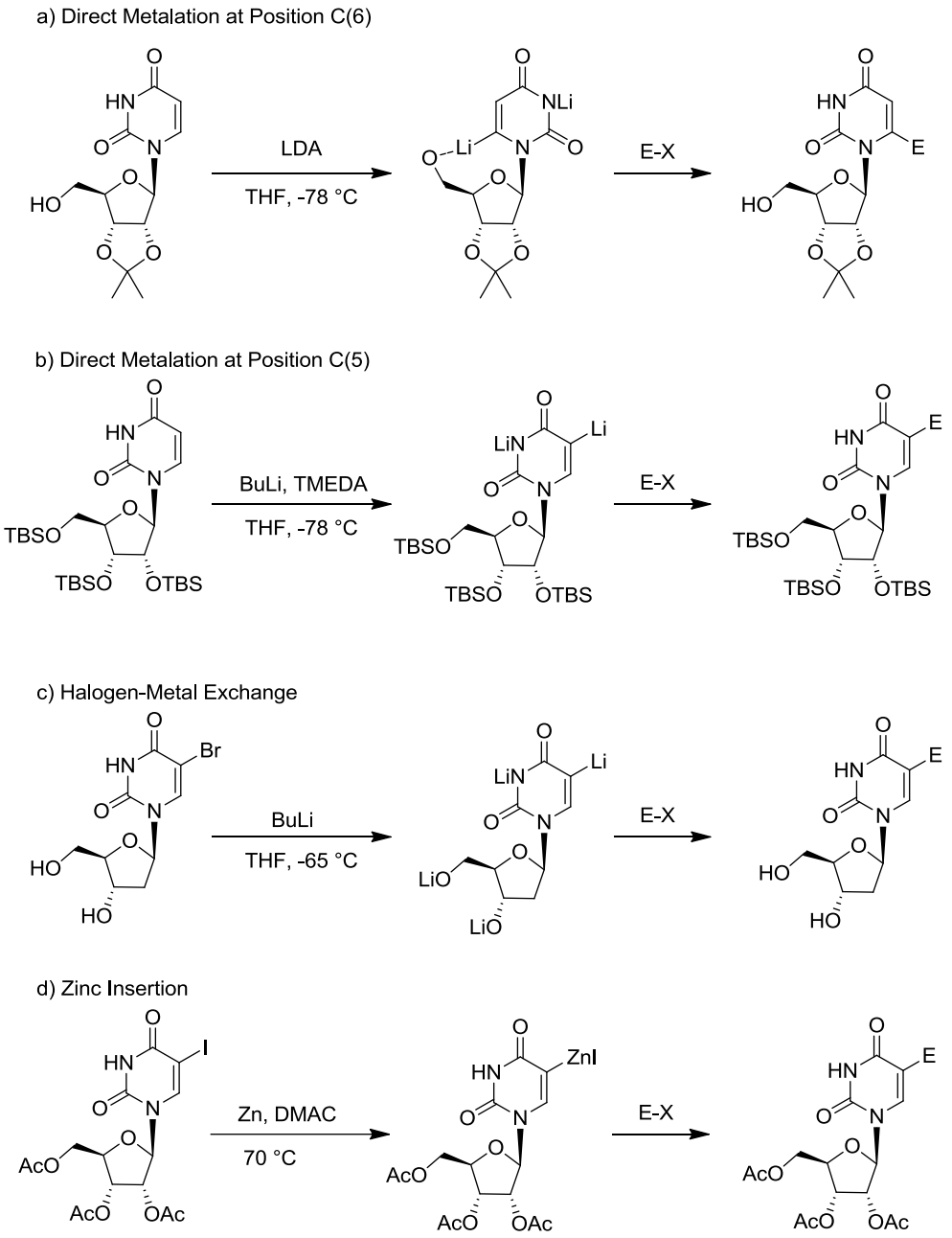
Scheme 20: Functionalized uracils and uridines with pharmaceutical application.

1.1.2. Current State of the Art for the Metalation of Uracils and Uridines

As uridine derivatives are an important pharmaceutical core structure, the functionalization of their heterocyclic system is of essential synthetic interest and has been studied thoroughly in the literature.[53]

Direct metalation of uridine **12** using lithium bases was developed at the C(5)- and C(6)-positions by the group of *Miyasaka* (Scheme 21).[54,55] The regioselectivity of the direct lithiation was proposed to be depending on the coordination effect of the hydroxylgroup at position C´(5) of the sugar moiety. The free hydroxyl group was able to direct the metalation to position C(6) by coordination of the LDA base. In contrast, introduction of a bulky silyl protecting group suppressed the coordination and the metalation occured at the more activated C(5)-position. As a result, uridine was metalated in a very selective manner. However, the use of highly reactive lithium bases allowed only a limited choice of electrophiles and lead to moderate product yields. Furthermore, functionalization of protected uridine was achieved by halogen-metal exchange[56] or zinc insertion[57] and subsequent reactions with electrophiles, but the products were obtained only in poor or mediocre yields.

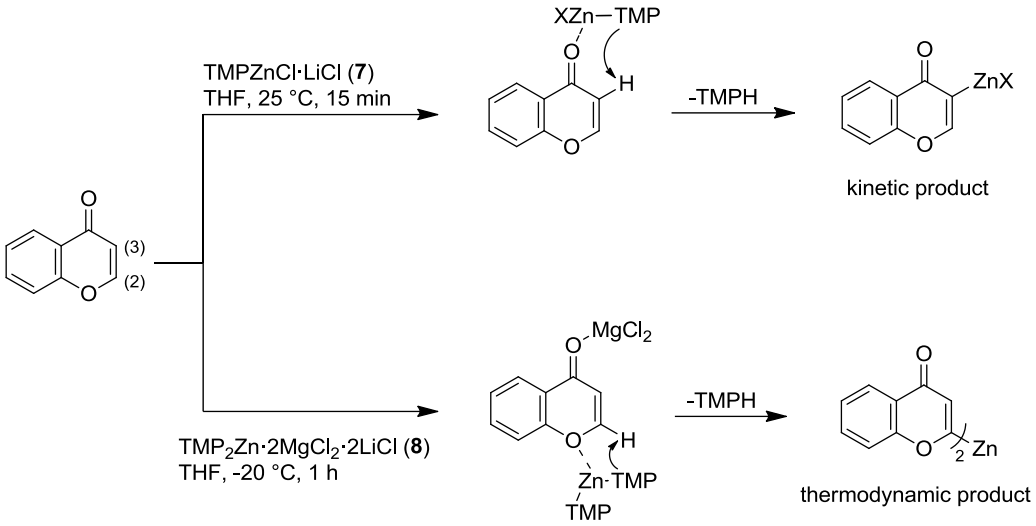
[53] *Comprehensive Heterocyclic Chemistry III*, *Pyridazines and their Benzo Derivatives* (Eds.: R. K. Alan, A. R. Christopher, F. V. S. Eric, J. K. T. Richard), Elsevier, Oxford, **2008**, p. 1.
[54] a) H. Tanaka, I. Nasu, T. Miyasaka, *Tetrahedron Lett*. **1979**, *20*, 4755. b) H. Tanaka, H. Hayakawa, T. Hiyasaka, *Tetrahedron* **1982**, *38*, 2635. c) M. Shimizu, H. Tanaka, H. Hayakawa, T. Miyasaka, *Tetrahedron Lett*. **1990**, *31*, 1295.
[55] a) H. Hayakawa, H. Tanaka, K. Obi, M. Itoh, T. Miyasaka. *Tetrahedron Lett.* **1987**, *28*, 87. b) M. Shimizu, H. Tanaka, H. Hayakawa, T. Miyasaka, *Tetrahedron Lett.* **1990**, *31*, 1295.
[56] T. L. V. Ulbricht, *Tetrahedron* **1959**, *6*, 225.
[57] a) T. M. Stevenson, B. A. S. Prasad, J. R. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375. b) B. A. S. Prasad, T. M. Stevenson, J. R. Citineni, V. Nyzam, P. Knochel, *Tetrahedron* **1997**, *53*, 7237.



Scheme 21: Reported examples of the metalation of uridine.

1.1.3. General Concept: Metalation in the Presence of Two Directing Groups

The group of *Knochel* developed a new procedure for the regioselective metalation of chromones (Scheme 22).[41a] This scaffold containes two different directing groups, the vinyl-ethereal oxygen and the carbonyl oxygen, which are next to two acidic protons in C(2)- and C(3)-position, respectively.



Scheme 22*:* Regioselective metalation of chromone in position C(2) or C(3) depending on the presence of the Lewis acid $MgCl_2$.

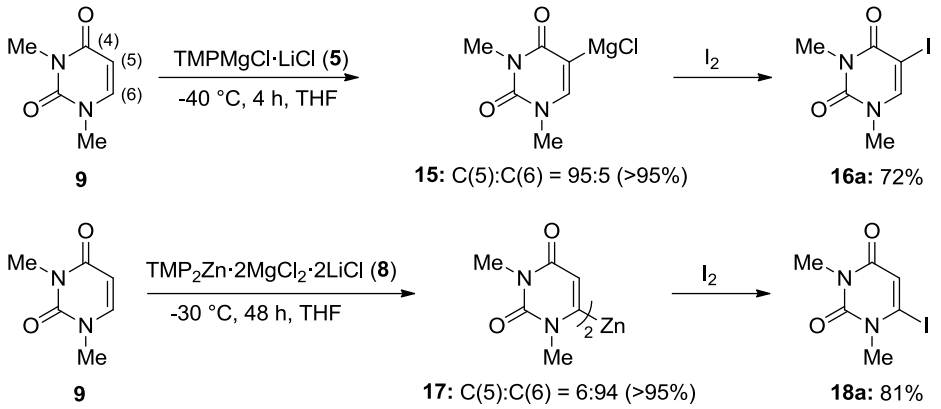
The carbonyl group served as the stronger directing group, lead to the coordination of the TMPZnCl·LiCl base (**7**) at the carbonyl oxygen and directed the metalation in position C(3) to furnish the kinetic product. However, in the presence of a stronger Lewis acid such as $MgCl_2$ the carbonyl coordination side was occupied and the metalation with the $TMP_2Zn·2MgCl_2·2LiCl$ base (**8**) was directed at the more acidic position C(2), which provided the thermodynamic product. Analogously, the concept could be applied for the metalation of the nucleobase uracil and the nucleosides uridine and cytidine.

1.2. Regioselective Metalation of Uracil

1.2.1. Optimized Metalation Conditions for Uracil

As it was anticipated, the concept of the metalation of chromones could be extended to uracil. First of all, the two lactam groups of the scaffold were protected at the nitrogen atoms. Hereby, methyl was choosen as a protecting group due to its small steric demand and the absence of additional coordination effects. Second of all, the optimized metalation conditions were developed by *Klier* and furnished the regioselectively functionalized C(5)- or C(6)-products (**16a**, **18a**) by quenching with iodine (Scheme 23).[58]

[58] Project was developed in cooperation with L. M. Klier (see: L. M. Klier, Dissertation, LMU-München, **2015**).

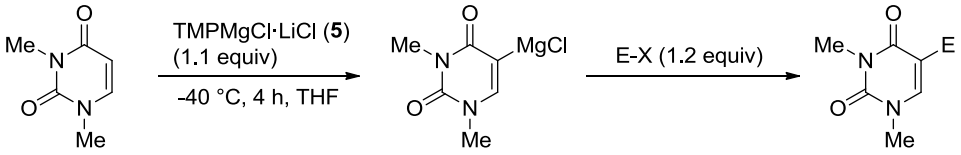


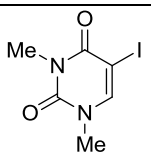
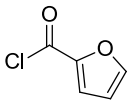
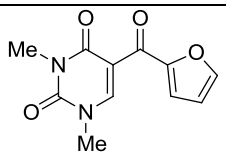
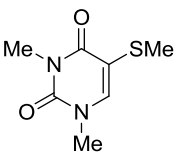
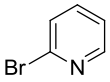
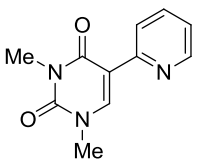
Scheme 23: Optimized metalation conditions for uracil.

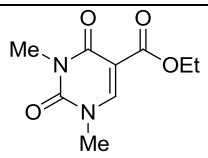
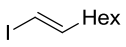
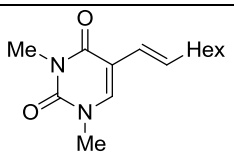
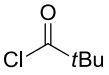
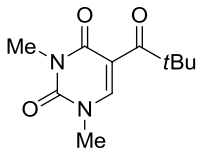
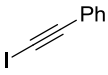
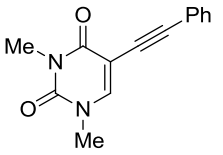
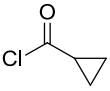
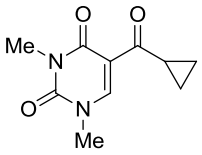
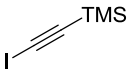
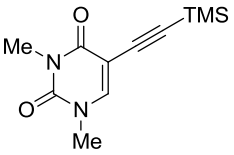
1.2.2. Uracil Reaction Scope

With the metalation conditions in hand, the scope of the reaction with different electrophiles was explored. Thus, methyl protected uracil **9** reacted with TMPMgCl·LiCl (**5**), lead to a regiospecific metalation at position C(5). Quenching with different electrophiles provided products **16a-j** in moderate to good yields (Table 1). Reaction of **15** with dimethyl disulfide afforded the thioether **16b** in 56% yield (entry 2), whereas reaction with ethyl chloroformate furnished the ester **16c** in 66% yield (entry 3).

Table 1: Metalation of 1,3-dimethyluracil in position C(5) and subsequent reactions with electrophiles.



Entry	Electrophile	Product/Yield[a]	Entry	Electrophile	Product/Yield[a]
1	I_2	 **16a:** 72%	6		 **16f:** 66%[b]
2	S_2Me_2	 **16b:** 56%	7		 **16g:** 48%[c,d]

3	$ClCO_2Et$	 **16c:** 66%	8		 **16h:** 79%[c,d]
4		 **16d:** 83%[b]	9		 **16i:** 54%[b]
5		 **16e:** 71%[b]	10		 **16j:** 74%[b]

[a] Isolated yield of analytically pure products. [b] CuCN·2LiCl was added. [c] $ZnCl_2$ was added. [d] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (2 mol%) and $P(2\text{-furyl})_3$ (4 mol%).

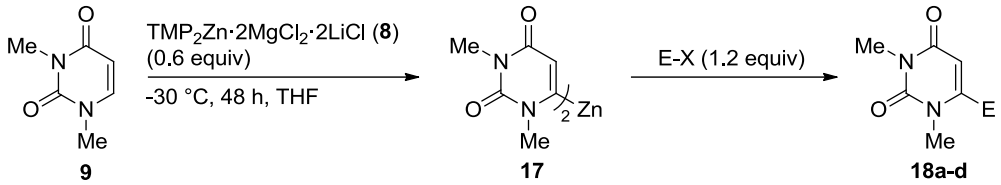
Transmetalation of **15** with CuCN·2LiCl and subsequent acylations with various acid chlorides provided aliphatic or hetero aromatic ketones **16d-f** in 66-83% yield (entries 4-6). Transmetalation of **15** with $ZnCl_2$ and subsequent Pd-catalyzed *Negishi*[59] cross-couplings (2 mol% $Pd(dba)_2$, 4 mol% $P(2\text{-furyl})_3$) with heteroaromatic or alkenyl halides gave the cross-coupling products **16g-h** (48-79%, entries 7-8). Additionally, Cu-catalyzed alkynylation[60] of **15** with CuCN·2LiCl and iodoacetylene derivatives afforded the highly functionalized acetylenes **16i-j** in 54-74% yield (entries 9-10).

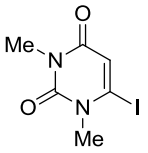
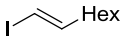
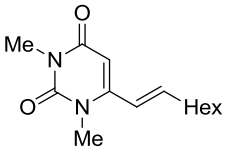
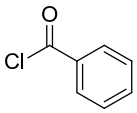
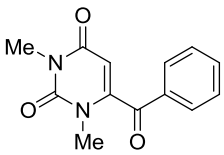
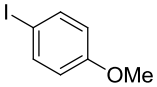
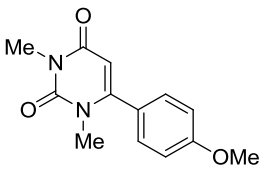
The reaction of methyl protected uracil **9** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**8**) at –30 °C provided the bis heterocyclic zinc reagent 1**7** allowing the direct functionalization at position C(6) (Table 2). Iodolysis of the zinc reagent **17** provided 6-iodouracil (**18a**) in 81% yield (entry 1). Similarly, copper-mediated acylation with benzoyl chloride afforded the C(6)-functionalized uracil derivative **18b** (84%, entry 2). Moreover, Pd-catalyzed *Negishi* cross-coupling (2 mol% $Pd(dba)_2$, 4 mol% $P(2\text{-furyl})_3$) with 1-iodooct-1-ene or 4-iodoanisole or furnished the expected C(6)-substituted uracils **18c** (74%, entry 3) and **18d** (84%, entry 4).

[59] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

[60] a) P. Knochel, N. Millot, A. L. Rodriguez, *Org. React.* **2001**, *58*, 417. b) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**, p. 1. c) M. C. P. Yeh, S. C. Berk, J. Talbert, P. Knochel, *J. Org. Chem.* **1988**, *53*, 2390.

Table 2: Metalation of 1,3-dimethyluracil in position C(6) and subsequent reactions with electrophiles.

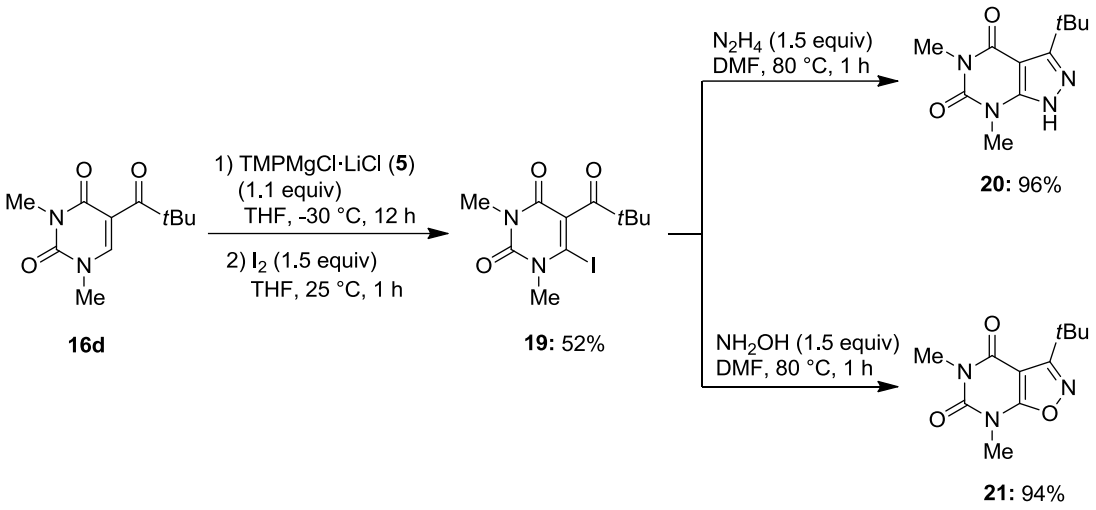


Entry	Electrophile	Product/Yield[a]	Entry	Electrophile	Product/Yield[a]
1	I_2	 **18a:** 81%	3		 **18c:** 74%[c]
2		 **18b:** 84%[b]	4		 **18d:** 84%[c]

[a] Isolated yield of analytically pure products. [b] CuCN·2LiCl was added. [c] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (2 mol%) and $P(2\text{-furyl})_3$ (4 mol%).

1.2.3. Preparation of 5,6-Disubstituted Uracil Derivatives

We further examined the prospect of a second metalation of a C(5)-substituted uracil derivative in order to prepare 5,6-disubstituted coumpounds. Metalation of halogen substituted or arylated uracils (**16a**, **16g**) using various TMP-bases and reaction temperatures gave limited results in terms of metalated species, as observed by TLC or ^{1}H-NMR of reaction aliquots quenched with iodine. However, it was observed that metalation was successful when the substituent at C(5) had a strong directing effect, for example the uracil **16d** containing a keto-group. The metalation of uracil **16d** with TMPMgCl·LiCl (**5**, -30 °C, 12 h) and subsequent iodolysis provided the disubstituted uracil **19** in moderate 52% yield (Scheme 24). Using this substrate two straight forward ring-closing reactions were performed when **19** was treated with hydrazine or hydroxylamine for 1 h at 80 °C in DMF to provide the pyrazole **20** and the isoxazole **21** in very good 94-96% yield.

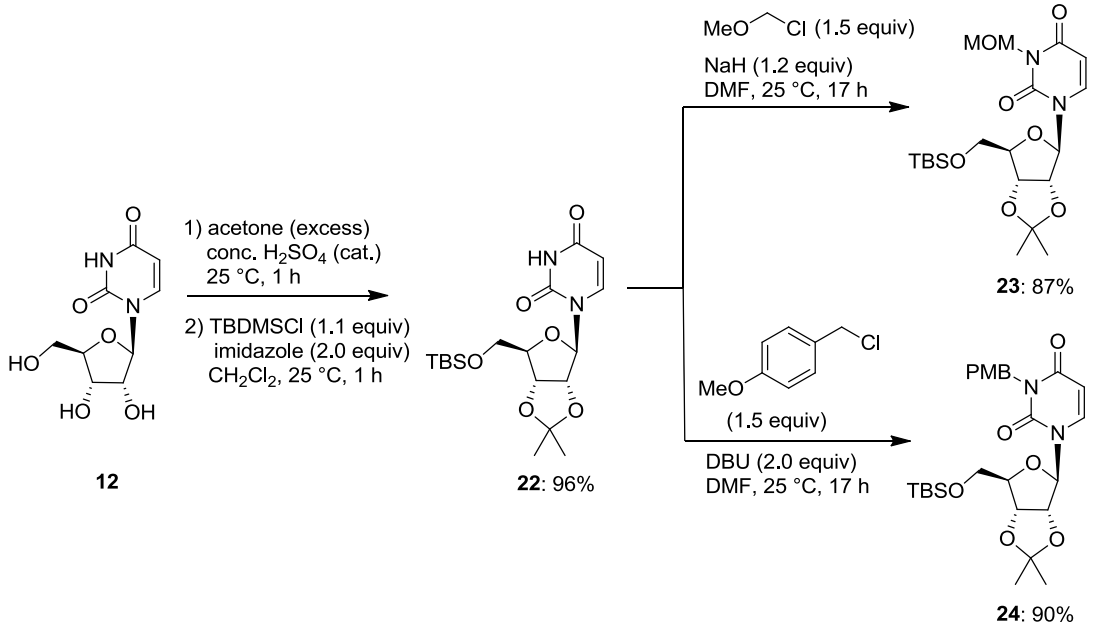


Scheme 24: Preparation of pyrazole and isoxazole derivatives **20** and **21**.

1.3. Regioselective Metalation of Uridine and Cytidine

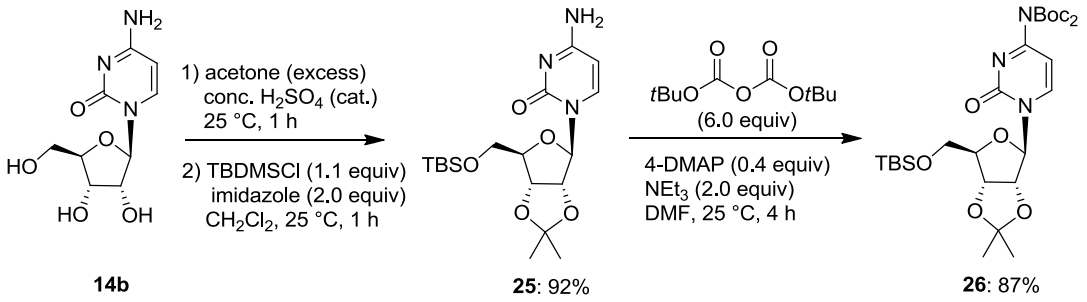
1.3.1. Protection of Uridine and Cytidine

First, the sugar moieties of the nucleosides uridine (**12**) and cytidine (**14b**) were protected in two straight forward steps. At the C'(3)- and C'(4)-hydroxy group an acetal moiety was introduced. Subsequent protection at the C'(5)-hydroxy group with a bulky TBDMS (*tert*-butyldimethylsilyl) group furnished the sugar protected uridine **22** or cytidine **25** in 92-96% yield (Scheme **25**, Scheme 26).



Scheme 25: Full protection of uridine (**12**).

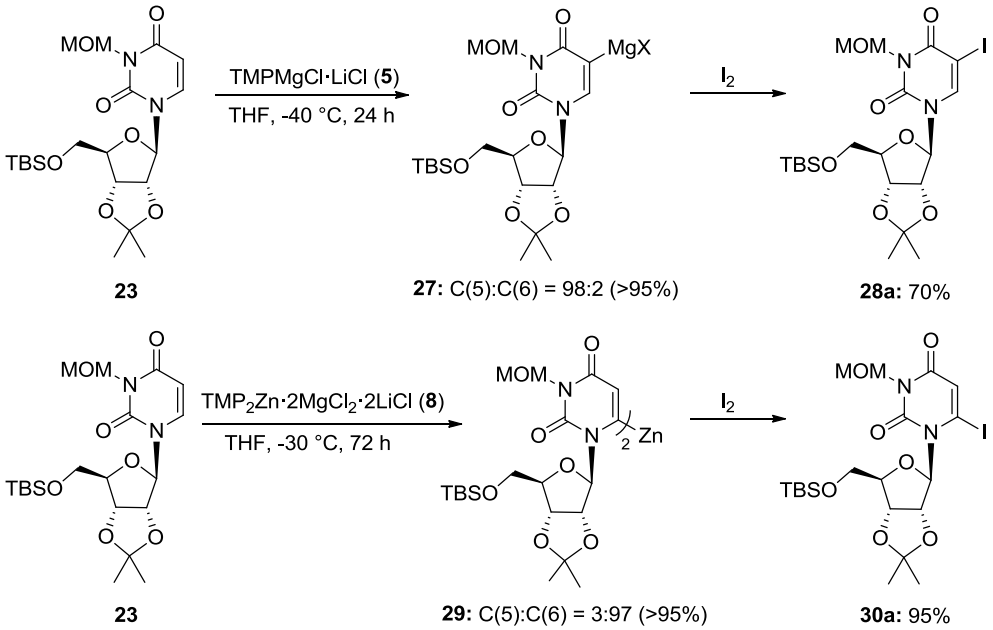
Second, the pyrimidine scaffold of uridine was protected with two different groups, furnishing the MOM(methoxymethyl)-protected uridine (**23**) or the PMB(4-methoxybenzyl ether)-protected uridine (**24**) in excellent yields (87-90%). Additionally, the amine function of the cytidine (**25**) was treated with an excess of di-*tert*-butyl dicarbonate (Boc_2O), providing the fully protected cytidine derivative (**26**, Scheme 26).[61]



Scheme 26: Full protection of cytidine (**14b**).

1.3.2. Optimization of the Reaction Conditions for Uridine Metalation

Analogous to the metalation of uracil, the concept was transfered for the functionalization of the uridine scaffold (**23**, **24**) in a regiospecific manner. Metalation of **23** with TMPMgCl·LiCl (**5**) yielded the C(5)-magnesiated intermediate **27** almost exclusively after 24 h, as confirmed by ^{1}H-NMR of the iodolysis product **28a** (Scheme 27).



Scheme 27: Optimized metalation conditions for uridine (**23**).

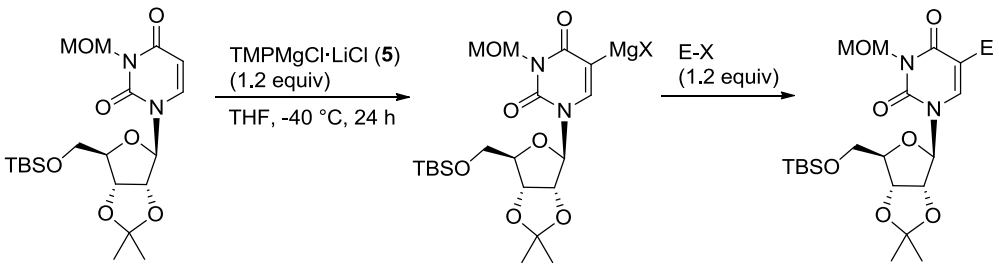
[61] S. He, H. Zhao, X. Guo, G. Xin, B. Huang, L. Ma, X. Zhou, R. Zhang, D. Du, X. Wu, Z. Xing, W. Huang, Q. Chen, Y. He, *Tetrahedron* **2013**, *69*, 9245.

Metalation of **23** with $TMP_2Zn \cdot 2LiCl \cdot 2MgCl_2$ (**8**) provided the C(6) zincated uridine **29** after 72 h. The regioselectivity of the metalation product was confirmed by ^{1}H-NMR of the iodolysis product **30a.**

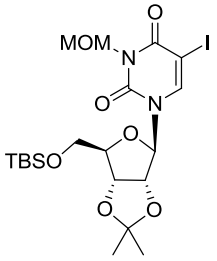
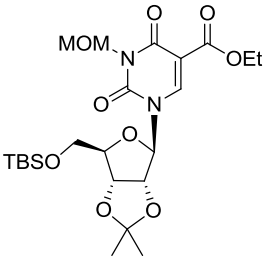
1.3.3. Functionalization of Protected Uridines

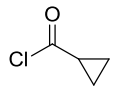
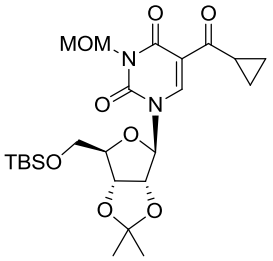
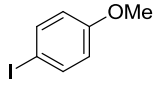
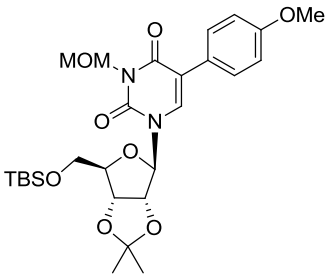
With the optimized metalation conditions in hand, various products of C(5)- and C(6)-functionalized uridines were prepared. Reaction of the C(5)-magnesiated uridine **27** with different electrophiles lead to products **28a-d** (Table 3).

Table 3: Metalation of MOM-protected uridine in position C(5) and subsequent reactions with electrophiles.



23 **27** **28a-d**

Entry	Electrophile	Product/Yield[a]
1	I_2	 **28a:** 70%
2	$ClCO_2Et$	 **28b:** 44%

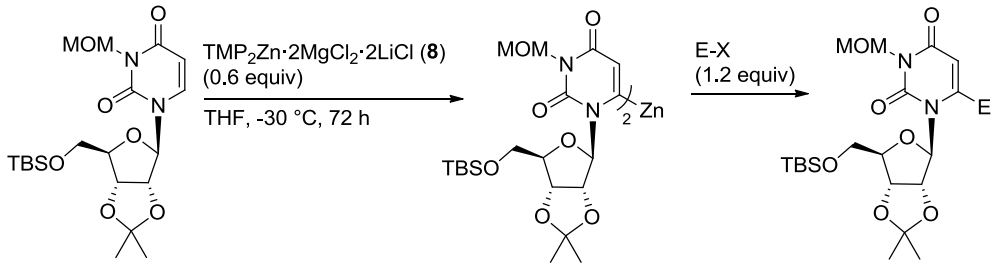
3		 **28c:** 71%[b]
4		 **28d:** 81%[c,d]

[a] Isolated yield of analytically pure products. [b] CuCN·2LiCl was added. [c] $ZnCl_2$ was added. [d] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (2 mol%) and $P(2\text{-furyl})_3$ (4 mol%).

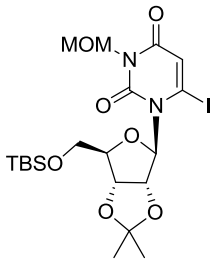
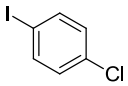
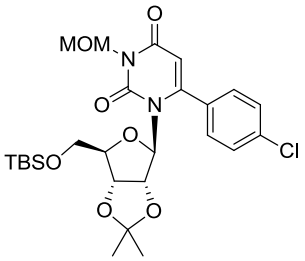
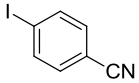
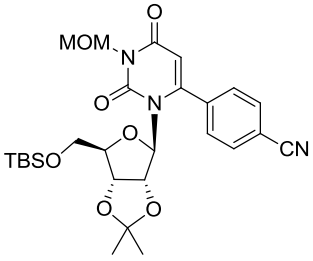
Thus, quenching with iodine or chloroformate furnished the C(5)-iodo derivative **28a** (70%, entry 1) and the ester **28b** (44%, entry 2), respectively. Moreover, copper-mediated acylation with cyclopropanecarbonyl chloride afforded the C(5)-functionalized uridine derivative **28c** in 71% yield (entry 3). Additionally, after transmetalation of **27** to zinc, Pd-catalyzed *Negishi* cross-coupling (2 mol% $Pd(dba)_2$, 4 mol% $P(2\text{-furyl})_3$) with 4-iodoanisole provided the product **28d** (81%, entry 4).

The metalation with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**8**) provided the C(6)-zincated uridine **29**, which was reacted with iodine to provide the C(6)-iodo derivative **30a** in 95% yield (Table 4, entry 1). Furthermore, Pd-catalyzed *Negishi* cross-coupling reactions (2 mol% $Pd(dba)_2$, 4 mol% $P(2\text{-furyl})_3$) with 1-chloro-4-iodobenzene or 4-iodobenzonitrile afforded the products **30b-c** in 69-84% yield (entries 2-3).

Table 4: Metalation of MOM-protected uridine in position C(6) and subsequent reactions with electrophiles.



23 **29** **30a-c**

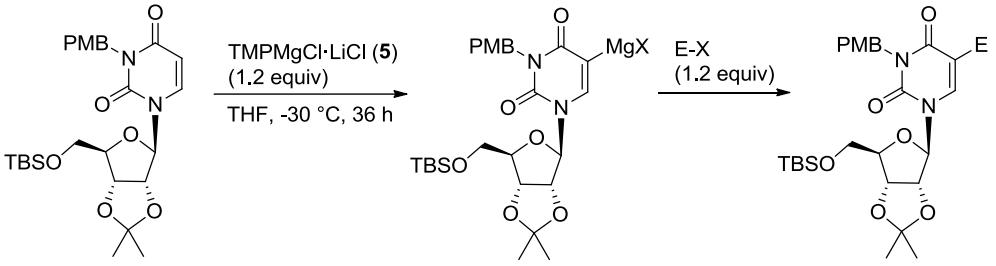
Entry	Electrophile	Product/Yield[a]
1	I_2	 **30a:** 95%
2		 **30b:** 84%[b]
3		 **30c:** 69%[b]

[a] Isolated yield of analytically pure products. [b] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (2 mol%) and $P(2\text{-furyl})_3$ (4 mol%).

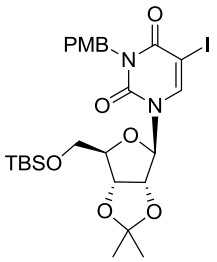
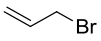
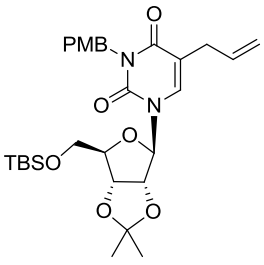
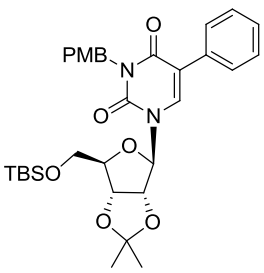
Similarly, a metalation method for the PMB-protected uridine **24** was developed and regioselective C(5)-magnesation provided the metalated species **31** at -30 °C in 36 h. Subsequent quenching with iodine afforded the C(5)-iodo derivative **32a** in 66% yield (Table ***5***, entry1). Compared to the MOM-protected iodo uridine **28a**, the reaction displayed similar yield, but extended reaction time for the metalation. Copper-mediated allylation with allyl

bromide afforded the C(5)-functionalized uridine derivative **32b** in 79% yield (entry 2) and transmetalation to the zinc species, followed by Pd-catalyzed cross-coupling reaction (2 mol% $Pd(dba)_2$, 4 mol% P(2-furyl)$_3$) with iodobenzene afforded the product **32c** in 72% yield (entry 3).

Table 5: Metalation of PMB-protected uridine in position C(5) and subsequent reactions with electrophiles.



24 **31** **32a-c**

Entry	Electrophile	Product/Yield[a]
1	I_2	 **32a:** 66%
2		 **32b:** 79%[b]
3		 **32c:** 72%[c,d]

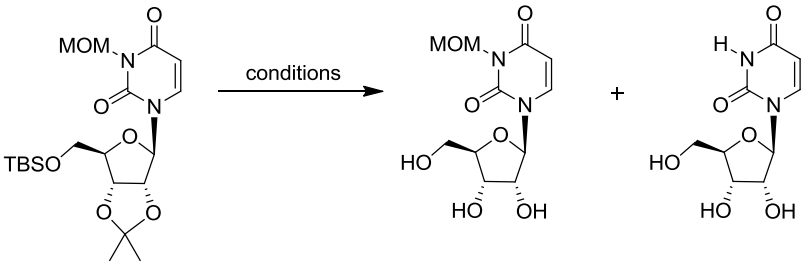
[a] Isolated yield of analytically pure products. [b] CuCN·2LiCl was added. [c] $ZnCl_2$ was added. [d] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (2 mol%) and P(2-furyl)$_3$ (4 mol%).

1.3.4. Deprotection of Uridine

In order to prepare compounds with potential biological interest, we investigated the removal of all protecting groups of the functionalized uridines of type **28** and **30**. Cleavage of the acetal group and the silyl ether has been accomplished under weakly acidic conditions.[62] However, the deprotection of *N*-MOM-protected amides could be only performed by using strong acids.[63]

Thus, different deprotecting conditions were tested on the unsubstituted uridine **23** (Table 6). First of all, a number of acidic conditions were examinated (entries 1-5) and showed, that the protecting groups on the sugar moiety were selectively cleaved to furnish uridine **33**.

Table 6: Screening of deprotection conditions for MOM-protected uridine.



23 **33** **34**

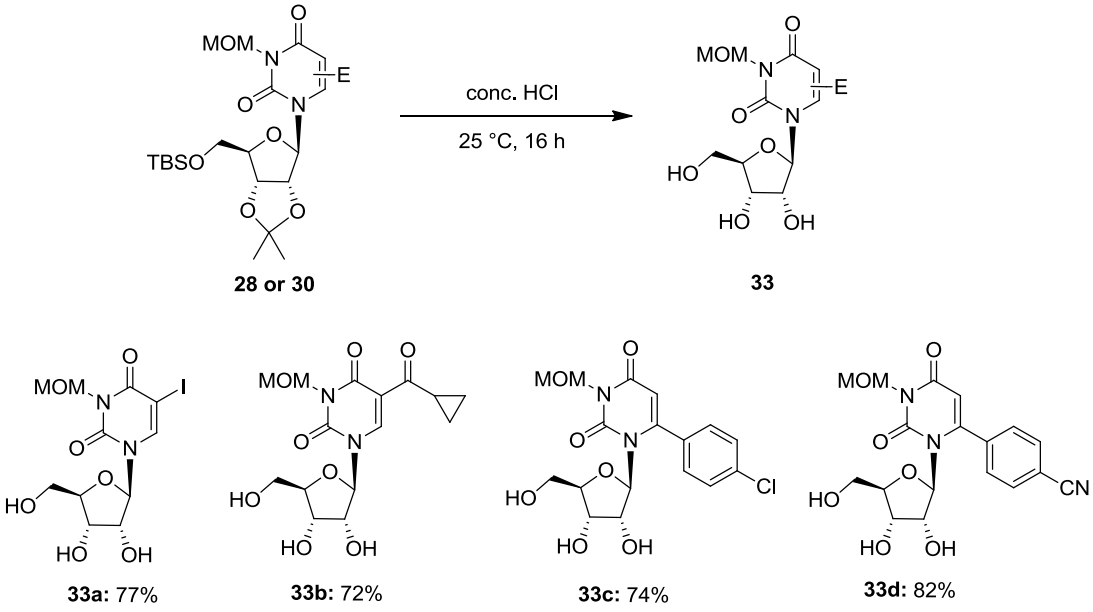
Entry	Reagent (equiv)	Reaction conditions	Isolated yield of **33**[a]	Isolated yield of **34**[a]
1	2.0 M HCl (excess)	25 °C, 16 h	87%	-
2	conc. HCl (excess)	25 °C, 16 h	88%	-
3	conc. HCl (excess)	60 °C, 16 h	40%	25%
4	70% aq. TFA (excess)	25 °C, 16 h	74%	-
5	*p*-TolSO_2Na (2.0) 2.0 M HCl (2.5)	MeCN, 25 °C, 27 h	62%	-
6	$ZrCl_4$ (0.5)	*i*PrOH, 80 °C, 24 h	-	-
7	BBr_3	CH_2Cl_2, -78 to 25 °C, 24 h	-	-

[a] Isolated yield of analytically pure products.

[62] Y.-C. Shih, Y.-Y. Yang, C.-C. Lin, T.-C. Chien, *J. Org. Chem*, **2013**, *78*, 4027.

[63] a) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp, *Angew. Chem., Int. Ed.* **1999**, *38*, 2934. b) S. Yokoshima, H. Tokuyama, T. Fukuyama, *Angew. Chem., Int. Ed.* **2000**, *39*, 4073. c) D. M. Barnes, J. Barkalow, D. J. Plata, *Org. Lett*. **2009**, *11*, 273. d) P. S. Baran, C. A. Guerrero, B. D. Hafensteiner, N. B. Ambhaikar, *Angew. Chem., Int. Ed.* **2005**, *44*, 3892.

The best result was obtained working with concentrated HCl as a solvent at 25 °C (88% yield of **33**, entry 2). However, the cleavage of the MOM-group was only partly achieved under harsh acidic conditions at 60 °C with concentrated HCl (25% yield of **34**, entry 3) in combination with decomposition of the uridine scaffold. Moreover, the use of Lewis acid conditions by treatment with $ZrCl_4$[64] or BBr_3[65] provided no desired product (entries 6-7).
With the optimized conditions for the sugar moiety, we readily performed a selective deprotection to afford the MOM-protected nucleosides **33a-d** in 72-82% yield (Scheme 28).



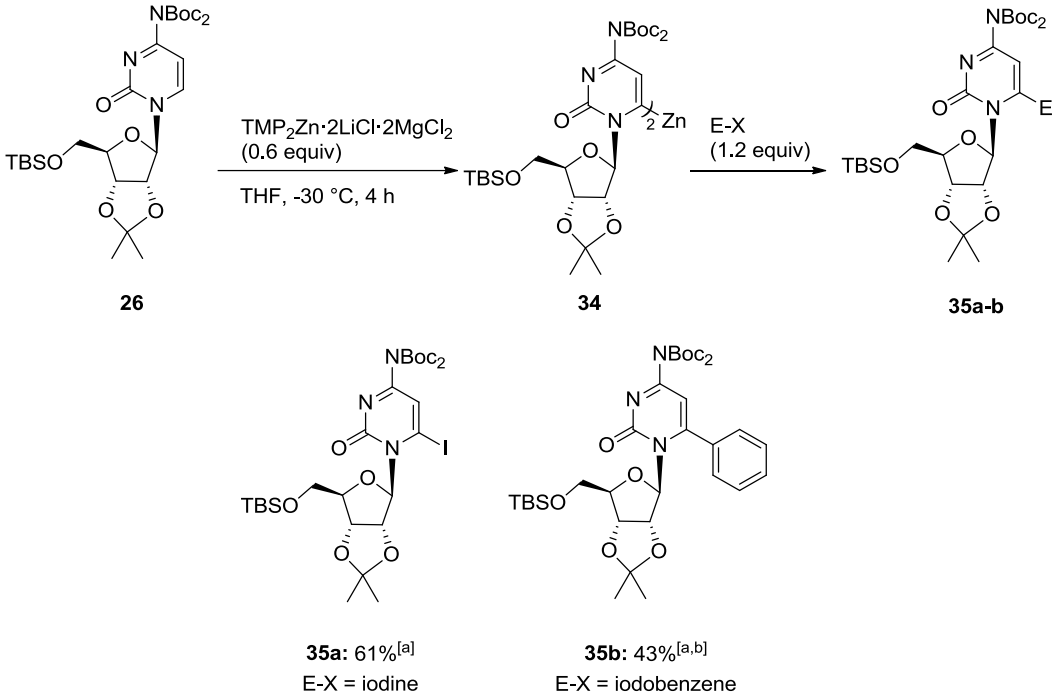
Scheme 28: Deprotection of substituted uridines leading to nucleosides **33a-d**.

1.4. Metalation of Cytidine

1.4.1. Metalation Conditions for Cytidine

The metalation procedure was extended to the bis-Boc protected cytidine (**26**) and treatment with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**8**) at –30 °C in THF for 4 h provided the C(6)-zincated species **34** as single regioisomer (Scheme 29). Subsequent quenching with iodine furnished iodo product **15a** in 61% yield. Moreover, a palladium-catalyzed cross-coupling of the metalated spezies **34** with $Pd(dba)_2$ (2 mol%), $P(2\text{-furyl})_3$ (4 mol%) and iodobenzene furnished the C(6)-arylated product **15b** in 43% yield.

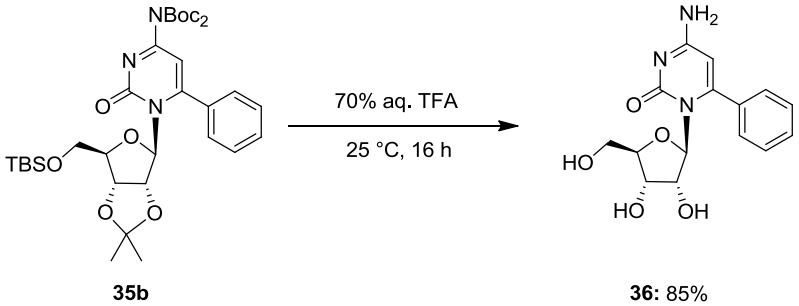
[64] G. V. M. Sharma, K. L. Reddy, P. S. Lakshmi, P. Radha Krishna, *Tetrahedron* **2004**, *45*, 9229.
[65] E. Sotelo, A. Coelho, E. Ravina, *Tetrahedron Lett.* **2001**, *42*, 8633.



Scheme 29: Metalation of bis-Boc-protected cytidine in position C(6) and subsequent reaction with electrophiles. [a] Isolated yield of analytically pure products. [b] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (2 mol%) and $P(2\text{-furyl})_3$ (4 mol%).

1.4.2. Deprotection of Cytidine

A full deprotection method for cytidine derivative **35b** was employed under acidic conditions (CF_3COOH, 70% in H_2O) at 25 °C and resulting in the formation of the arylated cytidine **36** in 85% yield (Scheme 30).



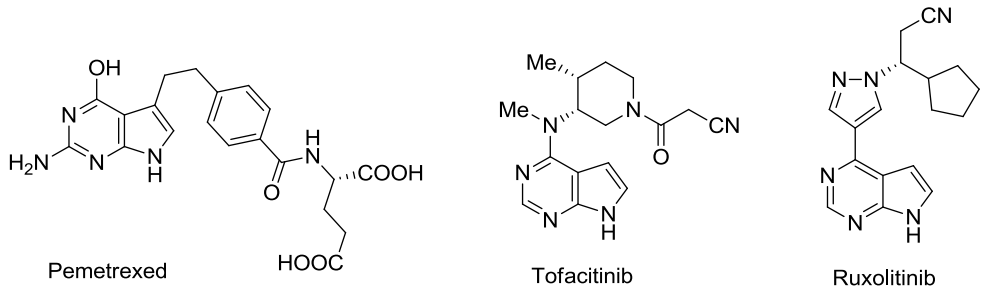
Scheme 30: Deprotection of the substituted cytidine **35b** leading to the nucleosides derivative **36**.

2. PREPARATION OF FUNCTIONALIZED PYRROLO[2,3-*D*]PYRIMIDINES *VIA* AN INTRAMOLECULAR COPPER-MEDIATED CARBOMAGNESIATION OF YNAMIDES

2.1. Introduction

2.1.1. Natural Products

Heterocyclic fused-pyrimidines are key structures in various natural alkaloids, which displays a multitude of biological activities. One of the most abundant and important heterocycles from this class are pyrrolopyrimidines, where a pyrimidine scaffold is fused to a pyrrole ring. This introduction is focused on the pyrrolo[2,3-*d*]pyrimidine isomer and its occurrence in numerous biologically-relevant molecules or phamaceuticals.[66] An example of a moleculs containing this core structure is Pemetrexed[67], a chemotherapy drug manufactured by Eli Lilly (Scheme 31). Moreover, Tofacitinib an inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3) can be used for treatment of rheumatoid arthritis.[68] Additionally, Ruxolitinib is a drug for the treatment of intermediate or high-risk myelofibrosis, a type of bone marrow cancer.[69,70]

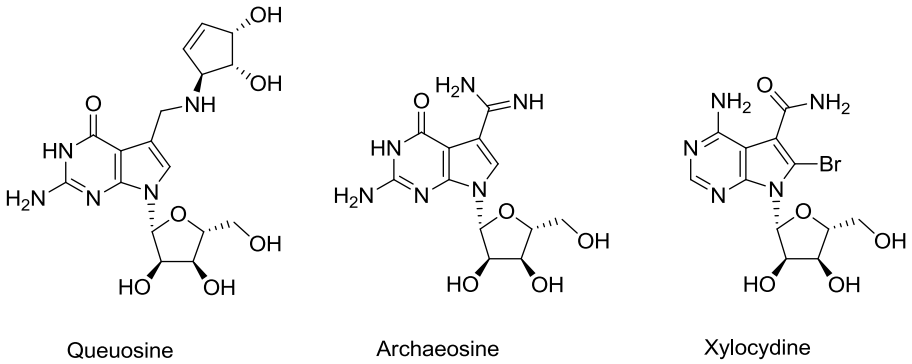


Scheme 31: Selected pharmaceutical relevant pyrrolopyrimidines.

Furthermore, a number of nucleoside modifications in the RNA are based on the pyrrolopyrimidne scaffold. Two of these modifications, Queuosine and Archaeosine, are

[66] For a general review, see: a) L. M. De Coen, T. S. A. Heugebaert, D. Garcia, C. V. Stevens, *Chem. Rev.* **2016**, *116*, 80. b) F. Seela, X. Peng, S. Budow, *Curr. Org. Chem.* **2007**, *11*, 427. c) E. Altmann, L. Widler, M. Missbach, *Mini Rev. Med. Chem.* **2002**, *2*, 201.
[67] E. C. Taylor, B. Liu, *J. Org. Chem.* **2003**, *68*, 9938.
[68] Tofacitinib. *Drugs R. D.* **2010**, *10*, 271.
[69] R.A. Mesa, U. Yasothan, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2012**, *11*, 103.
[70] Alan R. Katritzky in *Comprehensive heterocyclic chemistry*, (Ed: Alan R. Katritzky), Elsevier Books, **2008**, p.1.

present in the transfer-RNA of both bacteria and eukaryotes (Scheme 32).[71] Another natural nucleoside, Xylocydine, is a nanomolar CDK (cyclin-dependant kinase) inhibitor.[72]



Scheme 32: RNA nucleosides Quenosine, Archaeosine and Xylocydine.

Moreover, the marine alkaloids rigidin A, B, C, D and E (**37a-e**) represent another important class of molecules based on pyrrolopyrimidines (Scheme 33). The family of alkaloids was first isolated in 1990 from the tunicate *Eudistoma* cf. *rigida* found near Okinawa and New Guinea.[73] These compounds were shown to exhibit cytotoxicity against murine leukemia L1210 cells, while rigidin A was also found to possess anticalmodulin activity.[74] As a result of miniscule isolation yields of these natural products (0.0015% for A, 0.00031% for B, 0.00008% for C, 0.00004% for D, and 0.018% for E based on dry weight) synthetic routes for rigidins are highly desirable.

Before 2012, the synthetic accomplishments in the rigidin area included three total syntheses of rigidin A[75,76,77] and one of rigidin E.[77,78] However, all of these approaches involved long multistep synthetic routes with low overall yields.

[71] a) D. Iwata-Reuyl, *Bioorg.Chem.* **2003**, *31*, 24. b) M. Watanabe, M. Matsuo, S. Tanaka , H. Akimoto, S. Asahil, S. Nishimural, J. R. Katze, T. Hashizume, P. F. Crain, J. A. McCloske, N. Okada, *J. Bio. Chem.* **1997**, *272*, 20146.

[72] S. J. Cho, S. S. Lee, Y. J. Kim, B. D. Park, J. S. Choi, L. Liu, Y. M. Ham, K. B. Moon, S. K. Lee, *Cancer Lett.* **2010**, *287*,196.

[73] J. Kabayashi, J. Cheng, Y. Kikuchi, M. Ishibashi, S. Yamamura, Y. Ohizumi, T. Ohta, S. Nozoe, *Tetrahedron Lett.* **1990**, 31, 4617.

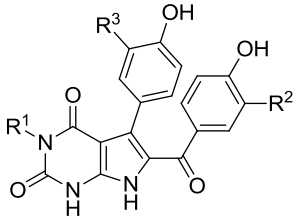
[74] a) M. Tsuda, K. Nozawa, K. Shimbo, J. Kobayashi, *J. Nat. Prod.*, **2003**, *66*, 292. b) R. A. Davis, L. V. Christensen, A. D. Richardson, R. M. da Rocha, C. M. Ireland, *Mar. Drugs*, **2003**, *1*, 27. c) R. Scott, A. Kornienko, *ChemMedChem*, **2014**, *9*, 1428.

[75] E. D. Edstrom, Y. Wei, *J. Org. Chem.* **1993**, *58*, 403.

[76] a) T. Sakamoto, Y. Kondo, S. Sato, H. Yamanaka, *J. Chem. Soc. Perkin Trans.* **1996**, *1*, 459. b) T. Sakamoto, Y. Kondo, S. Sato, H. Yamanaka, *Tetrahedron Lett.* **1994**, *35*, 2919.

[77] J. T. Gupton, E. J. Banner, A. B. Scharf, B. K. Norwood, R. P. F. Kanters, R. N. Dominey, J. E. Hempel, A. Kharlamova, I. Bluhn-Chertudi, C. Hickenboth, *Tetrahedron* **2006**, *62*, 8243.

[78] B. Cao, H. Ding, R. Yang, X. Wang, Q. Xiao, *Mar. Drugs* **2012**, *10*, 1412.



	R^1	R^2	R^3
37a: rigidin A	H	H	H
37b: rigidin B	H	OMe	H
37c: rigidin C	H	H	OMe
37d: rigidin D	H	OMe	OMe
37e: rigidin E	Me	H	H

Scheme 33: Structure of rigidin A-E (**37a-e**).

A more efficient approach was developed by *Magedov* in one-pot multicomponent reations to rapidly access the rigidins A-D and various structural variants of this heterocyclic scaffold.[79]

2.1.2. Carbocupration Development

Carbocuprations[80] are powerful addition reactions for the construction of complex stereodefined organic molecules[81] and their intramolecular version is very attractive for constructing heterocyclic organometallics.[82] Recently, *Kunz* and *Knochel* described a general preparation of functionalized benzo[*b*]thiophenes and benzo[*b*]thieno[2,3-*d*]thiophenes *via* an intramolecular catalytic carbocupration reaction.[83] Based on this work, a preparation of functionalized indoles and azaindoles of type **38** by copper-mediated carbomagnesation was developed by *Fischmuth* and *Knochel* (Scheme 34).[43]

[79] a) L. V. Frolova, N. M. Evdokimov, K. Hayden, I. Malik, S. Rogelj, A. Kornienko, I. V. Magedov, *Org. Lett.* **2011**, *13*, 1118. b) L. V. Frolova, I. V. Magedov, A. E. Romero, M. Karki, I. Otero, K. Hayden, N. M. Evdokimov, L. M. Y. Banuls, S. K. Rastogi, W. R. Smith, L. Shi-Long, R. Kiss, C. B. Shuster, E. Hamel, T. Betancourt, S. Rogelj, A. Kornienko *J. Med. Chem.* **2013**, *56*, 6886.

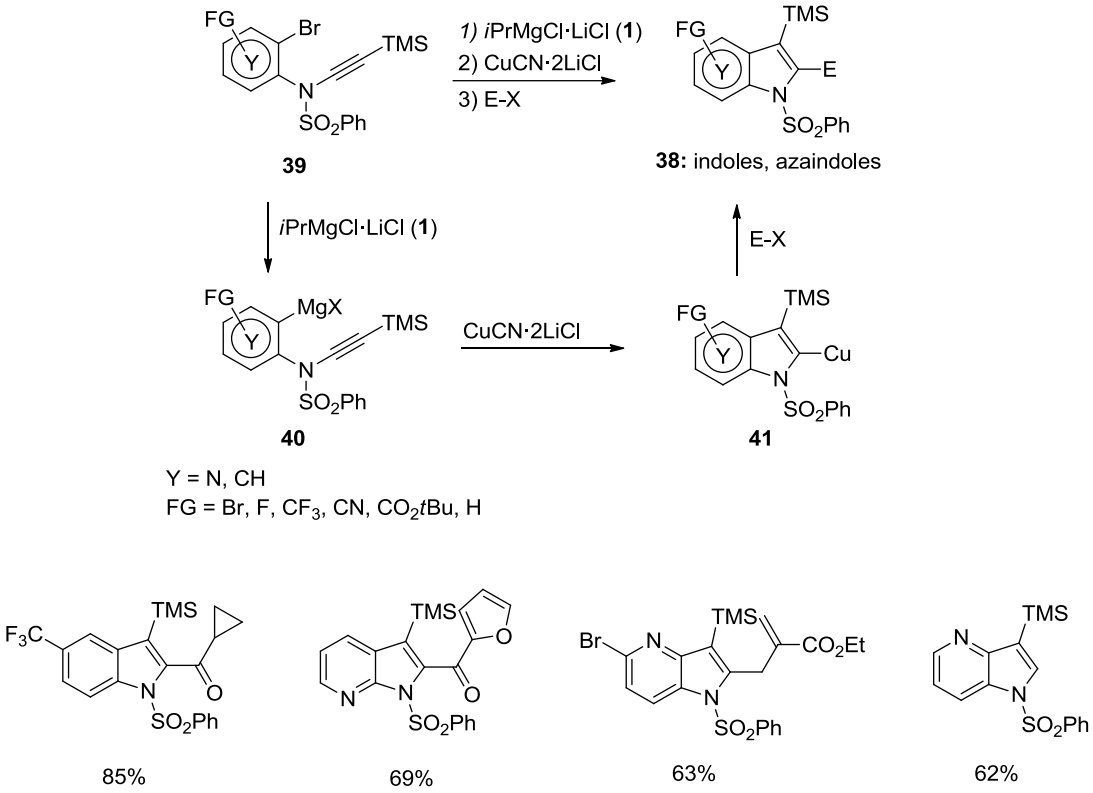
[80] a) J. P. Das, H. Chechik, I. Marek, *Nat. Chem*. **2009**, *1*, 128. b) A. Abramovitch, I. Marek, *Eur. J. Org. Chem*. **2008**, 4924. c) Y. Minko, M. Pasco, H. Chechik, I. Marek, *Beilstein J. Org. Chem.* **2013**, *9*, 526. For reviews on carbocupration reactions see also: d) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841. e) A. Basheer, I. Marek, *Beilstein J. Org. Chem*. **2010**, *6*, No. 77. f) N. Chinkov, D. Tene, I. Marek in *Metal-Catalyzed Cross-Coupling Reactions* (Ed.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2004**, p. 1. g) N. Krause in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, p. 1.

[81] a) C. Germon, A. Alexakis, J. F. Normant, *Synthesis* **1984**, 40. b) E. Nakamura, S. Mori, *Angew. Chem. Int. Ed.* **2000**, *39*, 3750. c) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796. d) Y. Minko, M. Pasco, L. Lercher, I. Marek, *Nat. Protoc.*, **2013**, *8*, 749. e) L. Ackermann, *Angew. Chem. Int. Ed*. **2011**, *50*, 3842. f) R. Jeyachandran, H. K. Potukuchi, L. Ackermann, *Beilstein J. Org. Chem.* **2012**, *8*, 1771. g) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954. h) G. Lefevre, G. Franc, A. Tlili, C. Adamo, M. Taillefer, I. Ciofini, A. Jutand, *Organometallics* **2012**, *31*, 7694. A. Tlili, F. Monnier, M. Taillefer, *Chem. Commun.* **2012**, *48*, 6408. i) G. Danoun, A. Tlili, F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12815.

[82] a) Z. Shen, X. Lu, *Adv. Synth. Catal*. **2009**, *351*, 3107. b) V. Kavala, D. Janreddy, M. J. Raihan, C.-W. Kuo, C. Ramesh, C.-F. Yao, *Adv. Synth. Catal.* **2012**, *354*, 2229.

[83] T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

The latter method offered a mild and general one-pot preparation of highly functionalized heterocycles *via* a five-endo-dig[84] intramolecular carbocupration starting from bromine-magnesium exchange with *i*PrMgCl·LiCl (**1**) of the corresponding bromo-ynamide (**39**)[85] to furnished the magnesium species **40**. Subsequent transmetalation with CuCN·2LiCl lead to cuprated heterocylic intermediates of type **41** and quenching with various electrophiles gave access to substituted indoles and azaindoles in good yields.



Scheme 34: Preparation of indoles, 4-, 5-, 6-, and 7-azaindoles and selected examples *via* copper-mediated carbomagnesiation of ynamides of type **39**.

[84] a) I. L. Kruse, J. E. Baldwin, *J. C. S. Chem. Commun.* **1976**, *18*, 734. b) R. C. Thomas, I. L. Kruse, L. Silberman, E. J. Baldwin, *J. Org. Chem.* **1977**, *42*, 3846.

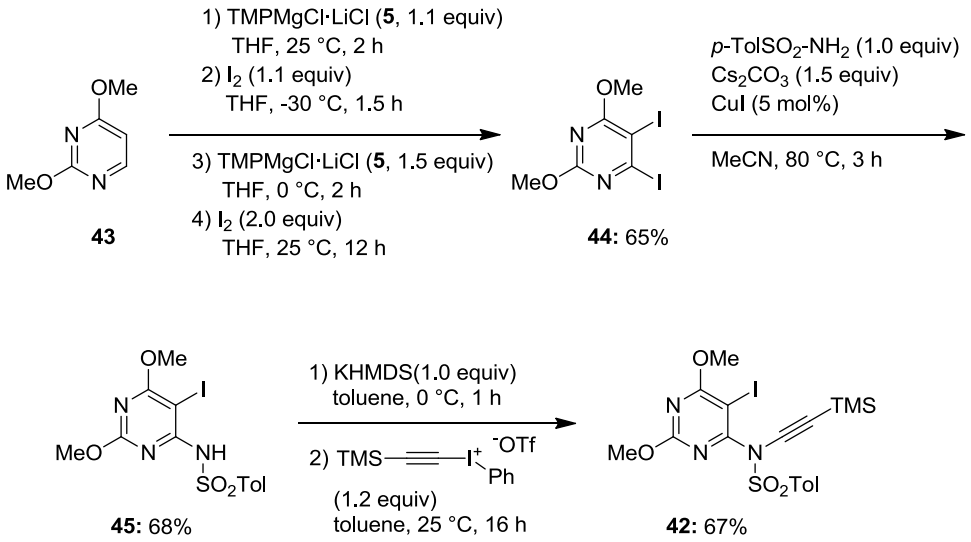
[85] Review: a) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840. b) K. A. DeKorver, H. Li, A.G. Lohse, R. Hayashi, Z. Lu, Y. Zhan, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064. c) A. Coste, G. Karthikeyan, F. Couty, G. Evano, *Angew. Chem. Int. Ed.* **2009**, *48*, 4381. d) K. Jouvin, J. Heimburger, G. Evano, *Chem. Sci.* **2012**, *3*, 756. e) J.Y. Kim, S.H. Kim, S. Chang, *Tetrahedron Lett.* **2008**, *49*, 1745. f) F. Nissen, V. Richard, C. Alayrac, B. Witulski, *Chem. Commun.* **2011**, *47*, 6656. g) S. Balieu, K. Toutah, L. Carro, L.-M. Chamoreau, H. Rousselière, C. Courillon, *Tetrahedron Lett.* **2011**, *52*, 2876.

2.2. Preparation of Pyrrolo[2,3-*d*]pyrimidines

2.2.1. Preparation of Functionalized Ynamides

We applied this mild, intramolecular copper-mediated carbomagnesiation procedure for the synthesis of functionalized pyrrolo[2,3-*d*]pyrimidines and have further investigated the preparation of a relevant natural product, the marine alkaloid rigidin A.

Firstly, we prepared the *N*-sulfonyl ynamide **42** derived from 2,4-dimethoxypyrimidine (**43**) by consecutive magnesation-iodolysis sequences[86] using TMPMgCl·LiCl (**5**) and iodine afforded 5,6-diiodo-dimethoxypyrimidine (**44**) in 65% overall yield (Scheme 35). Copper-catalyzed amination[87] with *p*-toluenesulfonamide in the presence of Cs_2CO_3 in MeCN provided pyrimidyl *N*-sulfonylamide (**45**) in 68% yield. After deprotonation with KHMDS (KHMDS = potassium hexamethyldisilazane), treatment with phenyl((trimethylsilyl)ethynyl)iodonium triflate[88] afforded the 6-substituted pyrimidyl *N*-sulfonyl ynamide (**42**) in 67% yield.



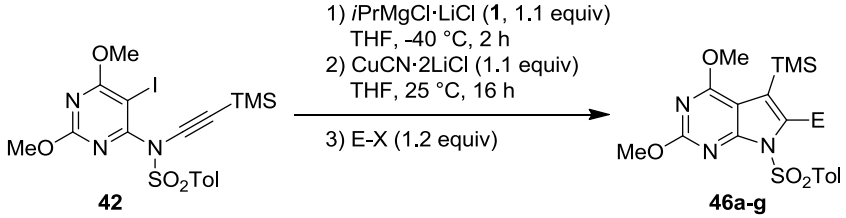
Scheme 35: Preparation of TMS-substituted ynamides of type **42**.

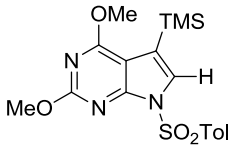
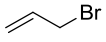
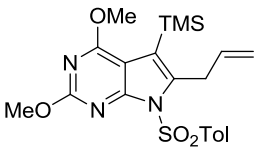
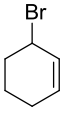
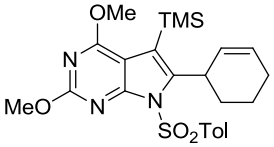
[86] M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008,** *6*, 3237.
[87] Y.-C. Teo, F.-F. Yong, *Synlett* **2011**, 837.
[88] a) P. Murch, B. L. Williamson, P. J. Stang, *Synthesis* **1994**, 1255. b) B. Witulski, T. Stengel, *Angew. Chem. Int. Ed.* **1998**, *37*, 489. c) K. Tanaka, K. Takeishi, *Synthesis* **2007**, 2920.

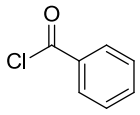
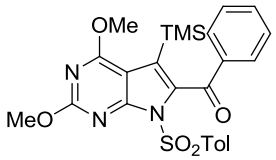
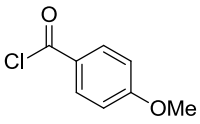
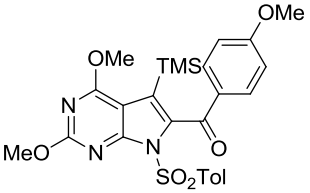
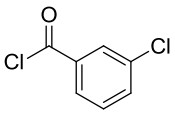
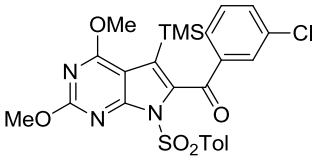
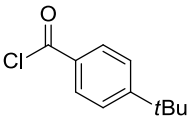
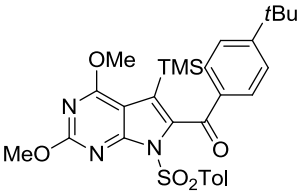
2.2.2. Preparation of Functionalized Pyrrolo[2,3-*d*]pyrimidines

Compound **42** was then submitted to an iodine-magnesium exchange using *i*PrMgCl·LiCl (**1**, THF, -40 °C, 2 h) (Scheme 35). The intermediate magnesium reagent of type **40** was transmetalated to the corresponding copper species using CuCN·2LiCl. Then a smooth *trans*-carbocupration proceeded at 25 °C within 16 h lead to a heterocyclic intermediate of type **41**. After hydrolysis, the pyrrolo[2,3-*d*]pyrimidine (**46a**) was obtained in 67% isolated yield (Table 7, entry 1). Allylation of the copper intermediate of type **41** with allyl bromide or 2-cyclohexenyl bromide provided the allylated products (**46b-c**) in 57-81% yield (entries 2-3). Moreover, acylation with benzoyl chloride furnished the substituted benzoylated *N*-heterocycle (**46d**) in 67% yield (entry 4). Furthermore, quenching with various substituted aromatic acid chlorides provided the corresponding 2-acylated pyrrolo[2,3-*d*]pyrimidines **46e-g** in 53-77% yield (entries 5-7).

Table 7: Functionalized pyrrolo[2,3-*d*]pyrimidines of type **46** obtained by copper-mediated carbomagnesiation of ynamide **42** and subsequent reactions with various electrophiles (E-X).



Entry	Electrophile	Product/Yield[a]
1	H_2O	 **46a**: 67%
2		 **46b**: 81%
3		 **46c**: 57%

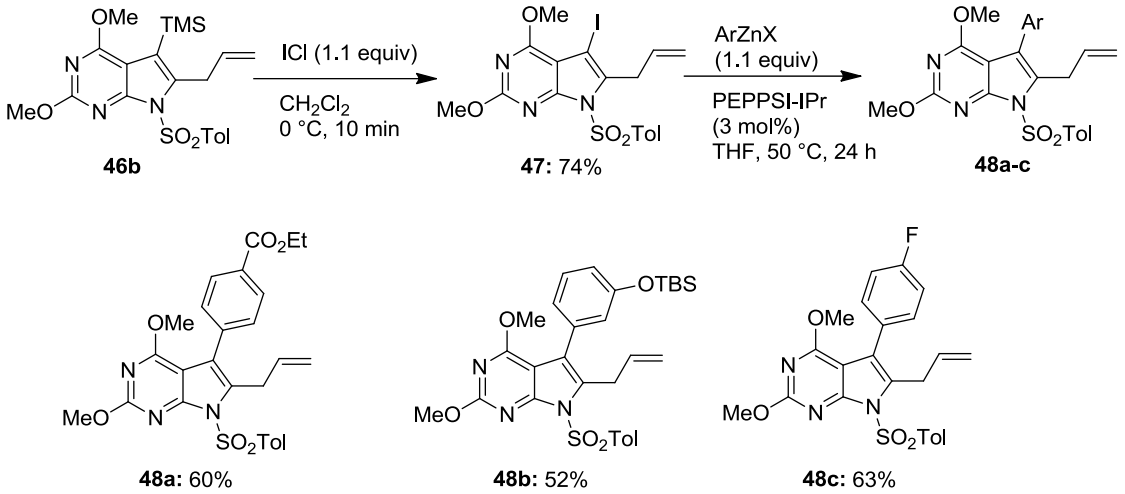
4		 **46d**: 67%
5		 **46e**: 71%
6		 **46f**: 77%
7		 **46g**: 53%

[a] Isolated yield of analytically pure products.

2.2.3. Further Functionalizations

We have further shown that the 3-TMS-substituted pyrrolo[2,3-*d*]pyrimidine (**46b**) can be readily converted into the corresponding iodide (**47**) by using ICl[89] in CH_2Cl_2 (0 °C, 10 min) in 74% yield. The iodoindole **47** undergoes *Negishi* cross-couplings with various freshly prepared arylzinc reagents using PEPPSI-IPr[90] (3 mol%) furnished *meta*- and *para*-substituted, arylated products (**48a-c**) as highly functionalized *N*-heterocycles in 52-63% yield (Scheme 36).

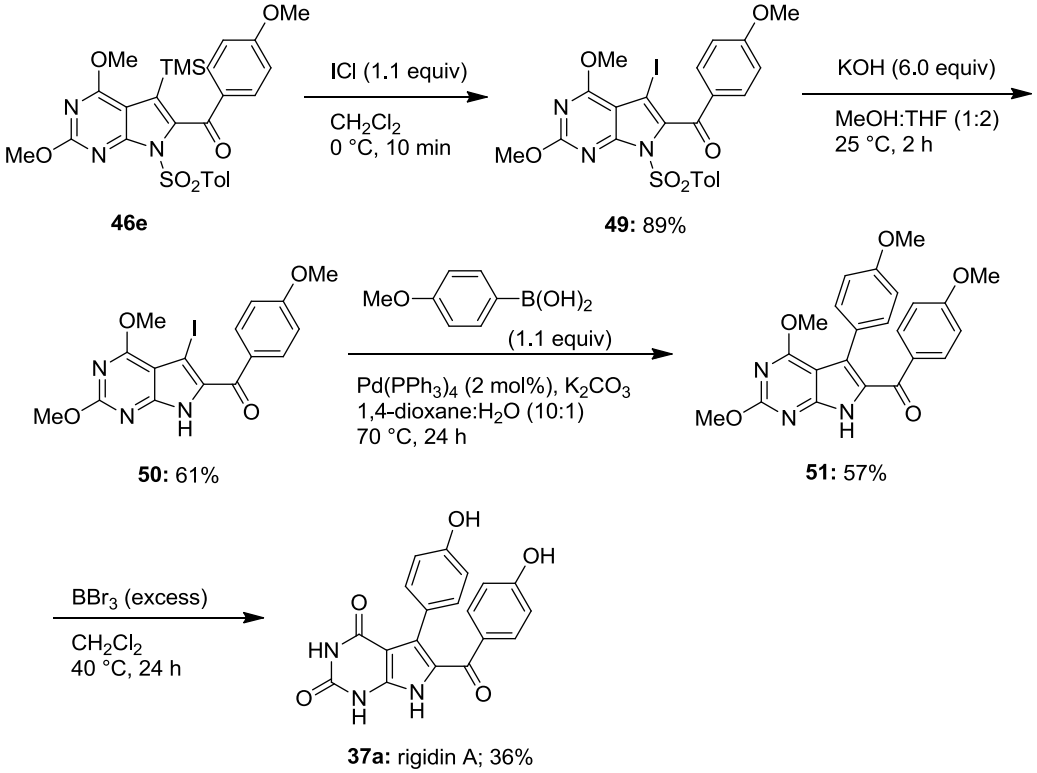
[89] Z. Bo, A. D. Schlüter, *J. Org. Chem*. **2002**, *67*, 5327.
[90] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743. b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Eur. J. Chem.* **2006**, *12*, 4749. c) L. C. McCann, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 4386.



Scheme 36: Transformation of the TMS-substituted indole **46b** to the iodine **47** and subsequent *Negishi* cross-couplings.

2.3. Synthesis of Rigidin A

With these results in hand, we applied the methodology to a synthesis of the marine natural product rigidin A (**37a**; Scheme 37). Thus, iodolysis of **46e** with ICl furnished the 3-iodo-derivative (**49**) in 89% yield.



Scheme 37: Synthesis of rigidin A (**37a**).

Removal of the sulfonamide group with KOH in a mixture of MeOH:THF provided the pyrrolo[2,3-*d*]pyrimidine (**50**) in 61% yield. The *N*-heterocycle **50** was further converted to rigidin A (**37a**) according to the procedure of Sakamoto[76a] in two steps. Thus, a Suzuki-reaction[91] with 4-anisylboronic acid catalyzed by $Pd(PPh_3)_4$ (2 mol%) afforded the fully substituted heterocycle **51** (57% yield), followed by a deprotection of all four methoxy-substituents with an excess of BBr_3[92] lead to rigidin A (**37a**) in five steps starting from the *N*-sulfonyl ynamide (**42**) in ca. 8% overall yield.

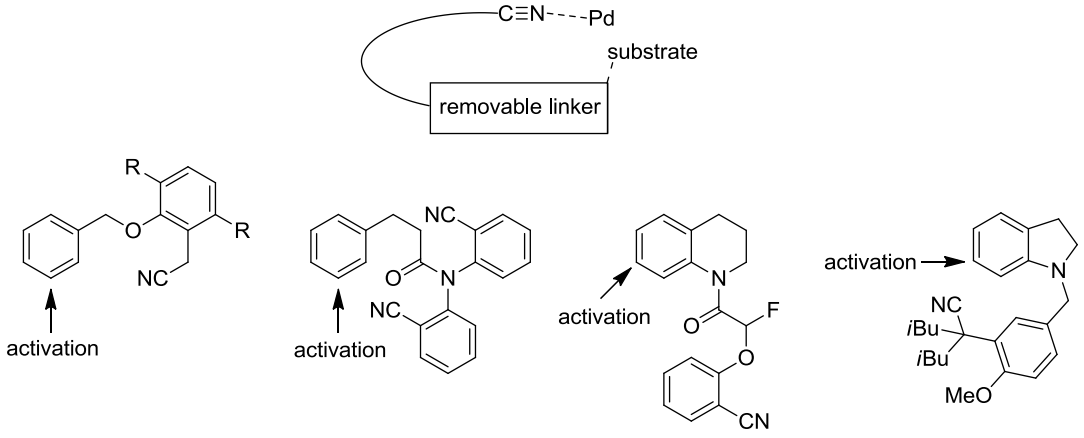
[91] N. Miyaura, A. Suzuki, Chem. Rev. **1995**, *95*, 2457.
[92] a) F. L. Benton, T. E. Dillon, *J. Am. Chem. Soc.* **1942**, *64*, 1128. b) J. F. W. McOmie, M. L. Watts, D. E. West, *Tetrahedron* **1968**, *24*, 2289. c) C. Sousa, P. J. Silva, *Eur. J. Org. Chem.* **2013**, 5195.

3. REGIOSELECTIVE PREPARATION OF TETRASUBSTITUTED FLUOROBENZENES

3.1. Overview of Remote *meta*- or *para*-selective Functionalizations

Achieving site selectivity in carbon-hydrogen (C-H) functionalization reactions is a significant challenge in organic chemistry, especially when the target C-H bond is distant from existing functional groups. The usual approach is to use the electronic and/or coordinative characteristics of a directing group, which lead to *ortho*-selectivity through the formation of conformationally rigid six- or seven-membered cyclic transition states. However, *meta*-selective C-H functionalizations still remain a big challenge.

The group of *Yu* reported a class of easily removable nitrile-containing templates that directed the activation of *meta*-C-H bonds (Scheme 38). These templates are conformationally locked by their substituents and enabled cyclopalladation reactions to selective functionalize certain arenes,[93] aromatic amines[94] and aromatic amides.[95]



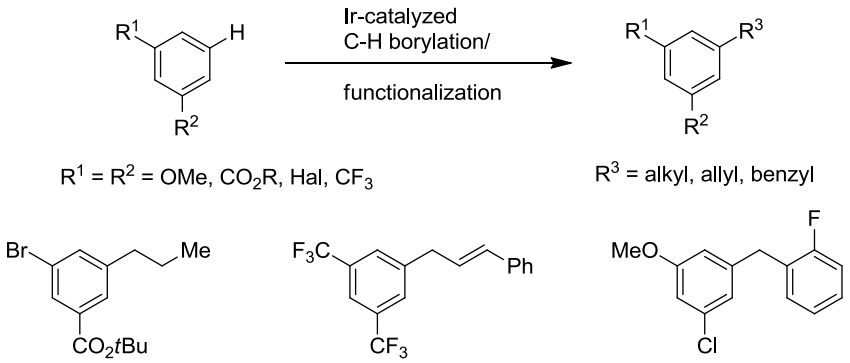
Scheme 38: Selected examples of remote *meta*-C-H bond activation using nitrile containing templates.

[93] a) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 10807. b) L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056. c) S. Lee, H. Lee, K. L. Tan, *J. Am. Chem. Soc.* **2013**, *135*, 18778. d) D. Leow1, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518.

[94] R.-Y. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215.

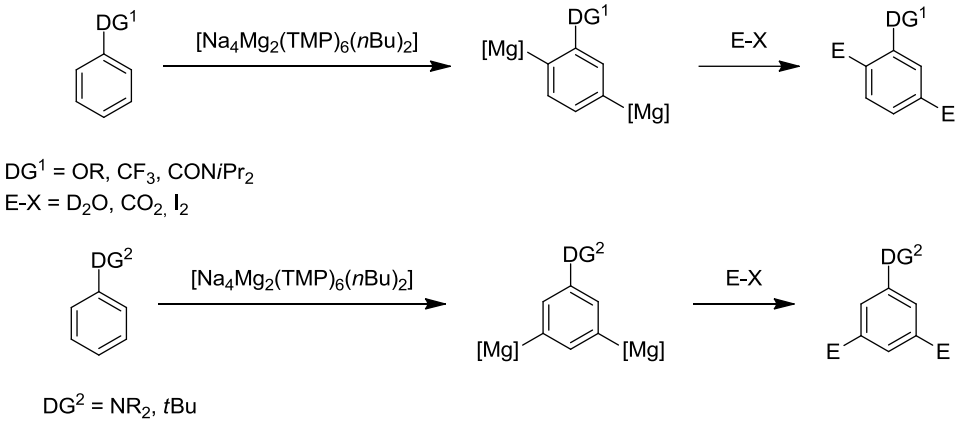
[95] X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015**, *519*, 334.

Moreover, *Hartwig* reported a one-pot method for sterically controlled *meta*-selective functionalizations of arenes through Ir-catalyzed C-H borylations, followed by Pd- or Ni-catalyzed cross-couplings of the resulting arylboronate esters with alkyl, allyl and benzoyl electrophiles (Scheme 39).[96]



Scheme 39: Selective examples of *meta*-functionalization through sterical demanding Ir-catalyzed C-H borylation.

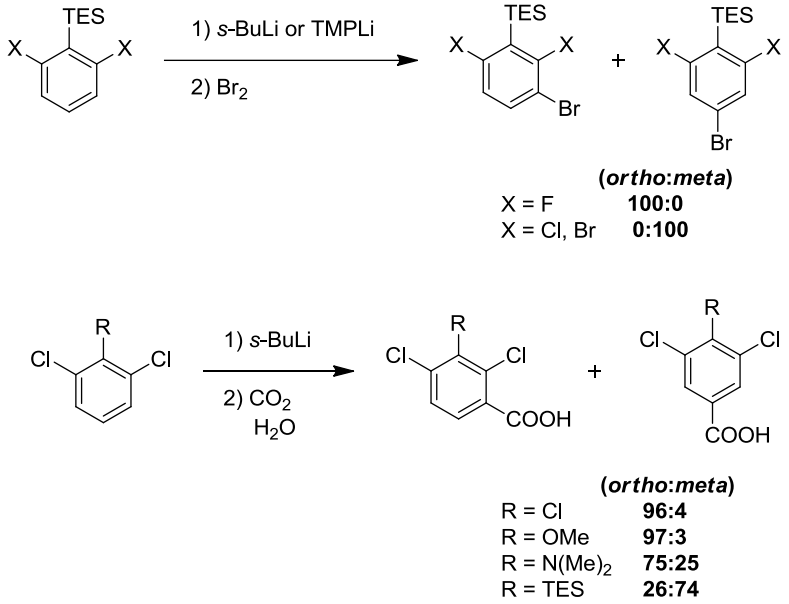
Furthermore, a few examples of remote metalation methods are reported in the literature. The group of *Mulvey* developed a protocol by which the metalating agent, a sodium-magnesium mixed TMP-base, enabled *ortho-meta'* or *meta-meta'* dimetalation, depending on the nature of the directing group (Scheme 40).[97] Moreover, several of these complexe bimetalic reagents were developed and enabled unconventional metalation pattern.[98]



Scheme 40: Site-selective metalation using mixed TMP-bases.

[96] a) D. W. Robbins, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 933. b) Y.-N. Wang, X.-Q. Guo, X.-H. Zhu, R. Zhong, L.-H. Cai, X.-F. Hou, *Chem. Commun.* **2012**, *48*, 10437.
[97] A. J. Martínez-Martínez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834.
[98] a) R. E. Mulvey, *Acc. Chem. Res.* **2009**, *42*, 743. b) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 3775.

However, remote selectivity can be also influenced by the sterical demand of functional groups suppressing common metalation sites on the aromatic scaffold. In fundamental work from *Schlosser* on metalation of haloarenes[99] a few examples of *meta*-selective metalation patterns were reported (Scheme 41).[100] The selectivity of the metalation of substituted 2,6-dihaloarenes depended on the sterical demand of the three substituents. Especially, introduction of the bulky triethylsilyl group directed the metalation to the less basic *meta*-position due to a so called "buttressing effect".[101]



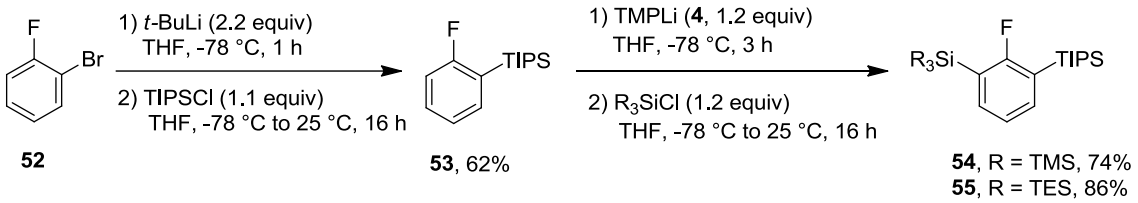
Scheme 41: Examples of *meta*-selective metalations of haloarenes.

3.2. Preparation of Bis Silylbenzene Derivatives

Taking aforementioned strategies into account, we envisioned a new protocol for the *para*-metalation of 2,6-bis silyl fluoroarenes. At first, we prepared the starting material by performing a bromine-lithium exchange with *t*-BuLi on 2-bromofluorobenzene (**52**) and trapping with triisopropylsilyl chloride (TIPSCl) afforded the silyl compound **53** in 62% yield (Scheme 42).

[99] a) C. Heiss, T. Rausis, M. Schlosser, *Synthesis* **2005**, 617. c) T. Rausis, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 3351. d) C. Heiss, E. Marzi, F. Mongin, M. Schlosser, *Eur. J. Org. Chem.* **2007**, 669.
[100] a) M. Schlosser, C. Heiss, *Eur. J. Org. Chem.* **2003**, 4618. b) C. Heiss, E. Marzi, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 4625. c) C. Heiss, F. Leroux, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 5242. d) M. Schlosser, C. Heiss, E. Marzi, R. Scopelliti, *Eur. J. Org. Chem.* **2006**, 4398.
[101] J. Gorecka, C. Heiss, R. Scopelliti, M. Schlosser, *Org. Lett.* **2004**, *6*, 4591.

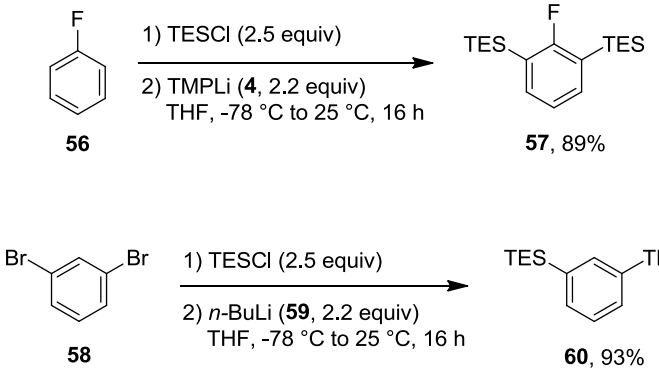
Subsequent metalation with TMPLi (**4**) at the activated position *ortho* to fluorine and quenching with different silyl chlorides provided the bis silyl derivatives **54** and **55** in 74-86% yield.



52 **53**, 62% **54**, R = TMS, 74% **55**, R = TES, 86%

Scheme 42*:* Preparation of bis silyl arenes bearing various trialkylsilyl groups.

Furthermore, two symmetric silyl groups were introduced on fluorobenzene (**56**) in a one-pot procedure. The addition of TMPLi (**4**, 2.2 equiv) in the presence of triethylsilyl chloride (TESCl, 2.5 equiv)[102] afforded the bis silyl arene **57** in 89% yield (Scheme 43). Additionally, double bromine-lithium exchange of dibromobenzene **58** with *n*-BuLi (**59**) was trapped *in situ* with TESCl (2.5 equiv) and furnished the bis silyl arene **60** in 93% yield.



56 **57**, 89%

58 **60**, 93%

Scheme 43: Preparation of bis silyl arenes with equal trialkylsilyl groups.

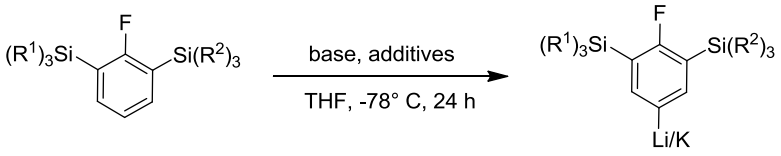
3.3. Optimization of Reaction Conditions for *para*-selective Metalation

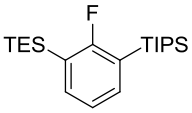
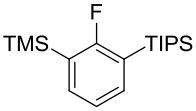
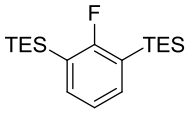
A new metalation protocol that enables *meta*-selective functionalization of fluoroarenes was investigated. In the preliminary experiments, we treated bis silyl arene **55** with *n*-BuLi (**59**) in THF at -78 °C for 24 h, but no conversion was observed (Table 8, entry 1). Also the addition of stoichiometric amount of potassium *tert*-butoxide (KO*t*Bu), to generate a kinetic enhanced and so called "superbase" did not increase the conversion rate (entry 2).[103] To our delight,

[102] S. Lulinski, J. Serwatowski, *J. Org. Chem.* **2003**, *68*, 9384.
[103] F. Mongin, R. Maggi, M. Schlosser, *Chimia* **1996**, *50*, 650.

switching to *s*-BuLi (**2**) furnished the desired product with low 10% conversion (entry 3). Moreover, moderate conversions (28-45%, entries 4-6) were achieved by the addition of coordinative nitrogen ligands, which break up the aggregates of the lithium base and enhance their reactivity.[104] Especially the mixture of *s*-BuLi (**2**), KO*t*Bu and PMDTA (*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine) proofed to be capable for deprotonation in position C(4) of the bis silyl arene **55** (entry 6). Decreasing the steric demand of the silyl group to the trimethysilyl (TMS) derivative **54** resulted in a regioselectivity switched metalation in position C(3) (entry 7). However, performing the reaction on TES-derivative (**57**), metalation occured selectively in the desired *meta*-position with 47% conversion (entry 8).

Table 8: Optimization of reaction conditions: screening of base, additives and size of the alkyl silyl group.



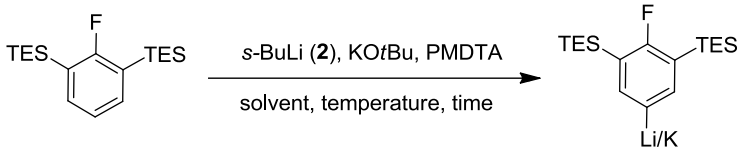
Entry	Silyl arene	Base (equiv)	Additives (equiv)	Conversion[a,b]
1	 **55**	*n*-BuLi (1.5)	-	-
2	**55**	*n*-BuLi (1.5)	KO*t*Bu (1.5)	traces
3	**55**	*s*-BuLi (1.5)	KO*t*Bu (1.5)	10%
4	**55**	*s*-BuLi (1.5)	KO*t*Bu (1.5), NEt_3 (1.5)	28%
5	**55**	*s*-BuLi (1.5)	KO*t*Bu (1.5), TMEDA (1.5)	34%
6	**55**	*s*-BuLi (1.5)	KO*t*Bu (1.5), PMDTA (1.5)	45%[b]
7	 **54**	*s*-BuLi (1.5)	KO*t*Bu (1.5), PMDTA (1.5)	65%[b] (*ortho* product)
8	 **57**	*s*-BuLi (1.5)	KO*t*Bu (1.5), PMDTA (1.5)	47%[b]

[a] GC yield after quenching with S_2Me_2 (3.0 equiv). [b] Regioselectivity was checked by ^{1}H-NMR.

[104] F. Faigl, E. Marzi, M. Schlosser, *Chem. Eur. J.* **2000**, *6*, 771.

To further improve the conversion, we evaluated the role of the solvent (Table 9, entries 1-4).[105] The metalation of bis triethylsilyl arene **57** was performed in different ethereal solvents or *i*hexane and the highest conversion was observed in diethyl ether (56%, entry 1). Moreover, performing the reaction at a temperature of -65 °C led to 76% conversion (entry 5). At -50 °C the conversion dropped significantly due to deprotonation of the solvent (entry 6). Finally, we observed an optimum of 2.5 equivalents of base and additives (entries 6-8) and examined an optimal reaction time of 20 h to afford the metalated species **61** (entries 9-11).

Table 9: Optimization of reaction conditions: Screening of solvent, temperature, time and equivalent of base and additives.



57 **61**

Entry	Base (equiv)	Additives [a]	Solvent	Temp. (°C)	time (h)	Conversion[b]
1	*s*-BuLi (1.5)	Ko*t*Bu, PMDTA	Et_2O	-78	24	56%
2	*s*-BuLi (1.5)	KO*t*Bu, PMDTA	MTBE	-78	24	41%
3	*s*-BuLi (1.5)	KO*t*Bu, PMDTA	Bu_2O	-78	24	18%
4	*s*-BuLi (1.5)	KO*t*Bu, PMDTA	*i*hexane	-78	24	traces
5	*s*-BuLi (1.5)	KO*t*Bu, PMDTA	Et_2O	-65	24	76%
6	*s*-BuLi (1.5)	KO*t*Bu, PMDTA	Et_2O	-50	24	39%
7	*s*-BuLi (2.5)	KO*t*Bu, PMDTA	Et_2O	-65	24	86%
8	*s*-BuLi (4.0)	KO*t*Bu, PMDTA	Et_2O	-65	24	85%
9	*s*-BuLi (2.5)	KO*t*Bu, PMDTA	Et_2O	-65	36	74%
10	***s*-BuLi (2.5)**	**KO*t*Bu, PMDTA**	**Et_2O**	**-65**	**20**	**88% (71%[c] isolated yield)**
11	*s*-BuLi (2.5)	KO*t*Bu, PMDTA	Et_2O	-65	16	82%

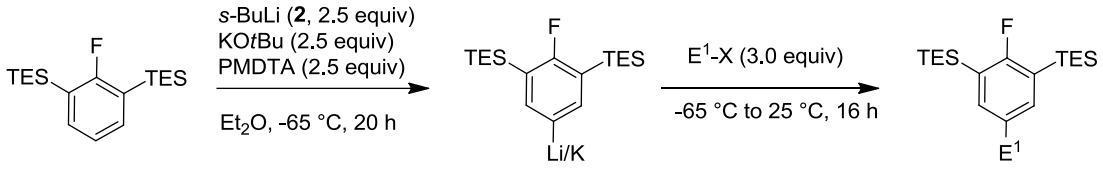
[a] Additives were used with the same equivalents as the base. [b] GC yield after quenching with S_2Me_2 (3.0 equiv). [c] Regioselectivity was checked by ^{1}H-NMR.

[105] A. J. Bridges, W. C. Patt, T. M. Stickney, *J. Org. Chem.* **1990**, *55*, 773.

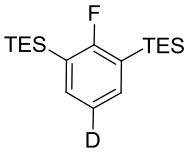
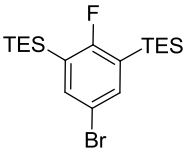
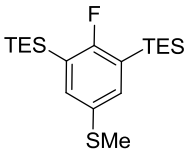
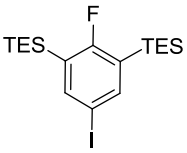
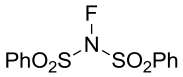
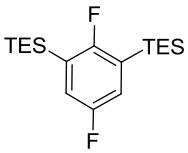
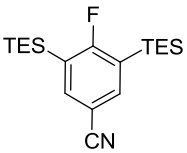
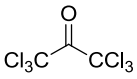
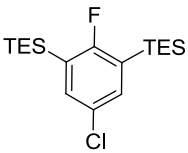
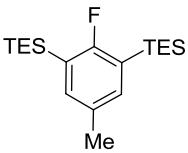
3.4. Functionalization in *para*-Position

With the optimized conditions in hand, we metalated fluoroarene **57** with a mixture of *s*-BuLi (**2**), KO*t*Bu and PMDTA in Et_2O at -65 °C in 20 h and subsequently reacted it with numerous electrophiles providing remote *para*-substituted arenes of type **62** (Table 10). Thus, metalated species **61** was quenched with deuterium oxide lead to the deuterated product **62a** in 78% yield (entry 1).

Table 10: Metalation of bis silyl fluoroarene **57** in *para*-position C(4) and subsequent reactions with electrophiles.



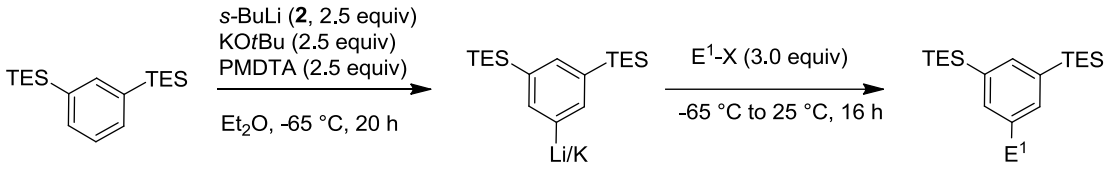
57 **61** **62a-h**

Entry	Electrophile	Product/Yield[a]	Entry	Electrophile	Product/Yield[a]
1	D_2O	 **62a**, 78%	5	Br_2	 **62e**, 61%
2	S_2Me_2	 **62b**, 71%	6	I_2	 **62f**, 64%
3		 **62c**, 50%	7		 **62g**, 50%
4		 **62d**, 55%	8	Me-I	 **62h**, 68%

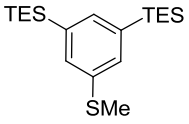
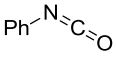
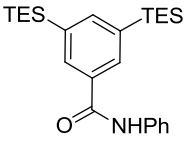
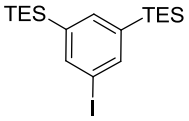
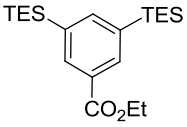
[a] Isolated yield of analytically pure products.

Also reaction with dimethyl disulfide provided the thioether **62b** in 71% yield (entry 2). Furthermore, several halogens were introduced (entries 3-6). Thus, reaction of the metalated species **61** with *N*-fluorobenzenesulfonimide (NFSI)[106] furnished the difluoro derivative **62c** in 50% yield. Additionally, treatment with hexachloroacetone, bromine or iodine afforded the *para*-halogenated compounds **62d-f** in 55-64% yields. Moreover, the use of dimethylmalononitrile[107] resulted in formation of benzonitrile **62g** in 50% yield (entry 7). Finally, quenching with methyl iodide furnished the alkylated product **62h** in 68% yield (entry 8).

Table 11: Metalation of bis silyl arene **60** in *meta*-position C(5) and subsequent reactions with electrophiles.



60 **63** **64a-d**

Entry	Electrophile	Product/Yield[a]	Entry	Electrophile	Product/Yield[a]
1	S_2Me_2	 **64a**, 57%	3		 **64c**, 40%
2	I_2	 **64b**, 46%	4	$ClCO_2Et$	 **64d**, 35%

[a] Isolated yield of analytically pure products.

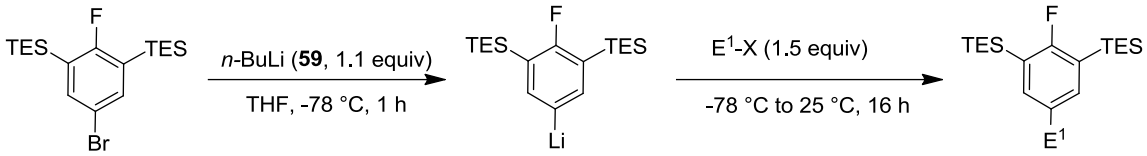
Similary, this concept was extended to functionalize selectively the unactivated 1,3-bis silyl arene **60** in remote *meta*-position under the same reaction conditions. Thus, the metalated species **63** was converted to 1,3,5-substituted arens of type **64** in 35-57% yield (Table 11). The metalated species **63** reacted under standard metalation conditions with dimethyl disulfide to provide the thioether **64a** in 57% yield (entry 1).

[106] F. A. Davis, P.V. N. Kasu, *Tetrahedron Lett.* **1998**, *39*, 6135.
[107] J. T. Reeves, C. A. Malapit, F. G. Buono, K. P. Sidhu, M. A. Marsini, C. A. Sader, K. R. Fandrick, C. A. Busacca, C. H. Senanayake, *J. Am. Chem. Soc.* **2015**, *137*, 9481.

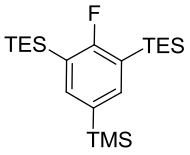
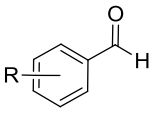
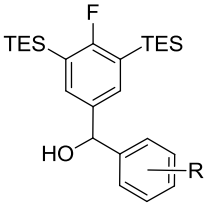
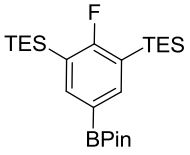
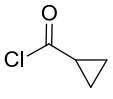
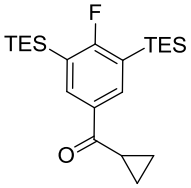
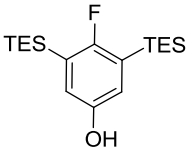
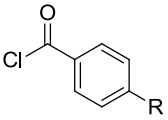
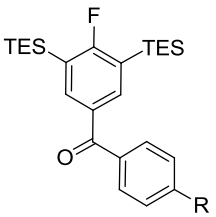
Iodolysis produced the expected halogenated product **64b** in 46% yield (entry 2). Moreover, quenching with phenylisocyanate or ethyl chloroformate lead to the desired amide **64c** and ester **64d** in 35-40% yield (entries 3-4).

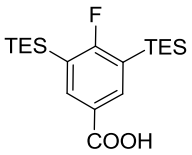
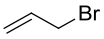
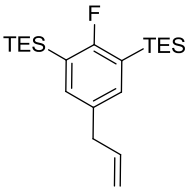
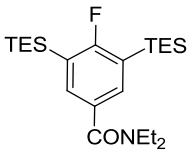
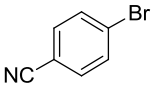
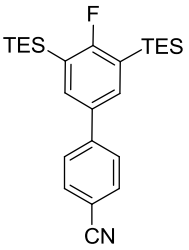
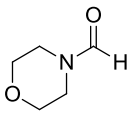
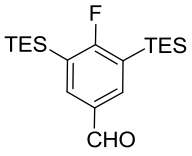
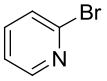
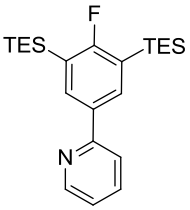
However, only a few electrophiles furnished the *para*-substituted arenes of type **62** in good yields (Table 10). Thus, we performed bromine-lithium exchange with *n*-BuLi (**59**) at -78 °C of bromoarene **62e** to generate the metalated species **65** without the addition of KO*t*Bu or PMDTA. Subsequent reaction with various electrophiles afforded C(4)-substituted derivatives of type **66** in 56-92% yield (Table 12).

Table 12: Bromine-lithium exchange of bromoarene **62e** in position C(4) and subsequent reactions with electrophiles.



62e **65** **66a-n**

Entry	Electrophile	Product/Yield[a]	Entry	Electrophile	Product/Yield[a]
1	TMS-Cl				
		66a, 92%	7	R = 4-SMe	**66g**, 69%
			8	R = 3-Cl	**66h**, 74%
2	*i*PrO-Bpin		9		
		66b, 88%			**66i**, 76%[b]
3	$B(OMe)_3$ NaOH, H_2O_2				
		66c, 80%	10	R = *t*Bu	**66j**, 72%[b]
			11	R = SMe	**66k**, 56%[b]

4	CO_2 (excess)	 **66d**, 71%	12		 **66l**, 77%[b]
5	$ClCONEt_2$	 **66e**, 85%	13		 **66m**, 85%[c,d]
6		 **66f**, 65%	14		 **66n**, 74%[c,d]

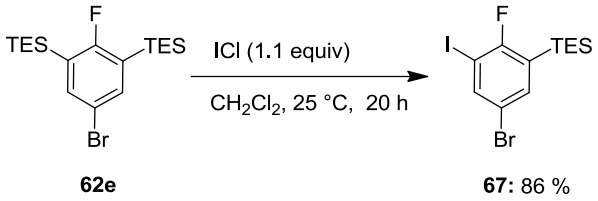
[a] Isolated yield of analytically pure products. [b] CuCN·2LiCl (1.2 equiv) was added. [c] $ZnCl_2$ was added. [d] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (3 mol%) and $P(2\text{-furyl})_3$ (6 mol%).

Therefore the lithiated arene **65** reacted with trimethylsilyl chloride to afford trisilyl compound **66a** in 92% yield (entry 1). Moreover, reaction with boronic esters furnished the pinacol ester **66b** (88%, entry 2) and provided after basic workup with hydrogen peroxide the free alcohol **66c** (80%, entry 3). Also treatment with several carbonyl electrophiles were performed and the metalated species **65** reacted with dry ice, carbamoyl chloride or morpholine-carbaldehyde to afford the carboxylic acid, the amide or the aldehyde (**66d-f**, 65-85%, entries 4-6). Similary, **65** reacted with various aromatic aldehydes to give the corresponding alcohols (**66g-h**, 69-74% yield, entries 7-8). Transmetalation of **65** with CuCN·2LiCl and subsequent acylation with various acid chlorides provided aliphatic or aromatic ketones **66i-k** in 56-76% yield (entries 9-11).

Furthermore, copper-mediated allylation with allyl bromide afforded the arene **66l** in 77% yield (entry 12). In addition, transmetalation of **65** with $ZnCl_2$ and subsequent Pd-catalyzed *Negishi*[108] cross-couplings (3 mol% $Pd(dba)_2$, 6 mol% $P(2\text{-furyl})_3$) with 4-bromobenzonitrile or 2-bromopyridine lead to the cross-coupling products (**66m-n**, 74-85% yield, entries 13-14).

3.5. Functionalization in *ortho*-Position

In addition, we have shown, that 4-bromoarene (**62e**) can be selectively converted into the corresponding mono iodide (**67**) by using ICl (1.1 equiv) in CH_2Cl_2 (25 °C, 20 h) in 86% yield (Scheme 44).



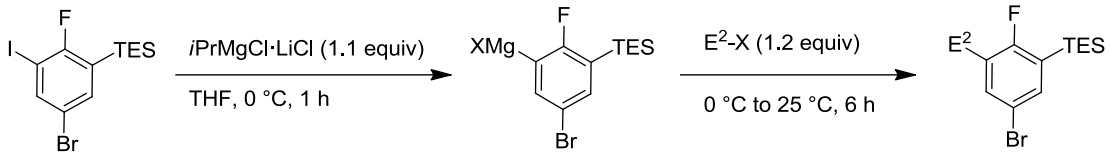
62e **67:** 86 %

Scheme 44: Mono-iodination of **62e**.

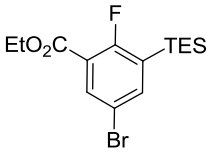
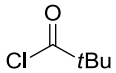
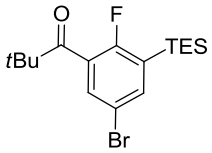
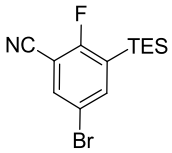
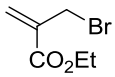
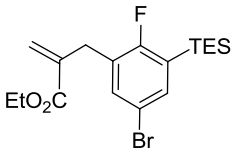
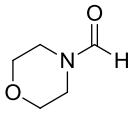
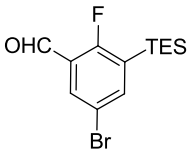
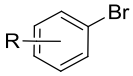
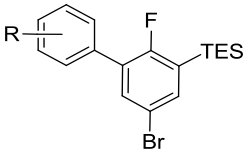
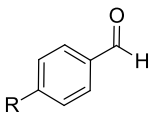
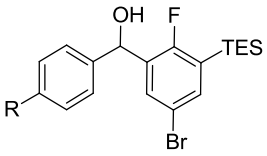
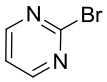
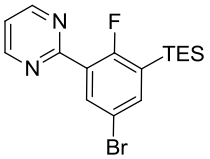
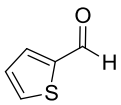
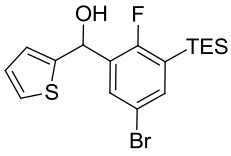
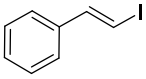
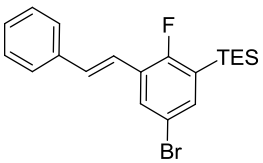
The 2-iodo-arene **67** enabled a selective iodine-magnesium exchange with *i*PrMgCl·LiCl (**1**) at 0 °C in 1 h and subsequent reactions of the magnesium species **68** with various electrophiles provided *ortho*-functionalized products of type **69a-m** (Table 13). Thus, trapping the magnesium species **68** with ethyl chloroformate furnished the ester **69a** in 74% yield (entry 1) and reaction with dimethylmalononitrile gave the benzonitrile **69b** in 79% yield (entry 2). Moreover, treatment with 4-formylmorpholine resulted in the formation of the aldehyde **69c** in 58% yield (entry 3). Quenching the magnesium species **68** with several aromatic or heteroaromatic aldehydes afforded alcohols **69d-g** in moderate yields (entries 4-7, 20-64%). After transmetalation with CuCN·2LiCl and subsequent acylation or allylation the keton **69h** (entry 8, 87% yield) or the acrylate **69i** (entry 9, 81% yield) were produced. Finally, palladium-catalyzed *Negishi* cross-couplings (after transmetalation with $ZnCl_2$) with various aromatic bromides, heteroaromatic bromides and vinyl iodides were readily performed and provided the *ortho*-substituted products **69j-m** in 65-85% yield (entries 10-13).

[108] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298. b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

Table 13: Selective iodine-magnesium exchange of arene **67** in *ortho*-position C(2) and subsequent reactions with electrophiles.



67 **68** **69a-m**

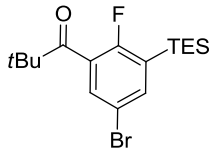
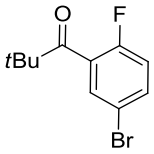
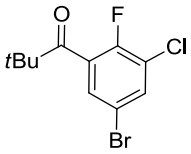
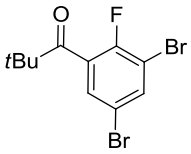
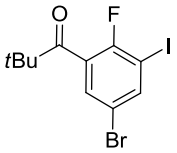
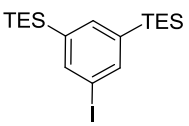
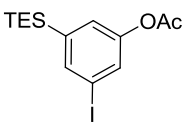
Entry	Electrophile	Product/Yield[a]	Entry	Electrophile	Product/Yield[a]
1	$ClCO_2Et$		8		
		69a, 74%			**69h**, 87%[b]
2			9		
		69b, 79%			**69i**, 81%[b]
3					
		69c, 58%	10	R = 4-OMe	**69j**, 71%[c,d]
			11	R = 3-OTBS	**69k**, 78%[c,d]
			12		
4	R = Cl	**69d**, 40%			**69l**, 65%[c,d]
5	R = OMe	**69e**, 44%			
6	R = CN	**69f**, 64%			
7			13		
		69g, 20%			**69m**, 85%[c,d]

[a] Isolated yield of analytically pure products. [b] CuCN·2LiCl (1.2 equiv) was added. [c] $ZnCl_2$ was added. [d] Obtained by a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (3 mol%) and $P(2\text{-furyl})_3$ (6 mol%).

3.6. Desilylation Reactions

We already have shown, that triethylsilyl arenes of type **62** or **66** can be versatile starting materials for *ortho*-functionalized products after cleavage of the silyl group with ICl to form the corresponding iodide. We were able to extend these studies to other *ipso*-desilylation procedures (Table 14).

Table 14: Various *ispo*-desilylation reactions.

Entry	Educt	Reagent (equiv) Conditions	Product/Yield[a]
1	 **69h**	TBAF (1.2) THF, 0 °C, 2 h	 **70**, 91%
2	**69h**	Cl_6C_2 (2.0) CsF (2.0) DMF, 25 °C, 3 h	 **71**, 88%
3	**69h**	$Cl_4Br_2C_2$ (2.0) CsF (2.0) DMF, 60 °C, 16 h	 **72**, 83%
4	**69h**	ICl (1.1) CH_2Cl_2, 25 °C, 20 h	 **73**, 88%
5	 **64b**	$PhI(OCOCF_3)_2$ (1.5) $Pd(OAc)_2$ (5 mol%) AcOH, 80 °C, 20 h	 **74**, 65%

[a] Isolated yield of analytically pure products.

Primarily, we deprotected the silyl arene **69h** with tetra-*n*-butylammonium fluoride (TBAF) in THF under mild conditions to furnish the trisubstituted arene **70** in 91% yield (entry 1). No desilylation of arene **69h** was provided though reactions with bromine, pyridinium bromide perbromide ($PyHBr_3$),[109] *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS)[110] were tested. However, using a dry fluoride-source in combination with halogen electrophiles was the method of choice.[111] The TES-group was removed by using CsF in DMF in the presence of C_2Cl_6 or $C_2F_4Br_2$ and furnished the chloride **71** (entry 2, 88% yield) and the bromide **72** (entry 3, 83% yield), respectively. Additionally, a smooth *ipso*-desilylation with ICl was performed to generate the iodide **73** in 88% yield (entry 4). Moreover, desilylative acetoxylation with $PhI(OCOCF_3)_2$ (1.5 equiv) was proceeded in the presence of catalytic amount of $Pd(OAc)_2$ and afforded the 1,3,5-trisubstituted arene **74** in 65% yield (entry 5).[112] However, substituents in *ortho*-position to the TES-group inhibited the acetoxylation reaction.

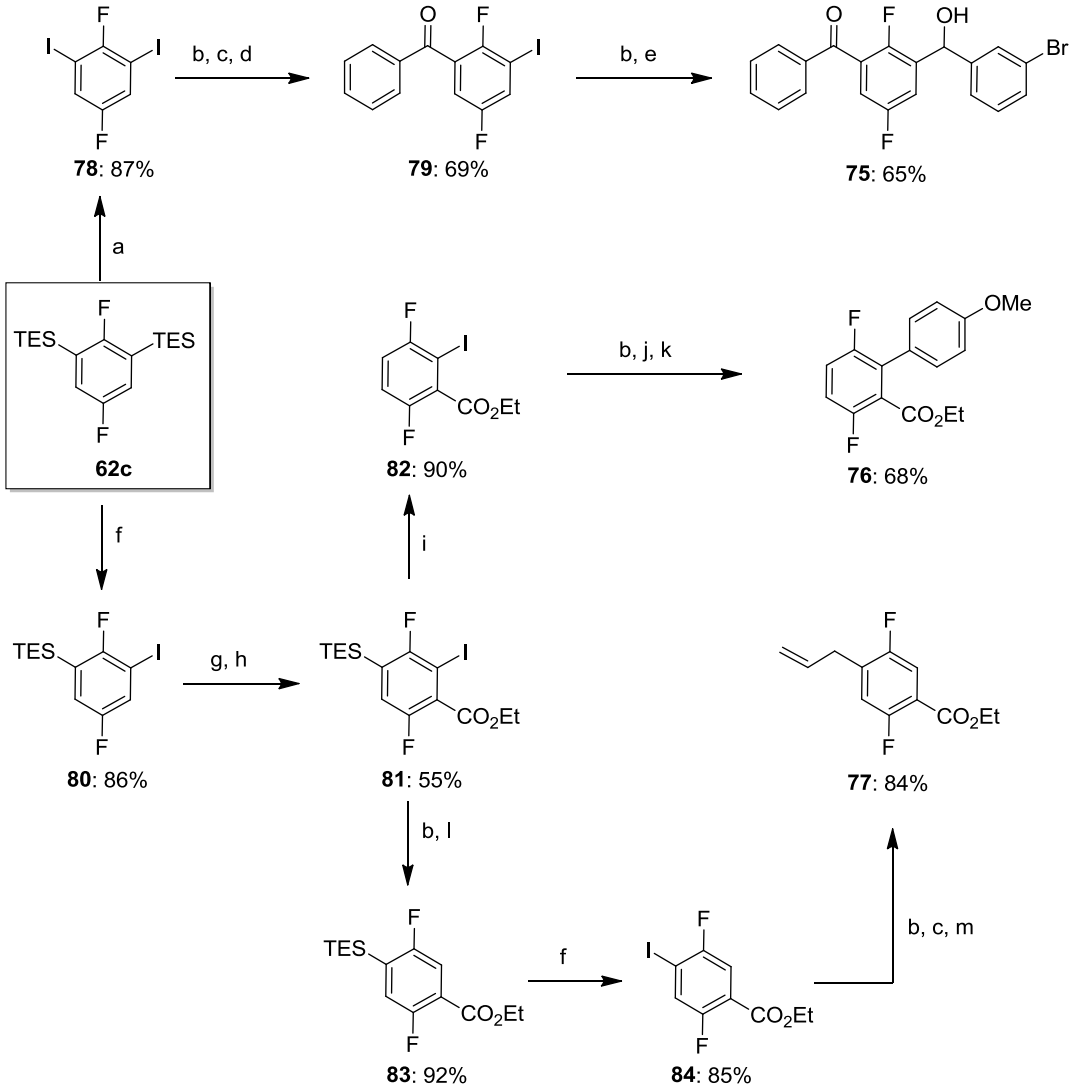
3.7. Preparation of Tetrasubstituted Fluorobenzenes

To demonstrate the superiority of these organometallic methods, we prepared selectively three different tetrasubstituted 1,4-difluorobenzene derivatives by relying on the same toolbox of organometallic procedures, that had already proven successfully in previous chapters. Starting from difluoro compound **62c**, we have made three substitution patterns **75**, **76** and **77** showing the flexibility of these methods by introducing different electrophiles to the 1,4-difluoro core structure (Scheme 45). Thus, bis silyl compound **62c** was fully desilylated by ICl (3.0 equiv) at 25 °C furnished the diiodo derivative **78** in 87% yield. Iodine-magnesium exchange reaction with *i*PrMgCl·LiCl (**1**) at 0 °C and subsequent copper-mediated acylation with benzoyl chloride afforded ketone **79** in 69% yield. A second iodine-magnesium exchange reaction with *i*PrMgCl·LiCl (**1**) at 0 °C and trapping with 3-bromobenzaldehyde provided the 2,6-substituted 1,4-difluorobenzene **75** in 65% yield.

The two other desired compounds were prepared starting with a mono deprotection of arene **62c** with ICl (1.0 equiv) to afford the mono iodinated compound **80** in 86% yield. Deprotonation with TMPMgCl·LiCl (**5**) at -20 °C in 4 h and further reaction with ethyl cyanoformate provided the highly functionalized ester **81** in 55% yield. Full desilylation was

[109] K. Groom, S. M. S. Hussain, J. Morin, C. Nilewski, T. Rantanen, V. Snieckus, *Org. Lett.* **2014**, *16*, 2378.
[110] Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, *7*, 2523.
[111] C. L. Fraser, N. R. Anastasi, J. J. S. Lamba, *J. Org. Chem.* **1997**, *62*, 9314.
[112] K. Gondo, J. Oyamada, T. Kitamura, *Org. Lett.* **2015**, *17*, 4778.

achieved with TBAF in THF to provide the tetrasubstituted benzene **82** in 90% yield. Subsequent iodine-magnesium exchange with *i*PrMgCl·LiCl (**1**) and transmetalation with $ZnCl_2$ enabled a palladium catalyzed *Negishi* cross-coupling with 4-iodoanisole to furnish the 2,3-substituted 1,4-difluorobenzene **76** in 68% yield.



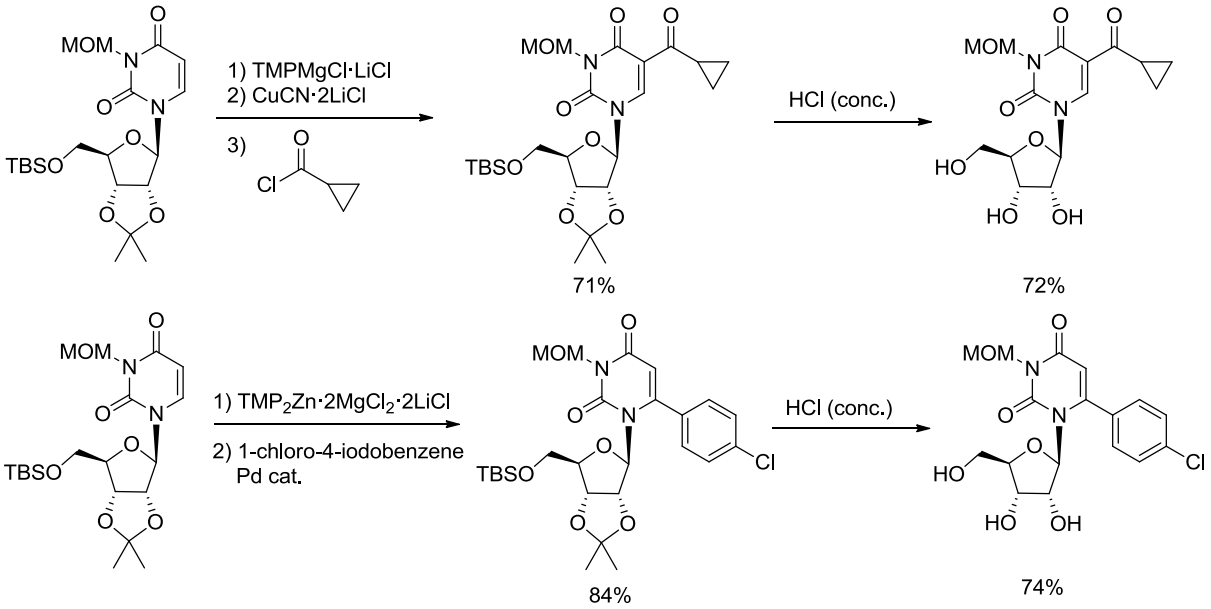
Scheme 45: Preparation of different tetrasubstituted 1,4-difluorobenzene derivatives. [a] ICl (3.0 equiv), CH_2Cl_2, 25 °C, 20 h; [b] *i*PrMgCl·LiCl (**1**, 1.1 equiv), THF, 0 °C, 1 h; [c] CuCN·2LiCl (1.2 equiv); [d] PhCOCl (1.2 equiv), 25 °C, 6 h; [e] 3-BrPhCHO (1.2 equiv), 25 °C, 12 h; [f] ICl (1.0 equiv), CH_2Cl_2, 25 °C, 20 h; [g] TMPMgCl·LiCl (**5**, 1.2 equiv), THF, -20 °C, 4 h; [h] $NCCO_2Et$ (1.2 equiv), 25 °C, 2 h; [i] TBAF (1.2 equiv), THF, 0 °C, 2 h; [j] $ZnCl_2$ (1.2 equiv); [k] $Pd(dba)_2$ (3 mol%), P(2-furyl)$_3$ (6 mol%), 4-iodoanisole (1.2 equiv), 25 °C, 4 h; [l] sat. aq. NH_4Cl; [m] allyl bromide (1.2 equiv), 25 °C, 6 h.

Finally, the synthesis of the third desired compound was accomplished by deiodination of **81** using *i*PrMgCl·LiCl (**1**) followed by a sequent quench with aq. NH_4Cl solution to provide the tetrasubstituted benzene **83** in 92% yield. A subsequent desilylation with ICl (1.0 equiv) afforded the iodo compound **84** in 85% yield. Additional iodine-magnesium exchange with *i*PrMgCl·LiCl (**1**) and copper-mediated allylaltion with allyl bromide furnished the 2,5-substituted 1,4-difluorobenzene **77** in 84% yield.

4. SUMMARY

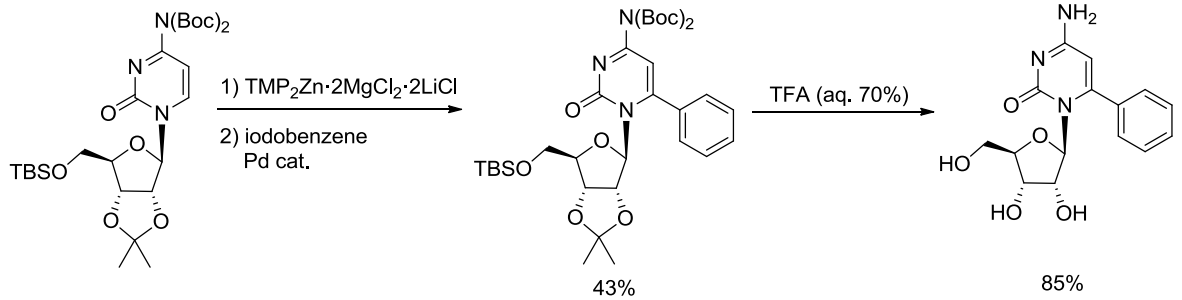
4.1. Metalation and Deprotection of Uracils, Uridines and Cytidine

In summary, we have shown that the Lewis acid $MgCl_2$ allowed control of the metalation regioselectivity of uridines and subsequent reactions with various electrophiles provided easy access to functionalized nucleosides (Scheme 46). In the absence of a Lewis acid, metalation of uridine derivatives with TMPMgCl·LiCl occured at the position C(5). In the presence of $MgCl_2$, zincation using $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ occured at the position C(6). Further deprotection with HCl afforded various MOM-protected uridines.



Scheme 46: Regioselective functionalization of uridine.

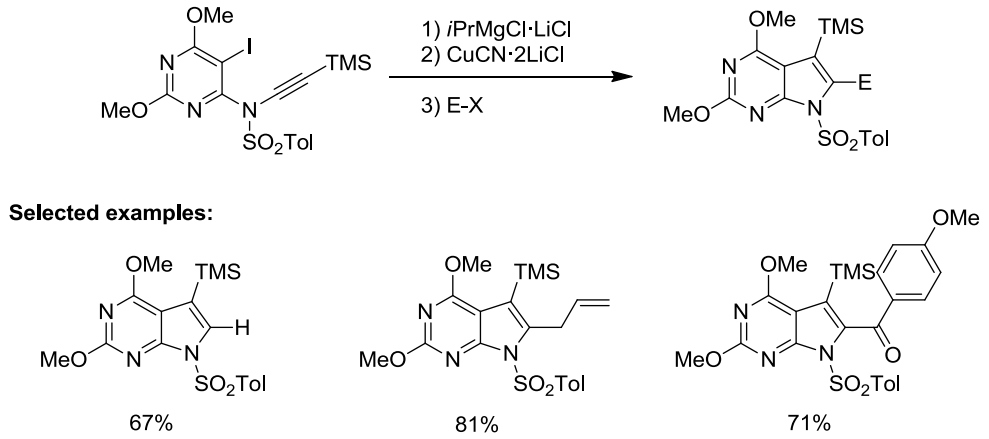
Additionally, using $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ also allowed to functionalize cytidine derivatives at the position C(6) and deprotection with TFA furnished the fully deprotected cytidine derivative (Scheme 47).



Scheme 47: Regioselective functionalization and deprotection of cytidine.

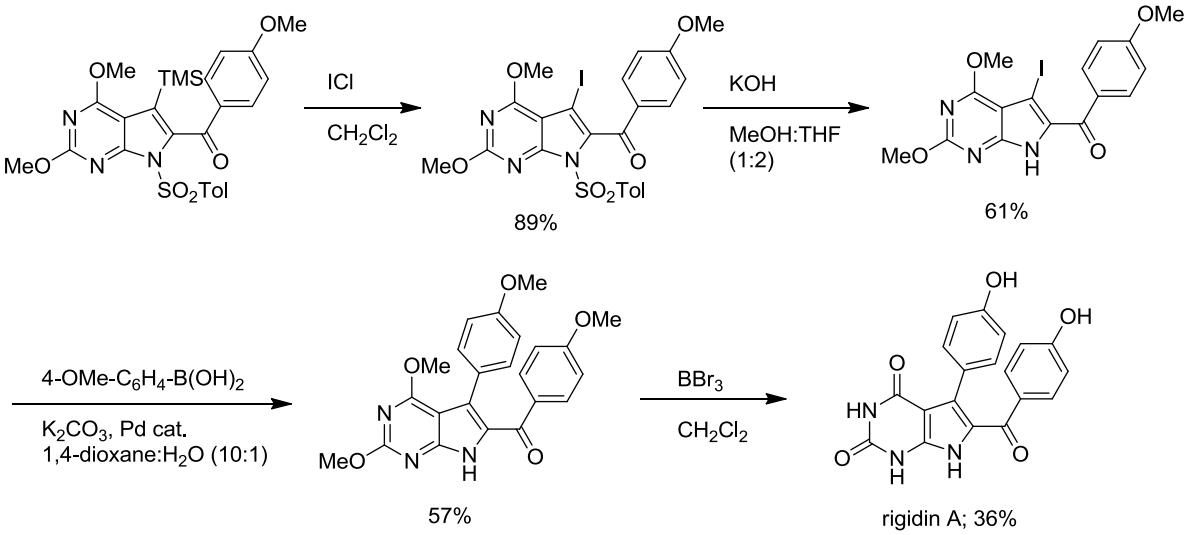
4.2. Preparation of Functionalized Pyrrolo[2,3-*d*]pyrimidines *via* an Intramolecular Copper-mediated Carbomagnesiation of Ynamides

A mild and general intramolecular copper-mediated carbomagnesiation procedure for the synthesis of higly functionalized pyrrolo[2,3-*d*]pyrimidines starting from the readily available ynamide was performed (Scheme 48).



Scheme 48: Preparation of pyrrolo[2,3-*d*]pyrimidines by a copper-mediated cyclization reaction starting from iodo-ynamides.

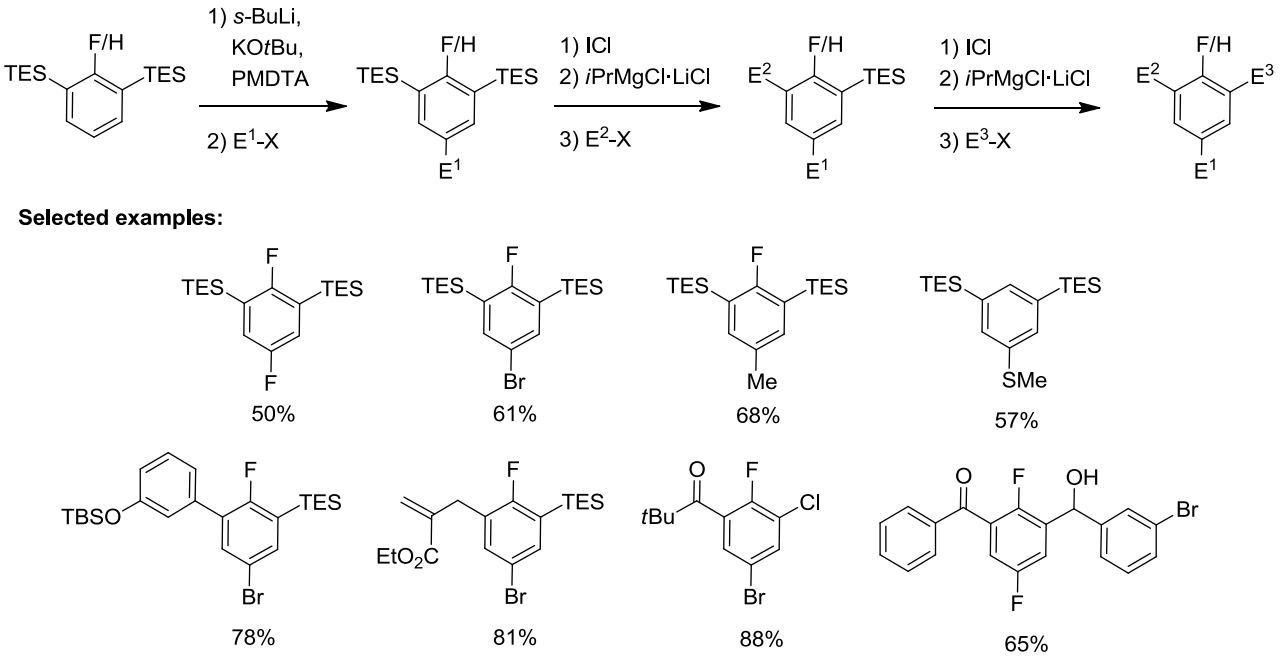
Further functionalization of these *N*-heterocycles gave access to a synthetic route of the marine alkaloid rigidin A (Scheme 49).



Scheme 49: Synthesis of rigidin A.

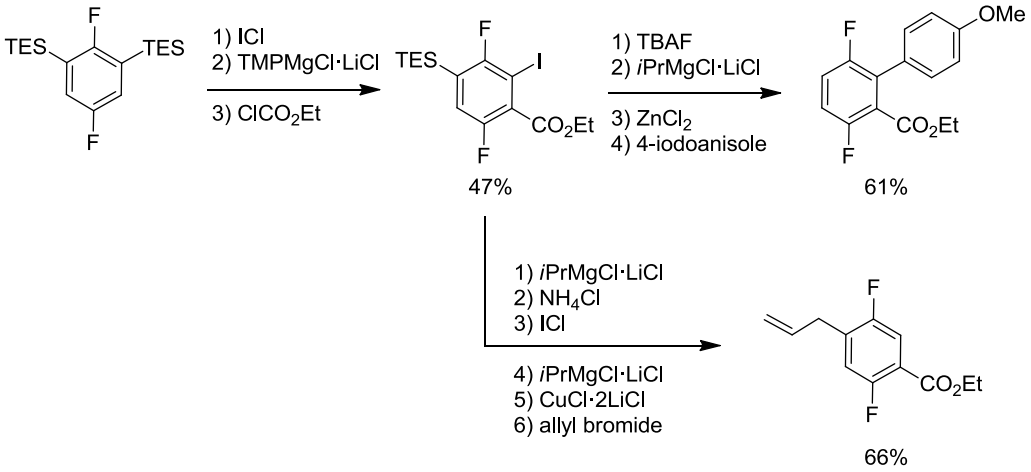
4.3. Regioselective Preparation of Tetrasubstituted Fluorobenzenes

Furthermore, a new synthetic protocol for a regioselective remote metalation of benzenes was developed (Scheme 50). The presence of two sterical demanding triethylsilyl groups forced the lithiation in *meta*- or *para*-position. Subsequent trapping with electrophiles provided rather unusual substitution pattern. Further desilylation reactions and regioselective functionalization with *via* halogen-magnesium exchange with *i*PrMgCl·LiCl afforded various 2,6-tetrasubstituted 1,4-dihalobenzene derivatives.



Scheme 50: Regioselective functionalization in remote *meta*- or *para*-position and preparation of 2,6-tetrasubstituted 1,4-dihalobenzene derivatives.

Moreover, we selectively prepared the additional two other tetrasubstituted 1,4-difluorobenzene derivatives with different substitution patterns starting with a metalation using TMPMgCl·LiCl. Following desilylation or exchange reactions allowed a short access to the 2,3-substituted or 2,5-substituted 1,4-difluorobenzene derivatives within a few steps (Scheme 51).



Scheme 51: Regioselective preparation of 2,3-tetrasubstituted and 2,5-tetrasubstituted 1,4-difluorobenzene derivatives.

C. EXPERIMENTAL SECTION

1. General Considerations

All reactions are carried out under argon atmosphere in flame-dried glassware. Syringes which are used to transfer anhydrous solvents or reagents are purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refere to isolated yields of compounds estimated to be pure as determined by ^{1}H-NMR (25 °C) and capillary GC. The products are prepared corresponding to known literature procedures. The analytical data for known compounds match the literature data.

1.1. Solvents

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

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

1,4-Dioxane was predried over $CaCl_2$ and distilled from Na.

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

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

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

PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) was dried over KOH and distilled.

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 argon atmosphere.

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

Triethylamine was dried over KOH and distilled.

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

1.2. Preparation of Reagents

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

TMPH was distilled under argon prior to use.

Preparation of CuCN·2LiCl solution:

CuCN·2LiCl solution (1.0 M in THF) was prepared by drying CuCN (7.17 g, 80 mmol) and LiCl (6.77 g, 160 mmol) in a *Schlenk*-tube under vacuum at 140 °C for 5 h. After cooling, dry THF (80 mL) was added and stirring was continued until all salts were dissolved.

Preparation of $ZnCl_2$ solution:

$ZnCl_2$ solution (1.0 M in THF) was prepared by drying $ZnCl_2$ (136.3 g, 100 mmol) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, dry THF (100 mL) was added and stirring was continued until all salts were dissolved.

Preparation of TMPMgCl·LiCl (7):

In a dry and argon-flushed *Schlenk*-flask TMPH (2,2,6,6-tetramethylpiperidine, 14.8 g, 105 mmol) was added to *i*PrMgCl·LiCl (**6**) (71.4 mL, 1.40 M in THF, 100 mmol) at 23 °C and the mixture was stirred for 3 days at 23 °C. The freshly prepared TMPMgCl·LiCl (**7**) was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of $TMP_2MgCl·LiCl$ (8):

$TMP_2Mg·2LiCl$ solution (0.6 M in THF) was prepared by the slow addition of *n*-BuLi (4.26 mL, 2.35 M in hexane, 10 mmol) to a solution of TMPH (1.41 g, 10 mmol) in THF (10 mL) at -40 °C. After stirring for 30 min the mixture was warmed up to 0 °C and TMPMgCl·LiCl (**7**) (8.3 mL, 1.2 M in THF, 10 mmol) was added dropwise. The resulting mixture was stirred for 30 min, warmed up to 23 °C and the solvent was evaporated under vacuum (10^{-3} mbar). THF was then added slowly under vigorous stirring until the salts were completely dissolved.

Preparation of TMPLi (4):

TMPLi solution (0.63 M in THF) was prepared by slow addition of *n*-BuLi (2.17 mL, 5.0 mmol, 2.3 M in hexane) to a solution of TMPH (706 mg, 0.85 mL, 5.0 mmol) in THF (5 mL) at -40 °C and stirred for 30 min at -40 °C.

***i*PrMgCl·LiCl** (**1**) was purchased as a solution in THF from Rockwood Lithium GmbH.

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

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

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

Content determination of organometallic reagent:

***n*-BuLi** was titrated using *i*PrOH and 1,10-phenanthroline as indicator in THF. [113]

Organomagnesium reagents were titrated using I_2 in THF.

$TMP_2Mg·2LiCl$ and **TMPMgCl·LiCl** were titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF at -40 °C.

TMPLi was titrated using *N*-benzylbenzamide in THF.[114]

[113] H.-S. Lin, A Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[114] A.F. Burchat, J.M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281.

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 bonds are 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), DMSO-d_6 (δ 2.50 ppm for ^{1}H-NMR and δ 39.5 ppm for ^{13}C-NMR). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), m (multiplet), q (quartet), quint (quintet), sxt (sextet), oct (octet), as well as br (broad).

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:

- Phosphomolybdic 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. URACIL, URIDINE, CYTIDINE

2.1. Typical Procedures

Typical Procedure for the Metalation of Uracil in C(5) Position using TMPMg·LiCl (5) (TP1):
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with 1,3-dimethyluracil (1.0 equiv) in dry THF (0.5 M solution). TMPMgCl·LiCl was added at -40 °C and stirred at this temperature for 4 h (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in THF).

Typical Procedure for Allylation or Acylation Reactions (TP2):
To the freshly prepared magnesium or zinc reagent was added CuCN·2LiCl (1.1 equiv, 1.0 M in THF) and the reaction mixture was stirred for 15 min at the indicated temperature The respective allyl bromide or acyl chloride was added and the reaction mixture was stirred for the indicated time and temperature. The reaction mixture was quenched with concentrated aqueous NH_4Cl:NH_3-solution (19:1), extracted three times with EtOAc. The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for Cross-Coupling Reactions (TP3):
To the freshly prepared magnesium reagent was added $ZnCl_2$ (1.1 equiv, 1.0 M in THF) and the reaction mixture was stirred for 15 min at 0 °C. The catalytic system and the aryl or vinyl halide (1.0 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with saturated aqueous NH_4Cl-solution, extracted three times with EtOAc, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for the Metalation of Uracil in C(6) Position using $TMP_2Zn·2MgCl_2·2LiCl$ (8) (TP4):
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum was charged with 1,3-dimethyluracil (1.0 equiv) in dry THF (0.5 M solution). $TMP_2Zn·2MgCl_2·2LiCl$ was added at -30 °C and stirred at this temperature for 48 h (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in THF).

Typical Procedure for the Metalation of Uridine in C(5) Position using TMPMg·LiCl (5) (TP5):
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum was charged with 5'-O-*tert*-butyldimethylsilyl-4-(4-methoxybenzyl)-2',3'-O-isopropylidene uridine (1.0 equiv) in dry THF (0.5 M solution). TMPMgCl·LiCl was added at -40 °C and stirred at this

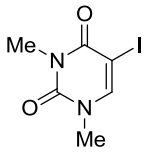
temperature for 24 h (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in THF).

Typical Procedure for the Metalation of uridine in C(6) position using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (8) (TP6):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum was charged with 5'-O-*tert*-butyldimethylsilyl-4-(4-methoxybenzyl)-2',3'-O-isopropylidene uridine (1.0 equiv) in dry THF (0.5 M solution). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ was added at -30 °C and stirred at this temperature for 72 h (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in THF).

2.2. Synthesis of 1,3-Dimethyluracil Derivatives

5-Iodo-1,3-dimethyluracil (16a)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. After the completion of the metalation iodine (280 mg, 1.1 mmol, 1.1 equiv) was added dropwise at -40 °C and allowed to warm up to room temperature within 6 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 8:2:0.05) afforded **16a** (192 mg, 72%) as a colorless solid.

m.p.: 227 - 229 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.23 (s, 1H), 3.28 (s, 3H), 3.19 (s, 3H).

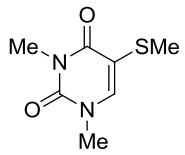
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 160.7, 151.6, 149.4, 66.7, 36.9, 29.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3050, 2955, 1688, 1634, 1616, 1509, 1475, 1441, 1425, 1391, 1352, 1340, 1262, 1222, 1143, 1070, 1011, 957, 944, 814, 752.

MS (EI, 70 eV): m/z (%) = 266 (100), 208 (13), 167 (19).

HRMS ($C_6H_7IN_2O_2$): calc.: 265.9552; found: 265.9548 (M^+).

5-(Methylthio)-1,3-dimethyluracil (16b)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. After the completion of the metalation dimethyl disulfide (103 mg, 1.1 mmol, 1.1 equiv) was added dropwise at -40 °C and allowed to warm up to room temperature within 6 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 7:3:0.05) afforded **16b** (104 mg, 56%) as a colorless solid.

m.p.: 187 - 189 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.42 (s, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.33 (s, 3H).

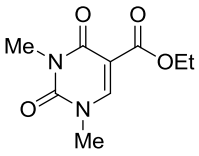
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.7, 153.0, 144.7, 66.7, 39.8, 31.4, 17.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3049, 2940, 1672, 1633, 1616, 1510, 1458, 1418, 1386, 1270, 1220, 1196, 1144, 1092, 1004, 968, 858, 786, 742, 668.

MS (EI, 70 eV): m/z (%) = 186 (100), 171 (25), 140 (36), 83 (12), 42 (74).

HRMS ($C_7H_{10}N_2O_2S$): calc.: 186.0463; found: 186.0474 (M^+).

5-Carboxylic acid ethyl ester-1,3-dimethyluracil (16c)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. After the completion of the metalation ethyl chloroformate (120 mg, 1.1 mmol, 1.1 equiv) was added dropwise at -40 °C and allowed to warm up to room temperature within 6 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 7:3:0.05) afforded **16c** (140 mg, 66%) as a colorless solid.

m.p.: 113.1 - 114.8 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.18 (d, J = 1.6 Hz, 1H), 4.37 – 4.30 (m, 2H), 3.49 (d, J = 1.5 Hz, 3H), 3.36 (d, J = 1.4 Hz, 3H), 1.39 – 1.32 (m, 3H).

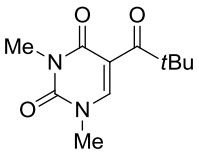
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.2, 159.2, 151.1, 149.9, 104.4, 61.3, 37.8, 28.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 2986, 2956, 2920, 1738, 1696, 1656, 1616, 1522, 1444, 1372, 1330, 1300, 1252, 1210, 1130, 1076, 1036, 966, 906, 872, 792, 762, 694.

MS (EI, 70 eV): m/z (%) = 212 (25), 167 (85), 140 (100), 110 (9), 97 (11), 83 (17), 71 (11), 57 (16), 53 (9), 42 (61).

HRMS ($C_9H_{12}N_2O_4$): calc.: 212.0797; found: 212.0800 (M^+).

5-(Pivaloyl)-1,3-dimethyluracil (16d)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP2** with CuCN·2LiCl (1.2 mL, 1.2 mmol, 1.0 M in THF, 1.2 equiv) and pivaloyl chloride (54 mg, 1.2 mmol, 1.2 equiv) and allowed to warm to 25 °C in 16 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **16d** (186 mg, 83%) as a colorless solid.

m.p.: 103 - 105 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.95 (s, 1H), 3.33 (s, 3H), 3.17 (s, 3H), 1.17 (s, 9H).

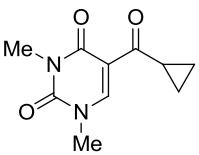
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 206.1, 160.8, 151.3, 146.3, 114.0, 44.5, 37.2, 28.1, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3067, 2963, 2926, 2872, 1777, 1705, 1651, 1609, 1520, 1478, 1443, 1390, 1356, 1342, 1284, 1221, 1179, 1049, 1026, 986, 967, 941, 934, 846, 794, 785, 760, 738, 663.

MS (EI, 70 eV): m/z (%): 224 (28), 167 (100), 140 (34), 57 (13), 42 (66), 40 (16).

HRMS ($C_{11}H_{16}N_2O_3$): calc.: 224.2563; found: 224.1157 (M^+).

5-(Cyclopropanecarbonyl)-1,3-dimethyluracil (16e)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP2** with CuCN·2LiCl (1.2 mL, 1.2 mmol, 1.0 M in THF, 1.2 equiv) and

cyclopropanecarbonyl chloride (125 mg, 1.2 mmol, 1.2 equiv) and allowed to warm to 25 °C in 16 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **16e** (148 mg, 71%) as a colorless solid.

m.p.: 154 - 156 °C.

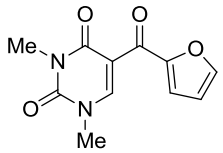
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.25 (s, 1H), 3.52 (s, 3H), 3.43 – 3.30 (m, 1H), 3.27 (s, 3H), 1.00 – 0.94 (m, 2H), 0.93 – 0.88 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 196.1, 161.4, 149.8, 149.7, 110.8, 36.9, 27.2, 18.4, 11.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3103, 3057, 3006, 2958, 1704, 1659, 1644, 1594, 1516, 1476, 1442, 1424, 1417, 1391, 1351, 1338, 1197, 1186, 1119, 1086, 1071, 1064, 1047, 1030, 996, 987, 972, 887, 778, 758, 693, 665.

HRMS (ESI) ($C_{10}H_{12}N_2O_3$): calc.: 208.2139; found: 208.2139 (M^+).

5-(Furan-2-carbonyl)-1,3-dimethyluracil (16f)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP2** with CuCN·2LiCl (1.2 mL, 1.2 mmol, 1.0 M in THF, 1.2 equiv) and 2-furoyl chloride (157 mg, 1.2 mmol, 1.2 equiv) and allowed to warm to 25 °C in 16 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 8:2:0.05) afforded **16f** (154 mg, 66%) as a colorless solid.

m.p.: 139 - 140 °C.

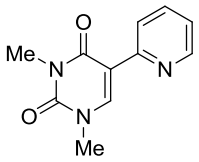
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.28 (s, 1H), 8.01 (dd, *J* = 1.75, 0.78 Hz, 1 H), 7.38 (dd, *J* = 3.70, 0.78 Hz, 1 H), 6.71 (dd, *J* = 3.61, 1.66 Hz, 1 H), 3.37 (s, 3H), 3.17 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 177.0, 160.4, 152.0, 151.3, 149.1, 148.6, 121.4, 113.0, 111.3, 37.4, 28.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3142, 3129, 3097, 2952, 1706, 1695, 1658, 1647, 1600, 1554, 1520, 1470, 1458, 1437, 1401, 1390, 1364, 1297, 1243, 1208, 1167, 1121, 1097, 1041, 998, 940, 923, 893, 881, 863, 818, 787, 773, 753, 697, 683.

HRMS (ESI) ($C_{11}H_{10}N_2O_4$): calc.: 234.2110; found: 234.0623 (M^+).

5-(Pyridin-2-yl)-1,3-dimethyluracil (16g)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv), $Pd(dba)_2$ (11 mg, 2 mol%) and $P(2\text{-furyl})_3$ (9 mg, 4 mol%) and 2-bromopyridine (190 mg, 1.2 mmol, 1.2 equiv) at 25 °C in 16 h. The mixture was quenched with sat. aq. NaCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 8:2:0.05) afforded **16g** (104 mg, 48%) as a colorless solid.

m.p.: 205 - 207 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.68 – 8.64 (m, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.97 (ddd, *J* = 8.0, 2.3, 1.7 Hz, 1H), 7.38 (s, 1H), 7.34 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 3.52 (s, 3H), 3.45 (s, 3H).

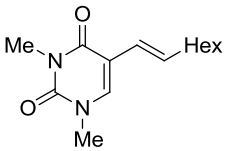
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.1, 151.3, 149.0, 148.4, 140.6, 136.2, 129.0, 123.1, 111.1, 37.3, 28.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1688, 1646, 1632, 1565, 1508, 1480, 1456, 1432, 1408, 1367, 1349, 1293, 1210, 1126, 1044, 1005, 970, 910, 817, 780, 771, 753, 717, 669.

MS (EI, 70 eV): m/z (%) = 218 (9), 217 (100), 160 (10), 159 (80), 119 (17), 104 (9), 91 (11), 73 (9), 44 (20), 42 (32).

HRMS ($C_{11}H_{11}N_3O_2$): calc.: 217.2239; found: 217.0841 (M^+).

5-(*E*)-(Oct-1-en-1-yl)-1,3-dimethyluracil (16h)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv), $Pd(dba)_2$ (11 mg, 2 mol%) and $P(2\text{-furyl})_3$ (9 mg, 4 mol%) and (*E*)-1-iodooct-1-ene (286 mg, 1.2 mol, 1.2 equiv) at 25 °C in 6 h. The mixture was quenched with sat. aq. NaCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **16h** (198 mg, 79%) as a colorless solid.

m.p.: 182.4 - 183.1 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.07 (s, 1H), 6.28 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.13 – 6.00 (m, 1H), 3.35 (s, 3H), 3.30 (s, 3H), 2.08 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.35 (m, 2H), 1.23 (m, 6H), 0.85 – 0.76 (m, 3H).

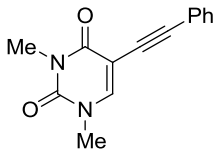
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.5, 151.2, 137.9, 132.5, 120.7, 111.9, 37.0, 33.4, 31.7, 29.2, 28.9, 28.0, 22.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2856, 1698, 1658, 1454, 1368, 1290, 1260, 1172, 1088, 968, 928, 840, 758, 690, 658.

MS (EI, 70 eV): m/z (%) = 250 (51), 221 (11), 207 (13), 193 (42), 179 (86), 166 (13), 153 (100), 122 (31), 94 (21), 81 (13), 67 (13), 55 (20), 53 (11), 43 (51), 42 (43).

HRMS ($C_{14}H_{22}N_2O_2$): calc.: 250.1681; found: 250.1675 (M^+).

5-(Phenylethynyl) -1,3-dimethyluracil (16i)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, $ZnCl_2$ (1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv) was added and stirred for 1 h at -20 °C. CuCN·LiCl (1.2 ml, 1.2 mmol, 1.0 M, 1.2 equiv) and (iodoethynyl)benzene (274 mg, 1.2 mol, 1.2 equiv) were added was stirred at 25 °C for 16 h. The mixture was quenched with sat. aq. NaCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **16i** (130 mg, 54%) as a colorless solid.

m.p.: 166.5 - 167.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.50 (s, 1H), 7.49 – 7.46 (m, 2H), 7.32 – 7.28 (m, 3H), 3.43 (s, 3H), 3.38 (s, 3H).

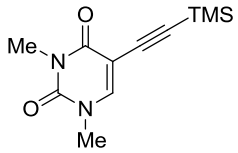
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.6, 150.9, 145.1, 131.6, 128.5, 128.3, 122.7, 99.2, 93.3, 80.5, 37.3, 28.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2950, 2854, 1700, 1648, 1446, 1370, 1346, 1306, 1216, 1152, 1082, 1042, 992, 952, 906, 860, 836, 792, 750, 688.

MS (EI, 70 eV): m/z (%) = 240 (100), 211 (2), 182 (15), 153 (5), 140 (6), 126 (14), 114 (37), 91 (2), 86 (2), 74 (2), 63 (5), 42 (25).

HRMS ($C_{14}H_{12}N_2O_2$): calc.: 240.0899; found: 240.0889 (M^+).

5-((Trimethylsilyl)ethynyl)-1,3-dimethyluracil (16j)



According to **TP1** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (1.0 ml, 1.1 mmol, 1.10 M, 1.1 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, $ZnCl_2$ (1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv) was added and stirred for 1 h at -20 °C. CuCN·LiCl (1.2 ml, 1.2 mmol, 1.0 M, 1.2 equiv) and (iodoethynyl)trimethylsilane (269 mg, 1.2 mol, 1.2 equiv) were added was stirred at 25 °C for 16 h. The mixture was quenched with sat. aq. NaCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **16j** (130 mg, 74%) as a colorless solid.

m.p.: 172.8 - 174.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 7.45 (s, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 0.20 (s, 9H).

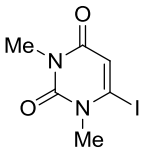
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.6, 150.9, 146.0, 99.2, 99.1, 95.6, 37.3, 28.3, -0.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2954, 2902, 2148, 1704, 1646, 1454, 1392, 1348, 1248, 1182, 1094, 1048, 984, 958, 922, 842, 766, 702, 666.

MS (EI, 70 eV): m/z (%) = 236 (25), 221 (100), 207 (4), 193 (6), 164 (10), 123 (33), 107 (12), 93 (9), 79 (8).

HRMS ($C_{11}H_{16}N_2O_2Si$): calc.: 236.0981; found: 236.1054 (M^+).

6-Iodo-1,3-dimethyluracil (18a)



According to **TP4** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn·2MgCl_2·2LiCl$ (0.84 ml, 0.6 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 48 h at this temperature. After the completion of the metalation iodine (307 mg, 1.2 mmol, 1.2 equiv) was added dropwise at -30 °C and allowed to warm to to 25 °C within 6 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **18a** (216 mg, 81%) as a colorless solid.

m.p.: 183 - 184 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 6.41 (s, 1H), 3.52 (s, 3H), 3.10 (s, 3H).

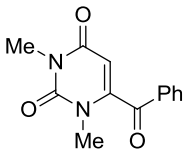
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.2, 150.0, 117.0, 113.0, 41.7, 28.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3050, 2955, 1688, 1634, 1616, 1509, 1475, 1441, 1425, 1391, 1352, 1340, 1262, 1222, 1143, 1070, 1011, 957, 944, 814, 752.

MS (EI, 70 eV): m/z (%) = 267 (6), 266 (95), 83 (4), 82 (100), 57 (6), 54 (8), 52 (6).

HRMS ($C_6H_7IN_2O_2$): calc.: 265.9552; found: 265.9536 (M^+).

6-Benzoyl-1,3-dimethyluracil (18b)



According to **TP4** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.84 ml, 0.6 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 48 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP2** with CuCN·2LiCl (1.2 mL, 1.2 mmol, 1.0 M in THF, 1.2 equiv) and benzoyl chloride (169 mg, 1.2 mmol, 1.2 equiv) and allowed to warm to 25 °C in 16 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 8:2:0.05) afforded **18b** (204 mg, 84%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.13 – 7.92 (m, 2H), 7.89 – 7.70 (m, 1H), 7.70 – 7.46 (m, 2H), 5.85 (s, 1H), 3.21 (s, 3H), 3.09 (s, 3H).

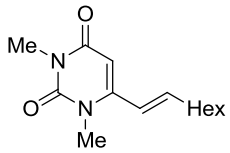
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 189.5, 162.1, 151.9, 150.3, 136.0, 134.3, 130.7, 129.8, 100.9, 33.7, 28.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3706, 3086, 3064, 2954, 1705, 1651, 1594, 1580, 1519, 1476, 1446, 1432, 1399, 1364, 1312, 1252, 1210, 1180, 1159, 1073, 1053, 1024, 994, 914, 844, 827, 805, 758, 726, 699, 687, 668.

MS (EI, 70 eV): m/z (%) = 244 (62), 216 (37), 215 (42), 159 (19), 158 (21), 105 (100), 82 (81), 77 (63).

HRMS ($C_{13}H_{12}N_2O_3$): calc.: 244.0848; found: 244.0845 (M^+).

6-(*E*)-(Oct-1-en-1-yl)-1,3-dimethyluracil (18c)



According to **TP4** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (0.84 ml, 0.6 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 48 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv), $Pd(dba)_2$ (11 mg, 2 mol%) and $P(2\text{-furyl})_3$ (9 mg, 4 mol%) and (*E*)-1-iodooct-1-ene (286 mg, 1.2 mol, 1.2 equiv) at 25 °C in 6 h. The mixture was quenched with sat. aq. NaCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **18c** (185 mg, 74%) as a colorless solid.

m.p.: 67 - 68 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 6.33 (m, 1H), 6.13 (m, 1H), 5.74 (m, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 2.21 – 2.16 (m, 2H), 1.57 – 1.18 (m, 8H), 0.96 – 0.76 (m, 3H).

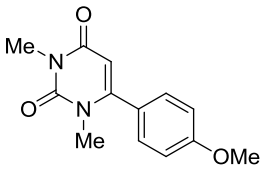
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.69, 152.35, 152.07, 142.13, 121.29, 98.42, 32.92, 32.25, 31.48, 28.69, 28.33, 27.84, 22.47, 14.09.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 3019, 2919, 2864, 2864, 2854, 2834, 1692, 1657, 1637, 1572, 1509, 1452, 1428, 1372, 1341, 1308, 1296, 1288, 1248, 1235, 1221, 1189, 1173, 1154, 1132, 1089, 1058, 1026, 999, 975, 948, 931, 918, 893, 883, 862, 853, 821, 785, 767, 752, 738, 726, 674.

MS (EI, 70 eV): m/z (%) = 250 (60), 207 (12), 194 (13), 193 (100), 180 (11), 167 (30).

HRMS ($C_{14}H_{22}N_2O_2$): calc.: 250.1681; found: 250.1683 (M^+).

6-(4-Methoxyphenyl)-1,3-dimethyluracil (18d)



According to **TP4** 1,3-dimethyluracile (**9**, 140 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (0.84 ml, 0.6 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 48 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (1.2 mL, 1.0 M in THF, 1.2 mmol, 1.2 equiv), $Pd(dba)_2$ (11 mg, 2 mol%) and $P(2\text{-furyl})_3$ (9 mg, 4 mol%) and 4-iodoanisole (281 mg, 1.2 mmol, 1.2 equiv) at 25 °C in 16 h. The mixture was quenched with sat. aq. NaCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash

chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 8:2:0.05) afforded **18d** (207 mg, 84%) as a colorless solid.

m.p.: 88 - 89 °C.

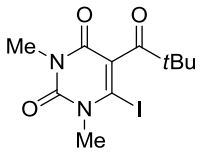
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.34 (d, J = 8.80 Hz, 2H), 7.01 (d, J = 8.80 Hz, 2H), 5.59 (s, 1H), 3.82 (s, 3H), 3.29 (s, 3H), 3.19 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.2, 161.2, 155.8, 152.6, 129.3, 125.3, 113.9, 101.0, 54.59, 33.84, 27.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2923, 2869, 2846, 1699, 1687, 1645, 1603, 1570, 1514, 1443, 1429, 1414, 1391, 1368, 1299, 1254, 1226, 1206, 1178, 1164, 1151, 1119, 1027, 1015, 1010, 1001, 846, 839, 813, 791, 761, 738, 716, 704, 699, 688, 659.

HRMS (ESI) ($C_{13}H_{14}N_2O_3$): calc.: 246.1004; found: 246.0996 (M^+).

6-Iodo-1,3-dimethyl-5-pivaloyl uracil (19)



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with 5-pivaloyl-1,3-dimethyl-uracil (**16d**, 123 mg, 0.54 mmol, 1.0 equiv) in dry THF (0.5 mL). TMPMgCl·LiCl was added at -30 °C and stirred at this temperature for 12 h. After the completion of the metalation iodine (207 mg, 0.81 mmol, 1.5 equiv) was added dropwise at -30 °C and allowed to warm to room temperature. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **19** (98 mg, 52%) as a colorless solid.

m.p.: 151 - 153 °C.

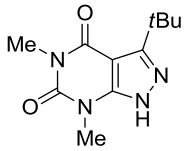
^{1}H-NMR (200 MHz, $CDCl_3$): δ / ppm = 3.73 (s, 3H), 3.33 (s, 3H), 1.34 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 207.3, 165.2, 149.0, 124.2, 112.7, 45.1, 34.7, 28.0, 27.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3048, 2957, 1694, 1638, 1618, 1507, 1455, 1440, 1426, 1377, 1352, 1320, 1252, 1220, 1143, 1048, 1011, 950, 814, 756.

HRMS (ESI) ($C_{11}H_{15}IN_2O$): calc.: 350.0128; found: 350.0140 (M^+).

3-(*tert*-Butyl)-5,7-dimethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (20)



To a solution of 6-iodo-1,3-dimethyl-5-pivaloyl uracil (**19**, 35 mg, 0.10 mmol, 1.0 equiv) in dry DMF (1 mL) was N_2H_4 (1 M in THD, 0.15 mL, 0.15 mmol, 1.5 equiv) added. The reaction mixture was stirred for 1 h at 60 °C. Upon completion, the reaction was quenched with sat. aq. NaCl (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 3:1:0.05) afforded **20** (23 mg, 0.096 mmol, 96%) as a colorless solid.

m.p.: 255 - 257 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ / ppm = 10.21 (s, 1H), 3.52 (s, 3H), 3.40 (s, 3H), 1.53(s, 9H).

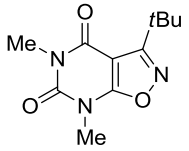
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.9, 155.4, 152.5, 152.0, 97.3, 32.7, 29.7, 28.1, 27.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3222, 3165, 3129, 3073, 3042, 2988, 2965, 2919, 2876, 2854, 1706, 1661, 1596, 1522, 1492, 1436, 1426, 1417, 1405, 1367, 1351, 1307, 1294, 1241, 1010, 981, 925, 786, 774, 743, 708.

MS (EI, 70 eV): m/z (%) = 237 (13), 236 (81), 235 (23), 222 (16), 221 (100), 137 (13).

HRMS ($C_{11}H_{16}N_4O_2$): calc.: 236.1273; found: 236.1216 (M^+).

3-(*tert*-Butyl)-5,7-dimethylisoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (21)



To a solution of 6-iodo-1,3-dimethyl-5-pivaloyl uracil (**19**, 35 mg, 0.10 mmol, 1.0 equiv) in dry DMF (1 mL) was $NH_2OH{\cdot}HCl$ (11 mg, 0.15 mmol, 1.5 equiv) added. The reaction mixture was stirred for 1 h at 60 °C. Upon completion, the reaction was quenched with sat. aq. NaCl (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 4:1:0.05) afforded **21** (22 mg, 0.094 mmol, 94%) as a colorless solid.

m.p.: 230 - 232 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ / ppm = 3.49 (s, 3H), 3.37 (s, 3H), 1.52(s, 9H).

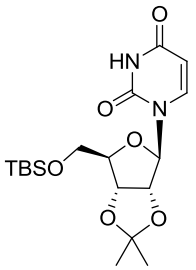
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 185.8, 158.8, 155.0, 151.0, 98.0, 35.4, 30.3, 28.3, 27.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2976, 2930, 2874, 2857, 2361, 2340, 1724, 1673, 1613, 1551, 1497, 1424, 1372, 1362, 1302, 1272, 1250, 1182, 1012, 786, 742.

MS (EI, 70 eV): m/z (%) = 237 (40), 222 (79), 196 (12), 195 (33), 182 (23), 181 (50), 126 (12), 125 (14), 124 (42), 67 (812), 58 (34), 57 (90), 56 (16), 55 (14), 53 (14), 43 (36).
HRMS ($C_{11}H_{15}N_3O_3$): calc.: 237.1113; found: 236.1066 (M^+).

2.3. Protection of Uridine and Cytidine

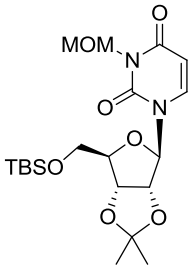
5'-O-*tert*-Butyldimethylsilyl-2',3'-O-isopropylidene uridine (22)



A stirred suspension of uridine (**12**, 10 g, 41 mmol, 1.0 equiv) in dry acetone (200 mL) was treated with conc. H_2SO_4 (0.5 mL) dropwise at 25 °C and the resulting mixture was stirred further for 1 h and neutralized with Et_3N. Evaporation of the solvent and washing one time with acetone gave 2',3'-O-isopropyliden uridine as a crude white solid.
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the cruede 2',3'-O-isopropyliden uridine in dry CH_2Cl_2 (250 mL) and was treated with imidazole (5.6 g, 82 mmol, 2.0 equiv) and TBDMSCl (6.79 g, 45.1 mmol, 1.1 equiv) at 0 °C. The reaction mixture was brought to 25 °C and stirred for 1 h. The solvent was evaporated under vacuum and the solid taken into ethyl acetate (30 mL), washed with water (15 mL), sat. NaCl-solution (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH, 20:1:) afforded **22** (15.7 g, 96%) as a colorless foam.

m.p.: 137.1 - 138.8 °C.
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.43 – 8.35 (m, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 2.8 Hz, 1H), 5.67 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.80 – 4.72 (m, 1H), 4.67 (dd, *J* = 6.2, 2.8 Hz, 1H), 4.31 (q, *J* = 2.7 Hz, 1H), 3.91 (dd, *J* = 11.5, 2.4 Hz, 1H), 3.79 (dd, *J* = 11.5, 2.9 Hz, 1H), 1.58 (d, *J* = 0.8 Hz, 3H), 1.35 (d, *J* = 0.9 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.72, 149.87, 140.46, 114.12, 102.13, 91.90, 86.62, 85.38, 80.26, 63.33, 27.27, 25.83, 25.34, 18.33, -5.45, -5.56.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2856, 2804, 1778, 1690, 1462, 1398, 1368, 1332, 1298, 1268, 1210, 1126, 1090, 1062, 998, 968, 862, 830, 776, 732, 688, 658.
HRMS (ESI) ($C_{17}H_{27}N_2O_6Si$): calc. 383.1683; found 383.1647 (M^+-Me).

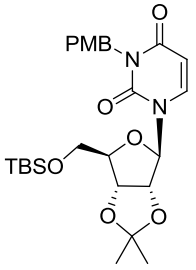
5'-O-*tert*-Butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (23)



To a solution of **22** (1.92 g, 5.00 mmol, 1.0 equiv) and NaH (240 mg, 60% in paraffin oil, 6.0 mmol, 1.2 equiv) in 10 mL dry DMF methoxymethyl chloride (604 mg, 7.5 mmol, 1.5 equiv) was added. After 17 h of stirring at 25 °C the solvent was removed *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc, 4:1) afforded **23** (1.92 g, 87%) as a colorless oil.

^{1}H-NMR (600 MHz, DMSO-d_6): δ / ppm = 7.67 (d, J = 8.2 Hz, 1H), 5.94 (d, J = 2.6 Hz, 1H), 5.72 (d, J = 8.2 Hz, 1H), 5.39 – 5.32 (m, 2H), 4.73 (dd, J = 6.1, 2.7 Hz, 1H), 4.69 (dd, J = 6.1, 2.6 Hz, 1H), 4.35 (q, J = 2.7 Hz, 1H), 3.91 (dd, J = 11.5, 2.3 Hz, 1H), 3.78 (dd, J = 11.6, 3.0 Hz, 1H), 3.43 (s, 3H), 1.58 (s, 3H), 1.35 (d, J = 0.9 Hz, 3H), 0.88 (s, 9H), 0.07 (d, J = 3.9 Hz, 6H).
^{13}C-NMR (150 MHz, DMSO-d_6): δ / ppm = 162.66, 151.00, 139.10, 113.92, 101.58, 93.13, 86.96, 85.73, 80.42, 71.80, 63.40, 57.86, 27.25, 25.81, 25.32, 18.29, -5.59.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2988, 2953, 2932, 2899, 2886, 2858, 1718, 1666, 1453, 1409, 1361, 1254, 1211, 1157, 1126, 1082, 1005, 968, 939, 914, 832, 806, 774, 717, 682.
HRMS (ESI) ($C_{19}H_{31}N_2O_7Si$): calc.: 427.1901; found: 427.1900 (M^+-Me).

5'-O-*tert*-Butyldimethylsilyl-4-(4-methoxybenzyl)-2',3'-O-isopropylidene uridine (24)



To a solution of **22** (1.92 g, 5.00 mmol, 1.0 equiv) and 1,8-diazabicycloundec-7-ene (1.56 g, 10.0 mmol, 2.0 equiv) in 20 mL dry DMF 4-methoxybenzyl chloride (1.14 g, 7.5 mmol, 1.5 equiv) was added. After 17 h of stirring at 25 °C the solvent was removed *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc, 4:1) afforded **24** (2.27 g, 90%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.62 (d, J = 8.1 Hz, 1H), 7.46 – 7.42 (m, 2H), 6.82 – 6.78 (m, 2H), 5.93 (d, J = 2.6 Hz, 1H), 5.70 (d, J = 8.1 Hz, 1H), 5.07 (d, J = 13.6 Hz, 1H), 4.98 (d, J = 13.6 Hz, 1H), 4.73 (dd, J = 6.2, 2.8 Hz, 1H), 4.66 (dd, J = 6.2, 2.6 Hz, 1H), 4.32 (q, J = 2.7 Hz, 1H), 3.89 (dd, J

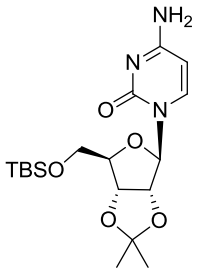
= 11.5, 2.4 Hz, 1H), 3.77 – 3.74 (m, 4H), 1.57 (d, *J* = 0.8 Hz, 3H), 1.35 (d, *J* = 0.8 Hz, 3H), 0.86 (s, 9H), 0.05 (d, *J* = 4.5 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.63, 159.04, 150.84, 138.14, 130.78, 128.98, 113.91, 113.63, 101.64, 93.06, 86.93, 85.81, 80.35, 63.31, 55.20, 43.48, 27.25, 25.78, 25.34, 18.25, -5.49.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2988, 2954, 2931, 2858, 1710, 1663, 1613, 1585, 1512, 1453, 1384, 1344, 1298, 1246, 1212, 1177, 1157, 1128, 1078, 1035, 1005, 967, 907, 832, 806, 775, 729.

HRMS (ESI) ($C_{25}H_{35}N_2O_7Si$): calc.: 503.2214; found: 503.2216 (M^+-Me).

5'-O-*tert*-Butyldimethylsilyl-2',3'-O-isopropylidene cytidine (25)



A stirred suspension of cytidine (**14b**, 10 g, 41 mmol, 1.0 equiv) in dry acetone (200 mL) was treated with conc. H_2SO_4 (0.5 mL) dropwise at 25 °C and the resulting mixture was stirred further for 1 h and neutralized with Et_3N. Evaporation of the solvent and washing one time with acetone gave 2',3'-O-isopropyliden cytidine as a cruede white solid.

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the cruede 2',3'-O-isopropyliden cytidine in dry CH_2Cl_2 (250 mL) and was treated with imidazole (5.6 g, 82 mmol, 2.0 equiv) and TBDMSCl (6.79 g, 45.1 mmol, 1.1 equiv) at 0 °C. The reaction mixture was brought to 25 °C and stirred for 1 h. The solvent was evaporated under vacuum and the solid was dissolved in ethyl acetate (30 mL), washed with water (15 mL), sat. NaCl-solution (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH, 15:1:) afforded **25** (15.0 g, 92%) as a colorless solid.

m.p.: 110.7 - 112.9 °C.

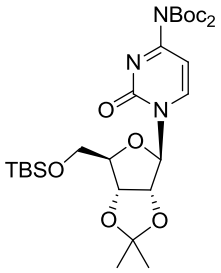
^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.57 (d, *J* = 7.4 Hz, 1H), 7.15 (br, 2H), 5.69 (d, *J* = 2.0 Hz, 1H), 5.61 (d, *J* = 7.4 Hz, 1H), 4.74 (dd, *J* = 6.3, 2.0 Hz, 1H), 4.62 (dd, *J* = 6.3, 3.7 Hz, 1H), 3.99 (dt, *J* = 4.9, 3.9 Hz, 1H), 3.73 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.65 (dd, *J* = 11.2, 5.1 Hz, 1H), 1.38 (s, 3H), 1.19 (s, 3H), 0.77 (s, 9H), -0.05 (d, *J* = 1.2 Hz, 6H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ / ppm = 166.34, 155.29, 143.11, 113.05, 94.40, 93.16, 87.30, 81.01, 63.73, 55.36, 27.53, 26.23, 25.66, 18.43, -4.99.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3332, 3126, 2930, 2858, 2740, 2644, 1640, 1488, 1374, 1254, 1212, 1122, 1078, 968, 926, 834, 778, 720, 680.

HRMS (ESI) ($C_{18}H_{32}N_3O_5Si$): calc. 398.2106; found 398.2108 ($M+H^+$).

5'-O-*tert*-Butyldimethylsilyl-4-(bis(*tert*-butoxycarbonylamino))-2',3'-O-isopropylidene cytidine (26)



Boc_2O (1.78 g, 8.16 mmol, 6.0 eq.) was added to a solution of **25** (540 mg, 1.36 mmol, 1.0 equiv), 4-(dimethylamino)-pyridine (75 mg, 0.55 mmol, 0.4 equiv) and NEt_3 (275 mg, 2.72 mmol, 2.0 equiv) in 2 mL dry THF. The reaction mixture was stirred at 25 °C for 4 h. The mixture was quenched with sat. aq. NaCl (50 mL), extracted with EtOAc (3 x 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc, 6:1) afforded **26** (706 mg, 87%) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.92 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 5.83 (d, J = 1.9 Hz, 1H), 4.70 (dd, J = 6.1, 1.9 Hz, 1H), 4.65 (dd, J = 6.1, 3.3 Hz, 1H), 4.31 – 4.24 (m, 1H), 3.86 (dd, J = 11.5, 2.7 Hz, 1H), 3.72 (dd, J = 11.5, 3.8 Hz, 1H), 1.50 (s, 3H), 1.47 (s, 18H), 1.26 (s, 3H), 0.80 (s, 9H), -0.01 (d, J = 1.2 Hz, 6H).

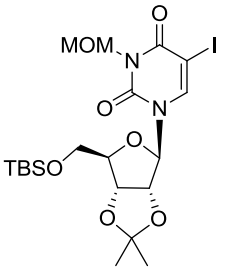
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.50, 154.07, 149.52, 144.29, 113.70, 95.66, 94.23, 88.03, 86.03, 84.85, 80.19, 63.33, 27.69, 27.24, 25.88, 25.32, 18.33, -5.37, -5.48.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2932, 1778, 1744, 1680, 1626, 1525, 1455, 1370, 1319, 1256, 1211, 1156, 1117, 1081, 10005, 960, 925, 835, 810, 781, 736, 682, 662.

HRMS (ESI) ($C_{24}H_{38}N_3O_9Si$): calc.: 540.2377; found: 540.2463 (M^+-*t*Bu).

2.4. Functionalization of Uridine

Preparation of Uridine Derivative (28a)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 24 h at this temperature. The mixture was quenched with iodine (77 mg, 0.3 mmol, 1.2 equiv) and warmed up to 25 °C within 2 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL), extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc:*i*hexane/NEt_3 2:8:0.05) afforded **28a** (99 mg, 70%) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ / ppm = 7.97 (s, 1 H), 5.83 (d, J = 1.94 Hz, 1 H), 5.47 - 5.38 (m, 2 H), 4.75 - 4.69 (m, 2 H), 4.45 - 4.41 (m, 1 H), 3.95 - 3.89 (m, 1 H), 3.82 - 3.76 (m, 1 H), 3.43 (s, 3 H), 1.58 (s, 3 H), 1.36 (s, 3 H), 0.91 - 0.89 (m, 9 H), 0.11 (d, J=0.83 Hz, 6 H).

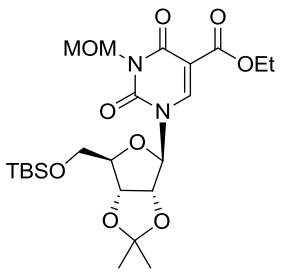
^{13}C-NMR (75 MHz, $CDCl_3$) δ / ppm = 159.8, 150.6, 143.6, 113.8, 94.4, 87.2, 85.9, 80.9, 73.5, 67.8, 63.5, 58.2, 27.2, 26.0, 25.2, 18.4, -5.1, -5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3459, 2953, 2929, 2856, 2228, 1713, 1661, 1608, 1503, 1459, 1408, 1382, 1373, 1361, 1254, 1212, 1157, 1126, 1083, 1068, 1018, 969, 939, 916, 833, 815, 778, 730, 686, 675, 665.

MS (70 eV, EI): m/z (%) = 553 (8), 511 (100), 451 (20) 339 (84), 309 (20), 307 (20), 277 (44), 229 (42), 171 (65), 143 (34), 129 (75).

HRMS ($C_{19}H_{30}IN_2O_7Si$): calc.: 553.0867; found: 553.0869 (M^+-Me).

Preparation of Uridine Derivative (28b)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 24 h at this temperature. The mixture was quenched with ethyl choroformate (33 mg, 0.3 mmol, 1.2 equiv) and warmed up to -10 °C within 4 h. The mixture was quenched with sat. aq. NH_4Cl (10 mL), extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc:*i*hexane/NEt_3 2:8:0.05) afforded **28b** (57 mg, 44%) as a yellow liquid.

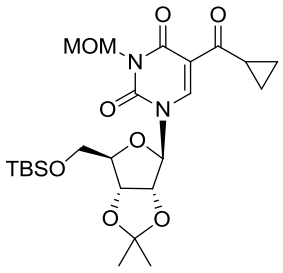
^{1}H-NMR (300 MHz, $CDCl_3$) δ / ppm = 8.49 (s, 1 H), 5.72 (d, *J* = 1.94 Hz, 1 H), 5.37 (q, *J* = 9.40 Hz, 2 H), 4.84 (dd, *J* = 5.81, 2.21 Hz, 1 H), 4.71 (d, *J* = 6.08 Hz, 1 H), 4.55 (s, 1 H), 4.39 - 4.19 (m, 2 H), 3.96 - 3.87 (m, 1 H), 3.84 - 3.73 (m, 1 H), 3.43 (s, 3 H), 1.57 (s, 3 H), 1.36 (s, 3 H), 1.34 (t, *J* = 7.19. 3 H), 0.80 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ / ppm = 163.0, 158.8, 150.4, 146.7, 133.5, 103.9, 96.6, 88.5, 86.4, 81.6, 72.1, 63.9, 61.2, 58.1, 27.0, 25.7, 25.0, 18.2, 14.3, -5.6, -5.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2966, 2949, 2934, 2857, 1752, 1735, 1728, 1709, 1675, 1624, 1532, 1454, 1373, 1365, 1355, 1266, 1227, 1217, 1188, 1158, 1123, 1091, 1029, 970, 918, 861, 835, 797, 778.

HRMS (ESI, $C_{23}H_{39}N_2O_9Si$): calc.: 515.2347; found: 515.2424 (M^+).

Preparation of Uridine Derivative (28c)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 24 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP2** with CuCN·2LiCl (0.3 mL, 0.3 mmol, 1.0 M in THF, 1.2 equiv) and cyclopropanecarbonyl chloride (32 mg, 0.3 mmol, 1.2 equiv) and allowed to warm to 25 °C in 16 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **28c** (91 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ / ppm = 8.45 (s, 1 H), 5.75 (d, *J* = 2.49 Hz, 1 H), 5.42 (q, *J* = 9.40 Hz, 2 H), 4.83 (dd, *J* = 5.94, 2.35 Hz, 1 H), 4.71 (dd, *J* = 5.94, 1.52 Hz, 1 H), 4.59 - 4.48 (m, 1 H),3.87 (dd, *J* = 11.61, 3.04 Hz, 1 H), 3.77 (dd, *J* = 11.61, 3.04 Hz, 1 H), 3.46 (s, 3 H), 3.29 (tt, *J* = 7.84, 4.60 Hz, 1 H), 1.58 (s, 3 H),1.36 (s, 3 H), 1.18 - 1.14 (m, 2 H), 1.03 - 0.97 (m, 2 H), 0.80 (s, 9H), 0.04 (s, 3 H), 0.02 (s, 3 H).

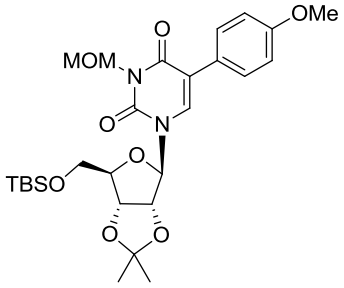
^{13}C-NMR (75 MHz, $CDCl_3$) δ / ppm = 196.8, 161.1, 150.5, 145.6, 113.4, 111.5, 96.5, 88.4, 86.4, 81.6, 72.2, 63.8, 58.0, 27.0, 25.8, 25.1, 19.4, 18.2, 12.7, -5.6, -5.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 2951, 2931, 2856, 1720, 1678, 1659, 1594, 1453, 1410, 1384, 1362, 1351, 1321, 1288, 1272, 1252, 1212, 1158, 1122, 1090, 1053, 1021, 990, 969, 919, 872, 860, 833, 814, 780.

MS (70 eV, EI): m/z (%) = 511 (2), 454 (26), 453 (100), 395 (11), 282 (12), 281 (57), 251 (12), 249 (15), 229 (12), 249 (15), 229 (12), 219 (21), 171 (33), 143 (16), 129 (25), 117 (13).

HRMS ($C_{24}H_{40}N_2O_8Si$): calc.: 511.2470; found: 510.2464 ($M+H^+$).

Preparation of Uridine Derivative (28d)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -40 °C and the reaction mixture was stirred for 24 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (0.3 mL, 1.0 M in THF, 0.3 mmol, 1.2 equiv), $Pd(dba)_2$ (2.7 mg, 2 mol%) and $P(2\text{-furyl})_3$ (2.2 mg, 4 mol%) and 4-iodoanisole (72 mg, 0.3 mol, 1.2 equiv) at 25 °C in 6 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **28d** (111 mg, 81%) as a colorless solid.

m.p.: 112 - 113 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ / ppm = 7.56 (s, 1 H), 6.88 (m, 2 H), 7.38 (m, 2 H), 5.88 (d, *J* = 2.73 Hz, 1 H), 5.43 (q, *J* = 9.55 Hz, 2 H), 4.83 (dd, *J* = 6.24, 2.73 Hz, 1 H), 4.73 (dd, *J* = 6.24, 2.73 Hz, 1 H), 4.35 (q, *J* = 2.73 Hz, 1 H), 3.79 (s, 3 H), 3.75 - 3.89 (m, 2 H), 3.45 (s, 3 H), 1.58 (s, 3 H), 1.35 (s, 3 H), 0.76 (s, 9 H), -0.04 (s, 3 H), -0.11 (s, 3 H).

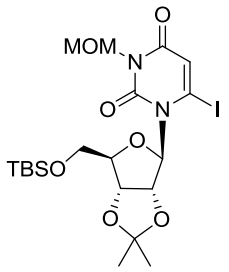
^{13}C-NMR (101 MHz, $CDCl_3$) δ / ppm = 162.1, 159.4, 150.6, 135.9, 126.7, 125.2, 114.2, 113.9, 113.8, 94.2, 87.1, 85.4, 80.8, 72.3, 63.5, 58.0, 55.3, 27.2, 25.8, 25.3, 18.3, -5.5, -5.64.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 2952, 2930, 2856, 1712, 1658, 1609, 1576, 1514, 1453, 1413, 1382, 1373, 1290, 1247, 1212, 1179, 1157, 1126, 1080, 1032, 1005, 970, 918, 831, 812, 795, 779, 760, 733, 701, 679, 666.

MS (70 eV, EI): m/z (%) = 548 (27), 492 (29), 491 (96), 319 (95), 287 (28), 257 (21), 230 (30).

HRMS ($C_{27}H_{40}N_2O_8Si$): calc.: 548.2554; found: 548.2553 (M^+).

Preparation of Uridine Derivative (30a)



According to **TP6** 5'-O-*tert*-butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.21 ml, 0.15 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 72 h at this temperature. The mixture was quenched with iodine (77 mg, 0.3 mmol, 1.2 equiv) and warmed up to 25 °C within 2 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL), extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **30c** (94 mg, 69%) as a colorless oil.

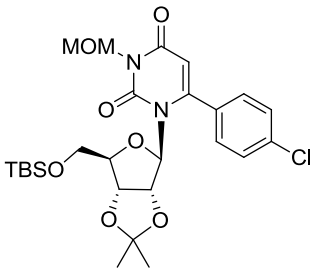
^{1}H-NMR (300 MHz, $CDCl_3$) δ / ppm = 6.51 (s, 1 H), 6.09 (d, J = 1.11 Hz, 1 H), 5.28 (s, 2 H), 5.20 (dd, J = 6.50, 1.24 Hz, 1 H), 4.86 (dd, J = 6.36, 4.42 Hz, 1 H), 4.21 - 4.14 (m, 1 H), 3.82 - 3.77 (m, 2 H), 3.42 (s, 3 H), 1.56 (s, 3 H), 1.34 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ / ppm = 160.5, 148.0, 116.4, 113.8, 112.3, 102.6, 89.8, 84.4, 82.0, 72.3, 64.0, 58.0, 27.2, 25.9, 25.4, 18.5, -5.3, -5.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2986, 2952, 2929, 2884, 2855, 1719, 1665, 1584, 1435, 1424, 1372, 1363, 1347, 1332, 1252, 1207, 1196, 1156, 1131, 1082, 1064, 1005, 948, 917, 876, 833, 816, 770, 673, 662.

HRMS (ESI) ($C_{19}H_{30}IN_2O_7Si$): calc.: 553.0867; found: 553.0868 (M^+-Me).

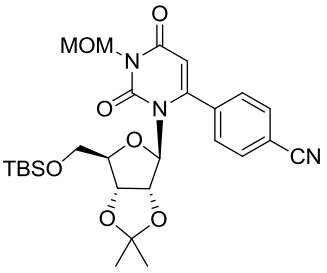
Preparation of Uridine Derivative (30b)



According to **TP6** 5'-O-*tert*-butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.21 ml, 0.15 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 72 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** $Pd(dba)_2$ (2.7 mg, 2 mol%) and $P(2\text{-furyl})_3$ (2.2 mg, 4 mol%) and 1-chloro-4-iodobenzene (71 mg, 0.3 mol, 1.2 equiv) at 25 °C in 6 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **30b** (116 mg, 84%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ / ppm = 7.51 - 7.40 (m, 4 H), 5.66 (s, 1 H), 5.43 (d, *J* = 1.38 Hz, 1 H), 5.37 (s, 2 H), 5.21 (dd, *J* = 6.50, 1.52 Hz, 1 H), 4.84 (dd, *J* = 6.36, 4.42 Hz, 1 H), 4.08 – 4.02 (m, 1 H), 3.86 - 3.82 (m, 2 H), 3.47 (s, 3 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ / ppm = 16.6, 154.0, 151.1, 167.0, 130.9, 129.6, 129.4, 113.6, 103.9, 93.6, 89.3, 84.1, 82.1, 71.9, 64.1, 58.0, 27.1, 25.9, 25.4, 18.4, -5.2, -5.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 2952, 2929, 2884, 2855, 1717, 1671, 1621, 1493, 1471, 1440, 1405, 1383, 1372, 1357, 1252, 1208, 1159, 1140, 1088, 1067, 1015, 969, 954, 901, 868, 834, 774, 729, 681, 667, 663.
HRMS (ESI) ($C_{26}H_{37}ClN_2O_7Si$): calc.: 553.2059; found: 553.2152 (M^+).

Preparation of Uridine Derivative (30c)

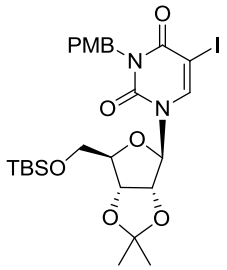


According to **TP6** 5'-O-*tert*-Butyldimethylsilyl-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (**23**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.21 ml,

0.15 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 72 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** $Pd(dba)_2$ (2.7 mg, 2 mol%) and $P(2\text{-furyl})_3$ (2.2 mg, 4 mol%) and 4-iodobenzenonitrile (70 mg, 0.3 mol, 1.2 equiv) at 25 °C in 6 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **30c** (94 mg, 69%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ / ppm = 7.81 - 7.78 (m, 2 H), 7.61 (s, 2 H), 5.66 (s, 1 H), 5.35 (s, 2 H), 5.27 (d, *J* = 1.56 Hz, 1 H), 5.20 (dd, *J* = 6.43, 1.36 Hz, 1 H), 4.82 (dd, *J* = 6.43, 4.48 Hz, 1 H), 4.05 - 4.00 (m, 1 H), 3.82 - 3.80 (m, 2 H), 3.46 (s, 3 H), 1.36 (s, 3 H), 1.27 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ / ppm = 161.3, 153.0, 150.9, 136.7, 132.8, 129.0, 117.7, 114.7, 113.7, 104.3, 93.8, 89.4, 83.9, 81.9, 72.0, 64.0, 58.1, 27.0, 25.9, 25.3, 18.4, -5.2, -5.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2931, 2856, 1718, 1671, 1624, 1605, 1504, 1471, 1441, 1406, 1387, 1384, 1373, 1356, 1270, 1253, 1207, 1159, 1140, 1084, 1067, 1021, 1006, 970, 952, 939, 916, 901, 868, 833, 816, 775, 731, 684, 664.
HRMS (ESI) ($C_{27}H_{36}N_3O_7Si$): calc.: 542.2323; found: 542.2325 (M^+-H).

Preparation of Uridine Derivative (32a)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(4-methoxybenzyl)-2',3'-O-isopropylidene uridine (**24**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 36 h at this temperature. The mixture was quenched with iodine (77 mg, 0.3 mmol, 1.2 equiv) and warmed up to 25 °C within 2 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL), extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc:*i*hexane/NEt_3 2:8:0.05) afforded **32a** (106 mg, 66%) as a yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 (s, 1H), 7.49 – 7.44 (m, 2H), 6.82 – 6.76 (m, 2H), 5.85 – 5.76 (m, 1H), 5.15 – 5.00 (m, 2H), 4.72 – 4.67 (m, 2H), 4.39 (tt, *J* = 2.6, 1.3 Hz, 1H), 3.88 (dd, *J* =

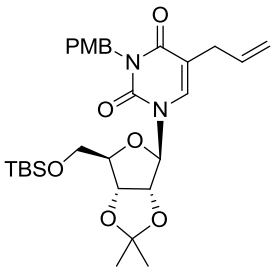
11.7, 2.2 Hz, 1H), 3.78 – 3.76 (m, 1H), 3.75 (s, 3H), 1.58 (d, *J* = 0.8 Hz, 3H), 1.35 (d, *J* = 0.7 Hz, 3H), 0.84 (s, 9H), 0.07 (d, *J* = 2.5 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.68, 159.22, 150.53, 142.65, 131.16, 128.47, 113.82, 113.66, 94.35, 87.20, 85.96, 80.80, 68.03, 63.41, 55.20, 45.24, 27.16, 25.93, 25.22, 18.30, -5.11, -5.46.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2933, 2860, 2224, 1710, 1668, 1608, 1503, 1477, 1408, 1382, 1361, 1254, 1212, 1157, 1083, 1068, 1028, 969, 933, 833, 815, 778, 686, 668.

HRMS (ESI) ($C_{26}H_{38}IN_2O_7Si$): calc.: 645.1495; found: 645.1487 ($M+H^+$).

Preparation of Uridine Derivative (32b)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(4-methoxybenzyl)-2',3'-O-isopropylidene uridine (**24**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 36 h at this temperature. Subsequently, the allylation reaction was accomplished according to **TP2** with CuCN·2LiCl (0.3 mL, 0.3 mmol, 1.0 M in THF, 1.2 equiv) and allyl bromide (36 mg, 0.3 mmol, 1.2 equiv) and allowed to warm to 25 °C in 16 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **32b** (110 mg, 79%) as a colorless oil.

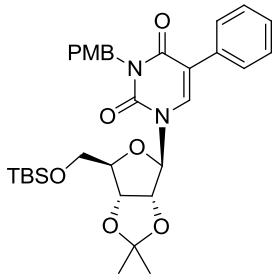
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 – 7.41 (m, 2H), 7.18 (t, *J* = 1.1 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.88 – 5.78 (m, 1H), 5.77 (d, *J* = 2.7 Hz, 1H), 5.14 – 4.95 (m, 4H), 4.77 (dd, *J* = 6.3, 2.7 Hz, 1H), 4.72 (dd, *J* = 6.3, 2.9 Hz, 1H), 4.27 (dt, *J* = 4.0, 3.0 Hz, 1H), 3.83 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.75 (m, 4H), 3.12 – 2.99 (m, 2H), 1.56 (d, *J* = 0.7 Hz, 3H), 1.34 (d, *J* = 0.8 Hz, 3H), 0.84 (s, 9H), 0.03 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.70, 159.02, 150.69, 135.14, 134.55, 130.81, 129.04, 117.10, 113.95, 113.62, 112.25, 94.07, 86.91, 85.11, 80.78, 63.39, 55.18, 43.80, 31.50, 27.20, 25.82, 25.34, 18.27, -5.38, -5.51.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 2951, 2931, 2856, 1720, 1678, 1659, 1594, 1453, 1410, 1384, 1362, 1351, 1321, 1288, 1272, 1252, 1212, 1158, 1122, 1090, 1053, 1021, 990, 969, 919, 872, 860, 833, 814, 780.

HRMS (ESI) ($C_{29}H_{43}N_2O_7Si$): calc.: 559.2841; found: 559.2835 ($M+H^+$).

Preparation of Uridine Derivative (32c)



According to **TP5** 5'-O-*tert*-butyldimethylsilyl-4-(4-methoxybenzyl)-2',3'-O-isopropylidene uridine (**24**, 111 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and TMPMgCl·LiCl (**5**, 0.27 mL, 1.1 M in THF, 0.3 mmol, 1.2 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 36 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** with $ZnCl_2$ (0.3 mL, 1.0 M in THF, 0.3 mmol, 1.2 equiv), $Pd(dba)_2$ (2.7 mg, 2 mol%) and $P(2\text{-furyl})_3$ (2.2 mg, 4 mol%) and iodobenzene (61 mg, 0.3 mol, 1.2 equiv) at 25 °C in 6 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **32c** (107 mg, 72%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.58 (s, 1H), 7.53 – 7.50 (m, 2H), 7.45 – 7.42 (m, 2H), 7.37 – 7.33 (m, 3H), 7.31 – 7.28 (m, 1H), 6.82 – 6.79 (m, 2H), 5.91 (d, *J* = 2.8 Hz, 1H), 5.16 (d, *J* = 13.6 Hz, 1H), 5.08 (d, *J* = 13.5 Hz, 1H), 4.80 (dd, *J* = 6.3, 2.8 Hz, 1H), 4.73 (dd, *J* = 6.3, 2.7 Hz, 1H), 4.35 (dt, *J* = 3.6, 2.6 Hz, 1H), 3.87 (dd, *J* = 11.5, 2.7 Hz, 1H), 3.75 (s, 3H), 1.60 (s, 3H), 1.37 (s, 3H), 0.73 (d, *J* = 0.7 Hz, 9H), -0.07 (s, 3H), -0.15 (s, 3H).

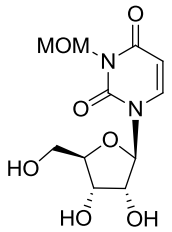
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 161.76, 159.08, 150.52, 135.75, 133.15, 131.13, 129.04, 128.53, 128.36, 127.78, 114.56, 113.95, 113.62, 94.04, 87.04, 85.61, 80.71, 63.38, 55.20, 44.02, 27.22, 25.73, 25.31, 18.19, -5.65.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2990, 2962, 2856, 1727, 1688, 1659, 1594, 1453, 1410, 1400, 1362, 1355, 1272, 1252, 1218, 1158, 1122, 1053, 1021, 994, 969, 919, 872, 833, 780.

HRMS (ESI) ($C_{31}H_{39}N_2O_7Si$): calc.: 579.2527; found: 579.2520 (M-Me).

2.5. Deprotection of Uridine

Preparation of 4-(Methoxymethyl)-2',3'-O-isopropylidene uridine (33)



33 was prepared from uridine derivative **23** (111 mg, 0.25 mmol), dissolved in conc. HCl (0.5 ml) and stirred for 16 h at room temperature. The crude product was concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH 10:1) afforded **33** (64 mg, 88%) as a colorless oil.

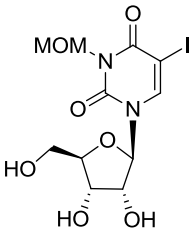
^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.91 (d, J = 8.2 Hz, 1H), 5.74 – 5.69 (m, 2H), 5.13 – 5.06 (m, 2H), 3.96 (t, J = 5.0 Hz, 1H), 3.89 (t, J = 4.7 Hz, 1H), 3.78 (dt, J = 4.2, 3.1 Hz, 1H), 3.56 (dd, J = 12.1, 3.1 Hz, 1H), 3.48 (dd, J = 12.1, 3.2 Hz, 1H), 3.19 (s, 3H).

^{13}C-NMR (101 MHz, DMSO-d_6): δ / ppm = 162.46, 151.42, 140.51, 101.43, 89.30, 85.33, 74.17, 71.74, 70.13, 61.10, 57.40.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3010, 2945, 2935, 2924, 2874, 2360, 2255, 2120, 1680, 1651, 1588, 1534, 1512, 1430, 1400, 1363, 1333, 1268, 1178, 1133, 1079, 1060, 1019, 975, 955, 942, 869, 774, 684, 652.

HRMS (ESI) ($C_{11}H_{16}N_2O_7$): calc.: 288.0958, found: 288.0944 (M^+).

Preparation of 5-Iodo-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (33a)



33a was prepared from uridine derivative **28a** (90 mg, 0.16 mmol), dissolved in conc. HCl (0.5 ml) and stirred for 16 h at room temperature. The crude product was concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH 12:1) afforded **33** (51 mg, 77%) as a colorless oil.

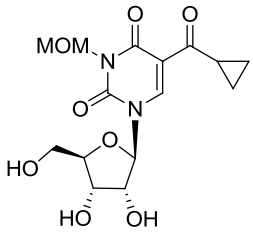
^{1}H-NMR (800 MHz, DMSO-d_6): δ / ppm = 8.62 (s, 1H), 5.74 (d, J = 4.1 Hz, 1H), 5.47 (d, J = 5.2 Hz, 1H), 5.32 (t, J = 4.6 Hz, 1H), 5.25 – 5.20 (m, 2H), 5.09 (d, J = 5.6 Hz, 1H), 4.05 (q, J = 4.8 Hz, 1H), 4.00 (q, J = 5.3 Hz, 1H), 3.89 (dt, J = 5.3, 2.6 Hz, 1H), 3.72 (ddd, J = 12.0, 4.8, 2.8 Hz, 1H), 3.61 – 3.57 (m, 1H), 3.28 (s, 3H).

^{13}C-NMR (200 MHz, DMSO-d_6): δ / ppm = 158.96, 149.82, 143.82, 88.84, 83.93, 73.40, 72.19, 68.32, 67.53, 59.16, 56.42.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 3325, 3086, 3077, 3008, 2948, 2935, 2923, 2874, 2824, 2454, 2360, 2253, 2126, 1696, 1651, 1610, 1558, 1539, 1522, 1506, 1438, 1402, 1363, 1346, 1331, 1268, 1227, 1208, 1176, 1172, 1135, 1102, 1079, 1063, 1042, 1019, 973, 955, 942, 931, 901, 868, 826, 774, 766, 754, 724, 718, 684, 670, 652.

HRMS (ESI) ($C_{11}H_{16}IN_2O_7$): calc.: 412.0004; found: 414.9999 ($M+H^+$).

Preparation of 5-(Cyclopropanecarbonyl)-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (33b)



33b was prepared from uridine derivative **28c** (82 mg, 0.16 mmol), dissolved in conc. HCl (0.5 ml) and stirred for 16 h at room temperature. The crude product was concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH 10:1) afforded **33b** (41 mg, 72%) as a colorless solid.

m.p.: 87.3 - 88.9 °C.

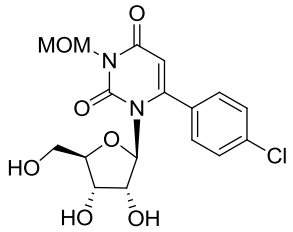
^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 8.83 (s, 1H), 5.82 (d, J = 3.8 Hz, 1H), 5.52 (d, J = 5.2 Hz, 1H), 5.29 – 5.22 (m, 2H), 5.18 (t, J = 4.4 Hz, 1H), 5.13 (d, J = 5.6 Hz, 1H), 4.10 (q, J = 4.5 Hz, 1H), 3.98 (q, J = 5.1 Hz, 1H), 3.93 (dt, J = 5.4, 2.7 Hz, 1H), 3.70 (ddd, J = 11.7, 4.4, 2.6 Hz, 1H), 3.61 – 3.54 (m, 1H), 3.32 (s, 3H), 3.11 (tt, J = 6.7, 5.5 Hz, 1H), 1.01 – 0.91 (m, 4H).

^{13}C-NMR (200 MHz, DMSO-d_6): δ / ppm = 195.12, 159.78, 149.55, 144.98, 111.14, 89.37, 84.11, 73.64, 71.13, 68.53, 59.41, 56.44, 18.24, 10.99.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3485, 3389, 3269, 3092, 3069, 2990, 2952, 2933, 2827, 2714, 2253, 2129, 1723, 1677, 1620, 1557, 1524, 1454, 1433, 1408, 1350, 1300, 1273, 1259, 1235, 1200, 1175, 1157, 1135, 1104, 1095, 1082, 1064, 1045, 1021, 1003, 990, 958, 918, 910, 898, 881, 872, 853, 822, 802, 790, 763, 744, 719, 689, 676, 667.

HRMS (ESI) ($C_{15}H_{20}N_2NaO_8$): calc.: 379.1112; found: 379.1112 ($M+Na^+$).

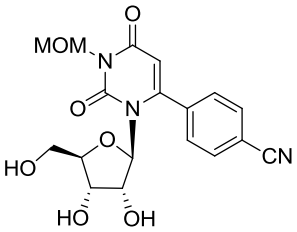
Preparation of 6-(4-Chlorophenyl)-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (33c)



33c was prepared from uridine derivative **30b** (103 mg, 0.18 mmol), dissolved in conc. HCl (0.5 ml) and stirred for 16 h at room temperature. The crude product was concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH 12:1) afforded **33c** (54 mg, 74%) as a colorless oil.

^{1}H-NMR (800 MHz, DMSO-d_6): δ / ppm = 7.65 – 7.61 (m, 2H), 7.57 – 7.54 (m, 2H), 5.73 (s, 1H), 5.23 – 5.18 (m, 2H), 5.08 (d, *J* = 5.2 Hz, 1H), 5.03 (d, *J* = 3.7 Hz, 1H), 4.89 (d, *J* = 6.3 Hz, 1H), 4.64 (t, *J* = 5.7 Hz, 1H), 4.56 (ddd, *J* = 6.2, 5.2, 3.8 Hz, 1H), 4.04 (q, *J* = 6.1 Hz, 1H), 3.62 – 3.56 (m, 2H), 3.48 – 3.43 (m, 1H), 3.32 (s, 3H).
^{13}C-NMR (200 MHz, DMSO-d_6): δ / ppm = 160.39, 153.39, 149.86, 134.59, 130.94, 128.30, 102.48, 93.75, 84.30, 78.50, 70.69, 70.21, 69.24, 61.43, 56.48.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3364, 3091, 2938, 2830, 2360, 2342, 1716, 1700, 1695, 1661, 1622, 1616, 1592, 1576, 1569, 1564, 1558, 1549, 1539, 1533, 1525, 1521, 1517, 1506, 1491, 1472, 1442, 1418, 1404, 1387, 1353, 1245, 1201, 1188, 1144, 1088, 1046, 1023, 1014, 950, 902, 823, 782, 765, 730, 712, 673, 668, 661.
HRMS (ESI) ($C_{17}H_{20}ClN_2O_7$): calc.: 399.0961; found: 399.0955 ($M+H^+$).

Preparation of 6-(4-benzonitril)-4-(methoxymethyl)-2',3'-O-isopropylidene uridine (33d)



33d was prepared from uridine derivative **30c** (86 mg, 0.16 mmol), dissolved in conc. HCL (0.5 ml) and stirred for 16 h at room temperature. The crude product was concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH 12:1) afforded **33d** (50 mg, 82%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 8.03 – 7.98 (m, 2H), 7.64 – 7.60 (m, 2H), 5.75 (s, 1H), 5.21 (d, *J* = 1.4 Hz, 2H), 5.10 (d, *J* = 5.2 Hz, 1H), 5.04 (d, *J* = 3.6 Hz, 1H), 4.90 (d, *J* = 6.3 Hz, 1H),

4.68 (t, *J* = 5.6 Hz, 1H), 4.56 (ddd, *J* = 6.3, 5.2, 3.6 Hz, 1H), 4.04 (q, *J* = 6.2 Hz, 1H), 3.64 – 3.53 (m, 2H), 3.46 (dt, *J* = 10.8, 6.0 Hz, 1H), 3.33 (s, 3H).

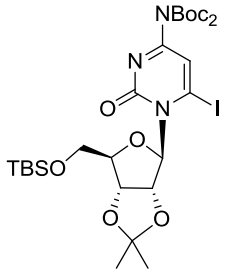
^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 167.40, 161.49, 154.96, 150.96, 136.31, 135.71, 128.29, 103.50, 94.95, 85.38, 71.80, 71.36, 70.32, 62.55, 57.57, 46.08.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3401, 3333, 3086, 3077, 3006, 2948, 2936, 2826, 2360, 2327, 2253, 2126, 1697, 1654, 1651, 1612, 1559, 1521, 1506, 1438, 1402, 1362, 1349, 1269, 1227, 1207, 1177, 1100, 1079, 1059, 1042, 1019, 998, 974, 954, 942, 931, 901, 867, 825, 766, 754, 735, 724, 718, 670, 658, 653.

HRMS (ESI) ($C_{18}H_{20}N_3O_7$): calc.: 390.1296; found: 390.1258 ($M+H^+$).

2.6. Functionalization and Deprotection of Cytidine

Preparation of Cytidine Derivative (35a)



5'-O-*tert*-Butyldimethylsilyl-4-(bis(*tert*-butoxycarbonylamino))-2',3'-O-isopropylidene cytidine (**26**, 149 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.21 ml, 0.15 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 4 h at this temperature. The reaction mixture was quenched with iodine (77 mg, 0.3 mmol, 1.2 equiv) and warmed up to 25 °C within 2 h. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **35a** (129 mg, 61%) as a colorless oil.

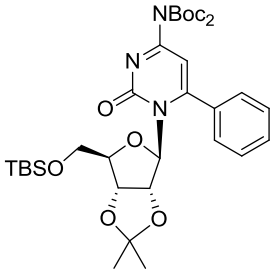
^{1}H-NMR (400 MHz, Acetone-d_6): δ / ppm = 7.65 (s, 1 H), 6.23 (d, *J* = 0.98 Hz, 1 H), 5.26 (dd, *J* = 6.46, 1.17 Hz, 1 H), 5.26 (dd, *J* = 6.46, 1.17 Hz, 1 H), 4.87 (dd, *J* = 6.36, 3.81 Hz, 1 H), 4.16 (td, *J*=6.55, 3.72 Hz, 1 H), 3.85 (s, 1 H), 3.83 (d, *J*=1.17 Hz, 1 H), 1.54 (s, 18 H), 1.50 (s, 3 H), 1.32 (s, 3 H), 0.87 (s, 9 H), 0.02 (s, *J* = 1.17, 3 H), 0.02 (s, *J*=1.17, 3 H).

^{13}C-NMR (100 MHz, Acetone-d_6): δ / ppm = 161.3, 151.5, 149.0, 118.3, 112.8, 109.8, 103.0, 90.9, 84.8, 84.4, 82.9, 64.1, 26.9, 26.5, 25.4, 24.5, 18.0, -5.8, -6.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3426, 3265, 2977, 2934, 1710, 1638, 1549, 1495, 1421, 1369, 1273, 1254, 1146, 1102, 1065, 1043, 1013, 868, 803, 767, 734, 661.

HRMS (ESI) ($C_{28}H_{47}IN_3O_9Si$): calc.: 724.2126; found: 724.2122 (M^+).

Preparation of Cytidine Derivative (35b)



5'-O-*tert*-Butyldimethylsilyl-4-(bis(*tert*-butoxycarbonylamino))-2',3'-O-isopropylidene cytidine (**26**, 149 mg, 0.25 mmol, 1.0 equiv) was dissolved in dry THF and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.21 ml, 0.15 mmol, 0.71 M, 0.6 equiv) was added dropwise at -30 °C and the reaction mixture was stirred for 4 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP3** $Pd(dba)_2$ (2.7 mg, 2 mol%) and P(2-furyl)$_3$ (2.2 mg, 4 mol%) and iodobenzene (61 mg, 0.3 mol, 1.2 equiv) at 25 °C in 12 h. The mixture was quenched with sat. aq. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc:NEt_3, 9:1:0.05) afforded **35b** (72 mg, 43%) as a colorless oil.

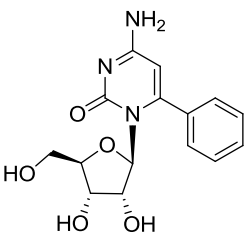
^{1}H-NMR (300 MHz, Acetone-d_6): δ / ppm = 7.62 (s, 5 H). 5.63 (s, 1 H), 6.91 (s, 1 H), 5.28 (dd, *J* = 6.50, 1.24 Hz, 1 H), 4.88 (dd, *J* = 6.36, 3.87 Hz, 1 H), 4.01 - 4.12 (m, 1 H), 3.94 (s, 1 H), 3.91 (s, 1 H), 1.57 (s, 18 H), 1.32 (s, 3 H), 1.27 (s, 3 H), 0.91 (s, 9 H),0.07 (s, 3 H), 0.07 (s, 3 H).

^{13}C-NMR (300 MHz, Acetone-d_6): δ / ppm = 161.62, 160.71, 153.9, 149.4, 133.6, 130.7, 129.0, 128.5, 112.5, 97.5, 93.9, 90.6, 84.5, 84.2, 83.1, 64.3, 27.0, 26.4, 25.4, 22.4, 18.0, -5.8, -5.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2952, 2932, 2929, 2887, 2856, 1781, 1745, 1685, 1608, 1596, 1574, 1537, 1492, 1467, 1461, 1413, 1395, 1370, 1308, 1284, 1251, 1209, 1159, 1131, 1092, 1057, 1033, 973, 879, 837, 816, 789, 776, 701.

HRMS (ESI) ($C_{34}H_{52}N_3O_9Si$): calc.: 674.3467; found: 674.3465 ($M+H^+$).

Preparation of 5-Phenyl-cytidine (36)



36 was prepared from cytidine derivative **35b** (67 mg, 0.10 mmol), dissolved in trifluoroacetic acid (1 ml, 70% in H_2O) and stirred for 16 h at room temperature. The crude product was concentrated *in vacuo*. Purification by flash chromatography on silica gel ($CHCl_3$:MeOH 12:1) afforded **35b** (27 mg, 85%) as a colorless solid.

m.p.: 85.5 - 87.3 °C

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.54 – 7.51 (m, 3H), 7.49 – 7.47 (m, 2H), 7.34 (d, *J* = 9.2 Hz, 2H), 5.61 (s, 1H), 5.12 (d, *J* = 4.3 Hz, 1H), 4.98 (d, *J* = 5.4 Hz, 1H), 4.82 (dd, *J* = 7.6, 3.8 Hz, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 4.64 (td, *J* = 5.9, 4.4 Hz, 1H), 4.08 (q, *J* = 5.7 Hz, 1H), 3.63 – 3.58 (m, 2H), 3.45 (ddd, *J* = 11.5, 7.6, 4.8 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 165.27, 157.37, 156.25, 134.50, 130.33, 129.23, 128.51, 96.82, 93.94, 85.78, 71.20, 70.82, 62.85.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3346, 3212, 1678, 1635, 1530, 1494, 1444, 1426, 1382, 1265, 1202, 1178, 1128, 1049, 1024, 1000, 904, 825, 800, 765, 719, 703, 668.

HRMS (ESI) ($C_{15}H_{18}N_3O_5$): calc.: 320.1241; found: 320.1243 ($M+H^+$).

3. PREPARATION OF FUNCTIONALIZED PYRROLO(2,3-*D*)PYRIMIDINE VIA AN INTRAMOLECULAR COPPER-MEDIATED CARBOMAGNESIATION OF YNAMIDES

3.1. Typical Procedures

Typical Procedure for Halogen-Magnesium-Exchange Reactions (TP1):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the starting aryl iodine in THF (0.2-1.0 M solution) and cooled to the indicated temperature. Then *i*PrMgCl·LiCl was added and the reaction mixture was stirred for the indicated time (the completion of the reaction was checked by HPLC analysis of reaction aliquots quenched with half concentrated aqueous NH_4Cl-solution).

Typical Procedure for the Copper-Mediated Cyclization Reaction (TP2):

After the completion of the iodine/magnesium-exchange (**TP1**), THF was added (0.05-0.2 M solution), CuCN·2LiCl solution (1.1 equiv, 1.0 M in THF) was added to the reaction mixture at the indicated temperature and stirred for the indicated time (the completion of the reaction was checked by HPLC analysis of reaction aliquots quenched with sat. aqueous NH_4Cl/NH_3-solution; typically two peaks with slightly differing retention time could be detected, corresponding to the open-chain and cyclized form).

Typical Procedure for Allylation or Acylation Reactions (TP3):

To the freshly prepared magnesium reagent was added CuCN·2LiCl (1.1 equiv, 1.0 M in THF) and the reaction mixture was stirred for 15 min at the indicated temperature unless copper was already present in the mixture from the cyclization step. The respective allyl bromide or acyl chloride was added and the reaction mixture was stirred for the indicated time at the indicated temperature. The reaction mixture was quenched with concentrated aqueous NH_4Cl:NH_3-solution (19:1), extracted three times with EtOAc, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for the Conversion of the TMS-Group to Iodide (TP4):

To the respective TMS-substituted compound (approx. 0.2 M in CH_2Cl_2) was added iodine monochloride (1.1 equiv) at 0 °C and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. $Na_2S_2O_3$-solution, extracted three times with CH_2Cl_2, the organic layers dried

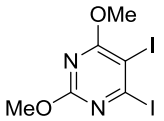
($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for Cross-Coupling Reactions (TP5):

To the freshly prepared magnesium reagent was added $ZnCl_2$ (1.1 equiv, 1.0 M in THF) and the reaction mixture was stirred for 15 min at 25 °C. The catalytic system and the heteroaryl iodide (1.0 equiv) were added and the reaction mixture was warmed to 50 °C. After stirring for the indicated time, the reaction mixture was quenched with half concentrated aqueous NH_4Cl-solution, extracted three times with EtOAc, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

3.2. Preparation of Functionalized Ynamides

4,5-Diiodo-2,6-dimethoxypyrimidine (44)



2,4-Dimethoxypyrimidine (**43**, 14.0 g, 100 mmol, 1.0 equiv) was dissolved in dry THF (100 ml). TMPMgCl·LiCl (98 ml, 110 mmol, 1.13 M, 1.1 equiv) was added dropwise at room temperature and the reaction mixture was stirred for 2 h at this temperature. After the completion of the metalation iodine (28.0 g, 110 mmol, 1.1 equiv) was added dropwise at −30 °C and the mixture was stirred 1.5 h at this temperature. Afterwards TMPMgCl·LiCl (133 ml, 150 mmol, 1.13 M, 1.5 equiv) was added dropwise. The mixture was warmed to 0 °C and stirred for 2 h. Iodine (51.4 g, 200 mmol, 2.0 equiv) dissolved in 50 mL THF was added at 25 °C and the mixture was stirred for 12 h at room temperature. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (50 mL) at 0 °C, extracted with Et_2O (3 x 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*i*hexane:EtOAc, 8:1) afforded **44** (25.48 g, 65%) as a pale yellow solid.

m.p.: 145.4 - 147.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 3.97 (s, 3H), 3.95 (s, 3H).

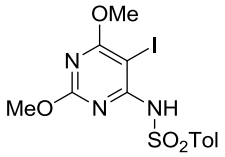
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 168.9, 163.6, 141.9, 84.2, 55.9, 55.7.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3025, 2994, 2948, 2864, 1517, 1477, 1450, 1378, 1340, 1293, 1222, 1196, 1102, 1020, 997, 930, 807, 774.

MS (EI, 70 eV): m/z (%) = 392(100), 391(25), 363(10), 362(17), 265(10), 250(29), 208(11), 193(14).

HRMS ($C_6H_6I_2N_2O_2$): calc.: 391.8519; found: 391.8533 (M^+).

***N*-(5-Iodo-2,4-dimethoxypyrimidin-6-yl)-6-methylbenzenesulfonamide (45)**



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with 5,6-diiodopyrimidine (**44**, 1.4 g, 3.6 mmol, 1.02 equiv), toluolsulfonamine (623 mg, 3.5 mmol, 1.0 equiv), cesium carbonate (1.04 g, 5.4 mmol, 1.5 equiv) and CuI (33.2 mg, 0.175 mmol, 0.05 equiv) in dry MeCN (50 mL). The mixture was heated under reflux for 3 h, cooled to 25 °C and NaOH (25 mL, 2 M) was added. The organic phase was washed with H_2O (3 x 25 mL) and the collected aqueous phase was treated with HCL (50 mL, 2 M) and the crude product was seperated by filtration to yield *N*-(5-iodo-2,6-dimethoxypyrimidin-4-yl)-4-methylbenzenesulfonamide **45** as a white solid. The aqueous phase was extracted three times with CH_2Cl_2 (3 x 50 mL), dried over Na_2SO_4, concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 4:1:0.1) afforded *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methylbenzenesulfonamide (**45**, 1.06 g, 68%) as a white powder.

m.p.: 192.0 - 194.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.95 (d, *J* = 8.3 Hz, 2H), 7.74 (s, 1H), 7.29 (d, *J* = 7.4 Hz, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 2.41 (s, 3H).

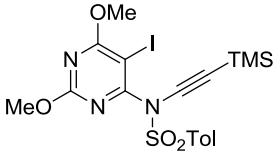
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 169.51, 164.84, 158.27, 144.62, 136.43, 129.38, 128.35, 55.41, 53.29, 21.62.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3344, 3016, 2999, 2959, 2923, 2898, 2867, 1557, 1488, 1460, 1424, 1373, 1316, 1267, 1203, 1186, 1160, 1116, 1081, 1042, 1021 1000, 968, 943, 869, 815, 778, 714, 696, 675, 653.

MS (EI, 70 eV): m/z (%) = 458 (9), 435 (100), 223 (7), 103 (6).

HRMS ($C_{13}H_{14}IN_3NaO_4S$): calc.: 457.9750; found: 457.9641 ($M+Na^+$).

***N*-(5-Iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-N-((trimethylsilyl)ethynyl)-benzenesulfonamide (42)**



In a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, potassium hexamethyldisilazane (14.3 mL, 10.0 mmol, 0.7 M in toluene) was added to a solution of *N*-(5-iodo-

2,4-dimethoxypyrimidin-6-yl)-6-methylbenzenesulfonamide (**45**, 4.35 g, 10.0 mmol, 1.0 equiv) in toluene (100 mL) at 0 °C. After 1 h, phenyl((trimethylsilyl)-ethynyl)iodonium triflate (5.39 g, 12.0 mmol, 1.2 equiv) was added in several portions. The resulting mixture was stirred for 16 h at 25 °C. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfon-amide (**42**, 3.56 g, 67%) as a white solid.

m.p.: 148.0 - 149.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.84 – 7.78 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 3.90 (s, 3H), 3.70 (s, 3H), 2.32 (s, 3H), 0.00 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 171.73, 165.17, 161.41, 145.24, 135.00, 129.31, 129.18, 127.81, 91.63, 68.94, 56.09, 55.52, 21.82, 0.00.

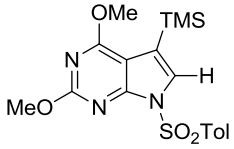
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2164, 1596, 1564, 1535, 1485, 1457, 1372, 1352, 1306, 1249, 1173, 1106, 1088, 1053, 1019, 992, 934, 842, 812, 760, 724, 703.

MS (EI, 70 eV): m/z (%) = 531 (9), 515 (23), 467 (78), 452 (78), 436 (14), 376 (25), 362 (46), 325 (13), 310 (10), 234 (16), 213 (15), 181 (15), 149 (100), 124 (34), 100 (26), 91 (67), 89 (64), 73 (34).

HRMS ($C_{18}H_{22}IN_3O_4SSi$): calc.: 531.0145; found: 531.0141 (M^+).

3.3. Preparation of Pyrrolo(2,3-*d*)pyrimidine Derivatives

2,4-Dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (46a)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h. The reaction mixture was quenched with concentrated aqueous NH_4Cl:NH_3-solution (19:1), extracted three times with EtOAc, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 19:1) afforded 2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7H-pyrrolo[2,3-*d*]pyrimidine (**46a**, 136 mg, 67%) as a white solid.

m.p.: 131.2 - 131.9 °C.

^{1}H-NMR (300 MHz, Acetone- d_6): δ / ppm = 8.17 – 8.08 (m, 2H), 7.51 – 7.43 (m, 2H), 7.39 (d, *J* = 0.7 Hz, 1H), 4.06 (d, *J* = 0.8 Hz, 3H), 4.00 (d, *J* = 0.8 Hz, 3H), 2.41 (s, 3H), 0.30 (s, 9H).

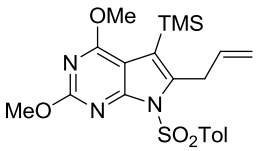
^{13}C-NMR (75 MHz, Acetone- d_6): δ / ppm = 165.12, 162.62, 153.97, 146.04, 134.94, 129.78, 128.43, 127.14, 113.28, 105.75, 54.40, 53.32, 20.63, -1.77.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2931, 2900, 1741, 1596, 1566, 1495, 1471, 1402, 1357, 1285, 1247, 1222, 1177, 1125, 1086, 1041, 985, 948, 870, 838, 813, 792, 758, 703.

MS (EI, 70 eV): m/z (%) = 405 (66), 390 (5), 360 (9), 341 (11), 326 (12), 250 (100), 235 (20), 220 (20), 178 (7), 155 (11), 149 (9), 100 (9), 89 (29).

HRMS ($C_{18}H_{23}N_3O_4SSi$): calc.: 405.1179; found: 405.1171 (M^+).

6-Allyl-2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (46b)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h and a subsequent allylation reaction was performed according to **TP3** using allyl bromide (73 mg, 0.6 mmol, 1.2 equiv) at -20 °C. The reaction mixture was allowed to warm slowly to 25 °C within 12 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 8:1:0.1) afforded the 6-allyl-2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**46b**, 158 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, Acetone- d_6): δ / ppm = 8.14 – 8.11 (m, 2H), 7.46 – 7.43 (m, 2H), 6.18 (ddt, *J* = 17.3, 10.2, 5.0 Hz, 1H), 5.17 (dq, *J* = 10.3, 1.8 Hz, 1H), 4.90 (dq, *J* = 17.3, 1.9 Hz, 1H), 4.05 (m, 5H), 3.97 (s, 3H), 2.42 (s, 3H), 0.36 (s, 9H).

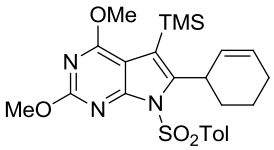
^{13}C-NMR (75 MHz, Acetone- d_6): δ / ppm = 162.93, 160.56, 154.91, 144.45, 139.15, 136.45, 135.19, 128.23, 127.50, 113.94, 110.37, 103.52, 53.27, 51.91, 19.51, -0.78.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2155, 1593, 1570, 1521, 1469, 1361, 1278, 1242, 1192, 1148, 1090, 1020, 993, 921, 890, 839, 795, 736, 703.

MS (EI, 70 eV): m/z (%) = 445 (34), 290 (100), 275 (33), 260 (8), 218 (5), 89 (24), 73 (15).

HRMS ($C_{21}H_{27}N_3O_4SSi$): calc.: 445.1492; found: 445.1485 (M^+).

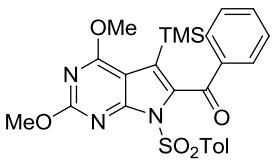
6-(Cyclohex-2-en-1-yl)-2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (46c)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h and a subsequent allylation reaction was performed according to **TP3** using 2-cyclohexenyl bromide (97 mg, 0.6 mmol, 1.2 equiv) at -20 °C. The reaction mixture was allowed to warm slowly to 25 °C within 12 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 8:1:0.1) afforded the 6-allyl-2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**46c**, 150 mg, 62%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.04 – 7.99 (m, 2H), 7.27 – 7.23 (m, 2H), 5.79 (dddd, *J* = 8.1, 5.2, 3.6, 1.6 Hz, 1H), 5.71 (dtt, *J* = 10.0, 2.6, 1.2 Hz, 1H), 4.33 (ddd, *J* = 12.7, 6.0, 3.2 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.53 (q, *J* = 12.7 Hz, 1H), 2.38 (s, 3H), 2.30 – 2.19 (m, 1H), 2.11 – 2.01 (m, 1H), 2.01 – 1.88 (m, 2H), 1.80 – 1.63 (m, 1H), 0.32 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 164.02, 161.27, 156.33, 147.36, 144.71, 136.87, 129.21, 129.08, 128.47, 126.79, 112.29, 105.13, 54.92, 53.38, 38.23, 29.29, 24.24, 23.35, 21.62, 1.81.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2930, 1592, 1569, 1496, 1470, 1361, 1308, 1289, 1236, 1212, 1192, 1176, 1146, 1129, 1090, 1046, 1018, 982, 949, 919, 892, 839, 813, 764, 730, 703.
MS (EI, 70 eV): m/z (%) = 485 (4), 405 (3), 330 (67), 315 (4), 264 (3), 250 (4), 88 (6), 73 (11), 70 (13), 61 (17), 45 (16), 43 (100).
HRMS ($C_{24}H_{31}N_3O_4SSi$): calc.: 485.1805; found: 485.1791 (M^+).

(2,4-Dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(phenyl)methanone (46d)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange

was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h and a subsequent acylation reaction was performed according to **TP3** using benzylcarbonyl chloride (84.6 mg, 0.6 mmol, 1.2 equiv) at -20 °C. The reaction mixture was allowed to warm slowly to 25 °C within 12 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 10:1:0.1) afforded the (2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(phenyl)methanone (**46d**, 171 mg, 67%) as a colorless solid.

m.p.: 199.2 - 200.2°C

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.87 (m, 2H), 7.86 – 7.77 (m, 2H), 7.58 – 7.48 (m, 1H), 7.40 (td, *J* = 7.3, 1.2 Hz, 2H), 7.22 – 7.15 (m, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 2.31 (s, 3H), 0.00 (s, 9H).

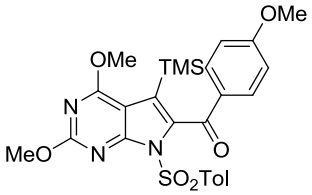
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 190.93, 165.43, 162.71, 154.98, 145.68, 138.53, 136.34, 134.56, 133.67, 129.57, 129.44, 128.86, 128.68, 113.84, 105.61, 55.13, 53.82, 21.71, 0.03.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3162, 3144, 3067, 3027, 2958, 2924, 2851, 2654, 2608, 2592, 2544, 1715, 1675, 1593, 1571, 1471, 1450, 1376, 1361, 1315, 1286, 1251, 1193, 1155, 1120, 1086, 1033, 1009, 944, 841, 813, 797, 766, 733, 682, 608.

MS (EI, 70 eV): m/z (%) = 509 (74), 494 (35), 354 (100), 339 (22), 310 (7), 297 (23), 280 (5), 135 (4), 105 (12), 91 (19).

HRMS ($C_{25}H_{27}N_3O_5SSi$): calc.: 509.1441; found: 509.1451 (M^+).

(2,4-Dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)methanone (46e)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h and a subsequent acylation reaction was performed according to **TP3** using 4-methoxybenzylcarbonyl chloride (105 mg, 0.6 mmol, 1.2 equiv) at -20 °C. The reaction mixture was allowed to warm slowly to 25 °C within 12 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 8:1:0.1)

afforded the (2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)-methanone (**46e**, 191 mg, 71%) as a colorless solid.

m.p.: 208.5 - 210.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.96 (d, *J* = 8.0 Hz, 2H), 7.86–7.76 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.81 (d, *J* = 1.2 Hz, 3H), 2.31 (s, 3H), 0.00 (s, 9H).

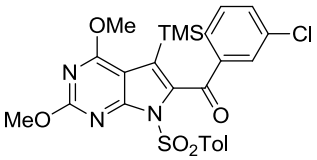
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 189.52, 165.34, 164.00, 162.57, 154.89, 145.60, 136.62, 134.59, 131.91, 131.90, 129.42, 128.84, 113.93, 113.17, 105.52, 55.52, 55.10, 53.79, 21.71, 0.01.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3054, 3028, 2956, 2925, 2851, 2730, 2661, 2563, 2232, 1682, 1668, 1598, 1570, 1512, 1495, 1471, 1454, 1427, 1374, 1289, 1257, 1209, 1193, 1165, 1121, 1086, 1027, 1009, 944, 870, 842, 817, 794, 772, 682, 665, 634, 615.

MS (EI, 70 eV): m/z (%) = 539 (38), 524 (19), 384 (71), 370 (100), 324 (10), 155 (9), 135 (21), 91 (40), 77 (6), 65 (9).

HRMS ($C_{26}H_{29}N_3O_6SSi$): calc.: 539.1546; found: 539.1523 (M^+).

(3-Chlorophenyl)(2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)methanone (46f)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h and a subsequent acylation reaction was performed according to **TP3** using 3-chlorobenzylcarbonyl chloride (105 mg, 0.6 mmol, 1.2 equiv) at -20 °C. The reaction mixture was allowed to warm slowly to 25 °C within 12 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 8:1:0.1) afforded the ((3-chlorophenyl)(2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)methanone (**46f**, 209 mg, 77%) as a colorless solid.

m.p.: 184.1 - 185.6 °C.

^{1}H-NMR (300 MHz, Acetone-d_6): δ / ppm = 7.89 – 7.84 (m, 2H), 7.82 (t, *J* = 1.9 Hz, 1H), 7.76 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.68 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.41 – 7.35 (m, 2H), 4.02 (s, 3H), 3.97 (s, 3H), 2.34 (s, 3H), 0.05 (s, 9H).

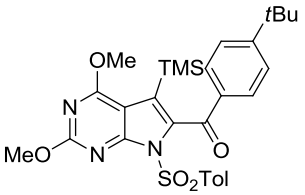
^{13}C-NMR (75 MHz, Acetone- d_6): δ / ppm = 190.56, 167.04, 164.67, 156.72, 148.02, 141.95, 137.31, 136.18, 135.94, 135.11, 132.38, 131.31, 130.16, 130.09, 129.51, 115.88, 106.77, 56.24, 55.04, 22.26, 0.90.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 2955, 2928, 2710, 2660, 2596, 2551, 1694, 1592, 1572, 1471, 1377, 1360, 1292, 1250, 1193, 1157, 1122, 1086, 1033, 1009, 954, 920, 898, 877, 842, 814, 750, 734, 704, 682, 665, 602.

MS (EI, 70 eV): m/z (%) = 543 (56), 528 (32), 388 (100), 374 (23), 331 (31), 328 (13), 280 (3), 139 (7), 91 (11).

HRMS ($C_{25}H_{26}ClN_3O_5SSi$): calc.: 543.1051; found: 543.1029 (M^+).

(4-(*tert*-Butyl)phenyl)(2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)methanone (46g)



The title compound was prepared from *N*-(5-iodo-2,4-dimethoxypyrimidin-6-yl)-6-methyl-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (**42**, 266 mg, 0.5 mmol, 1.0 equiv). A Br/Mg-exchange was performed according to **TP1** with *i*PrMgCl·LiCl (0.45 mL, 1.22 M, 0.55 mmol, 1.1 equiv) at -40 °C within 2 h (1.0 M). After addition of THF (5 mL), CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.1 equiv) mediated cyclization was performed according to **TP2** at 25 °C in 24 h and a subsequent acylation reaction was performed according to **TP3** using 4-tertbutylbenzylcarbonyl chloride (102 mg, 0.6 mmol, 1.2 equiv) at -20 °C. The reaction mixture was allowed to warm slowly to 25 °C within 12 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:NEt_3 = 12:1:0.1) afforded the (4-(*tert*-butyl)phenyl)(2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-methanone (**46g**, 150 mg, 53%) as a colorless solid.

m.p.: 197.3 - 198.0 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.94 – 7.85 (m, 2H), 7.78 – 7.68 (m, 2H), 7.42 – 7.34 (m, 2H), 7.21 – 7.15 (m, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 2.30 (s, 3H), 1.27 (d, *J* = 1.4 Hz, 9H), 0.00 (s, 9H).

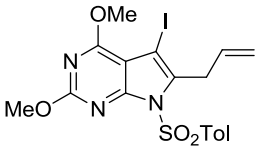
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 190.60, 165.40, 162.65, 157.47, 154.99, 145.58, 136.71, 136.05, 134.65, 129.39, 128.86, 125.61, 113.58, 105.59, 55.12, 53.79, 35.25, 31.11, 21.70, 0.05.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3172, 3120, 3069, 2961, 2870, 2670, 2600, 2556, 1790, 1715, 1681, 1593, 1470, 1378, 1317, 1286, 1249, 1213, 1166, 1121, 1087, 1033, 1010, 946, 843, 814, 778, 734, 706, 682, 663.

MS (EI, 70 eV): m/z (%) = 565 (39), 550 (22), 410 (100), 394 (44), 380 (30), 366 (9), 350 (12), 337 (19), 161 (11), 91 (13).

HRMS ($C_{29}H_{35}N_3O_5SSi$): calc.: 565.2067; found: 565.2042 (M^+).

6-Allyl-5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (47)



According to **TP4** iodine monochloride (179 mg, 1.1 mmol, 1.1 equiv) was added at 0 °C to a solution of 6-allyl-2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**46b**, 445 mg, 1.0 mmol, 1.0 equiv) in dry CH_2Cl_2 (5 mL) and stirred for 10 min at this temperature. The reaction mixture was quenched with sat. $Na_2S_2O_3$-solution, extracted three times with CH_2Cl_2, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (*i*hexane:EtOAc:NEt_3 = 8:1:0.1) to afforded 6-allyl-5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**47**, 371 mg, 74%) as a colorless solid.

m.p.: 167.9 - 170.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.97 – 7.94 (m, 2H), 7.32 – 7.29 (m, 2H), 5.05 (dddd, *J* = 9.2, 7.3, 5.7, 4.9 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.98 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.90 (dd, *J* = 15.1, 5.8 Hz, 1H), 3.72 (dd, *J* = 15.1, 9.2 Hz, 1H), 2.42 (s, 3H).

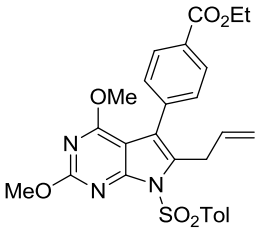
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.91, 160.75, 153.49, 144.80, 133.97, 133.79, 128.49, 127.17, 102.32, 64.60, 54.05, 53.17, 49.58, 36.19, 29.47, 20.61.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2992, 2955, 2924, 2852, 1577, 1469, 1394, 1372, 1317, 1296, 1275, 1221, 1177, 1142, 1084, 1050, 1020, 998, 942, 909, 858, 817, 789, 750, 734, 694, 681.

MS (EI, 70 eV): m/z (%) = 499 (26), 381 (27), 379 (45), 345 (41), 344 (100), 317 (12), 252 (17), 216 (40), 202 (13), 188 (12), 159 (9), 145 (13), 127 (11), 91 (37), 65 (15), 43 (67).

HRMS ($C_{18}H_{18}IN_3O_4S$): calc.: 499.0063; found: 499.0079 (M^+).

Ethyl 4-(6-allyl-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)benzoate (48a)

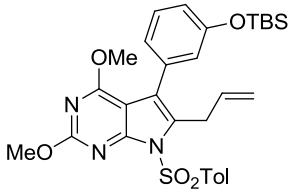


(4-(Ethylester)phenyl)magnesium chloride/lithium chloride was prepared by adding *i*PrMgCl·LiCl (0.16 mL, 0.17 mmol, 1.05 M in THF, 1.1 equiv) to a solution of (4-iodophenyl)ethylester (42 mg,

0.15 mmol, 1.0 equiv) in dry THF (0.2 mL) at 0 °C and stirring the reaction mixture at this temperature for 1 h. The title compound was prepared according to **TP5** with $ZnCl_2$ (0.18 mL, 0.18 mmol, 1.0 M in THF, 1.1 equiv), 6-allyl-5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**47**, 75 mg, 0.15 mmol, 1.0 equiv) and PEPPSI-IPr (3.1 mg, 3 mol%) at 50 °C in 24 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 9:1) afforded **48a** (47 mg, 60%) as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 – 8.13 (m, 2H), 8.09 – 8.08 (m, 2H), 7.45 – 7.44 (m, 2H), 7.33 – 7.32 (m, 2H), 6.19 – 6.15 (m, 1H), 5.19 (dq, *J* = 10.2, 1.6 Hz, 1H), 4.98 (dq, *J* = 17.3, 1.7 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 4.05 (s, 3H), 3.87 (s, 3H), 3.80 (dt, *J* = 5.3, 1.7 Hz, 2H), 2.44 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 165.41, 163.07, 160.65, 153.18, 144.30, 136.40, 135.42, 134.88, 131.23, 129.18, 128.32, 128.16, 127.81, 127.68, 116.89, 115.24, 59.90, 53.97, 52.85, 28.76, 28.58, 20.60, 13.26.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 2956, 2925, 2854, 1716, 1598, 1581, 1472, 1369, 1335, 1270, 1175, 1147, 1091, 1015, 966, 926, 859, 814, 795, 754, 704, 667.
MS (EI, 70 eV): m/z (%) = 521 (10), 366 (32), 338 (3), 326 (3), 293 (4), 267 (3), 91 (6), 61 (18), 45 (15), 43 (100).
HRMS ($C_{27}H_{27}N_3O_6S$): calc.: 521.1621; found: 521.1624 (M^+).

6-Allyl-5-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (48b)



(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)magnesium chloride/lithium chloride was prepared by adding *i*PrMgCl·LiCl (0.21 mL, 0.22 mmol, 1.05 M in THF, 1.1 equiv) to a solution of (3-bromophenoxy)(*tert*-butyl)dimethylsilane (57 mg, 0.20 mmol, 1.0 equiv) in dry THF (0.2 mL) at 0 °C and stirring the reaction mixture at this temperature for 1 h. The title compound was prepared according to **TP5** with $ZnCl_2$ (0.22 mL, 0.22 mmol, 1.0 M in THF, 1.1 equiv), 6-allyl-5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**47**, 100 mg, 0.20 mmol, 1.0 equiv) and PEPPSI-IPr (4.1 mg, 3 mol%) at 50 °C in 24 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 12:1) afforded **48b** (60 mg, 52%) as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 - 7.77 (m, 2H), 7.10 - 7.03 (m, 3H), 6.71 - 6.62 (m, 3H), 5.89 - 5.81 (m, 1H), 4.97 - 4.88 (m, 1H), 4.68 - 4.62 (m, 1H), 3.80 - 3.73 (m, 4 H), 3.62 (s, 3H), 3.49 - 3.44 (m, 1H), 2.20 (s, 3H), 0.78 (s, 9H), 0.00 (s, 6H).

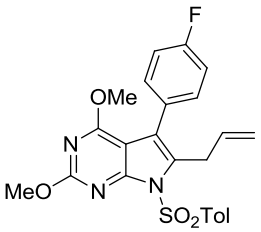
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 164.57, 162.05, 155.23, 154.79, 145.52, 135.58, 134.06, 133.52, 131.34, 129.48, 129.32, 128.91, 128.62, 128.54, 128.20, 119.73, 116.78, 101.47, 55.05, 54.02, 50.49, 34.73, 25.68, 21.68, -4.29.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2928, 2856, 1725, 1666, 1594, 1574, 1473, 1365, 1284, 1250, 1225, 1191, 1172, 1146, 1088, 1002, 963, 905, 829, 812, 782, 732, 665.

MS (EI, 70 eV): m/z (%) = 579 (3), 499 (9), 459 (8), 424 (14), 344 (24), 304 (32), 290 (9), 212 (10), 139 (17), 91 (28), 61 (21), 45 (15), 43 (100).

HRMS ($C_{30}H_{37}N_3O_5SSi$): calc.: 579.2223; found: 579.2204 (M^+).

6-Allyl-5-(4-fluorophenyl)-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (48c)



(4-fluoro-phenyl)magnesium chloride/lithium chloride was prepared by adding *i*PrMgCl·LiCl (0.21 mL, 0.22 mmol, 1.05 M in THF, 1.1 equiv) to a solution of 1-fluoro-4-iodobenzene (44 mg, 0.20 mmol, 1.0 equiv) in dry THF (0.2 mL) at 0 °C and stirring the reaction mixture at this temperature for 1 h. The title compound was prepared according to **TP5** with $ZnCl_2$ (0.22 mL, 0.22 mmol, 1.0 M in THF, 1.1 equiv), 6-allyl-5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**47**, 100 mg, 0.20 mmol, 1.0 equiv) and PEPPSI-IPr (4.1 mg, 3 mol%) at 50 °C in 24 h. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 12:1) afforded **48c** (59 mg, 63%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.12 – 8.07 (m, 2H), 7.32 – 7.27 (m, 4H), 7.09 – 7.03 (m, 2H), 6.14 (ddt, *J* = 17.3, 10.4, 5.3 Hz, 1H), 5.15 (dq, *J* = 10.2, 1.6 Hz, 1H), 4.94 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.02 (s, 3H), 3.83 (s, 3H), 3.75 (dt, *J* = 5.3, 1.8 Hz, 2H), 2.41 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 164.19, 162.26 (d, *J* = 247.1 Hz), 161.67, 154.16, 145.29, 136.68, 136.07, 132.00, 131.88 (d, *J* = 10.2 Hz), 129.23, 128.75, 128.53, 117.82, 116.17, 114.69 (d, *J* = 22.8 Hz), 101.08, 55.03, 53.91, 29.81, 21.67.

^{19}F-NMR (375 MHz, $CDCl_3$) δ / ppm = -114.75.

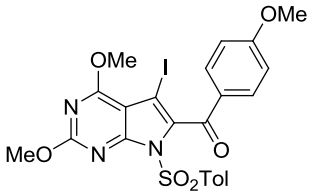
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2927, 2854, 1724, 1596, 1576, 1508, 1473, 1386, 1372, 1334, 1294, 1264, 1222, 1192, 1145, 1091, 1013, 994, 912, 838, 813, 794, 759, 703, 667.

MS (EI, 70 eV): m/z (%) = 467 (21), 312 (100), 296 (4), 265 (4), 239 (7), 216 (3), 172 (2), 145 (2), 91 (7), 72 (3), 65 (3), 43 (6).

HRMS ($C_{24}H_{22}FN_3O_4S$): calc.: 467.1315; found: 467.1313 (M^+).

3.4. Synthesis of Rigidin A

(5-Iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)methanone (49)



According to **TP4** iodine monochloride (393 mg, 2.42 mmol, 1.1 equiv) was added at 0 °C to a solution of (2,4-dimethoxy-7-tosyl-5-(trimethylsilyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)-methanone (**46e**, 1.19 g, 2.2 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) and stirred for 10 min at this temperature. The reaction mixture was quenched with sat. $Na_2S_2O_3$-solution, extracted three times with CH_2Cl_2, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (*i*hexane:EtOAc:NEt_3 = 6:1:0.1) to afford (5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)methanone (**49**, 1.16 g, 89%) as a colorless solid.

m.p.: 200.1 - 201.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J*=8.1 Hz, 2H), 7.88 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 6.93 (d, *J*=8.4 Hz, 2H), 4.03 (s, 3H), 4.01 (s, 3H), 3.84 (s, 3H), 2.36 (s, 3H).

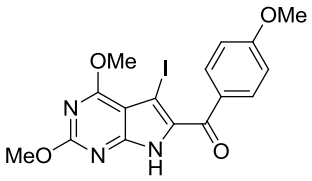
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 187.11, 165.14, 164.49, 162.78, 153.97, 146.10, 134.19, 133.86, 132.60, 129.64, 129.62, 129.05, 114.26, 103.61, 59.79, 55.63, 55.34, 54.44, 21.81.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935, 1653, 1593, 1574, 1506, 1475, 1456, 1421, 1401, 1380, 1361, 1306, 1279, 1260, 1214, 1166, 1152, 1121, 1089, 1059, 1026, 972, 932, 907, 866, 850, 814, 790, 756, 731, 702, 682, 667.

MS (EI, 70 eV): m/z (%) = 593 (5), 439 (35), 313 (36), 299 (24), 246 (12), 152 (28), 142 (55), 135 (100), 126 (25), 123 (15), 108 (12), 91 (55), 77 (31), 65 (21).

HRMS ($C_{23}H_{20}IN_3O_6S$): calc.: 593.0117; found: 593.0117 (M^+).

(5-Iodo-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)methanone (50)



In a 50 mL flasked, equipped with a magnetic stirrer and a septum, (5-iodo-2,4-dimethoxy-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)methanone (**49**, 356 mg, 0.6 mmol, 1.0 equiv) and KOH (202 mg, 3.6 mmol, 6.0 equiv) were dissolved in THF:MeOH (2:1, 10 mL) and stirred at 25 °C for 2 h. The reaction mixture was quenched with sat. NH_4Cl-solution, extracted three times with CH_2Cl_2, the organic layers dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (*i*hexane:EtOAc:NEt_3 = 4:1:0.05) to afford (5-iodo-2,4-dimethoxy-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(4-methoxyphenyl)methanone (**50**, 161 mg, 61%) as a colorless solid.

m.p.: 198.3 - 200.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.74 (s, 1H), 7.74 (d, *J*=8.5 Hz, 2H), 6.90 (d, *J*=8.5 Hz, 2H), 4.08 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H).

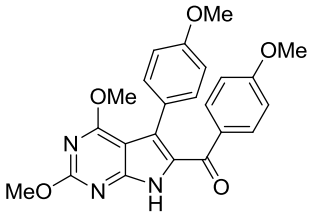
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 186.67, 166.43, 163.66, 163.45, 153.75, 132.48, 132.28, 129.31, 113.80, 105.32, 60.59, 55.56, 55.05, 54.31.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3140, 3075, 3000, 2945, 2910, 2870, 2842, 2805, 1636, 1616, 1597, 1478, 1447, 1422, 1388, 1358, 1318, 1282, 1254, 1192, 1169, 1149, 1111, 1085, 1028, 976, 932, 843, 788, 767, 743, 702, 676.

MS (EI, 70 eV): m/z (%) = 439 (100), 407 (15), 330 (14), 312 (70), 281 (9), 204 (10), 176 (8), 135 (54), 92 (12), 77 (17).

HRMS ($C_{16}H_{14}IN_3O_4$): calc.: 439.0029; found: 439.0032 (M^+).

(2,4-dimethoxy-5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-6-yl)(4-methoxyphenyl)methanone (51)



In a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, (5-iodo-2,4-dimethoxy-7*H*-pyrrolo[2,3-d]pyrimidin-6-yl)(4-methoxyphenyl)methanone (**50**, 155 mg, 0.35 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (8 mg, 0.017 mmol, 5 mol%), K_2CO_3 (193 mg, 1.40 mmol, 4.0 equiv) and (4-methoxyphenyl)boronic acid (64 mg, 0.42 mmol, 1.2 equiv) were dissolved in 1,4-Dioxane:H_2O

(10:1, 11 ml). The resulting mixture was stirred for 24 h at 70 °C. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc:MeOH = 2:1:0.05) afforded (2,4-dimethoxy-5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-6-yl)(4-methoxyphenyl)methanone (**51**, 84 mg, 57%) as a white solid.

m.p.: 155.2 - 158.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.29 (s, 1H), 7.38 (d, *J*=8.5 Hz, 2H), 7.05 (d, *J*=8.3 Hz, 2H), 6.57 (d, *J*=8.3 Hz, 2H), 6.50 (d, *J*=8.5 Hz, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.67 (s, 3H).

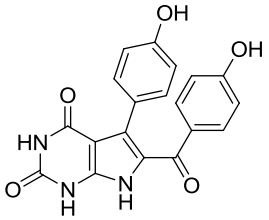
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 187.18, 167.05, 163.86, 162.45, 158.92, 153.40, 132.62, 131.65, 129.66, 127.98, 125.21, 124.08, 112.93, 112.87, 101.09, 55.35, 55.24, 54.97, 54.13.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3265, 3076, 6053, 3002, 2985, 2939, 2836, 1596, 1565, 1532, 1511, 1496, 1476, 1457, 1437, 1424, 1391, 1365, 1278, 1245, 1215, 1196, 1162, 1140, 1112, 1079, 1035, 1018, 987, 956, 932, 866, 846, 832, 797, 773, 744, 724, 667.

MS (EI, 70 eV): m/z (%) = 419 (100), 402 (5), 388 (5), 269 (6), 209 (4), 135 (32), 77 (9).

HRMS ($C_{23}H_{21}N_3O_5$): calc.: 419.1481; found: 419.1477 (M^+).

Rigidine A (37a)



In a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, (2,4-dimethoxy-5-(4-methoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-6-yl)(4-methoxyphenyl)methanone (**51**, 80 mg, 0.19 mmol, 1.0 equiv) were dissolved in dry CH_2Cl_2 (25 ml) and cooled to -78°C. A solution of boron tribromide (3.81 mL, 1.0 M in CH_2Cl_2, 3.81 mmol, 20.0 equiv) was added to the reaction mixture slowly over 5 min. The reaction mixture was warmed to 40 °C and then stirred for 24 h at this temperature. After cooling the reaction mixture to -78 °C an additional amount of boron tribromide solution (0.95 mL, 1.0 M in CH_2Cl_2, 0.95 mmol, 5.0 equiv) was added slowly over 3 min and the reaction mixture was allowed to warm to 25 °C and stirred for 20 h. The reaction mixture was cooled in an ice/water bath and quenched with slow addition of methanol (10 ml). This mixture was stirred in an ice bath for 5 h and 20 mL of water was added followed by the careful addition of 5% aqueous NaOH (5 mL) to a pH of 6. This solution was allowed to warm to 25 °C and stirred for 16 h. The solvents were removed *in vacuo* and the resulting aqueous mixture was extracted three times with CH_2Cl_2, the organic layers dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by reverse phase column chromatography with acetonitrile/water gradient to afford rigidine A (**37a**, 22 mg, 0.061 mmol, 32%) as a light yellow solid.

m.p.: > 320 °C (decomp.).

^{1}H-NMR (300 MHz, DMSO-d_6): δ / ppm = 11.73 (br s, 1H), 11.17 (br s, 1H), 10.62 (br s, 1H), 9.99 (br s, 1H), 9.72 (br s, 1H), 7.30 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.48 (d, J = 9.0 Hz, 2H), 6.45 (d, J = 9.0 Hz, 2H).

^{13}C-NMR (75 MHz, DMSO-d_6): δ / ppm = 185.7, 161.2, 160.2, 156.9, 151.1, 141.6, 132.7, 132.0, 129.1, 128.5, 125.4, 123.2, 114.8, 114.3, 98.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3215, 1695, 1568, 1434, 1413, 1258.

HRMS (ESI, $C_{19}H_{12}N_3O_5$): calc.: 362.0855; found: 362.0774 (M^+).

4. REGIOSELECTIVE PREPARATION OF TETRASUBSTITUTED FLUOROBENZENES

4.1. Typical Procedures

Typical Procedure for the Metalation using *s*-BuLi (TP1):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with freshly sublimated KO*t*Bu (2.5 equiv) and freshly destilled PMDTA (*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine) (2.5 equiv) in dry Et_2O (0.5 M solution) and stirred for 10 min at 25 °C. The slurry mixture was cooled to -65 °C and *s*-Buli (2.5 equiv) was added slowly and stirred for 15 min at the same temperature. Then the bissilylbenzene was added and the reaction mixture was stirred for 20 h at -65 °C (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with dimethyl disulfide in Et_2O).

Typical Procedure for Halogen-Lithium Exchange Reactions (TP2):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the starting aryl bromide in THF (0.5-1.0 M solution) and cooled to -78 °C. Then *n*-BuLi (1.1 equiv) was added and the reaction mixture was stirred for the indicated time (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with saturated aqueous NH_4Cl-solution).

Typical Procedure for Allylation or Acylation Reactions (TP3):

To the freshly prepared lithium/magnesium reagent was added CuCN·2LiCl (1.2 equiv, 1.0 M in THF) and the reaction mixture was stirred for 30 min at the indicated temperature. The respective allyl bromide or acyl chloride was added and the reaction mixture was stirred for the indicated time at the indicated temperature. The reaction mixture was quenched with concentrated aqueous NH_4Cl:NH_3-solution (19:1), extracted three times with EtOAc, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for Cross-Coupling Reactions (TP4):

To the freshly prepared lithium/magnesium reagent was added $ZnCl_2$ (1.2 equiv, 1.0 M in THF) and the reaction mixture was stirred for 30 min at the indicated temperature. The catalytic system and the aryl iodide/bromide (1.2 equiv) were added and the reaction mixture was warmed to 25 °C. After stirring for the indicated time, the reaction mixture was quenched with half concentrated aqueous NH_4Cl-solution, extracted three times with EtOAc, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for the Conversion of the TES-Group to Iodide (TP5):

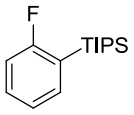
To the respective TES-substituted compound (approx. 0.2 M in CH_2Cl_2) was added iodine monochloride (1.1 equiv) at 0 °C and the mixture was stirred for 20 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$-solution, extracted three times with CH_2Cl_2, the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel.

Typical Procedure for Halogen-Magnesium Exchange Reactions (TP6):

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with the starting aryl iodine in THF (0.2-1.0 M solution) and cooled to the indicated temperature. Then *i*PrMgCl·LiCl was added and the reaction mixture was stirred for the indicated time (the completion of the reaction was checked by GC analysis of reaction aliquots quenched with saturated aqueous NH_4Cl-solution).

4.2. Preparation of Bis Silylbenzene Derivatives

(2-Fluorophenyl)triisopropylsilane (53)



A solution of 1-bromo-2-fluorobenzene (**52**, 6.56 g, 37.5 mmol, 1.0 equiv) in THF (40 mL) was added to a dry and argon-flushed *Schlenk* flask, equipped with a septum and a magnetic stirring bar, cooled to -78 °C and *t*-BuLi (50.0 ml, 1.65 M in *i*hexane, 82.5 mmol, 2.2 equiv) was added dropwise. The reaction mixture was stirred for 1.5 h at -78 °C. Afterwards triisopropylsilyl chloride (7.96 g, 41.3 mmol, 1.1 equiv) was added slowly and the solution was allowed to warm to 25 °C within 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (pentane) afforded the compound **53** (5.86 g, 62%) as a colorless oil.

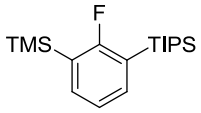
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.53 (m, 1H), 7.42 (m, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 1.58 (hept, J = 7.6 Hz, 3H), 1.20 (d, J = 7.9 Hz, 18H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.57 (d, J = 241.0 Hz), 136.85 (d, J = 12.2 Hz), 131.00 (d, J = 8.5 Hz), 123.62 (d, J = 2.7 Hz), 115.03 (d, J = 27.3 Hz), 18.7, 11.4.
^{19}F-NMR (375 MHz, $CDCl_3$): δ / ppm = -96.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 3014, 2944, 2891, 2866, 2727, 1915, 1795, 1698, 1600, 1563, 1468, 1432, 1384, 1367, 1332, 1284, 1256, 1202, 1156, 1115, 1078, 1018, 996, 941, 920, 882, 856, 820, 756, 730, 717, 673.

MS (EI, 70 eV): *m/z* (%) = 252 (1), 209 (3), 167 (24), 139 (100), 125 (22), 91 (12), 77 (19), 63 (12), 47 (25), 43 (28).

HRMS ($C_{15}H_{25}FSi$): calc.: 252.1710, found: 252.1703 (M^+).

Trimethyl(2-fluoro-3-(triisopropylsilyl)phenyl)silane (54)



A dry and argon-flushed *Schlenk* flask, equipped with a septum and a magnetic stirring bar, was filled with TMPH (182 mg, 1.3 mmol, 1.3 equiv) dissolved in THF (2 mL) and cooled to -20 °C. *n*-BuLi (**59**, 0.50 mL, 1.2 mmol, 1.2 equiv, 2.40 M in *i*hexane) was added dropwise and the reaction mixture was stirred for 20 min at -20 °C and then 15 min at 0 °C. After cooling to -78 °C (2-fluorophenyl)triisopropylsilane (**53**, 252 mg, 1.0 mmol, 1.0 equiv) dissolved in THF (15 mL) was added and the suspension was stirred for 4 h at -78 °C. Then trimethylsilyl chloride (141 mg, 1.5 mmol, 1.5 equiv) solved in THF (5 mL) was added and the mixture was allowed to warm to 25 °C for 16 h. The suspension was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with *i*hexane (3 × 50 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded the compound **54** (240 mg, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.51 – 7.40 (m, 2H), 7.15 (td, *J* = 7.2, 1.7 Hz, 1H), 1.12 (d, *J* = 7.5 Hz, 18H), 0.34 (s, 3H), 0.33 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.10 (d, *J* = 236.2 Hz), 138.31 (d, *J* = 12.6 Hz), 136.24 (d, *J* = 11.9 Hz), 125.36 (d, *J* = 36.9 Hz), 123.31 (d, *J* = 2.6 Hz), 119.95 (d, *J* = 37.1 Hz), 18.63 (d, *J* = 1.0 Hz), 11.36 (d, *J* = 1.7 Hz), -1.10 (d, *J* = 1.8 Hz).

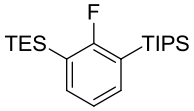
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -115.07

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946, 2892, 2866, 1586, 1554, 1464, 1381, 1249, 1215, 1191, 1151, 1128, 1072, 1018, 996, 920, 882, 838, 762, 694, 676, 646, 597, 578, 555.

MS (EI, 70 eV): m/z (%) = 324 (3), 239 (57), 225 (2), 211 (100), 197 (18), 189 (20), 161 (9), 147 (43), 133 (10), 119 (5), 105 (2), 98 (3), 77 (12), 73 (57), 59 (10).

HRMS ($C_{18}H_{33}FSi_2$): calc.: 324.2105, found: 324.2102 (M^+).

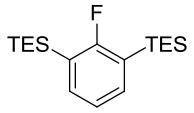
Triethyl(2-fluoro-3-(triisopropylsilyl)phenyl)silane (55)



A dry and argon-flushed *Schlenk* flask, equipped with a septum and a magnetic stirring bar, was filled with TMPH (1.28 g, 9.01 mmol, 1.3 equiv) dissolved in THF (9 mL) and cooled to -20 °C. *n*-BuLi (**59**, 3.47 mL, 8.32 mmol, 1.2 equiv, 2.40 M in *i*hexane) was added dropwise and the reaction mixture was stirred for 20 min at -20 °C and then 15 min at 0 °C. After cooling to -78 °C (2-fluorophenyl)triisopropylsilane (**53**, 1.75, 6.93 mmol, 1.0 equiv) dissolved in THF (15 mL) was added and the suspension was stirred for 4 h at -78 °C. Then triethylsilyl chloride (1.57 g, 10.4 mmol, 1.5 equiv) suspended in THF (5 mL) was added and the mixture was allowed to warm to 25 °C within 16 h. The suspension was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with *i*hexane (3 × 50 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded the compound (**55**, 2.20 g, 86%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48 (m, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 1.52 (spt, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 7.7 Hz, 18H) 1.10 – 0.87 (m, 15H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 172.14 (d, *J* = 236.1 Hz), 138.20 (d, *J* = 12.6 Hz), 137.24 (d, *J* = 12.4 Hz), 123.35 (d, *J* = 2.6 Hz), 122.35 (d, *J* = 38.1 Hz), 119.87 (d, *J* = 37.6 Hz), 18.66, 11.39, 11.37, 7.45, 3.56, 3.54.
^{19}F-NMR (375 MHz, $CDCl_3$): δ / ppm = -81.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3043, 2951, 2889, 2867, 2729, 1936, 1885, 1696, 1579, 1554, 1462, 1417, 1380, 1281, 1255, 1239, 1214, 1189, 1150, 1122, 1072, 1017, 1004, 972, 920, 882, 818, 801, 767, 747, 729, 721, 696, 676.
MS (EI, 70 eV): *m/z* (%) = 366 (1), 295 (100), 281 (18), 267 (97), 253 (42), 239 (87), 189 (19), 169 (31), 161 (36), 147 (24), 133 (26), 115 (15), 105 (43), 87 (20), 77 (50), 59 (27), 43 (15).
HRMS ($C_{21}H_{39}FSi_2$): calc.: 366.2574, found: 366.2590 (M^+).

(2-Fluoro-1,3-phenylene)bis(triethylsilane) (57)

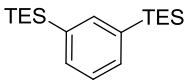


In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with fluorobenzene (**56**, 1.92 g, 20 mmol, 1.0 equiv) and TES-Cl (7.53 g, 50 mmol, 2.5 equiv) in 30 mL THF. The solution was cooled down to -78 °C and TMPLi (**4**, 67.7 ml, 0.65 M in hexane, 44 mmol, 2.2 equiv) was added dropwise. The reaction mixture was allowed to warm to 25 °C within 8 h, quenched with sat. aq. NH_4Cl (100 mL) and extracted with *i*hexane (3 × 50 mL). The combined

organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (2-fluoro-1,3-phenylene)bis(triethylsilane (**57**, 5.77 g, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33 (dd, *J* = 7.2, 5.7 Hz, 2H), 7.05 (td, *J* = 7.2, 1.7 Hz, 1H), 0.89 (t, *J* = 7.6 Hz, 18H), 0.81 – 0.71 (m, 12H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.16 (d, *J* = 236.0 Hz), 137.33 (d, *J* = 12.3 Hz), 123.43 (d, *J* = 2.7 Hz), 122.11 (d, *J* = 37.1 Hz), 7.40, 3.55, 3.54.
^{19}F NMR (376 MHz, $CDCl_3$): δ / ppm = -84.72.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 1582, 1555, 1458, 1417, 1384, 1278, 1239, 1215, 1190, 1150, 1126, 1004, 973, 818, 773, 748, 718, 684.
MS (EI, 70 eV): m/z (%) = 324 (5), 295 (2), 267 (85), 239 (100), 225 (6), 211 (55), 183 (11), 161 (34), 133 (24), 119 (12), 105 (37), 91 (19), 77 (22), 59 (13).
HRMS ($C_{18}H_{33}FSi_2$): calc.: 324.2105, found: 324.2118 (M^+).

1,3-Bis(triethylsilyl)benzene (60)

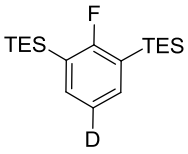


In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with 1,3-dibromobenzene (**58**, 7.02 g, 30 mmol, 1.0 equiv) and TES-Cl (11.29 g, 75 mmol, 2.5 equiv) in 50 mL THF. The solution was cooled down to -78 °C and *n*-BuLi (**59**, 31.4 ml, 2.1 M in hexane, 66 mmol, 2.2 equiv) was added dropwise. The reaction mixture was allowed to warm to 25 °C within 8 h, quenched with sat. aq. NH_4Cl (100 mL) and extracted with *i*hexane (3 × 50 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded 1,3-bis(triethylsilyl)benzene (**60**, 8.54 g, 93%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.55 (td, *J* = 1.3, 0.8 Hz, 1H), 7.42 (dd, *J* = 1.4, 0.5 Hz, 1H), 7.40 (d, *J* = 1.3 Hz, 1H), 7.26 (ddd, *J* = 7.7, 6.9, 0.7 Hz, 1H), 0.96 – 0.86 (m, 18H), 0.78 – 0.67 (m, 12H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.17, 136.11, 134.52, 126.90, 7.42, 3.42.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2910, 2875, 1458, 1416, 1361, 1237, 1106, 1003, 779, 729, 714, 685.
MS (EI, 70 eV): m/z (%) = 306 (5), 277 (100), 249 (67), 235 (4), 221 (55), 207 (2), 191 (9), 177 (3), 165 (11), 149 (2), 137 (15), 124 (3), 110 (13), 96 (22), 82 (17), 68 (10), 55 (8).
HRMS ($C_{18}H_{34}Si_2$): calc.: 306.2199; found: 306.2194 (M^+).

4.3. Functionalization in *para*-Position *via* Metalation with *s*-BuLi

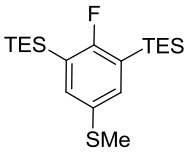
(5-Deuterium-2-fluoro-1,3-phenylene)bis(triethylsilane) (62a)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with MeOD-d_4 (108 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded a mixture of (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 71 mg, 22%) and (5-deuterium-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62a**, 252 mg, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 (dd, J = 6.5, 3.0 Hz, 2H), 7.04 (td, J = 7.1, 1.7 Hz, 0.22 H), 0.88 (t, J = 7.7 Hz, 18H), 0.82 – 0.72 (m, 12H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 172.16 (d, J = 236.1 Hz), 137.23 (d, J = 12.3 Hz), 123.53 – 121.78 (m), 7.40, 3.55, 3.54.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -84.73.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2875, 2124, 1582, 1545, 1457, 1417, 1377, 1334, 1281, 1239, 1214, 1190, 1150, 1122, 1061, 1004, 973, 914, 901, 856, 816, 749, 719, 684, 648, 583, 555.
MS (EI, 70 eV): m/z (%) = 325 (8), 296 (4), 268 (100), 240 (93), 212 (60), 184 (9), 162 (38), 156 (30), 134 (26), 115 (6), 105 (35), 91 (18), 77 (28), 71 (7), 59 (12).
HRMS ($C_{18}H_{32}DFSi_2$): calc.: 325.2168, found: 325.2182 (M^+).

(2-Fluoro-5-(methylthio)-1,3-phenylene)bis(triethylsilane) (62b)

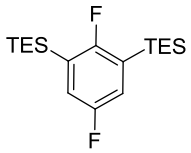


The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h.

The reaction mixture was quenched with dimethyl disulfide (283 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (2-fluoro-5-(methylthio)-1,3-phenylene)bis(triethylsilane) (**62b**, 262 mg, 71%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.24 (s, 1H), 7.23 (s, 1H), 2.40 (s, 3H), 0.94 – 0.84 (m, 18H), 0.82 – 0.70 (m, 12H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.68 (d, J = 235.4 Hz), 136.81 (d, J = 12.6 Hz), 132.14 (d, J = 2.9 Hz), 123.34 (d, J = 38.4 Hz), 17.54, 7.38, 3.49, 3.48.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -89.80.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2874, 1566, 1458, 1418, 1386, 1270, 1220, 1196, 1144, 1092, 1004, 968, 858, 786, 742, 668.
MS (EI, 70 eV): m/z (%) = 370 (100), 313 (18), 285 (53), 227 (6), 221 (5), 201 (30), 179 (30), 142 (9), 128 (16), 114 (18), 105 (33), 87 (11), 77 (31), 59 (12).
HRMS ($C_{19}H_{35}FSSi_2$): calc.: 370.1982, found: 370.1981 (M^+).

(2,5-Difluoro-1,3-phenylene)bis(triethylsilane) (62c)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with *N*-fluorobenzenesulfonimide (946 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (2,5-difluoro-1,3-phenylene)bis(triethylsilane) (**62c**, 172 mg, 50%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.04 (dd, J = 8.0, 3.9 Hz, 2H), 1.02 – 0.92 (m, 18H), 0.90 – 0.79 (m, 12H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.44 (dd, J = 231.5, 1.2 Hz), 158.89 (dd, J = 244.5, 2.2 Hz), 137.33 (d, J = 12.3 Hz), 124.71 (dd, J = 41.3, 3.7 Hz), 122.79 (dd, J = 22.0, 13.6 Hz), 7.31, 3.35, 3.33.

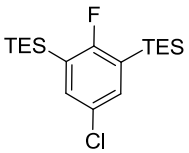
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -92.73, -122.12.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 2833, 2813, 1757, 1712, 1694, 1659, 1642, 1592, 1575, 1515, 1457, 1417, 1386, 1313, 1277, 1239, 1192, 1174, 1126, 1094, 1061, 1004, 974, 881, 819, 785, 741, 718, 689.

MS (EI, 70 eV): m/z (%) = 342 (4), 285 (34), 257 (46), 231 (25), 188 (27), 173 (18), 155 (9), 149 (11), 141 (14), 133 (24), 127 (14), 111 (27), 105 (10), 97 (36), 95 (18), 85 (51), 77 (18), 71 (76), 57 (100), 43 (57).

HRMS ($C_{18}H_{32}F_2Si_2$): calc.: 342.2011; found: 342.1996 (M^+).

(5-Chloro-2-fluoro-1,3-phenylene)bis(triethylsilane) (62d)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with 1,1,1,3,3,3-hexachloroacetone (794 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (5-chloro-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62d**, 197 mg, 55%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.29 (s, 1H), 7.28 (s, 1H), 0.95 (dd, J = 9.6, 6.1 Hz, 18H), 0.86 – 0.79 (m, 12H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.22 (d, J = 235.9 Hz), 137.31 (d, J = 13.8 Hz), 136.48 (d, J = 14.9 Hz), 129.27, 125.02 (d, J = 40.7 Hz), 7.28, 3.32.

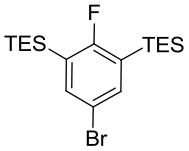
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -89.26.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 1573, 1549, 1457, 1417, 1379, 1321, 1296, 1271, 1239, 1210, 1192, 1135, 1112, 1086, 1061, 1004, 974, 884, 855, 818, 781, 744, 722, 675.

MS (EI, 70 eV): m/z (%) = 358 (21), 301 (80), 273 (100), 267 (19), 245 (60), 239 (16), 211 (14), 195 (20), 189 (50), 166 (22), 161 (16), 133 (24), 122 (17), 115 (14), 105 (48), 87 (21), 77 (45). 59 (18).

HRMS ($C_{18}H_{32}ClFSi_2$): calc.: 358.1715; found: 358.1712 (M^+).

(5-Bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (62e)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with a solution of bromine (479 mg, 3.0 mmol, 3.0 equiv) in 5 mL Et_2O and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 246 mg, 61%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.36 (s, 1H), 7.35 (s, 1H), 0.91 – 0.86 (m, 18H), 0.80 – 0.71 (m, 12H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.76 (d, *J* = 236.1 Hz), 139.43 (d, *J* = 12.9 Hz), 125.80 (d, *J* = 39.7 Hz), 117.60 (d, *J* = 2.9 Hz), 7.30, 3.37, 3.35.

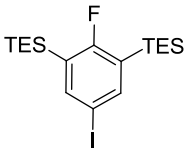
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -88.68.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 1572, 1458, 1417, 1379, 1270, 1239, 1211, 1194, 1120, 1078, 1004, 974, 883, 816, 780, 744, 720, 687, 650, 615.

MS (EI, 70 eV): m/z (%) = 404 (17), 402 (15), 347 (69), 319 (85), 291 (58), 241 (25), 233 (33), 189 (28), 145 (17), 131 (29), 105 (100), 77 (67).

HRMS ($C_{18}H_{32}BrFSi_2$): calc.: 402.1210; found: 402.1200 (M^+).

(5-Iodo-2-fluoro-1,3-phenylene)bis(triethylsilane) (62f)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with a solution of bromine (479 mg, 3.0 mmol, 3.0 equiv) in 5 mL Et_2O and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical

purification on silica gel (pentane) afforded (5-iodo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62f**, 288 mg, 64%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (s, 1H), 7.63 (s, 1H), 0.97 (td, *J* = 8.2, 7.8, 1.2 Hz, 18H), 0.84 (dtt, *J* = 7.9, 7.0, 1.0 Hz, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 171.60 (d, *J* = 236.8 Hz), 145.52 (d, *J* = 12.5 Hz), 126.54 (d, *J* = 38.9 Hz), 89.50 (d, *J* = 2.8 Hz), 7.31, 3.37, 3.36.

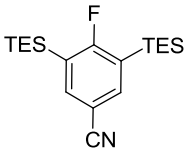
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -87.69.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2910, 2875, 1567, 1457, 1417, 1381, 1308, 1267, 1238, 1214, 1195, 1115, 1060, 1003, 974, 907, 882, 778, 745, 720, 686.

MS (EI, 70 eV): m/z (%) = 450 (33), 421 (9), 393 (81), 365 (100), 337 (58), 309 (11), 301 (5), 287 (31), 279 (9), 259 (25), 209 (5), 181 (7), 168 (15), 154 (14), 133 (10), 115 (10), 105 (45), 87 (17), 77 (27), 59 (12).

HRMS ($C_{18}H_{32}FISi_2$): calc.: 450.1071; found: 450.1073 (M^+).

4-Fluoro-3,5-bis(triethylsilyl)benzonitrile (62g)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with 2,2-dimethylmalononitrile (282 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 70:1) afforded (4-fluoro-3,5-bis(triethylsilyl)benzonitrile) (**62g**, 175 mg, 50%) as a colorless solid.

m.p.: 26.2 - 26.9 °C.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.70 (s, 1H), 7.69 (s, 1H), 1.02 – 0.94 (m, 18H), 0.89 – 0.85 (m, 12H).

^{13}C-NMR (200 MHz, $CDCl_3$): δ / ppm = 173.83 (d, *J* = 245.3 Hz), 141.55 (d, *J* = 15.0 Hz), 124.86 (d, *J* = 40.3 Hz), 119.20, 108.43 (d, *J* = 3.9 Hz), 7.24, 3.23, 3.22.

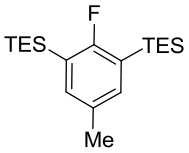
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -75.62.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 2953, 2911, 2875, 2361, 2341, 2231, 2183, 1862, 1809, 1567, 1514, 1456, 1417, 1392, 1309, 1280, 1231, 1200, 1106, 1004, 977, 934, 903, 787, 753, 740, 719, 694.

MS (EI, 70 eV): m/z (%) = 349 (4), 320 (25), 292 (77), 264 (100), 236 (43), 194 (3), 180 (36), 158 (10), 130 (6), 117 (9), 105 (15), 87 (4), 77 (21), 71 (4), 59 (8), 43 (20).

HRMS ($C_{19}H_{32}FNSi_2$): calc.: 349.2057; found: 349.2055 (M^+).

(2-Fluoro-5-methyl-1,3-phenylene)bis(triethylsilane) (62h)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (2-fluoro-1,3-phenylene)bis(triethylsilane) (**57**, 324 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with methyl iodine (426 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (2-fluoro-5-methyl-1,3-phenylene)bis(triethylsilane) (**62h**, 230 mg, 68%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.16 (d, J = 0.8 Hz, 1H), 7.15 (d, J = 0.8 Hz, 1H), 2.31 (d, J = 1.0 Hz, 3H), 0.99 – 0.93 (m, 18H), 0.83 (pd, J = 7.8, 1.1 Hz, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 170.48 (d, J = 233.7 Hz), 137.70 (d, J = 12.2 Hz), 132.11, 123.42, 121.69 (d, J = 36.9 Hz), 20.78, 7.41, 3.53.

^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -90.80.

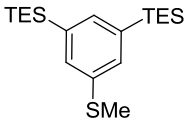
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2893, 2864, 2727, 1936, 1887, 1696, 1589, 1554, 1462, 1417, 13802 1266, 1255, 1222, 1214, 1189, 1151, 1114, 1072, 1019, 1004, 972, 924, 878, 816, 801, 767, 729, 694, 672.

MS (EI, 70 eV): *m/z* (%) = 338 (22), 281 (100), 267 (29), 253 (80), 239 (31), 225 (77), 211 (20), 195 (12), 175 (75), 167 (15), 161 (23), 147 (48), 133 (14), 112 (21), 105 (52), 98 (24), 87 (20), 84 (13), 77 (51), 59 (20), 43 (36).

HRMS (EI) ($C_{19}H_{35}FSi_2$): calc.: 338.2261, found: 338.2261 (M^+).

4.4. Functionalization in *meta*-Position *via* Metalation with *s*-BuLi

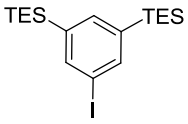
(5-Methylthio)-1,3-bis(triethylsilyl)benzene (64a)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (1,3-bis(triethylsilyl)benzene (**60**, 306 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with dimethyl disulfide (283 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (5-methylthio)-1,3-bis(triethylsilyl)benzene (**64a**, 201 mg, 57%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.29 – 7.27 (m, 1H), 7.26 (d, J = 1.0 Hz, 2H), 2.43 (s, 3H), 0.87 (td, J = 7.8, 1.1 Hz, 18H), 0.71 (qd, J = 7.5, 1.4 Hz, 12H).
^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 137.47, 136.78, 136.55, 132.21, 15.16, 7.68, 3.20.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2909, 2874, 2809, 1548, 1522, 1507, 1457, 1416, 1378, 1363, 1321, 1310, 1236, 1141, 1119, 1067, 1003, 967, 854, 795, 716, 688.
MS (EI, 70 eV): m/z (%) = 352 (98), 323 (89), 295 (65), 267 (100), 182 (12), 147 (12), 133 (25), 119 (29), 111 (9), 105 (27), 97 (14), 91 (14), 85 (38), 71 (48), 57 (67), 43 (41).
HRMS ($C_{19}H_{36}SSi_2$): calc.: 352.2076; found: 352.2074 (M^+).

(5-Iodo)-1,3-bis(triethylsilyl)benzene (64b)



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (1,3-bis(triethylsilyl)benzene (**60**, 306 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with iodine (768 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (5-iodo)-1,3-bis(triethylsilyl)benzene (**64b**, 199 mg, 46%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69 (d, *J* = 1.0 Hz, 2H), 7.45 (t, *J* = 1.0 Hz, 1H), 0.95 – 0.85 (m, 18H), 0.77 – 0.65 (m, 12H).

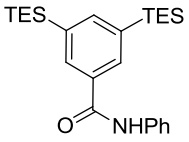
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.85, 140.14, 138.70, 96.72, 7.32, 3.27.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2907, 2872, 2828, 2806, 1552, 1528, 1455, 1413, 1366, 1345, 1307, 1235, 1134, 1099, 1002, 972, 860, 787, 717, 688.

MS (EI, 70 eV): m/z (%) = 432 (13), 403 (100), 391 (6), 375 (45), 347 (44), 290 (5), 263 (7), 187 (10), 173 (13), 163 (7), 159 (16), 145 (13), 131 (6), 105 (4), 87 (12), 71 (3), 59 (8).

HRMS ($C_{18}H_{33}ISi_2$): calc.: 432.1165; found: 432.1161 (M^+).

***N*-Phenyl-3,5-bis(triethylsilyl)benzamide (64c)**



The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (1,3-bis(triethylsilyl)benzene (**60**, 306 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with isocyanatobenzene (357 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded *N*-phenyl-3,5-bis(triethylsilyl)benzamide (**64c**, 170 mg, 40%) as a colorless solid.

m.p.: 145.9 - 147.8 °C.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.93 (s, 1H), 7.80 (s, 1H), 7.77 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 1.00 (m, 18H), 0.89 – 0.83 (m, 12H).

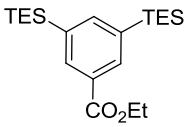
^{13}C-NMR (200 MHz, $CDCl_3$): δ / ppm = 165.90, 142.55, 137.02, 136.29, 132.67, 131.78, 128.05, 123.47, 119.16, 6.36, 2.30.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3287, 3270, 2953, 2909, 2874, 1640, 1600, 1573, 1537, 1500, 1442, 1415, 1378, 1331, 1316, 1268, 1238, 1179, 1141, 1103, 1079, 1003, 960, 926, 900, 796, 754, 717, 687.

MS (EI, 70 eV): m/z (%) = 425 (22), 396 (41), 368 (25), 340 (17), 333 (100), 310 (2), 221 (5), 196 (3), 183 (8), 170 (5), 155 (11), 141 (12), 127 (6), 115 (5), 87 (18), 59 (6).

HRMS ($C_{25}H_{39}NOSi_2$): calc.: 425.2570; found: 425.2564 (M^+).

Ethyl 3,5-bis(triethylsilyl)benzoate (64d)

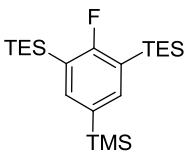


The title compound was prepared according to **TP1** from KO*t*Bu (280.5 mg, 2.5 mmol, 2.5 equiv), PMDTA (434 mg, 2.5 mmol, 2.5 equiv), *s*-BuLi (1.85 ml, 1.35 M in *i*hexane, 2.5 mmol, 2.5 equiv) and (1,3-bis(triethylsilyl)benzene (**60**, 306 mg, 1.0 mmol, 1.0 equiv) at -65 °C in 20 h. The reaction mixture was quenched with ethyl chloroformate (313 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (pentane) afforded ethyl 3,5-bis(triethylsilyl)benzoate (**64d**, 133 mg, 35%) as a colorless oil.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 1.2 Hz, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 7.28 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 0.95 – 0.85 (m, 18H), 0.86 – 0.79 (m, 12H).
^{13}C-NMR (200 MHz, $CDCl_3$): δ / ppm = 197.55, 143.46, 139.44, 134.94, 134.48, 59.80, 13.37, 6.35, 2.29, 2.28.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2912, 2874, 1748, 1686, 1578, 1456, 1422, 1388, 1292, 1218, 1160, 1102, 1010, 960, 912, 783, 752, 654.
MS (EI, 70 eV): m/z (%) = 349 (30), 321 (11), 293 (13), 113 (18), 111 (11), 97 816), 90 (20), 83 (28), 71 (62), 57 (70), 44 (100), 41 (43).
HRMS ($C_{19}H_{33}O_2Si_2$): calc.: 349.2025; found: 349.2015 (M^+-Et).

4.5. Functionalization in *para*-Position *via* Exchange with *n*-BuLi

(2-Fluoro-5-(trimethylsilyl)-1,3-phenylene)bis(triethylsilane) (66a)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with trimethylsilyl chloride (49 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and

concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (2-fluoro-5-(trimethylsilyl)-1,3-phenylene)bis(triethylsilane) (**66a**, 109 mg, 92%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.54 (s, 1H), 7.53 (s, 1H), 0.97 (t, *J* = 7.7 Hz, 18H), 0.87 – 0.82 (m, 12H), 0.26 (s, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 173.17 (d, *J* = 238.1 Hz), 142.60 (d, *J* = 13.5 Hz), 134.16, 121.15 (d, *J* = 36.3 Hz), 7.42, 3.63, -0.93.

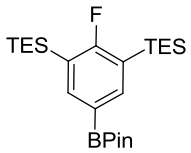
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -84.30.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 1574, 1566, 1458, 1417, 1381, 1237, 1222, 1198, 1140, 1099, 1011, 972, 823, 777, 748, 719, 674, 620.

MS (EI, 70 eV): *m/z* (%) = 396 (4), 381 (31), 353 (16), 339 (71), 311 (48), 283 (52), 275 (20), 246 (22), 218 (46), 162 (9), 141 (11), 127 (9), 97 (12), 87 (18), 83 (10), 77 (10), 71 (14), 59 (15), 57 (30), 42 (100), 39 (17).

HRMS ($C_{21}H_{41}FSi_3$): calc.: 396.2500, found: 396.2498 (M^+).

(2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-phenylene)bis(triethylsilane) (66b)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with *i*PrO-BPin (93 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 100:1) afforded (2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-phenylene)bis(triethylsilane) (**66b**, 119 mg, 88%) as a colorless solid.

m.p.: 62.8 - 64.2 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.83 (s, 1H), 7.82 (s, 1H), 1.32 (s, 12H), 0.97 – 0.91 (m, 18H), 0.84 (dt, *J* = 9.2, 7.4 Hz, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 174.50 (d, *J* = 240.5 Hz), 144.62 (d, *J* = 14.4 Hz), 144.40, 121.27 (d, *J* = 37.1 Hz), 83.59, 24.85, 7.39, 3.48.

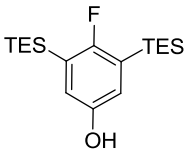
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -58.28.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2909, 2872, 1567, 1455, 1425, 1369, 1345, 1311, 1271, 1254, 1240, 1220, 1193, 1128, 1004, 964, 911, 852, 832, 787, 755, 723, 701, 667.

MS (EI, 70 eV): *m/z* (%) = 450 (2), 421 (13), 393 (100), 365 (33), 351 (5), 337 (49), 321 (32), 293 (5), 281 (11), 265 (12), 237 (11), 209 (5), 181 (10), 168 (7), 154 (5), 105 (5), 87 (9), 83 (12), 77 (11), 59 (6), 41 (6).

HRMS (**$C_{24}H_{44}BFO_2Si_2$**)**:** calc.: 450.2957, found: 450.2970 (M^+).

4-Fluoro-3,5-bis(triethylsilyl)phenol (66c)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with trimethyl borate (47 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 6 h. The reaction mixture was cooled to -70°C, NaOH (2 mL, 3 M) and H_2O_2 (2 mL, 30% in H_2O) was added simultaneously and allowed to warm to 25 °C within 16 h. The mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 20:1) afforded 4-fluoro-3,5-bis(triethylsilyl)phenol (**66c**, 82 mg, 80%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 9.17 (s, 1H), 6.76 (d, J = 4.3 Hz, 2H), 0.96 – 0.87 (m, 18H), 0.81 – 0.70 (m, 12H).

^{13}C-NMR (150 MHz, DMSO-d_6): δ / ppm = 165.09 (d, J = 225.2 Hz), 153.46 (d, J = 1.7 Hz), 123.29 (d, J = 12.5 Hz), 122.41 (d, J = 39.1 Hz), 7.75, 3.55, 3.53.

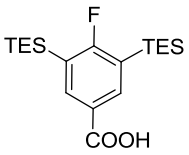
^{19}F NMR (375 MHz, DMSO-d_6): δ / ppm = -100.24.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3293, 2954, 2910, 2876, 1593, 1572, 1457, 1416, 1389, 1314, 1238, 1205, 1183, 1099, 1004, 974, 873, 789, 763, 737, 717, 690.

MS (EI, 70 eV): *m/z* (%) = 340 (85), 283 (55), 255 (100), 227 (72), 197 (12), 189 (74), 177 (26), 171 (39), 160 (14), 149 (35), 133 (31), 113 (16), 105 (19), 99 (17), 87 (17), 77 (30), 59 (16), 43 (17).

HRMS (**$C_{18}H_{33}FOSi_2$**)**:** calc.: 340.2054, found: 340.2050 (M^+).

4-Fluoro-3,5-bis(triethylsilyl)benzoic acid (66d)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in

*i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture poured on freshly crushed dry ice, allowed to warm to 25 °C within 4 h and sat. aq. NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded (2-fluoro-5-(methylthio)-1,3-phenylene)bis(triethylsilane) (**66d**, 78 mg, 0.66 mmol, 71%) as a colorless solid.

m.p.: 110.5 - 112.2 °C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 12.92 (s, 1H), 7.94 (s, 1H), 7.93 (s, 1H), 0.88 – 0.78 (m, 18H), 0.79 – 0.69 (m, 12H).

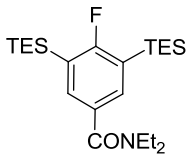
^{13}C-NMR (101 MHz, DMSO-d_6): δ / ppm = 174.51 (d, *J* = 241.4 Hz), 167.22, 139.57 (d, *J* = 14.1 Hz), 127.16 (d, *J* = 2.5 Hz), 122.44 (d, *J* = 38.6 Hz), 7.62, 3.41, 3.40.

^{19}F NMR (375 MHz, DMSO-d_6): δ / ppm = -80.38.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2914, 2874, 2734, 2652, 2554, 1686, 1576, 1456, 1418, 1382, 1290, 1220, 1162, 1102, 1004, 960, 902, 784, 752, 714, 652.

HRMS (ESI) ($C_{19}H_{32}FO_2Si_2$): calc.: 367.1930, found: 367.1937 (M^+-H).

***N*,*N*-Diethyl-4-fluoro-3,5-bis(triethylsilyl)benzamide (66e)**



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with diethylcarbamic chloride (61 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 40:1) afforded *N*,*N*-diethyl-4-fluoro-3,5-bis(triethylsilyl)benzamide (**66e**, 108 mg, 85%) as a colorless oil.

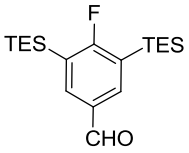
^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.39 (s, 1H), 7.38 (s, 1H), 3.54 (s, 2H), 3.23 (s, 2H), 1.24 (m, 3H), 1.16 – 1.10 (m, 3H), 0.94 (t, *J* = 7.7 Hz, 18H), 0.87 – 0.79 (m, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 172.31 (d, *J* = 239.7 Hz), 171.47, 135.56 (d, *J* = 13.0 Hz), 132.43, 122.47 (d, *J* = 38.2 Hz), 43.37, 39.43, 14.23, 12.91, 7.33, 3.38.

^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -83.75.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2875, 1634, 1572, 1540, 1522, 1507, 1457, 1426, 1389, 1348, 1314, 1286, 1239, 1220, 1195, 1116, 1069, 1004, 974, 946, 904, 831, 799, 749, 721, 689.
MS (EI, 70 eV): *m/z* (%) = 423 (73), 394 (100), 366 (59), 351 (43), 338 (90), 310 (62), 237 (6), 209 (14), 175 (5), 161 (10), 153 (6), 140 (7), 133 (14), 126 (6), 105 (8), 87 (10), 77 (13), 59 (9).
HRMS ($C_{23}H_{42}FNOSi_2$): calc.: 423.2789, found: 423.2787 (M^+).

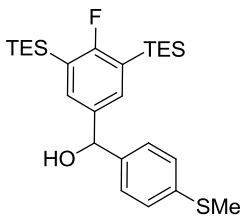
4-Fluoro-3,5-bis(triethylsilyl)benzaldehyde (66f)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with with morpholine-4-carbaldehyde (52 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 4-fluoro-3,5-bis(triethylsilyl)benzaldehyde (**66f**, 69 mg, 65%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 9.96 (s, 1H), 7.91 (s, 1H), 7.90 (s, 1H), 0.99 – 0.92 (m, 18H), 0.89 – 0.83 (m, 12H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 191.46, 175.67 (d, *J* = 246.5 Hz), 139.89 (d, *J* = 16.6 Hz), 132.22 (d, *J* = 13.3 Hz), 123.89 (d, *J* = 40.1 Hz), 7.29, 3.30.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -75.00.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2933, 2913, 2876, 1694, 1568, 1458, 1417, 1391, 1365, 1217, 1194, 1095, 1004, 929, 897, 795, 772, 754, 720, 688.
MS (EI, 70 eV): *m/z* (%) = 352 (2), 323 (18), 295 (85), 267 (100), 239 (58), 211 (11), 183 (25), 161 (10), 133 (8), 105 (17), 77 (13).
HRMS ($C_{17}H_{28}FOSi_2$): calc.: 323.1663, found: 323.1664 (M^+-Et).

(4-Fluoro-3,5-bis(triethylsilyl)phenyl)(4-(methylthio)phenyl)methanol (66g)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with 4-(methylthio)benzaldehyde (69 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 30:1) afforded (4-fluoro-3,5-bis(triethylsilyl)phenyl)(4-(methylthio)phenyl)methanol (**66g**, 99 mg, 69%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 (d, *J* = 0.6 Hz, 1H), 7.37 (d, *J* = 0.6 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.30 – 7.22 (m, 2H), 5.82 (s, 1H), 2.50 (s, 3H), 0.96 (t, *J* = 7.7 Hz, 18H), 0.86 – 0.80 (m, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 171.66 (d, *J* = 236.5 Hz), 140.85, 138.16 (d, *J* = 2.9 Hz), 137.56, 135.70 (d, *J* = 12.8 Hz), 126.95, 126.66, 122.35 (d, *J* = 37.8 Hz), 75.71 (d, *J* = 1.4 Hz), 15.94, 7.43, 3.52, 3.51.

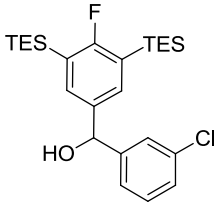
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -87.06.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3277, 2953, 2909, 2874, 1599, 1576, 1494, 1457, 1390, 1316, 1283, 1237, 1194, 1100, 1006, 968, 922, 902, 824, 788, 748, 715, 688.

MS (EI, 70 eV): *m/z* (%) = 476 (57), 460 (14), 445 (16), 419 (61), 403 (17), 391 (88), 375 (35), 363 (43), 325 (50), 297 (17), 269 (13), 195 (16), 167 (13), 153 (41), 145 (20), 137 (24), 105 (19), 87 (14), 77 (36), 59 (14), 44 (100).

HRMS ($C_{26}H_{41}FOSSi_2$): calc.: 476.2401, found: 476.2388 (M^+).

(3-Chlorophenyl)(4-fluoro-3,5-bis(triethylsilyl)phenyl)methanol (66h)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. The reaction mixture was quenched with 3-chlorobenzaldehyde (63 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 40:1) afforded (3-chlorophenyl)(4-fluoro-3,5-bis(triethylsilyl)phenyl)methanol (66h, 103 mg, 74%) as a colorless solid.

m.p.: 59.9 - 61.2 °C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.43 – 7.41 (m, 3H), 7.37 – 7.30 (m, 2H), 7.27 (dt, *J* = 7.1, 2.1 Hz, 1H), 6.06 (d, *J* = 4.2 Hz, 1H), 5.76 (d, *J* = 4.2 Hz, 1H), 0.89 (t, *J* = 7.7 Hz, 18H), 0.82 – 0.71 (m, 12H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 175.83 (d, *J* = 234.2 Hz), 153.41, 145.35 (d, *J* = 2.7 Hz), 140.77 (d, *J* = 12.5 Hz), 138.04, 135.24, 131.82, 131.09, 129.92, 126.07 (d, *J* = 37.5 Hz), 78.11, 12.45, 8.36, 8.34.

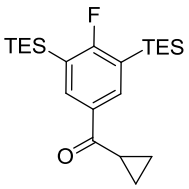
^{19}F NMR (375 MHz, DMSO-d_6): δ / ppm = -84.48.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3283, 2954, 2909, 2876, 1597, 1576, 1457, 1433, 1417, 1390, 1312, 1284, 1237, 1195, 1100, 1078, 1006, 973, 928, 880, 855, 785, 750, 720, 688, 654.

MS (EI, 70 eV): *m/z* (%) = 464 (12), 407 (100), 379 (70), 351 (55), 333 (7), 313 (66), 303 (7), 277 (7), 257 (9), 229 (11), 193 (11), 165 (16), 147 (8), 138 (13), 105 (11), 87 (18), 77 (25), 59 (14).

HRMS (**$C_{25}H_{38}ClFOSi_2$**)**:** calc.: 464.2134, found: 464.2130 (M^+).

Cyclopropyl(4-fluoro-3,5-bis(triethylsilyl)phenyl)methanone (66i)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. Subsequently, the acylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.36 mL, 0.36 mmol, 1.0 M in THF, 1.2 equiv) and cyclopropanecarbonyl chloride (43 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded cyclopropyl(4-fluoro-3,5-bis(triethylsilyl)phenyl)methanone (**66i**, 89 mg, 76%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 8.07 (s, 1H), 8.07 (s, 1H), 2.63 (tt, *J* = 7.8, 4.5 Hz, 1H), 1.27 – 1.21 (m, 2H), 1.07 – 1.01 (m, 2H), 0.97 (m, 18H), 0.91 – 0.83 (m, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 199.89, 174.81 (d, *J* = 244.0 Hz), 137.96 (d, *J* = 15.9 Hz), 133.67, 122.77 (d, *J* = 39.3 Hz), 16.98, 11.59, 7.33, 3.41.

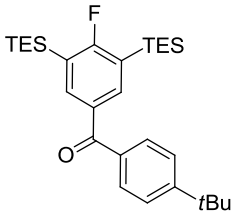
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -78.67.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 2812, 2361, 2341, 1751, 1670, 1567, 1521, 1506, 1457, 1417, 1379, 1289, 1238, 1218, 1144, 1105, 1063, 1043, 1014, 975, 913, 895, 873, 843, 785, 757, 738, 717, 688.

MS (EI, 70 eV): *m/z* (%) = 392 (4), 363 (23), 335 (100), 307 (67), 279 (54), 257 (4), 249 (3), 223 (15), 201 (5), 153 (3), 139 (9), 128 (3), 125 (6), 110 (3), 105 (5), 87 (9), 77 (15), 69 (9), 59 (10), 41 (5).

HRMS ($C_{22}H_{37}FOSi_2$): calc.: 392.2367, found: 392.2363 (M^+).

(4-(*tert*-Butyl)phenyl)(4-fluoro-3,5-bis(triethylsilyl)phenyl)methanone (66j)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. Subsequently, the acylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.36 mL, 0.36 mmol, 1.0 M in THF, 1.2 equiv) and 4-*tert*-butylbenzoyl chloride (88 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 30:1) afforded (4-(*tert*-butyl)phenyl)(4-fluoro-3,5-bis(triethylsilyl)phenyl)methanone (**66j**, 105 mg, 72%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88 (s, 1H), 7.86 (s, 1H), 7.82 – 7.74 (m, 2H), 7.54 – 7.49 (m, 2H), 1.40 (s, 9H), 1.03 – 0.94 (m, 18H), 0.93 – 0.82 (m, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 195.80, 174.46 (d, J = 243.4 Hz), 156.16, 139.89 (d, J = 14.0 Hz), 134.92, 133.36 (d, J = 2.7 Hz), 130.11, 125.19, 122.58 (d, J = 38.6 Hz), 35.13, 31.16, 7.38, 3.45, 3.43.

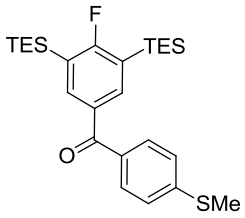
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -79.11.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2875, 2734, 2362, 1657, 1606, 1566, 1459, 1379, 1314, 1276, 1239, 1222, 1199, 1169, 1100, 1004, 975, 922, 848, 789, 770, 754, 722, 688, 663.

MS (EI, 70 eV): *m/z* (%) = 484 (7), 455 (93), 427 (100), 399 (86), 371 (65), 341 (6), 315 (11), 206 (8), 192 (26), 178 (29), 164 (11), 161 (12), 150 (23), 136 (14), 105 (7), 87 (5), 77 (13), 57 (18), 44 (15).

HRMS (**$C_{29}H_{45}FOSi_2$**)**:** calc.: 484.2993, found: 484.3003 (M^+).

(4-fluoro-3,5-bis(triethylsilyl)phenyl)(4-(methylthio)phenyl)methanone (66k)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. Subsequently, the acylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.36 mL, 0.36 mmol, 1.0 M in THF, 1.2 equiv) and 4-(thiomethyl)benzoyl chloride (560 mg, 3.0 mmol, 3.0 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded (4-fluoro-3,5-bis(triethylsilyl)phenyl)(4-(methylthio)phenyl)methanone (**66k**, 80 mg, 56%) as a colorless solid.

m.p.: 71.0 - 72.9 °C

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.82 (s, 1H), 7.82 (s, 1H), 7.75 – 7.73 (m, 2H), 7.30 – 7.29 (m, 2H), 2.55 (s, 3H), 0.99 – 0.93 (m, 18H), 0.88 – 0.81 (m, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 195.16, 174.43 (d, J = 243.6 Hz), 145.12, 139.77 (d, J = 15.9 Hz), 133.84, 133.22, 130.60, 124.76, 122.68 (d, J = 39.1 Hz), 14.85, 7.34, 3.39.

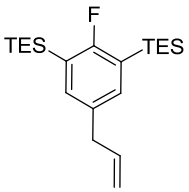
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -78.93.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2909, 2874, 1717, 1646, 1586, 1566, 1456, 1435, 1378, 1325, 1283, 1269, 1239, 1220, 1196, 1169, 1092, 1003, 969, 919, 840, 786, 762, 750, 719, 686, 660.

MS (EI, 70 eV): *m/z* (%) = 474 (4), 445 (7), 417 (7), 389 (8), 361 (7), 225 (6), 197 (8), 183 (7), 155 (11), 141 (12), 127 (16), 113 (19), 99 (28), 85 (65), 71 (82), 57 (100), 43 (46).

HRMS (**$C_{26}H_{39}FOSSi_2$**)**:** calc.: 474.2244, found: 474.2230 (M^+).

(5-Allyl-2-fluoro-1,3-phenylene)bis(triethylsilane) (66l)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. Subsequently, the allylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.36 mL, 0.36 mmol, 1.0 M in THF, 1.2 equiv) and allyl bromide (54 mg, 0.45 mmol, 1.5 equiv) and allowed to warm to 25 °C in 16 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (pentane) afforded (5-allyl-2-fluoro-1,3-phenylene)bis(triethylsilane) (**66l**, 95 mg, 87%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.17 (d, *J* = 0.8 Hz, 1H), 7.16 (d, *J* = 0.7 Hz, 1H), 6.03 – 5.90 (m, 1H), 5.07 (t, *J* = 1.5 Hz, 1H), 5.07 – 5.02 (m, 1H), 3.36 (m, 2H), 0.96 (dd, *J* = 8.2, 7.3 Hz, 18H), 0.86 – 0.79 (m, 12H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 170.83 (d, *J* = 234.9 Hz), 137.73, 137.32 (d, *J* = 14.2 Hz), 134.29, 121.91 (d, *J* = 38.2 Hz), 115.55, 39.52, 7.40, 3.53.

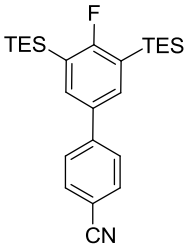
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -89.77.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2911, 2876, 1640, 1578, 1458, 1417, 1392, 1276, 1238, 1221, 1194, 1105, 1004, 974, 910, 876, 788, 747, 718, 688.

MS (EI, 70 eV): *m/z* (%) = 364 (24), 307 (100), 279 (78), 251 (74), 221 (12), 195 (47), 173 (54), 145 (25), 111 (19), 105 (49), 87 (20), 77 (58), 71 (19), 59 (21), 57 (37).

HRMS ($C_{21}H_{37}FSi_2$): calc.: 364.2418, found: 364.2401 (M^+).

4'-Fluoro-3',5'-bis(triethylsilyl)-[1,1'-biphenyl]-4-carbonitrile (66m)

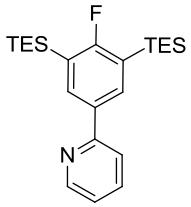


The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP4** with $ZnCl_2$ (0.36 mL, 0.36 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (5.2 mg,

3 mol%) and P(2-furyl)$_3$ (4.2 mg, 6 mol%) and 4-bromobenzonitrile (82 mg, 0.45 mmol, 1.5 equiv) at 25 °C in 4 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 4'-fluoro-3',5'-bis(triethylsilyl)-[1,1'-biphenyl]-4-carbonitrile (**66m**, 108 mg, 85%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.75 – 7.70 (m, 2H), 7.66 – 7.61 (m, 2H), 7.57 (s, 1H), 7.56 (s, 1H), 1.03 – 0.96 (m, 18H), 0.92 – 0.85 (m, 12H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 172.62 (d, J = 238.8 Hz), 145.65, 136.26 (d, J = 14.9 Hz), 134.59, 132.56, 127.70, 123.36 (d, J = 39.0 Hz), 118.98, 110.54, 7.40, 3.49.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -85.86.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2875, 2228, 1607, 1576, 1507, 1457, 1396, 1314, 1291, 1279, 1227, 1201, 1180, 1110, 1004, 974, 903, 864, 837, 77, 751, 721, 687, 668.
MS (EI, 70 eV): *m/z* (%) = 425 (49), 396 (66), 368 (100), 340 (89), 312 (70), 282 (11), 262 (20), 256 (80), 234 (31), 206 (29), 170 (8), 155 (21), 141 (18), 127 (17), 105 (46), 87 (13), 77 (47), 59 (16), 57 (12).
HRMS ($C_{25}H_{36}FNSi_2$): calc.: 425.2370, found: 425.2364 (M^+).

2-(4-Fluoro-3,5-bis(triethylsilyl)phenyl)pyridine (66n)



The title compound was prepared according to **TP2** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 121 mg, 0.3 mmol, 1.0 equiv) and *n*-BuLi (**59**, 0.13 ml, 2.60 M in *i*hexane, 0.33 mmol, 1.1 equiv) at -78 °C in 1 h. Subsequently, the cross-coupling was accomplished according to **TP4** with $ZnCl_2$ (0.36 mL, 0.36 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (5.2 mg, 3 mol%) and P(2-furyl)$_3$ (4.2 mg, 6 mol%) and 2-bromopyridine (71 mg, 0.45 mmol, 1.5 equiv) at 25 °C in 4 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 2-(4-fluoro-3,5-bis(triethylsilyl)phenyl)pyridine (**66n**, 89 mg, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.71 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 8.00 (s, 1H), 7.98 (s, 1H), 7.77 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.28 – 7.20 (m, 1H), 1.01 m, 18H), 0.92 (m, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 173.01 (d, *J* = 238.7 Hz), 157.57, 149.50, 136.83, 136.41 (d, *J* = 13.6 Hz), 134.63, 122.62 (d, *J* = 38.2 Hz), 121.69, 120.68, 7.47, 3.53, 3.51.

^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -85.72.

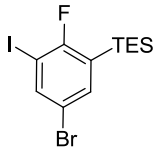
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2910, 2875, 1578, 1468, 1438, 1416, 1393, 1297, 1265, 1223, 1196, 1151, 1116, 1070, 1044, 1004, 974, 925, 903, 867, 792, 749, 718, 688.

MS (EI, 70 eV): *m/z* (%) = 401 (33), 372 (77), 344 (50), 316 (82), 288 (75), 238 (15), 228 (12), 208 (26), 181 (14), 143 (12), 129 (18), 115 (14), 111 (11), 104 (12), 97 (22), 85 (21), 77 (34), 57 (61), 44 (100).

HRMS ($C_{23}H_{36}FNSi_2$): calc.: 401.2370, found: 401.2365 (M^+).

4.6. Functionalization in *ortho*-Position *via* Exchange with *i*PrMgCl·LiCl

(5-Bromo-2-fluoro-3-iodophenyl)triethylsilane (67)



The title compound was prepared according to **TP5** from (5-bromo-2-fluoro-1,3-phenylene)bis(triethylsilane) (**62e**, 4.04 g, 10.0 mmol, 1.0 equiv) and iodine monochloride (1.77 g, 11 mmol, 1.1 equiv) at 25 °C in 20 h. Flash column chromatographical purification on silica gel (pentane) afforded (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 3.56 g, 86%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.79 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.31 (dd, *J* = 4.1, 2.4 Hz, 1H), 0.88 (td, *J* = 7.8, 1.3 Hz, 9H), 0.81 – 0.73 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.55 (d, *J* = 240.1 Hz), 142.11 (d, *J* = 2.2 Hz), 138.32 (d, *J* = 11.5 Hz), 127.15 (d, *J* = 36.9 Hz), 117.51 (d, *J* = 3.3 Hz), 82.50 (d, *J* = 33.2 Hz), 7.22, 3.17.

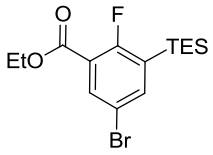
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -83.69.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2875, 1539, 1456, 1405, 1377, 1261, 1237, 1218, 1110, 1089, 1074, 1003, 973, 869, 836, 781, 725, 690, 648.

MS (EI, 70 eV): m/z (%) = 414 (28), 385 (6), 355 (85), 327 (100), 256 (31), 229 (66), 201 (21), 149 (15), 121 (8), 75 (10).

HRMS ($C_{12}H_{17}BrFISi$): calc.: 413.9312; found: 413.9314 (M^+).

Ethyl 5-bromo-2-fluoro-3-(triethylsilyl)benzoate (69a)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with ethyl cyanoformate (37 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded ethyl 5-bromo-2-fluoro-3-(triethylsilyl)benzoate (**69a**, 67 mg, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (dd, *J* = 6.5, 2.6 Hz, 1H), 7.56 (dd, *J* = 3.8, 2.6 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.98 – 0.89 (m, 9H), 0.85 (ddt, *J* = 8.2, 6.8, 1.1 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.87 (d, *J* = 254.4 Hz), 163.40 (d, *J* = 4.5 Hz), 142.57 (d, *J* = 13.4 Hz), 135.39 (d, *J* = 1.6 Hz), 128.85 (d, *J* = 35.7 Hz), 120.16 (d, *J* = 15.7 Hz), 116.70 (d, *J* = 3.3 Hz), 61.57, 14.20, 7.19, 3.15.

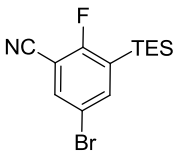
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -99.36.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 275, 1736, 1715, 1590, 1455, 1415, 1384, 1364, 1333, 1283, 1239, 1210, 1172, 1123, 1101, 1004, 975, 891, 862, 833, 786, 729, 693, 657.

MS (EI, 70 eV): m/z (%) = 360 (10), 331 (12), 315 (17), 303 (100), 275 (57), 247 (14), 229 (10), 216 (7), 203 (13), 196 (4), 139 (6), 123 (4), 105 (6), 77 (10), 47 (5).

HRMS ($C_{15}H_{22}BrFO_2Si$): calc.: 360.0556; found: 360.0544 (M^+).

5-Bromo-2-fluoro-3-(triethylsilyl)benzonitrile (69b)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with 2,2-dimethylmalononitrile (35 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture

was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 5-bromo-2-fluoro-3-(triethylsilyl)benzonitrile (**69b**, 62 mg, 79%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (dd, *J* = 5.7, 2.5 Hz, 1H), 7.68 (dd, *J* = 4.3, 2.5 Hz, 1H), 1.04 – 0.94 (m, 9H), 0.95 – 0.83 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.13 (d, *J* = 252.9 Hz), 143.44 (d, *J* = 12.9 Hz), 136.27, 128.95 (d, *J* = 33.0 Hz), 117.21 (d, *J* = 3.4 Hz), 113.03, 102.89 (d, *J* = 22.3 Hz), 7.12, 3.05.

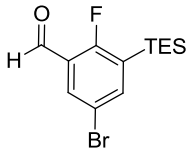
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -99.00.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2912, 2877, 2237, 1589, 1457, 1422, 1388, 1270, 1222, 1177, 1004, 975, 878, 828, 737, 710, 682.

MS (EI, 70 eV): m/z (%) = 313 (7), 284 (32), 256 (55), 228 (100), 208 (4), 201 (3), 176 (5), 149 (8), 130 (4), 102 (5), 77 (24), 59 (2), 47 (39).

HRMS ($C_{13}H_{17}BrFNSi$): calc.: 313.0298; found: 313.0278 (M^+).

5-Bromo-2-fluoro-3-(triethylsilyl)benzaldehyde (69c)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with morpholine-4-carbaldehyde (43 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 100:1) afforded ethyl 5-bromo-2-fluoro-3-(triethylsilyl)benzaldehyde (**69c**, 46 mg, 58%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.22 (s, 1H), 7.89 (dd, *J* = 6.2, 2.6 Hz, 1H), 7.59 (dd, *J* = 4.3, 2.6 Hz, 1H), 0.96 – 0.86 (m, 9H), 0.86 – 0.75 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 186.47 (d, *J* = 6.6 Hz), 167.80 (d, *J* = 252.5 Hz), 144.53 (d, *J* = 13.9 Hz), 132.07 (d, *J* = 2.5 Hz), 128.91 (d, *J* = 34.3 Hz), 124.88 (d, *J* = 13.7 Hz), 118.14 (d, *J* = 3.0 Hz), 7.20, 3.22.

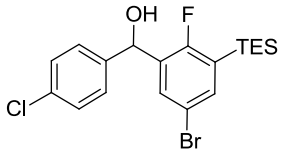
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -111.83.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2875, 1694, 1659, 1591, 1557, 1455, 1424, 1376, 1276, 1225, 1191, 1167, 1079, 1003, 976, 898, 830, 732, 690.

MS (EI, 70 eV): m/z (%) = 316 (15), 287 (13), 259 (79), 231 (100), 203 (13), 196(7), 152 (7), 123 (11), 116 (58), 103 (8), 85 (11), 77 (32), 71 (15), 57 (20), 47 (53), 45 (10).

HRMS ($C_{13}H_{18}BrFOSi$): calc.: 316.0294; found: 316.0282 (M^+).

(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(4-chlorophenyl)methanol (69d)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with 4-chlorobenzaldehyde (53 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded (5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(4-chlorophenyl)methanol (**69d**, 43 mg, 40%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.63 – 7.60 (m, 1H), 7.33 – 7.21 (m, 2H), 6.14 (d, *J* = 7.5 Hz, 2H), 5.81 (d, *J* = 7.4 Hz, 2H), 0.83 – 0.73 (m, 9H), 0.74 – 0.64 (m, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 162.74 (d, *J* = 240.3 Hz), 143.10, 136.91 (d, *J* = 12.7 Hz), 134.65 (d, *J* = 19.9 Hz), 132.21, 132.02 (d, *J* = 5.1 Hz), 128.72, 128.51 (d, *J* = 1.3 Hz), 126.50 (d, *J* = 34.9 Hz), 117.37 (d, *J* = 2.6 Hz), 67.66 (d, *J* = 2.3 Hz), 7.60, 3.27.

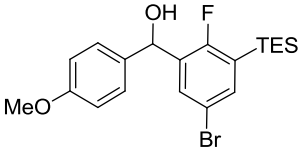
^{19}F NMR (300 MHz, DMSO-d_6): δ / ppm = -107.48.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3387, 2953, 2875, 2740, 2391, 2349, 2256, 2192, 2129, 1905, 1650, 1489, 1413, 1384, 1327, 1296, 1208, 1154, 1089, 1047, 1023, 994, 898, 880, 824, 762.

MS (EI, 70 eV): m/z (%) = 428 (30), 399 (32), 381 (57), 371 (100), 276 (58), 255 (21), 244 (13), 227 (15), 199 (23), 163 (28), 152 (27), 141 (22), 105 (50), 93 (15), 77 (82), 47 (14).

HRMS ($C_{19}H_{23}BrClFOSi$): calc.: 428.0374; found: 428.0367 (M^+).

(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(4-methoxyphenyl)methanol (69e)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with 4-methoxybenzaldehyde (51 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded (5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(4-methoxyphenyl)methanol (**69e**, 47 mg, 44%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.68 – 7.62 (m, 1H), 7.32 (dd, *J* = 4.2, 2.5 Hz, 1H), 7.30 – 7.24 (m, 2H), 6.89 – 6.83 (m, 2H), 6.02 (dd, *J* = 2.8, 1.4 Hz, 1H), 3.78 (s, 3H), 0.94 – 0.87 (m, 9H), 0.83 – 0.75 (m, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.98 (d, *J* = 241.0 Hz), 159.24, 137.27 (d, *J* = 13.0 Hz), 134.51, 132.63 (d, *J* = 19.2 Hz), 131.38, 127.63, 126.60 (d, *J* = 35.0 Hz), 117.40, 113.96, 69.45, 55.25, 7.24, 3.28.

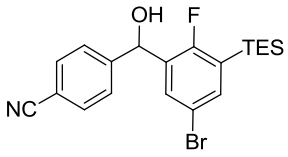
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -107.82.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 3000, 2953, 2908, 2874, 2834, 1677, 1610, 1510, 1455, 1413, 1385, 1333, 1303, 1247, 1208, 1155, 1111, 1033, 1005, 975, 898, 880, 828, 778, 725, 685.

MS (EI, 70 eV): m/z (%) = 424 (81), 377 (100), 365 (68), 349 (12), 273 (39), 257 (10), 165 (9), 138 (17), 109 (36), 77 (55), 47 (7).

HRMS ($C_{20}H_{26}BrFO_2Si$): calc.: 424.0869; found: 424.0867 (M^+).

(5-Bromo-2-fluoro-3-(triethylsilyl)phenyl)(4-isocyanophenyl)methanol (69f)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with 4-formylbenzonitrile (49 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded (5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(4-isocyanophenyl)methanol (**69f**, 67 mg, 64%) as a colorless solid.

m.p.: 98.2 - 100.1 °C.

^{1}H-NMR (800 MHz, DMSO-d_6): δ / ppm = 8.07 – 8.03 (m, 2H), 7.91 – 7.88 (m, 2H), 7.85 (dd, *J* = 6.2, 2.6 Hz, 1H), 7.72 (dd, *J* = 3.9, 2.5 Hz, 1H), 6.88 (s, 1H), 0.91 (t, *J* = 7.8 Hz, 9H), 0.82 (dd, *J* = 8.7, 7.4 Hz, 6H).

^{13}C-NMR (200 MHz, DMSO-d_6): δ / ppm = 191.23, 162.92 (d, *J* = 244.9 Hz), 141.88 (d, *J* = 13.9 Hz), 140.21, 134.62 (d, *J* = 3.7 Hz), 133.38, 130.24, 128.16 (d, *J* = 35.4 Hz), 127.61 (d, *J* = 22.0 Hz), 118.42, 117.66, 116.29, 7.58, 3.18.

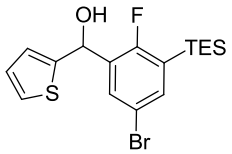
^{19}F NMR (300 MHz, DMSO-d_6): δ / ppm = -101.62.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3394, 3093, 3075, 2956, 2912, 2876, 2230, 1664, 1606, 1586, 1567, 1499, 1455, 1410, 1386, 1351, 1310, 1283, 1261, 1241, 1204, 1180, 1149, 1112, 1048, 1024, 1002, 971, 918, 888, 858, 836, 796, 775, 759, 733, 690.

MS (EI, 70 eV): m/z (%) = 419 (27), 388 (79), 360 (50), 340 (48), 332 (52), 314 (25), 304 (24), 252 (10), 224 (23), 217 (28), 190 (14), 176 (18), 130 (56), 105 (92), 77 (100), 47 (35).

HRMS ($C_{20}H_{23}BrFNOSi$): calc.: 419.0716; found: 419.0552 (M^+).

(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(thiophen-2-yl)methanol (69g)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with thiophene-2-carbaldehyde (42 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C for 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded ((5-bromo-2-fluoro-3-(triethylsilyl)phenyl)(thiophen-2-yl)methanol (**69g**, 20 mg, 20%) as a colorless oil.

^{1}H-NMR (800 MHz, DMSO-d_6): δ / ppm = 7.72 (dd, *J* = 6.5, 2.6 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.38 (dd, *J* = 4.0, 2.5 Hz, 1H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.85 (dt, *J* = 3.5, 1.0 Hz, 1H), 6.45 (d, *J* = 4.9 Hz, 1H), 6.13 (d, *J* = 4.8 Hz, 1H), 0.89 (dd, *J* = 8.2, 7.3 Hz, 9H), 0.80 (q, *J* = 8.7, 8.2 Hz, 6H).

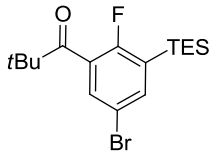
^{13}C-NMR (200 MHz, DMSO-d_6): δ / ppm = 162.65 (d, *J* = 240.6 Hz), 148.37, 137.10 (d, *J* = 13.6 Hz), 134.50 (d, *J* = 20.4 Hz), 131.81 (d, *J* = 6.1 Hz), 127.12, 126.59 (d, *J* = 35.4 Hz), 125.68, 124.38, 117.28 (d, *J* = 3.1 Hz), 64.45 (d, *J* = 3.6 Hz), 7.62, 3.27.

^{19}F NMR (375 MHz, DMSO-d_6): δ / ppm = -108.09.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3350, 2954, 2910, 2875, 1595, 1456, 1415, 1386, 1319, 1296, 1270, 1230, 1209, 1158, 1121, 1019, 1004, 880, 854, 829, 770, 725, 696.

MS (EI, 70 eV): m/z (%) = 400 (49), 371 (45), 353 (29), 341 (100), 324 (13), 315 (23), 297 (14), 292 (20), 263 (12), 251 (28), 233 (31), 171 (39), 115 (18), 111 (14), 105 (88), 85 (27), 77 (84), 45 (16).
HRMS ($C_{17}H_{22}BrFOSSi$): calc.: 400.0328; found: 400.0326 (M^+).

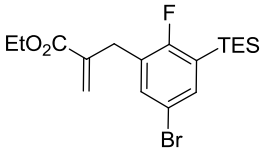
1-(5-Bromo-2-fluoro-3-(triethylsilyl)phenyl)-2,2-dimethylpropan-1-one (69h)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.30 mL, 0.30 mmol, 1.0 M in THF, 1.2 equiv) and pivaloyl chloride (45 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 1-(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)-2,2-dimethylpropan-1-one (**69h**, 81 mg, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, DMSO-d_6): δ / ppm = 7.60 (dd, J = 6.0, 2.5 Hz, 1H), 7.51 (dd, J = 4.3, 2.5 Hz, 1H), 1.14 (s, 6H), 0.89 (td, J = 6.9, 1.3 Hz, 9H), 0.86 – 0.76 (m, 6H).
^{13}C-NMR (100 MHz, DMSO-d_6): δ / ppm = 208.12 (d, J = 1.2 Hz), 160.72 (d, J = 238.5 Hz), 138.98 (d, J = 12.3 Hz), 131.70 (d, J = 5.3 Hz), 130.37 (d, J = 27.5 Hz), 127.30 (d, J = 35.3 Hz), 117.10 (d, J = 2.8 Hz), 44.97, 26.37, 7.55, 3.15.
^{19}F NMR (375 MHz, DMSO-d_6): δ / ppm = -104.04.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2910, 2876, 2736, 1700, 1588, 1458, 1406, 1278, 1224, 1172, 990, 878, 824, 768, 730, 696.
MS (EI, 70 eV): m/z (%) = 372 (4), 331 (3), 317 (100), 315 (94), 287 (7), 261 (3), 229 (2), 203 (8), 142 (7), 105 (16), 87 (9), 77 (22), 57 (19), 41 (10).
HRMS ($C_{17}H_{26}BrFOSi$): calc.: 372.0920; found: 372.0912 (M^+).

Ethyl 2-(5-bromo-2-fluoro-3-(triethylsilyl)benzyl)acrylate (69i)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the allylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.30 mL, 0.30 mmol, 1.0 M in THF, 1.2 equiv) and ethyl 2-(bromomethyl)acrylate (72 mg, 0.375 mmol, 1.5 equiv) and allowed to warm to 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded ethyl 2-(5-bromo-2-fluoro-3-(triethylsilyl)benzyl)acrylate (**69i**, 81 mg, 81%) as a colorless oil.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.35 (dd, *J* = 6.8, 2.5 Hz, 1H), 7.32 (dd, *J* = 4.1, 2.5 Hz, 1H), 6.30 (q, *J* = 1.0 Hz, 1H), 5.47 (p, *J* = 1.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.62 (d, *J* = 1.7 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.87 – 0.82 (m, 6H).

^{13}C-NMR (200 MHz, $CDCl_3$): δ / ppm = 165.46, 163.41 (d, *J* = 241.5 Hz), 137.20, 135.58 (d, *J* = 13.1 Hz), 133.84 (d, *J* = 5.7 Hz), 126.49 (d, *J* = 22.4 Hz), 125.53, 125.40 (d, *J* = 35.4 Hz), 115.82 (d, *J* = 3.3 Hz), 59.90, 30.08 (d, *J* = 3.3 Hz), 13.12, 6.27, 2.30.

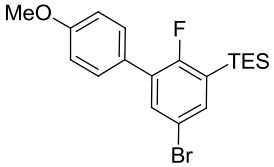
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -107.15.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2875, 1716, 1632, 1595, 1556, 1413, 1392, 1368, 1327, 1300, 1277, 1251, 1193, 1161, 1133, 1004, 948, 910, 870, 830, 816, 724, 662.

MS (EI, 70 eV): m/z (%) = 400 (20), 371 (12), 312 (41), 296 (16), 254 (53), 240 (100), 223 (15), 206 (23), 194 (15), 128 (18), 115 (81), 105 (65), 97 (14), 85 (23), 77 (66), 71 (30), 57 (42), 43 (40).

HRMS ($C_{18}H_{26}BrFO_2Si$): calc.: 400.0869; found: 400.0858 (M^+).

(5-Bromo-2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)triethylsilane (69j)

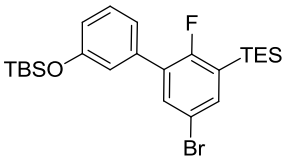


The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP4** with

$ZnCl_2$ (0.30 mL, 0.30 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (4.3 mg, 3 mol%), P(2-furyl)$_3$ (3.6 mg, 6 mol%) and 4-iodoanisole (70 mg, 0.30 mmol, 1.2 equiv) at 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 100:1) afforded (5-bromo-2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)triethylsilane (**69j**, 70 mg, 71%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.55 – 7.49 (m, 1H), 7.47 – 7.42 (m, 2H), 7.35 (dd, *J* = 3.9, 2.5 Hz, 1H), 7.00 – 6.94 (m, 2H), 3.84 (s, 3H), 0.97 (dd, *J* = 8.3, 7.3 Hz, 9H), 0.89 – 0.82 (m, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.83 (d, *J* = 241.8 Hz), 159.47, 136.60 (d, *J* = 14.5 Hz), 134.13, 130.18, 127.25 (d, *J* = 7.6 Hz), 127.02, 117.17, 113.94, 55.31, 7.32, 3.35.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -107.41.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2910, 2876, 2736, 1700, 1588, 1458, 1406, 1278, 1224, 1172, 990, 878, 824, 768, 730, 696.
MS (EI, 70 eV): m/z (%) = 394 (100), 337 (76), 309 (93), 286 (57), 229 (23), 215 (8), 199 (9), 182 (10), 178 (12), 165 (16), 155 (24), 139 (21), 77 (26), 47 (11).
HRMS ($C_{19}H_{24}BrFOSi$): calc.: 394.0764; found: 394.0764 (M^+).

((5'-Bromo-2'-fluoro-3'-(triethylsilyl)-[1,1'-biphenyl]-3-yl)oxy)(*tert*-butyl)dimethylsilane (69k)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP4** with $ZnCl_2$ (0.30 mL, 0.30 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (4.3 mg, 3 mol%), P(2-furyl)$_3$ (3.6 mg, 6 mol%) and (3-bromophenoxy)(*tert*-butyl)dimethylsilane (86 mg, 0.30 mmol, 1.2 equiv) at 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane) afforded ((5'-bromo-2'-fluoro-3'-(triethylsilyl)-[1,1'-biphenyl]-3-yl)oxy)(*tert*-butyl)dimethylsilane (**69k**, 96 mg, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 (dd, *J* = 7.0, 2.6 Hz, 1H), 7.33 (dd, *J* = 3.9, 2.5 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.02 (ddt, *J* = 7.7, 2.4, 1.2 Hz, 1H), 6.91 (q, *J* = 1.9 Hz, 1H), 6.79 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 0.96 – 0.87 (m, 18H), 0.85 – 0.74 (m, 6H), 0.16 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.82 (d, *J* = 242.6 Hz), 155.68, 137.20 (d, *J* = 12.7 Hz), 136.20 (d, *J* = 1.4 Hz), 134.35 (d, *J* = 4.0 Hz), 130.40 (d, *J* = 19.9 Hz), 129.38, 127.32 (d, *J* = 36.2 Hz), 122.02 (d, *J* = 3.0 Hz), 120.84 (d, *J* = 3.0 Hz), 119.68, 117.16 (d, *J* = 3.0 Hz), 25.71, 18.24, 7.33, 3.39, -4.38.

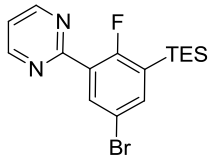
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -106.76.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2930, 2909, 2875, 2858, 1602, 1579, 1551, 1485, 1471, 1443, 1403, 1390, 1361, 1297, 1252, 1225, 1187, 1086, 1061, 1001, 955, 873, 839, 780, 722, 696, 675.

MS (EI, 70 eV): m/z (%) = 494 (82), 437 (46), 381 (47), 367 (30), 353 (100), 345 (13), 331 (21), 273 (11), 252 (11), 190 (16), 177 (63), 165 (17), 87 (26), 77 (21), 73 (48), 59 (14).

HRMS ($C_{24}H_{36}BrFOSi$): calc.: 494.1472; found: 494.1463 (M^+).

2-(5-Bromo-2-fluoro-3-(triethylsilyl)phenyl)pyrimidine (69l)



The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP4** with $ZnCl_2$ (0.30 mL, 0.30 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (4.3 mg, 3 mol%), $P(2\text{-furyl})_3$ (3.6 mg, 6 mol%) and 2-bromopyrimidine (48 mg, 0.30 mmol, 1.2 equiv) at 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane) afforded 2-(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)pyrimidine (**69l**, 59 mg, 65%) as a colorless oil.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 8.96 (d, *J* = 4.9 Hz, 2H), 8.12 (dd, *J* = 6.8, 2.7 Hz, 1H), 7.59 (dd, *J* = 3.6, 2.5 Hz, 1H), 7.54 (t, *J* = 4.9 Hz, 1H), 0.93 (dd, *J* = 8.2, 7.3 Hz, 9H), 0.88 – 0.83 (m, 6H).

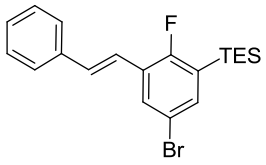
^{13}C-NMR (200 MHz, $CDCl_3$): δ / ppm =163.92 (d, *J* = 249.5 Hz), 161.73 (d, *J* = 6.3 Hz), 158.22, 139.90 (d, *J* = 14.0 Hz), 135.69, 129.23 (d, *J* = 87.1 Hz), 128.31, 128.27 (d, *J* = 53.1 Hz), 120.81, 117.05, 7.67, 3.25.

^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -103.77.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2910, 2875, 1592, 1566, 1549, 143, 1404, 1386, 1306, 1238, 1204, 1110, 1069, 1004, 976, 908, 884, 846, 814, 717, 680, 653.

MS (EI, 70 eV): m/z (%) = 366 (13), 337 (72), 309 (81), 281 (100), 234 (16), 202 (19), 181 (9), 168 (8), 155 (17), 131 (10), 128 (8), 103 (11), 77 (14), 69 (12), 57 (7), 43 (36).
HRMS ($C_{16}H_{20}BrFN_2Si$): calc.: 366.0563; found: 366.0548 (M^+).

(*E*)-(5-Bromo-2-fluoro-3-styrylphenyl)triethylsilane (69m)

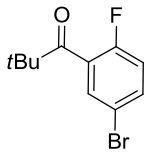


The title compound was prepared according to **TP6**, where (5-bromo-2-fluoro-3-iodophenyl)triethylsilane (**67**, 104 mg, 0.25 mmol, 1.0 equiv) was dissolved in THF (0.5 ml) and *i*PrMgCl·LiCl (**1**, 0.246 mL, 0.275 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP4** with $ZnCl_2$ (0.30 mL, 0.30 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (4.3 mg, 3 mol%), P(2-furyl)$_3$ (3.6 mg, 6 mol%) and (*E*)-(2-iodovinyl)benzene (69 mg, 0.30 mmol, 1.2 equiv) at 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane) afforded (*E*)-(5-bromo-2-fluoro-3-styrylphenyl)triethylsilane (**69m**, 83 mg, 85%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.73 (dd, *J* = 6.8, 2.5 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.36 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.23 – 7.09 (m, 2H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.89 – 0.81 (m, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.47 (d, *J* = 244.4 Hz), 144.96, 137.00, 136.86 (d, *J* = 14.9 Hz), 131.08 (dd, *J* = 212.0, 3.8 Hz), 128.69 (d, *J* = 6.3 Hz), 128.33, 128.18, 126.73, 125.95, 119.92 (d, *J* = 3.7 Hz), 117.34, 7.28, 3.29.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -107.41.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2908, 2873, 1597, 1551, 1494, 149, 1416, 1396, 1326, 1301, 1280, 1260, 1238, 1204, 1184, 1159, 1127, 1102, 1075, 1004, 961, 923, 871, 827, 726, 687.
MS (EI, 70 eV): m/z (%) = 390 (100), 333 (54), 282 (28), 223 (30), 205 (9), 189 (12), 178 (84), 152 (13), 139 (11), 125 (10), 105 (31), 91 (21), 77 (68), 47 (16).
HRMS ($C_{20}H_{24}BrFSi$): calc.: 390.0815; found: 390.0818 (M^+).

4.7. Desilylation Reactions

1-(5-Bromo-2-fluorophenyl)-2,2-dimethylpropan-1-one (70)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 1-(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)-2,2-dimethylpropan-1-one (**69h**, 162 mg, 0.43 mmol, 1.0 equiv) and dissolved in dry CH_2Cl_2 (2 ml). After cooling down to 0 °C, TBAF·$3H_2O$ (163 mg, 0.52 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 2 h at this temperature. After complete conversion, the mixture was quenched with H_2O (5 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 20:1) 1-(5-bromo-2-fluorophenyl)-2,2-dimethylpropan-1-one (**70**, 101 mg, 91%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 7.46 (ddd, *J* = 8.8, 4.6, 2.5 Hz, 1H), 7.27 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.97 (t, *J* = 8.8 Hz, 1H), 1.22 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 208.16 (d, *J* = 1.3 Hz), 156.90 (d, *J* = 247.2 Hz), 133.61 (d, *J* = 8.0 Hz), 130.74 (d, *J* = 21.9 Hz), 130.35 (d, *J* = 4.9 Hz), 117.71 (d, *J* = 23.9 Hz), 116.47 (d, *J* = 3.4 Hz), 45.00, 26.4.

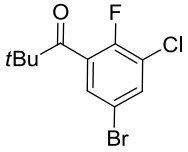
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -114.83.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2969, 2935, 2906, 2872, 1697, 1604, 1474, 1386, 1366, 1283, 1259, 1231, 1175, 1116, 1078, 1035, 971, 940, 880, 816, 771, 738, 701, 679.

MS (EI, 70 eV): m/z (%) = 258 (7), 201 (19), 97 (12), 94 (10), 83 (19), 71 (20), 69 (23), 61 (11), 57 (100), 55 (22), 43 (77).

HRMS ($C_{11}H_{12}BrFO$): calc.: 258.0056; found: 258.0033 (M^+).

1-(5-Bromo-3-chloro-2-fluorophenyl)-2,2-dimethylpropan-1-one (71)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 1-(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)-2,2-dimethylpropan-1-one (**69h**, 414 mg, 1.0 mmol, 1.0 equiv), hexachloroethane (473 mg, 2.0 mmol, 2.0 equiv) and caesium fluoride (304 mg, 2.0 mmol, 2.0 equiv) in dry DMF (2 ml). The reaction mixture was stirred for 3 h at 25 °C. After complete

conversion, the mixture was quenched with sat. aq. NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 1-(5-bromo-3-chloro-2-fluorophenyl)-2,2-dimethylpropan-1-one (**71**, 257 mg, 88%) as a colorless solid.

m.p.: 89.7 - 91.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 (dd, *J* = 6.3, 2.4 Hz, 1H), 7.21 (dd, *J* = 4.9, 2.4 Hz, 1H), 1.27 (d, *J* = 1.0 Hz, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 206.92 (d, *J* = 1.6 Hz), 152.72 (d, *J* = 249.0 Hz), 133.71, 131.52(d, *J* = 22.1 Hz), 128.59 (d, *J* = 4.1 Hz), 123.01 (d, *J* = 20.0 Hz), 116.49 (d, *J* = 4.2 Hz), 45.17, 26.41 (d, *J* = 1.8 Hz).

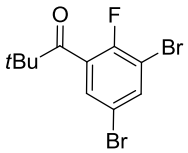
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -116.91.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 2967, 2933, 2909, 2870, 1697, 1663, 1594, 1564, 1477, 1451, 1418, 1390, 1368, 1283, 1244, 1218, 1194, 1172, 1108, 1090, 1040, 992, 938, 898, 866, 832, 785, 760, 718, 668.

MS (EI, 70 eV): m/z (%) = 291 (4), 237 (3), 149 (5), 135 (7), 127 (4), 111 (6), 109 (6), 97 (6), 67 (8), 57 (100), 44 (46), 41 (25).

HRMS ($C_{11}H_{11}BrFClO$): calc.: 291.9666; found: 291.9647 (M^+).

1-(3,5-Dibromo-2-fluorophenyl)-2,2-dimethylpropan-1-one (72)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 1-(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)-2,2-dimethylpropan-1-one (**69h**, 414 mg, 1.0 mmol, 1.0 equiv), 1,2-dibromotetrachloroethane (651 mg, 2.0 mmol, 2.0 equiv) and caesium fluoride (304 mg, 2.0 mmol, 2.0 equiv) in dry DMF (2 ml). The reaction mixture was stirred for 16 h at 60 °C. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 1-(3,5-dibromo-2-fluorophenyl)-2,2-dimethylpropan-1-one (**72**, 279 mg, 83%) as a colorless solid.

m.p.: 103.9 - 104.4 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.75 – 7.70 (m, 1H), 7.22 (ddd, *J* = 4.8, 2.4, 1.2 Hz, 1H), 1.24 (d, *J* = 1.1 Hz, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 206.91, 153.56 (d, *J* = 247.1 Hz), 136.37, 131.30 (d, *J* = 24.3 Hz), 129.29, 116.85, 110.83 (d, *J* = 24.5 Hz), 45.16, 26.40.

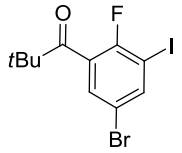
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -108.85.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 2979, 2938, 2874, 1744, 1690, 2589, 2556, 1481, 1435, 1399, 1385, 1364, 1340, 1278, 1243, 1224, 1199, 1158, 1039, 1018, 984, 938, 894, 872, 839, 822, 778, 757, 709, 656.

MS (EI, 70 eV): m/z (%) = 335 (5), 315 (2), 281 (15), 250 (3), 172 (5), 93 (8), 74 (2), 57 (100), 41 (18).

HRMS ($C_{11}H_{11}BrFO$): calc.: 335.9161; found: 3335.9166 (M^+).

1-(5-Bromo-2-fluoro-3-iodophenyl)-2,2-dimethylpropan-1-one (73)



The title compound was prepared according to **TP5** from 1-(5-bromo-2-fluoro-3-(triethylsilyl)phenyl)-2,2-dimethylpropan-1-one (**69h**, 75 mg, 0.2 mmol, 1.0 equiv) and iodine monochloride (42 mg, 0.22 mmol, 1.1 equiv). Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded 1-(5-bromo-2-fluoro-3-iodophenyl)-2,2-dimethylpropan-1-one (**73**, 68 mg, 88%) as a colorless solid.

m.p.: 116.6 - 118.0 °C

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.89 (dd, *J* = 5.3, 2.3 Hz, 1H), 7.23 (dd, *J* = 5.2, 2.3 Hz, 1H), 1.22 (d, *J* = 1.3 Hz, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 206.96, 155.99 (d, *J* = 245.0 Hz), 141.86, 130.44, 130.27, 117.22, 82.93 (d, *J* = 29.6 Hz), 45.12, 26.42.

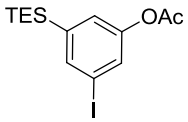
^{19}F NMR (300 MHz, $CDCl_3$): δ / ppm = -95.56.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2977, 2955, 2935, 2871, 2730, 2615, 2594, 2471, 1764, 1742, 1694, 1567, 1549, 1480, 1461, 1427, 1398, 1363, 1347, 1312, 1276, 1237, 1222, 1197, 1152, 1093, 1038, 1018, 1005, 982, 938, 911, 895, 872, 837, 775, 752, 734, 703, 683, 667.

MS (EI, 70 eV): m/z (%) = 383 (15), 326 (26), 298 (5), 200 (2), 172 (9), 127 (2), 93 (19), 57 (100), 41 (20).

HRMS ($C_{11}H_{11}BrFIO$): calc.: 383.9022; found: 383.9015 (M^+).

3-Iodo-5-(triethylsilyl)phenyl acetate (74)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with (5-iodo)-1,3-bis(triethylsilyl)benzene (**64b**, 236 mg, 0.54 mmol, 1.0 equiv), $PhI(OCOCF_3)_2$ (352 mg, 0.82 mmol, 1.5 equiv) and $Pd(OAc)_2$ (6.1 mg, 5 mol%) in AcOH (2 ml). The reaction mixture was stirred for 20 h at 80 °C. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 70:1) afforded 3-iodo-5-(triethylsilyl)phenyl acetate (**74**, 132 mg, 65%) as a colorless solid.

m.p.: 88.3 - 89.5 °C.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.64 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.47 (td, *J* = 1.9, 0.8 Hz, 1H), 7.14 (dt, *J* = 2.2, 0.9 Hz, 1H), 2.31 (s, 2H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.84 – 0.76 (m, 6H).

^{13}C-NMR (200 MHz, $CDCl_3$): δ / ppm = 169.04, 150.40, 142.43, 140.04, 130.91, 126.06, 94.38, 21.09, 7.24, 3.16.

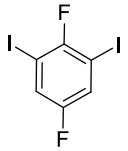
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2913, 2873, 2853, 1774, 1737, 1656, 1574, 1552, 1454, 1415, 1367, 1294, 1185, 1125, 1092, 1009, 971, 935, 901, 871, 831, 795, 755, 734, 721, 690.

MS (EI, 70 eV): m/z (%) = 376 (27), 347 (100), 334 (55), 319 (82), 291 (57), 277 (28), 249 (42), 150 (18), 121 (17), 97 (11), 85 (21), 83 (13), 71 (31), 61 (14), 55 (22), 43 (94).

HRMS ($C_{17}H_{21}IO_2Si$): calc.: 376.0355; found: 376.0356 (M^+).

4.8. Preparation of Tetrasubstituted Fluorobenzene Derivatives

2,5-Difluoro-1,3-diiodobenzene (78)



The title compound was prepared according to **TP5** from (2,5-difluoro-1,3-phenylene)bis(triethylsilane) (**62c**, 1.71 g, 5.0 mmol, 1.0 equiv) and iodine monochloride (2.45 g, 15.0 mmol, 3.0 equiv). Flash column chromatographical purification on silica gel (pentane) afforded 2,5-difluoro-1,3-diiodobenzene (**78**, 1.59 g, 87%) as a colorless solid.

m.p.: 46.8 - 48.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.50 (d, J = 4.5 Hz, 1H), 7.48 (d, J = 4.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 157.90 (dd, J = 252.5, 3.5 Hz), 157.37 (dd, J = 238.8, 3.4 Hz), 126.27 (d, J = 1.4 Hz), 126.02 (d, J = 1.4 Hz).

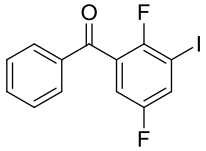
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -79.44, -116.14.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 1572, 1447, 1433, 1385, 1358, 1345, 1271, 1239, 1226, 1190, 1146, 1115, 1092, 1069, 1044, 953, 907, 862, 820, 763, 714, 685.

MS (EI, 70 eV): m/z (%) = 365 (100), 347 (18), 239 (19), 221 (4), 182 (3), 127 (9), 112 (40), 94 (7), 86 (1), 74 (4), 62 (16), 43 (3).

HRMS ($C_6H_2F_2I_2$): calc.: 365.8214; found: 365.8204 (M^+).

(2,5-difluoro-3-iodophenyl)(phenyl)methanone (79)



The title compound was prepared according to **TP6**, where 2,5-difluoro-1,3-diiodobenzene (**78**, 366 mg, 1.0 mmol, 1.0 equiv) was dissolved in THF (2 ml) and *i*PrMgCl·LiCl (**1**, 0.98 mL, 1.1 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the acylation reaction was accomplished according to **TP3** with CuCN·2LiCl (1.2 mL, 1.2 mmol, 1.0 M in THF, 1.2 equiv) and benzoyl chloride (169 mg, 1.5 mmol, 1.2 equiv) and allowed to warm to 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 70:1) afforded (2,5-difluoro-3-iodophenyl)(phenyl)methanone (**79**, 238 mg, 69%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.88 – 7.80 (m, 2H), 7.72 – 7.62 (m, 2H), 7.58 – 7.48 (m, 2H), 7.25 (ddd, *J* = 7.7, 4.8, 3.1 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 190.92 (d, *J* = 2.4 Hz), 158.04 (dd, *J* = 250.6, 3.1 Hz), 155.20 (dd, *J* = 246.5, 2.9 Hz), 136.22, 134.07, 129.83 (d, *J* = 1.1 Hz), 128.73, 128.49 (d, *J* = 2.1 Hz), 127.79 (dd, *J* = 20.9, 6.5 Hz), 117.10 (dd, *J* = 24.8, 2.9 Hz), 82.22 (dd, *J* = 29.8, 8.2 Hz).

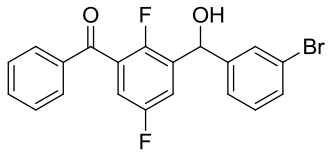
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -98.03, -115.96.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 3062, 3031, 2956, 2924, 2876, 2854, 1649, 1594, 1578, 1506, 1476, 1439, 1412, 1392, 1312, 1293, 1273, 1239, 1194, 1175, 1116, 1094, 1070, 1027, 996, 978, 938, 892, 860, 810, 760, 724, 694, 654, 614, 578, 562.

MS (EI, 70 eV): m/z (%) = 344 (80), 266 (15), 238 (4), 216 (2), 188 (2), 112 (14), 105 (100), 77 (35), 62 (3), 57 (2), 43 (2).

HRMS ($C_{13}H_7F_2IO$): calc.: 343.9510; found: 343.9504 (M^+).

(3-((3-bromophenyl)(hydroxy)methyl)-2,5-difluorophenyl)(phenyl)methanone (75)



The title compound was prepared according to **TP6**, where (2,5-difluoro-3-iodophenyl)(phenyl)methanone (**79**, 172 mg, 0.5 mmol, 1.0 equiv) was dissolved in THF (2 ml) and *i*PrMgCl·LiCl (**1**, 0.49 mL, 0.55 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with 3-bromobenzaldehyde (111 mg, 0.60 mmol, 1.2 equiv) and allowed to warm to 25 °C for 12 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 10:1) afforded (3-((3-bromophenyl)(hydroxy)methyl)-2,5-difluorophenyl)(phenyl)methanone (**75**, 132 mg, 65%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.80 – 7.71 (m, 2H), 7.63 – 7.55 (m, 3H), 7.43 (dd, *J* = 6.2, 2.6 Hz, 1H), 7.32 – 7.28 (m, 4H), 7.25 – 7.22 (m, 1H), 5.84 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 192.12 (d, *J* = 2.3 Hz), 160.76 (dd, *J* = 247.4, 3.1 Hz), 158.30 (dd, *J* = 244.5, 2.9 Hz), 146.39, 145.97, 136.57 (dd, *J* = 22.8, 6.8 Hz), 134.70, 131.12 (dd, *J* = 18.6, 7.5 Hz), 130.73, 129.85, 129.44, 129.41, 128.42 (dd, *J* = 22.9, 6.9 Hz), 125.93, 125.75, 121.98, 115.80 (dd, *J* = 18.3, 7.5 Hz), 62.53.

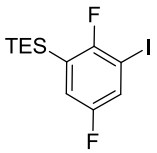
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -118.25, -121.06.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3386, 3074, 3060, 3024, 2950, 2933, 2880, 2854, 2190, 2101, 1651, 1592, 1516, 1480, 1442, 1392, 1312, 1290, 1241, 1194, 1175, 1091, 1066, 1026, 996, 968, 892, 860, 758, 722, 694, 570, 558.

MS (EI, 70 eV): m/z (%) = 402 (55), 323 (60), 286 (10), 257 (14), 245 (100), 218 (50), 183 (15), 169 (12), 157 (13), 140 (13), 119 (11), 105 (96), 84 (12), 77 (81), 66 (10).

HRMS ($C_{20}H_{13}BrF_2O_2$): calc.: 402.0067; found: 402.0055 (M^+).

(2,5-Difluoro-3-iodophenyl)triethylsilane (80)



The title compound was prepared according to **TP5** from (2,5-difluoro-1,3-phenylene)bis(triethylsilane) (**62c**, 3.42 g, 10.0 mmol, 1.0 equiv) and iodine monochloride (1.62 g, 10.0 mmol, 1.0 equiv). Flash column chromatographical purification on silica gel (pentane) afforded (2,5-difluoro-3-iodophenyl)triethylsilane (**80**, 3.05 g, 86%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.44 (ddd, *J* = 7.1, 4.9, 3.0 Hz, 1H), 7.02 (dt, *J* = 7.7, 3.2 Hz, 1H), 0.96 (td, *J* = 8.2, 7.7, 1.2 Hz, 9H), 0.90 – 0.78 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.60 (dd, *J* = 235.7, 2.2 Hz), 158.15 (dd, *J* = 249.3, 2.5 Hz), 140.52 (d, *J* = 2.0 Hz), 136.02 (d, *J* = 11.2 Hz), 126.65 (dd, *J* = 26.0, 2.6 Hz), 121.70 (dd, *J* = 21.3, 11.8 Hz), 7.17, 3.13.

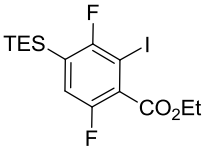
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -88.11, -118.38.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2912, 2876, 1538, 1450, 1403, 1374, 1281, 1242, 1224, 1109, 1084, 1074, 1000, 975, 869, 784, 727, 684.

MS (EI, 70 eV): m/z (%) = 354 (26), 325 (12), 297 (76), 285 (12), 279 (18), 269 (100), 257 (14), 251 (17), 198 (29), 173 (9), 169 (79), 151 (13), 141 (18), 102 (10), 87 (11), 77 (25), 75 (30).

HRMS ($C_{12}H_{17}F_2ISi$): calc.: 354.0112; found: 354.0104 (M^+).

Ethyl 3,6-difluoro-2-iodo-4-(triethylsilyl)benzoate (81)

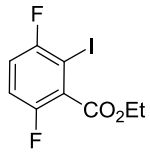


A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with (2,5-difluoro-3-iodophenyl)triethylsilane (**80**, 2.12 g, 6.0 mmol, 1.0 equiv) in dry THF (10 ml), TMPMgCl·LiCl (**5**, 6.55 mL, 7.2 mmol, 1.2 equiv, 1.10 M in THF) was added dropwise at -20 °C and stirred for 4 h at this temperature. The reaction mixture was quenched with ethyl cyanoformate

(714 mg, 7.2 mmol, 1.2 equiv) and allowed to warm to 25 °C within 2 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 100:1) afforded ethyl 3,6-difluoro-2-iodo-4-(triethylsilyl)benzoate (**81**, 1.41 g, 55%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.10 (dd, *J* = 8.1, 3.5 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.02 – 0.93 (m, 9H), 0.92 – 0.81 (m, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.27 (d, *J* = 2.2 Hz), 161.45 (dd, *J* = 236.8, 2.3 Hz), 154.60 (dd, *J* = 252.8, 2.5 Hz), 130.20 (dd, *J* = 21.8, 2.2 Hz), 127.56 (dd, *J* = 39.2, 4.0 Hz), 122.39 (dd, *J* = 21.6, 12.2 Hz), 80.81 (dd, *J* = 37.0, 3.0 Hz), 62.62, 14.12, 7.16, 3.09.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -83.89, -118.65.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2912, 2877, 1737, 1675, 1541, 1507, 1465, 1438, 1375, 1282, 1238, 1192, 1173, 1124, 1097, 1070, 876, 817, 784, 720, 696, 596, 569.
MS (EI, 70 eV): m/z (%) = 426 (53), 397 (9), 381 (38), 370 (30), 341 (100), 323 (9), 313 (16), 305 (12), 295 (7), 277 (6), 255 (4), 241 (18), 214 (27), 197 (6), 169 (15), 141 (16), 127 (7), 87 (7), 77 (9).
HRMS ($C_{15}H_{21}F_2IO_2Si$): calc.: 426.0324; found: 426.0323 (M^+).

Ethyl 3,6-difluoro-2-iodobenzoate (82)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with ethyl 3,6-difluoro-2-iodo-4-(triethylsilyl)benzoate (**81**, 426 mg, 1.0 mmol, 1.0 equiv) and dissolved in dry THF (2 ml). After cooling down to 0 °C, TBAF·$3H_2O$ (316 mg, 1.2 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 2 h at this temperature. After complete conversion, the mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded ethyl 3,6-difluoro-2-iodobenzoate (**82**, 281 mg, 90%) as a colorless oil.

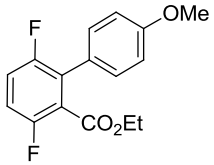
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 – 7.60 (m, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 162.51 (dd, *J* = 5.0, 2.3 Hz), 157.65 (dd, *J* = 249.0, 3.4 Hz), 157.05 (dd, *J* = 254.6, 3.1 Hz), 130.16 (dd, *J* = 25.6, 2.4 Hz), 120.01 (dd, *J* = 15.2, 7.5 Hz), 118.53 (d, *J* = 25.2 Hz), 83.02 (dd, *J* = 30.3, 8.2 Hz), 62.11, 14.17.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -94.93, -116.54.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 1716, 1610, 1583, 1451, 1422, 1391, 1366, 1298, 1239, 1188, 1133, 1115, 1077, 1017, 962, 869, 821, 765, 713.

MS (EI, 70 eV): m/z (%) = 312 (59), 297 (2), 284 (45), 266 (100), 239 (15), 140 (8), 112 (36), 96 (4), 88 (2), 81 (7), 70 (4), 62 (8), 43 (50).

HRMS ($C_9H_7F_2IO_2$): calc.: 311.9459; found: 311.9460 (M^+).

Ethyl 3,6-difluoro-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (76)



The title compound was prepared according to **TP6**, where ethyl 3,6-difluoro-2-iodobenzoate (**82**, 156 mg, 0.5 mmol, 1.0 equiv) was dissolved in THF (1 ml) and *i*PrMgCl·LiCl (**1**, 0.49 mL, 0.55 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the cross-coupling was accomplished according to **TP4** with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0 M in THF, 1.2 equiv), $Pd(dba)_2$ (8.6 mg, 3 mol%), $P(2\text{-furyl})_3$ (7.2 mg, 6 mol%) and 4-iodoanisole (139 mg, 0.60 mmol, 1.2 equiv) at 25 °C in 4 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 40:1) afforded ethyl 3,6-difluoro-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (**76**, 100 mg, 68%) as a colorless solid.

m.p.: 52.6 - 54.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.60 – 7.51 (m, 1H), 7.49 (dd, *J* = 8.8, 1.8 Hz, 2H), 7.31 (dd, *J* = 5.4, 3.2 Hz, 1H), 7.06 – 6.97 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.30 (dd, *J* = 247.3, 3.5 Hz), 159.86, 156.34 (dd, *J* = 249.8, 2.9 Hz), 153.60 (d, *J* = 2.7 Hz), 132.01 (dd, *J* = 27.1, 7.7 Hz), 130.24 (d, *J* = 3.3 Hz), 126.44 (d, *J* = 1.4 Hz), 121.09 (dd, *J* = 24.0, 4.3 Hz), 120.79 (dd, *J* = 23.8, 4.9 Hz), 116.27 (dd, *J* = 25.4, 1.5 Hz), 114.11, 61.73, 55.36, 14.22 .

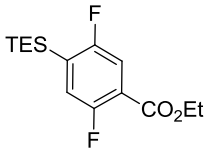
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -118.21, -121.06.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3401, 3090, 3072, 3017, 2994, 2967, 2940, 2911, 2840, 1764, 1714, 1610, 1516, 1481, 1459, 1436, 1408, 1393, 1365, 1332, 1286, 1262, 1246, 1218, 1181, 1151, 1114, 1018, 967, 936, 896, 870, 833, 820, 798, 772, 738, 714, 668.

MS (EI, 70 eV): m/z (%) = 292 (100), 264 (20), 247 (28), 221 (8), 204 (6), 187 (5), 175 (10), 123 (6), 57 (2), 43 (2).

HRMS ($C_{16}H_{14}F_2O_3$): calc.: 292.0911; found: 292.0906 (M^+).

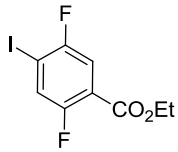
Ethyl 2,5-difluoro-4-(triethylsilyl)benzoate (83)



The title compound was prepared according to **TP6**, where ethyl 3,6-difluoro-2-iodo-4-(triethylsilyl)benzoate (**81**, 639 mg, 1.5 mmol, 1.0 equiv) was dissolved in THF (2 ml) and *i*PrMgCl·LiCl (**1**, 1.47 mL, 1.65 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 100:1) afforded ethyl 2,5-difluoro-4-(triethylsilyl)benzoate (**83**, 415 mg, 92%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.50 (dd, *J* = 7.9, 5.3 Hz, 1H), 7.10 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.97 – 0.93 (m, 9H), 0.88 – 0.81 (m, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 163.46, 162.25 (d, *J* = 237.9 Hz), 157.57 (d, *J* = 257.5 Hz), 132.53 – 131.84 (m), 123.61 (dd, *J* = 24.9, 13.6 Hz), 120.81 – 120.23 (m), 117.16 (d, *J* = 32.4 Hz), 61.53, 14.20, 7.15, 3.08.
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -94.87, -116.54.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2912, 2878, 1737, 1719, 1622, 1559, 1469, 1400, 1376, 1298, 1260, 1241, 1223, 1165, 1100, 1029, 1005, 897, 840, 783, 725, 710, 680, 595.
MS (EI, 70 eV): m/z (%) = 300 (6), 271 (3), 255 (14), 243 (100), 229 (3), 225 (3), 215 (89), 213 (31), 197 (21), 187 (14), 171 (4), 142 (8), 71 (22), 43 (38).
HRMS ($C_{15}H_{22}F_2O_2Si$): calc.: 300.1357; found: 300.1347 (M^+).

Ethyl 2,5-difluoro-4-iodobenzoate (84)



The title compound was prepared according to **TP5** from ethyl 2,5-difluoro-4-(triethylsilyl)benzoate (**83**, 300 mg, 1.0 mmol, 1.0 equiv) and iodine monochloride (178 mg, 1.1 mmol, 1.1 equiv). Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded ethyl 2,5-difluoro-4-iodobenzoate (**84**, 265 mg, 85%) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.58 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 162.81, 157.78 (d, *J* = 243.5 Hz), 157.17 (d, *J* = 262.1 Hz), 127.66 (d, *J* = 28.2 Hz), 87.06 (dd, *J* = 29.2, 10.2 Hz), 117.29 (d, *J* = 29.0 Hz), 61.88, 14.15.

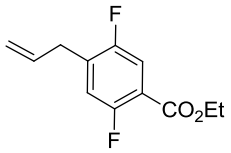
^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -99.63, -113.99.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2932, 1717, 1610, 1477, 1406, 1387, 1300, 1247, 1218, 1179, 1087, 1019, 971, 895, 863, 838, 765, 680.

MS (EI, 70 eV): m/z (%) = 312 (39), 284 (49), 267 (100), 239 (14), 221 (14), 183 (5), 157 (3), 140 (23), 120 (2), 112 (39), 101 (4), 85 (3), 74 (2), 62 (17), 45 (13), 43 (21).

HRMS ($C_9H_7F_2IO_2$): calc.: 311.9459; found: 311.9446 (M^+).

Ethyl 4-allyl-2,5-difluorobenzoate (77)



The title compound was prepared according to **TP6**, where ethyl 2,5-difluoro-4-iodobenzoate (**84**, 156 mg, 0.5 mmol, 1.0 equiv) was dissolved in THF (1 ml) and *i*PrMgCl·LiCl (**1**, 0.49 mL, 0.55 mmol, 1.1 equiv, 1.12 M in THF) was added at 0°C and stirred for 1 h at this temperature. Subsequently, the allylation reaction was accomplished according to **TP3** with CuCN·2LiCl (0.60 mL, 0.60 mmol, 1.0 M in THF, 1.2 equiv) and allyl bromide (73 mg, 0.6 mmol, 1.2 equiv) and allowed to warm to 25 °C in 6 h. After complete conversion, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatographical purification on silica gel (*i*hexane:EtOAc = 50:1) afforded ethyl 4-allyl-2,5-difluorobenzoate (**77**, 95 mg, 84%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.60 (dd, *J* = 9.5, 5.9 Hz, 1H), 7.00 (dd, *J* = 10.7, 5.8 Hz, 1H), 5.93 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.24 – 5.09 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.48 – 3.39 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.34 (dd, *J* = 4.3, 2.1 Hz), 157.87 (dd, *J* = 256.5, 2.4 Hz), 156.10 (dd, *J* = 243.0, 2.6 Hz), 134.34 (d, *J* = 18.9 Hz), 134.26 (d, *J* = 18.8 Hz), 133.92, 118.54 (dd, *J* = 25.2, 4.8 Hz), 117.97 (d, *J* = 1.7 Hz), 117.71, 61.51, 32.94 (dd, *J* = 2.3, 1.1 Hz), 14.22.

^{19}F NMR (375 MHz, $CDCl_3$): δ / ppm = -115.37, -123.50.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 2984, 2937, 2910, 2362, 1715, 1632, 1583, 1498, 1424, 1367, 1322, 1301, 1250, 1203, 1172, 1138, 1096, 1056, 995, 919, 896, 869, 780, 754, 708, 667.

MS (EI, 70 eV): m/z (%) = 226 (33), 198 (15), 181 (100), 153 (10), 151 (7), 133 (8), 127 (4), 107 (1).

HRMS ($C_{12}H_{12}F_2O_2$): calc.: 226.0805; found: 226.0807 (M^+).

D: APPENDIX

List of Abbreviations

Ac	Acetyl
aq.	aqueous
Ar	aryl
Boc	*tert*-butyloxycarbonyl
calc.	calculated
conc.	concentrated
d	doublet (NMR)/ day
dba	*trans,trans*-dibenzylideneacetone
dist.	distilled
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylforamide
DMSO	dimethyl sulfoxide
δ	chemical shifts in ppm
E	electrophile
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Hal	halogen
i-hexane	*iso*-hexane
hex	hexyl
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrometry
Hz	Hertz
*i*Pr	*iso*-propyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium *N,N*-diisopropylamide
M	molarity
m	*meta*
m.p.	melting point
Me	methyl
*n*Bu	*n*-butyl
Nf	nonaflate
MDPM	monomethoxydiphenylmethoxymethyl
min	minute
mmol	millimole

MOM	methoxymethyl acetal
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PEPPSI-IPr	[1,3-bis(2,6-di(isopropyl)-phenyl)imidazol-2-ylidene] (3-chloropyridyl)-palladium(II) dichloride
pin	pinacol
PMDTA	(*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine
Ph	phenyl
PG	protecting group
Piv	pivalyl
ppm	parts per million
prim	primary
R	organic substituent
sat.	saturated
sec	secoundary
SEM	(2-(Trimethylsilyl)ethoxy)methyl acetal
*s*Bu	*sec*-butyl
T	temperature
t	time
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TES	triethylsilyl
tf	triflate
tfp	tris-(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	tri(isopropylsilyl)
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine
TMP	2,2,6,6-tetramethyl-piperidyl
TMPH	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Tol	toluene
Ts	4-toluenesulfonyl
X	halide or pseudohalide