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Polyfunctionalizations of N-Heterocycles via Chemo- and Regioselective Metalations

von

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aus

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, und ohne unerlaubte Hilfe erarbeitet.

München, am 29.11.07

Nadège Boudet

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2. Gutachter: Prof. Dr. Thomas Carell

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Parts of this Ph. D. thesis have been published:

1) **Nadège Boudet**, Srinivas Reddy Dubbaka and Paul Knochel. **"**Amination of DNA and RNA units via Cuprated Pyrimidine and Purine Intermediates". *Org. Lett.* **2007**, *submitted.*

2) **Nadège Boudet**, Jennifer R. Lachs and Paul Knochel. "Multiple Regioselective Functionalization of Quinolines *via* Magnesiations". *Org. Lett.* **2007**, *9*, 5525-5528.

3) **Nadège Boudet**, Shohei Sase, Pradipta Sinha, Ching-Yuan Liu, Arkady Krasovskiy, and Paul Knochel. "Directed Ortho Insertion (DoI): a New Approach to Functionalized Aryl and Heteroaryl Zinc Reagents". *J. Am. Chem. Soc*. **2007**, *129*, 12358-12359.

4) Darunee Soorukram, **Nadège Boudet**, Vladimir Malakhov and Paul Knochel. "Preparation of Polyfunctionalized 2,6-Dimethoxypyrimidine Derivatives *via* Chemo- and Regioselective Direct Zinc Insertion". *Synthesis* **2007**, *24*, 3915-3922.

5) **Nadège Boudet** and Paul Knochel. "Chemo- and Regio-selective Functionalization of Uracil Derivatives. Application to the Synthesis of Oxipurinol and Emivirine". *Org. Lett*. **2006**, *8*, 3737-3740.

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Abbreviations

ABBREVIATIONS

Ac	acetyl
acac	acetyl acetonate
AcOH	acetic acid
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
BSA	N,O-bis(trimethylsilyl)acetamide
CDI	1,1'-carbonyldiimidazole
CDK	cyclin-dependent kinase
CH_2Cl_2	dichloromethane
Cy	cyclohexyl
d	double
dba	*trans*,*trans*-dibenzylideneacetone
DMA	dimethylacetal
DMF	*N*,*N*-dimethylformamide
DMGs	directing metalation groups
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DoI	directed *ortho* insertion
Eq.	equation
equiv	equivalent
EI	electron-impact
Et	ethyl
FG	functional group
GC	gas chromatography
GP	general procedure
h	hour
HIV	human immunodeficiency virus
HRMS	high resolution mass spectroscopy
Im-*H*	imidazole
i-Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
LDA	lithium diisopropylamide
LG	leaving group
LUMO	lowest unoccupied molecular orbital
M	molarity
m	meta

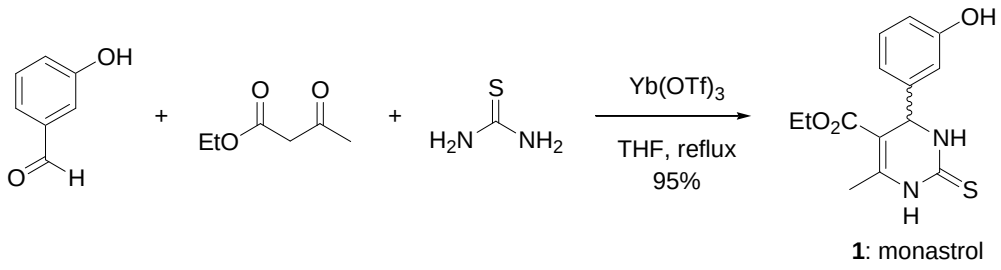
m	multiplet
Me	methyl
Mes	mesityl
Met	metal
min	minute
mol.	mole
mp.	melting point
MS	mass spectroscopy
NK3	neurokinin-3
NMP	N-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NNRTIs	nonnucleoside reverse transcriptase inhibitor
o	ortho
p	para
PEG	polyethylene glycol
pent	pentyl
PG	protecting group
Ph	phenyl
q	quartet
RNA	ribonucleic acid
rt	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
tfp	*tri*-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAU	(6-([3,4-trimethylene]-anilino)uracil)
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Ts	4-toluenesulfonyl

A: General Introduction

1. Overview

Polysubstituted heterocycles belong to the most important organic compounds both in view of their mere production quantity and of their economic importance. The methods for their synthesis form the bedrock of modern medicinal chemical and pharmaceutical research. For instance, N-heterocyclic organic compounds are extensively applied to modify the reactivity profile of antitumor compounds. Pyrroles, pyrimidines, indoles, quinolines, and purines are the heterocycles known to show interesting cytotoxicity profiles.

The search for a new drug often begins with the identification of a particular class of heterocycles having a potential for the desired biological activity. The second step is the functionalization of this class of heterocycle in order to obtain several candidates. The synthetic approaches towards polyfunctionalized heterocycles can be crudely divided into two categories. The first approach aims at the construction of a heterocyclic core after the substituents have been installed and functionalized. As an illustration of this approach, a transition-metal catalyzed Biginelli heterocyclization reaction for the synthesis of monastrol,[1] a potentially important chemotherapeutic for cancer, is shown in Scheme 1.



Scheme 1: The modern variant of Biginelli reaction for the synthesis of monastrol (**1**).

The second approach is based on a preformed heterocycle to which different substituents are attached in successive order. This approach is more flexible concerning the choice of the substituents and gives an easy access to various analogs. It may include traditional aromatic substitution chemistry, directed metalation methods, halogen–metal exchange reactions as well as cross-coupling reactions. The methods used should be reliable in terms of reactivity, functional tolerance and selectivity. To address these requirements, the organometallic

[1] (a) Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett.* **2002**, *43*, 5913.

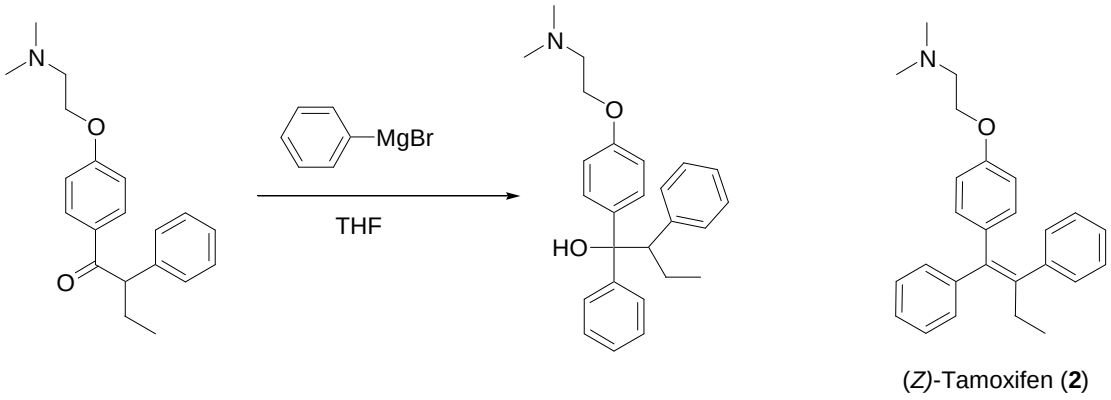
chemistry proved to be an excellent tool with a broad applicability.[2] Over the years, organometallic compounds, especially Grignard, copper and zinc reagents, facilitated the development of an arsenal of synthetic methods for efficient and selective reactions and have found numerous applications in industrial processes. In order to perform efficient C-C and C-N bond formations in heterocycle chemistry, there is still a need of new organometallic methods and reagents, which have to be chemo- and regioselective and as inexpensive and environmentally friendly as possible.

[2] For general review, see: (a) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F in *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH, Weinheim **2005**: 251; (b) Knochel, P.; Millot, P.; Rodriguez, A. L.; Tucker, C. E. in *Organic reactions*; Overman, L. E., Ed.; Wiley & Sons Inc., New York, **2001**.

2. Direct Preparation and Use of Organomagnesiated Aryl and Heteroaryl Compounds

2.1. Introduction

Since their first preparation in ethereal solution in 1901 by Victor Grignard, [3] organomagnesium reagents have obtained a key role in organic synthesis. Their easy synthesis, good stability and their excellent reactivity make Grignard reagents one of the most powerful tools for carbon-carbon formation used in industry[4] and academic laboratories. As an example, the Grignard reaction, using phenyl magnesium bromide, is a key step of the industrial production of *Tamoxifen* (**2**), [5] currently the world's largest selling drug for breast cancer (Scheme 2).



Scheme 2: Key step of the total synthesis of the drug *Z*-Tamoxifen (**2**)

Furthermore, organomagnesium reagents are also useful reactants for C-N bond formation[6] leading to polyfunctionalized amines, useful for pharmaceutical applications. Finally, transmetalations to more chemoselective organometallic species such as zinc, copper,[7] or titanium, allow additional fine-tuning of their reactivity pattern.

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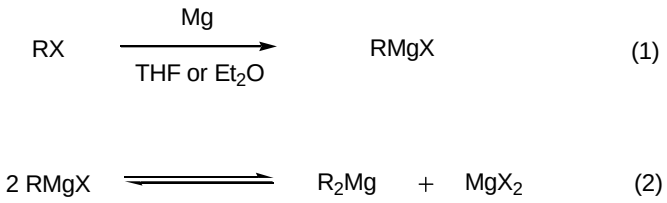
[3] Grignard, V. *Ann. Chim*. **1901**, *24*, 433.
[4] Bush, F. R.; De Antonis, D. M. Grignard Reagents- New Developments; Richey, H. G., Jr., Ed.; Wiley, New York, **2000**, pp.165-183.
[5] (a) Harper, M. J. K.; Walpole, A. L. *Nature* **1966**, *212*, 87; (b) Bedford, G. R.; Richardson, D. N. *Nature* **1966**, *212*,733; for a review of the pharmacology, see: (c) Heel, R. C.; Brogdon, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1978**, *16*, 1; (d) Harper, M. J. K.; Richardson, D. N.; Walpole, A. L.GB1013907, **1965**, Imperial Chemical Industries, Ltd.; (e) Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem*. **1982**, *47*, 2387; (f) McCague, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1011.
[6] For a review on recent amination procedures see: Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel. *Eur. J. Org. Chem*. **2007**, *25*, 4166.
[7] Lipshutz B. H.; Sengupta S. *Org. Reactions* **1992**, *41*, 135.

2.2. Direct oxidative addition of magnesium to organic halides

The most common used method for the preparation of Grignard reagents is the direct oxidative addition of magnesium metal to organic halides in an aprotic solvent like THF or diethyl ether (Scheme 3, Eq. 1).



Scheme 3: Synthesis of Grignard reagents by oxidative addition (Eq. 1) and Schlenk-equilibrium (Eq. 2).

The detailed mechanism of this reaction is still not clear, although a radical pathway is generally accepted.[8] In solution, a Grignard reagent (RMgX) is in equilibrium with R_2Mg and MgX_2 (Schlenk equilibrium, Scheme 3, Eq. 2), depending on temperature, solvent and the anion X^-.[9] Usually, magnesium metal is covered with an 'oxide layer' which mainly consists of $Mg(OH)_2$.[10] Thus, in order to shorten the induction period and obtain a better reproducibility of the reaction, the activation of the magnesium surface with reagents like 1,2-dibromoethane prior to reaction is normally desired.[11] For the synthesis of functionalized Grignard reagents bearing sensitive functional groups, highly reactive *Rieke* magnesium (Mg*)[12] can be used (Scheme 4). The direct trapping of Grignard reagent with an electrophile (Barbier-reaction)[13] can sometimes be used to overcome the stability problems.

[8] (a) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286; (b) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95; (c) Rogers, H. R.; Hill, C. L.; Fujuwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217; (d) Garst, J. F.; Ungvary, F. *Grignard Reagents* (Ed.: H. G. Richey, Jr.), Wiley, Chichester, **2000**, 185; (e) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, **1954**; (f) Hamdouchi, C.; Walborsky, H. M. *Handbook of Grignard-Reagents* (Eds: Silverman, G. S.; Rakita, P. E.), Marcel Dekker, New York, **1995**, 145; (g) Oshima, K. *Main Group Metals in Organic Synthesis* (Eds.: Yamamoto, H.; Oshima, K.), Wiley-VCH, Weinheim, **2004**.

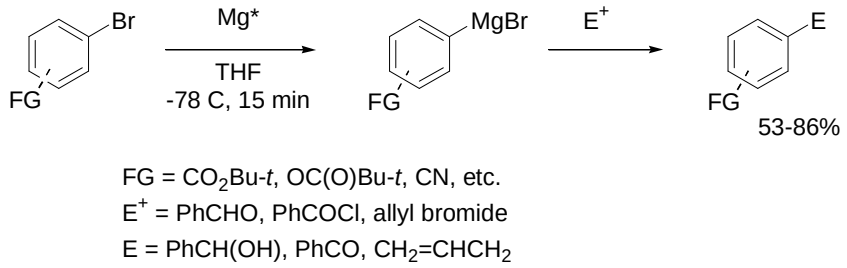
[9] Schlenk, W.; Schlenk Jr., W. *Chem. Ber.* **1929**, *62*, 920.

[10] Garst, J. F.; Seriaga, M. P. *Coord. Chem. Rev* . **2004**, *248*, 623.

[11] For relevant parameters controlling Grignard reagent formation, see: Lindsell, W. E. *Comprehensive Organometallic Chemistry I* (Eds. G. Wilkinson, F. G. S. Stone and G. E. Ebel), Vol. 1 , Chap. 3, Pergamon Press, Oxford, **1982**, pp. 155-252 and references therein.

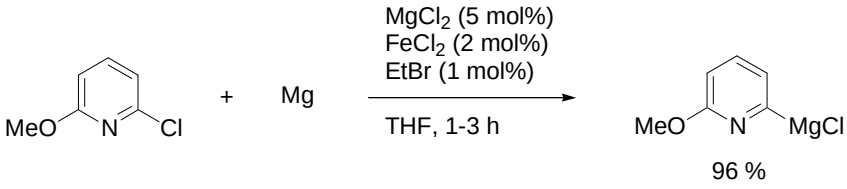
[12] (a) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925; (b) Rieke, R. D. *Aldrichim. Acta* **2000**, *33*, 52; (c) Rieke, R. D.; Sell, M. S.; Klein, W. R.; Chen, T.-A.; Brown, J. D.; Hansen, M. U. *Active Metals. Preparation, Characterization, Application*, Fürstner, A. (Ed.), Wiley-VCH, Weinheim (Germany), **1996**, p.1.

[13] Blomberg, C. *The Barbier Reaction and Related One-Step Processes* Springer, Berlin, Heidelberg, New York, **1993**.



Scheme 4: Preparation of functionalized Grignard reagents using *Rieke*-magnesium (Mg*).

Interestingly, low reactive aryl chlorides can be converted to the corresponding organomagnesium species through transition metal catalysis using 2 mol% $FeCl_2$ (Scheme 5).[14]

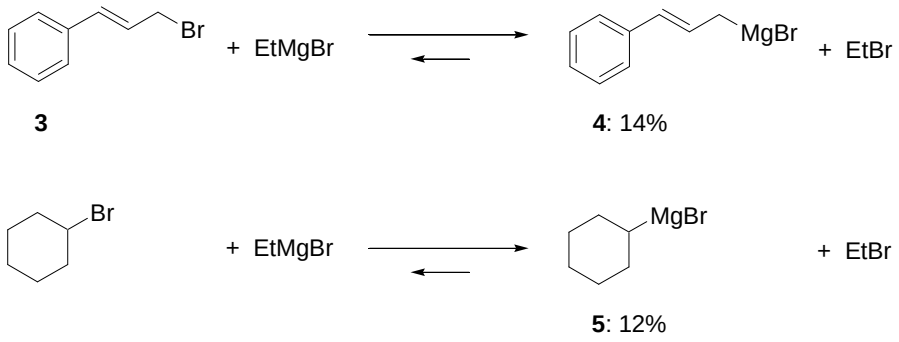


Scheme 5: Direct oxidative insertion of activated magnesium into aryl chloride.

2.3. The halogen/magnesium exchange reaction

The direct oxidative addition of magnesium has been used successfully for the preparation of organomagnesium compounds. However, the use of magnesium metal leads also to the reduction of electrophilic functional groups and involves exothermic reactions, which are not easy to control during industrial processes.[4] These limitations can be considerably reduced by using a halogen/magnesium exchange reaction. The first example was briefly reported in 1931 by *Prévost.* [15] The reaction of cinnamyl bromide (**3**) with EtMgBr furnished cinnamylmagnesium bromide **4** in a low yield. *Urion* reported the preparation of cyclohexylmagnesium bromide **5** in a similar way (Scheme 6). [16]

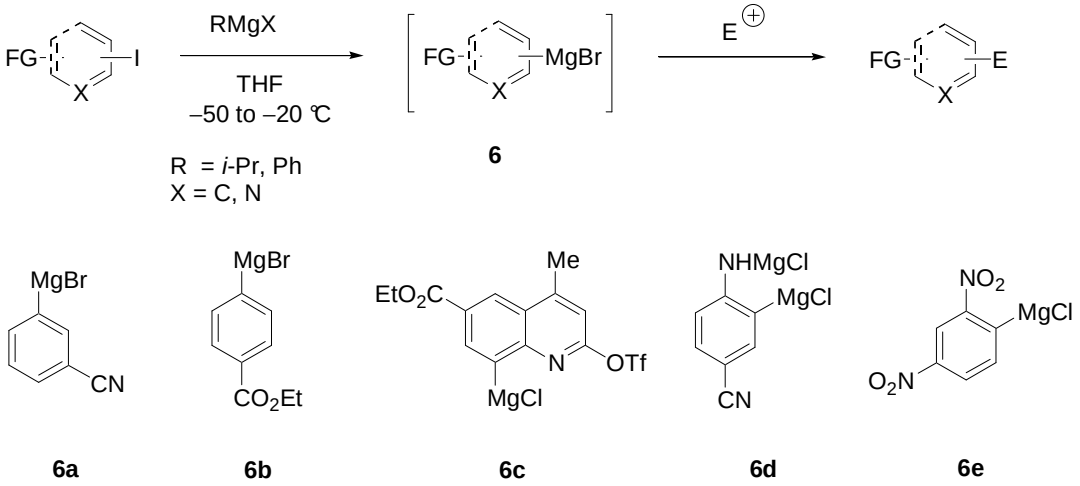
[14] Bogdanović, B.; Schwickardi, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.
[15] Prévost, C. *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[16] Urion, E. *Comp. Rend. Acad. Sci. Paris* **1934**, *198*, 1244.



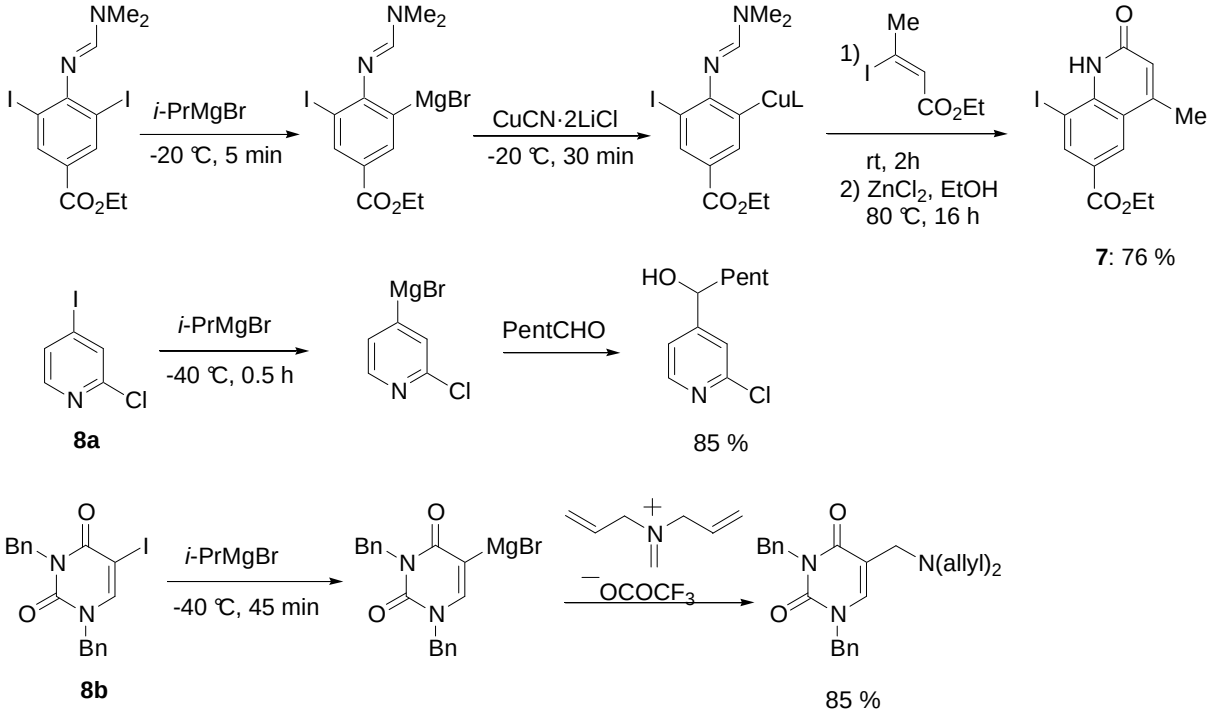
Scheme 6: First examples of a Br/Mg exchange.

The halogen/magnesium exchange is a reaction favoring the formation of the more stable organomagnesium compound (sp > sp^2(vinyl) > sp^2(aryl) > sp^3(prim.)> sp^3(sec.)). The mechanism of the exchange reaction is not yet fully clarified,[17a,b,c] but calculations show that it proceeds via a concerted 4-centered mechanism,[17d] in contrast to the halogen-lithium exchange that goes via the formation of a halogenate complex. In 1971, *Tamborski* showed that not only the electronic properties of the organic molecule play an important role in the formation-rate of the new Grignard reagent, but also the nature of the halogen atom.[18] The reactivity order (I > Br > Cl >> F) is influenced by the carbon-halogen bond strength and by the electronegativity and polarizability of the halide. In recent years, the halogen/magnesium exchange has been found to be the method of choice for the preparation of new polyfunctionalized organomagnesium reagents of considerable synthetic utility.[19] The reactivity of organomagnesium reagents is strongly dependent of the temperature: only reactive electrophiles such as aldehydes and most ketones react rapidly at temperature below 0 °C. Thus, performing the halogen/magnesium exchange at temperatures below 0 °C has the potential for the preparation of magnesiated reagents that bear reactive functional groups. In 1998, *Knochel* showed excellent functional group tolerance during a low-temperature I/Mg exchange reaction used for the preparation of functionalized aromatic Grignard reagents (Scheme 7, **6a** and **6b**).[20]

[17] (a) Bailey W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1; (b) Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc*. **1985**, *107*, 4101; (c) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc*. **1986**, *108*, 2449; (d) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.
[18] Tamborski, C.; Moore, G. J. *J. Organomet. Chem.* **1971**, *26*, 153.
[19] For a review on functionalized organomagnesium reagents see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 4302.
[20] (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed*. **1998**, *37*, 1701; (b) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Knochel, P. *Synlett* **2001**, 477.



Scheme 7: Functionalized arylmagnesium halides of type **6** prepared via an I/Mg exchange.

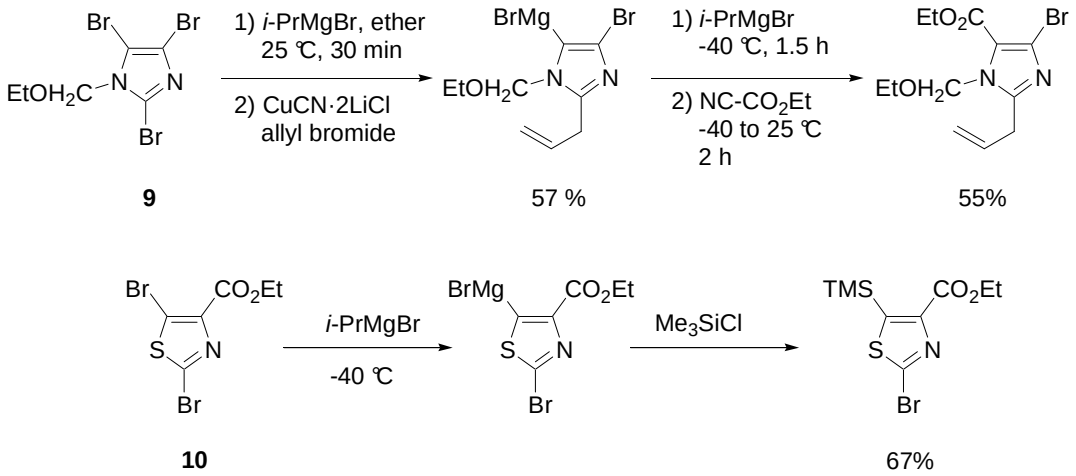


Scheme 8: I/Mg exchange using for the synthesis of functionalized heterocycles.

Many applications[19] have confirmed that the halogen/magnesium exchange proceeds under mild conditions and that various sensitive functional groups such as esters (**6c**,[21] Scheme 8), nitriles (**6d**), [22] iodides, imines, or even nitro group (**6e**) [23] are tolerated during the organomagnesium reagent formation. One interesting example is the preparation of the

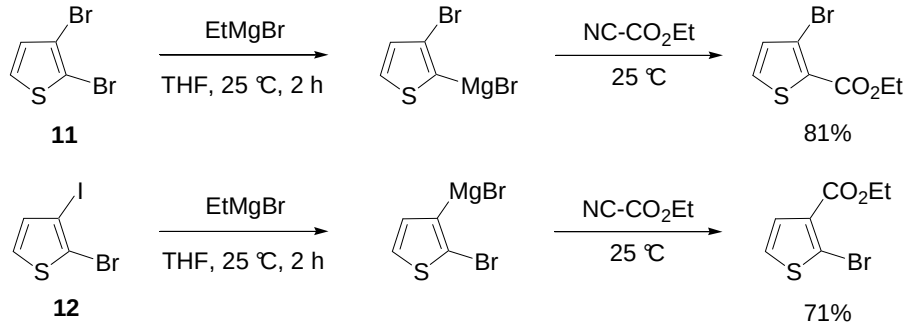
[21] Staubitz, A.; Dohle, W.; Knochel, P. *Synthesis* **2003**, 223.
[22] Varchi, G.; Kofink, C.; Lindsay, D. M.; Ricci, A.; Knochel, P. *Chem. Commun*. **2003**, 396.
[23] Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed*. **2002**, *41*, 1610.

functionalized α,β-unsaturated lactam **7** (Scheme 8).[24] The halogen/magnesium exchange is an attractive method for the generation of stable functionalized heteroarylmagnesium compounds. A variety of functionalized heteroarylmagnesium compounds bearing electron-withdrawing groups can be readily prepared by using I/Mg or Br/Mg exchange between -30 °C and -20 °C within few hours.[25] The electronic density of the heterocycle influences the halogen/magnesium-exchange rate: electron-poor heterocycles react faster and electron-withdrawing substituents strongly accelerate the exchange rate. Likewise, heteroaryl iodide such as 2-chloro-4-iodopyridine (**8a**)[26] or protected iodouracils (**8b**),[27] react very fast with *i*-PrMgBr in THF giving the corresponding magnesium compounds in high yields (Scheme 8). Polyhalogenated substrates usually undergo a single halogen-magnesium exchange (Schemes 9 and 10). After the first magnesiation, the electron density of the heterocycle increases and the subsequent second exchange reaction proceeds much slower. This very general behavior allows a high chemoselectivity for the Br/Mg exchange reaction of polyhalogenated compounds. Chelating groups, such as an ester or an ether, strongly influence the regioselectivity of the exchange reaction, as demonstrated by the reaction of *i*-PrMgBr with the tribromoimidazole **9** and the dibromothiazole **10** (Scheme 9).[28] Chemo and regio-selective Br/Mg exchange have also been observed in the dihalogenated thiophenes **11** and **12**, using EtMgBr at 25 °C (Scheme 10).[29]



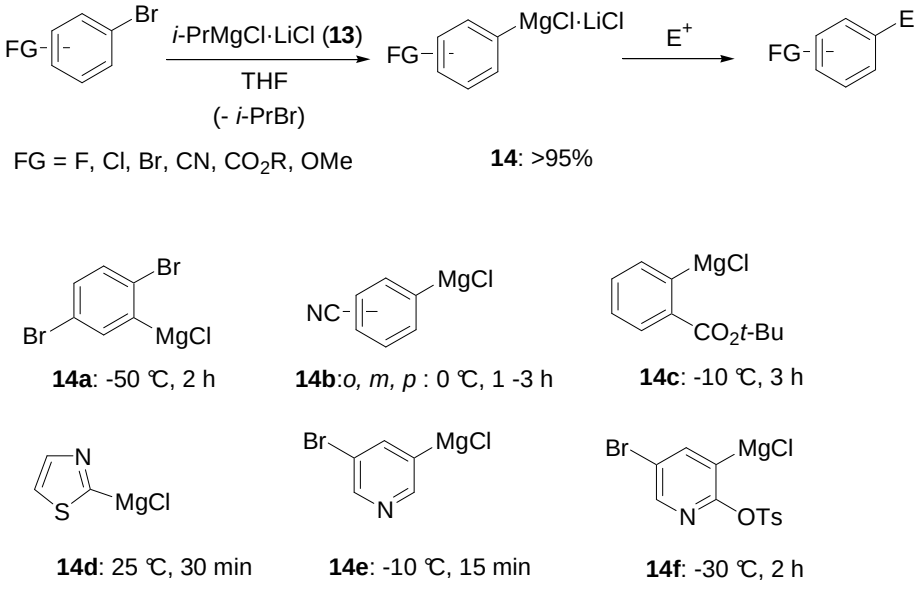
Scheme 9: Regioselective Br/Mg exchanges induced by chelating effect

[24] Dohle, W. PhD thesis, LMU München, **2002**.
[25] For review concerning the halogen/magnesium exchange on heterocycles, see: Hiriyakkanavar, I.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. comm.* **2006**, 583.
[26] (a) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, *7*, 1371; (b) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832.
[27] Abarbri, M.; Knochel, P. *Synlett* **1999**, 1577.
[28] (a) Lipshutz, B. H.; Hagen, W. Tetrahedron Lett. **1992**, *33*, 5865; (b) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F. ; Röttlander, M. ; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.
[29] Christophersen, C.; Begtrup, M.; Ebdrup, S.; Petersen H.; Vedsø, P. *J. Org. Chem.* **2003**, *68*, 9513.



Scheme 10: Regioselective I/Mg and Br/Mg exchange on dihalogenated thiophenes.

Inactived aryl bromides do not react with *i*-PrMgBr at a sufficient rate even at 25 °C. In some cases, the use of trialkylmagnesiate reagents (R_3MgLi) according to the work of *Oshima* allowed the magnesiation of less active system, such as 3-bromobenzonitrile.[30] However, a catalyzed version of the Br/Mg exchange, recently developed by *Knochel*, using 1 equivalent of LiCl, significantly broadered the range of suitable substrates for this process. [31] The mixed organometallic *i*PrMgCl·LiCl (**13**), allowed a fast Br/Mg exchange leading to the desired Grignard reagents of type **14** in high yields under mild conditions (Scheme 11).



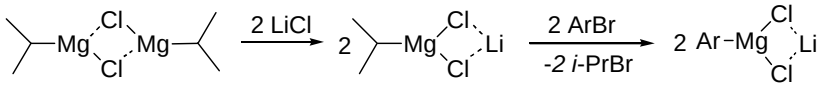
Scheme 11: LiCl-mediated Br/Mg exchange reaction of brominated aryls and heteroaryls.[31, 32]

[30] (a) Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1; (b) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem.* **2000**, *112*, 2594; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2481; (c) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333; (d) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2000**, *56*, 9601; (e) Yousef, R.I.; Rüffer, T.; Schmidt, H.; Steinborn, D. *J. Organomet. Chem.* **2002**, *655*, 111.

[31] Krasovskiy, A.; Knochel, P. *Angew. Chem.* **2004**, *116*, 3369; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

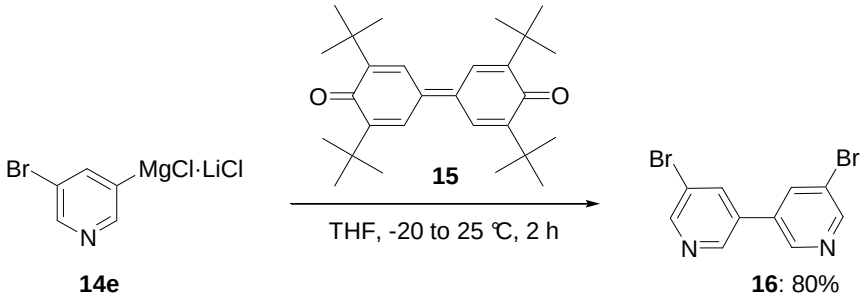
[32] Ren, H.; Knochel, P. *Chem. Commun.* **2006**, 726.

The necessity to use the stoichiometric complex **13**, leads to the postulate that the addition of LiCl breaks the aggregates of *i*-PrMgCl producing a highly reactive Grignard reagent (Scheme 12). *Knochel* has presented model calculations to correlate the structure of magnesium reagents with their reactivity in Br/Mg exchange reaction in the presence of LiCl.[17d]



Scheme 12: Catalysis of the Br/Mg-exchange reaction with LiCl.

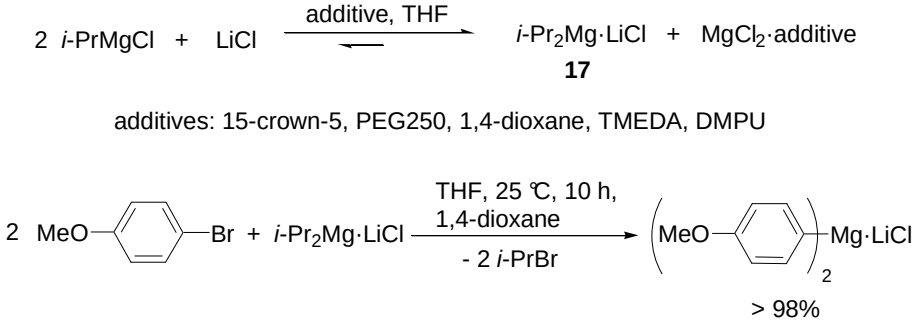
Using this catalyzed version of the Br/Mg exchange reaction, *Knochel* and *Mayr*[33] have recently reported the use of 3,3´,5,5´-tetra-*tert*-butyldiphenoquinone (**15**, Scheme 13) as an electron acceptor to allow the simple preparation of functionalized biaryls, diynes and dienes through coupling reactions of organomagnesiated reagents which are complexed with LiCl. As an example, the 5-bromopyridin-3-ylmagnesium chloride (**14e**) was coupled using **15** to lead to the corresponding bipyridine (**16**) in 80% yield (Scheme 13).



Scheme 13: Coupling of the organomagnesium reagent **14e**.

As an extension of the LiCl-mediated Br/Mg exchange reaction, the synthesis of the new Grignard reagent *i*-Pr_2Mg·LiCl (**17**)[17d] offered a new class of highly reactive exchange reagents. Using additives such as dioxane to shift the Schlenk equilibria, the reaction of **17** on electron rich aryl bromides undergo a fast conversion as shown in Scheme 14.

[33] Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5010.



Scheme 14: Preparation of *i*-Pr_2Mg·LiCl (**17**) and his reaction on 4-bromoanisole.

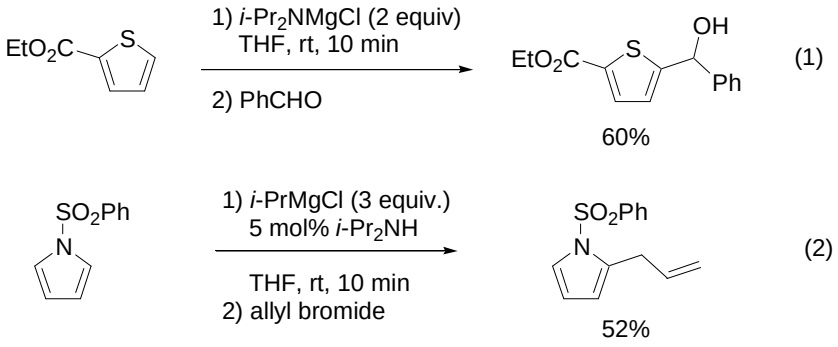
2.4. Metalation reactions with magnesium amide bases

The preparation of aryl and heteroaryl organometallics via directed metalations has found many applications in recent years, especially via the directed *ortho*-lithiation using lithium bases such as *sec*-BuLi or lithium 2,2,6,6-tetramethylpiperidide (TMPLi).[34] However, the use of lithium bases is often complicated by the undesired side reactions due to high reactivity of the products and therefore the low tolerance towards sensitive functional groups. These limitations reduce the scope of useful directing group. Magnesium amides of type R_2NMgCl, R_2NMgR or $(R_2N)_2Mg$, were developed as metalating reagents[35] to overcome these limitations, but their low kinetic basicity and low solubility have hampered more general applications. Nevertheless, interesting examples of the metalation of N-heterocyclic

[34] (a) Schlosser, M. *Angew. Chem.* **2005**, *117*, 380; *Angew. Chem. Int. Ed.* **2005**, *44*, 376; (b) Turck, A.; Plé, N., Mongin, F.; Quéguiner,G. *Tetrahedron* **2001**, *57*, 4489 (c) Schlosser, M. *Eur. J. Org. Chem.* **2001**, *21*, 3975; (d) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *Org. Lett.* **2005**, *7*, 2305; (e) Plaquevent, J.-C.; Perrard, T. ; Cahard, D. *Chem. Eur. J.* **2002**, *8*, 3300; (f) Chang, C.-C.; Ameerunisha, M. S. *Coord. Chem. Rev.* **1999**, *189*, 199; (g) Clayden, J. *Organolithiums: Selectivity for Synthesis* (Hrsg.: J. E. Baldwin, R. M. Williams), Elsevier, **2002**; (h)*"The Preparation of Organolithium Reagents and Intermediates"*: Leroux, F., Schlosser, M.; Zohar, E.; Marek, I. *Chemistry of Organolithium Compounds* (Hrsg.: Z. Rappoport, Marek, I.), Wiley, New York, **2004**, Chapt.1, S. 435; (i) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; (j) Queguiner, G.; Marsais , F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187; (k) Veith, M.; Wieczorek, S.; Fries, K.; Huch, V. *Z. Anorg. Allg. Chem.* **2000**, *626*, 1237.

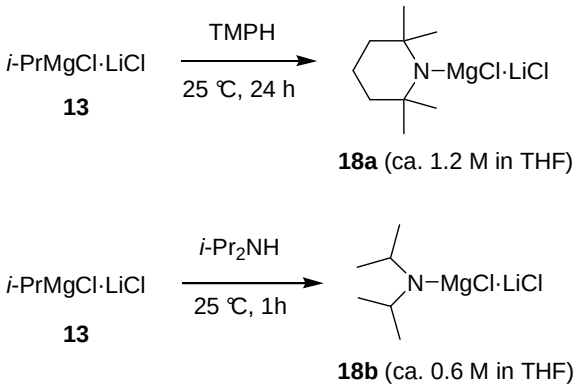
[35] (a) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; (b) Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, *7*, 3430; (c) Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295; (d) Kobayashi, K.; Kitamura, T.; Nakahashi, R.; Shimizu, A.; Yoneda, K.; Konishi, H. *Heterocycles* **2000**, *53*, 1021; (e) Westerhausen, M. *Dalton Trans.* **2006**, 4768. (f) Zhang M.-X. ; Eaton, P. E. *Angew. Chem. Int. Ed.* **2002**, *41*, 2169; (g) Kondo, Y.; Akihiro Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans.***1996**, *1*, 2331; (h) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.***1989**, *111*, 8016; (i) Eaton, P. E.; Zhang, M.-X.; Komiya C.-G. N.; Yang, Steele, I.; Gilardi, R. *Synlett.* **2003**, 1275; (j) Eaton, P. E.; Martin, R. M. *J. Org.* Chem. **1988**, 53, 2728; (k) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1*. **2001**, 442.

compounds, using excess (2-3 equiv) of Hauser bases (R_2NMgCl), showed selective deprotonations tolerating an ester function (Scheme 15).[36]



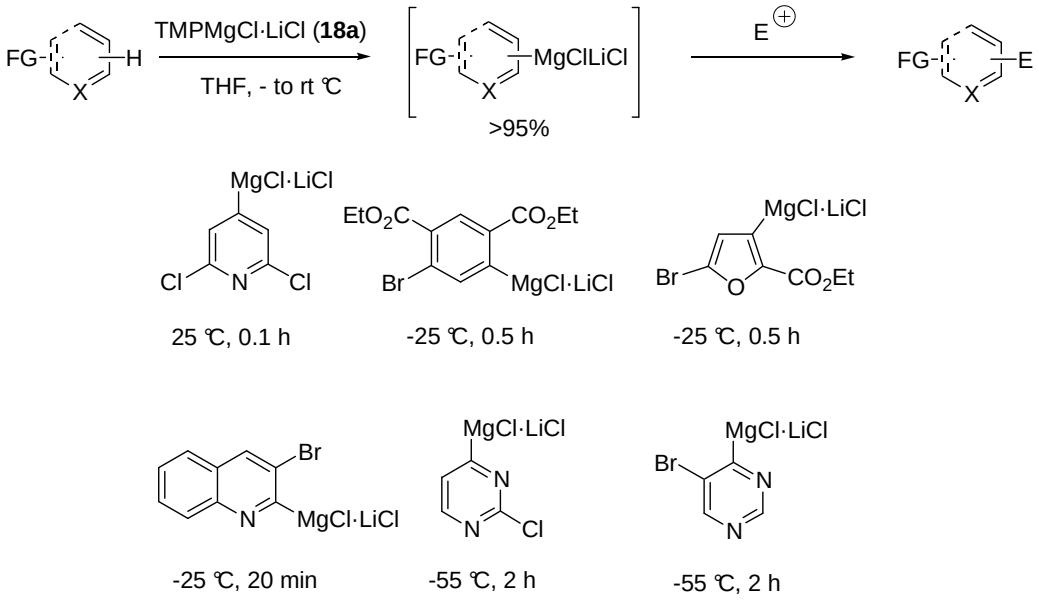
Scheme 15: Selective magnesiation of N-heterocycles.

Recently, a major improvement of this chemistry was achieved in our group when *Krasovskiy*, *Krasovskaya* and *Knochel* discovered the mixed Mg/Li-bases of type $R_2NMgCl{\cdot}LiCl$ (**18a** and **18b**, Scheme 16).[37] This new generation of bases possesses an excellent kinetic basicity, a very good solubility and excellent thermal stability allowing their long term storage in THF solution. TMPMgCl·LiCl (**18a**) used in nearly stoichiometric amounts permits the magnesiation of various aromatics and heteroaromatics with excellent regioselectivity at practical temperatures (Scheme 17).



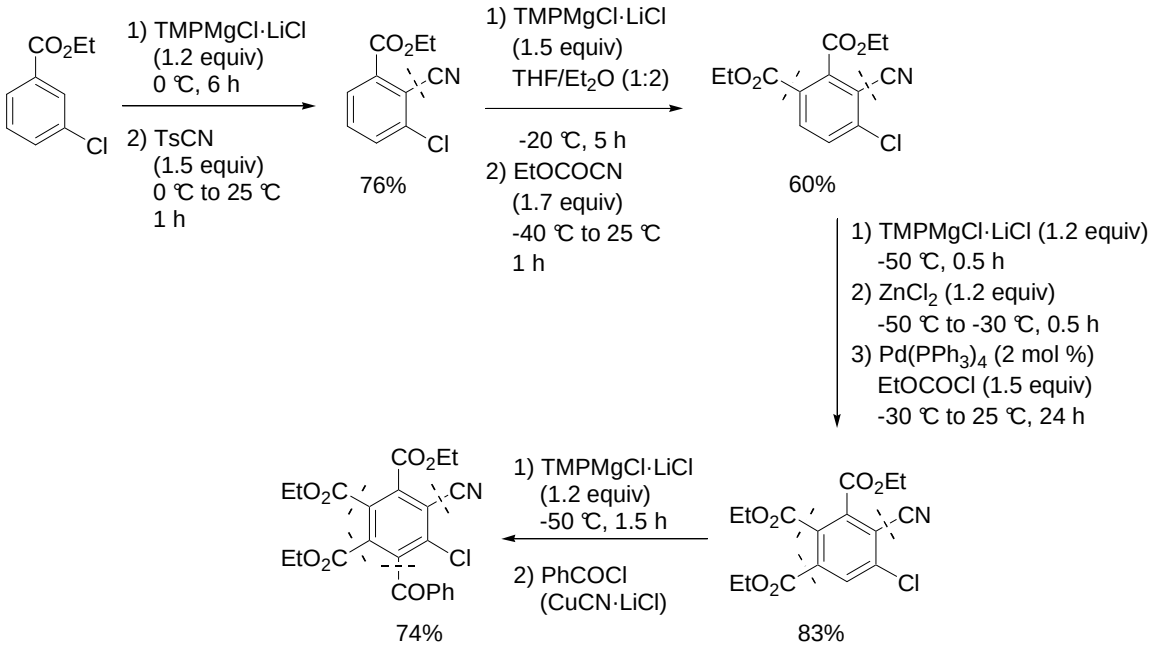
Scheme 16: Preparation of Mg/Li amide bases of type $R_2NMgCl{\cdot}LiCl$.

[36] (a) Kondo, Y.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331; (b) Dinsmore, A.; Billing, D. G.; Mandy, K. ; Michael, J. P.; Mogano, D.; Patil, S. *Org. Lett.* **2004**, *6*, 293.
[37] Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.



Scheme 17: Direct magnesiation of functionalized aryls and heteroaryls using **18a**.[37,38]

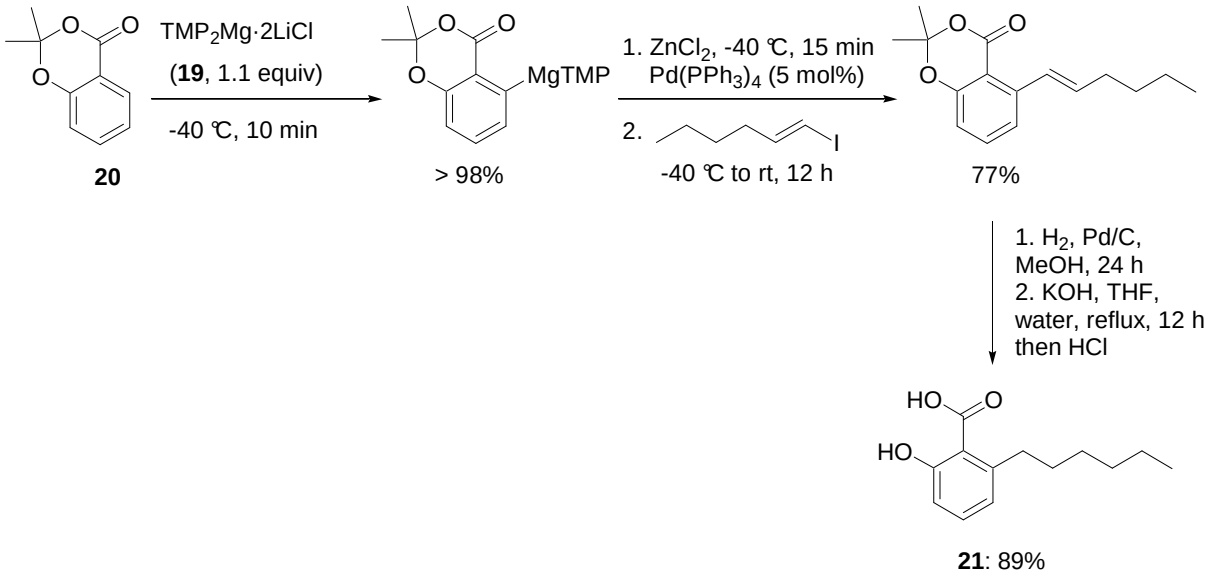
The successive direct magnesiations of highly functionalized aromatics bearing an ester, a nitrile or a ketone has been achieved using TMPMgCl·LiCl (**18a**, Scheme 18).[39] After quenching with electrophiles, highly functionalized and polysubstituted benzenes were obtained (Scheme 18).



Scheme 18: Successive magnesiations of 3-chlorobenzoate.

[38] Kienle, M.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, 1272.
[39] Lin, W.; Baron, O. *Org. Lett*. **2006**, *8*, 5673.

After the discovery of TMPMgCl·LiCl (**18a**), the chemistry of the corresponding magnesium bisamides complexed with lithium chloride, $TMP_2Mg·2LiCl$ (**19**), was further developed by *Clososki*, *Rohbogner* and *Knochel*.[40] This new class of bases displays a superior metalation power allowing the magnesiation of various polyfunctional aromatic or heteroaromatic reagents bearing functional groups such as an ester, a nitrile or a ketone. The efficiency of $TMP_2Mg·2LiCl$ (**19**) was demonstrated by the *ortho*-deprotonation of dimethyl-1,3-benzodioxan-4-one (**20**, Scheme 19) which led after the Negishi cross-coupling and hydrogenation, followed by the cleavage of the dioxanone, to 6-hexylsalicylic acid (**21**), a natural product found in essential oil of *Pelargonium sidoides* DC.



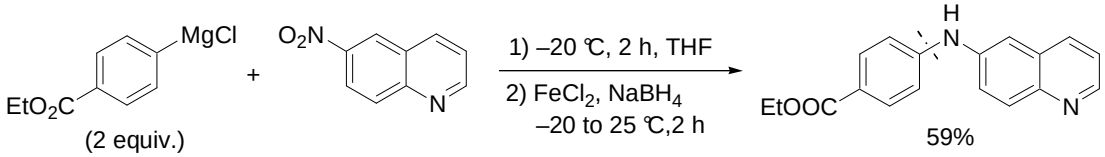
Scheme 19: Preparation of 6-hexylsalicylic acid (**21**) via the regioselective deprotonation using $TMP_2Mg·2LiCl$ (**19**).

2.5. Recent applications of Grignard reagents for a C-N bond formation

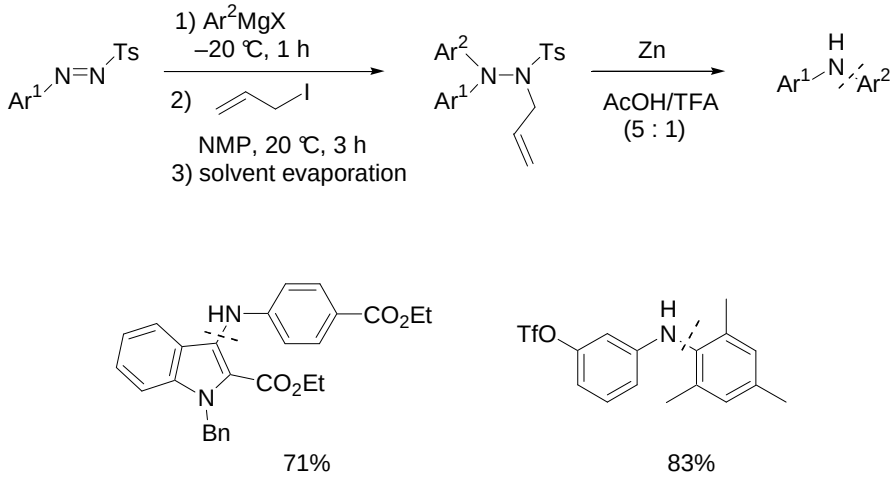
Functionalized aromatic and heteroaromatic amines are important building blocks for the synthesis of pharmaceuticals.[41] Beside, the transition metal-catalyzed amination protocols[6] using palladium, copper or nickel, the reaction of aromatic nitro compounds with Grignard reagents have proven to be a versatile alternative for the synthesis of functionalized

[40] Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem.* **2007**, *119*, 7825; *Angew. Chem. Int. Ed.* **2007**, *46*, 1.
[41] Czarnik, A. W. *Acc. Chem. Res*. **1996**, *29*, 112 and references cited therein.

diarylamines.[42] In this reaction the aromatic organometallic species acts as a nucleophile, while the nitroarene plays the role of an electrophile. Even heterocycles bearing a nitro group can be transformed successfully to the corresponding heterocyclic amines (Scheme 20). Alternatively, arylazo tosylates can be used in such electrophilic amination reactions (Scheme 21).[43]



Scheme 20: Electrophilic amination using a nitroarene and a Grignard reagent.

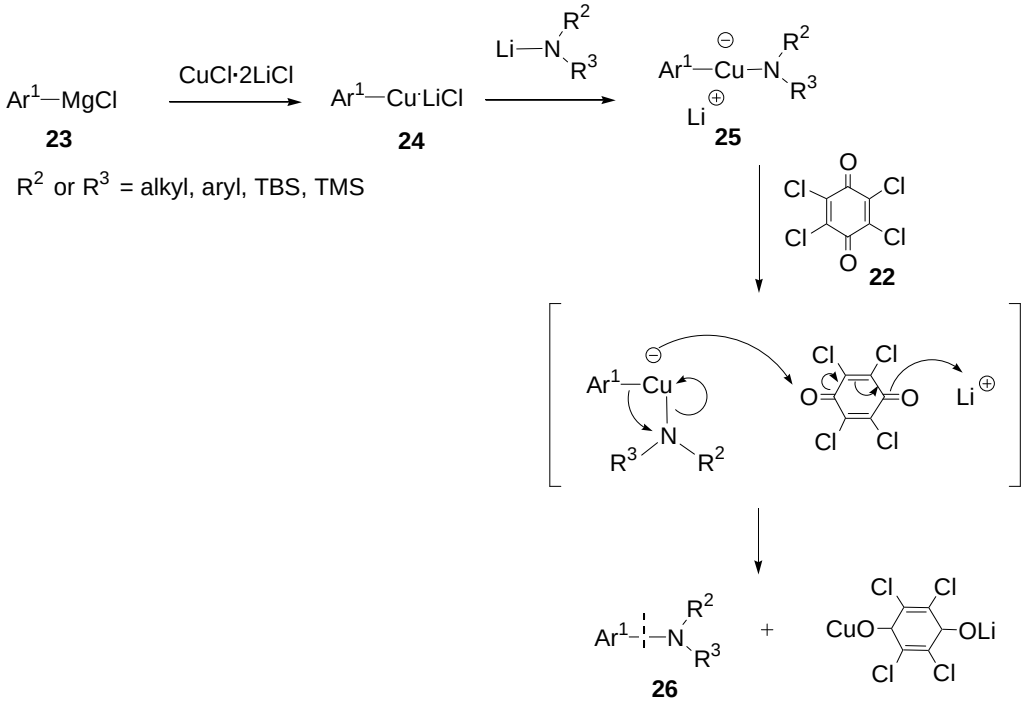


Scheme 21: Electrophilic amination using an aryzalo tosylate and a Grignard reagent.

The oxidative amination reaction of amidocuprates is a further complement to transition metal-catalyzed and electrophilic amination reactions. Previous studies by *H. Yamamoto, K. Maruoka*[44] and *A. Ricci* [45] focused on the oxidative coupling of lithium amidocuprates, leading to amines by molecular oxygen. Since the use of gaseous oxygen is not convenient for large-scale industrial reactions, *del Amo*, *Dubbaka*, *Krasovskiy* and *Knochel* developed a

[42] (a) Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390; (b) Ono, A.; Sasaki, H.; Yaginuma, F. *Chem. Ind. (London)* **1983**, 480.
[43] (a) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 897; (b) Sinha, P.; Knochel, P. *Synlett* **2006**, 3304.
[44] Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739.
[45] (a) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620; (b) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677; (c) Canè, F.; Brancaleoni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, 545; (d) Bernardi, P.; Dembech, P.; Fabbri, G. ; Ricci, A.; Seconi, G. *J. Org. Chem.* **1999**, *64*, 641.

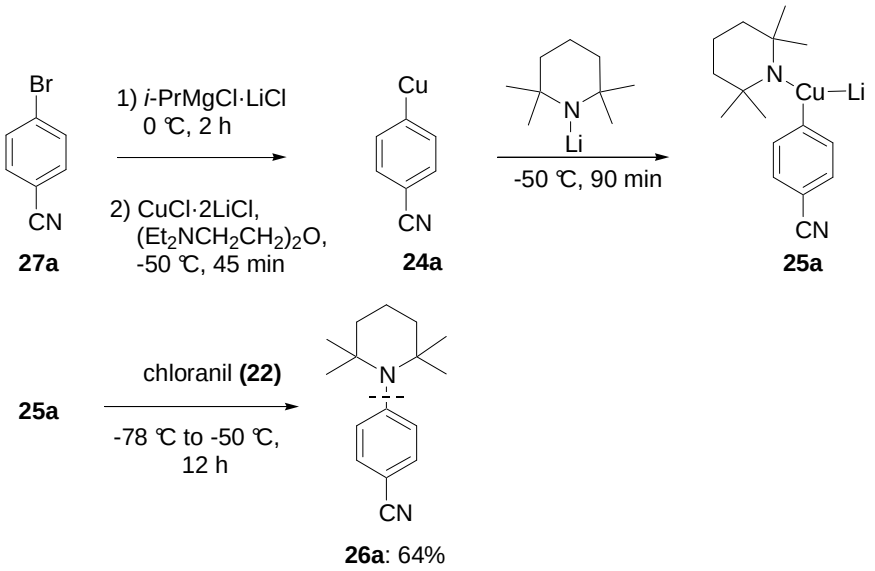
preparation of amines via the oxidative coupling of polyfunctional aryl and heteroaryl amidocuprates mediated by solid tetrachlorobenzoquinone (chloranil (**22**), Scheme 22).[38, 46] The transmetalation of Grignard reagent **23** with CuCl·2LiCl,[47] soluble in THF, provided the copper reagent **24**, which after treatment with a lithium amide resulted in the lithium amidocuprate of type **25**. This intermediate could be oxidized with chloranil (**22**) affording desired amines **26** (Scheme 22).



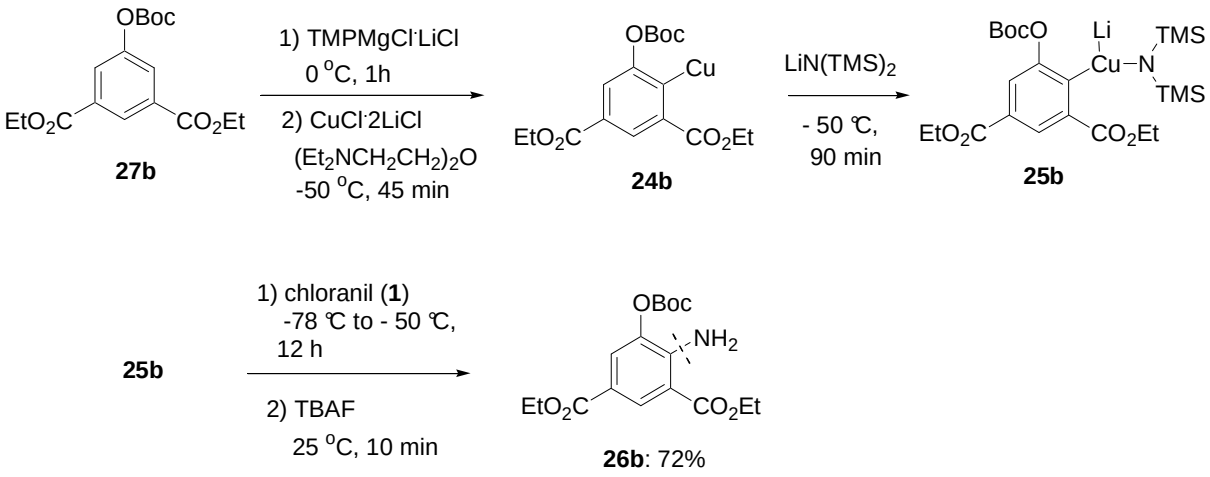
Scheme 22: Preparation of amines of type **26** via an oxidative coupling of amidocuprates using chloranil (**22**).

This method is well-suited for the preparation of primary, secondary and tertiary aromatic and heterocyclic amines. It tolerates a broad range of functional groups such an ester, a cyanide, a halide, and is not hampered by steric hindrance (Schemes 23 and 24). Using LiHMDS as lithium amide, a primary arylamine could be prepared as shown by the synthesis of the aminated isophtalic diester **26b** (Scheme 24).

[46] del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.
[47] $(Et_2NCH_2CH_2)_2O$ was added to CuCN·2LiCl. This additive was found to improve the yield of the amination reaction.



Scheme 23: Preparation of the sterically hindered tertiary amine **26a** through an oxidative amination with TMP-Li using chloranil (**22**).

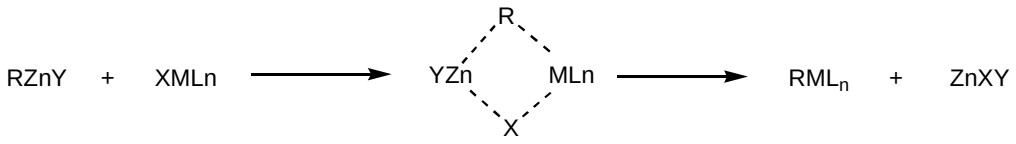


Scheme 24: Preparation of the primary arylamine **26b** through an oxidative amination with the cuprated polyfunctional aryl derivative **24b** and LiHMDS using chloranil (**22**).

3. Direct Preparation and Use of Organozincated Aryl and Heteroaryl Compounds.

3.1 Introduction

Organozinc reagents are known for more than 150 years, since the preparation of diethylzinc by *Frankland* in 1849 in Marburg (Germany).[48] These organometallic reagents were used to form new carbon-carbon bonds until *Grignard* [3] discovered in 1900 a convenient preparation of organomagnesium compounds. Over the years, some reactions were conventionally performed with zinc organometallics such as the Reformatsky reaction[49] or the Simmons-Smith cyclopropanation.[50] The intermediate organometallics (zinc enolate and zinc carbenoid) were more easy to handle and more selective than the corresponding magnesium species. In 1943, *Hunsdiecker* has shown that organozinc reagents bearing a long carbon chains terminated by an ester function can be prepared, [51] but it was only recently that *Knochel* has demonstrated the synthetic potential of these reagents.[52] Organozinc compounds are prone to undergo a broad range of transmetalations. This is due to the presence of empty low-lying *p*-orbitals which readily interact with the *d*-orbitals of many transition metal salts, leading to highly reactive intermediates such as organocopper[53] or palladium compounds[54] (Scheme 25).



Scheme 25: Transmetalation of organozincs reagents

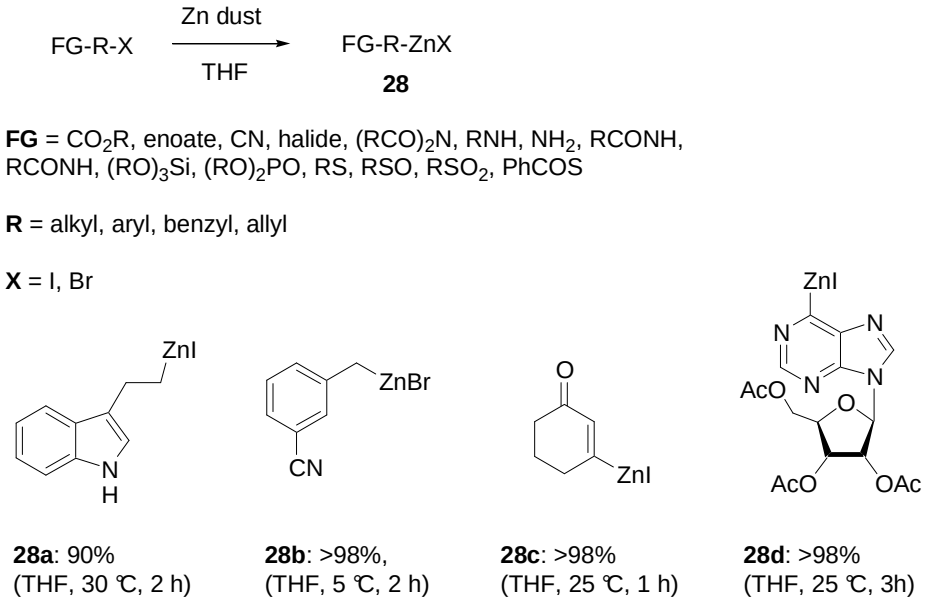
Moreover, the highly covalent character of the carbon-zinc bond makes organozinc species stable at the temperatures where the corresponding organomagnesiums and organolithiums

[48] Frankland, E. *Liebigs Ann. Chem*. **1849**, *71*, 171 and 173.
[49] (a) Reformatsky, S. *Chem. Ber*. **1887**, *20*, 1210; **1895**, *28*, 2842; (b) Fürstner, A. *Angew. Chem. Int. Ed*. **1993**, *32*, 164.
[50] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323; (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc*. **2003**, *125*, 2341.
[51] Hunsdiecker, H.; Erlbach, H., Vogt, E. **1942**, German patent 722467; *Chem. Abstr*. **1943**, *37*, 5080.
[52] (a) Knochel, P.; Singer, R. D. *Chem. Rev*. **1993**, *93*, 2117; (b) Knochel, P.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
[53] (a) Knochel, P. *Synlett* **1995**, 393; (b) Knochel, P.; Vettel, S.; Eisenberg, C. *Applied Organomet. Chem*. **1995**, *9*, 175; (c) Knochel, P.; Jones, P. *Organozinc reagents. A Practical Approach*, Oxford University Press, **1999**; (d) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React*. **2001**, *58*, 417; (e) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed*. **2000**, *39*, 4415.
[54] (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc*. **1980**, *102*, 3298; (b) Kobayashi, M.; Negishi, E. *J. Org. Chem*. **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res*. **1982**, *15*, 340.

undergo decomposition. Such combination of the high tolerance toward functionalities, facile transmetalation to many transition metal complexes and an excellent stability makes organozincs extremely valuable reagents for organic synthesis. The reactivity of organozinc halides strongly depends on the electronegativity of the carbon attached to zinc (alkynyl < alkyl < alkenyl ≤ aryl <benzyl< allyl). A stabilization of the negative carbanionic charge by inductive or mesomeric effects leads to a more ionic carbon-zinc bond and to a higher reactivity. The direct preparation of organozinc compounds can be achieved by an insertion of zinc dust into organic halides or by an I/Zn exchange of iodinated alkyl and aryl substrates.

3.2 The direct insertion of zinc metal into aryl and heteroaryl halides

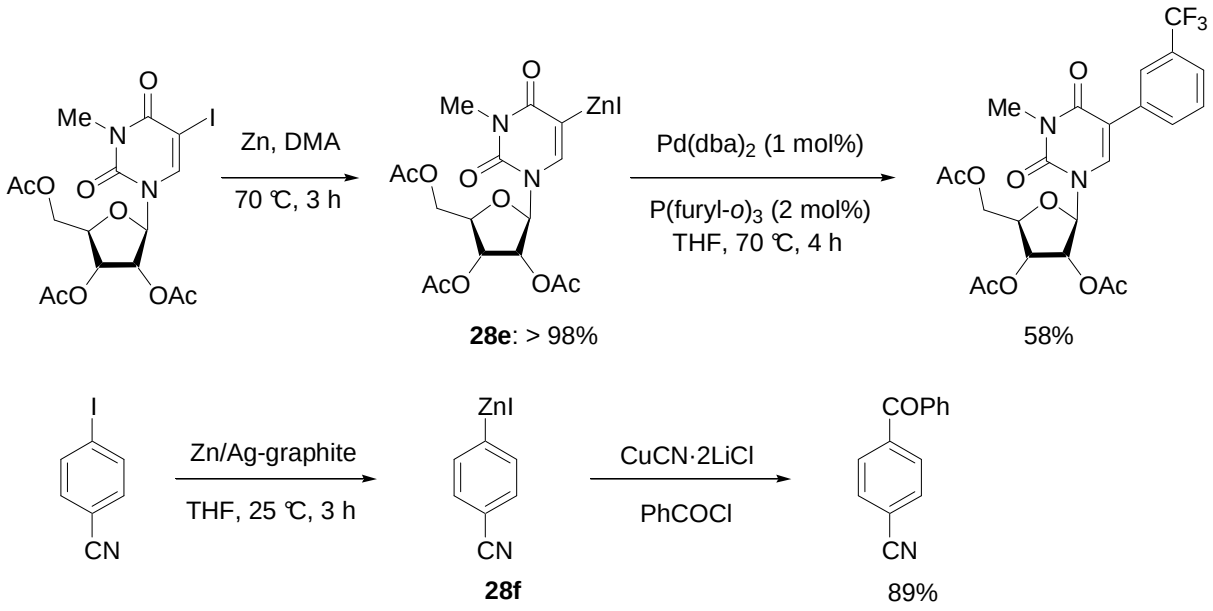
The oxidative addition of zinc dust into organic halides is an usual method for the preparation of functionalized organozinc halides, especially iodides (**28**, Scheme 26). This method of preparation tolerates several functionalities and is sensitive to the reaction conditions (solvent, concentration, and temperature), the nature of the halide and the method of zinc activation (Scheme 26).



Scheme 26: Direct insertion of zinc into functionalized organic halides.

As magnesium, zinc slowly oxidizes in air and is covered by an oxide layer. An efficient activation procedure consists of treating zinc with 1,2-dibromoethane in THF (reflux, 1-2 min), followed by the addition of TMSCl (1-2 mol%; reflux, 1 min).[2a, 52a, 53d] *Rieke* zinc

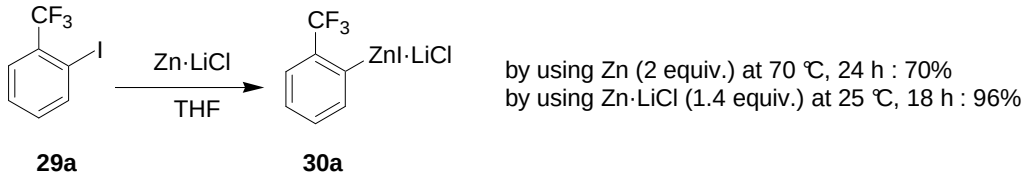
(Zn*)[55] prepared by the reduction of zinc chloride with lithium naphthalenide in THF, offers a second alternative to obtain highly reactive zinc. Over the last 20 years, using these two methods, a wide range of functionalized organozinc iodides was obtained including functionalized alkyl, allylic or benzylic compounds.[2] For instance, using activated zinc dust in THF, *Knochel* described the successful insertion into a non protected 3-(2-iodoethyl)indole,[56] functionalized benzylic[57] and alkenyl[58] iodides and, interestingly, into an iodinated nucleoside[59] (**28a-d**, Scheme 26). In general, the zinc insertion into a sp^2 C-I(Br) bond is more difficult than into a sp^3 C-I(Br) bond and requires either the use of polar solvents[60] or the use of *Rieke* zinc (Zn*). *Knochel* described the insertion into a 5-iodouridine derivative **28e** using activated zinc in the presence of DMA (Scheme 27). *Fürstner*, *Singer* and *Knochel* showed direct insertion into a reactive aryl bromide such as *p*-bromobenzonitrile[61] using Zn* (**28f**, Scheme 27).



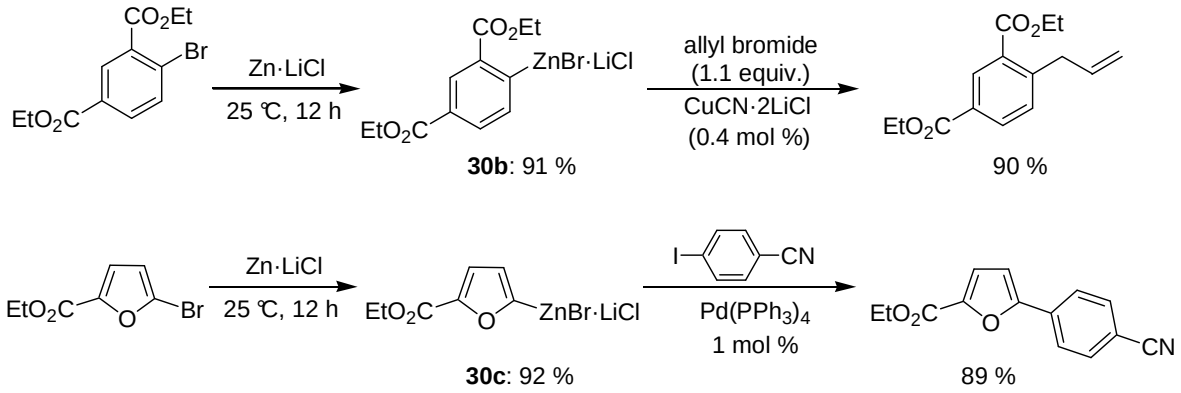
Scheme 27: Zinc insertion into sp^2 C-iodine bond.

[55] (a) *Organozinc Reagents*, Editors: P. Knochel, P. Jones, Oxford University Press, New York, **1999**; (b) Rieke, R. D.; Li, P. T.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323; (c) Arnold, R. T.; Kulenovic, S. T.; *Synth. Commun.* **1977**, *7*, 223.
[56] Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem*. **1991**, *56*, 5974.
[57] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem*. **1988**, *53*, 2390.
[58] Knochel, P.; Rao, C. J. *Tetrahedron* **1993**, *49*, 29.
[59] (a) Stevenson, T. M.; Prasad, A. S. B.; Citineni, J. R.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8375; (b) Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237.
[60] (a) Tagaki, K.; Hayama, N.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691; (b) Tagaki, K. *Chem. Lett.* **1993**, 469; (c) Tagaki, K.; Shimoishi, Y.; Sasaki, K. *Chem. Lett.* **1994,** 2055; (d) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.
[61] Fürstner, A.; Singer, R.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 1047.

Since the activity of Rieke Zn decreases with time, a new practical zinc insertion procedure was invented by *Krasovskiy, Malakhov, Gavryushin* and *Knochel* in 2006.[62] They found that the addition of LiCl during the insertion of zinc dust into organic bromides or iodides leads to a spectacular rate increase as shown by the example of *ortho*-trifluoromethylphenyl iodide (**29a**) providing the corresponding organozinc iodide at 25 °C (**30a**, Scheme 28). This method allows a simple, high-yielding preparation of a broad range of functionalized aryl and heteroarylzinc reagents such as the zincated diester **30b** and the furylzinc reagent **30c** (Scheme 29).



Scheme 28: The effect of LiCl on the zinc insertion into *ortho*-trifluoromethylphenyl iodide (**29a**).

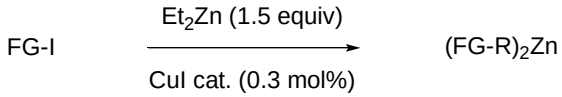


Scheme 29: Direct zinc insertion in the presence of LiCl into aromatic and heterocyclic bromides.

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

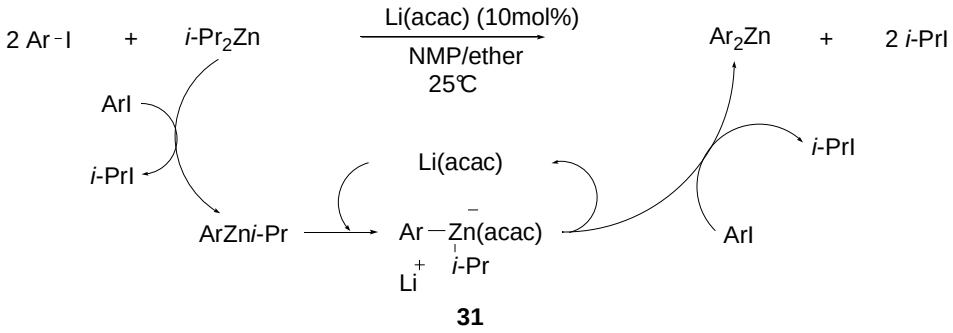
3.3 The iodine/zinc exchange reaction

The halide/zinc exchange allows the preparation of diorganozincs, which are more reactive than organozinc halides and are extensively used in asymmetric synthesis.[52a, 63] The I/Zn exchange reaction is a practical way for preparing polyfunctional diorganozincs $(FG–R)_2Zn$.[64] A wide range of polyfunctional primary alkyl iodides undergo this exchange if treated neat with diethyl zinc in the presence of a catalytic amount of copper(I) iodide or copper(I) cyanide (Scheme 30).[65] This reaction can also be catalyzed by Pd-complexes.[66]



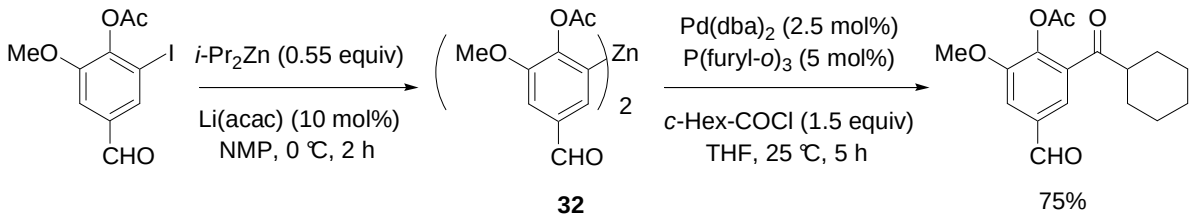
Scheme 30: Copper-catalyzed I/Zn exchange.

This method provides a general access to functionalized dialkylzincs but fails in the case of aromatic iodides. For performing an I/Zn exchange on aryl iodides, *Knochel* showed in 2004[67] that the addition of catalytic amounts of Li(acac) to an aryl iodide and *i*-Pr_2Zn allows the I/Zn exchange with the formation of Ar_2Zn and *i*-PrI. The "ate" intermediate **31** (Scheme 31) is similar to the one during the Br/Mg exchange catalyzed by LiCl.[17d, 31] This method affords an easy synthesis of functionalized diarylzinc derivative such as **32** bearing an aldehyde function (Scheme 32).



Scheme 31: Li (acac) catalyzed synthesis of diarylzincs.

[63] Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833.
[64] Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353.
[65] (a) Rozema, M. J.; Achyutha Rao, S.; Knochel, P. *J. Org. Chem*. **1992**, 57, 1956; (b) Rozema, M. J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett*. **1993**, *34*, 3115.
[66] Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc*. **1993**, *115*, 7027.
[67] Kneisel, F. F; Dochnahl, M.; Knochel, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 1017.



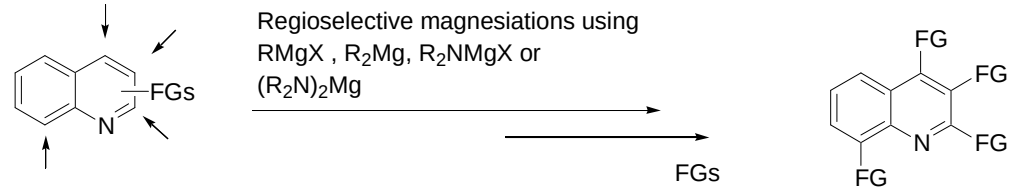
Scheme 32. Functionalized diarylzinc bearing an aldehyde function.

4. Objectives

We plan in this work to apply the newly developed preparations of organomagnesium and zinc reagents for the synthesis of various N-heterocyclic magnesium and zinc intermediates. Our aim was to perform successive selective functionalizations of N-heterocycles, and apply our methodology for the synthesis of biologically active compounds.

In a first project, our research was mainly focused on the functionalizations of quinolines, protected uracils, and purines, which are the classes of N-heterocycles where metalation and subsequent functionalization are still unexplored.
More precisely, our objectives were:

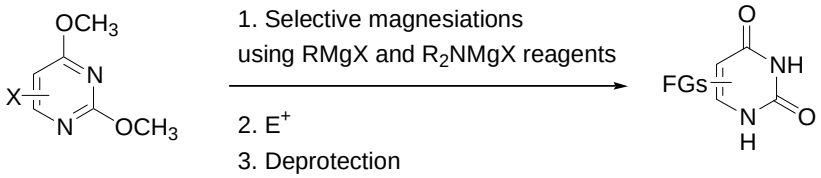
- The magnesiations and functionalizations of quinoline cores by the combination of selective Br/Mg exchanges as well as direct deprotonations (Scheme 33).



FG= -Br, -COOR, COR, -CN, -CHOHR, -OR, -NR_2, -SR, -Ar

Scheme 33: Multiple regioselective functionalizations of quinolines via magnesiations.

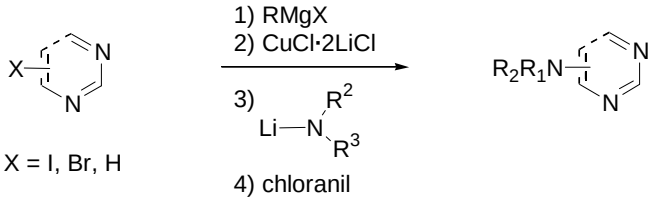
- The selective magnesiation of 2,4-dimethoxypyrimidine as a synthetic route to polyfunctionalized protected uracils (Scheme 34).



FG or E = -Br, -I, -COOR, COR, -CN, -CHOHR, -OR, -NR_2, -SR, -Ar
X = H, I, Br, Cl

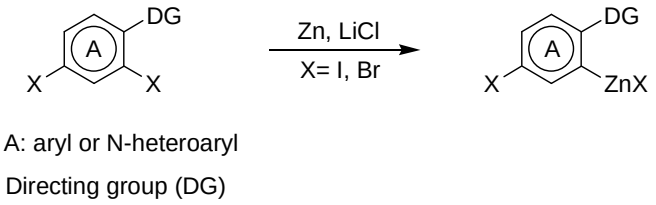
Scheme 34: Chemo- and regio-selective functionalization of uracil derivatives.

- The aminations of DNA and RNA units such as protected uracils, pyrimidines and purines, via selective magnesiations and cupration followed by the addition of lithium amides and the oxidative coupling with chloranil (Scheme 35).



Scheme 35: Amination of DNA and RNA units via cuprated purine and pyrimidine derivatives.

In the second project, it was planned to study the insertion of zinc dust in the presence of LiCl into polyhalogenated aryls and N-heterocycles, in order to access new zincated aromatic and heterocyclic compounds (Scheme 36).



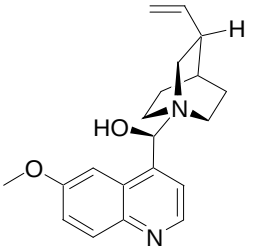
Scheme 36: LiCl-mediated regioselective zinc insertion of aryl and heteroaryl compounds.

B: Results and Discussion

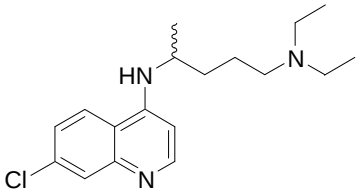
1. Functionalizations of Quinoline Moieties *via* Chemo- and Regioselective Magnesiations.

1.1 Introduction

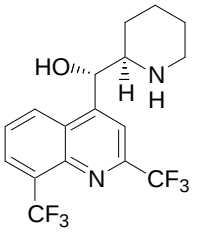
The functionalization of quinoline and its derivatives is a matter of great interest, since the basic structure of many antimalarial drugs is derived from quinine **33a** (Scheme 37). Quinine is the active ingredient of the bark of Cinchona tree, which has been used against malaria since the early 17th century. In 1820, quinine (**33a**) was isolated and replaced the crude bark for the treatment of malaria. It was of the first pure chemical compounds used as a drug. In the next century, various antimalarial drugs have been developed, including chloroquine **33b** and mefloquine **33c** (Scheme 37).[68]



33a: quinine



33b: chloroquine

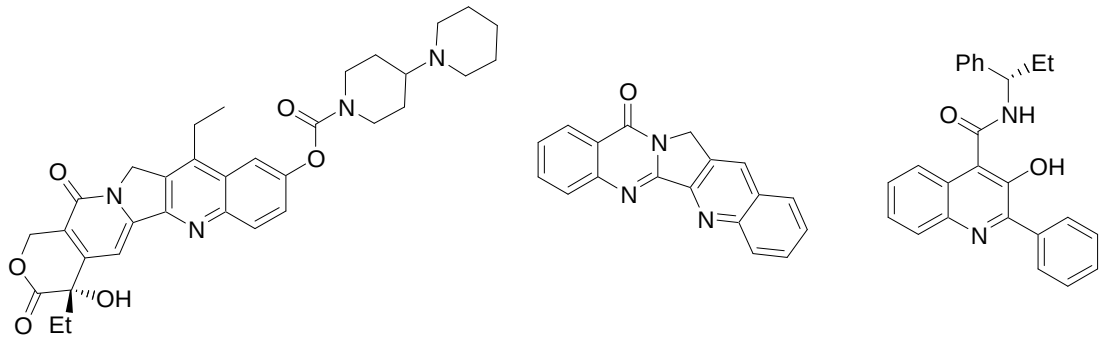


33c: mefloquine

Scheme 37: Quinine derived antimalarial drugs.

There is still an urgent need for the rapid development of an effective, safe and affordable chemotherapeutics against malaria in which the functionalization of quinoline and its derivatives would play an important role. Nowadays, the quinoline moiety is not only present as a substructure of the drugs for treatment of parasitic infections, but is also present in antitumor agents such as irinotecan (**33d**),[69] in P-selectin antagonists like luotonin A (**33e**),[70] or in potential NK3 receptor antagonists such as talnetant (**33f**)[71] (Scheme 38).[72]

[68] Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5274.
[69] Duffour, J.; Gourgou, S.; Desseigne, F.; Debrigode, C.; Mineur, L.; Pinguet, F.; Poujol, S.; Chalbos, P.; Bressole, F.; Ychou, M. *Cancer Chemotherapy and Pharmacology*. **2007**, *60*, 283.
[70] (a) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097; (b) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem*. **2007**, *72*, 6270.
[71] Elliott, J. M.; Carling, R. W.; Chambers, M.; Chicchi, G. G.; Hutson, P. H.; Jones, A. B.; MacLeod, A.; Marwood, R.; Meneses-Lorente, G.; Mezzogori, E.; Murray, F.; Rigby, M.; Royo, I.; Russell, M. G. N.; Sohal, B.; Tsao, K. L.; Williams, B. *Bioorg. Med. Chem Lett*. **2006**, *16*, 5748.
[72] Kaila, N.; Janz, K.; Debernardo, S.; Bedard, P. W.; Camphausen, R., T.; Tam, S.; Tsao, D. H. H.; Keith, J. C.; Nickerson-Nutter, C.; Shiling, A.; Young-Sciame, R.; Wang, Q. *J. Med. Chem*. **2007**, *50*, 21.



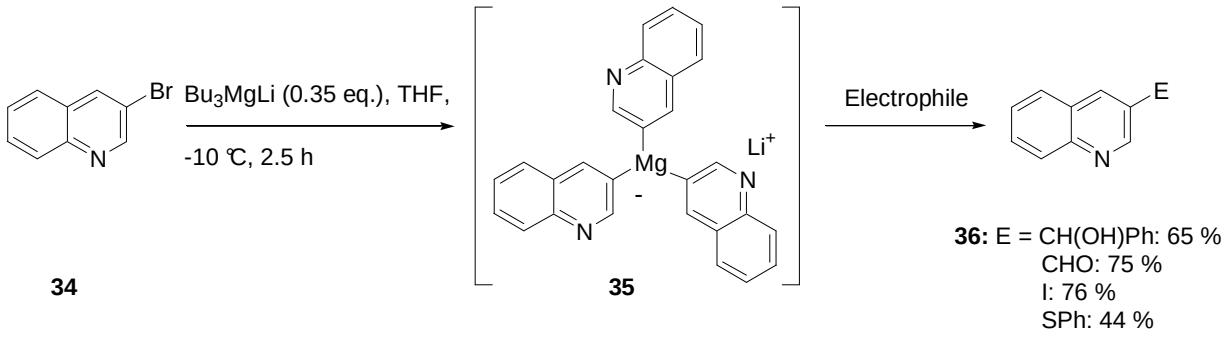
33d: irinotecan **33e**: luotonin A **33f**: talnetant

Scheme 38: Drugs containing the quinoline skeleton.

1.2 Functionalization of quinolines using selective Br/Mg exchange reactions

1.2.1 Functionalization of quinolines using halogen/metal exchanges

Quéguiner[73] has studied an exchange on 3-bromoquinoline (**34**) with reagents such as *i*-PrMgCl, *t*-BuMgCl, *i*-Pr_2Mg and *i*-PrTMPMg, but the corresponding 3-quinolylmagnesium derivatives could not be obtained. Due to the low LUMO energy, quinoline is prone to a nucleophilic attack, and the addition of a Grignard reagent to the quinoline ring was favoured

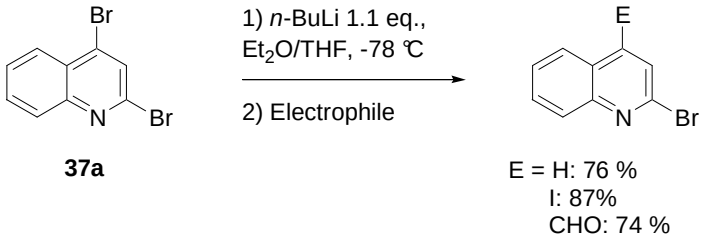


Scheme 39: Functionalization *via* lithium tri(quinolyl)magnesates shown for 3-bromoquinoline (**34**).

over the exchange reaction. *Quéguiner* could overcome these problems by treating the monobrominated quinoline **34** with Bu_3MgLi in THF at –10 °C to generate the corresponding lithium tri(quinolyl)magnesates **35** (Scheme 39). The resulting organomagnesium derivative

[73] Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.*, **2003**, *44*, 2033.

was quenched with various electrophiles, furnishing monofunctionalized quinolines of type **36**. Using the same method, the functionalizations at C4 and C2 positions were also studied by this group, providing monofunctionalized quinolines in moderate yields.[73] *Comins* achieved the functionalization at the C4-position by a regioselective Br/Li exchange reaction of 2,4-dibromoquinoline (**37a**).[74] When **37a** is treated with *n*-BuLi at –78 °C only the 4-lithiated species is observed (Scheme 40).



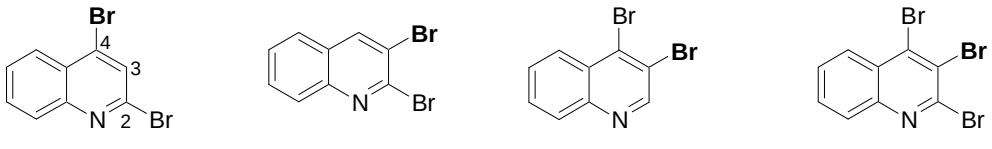
37a

Scheme 40: Regioselective bromine/lithium exchange on 2,4-dibromoquinoline (**37a**).

1.2.2 Regioselective Br/Mg exchange on di- and tribrominated quinolines

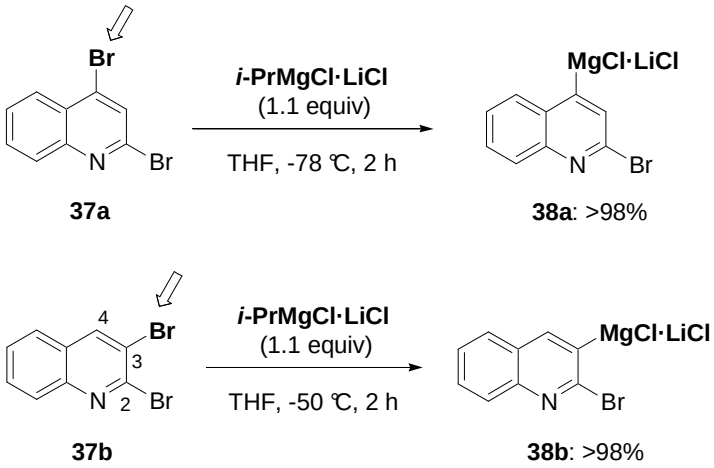
The Br/Mg exchange reactions using *i*-PrMgCl·LiCl (**13**) allows an efficient functionalization of brominated substrates,[31] so we focused first our attention on the regioselectivity of the Br/Mg exchange on the polybrominated quinolines of type **37** (Scheme 41). A similar study was performed by *Quéguiner* in 2000 on polybrominated pyridines and the obtained regioselectivity using *i*-PrMgCl was C3>C4>>C2.[75, 76] We have tested several magnesiation reagents on quinolines of type **37** in order to obtain a complete regioselective exchange. Thus, starting from 2,4-dibromoquinoline (**37a**)[77], the addition of *i*-PrMgCl·LiCl (**13**; 1.1 equiv, -78 °C, 2 h) gave quantitatively[78] and regioselectively[79] the corresponding 4-magnesiated 2-bromoquinoline (**38a**, Scheme 42). Similarly, the reaction of 2,3-dibromoquinoline (**37b**) with *i*-PrMgCl·LiCl (**13**;1.1 equiv, -50 °C, 2 h, Scheme 42) provided the corresponding 3-magnesiated 2-bromoquinoline (**38b**, Scheme 42).

[74] D. L. Comins, J. M. Nolan, I. D. Bori, *Tetrahedron Lett.* **2005**, *46*, 6697.
[75] Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.
[76] Mallet, M.; Quéguiner, G. *Tetrahedron* **1986**, *42*, 2253.
[77] Osborne, A. G.; Buley, J. M.; Clarke, H.; Dakin, R. C. H.; Price, P. I. *J. Chem. Soc., Perkin Trans. 1*. **1993**, *22*, 2747.
[78] The completion of the Br/Mg exchange reaction was checked by GC analysis of reaction of aliquots quenched with saturated NH_4Cl (aqueous).
[79] The regioselectivity of the Br/Mg exchange reaction was checked by ^1H NMR of the crude product quenched with saturated NH_4Cl (aqueous).



37a **37b** **37c** **37d**

Scheme 41: Polybrominated quinolines of type **37** as substrates for the regioselective Br/Mg exchange reactions.



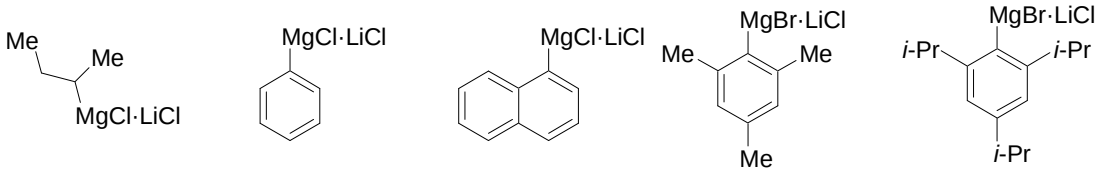
37a **38a**: >98%

37b **38b**: >98%

Scheme 42: Regioselective Br/Mg exchanges on 2,4- and 2,3-dibromoquinolines (**37a** and **37b**).

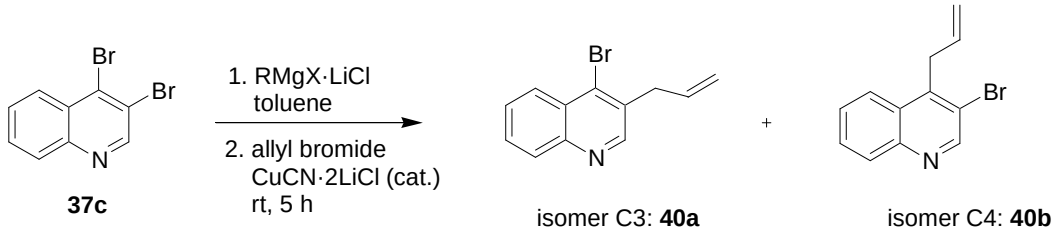
In contrast, the reactions of 3,4-dibromoquinoline (**37c**) or 2,3,4-tribromoquinoline (**37d**) with *i*-PrMgCl·LiCl (**13**) were not selective, giving a regioisomeric mixture (C3 and C4 positions) of Grignard reagents. Moreover, as the main side reaction, the addition of the Grignard at the C2 position was observed. Related selectivity problems have been observed with dibromopyridines. [59, 60] Starting from 3,4-dibromoquinoline (**37c**), more sterically hindered magnesiation reagents were tried such as *sec*-BuMgCl·LiCl (**39a**, Scheme 43), PhMgCl·LiCl (**39b**), 1-naphtylmagnesium chloride (**39c**), MesMgBr·LiBr (**39d**), and 1,3,5-triisopropylphenylmagnesium bromide (**39e**) (Scheme 44 and Table 1). The regioselectivity and the conversion of the reaction between **37c** and the Grignard reagents **39a-d** were checked by ^{1}H NMR of the crude product, obtained after quenching the reaction mixture with allyl bromide (1.5 equiv) in the presence of catalytic amount of CuCN·2LiCl (cat.)[57] (Scheme 44). Unfortunately, the lack of reactivity of the Grignard reagents **39a-d** led to long time reactions and a moderate selectivity (mixture of isomers C3 (**40a**) and C4 (**40b**), entries 1-6,

Table 1). The best regioselectivity (C3/C4, 6.5:1) was obtained with MesMgBr·LiBr (**39d**, entry 5).



39a **39b** **39c** **39d** **39e**

Scheme 43: Sterically hindered Grignard reagents.



37c isomer C3: **40a** isomer C4: **40b**

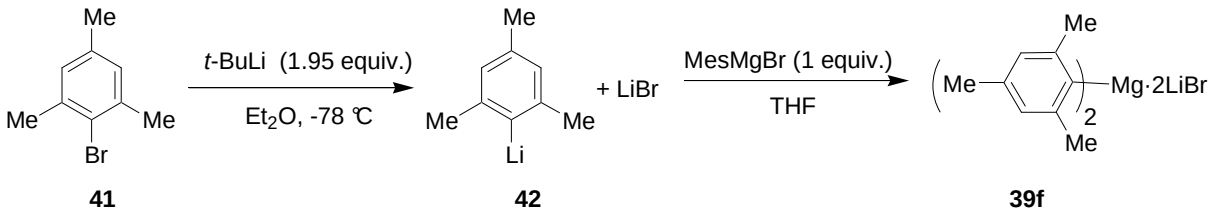
Scheme 44: Br/Mg exchange on **37c**.

Table 1: Br/Mg exchange on 3,4-dibromoquinoline (**37c**)

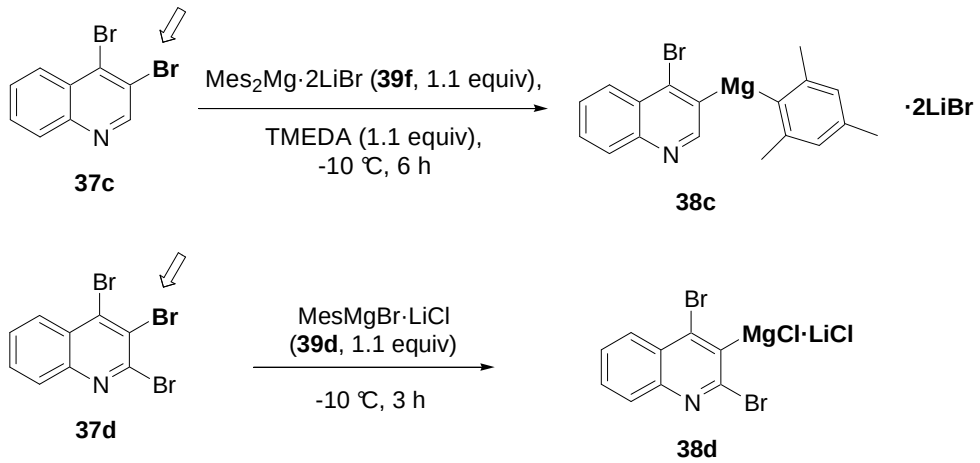
entry	Grignard reagent (1.1 equiv)	T/t [°C]/[h]	conv. (%)[a]	isomer **40a** : isomer **40b**[a]
1	*i*-PrMgCl·LiCl	-78 / 2	98	1.6 : 1
2	*sec*-BuMgCl·LiCl(**39a**)	-78 / 3	91	3.3 : 1
3	PhMgCl·LiCl(**39b**)	0 / 12	90	1.2 : 1
4	$C_{10}H_7MgCl·LiCl$ (**39c**)	0 / 24	56	2.5 : 1
5	MesMgBr·LiBr (**39d**)	0 / 24	95	6.5 : 1
6	$C_{15}H_{23}MgCl·LiCl$ (**39e**)	0-25 / 30	85	6 : 1
7	$Mes_2Mg·2LiBr$(**39f**)	-10 / 3	95	19 : 1
8	**$Mes_2Mg·2LiBr$ (39f) + TMEDA (1.1 equiv)**	**-10 / 6**	**96**	**>19 :1**

[a] The regioselectivity and the conversion were checked by ^1H NMR of the crude product obtained after quenching the reaction mixture with allyl bromide (1. 5 equiv) in presence of cat. amount of CuCN·2LiCl (cat.)

To overcome this problem, we have performed the synthesis of the corresponding dimesitylmagnesium·2LiBr complex **39f** ($Mes_2Mg·2LiBr$, Scheme 45). Diaryl or dialkyl Grignard are more reactive than their corresponding mono Grignard species.[17d] Starting from commercially available mesityl bromide (**41**), the addition of *t*-BuLi (1.95 equiv, Et_2O, -78 °C) provided the corresponding lithiated compound **42** in quantitative yield, which after evaporation of the solvent reacted with one equivalent of MesMgBr to furnish $Mes_2Mg·2LiBr$ (**39f**). The use of this new diaryl Grignard was found to be more effective, and a 19 : 1 mixture of the isomers C3 (**40a**)/C4 (**40b**) was obtained at -10 °C after 3 h (entry 7).[80] We have improved the regioselectivity by adding 1.1 equiv of TMEDA. This led to the complex **39f**·TMEDA of reduced reactivity, and furnished selectively the C3-magnesiated quinoline (entry 8, Table 1 and Scheme 46).



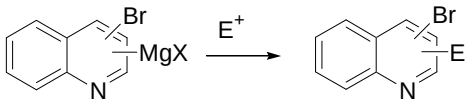
Scheme 45: Preparation of the diaryl Grignard reagent $Mes_2Mg·2LiBr$ (**39f**)



Scheme 46: Regioselective Br/Mg exchanges on 3,4-di- and 2,3,4-tri-bromoquinolines (**37c** and **37d**).

[80] 1.1 equivalent of $Mes_2Mg·2LiBr$ (**39f**) was necessary to obtain a complete conversion of the 3,4-dibromoquinoline.

Concerning the Br/Mg exchange on 2,3,4-tribromoquinoline (**37d**), the reaction of MesMgBr·LiCl (**39d** (1.1 equiv), -10 °C, 3 h) led to a completely regioselective magnesiation at C3 position providing the corresponding intermediate **38d** (Scheme 46). Compared to 3,4-dibromoquinoline, the presence of the bromine at C2 position increases the reactivity of the C3 position for the Br/Mg exchange, and MesMgBr·LiCl appeared to be sufficiently selective. The Grignard compounds **38a-d** (Schemes 42 and 46) were trapped with various electrophiles as shown in Scheme 47 and Table 2. Thus, the Grignard intermediate **38a** afforded after quenching with $PhSO_2SPh$[81] or tosyl cyanide the corresponding phenylsulfanyl quinoline (**43a**, 91%) or 4-cyano-2-bromoquinoline (**43b**, 85%) (entries 1 and 2). The transmetalation of the C4-magnesiated 2-bromoquinoline **38a** using CuCl·2LiCl (1.2 equiv, -50 °C, 1 h) followed by the addition of LiHMDS (2 equiv, -60 °C, 1 h) provided the corresponding amidocuprate which was oxidized using chloranil (1.2 equiv, -78 °C, 12 h) [46] and then deprotected with TBAF (2.0 equiv, 25 °C, 15 min) leading to the 4-amino-2-bromoquinoline (**43c**, entry 3) in 75% yield. The C3-magnesiated 2-bromoquinoline **38b** was quenched with tosyl cyanide or propionaldehyde and gave 3-cyano-2-bromoquinoline (**43d**, 84%) or the corresponding alcohol (**43e**, 76%) (entries 4 and 5 of Table 2). The C3-magnesiated 4-bromoquinoline (**38c**) provided after trapping with $PhSO_2SMe$[82] the thioether **43f** (entry 6, 79% yield). Interestingly, the diarylmagnesium reagent **38c** underwent after transmetalation with $ZnCl_2$ a Pd-catalyzed Negishi cross-coupling[54] with 4-iodobenzonitrile, and furnished the coupling product (**43g**) in 71% yield (entry 7). The reaction with C4-magnesiated 2,3-dibromoquinoline (**38d**) and tosyl cyanide afforded the corresponding quinoline **43h** (88%, entry 8). The Grignard intermediate **38d** was also quenched with ethyl cyanoformate giving the quinoline ester **43i** (90%, entry 9).

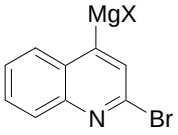
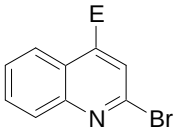
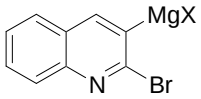
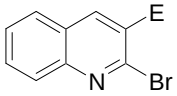
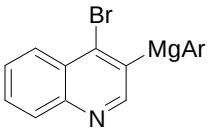
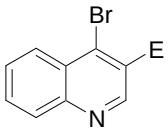
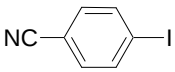
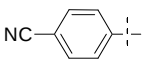
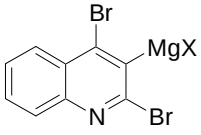
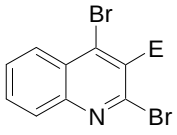


38a-d **43**

Scheme 47: Functionalization of the magnesiated quinolines of type **38a-d**.

[81] Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.
[82] Stoll, A. H.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed*. **2006**, *45*, 606.

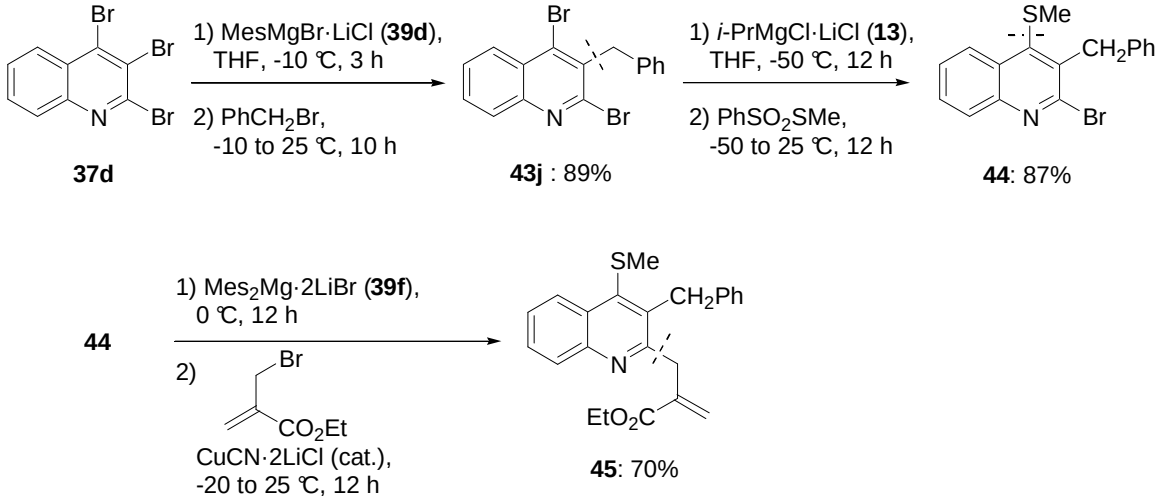
Table 2: Bromoquinolines of type **43** obtained by the reaction of brominated quinolines with an exchange Grignard reagent and an electrophile

entry	magnesium species of type **38** [a]	electrophile	product of type **43**	yield (%)[b]
	 **38a**			
1	**38a**	$PhSO_2SPh$	**43a**: E=SPh	91
2	**38a**	TsCN	**43b**: E=CN	85
3	**38a**	LiHMDS; chloranil	**43c**: E=NH_2	75[c]
	 **38b**			
4	**38b**	TsCN	**43d**: E=CN	84
5	**38b**	C_2H_5CHO	**43e**: E=CH(OH)C_2H_5	76
	 **38c**[d]			
6	**38c** [d]	$PhSO_2SMe$	**43f**: E= SMe	79
7	**38c** [d]		**43g**: E= 	71[e,f]
	 **38d**			
8	**38d**	TsCN	**43h**: E=CN	88
9	**38d**	NC-CO_2Et	**43i**: E=CO_2Et	90

[a] X = Cl·LiCl or Br·LiCl .[b] Isolated yield of analytically pure product. [c] Reaction performed after transmetalation with CuCl·2LiCl (1.2 equiv). [d] Ar = Mes·2LiBr. [e] Reaction performed after transmetalation with $ZnCl_2$. [f] 2 mol% of $Pd(dba)_2$ and 4 mol% of P-(*o*-furyl)$_3$ were added.

1.2.3 Successive regioselective Br/Mg exchanges on 2,3,4-tribromoquinoline (37d)

Remarkably, multiple selective exchanges can also be performed starting with the tribromoquinoline **37d**. Thus, the reaction of MesMgBr·LiCl (**39e**, 1.1 equiv, -10 °C, 3 h) with **37d** provided after quenching with benzyl bromide the corresponding benzylated quinoline **43j** in 89% yield (Scheme 48). This product **43j** underwent a second Br/Mg exchange reaction using **13** (1.1 equiv, -50 °C, 12 h) and led after quenching with $PhSO_2SMe$



Scheme 48: Successive regioselective Br/Mg exchange reactions at the **C3**, **C4** and **C2** positions.

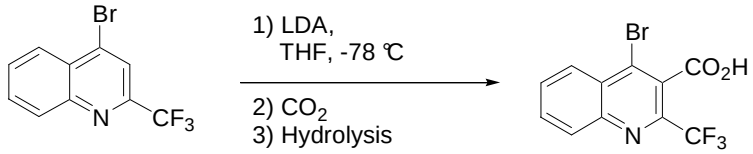
to 3,4-difunctionalized-2-bromoquinoline **44** in 87% yield. The third Br/Mg exchange was performed on **44** using $Mes_2Mg·2LiBr$ (**39f**, 1.2 equiv, 0 °C, 12 h) and a copper-catalyzed allylation with ethyl (2-bromomethyl)acrylate[83] afforded the highly functionalized quinoline **45** in 70% yield. This last exchange reaction completed the sequence of successive functionalization at C4, C3 and C2 positions.

[83] Villieras, J.; Rambaud, M. *Org. Synth*. **1988**, *66*, 220.

1.3 Functionalization of quinolines using a combination of selective magnesiations

1.3.1 Metalations of quinolines using lithium amide bases

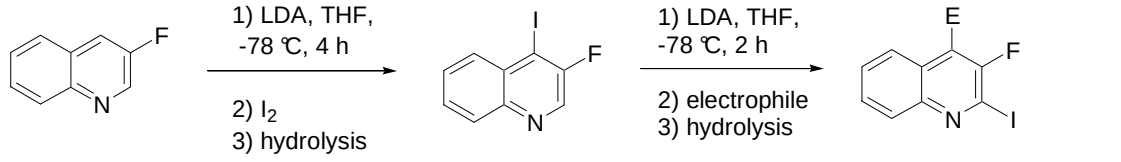
Strong bases like lithium amide reagents (LDA) can be used for the *ortho*-directed lithiation of 2-bromoquinoline.[84] *Schlosser* studied the "regioflexibility"[85] in the functionalization of polyhalogenated quinolines using LDA or LiTMP. As an example, the sequential treatment of 4-bromo-2-(trifluoromethyl)quinoline (**46**) with LDA and carbon dioxide provided the quinoline 3-carboxylic acid **47** in 88% yield (Scheme 49).



46 **47:** 88%

Scheme 49: C3 lithiation of 4-bromo-2-(trifluoromethyl)quinoline.

Quéguiner described the functionalization of the 4-position of 3-fluoroquinoline (**48**, Scheme 50) achieved by an intricate sequence of deprotonation reactions with LDA at –78 °C. The first deprotonation is followed by the trapping with iodine and leads to 3-fluoro-4-iodoquinoline (**49**) which can be then deprotonated in the 2-position and quenched with electrophiles, leading to 4-substituted dihalogenated quinoline derivatives **50** via a "halogen-dance" rearrangement (Scheme 50).[86]



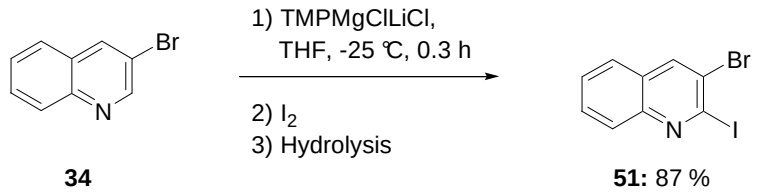
48 **49:** 94 % **50:** 74 - 98 %
E = H, I, Cl, CH(OH)Me, CH(OH)Ph, CHO

Scheme 50: Functionalization of the 4-position of **48** via two deprotonations and a halogen-dance.

[84] Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120.
[85] (a) Marull , M. ; Schlosser, M. *Eur. J. Org. Chem*. **2004**, 1008; (b) Marull , M. ; Schlosser, M. *Eur. J. Org. Chem*. **2003**, *8*, 1576.
[86] a) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéquiner, G. *Tetrahedron Lett.* **1998**, *39*, 6465; b) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéquiner, G. *Tetrahedron* **1999**, *55*, 12149.

1.3.2 Magnesiations of quinolines using deprotonations and Br/Mg exchanges

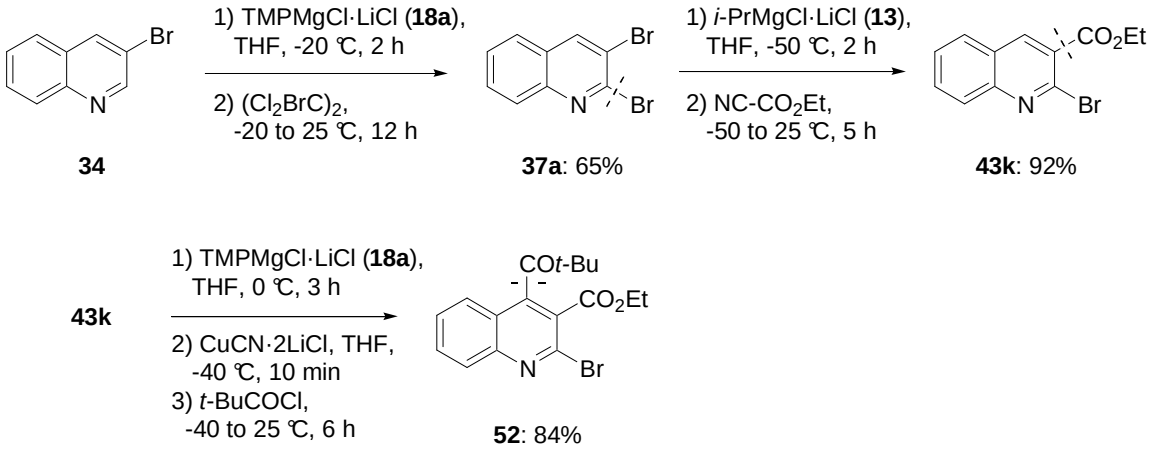
Recently, our group developed the new mixed Mg/Li amide bases TMPMgCl·LiCl (**18a**)[37] and $TMP_2Mg·2LiCl$ (**19**)[40] which allowed the direct magnesiation of some heteroaryl compounds such as 3-bromoquinoline (**34**) leading to the 2-functionalized quinoline **51** (Scheme 51).[37]



34 **51:** 87 %

Scheme 51: Direct C2-magnestion of 3-bromoquinoline (**34**).

We focused our attention on the direct magnesiation of quinolines using TMPMgCl·LiCl (**18a**), and $TMP_2Mg·2LiCl$ (**19**), which further enhanced both the scope of regioselective magnesiations as well as the tolerance toward sensitive functional groups, such as ketones or esters. Using the combination of this metalation reaction with the regioselective Br/Mg exchange on polybrominated quinolines, we may thus choose different pathways for polyfunctionalization and obtain a complete "regioflexibility".



34 **37a**: 65% **43k**: 92%

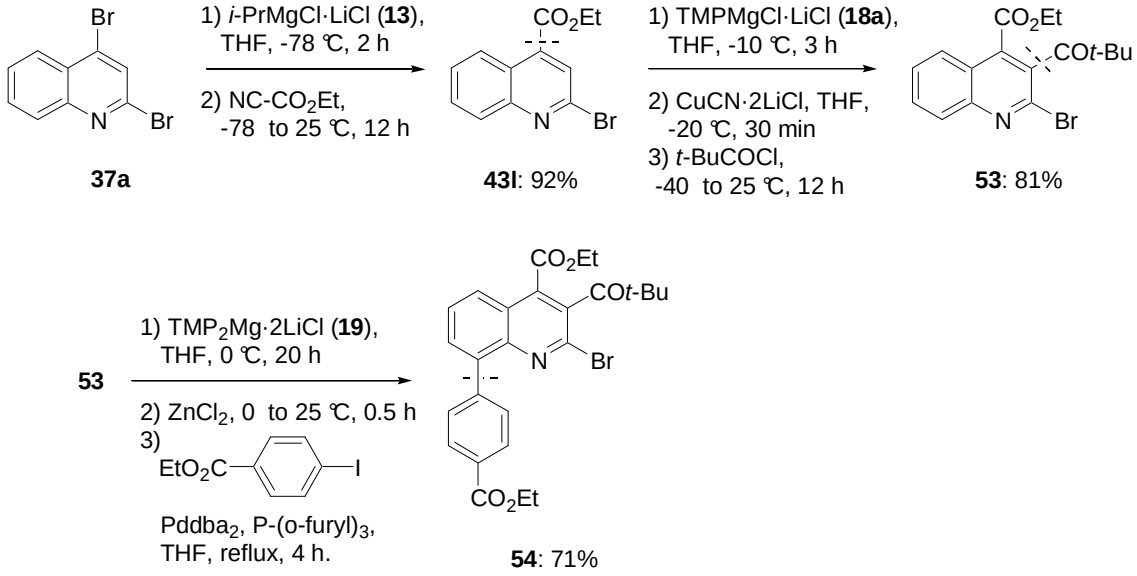
52: 84%

Scheme 52: Successive regioselective magnesiations at the **C2**, **C3** and **C4** positions.

Thus, a successive magnesiations in position C2, C3 and C4 could be achieved. Commercially available 3-bromoquinoline (**34**, Scheme 52) underwent a C2-deprotonation using TMPMgCl·LiCl (**18a**, 1.1 equiv, -20 °C, 2 h) and was quenched with 1,2-dibromo-1,1,2,2-

tetrachloroethane giving the 2,3-dibromoquinoline **37a** in 65% yield. The treatment of **37a** with *i*PrMgCl·LiCl (**13**), provided after the reaction with ethyl cyanoformate 2-bromoquinoline-3-carboxylic acid ethyl ester (**43k**) in 92% yield. Addition of TMPMgCl·LiCl (**18a**) to **43k** gave regioselectively the C4-magnesiated intermediate under mild conditions (0 °C, 3 h). Then, a smooth carboxylation in the presence of CuCN·2LiCl led to the quinoline **52** in 84% yield. Thus, the sequence of functionalization C2-C3-C4 was accomplished (Scheme 52).

The pertinent combination of Br/Mg exchanges and direct metalations allowed a regioselective functionalization of up to three new positions of the 2,4-dibromoquinoline (**37a**). Performing a Br/Mg exchange on **37a** with *i*-PrMgCl·LiCl (**13**, -78 °C, 2 h, Scheme 53) led after the reaction with ethyl cyanoformate, to the quinoline **43l** in 92% yield. Then, the regioselective deprotonation of **43l** at the C3-position using **18a** (-10 °C, 3 h) followed by a copper-mediated acylation[57] using pivaloyl chloride gave the quinoline derivative **53** in 81% yield. Remarkably, a second regioselective deprotonation on the quinoline **53** was performed at the position C8 (N-coordination), using the magnesium bisamide $TMP_2Mg·2LiCl$ [40, 87] under mild conditions (0 °C, 20 h). After the transmetalation with $ZnCl_2$, the Pd-catalyzed Negishi cross-coupling with ethyl 4-iodobenzoate furnished the highly functionalized quinoline **54** in 71% yield (Scheme 53).

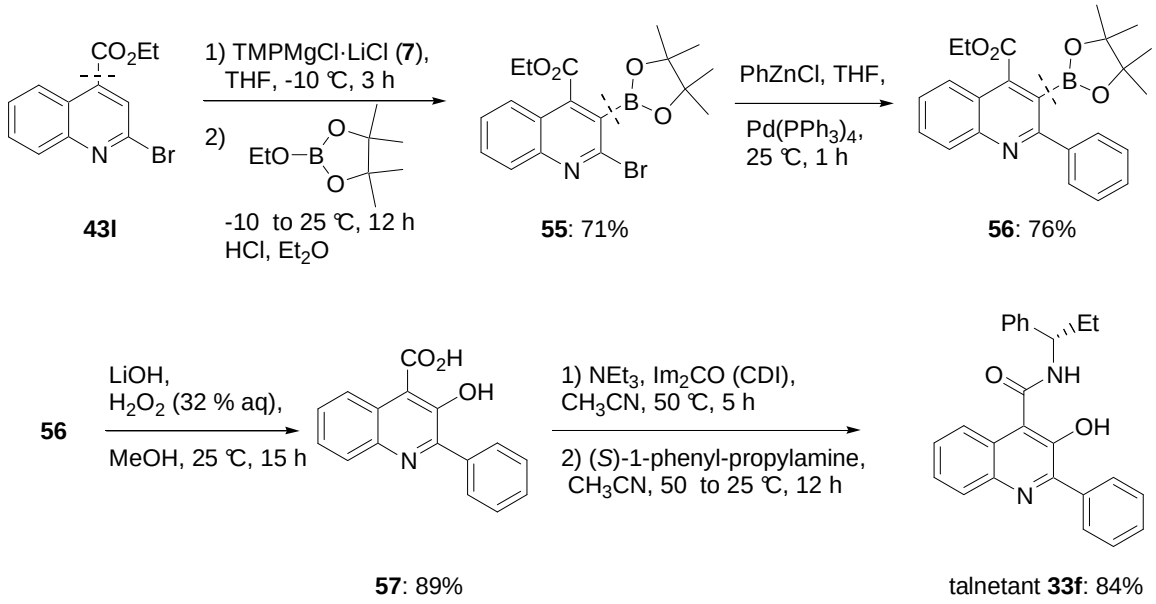


Scheme 53: Successive regioselective magnesiations at the **C4**, **C3** and **C8** positions.

[87] TMPMgCl·LiCl (**18a**) was found to be ineffective for this metalation.

1.3.3 An application to the synthesis of the NK3 receptor antagonist talnetant (33f)

As an application of our methodology, the total synthesis of talnetant (**33f**) was performed (Scheme 54). Talnetant is a neurokinin-3 receptor antagonist, it is under development by GlaxoSmithKline for the potential treatment of several disorders, including urinary incontinence, irritable bowel syndrome and schizophrenia.

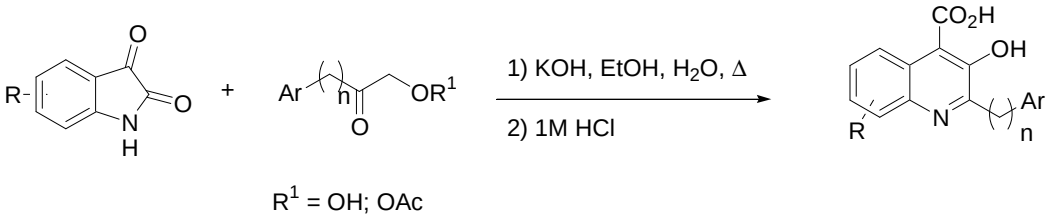


Scheme 54: Successive regioselective functionalizations of quinolines at the **C4**, **C3** and **C2** positions.

The treatment of 4-carbethoxy-2-bromoquinoline (**43l**) with TMPMgCl·LiCl (**18a**, -10 °C, 3 h), followed by quenching with ethyl pinacol borate[88] (1.5 equiv, -10 °C to 25 °C, 12 h) and acidic workup (1.2 equiv HCl in Et_2O)[89] furnished the corresponding pinacol boronic ester **55** in 71% yield (Scheme 54). Its Pd(0)-catalyzed cross-coupling with PhZnCl gave the corresponding functionalized boronic ester **56** in 76% yield. A basic oxidation using LiOH (6 equiv) and 30% aq H_2O_2 (3 equiv) in MeOH (25 °C, 15 h) afforded the acid **57** in 89% yield. Treatment[90] of **57** with NEt_3 (25 °C, 30 min), CDI (1.1 equiv, 50 °C, 5 h) and (*S*)-1-phenyl-propylamine (1.1 equiv, 50 °C to 25 °C, 12 h) in acetonitrile gave talnetant (**33f**) in 84% yield. By this method, we obtained a new sequence of functionalization, C4-C3-C2, and have found an alternative method to the Pfitzinger synthesis, the common method to obtain

[88] Ethyl pinacol borate was preferentially used instead of commercially isopropyl pinacol borate because of a transesterification side reaction.
[89] Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tet. Lett.* **1988**, *29*, 2631.
[90] Labaw, C. S.; Liu, P. PCT Int. Appl. **2007**, WO 2007016609.

quinoline salicylic acid series used as clinical candidate for P-selectin antagonists (Scheme 55). [91, 92]



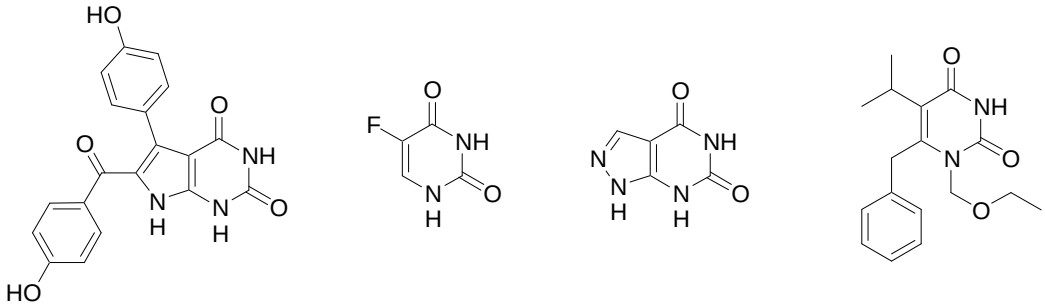
Scheme 55: Pfitzinger reaction used for the synthesis of quinoline salicylic acid.

[91] Pfitzinger, W. *J. Prakt. Chem.* **1886**, *33*, 100.
[92] Kaila, N.; Janz, K.; Huang, A.; Moretto, A.; DeBernardo, S.; Bedard, P. W.; Tam, S.; Clerin, V.; Keith, J. C. Jr.; Tsao, D. H. H.; Sushkova, N.; Shaw, G. D.; Camphausen, R. T.; Schaub, R. G.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 21.

2. Functionalizations of Protected Uracils via Chemo- and Regioselective Magnesiations

2.1. Introduction

Uracil derivatives are present among the natural products, like the marine alkaloid rigidin **58**[93] (Scheme 56), are mainly privileged structures in drug discovery[94] and display a broad spectrum of biological activities. For example, 5-fluorouracil (**59**)[95] is an important anticancer agent. Oxypurinol (**60**),[96] is a xanthine oxidase inhibitor, the active metabolite of the drug allopurinol. In recent years, several pathways were developed for the synthesis of analogues of emivirine (**61**), belonging to non-nucleoside reverse transcriptase inhibitors (NNRTIs)[97] that targets the retrovirus HIV-1 (Scheme 56).



58: rigidin **59**: 5-fluorouracil **60**: oxypurinol **61**: emivirine

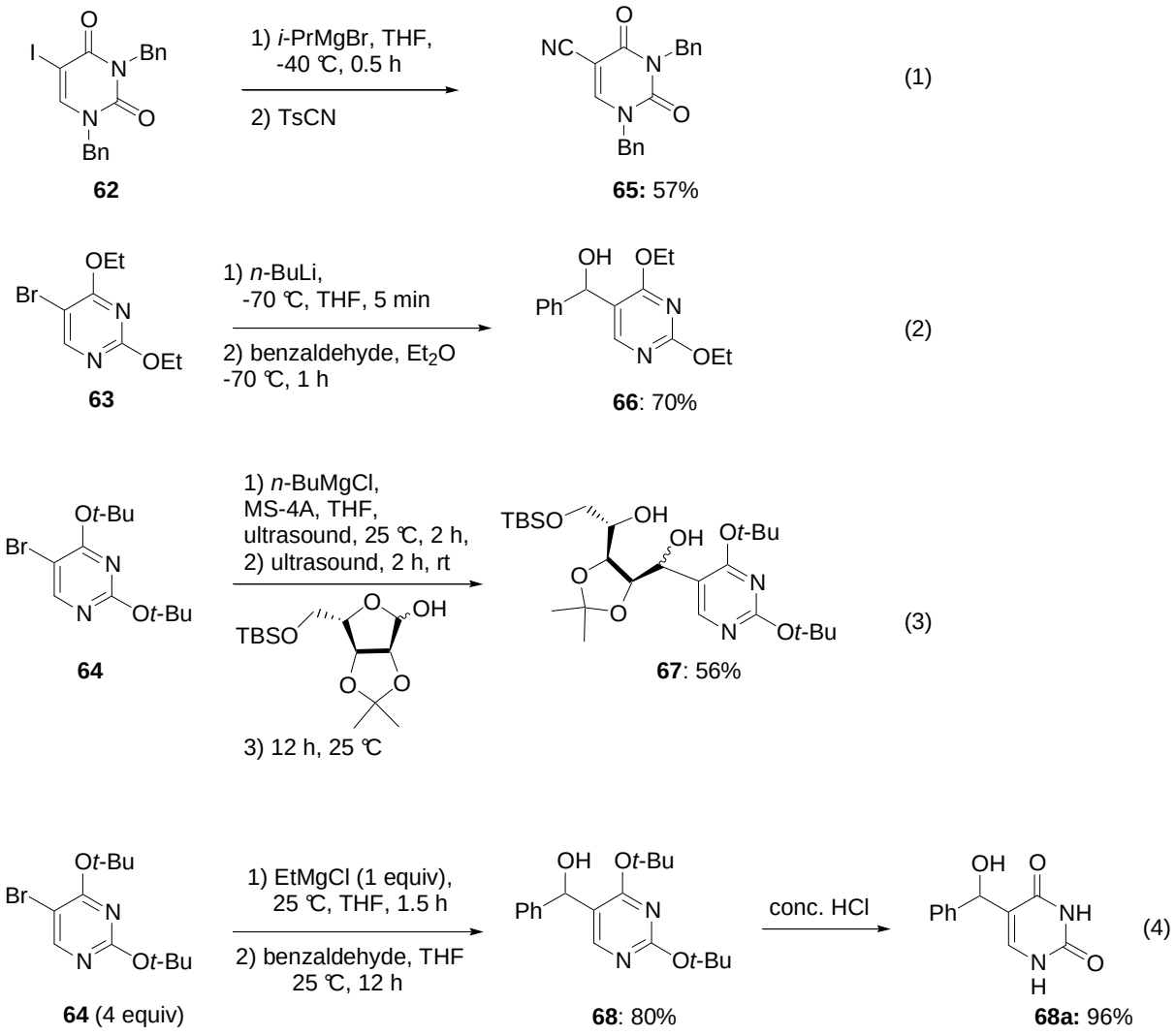
Scheme 56: Uracil derivatives as pharmacological agents.

[93] (a) Sakamoto, T.; Kondo, Y.; Sato, S.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1*. **1996**, *5*, 459; (b) Lagoja, I. M. *Chemistry & Biodiversity* **2005**, *2*, 1.
[94] Newkome, G. R.; Pandler, W. W.; *Contemporary Heterocyclic Chemistry*, Wiley, New York, **1982**.
[95] Cai, T. B.; Tang, X.; Nagorski, J.; Brauschweiger, P. G.; Wang, P. G. *Bioorganic & Medicinal Chemistry* **2003**, *11*, 4971.
[96] Nagamatsu, T.; Fujita, T.; Endo, K. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 33. Allopurinol is a well known drug clinically used for the treatment of gout and hyperuricemia. Oxypurinol is currently being developed by Cardiome Pharma for the treatment of allopurinol-intolerant hyperuricaemia (gout) and is in phase III trials for the treatment of congestive heart failure.
[97] (a) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem*. **1995**, *38*, 2860; (b) Pedersen, O. S.; Pedersen, E. B. *Antiviral Chem. Chemother*. **1999**, *10*, 2860.

2.2. Chemo and regioselective Br/Mg exchanges on protected uracils

2.2.1. Functionalization of protected uracils using halogen/metal exchange

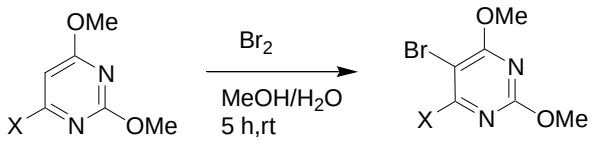
The functionalization of uracil derivatives at C4 or C5 generally requires the protection of the carbonyl groups.[98] Two ways of the amide group protection are often used. The N-alkylation (as with the uracil **62**) protected the nitrogens with benzyl or methyl groups, or the O-alkylation protected the oxygens such as in the 2,4-dialkylpyrimidine derivatives **63** and **64** (Scheme 57).



Scheme 57: Halogen/metal exchange on protected uracils.

[98] For a recent functionalization of unprotected uracil, see: Kopp, F.; Knochel, P. *Org. Lett*. **2007**, *9*, 1639.

Knochel described the I/Mg exchange on the protected uracil **62** which led to compound **65** after quenching with tosyl cyanide (Scheme 57, Eq. 1).[99] The harsh conditions for deprotection have limited the use of this route. 2,4-Dialkoxypyrimidine was first used as a starting material for the preparation of protected uracil by *Binkley* in 1963,[100] which described the Br/Li exchange on 5-bromo-diethoxypyrimidine (**63**) using *n*-BuLi. After quenching with benzaldehyde, the corresponding product **66** was obtained in high yield (Scheme 57, Eq. 2). Later, Br/Mg exchanges were studied by *Yokohama* on 5-bromo-2,4-di-*t*-butoxypyrimidine (**64**) using *n*-BuMgCl under ultrasonic irradiation to perform the synthesis of nucleoside derivatives (**67**, Eq. 3)[101] or using EtMgCl in the presence of a large excess of starting material (Eq. 4) to synthesize the alcohol uracil derivative **68**.[102] Interestingly, the corresponding product **68** was easily deprotected using conc. HCl affording the uracil **68a** in 96% yield. These methods allowed the preparation of various uracil derivatives but required low temperatures, activation and non-stoichiometric conditions, precluding the presence of sensitive functional groups. Recently, we have found a LiCl-catalyzed Br/Mg exchange reaction using *i*-PrMgCl·LiCl (**13**).[31] This reagent considerably accelerates the Br/Mg exchange reaction on aryl and heteroaryl bromides. We focused our studies on the general preparation of uracils, functionalized at C4 and C5 positions, starting from readily available protected uracils, which easily undergo deprotection. We chose 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**, Scheme 58) and 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) as starting materials, prepared respectively by bromination[103] of commercially available 4-chloro-dimethoxypyrimidine (**70a**), and readily available 4-bromo-dimethoxypyrimidine (**70b**).[104]



70a: X = Cl
70b: X = Br

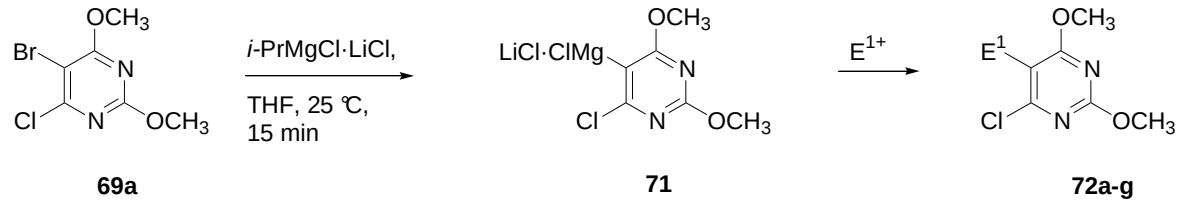
69a: X = Cl, 92%
69b: X = Br, 96%

Scheme 58: Preparation of starting materials **69a** and **69b**.

[99] Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F. ; Rottländer, M. ; Knochel, P. *J. Org. Chem*. **2000**, *65*, 4618.
[100] Rajkumar, T. V.; Binkley, S. B. *J. Med. Chem*. **1963**, *6*, 550.
[101] Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Yokohama, M. *J. Org. Chem*. **1998**, *63*, 7207.
[102] Shimura, A.; Momotake, A.; Togo, H.; Yokoyama, M. *Synthesis* **1999**, 495.
[103] Okafor, C. *J. Org. Chem*. **1973**, *38*, 4386.
[104] 4-Bromo-2,6-dimethoxypyrimidine (**70b**) was prepared following the literature procedure: White, J. D.; Hansen, J. D. *J. Org. Chem*. **2005**, *70*, 1963.

2.2.2. Chemoselective Br/Mg exchange on 5-bromo-4-chloro-2,6-dimethoxy-pyrimidine

The addition of *i*-PrMgCl·LiCl (**13**) to 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) at 25 °C in THF furnished within 15 min quantitatively[105] the magnesiated N-heterocycle **71** (Scheme 59, Table 3). This magnesium reagent reacts with a wide range of electrophiles providing new 5-functionalized 4-chloro-2,6-dimethoxypyrimidines of type **72a-g** in high yields (Scheme 59, Table 3). Thus, the addition of benzaldehyde or 2-methoxy-benzaldehyde



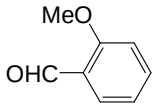
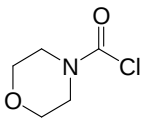
69a **71** **72a-g**

Scheme 59: Chemoselective functionalizations of 5-bromo-4-chloro-2,6-dimethoxy-pyrimidine (**69a**) at C5 position.

to the magnesiated species **71** led to the corresponding alcohols **72a** and **72b** respectively in 91 and 83% yield (entries 1 and 2 of Table 3). The reaction with acid chlorides like PhCOCl or a carbamoyl chloride provided the ketone **72c** in 86% yield and the amide **72d** in 85% yield (entries 3-4). Treatment of the magnesiated derivative **71** with TsCN afforded the heterocyclic nitrile **72e** in 89% yield (entry 5). The introduction of an ester group was best performed by the reaction with NC-CO_2Et leading to the ester **72f** in 87% yield (entry 6). The reaction with an activated bromide like benzyl bromide provided the expected product **72g** in 75% yield (entry 7).

[105] The completion of Br-Mg exchange was checked by GC analysis of reaction aliquots quenched with saturated NH_4Cl (aq.).

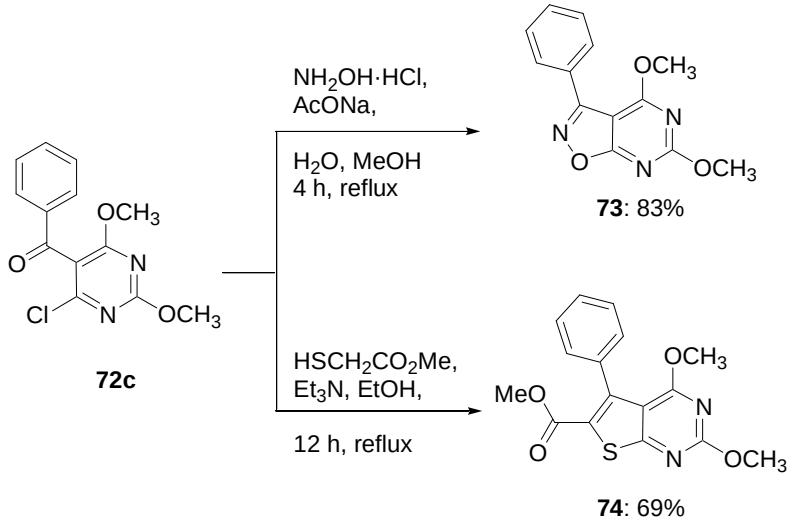
Table 3: Products of type **72**

entry	Grignard reagent [a]	electrophile	product of type **72**	yield (%)[b]
1	**71**	PhCHO	**72a**	91
2	**71**		**72b**	83
3	**71**	PhCOCl	**72c**	86
4	**71**		**72d**	85
5	**71**	TsCN	**72e**	89
6	**71**	$NC\text{-}CO_2Et$	**72f**	87
7	**71**	$PhCH_2Br$	**72g**	75

[a] X = Cl·LiCl. [b] Isolated yield of analytically pure product.

2.2.3. Application to the synthesis of annelated heterocycles and the xanthine oxidase inhibitor oxypurinol.

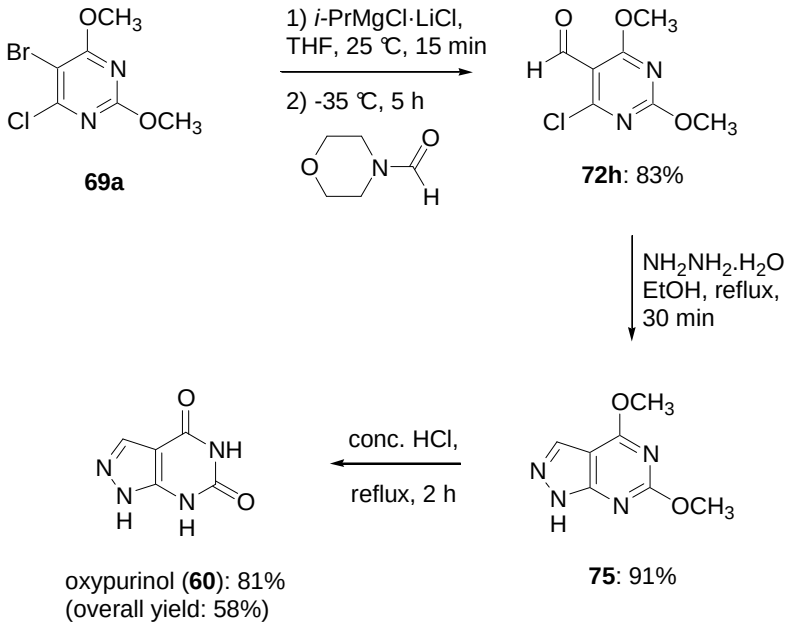
The pyrimidine **72c** can be easily converted into annelated heterocycles. Thus, the reaction between the chloroketone **72c** and hydroxylamine hydrochloride in a 1:1 mixture of H_2O/MeOH gave within 4 h the desired product **73** in 83% yield (Scheme 60). Interestingly, the addition of methyl mercaptoacetate to **72c** in the presence of triethylamine[106] provided the bicyclic S,N-heterocycle **74** in 69% yield (Scheme 60).



Scheme 60: Synthesis of annelated heterocycles starting from the acyluracil derivative (**72c**).

As an application, we also used an intramolecular cyclization to prepare the drug oxypurinol **60** (Scheme 61). Thus, the reaction of pyrimidine **69a** with *i*-PrMgCl·LiCl (**13** (1.05 equiv), 25 °C, 15 min) followed by the reaction with N-formylmorpholine provided the aldehyde **72h** in 83% yield. Treatment of **72h** with an excess of hydrazine monohydrate[107] led to pyrazolopyrimidine **75** in 91% yield (80 °C, 0.5 h). Deprotection using conc. HCl led to oxypurinol (**60**) in 81% yield.

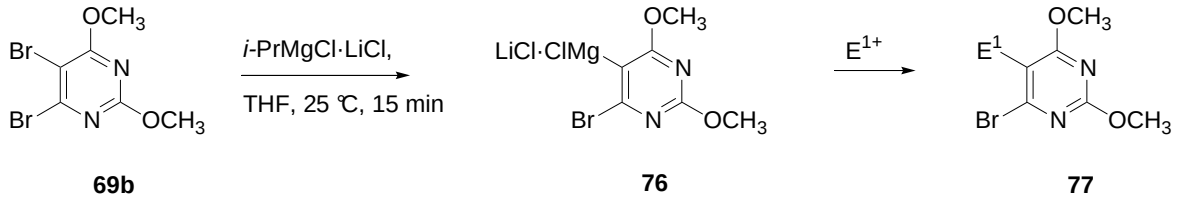
[106] Rahman, L. K. A.; Scrowston, R. M. *J. Chem. Soc., Perkin Trans. 1*. **1984**, *3*, 385.
[107] Nagamatsu, T. ; Fujita, T. ; Endo, K. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 33.



Scheme 61: Synthesis of oxypurinol (**60**).

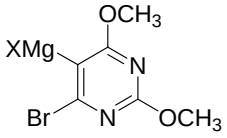
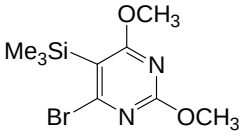
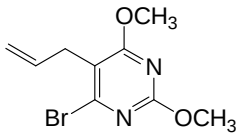
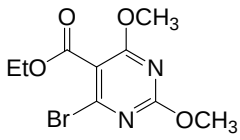
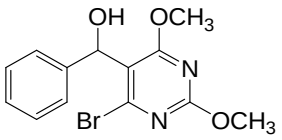
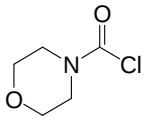
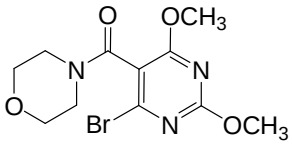
2.2.4. Regioselective Br/Mg exchange on 4,5-dibromo-2,6-dimethoxypyrimidine (69b).

The Br/Mg exchange on 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**), using *i*-PrMgCl·LiCl (**13** (1.05 equiv), 25 °C, 15 min) occurred regioselectively at C5, providing the corresponding magnesium species **76** (Scheme 62, Table 4). The reaction of **76** with various electrophiles gave the expected products **77i-m** in 70-91% yield (Table 4). The silylation and the direct allylation of the magnesium derivative **76** can be accomplished respectively with TMSCl and allyl bromide, leading to pyrimidines **77i** and **77j** in 91% yield (entries 1-2 of Table 4). Trapping the magnesium species **76** with ethyl cyanoformate, benzaldehyde or 4-morpholine-carbonyl chloride furnished the corresponding functionalized products **77k-m** in 70-95% yields (entries 3-5).



Scheme 62: Regioselective functionalizations of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) at C5 position.

Table 4: Products of type **77**

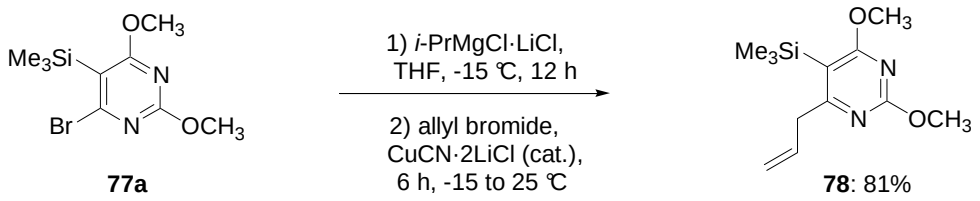
entry	Grignard reagent [a]	electrophile	product of type **72**	yield (%)[b]
		TMSCl		
1	**76**		**77a**	91
		allyl bromide		
2	**76**		**77b**	91
		$NC\text{-}CO_2Et$		
3	**76**		**77c**	81
		PhCHO		
4	**76**		**77d**	95
				
5	**76**		**77e**	70

[a] X = Cl·LiCl. [b] Isolated yield of analytically pure product.

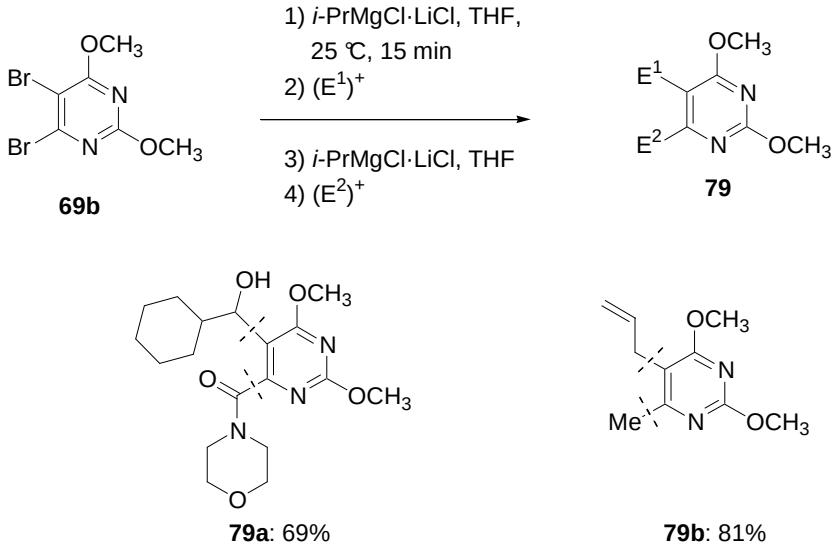
2.2.5. Successive Br/Mg exchanges on 4,5-dibromo-2,6-dimethoxypyrimidine (69b) and his application the synthesis of the anti-HIV drug emivirine.

A successive introduction of two different electrophiles in positions C4 and C5 of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) can be performed. Thus, the reaction of 4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (**77d**) with *i*-PrMgCl·LiCl (**13** (1.1 equiv), -15 °C, 12 h) furnished the corresponding Grignard reagent, which could be trapped with allyl bromide to give the expected product **78** in 81% yield (Scheme 63). Interestingly, difunctionalizations with two successive Br/Mg-exchange reactions using a "one-pot" procedure could also be performed. Thus, by using successively *c*-HexCHO and N-

morpholinecarbonyl chloride as electrophiles, the desired product **79a** was obtained in 69% overall yield. Similarly, by using allyl bromide and MeI, the 4,5-disubstituted pyrimidine **79b** was prepared in 81% yield (Scheme 64).



Scheme 63: Br/Mg exchange of 4-bromo-5-(trimethylsilyl)-2,6-dimethoxypyrimidine (**77a**).

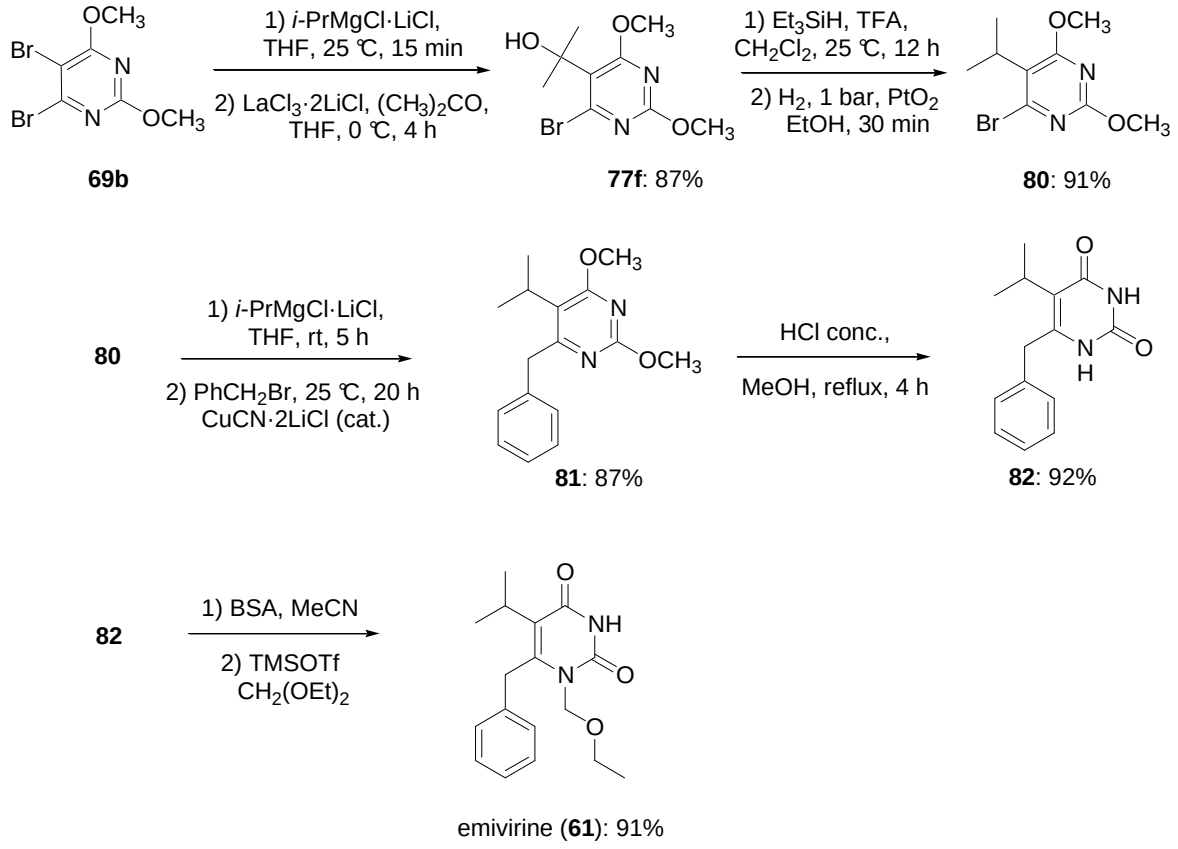


Scheme 64: Difunctionalizations of 4,5-dibromo-2,6-dimethoxypyrimidine via successive "one-pot" Br/Mg exchange reactions.

To illustrate the versatility of this method, a synthesis of the anti-HIV drug emivirine (**61**) was performed (Scheme 65). Treatment of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) with *i*-PrMgCl·LiCl (**13**) followed by the reaction with acetone in the presence of a solution of $LaCl_3 \cdot 2LiCl$ in THF,[108] led to the corresponding alcohol (**77f**) in 87% yield. This compound was partly reduced using triethylsilane and trifluoroacetic acid.[109] A mixture of the expected 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine (**80**) and the corresponding unsaturated

[108] Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
[109] Albert, J. S.; Aharony, D.; Andisik, D.; Barthlow, H.; Bernstein, P. R.; Bialecki, R. A.; Dedinas, R.; Dembofsky, B. T.; Hill, D.; Kirkland, K.; Koether, G. M.; Kosmider, B. J.; Ohnmacht, C.; Palmer, W.; Potts, W.; Rumsey, W.; Shen, L.; Shenvi, A.; Sherwood, S.; Warwick, P. J.; Russell, K. *J. Med. Chem.* **2002**, *45*, 3972.

product was obtained[110]. The product mixture was directly hydrogenated using PtO_2[111] (1 bar, 30 min) to obtain **80** in 91% yield. The second Br/Mg exchange was performed at 25 °C within 5 h, followed by the benzyl bromide addition, leading to the 4,5-dialkylated-2,6-dimethoxypyrimidine species (**81**) (20 h, 25 °C, 87%). An acidic hydrolysis in aqueous MeOH gave the corresponding uracil **82** in 92% yield after the recrystallization. Compound **82** was transiently silylated using BSA in MeCN and then N-alkylated [112] with diethoxymethane to furnish 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (**61,** emivirine) in 90% yield (Scheme 65).



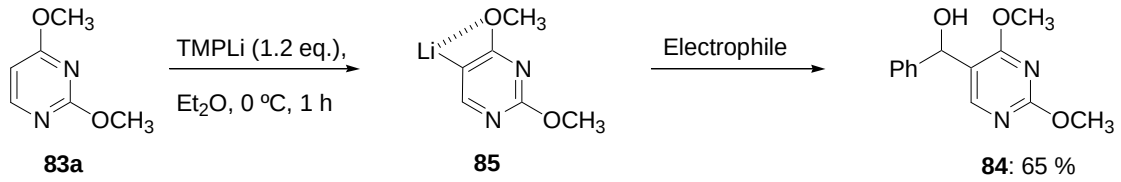
Scheme 65: Synthesis of the anti-HIV drug emivirine (**61**).

[110] A mixture of 17% of **80** and 83% of the corresponding dehydrated product was obtained by ^{1}H NMR analysis of the crude product.
[111] Tilley, J. W.; LeMahieu, R. A.; Carson, M.; Kierstead, R. W. *J. Med. Chem*. **1980**, *23*, 92.
[112] Therkelsen, F. D.; Hansen, A-L. L.; Pedersen, E. B.; Nielsen, *C. Org. Biomol. Chem*. **2003**, *1*, 2908.

2.3. Direct magnesiation of protected uracils

2.3 Deprotonation of 2,4-dimethoxypyrimidine (83a) using lithium amide bases

Using the amide base TMPMgCl·LiCl (**18a**),[37] we have investigated the deprotonation of commercially available 2,4-dimethoxypyrimidine (**83a**, Scheme 66). Our aim was to access regioselectively polyfunctionalized protected uracils. *J. Yamamoto* described the use of strong bases such as the lithium amide TMPLi which led to the *ortho*-directed lithiation of 2,4-dimethoxypyrimidine (**83a**) in order to obtain the 5-functionalized 2,4-dimethoxypyrimidine **84** (Scheme 66).[113] The chelating effect of the methoxy group in the intermediate **85** led to the thermodynamically most stable metal species.[114] With the use of lithium reagents, the range of potential electrophiles was strongly limited, and the 5-functionalized 2,4-dimethoxypyrimidines were obtained in moderate to low yields (4-65%). Very low yields were obtained using LDA, with recovery of the starting material.[113]

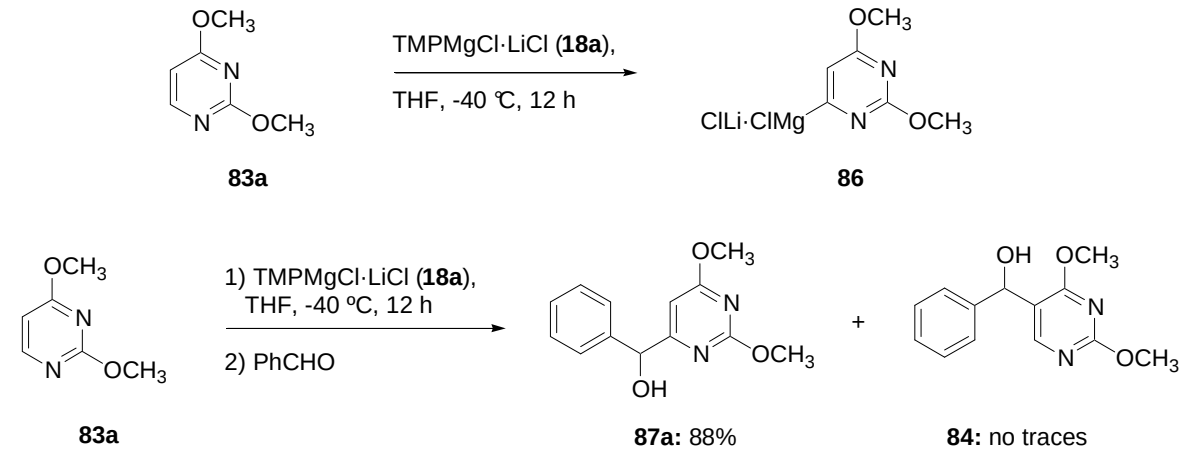


Scheme 66: *Ortho*-directed lithiation of 2,6-dimethoxypyrimidine.

2.3.1 Deprotonation of 2,4-dimethoxypyrimidine using TMPMgCl·LiCl (18a)

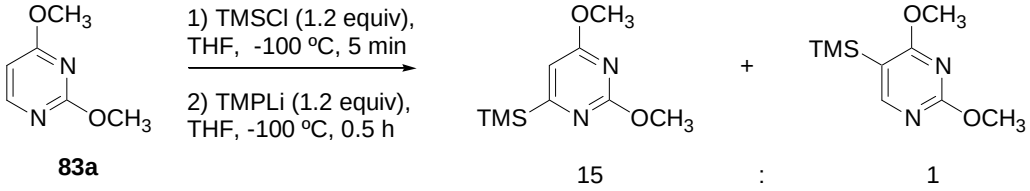
Surprisingly, through the treatment of commercially available 2,4-dimethoxypyrimidine (**83a**) with TMPMgCl·LiCl (**18a**) at –40 °C we easily got an access to the 6-magnesiated 2,4-dimethoxypyrimidine (**86**). Trapping of the resulting Grignard reagent **86** with benzaldehyde furnished the corresponding alcohol **87a** in 88 % yield (Scheme 67a). By the comparison of ^{1}H NMR[115] of the products **87a** and **84** (synthesized by *Yamamoto* using TMPLi (Scheme 66), we could show that we obtained the kinetic product, C6-isomer product (**87a**) and not the C5 product (**84**). Starting from **83a**, the reaction with TMPMgCl·LiCl at various temperatures such as -20 °C, 0 °C or 25 °C, and the quenching with several electrophiles, led to a regioisomeric C6/C5 mixture.

[113] (a) Wada, A.;Yamamoto, J.; Kanatomo, S. *Heterocycles* **1987**, *3*, 585; (b) Wada, A.; Yamamoto, J.; Hamoaka, Y.; Ohki, S.; Nagai, S.; Kanamoto, S. *J. Heterocycl. Chem*. **1990**, *27*, 1831.
[114] Turck, A. ; Plè, N.; Quéguiner, G. *Heterocycles* **1994**, *3*, 2149.
[115] 1H-NMR ($CDCl_3$): **84**: δ = 8.16 ppm (s, 1H at C6 position); **87a**: δ = 6.21 ppm (s, 1H at C5 position).



Scheme 67a: First regioselective 6-functionalization of 2,4-dimethoxypyrimidine (**83a**).

Remarkably, the reaction of 2,4-dimethoxypyrimidine (**83a**), in presence of TMSCl (1.5 equiv) in THF at -100°C (Barbier conditions reaction), with TMPLi (1.0 M in Et_2O) led after 0.5 h to a regioisomeric mixtures of the corresponding products C6/C5 = 15:1[116] (Scheme 67b). This result proved that using TMPLi a kinetic deprotonation of 2,4-dimethoxypyrimidine (**83a**) is also possible to occur at C6 position, but at lower temperature compared with TMPMgCl·LiCl.

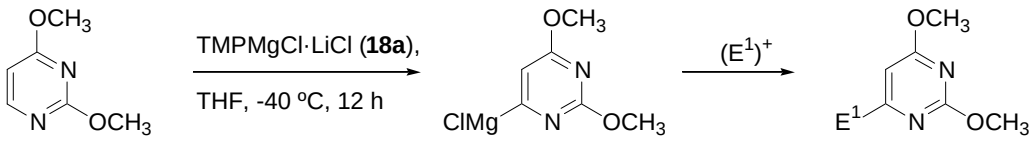


Scheme 67b: Deprotonation of 2,4-dimethoxypyrimidine (**83a**) at C6 position using TMPLi under Barbier conditions.

Keeping carefully the temperature at -40 °C during the deprotonation, we could quench the C6-magnesiated 2,4-dimethoxypyrimidine (**86**, Scheme 67) at low temperature with several electrophiles, obtaining the C6-functionalized protected uracils of type **87** (Scheme 68, Table 5, entries 1-4). Thus, the reaction of the Grignard intermediate **86** with iodine produced the 4-iodo-2,6-dimethoxypyrimidine (**87b**) in 87% yield (entry 1). A transmetalation of **86** with 1.1 equiv of CuCN·2LiCl and the treatment with pivaloyl chloride furnished the protected uracil

[116] The regioselectivity of the reaction was obtained by GC-MS analysis of the crude mixture obtained after quenching the reaction with NH_4Cl and extracting with Et_2O.

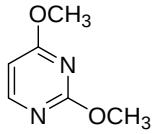
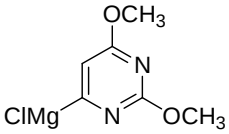
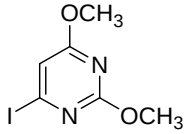
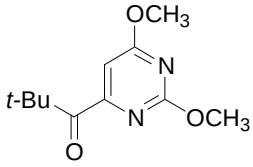
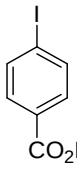
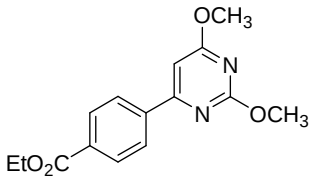
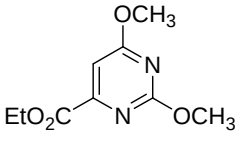
87c in 72% yield (entry 2). Starting from the Grignard intermediate **86** and using transmetalation with $ZnCl_2$ (1 M in THF, 1.1 equiv, 25 °C, 15 min) and the Pd-Negishi cross-coupling with ethyl 4-iodobenzoate we obtained the arylpyrimidine **87d** in 75% yield (entry 3). An ester function was also implemented on **83a** using ethyl cyanoformate, and ester derivative **87e** was prepared in 71% yield (entry 4).

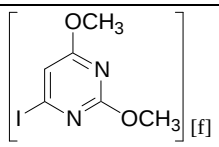
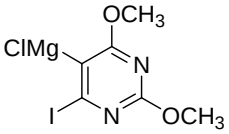
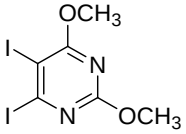
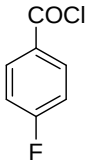
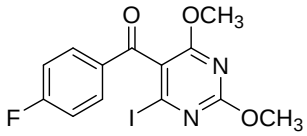
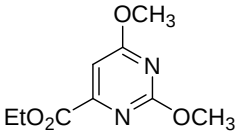
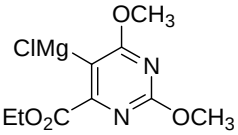
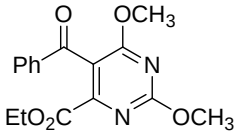


83a **86** **87b-e**

Scheme 68: C6-functionalization of 2,4-dimethoxypyrimidine (**83a**) using TMPMgCl·LiCl (**18a**).

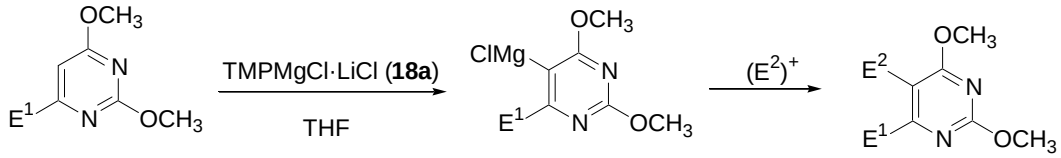
Table 5: Products of type **87** and **89**.

entry	reagent	(°C) ; [T]	magnesium reagent	electro-phile	product, yield (%)[a]
1	 **83a**	-40; [12]	 **86**	I_2	 **87b**: 87
2	**83a**	-40; [12]	**86**	*t*-BuCOCl	 **87c**: 72[c]
3	**83a**	-40; [12]	**86**		 **87d**: 75[e,d]
4	**83a**	-40; [12]	**86**	NC-CO_2Et	 **87e**: 71

5	 **87b**	-30 to 0; [2]	 **88a**	I_2	 **89a**: 87
6	**87b**	0; [1]	**88a**		 **89b**: 84[c]
7	 **87e**	-40; [2]	 **88b**	PhCOCl	 **89c**: 78[c]

[a] Isolated yield of analytically pure product; [b] Catalytic amount of CuCN·2LiCl was added; [c] 1 equiv. of CuCN·2LiCl was added; [d] The Grignard was transmetalated with 1.2 equiv. of $ZnCl_2$ in THF [e] 1 mol % of $Pd(Ph_3P)_4$ was added. [f] This reaction was made starting from **83a** in a "one pot" procedure.

2.3.2 Deprotonation of 6-functionalized 2,4-dimethoxypyrimidine using TMPMgCl·LiCl (18a)



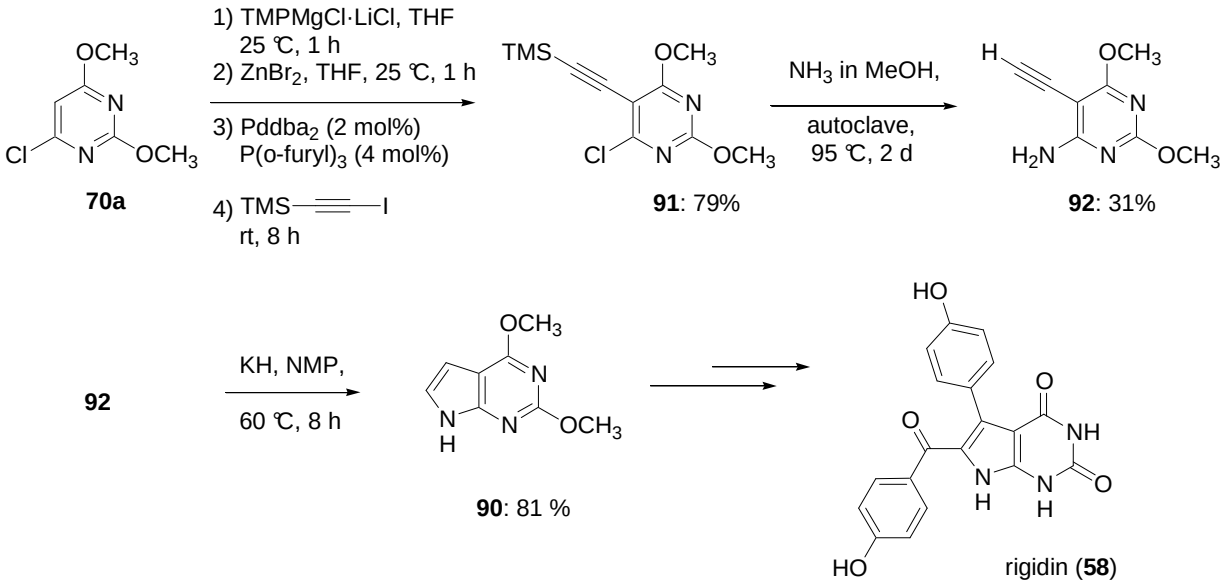
87 **88** **89**

Scheme 69: Functionalization of compounds of type **87** using TMPMgCl·LiCl (**18a**).

Interestingly, contrary to the regioselectivity C5>C4, obtained on 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) in the Br/Mg exchange reaction (Scheme 64), the direct deprotonation of 2,4-dimethoxypyrimidine (**83a**) with TMPMgCl·LiCl allowed us to introduce successively functional groups first at C6 and then at C5 positions (Scheme 69, Table 5, entries 5-7). The "one pot" successive diiodination of **83a** was performed using TMPMgCl·LiCl (-40 °C, 12 h) and iodine (1.2 equiv, -30 °C, 2 h) and provided the 4,5-diiodo-2,6-dimethoxypyrimidine (**89a**) (87% yield, entry 6). Starting from **87b**, the reaction with TMPMgCl·LiCl (0 °C, 1 h) followed by a copper(I)-catalyzed acylation with 4-fluorobenzoyl chloride led to the ketone derivative **89b** (84%, entry 7). Moreover, the use of this mixed Mg/Li amide base enhanced the tolerance toward sensitive functional groups such as an ester (entry 7). Thus, the reaction of TMPMgCl·LiCl (1.1 equiv, -40 °C, 2 h) on the

protected uracil ester **87e** led to the C5-magnesiated intermediate **88b**, which after a transmetalation with CuCN·2LiCl was quenched with benzoyl chloride and afforded the highly functionalized pyrimidine **89c** in 78% yield (entry 7).

The use of TMPMgCl·LiCl (**18a**) allowed us the direct functionalization of commercially available 4-chloro-2,6-dimethoxypyrimidine (**70a**). We used this substrate for the synthesis of the pyrrolopyrimidine **90**, a known precursor of the marine alkaloid rigidin (**58**, Scheme 70). [117] Thus, the addition of TMPMgCl·LiCl (**16**, 25 °C, 1 h) to 4-chloro-2,6-dimethoxypyrimidine (**70a**) gave after transmetalation with $ZnCl_2$, and the Pd-catalyzed coupling with iodoethynyl-trimethylsilane,[118] the corresponding cross-coupling product **91** in 79% yield (Scheme 70). A one-pot amination and deprotection of **91** using NH_3 in MeOH furnished the 6-amino-2,4-dimethoxypyrimidine (**92**) in 31% yield. This product was then successfully cyclized using the conditions developed by *Knochel*[119] to the pyrrolopyrimidine **90** in yield 81 % yield.



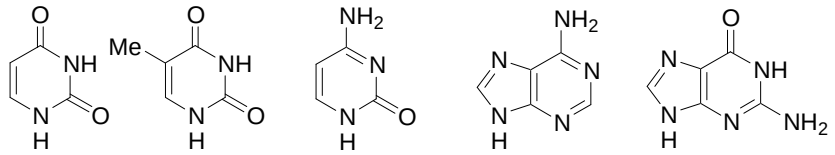
Scheme 70: Synthesis of the precursor **90** for the synthesis of rigidin (**58**)**.**

[117] Sakamoto, T.; Kondo, Y.; Sato, S.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1*. **1996**, *5*, 459. (b) Lagoja, I. M. *Chemistry & Biodiversity* **2005**, *2*, 1.
[118] For the preparation of iodoethynyl-trimethyl-silane, see: Al-Hassan, M. I. *J. Organomet. Chem.* **1989**, *372*, 183. This reagent was distilled and stored under argon at -4 °C.
[119] Rodriguez, A. L.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed*. **2000**, *39*, 2488.

3. Amination of DNA and RNA Units via Cuprated Pyrimidines and Purines Intermediates

3.1. Introduction

The chemical modification of DNA and RNA nucleotides **93a-e** (Scheme 71) is an important synthetic task, since modified DNA and RNA bases have interesting pharmaceutical properties and are important for the investigations of biochemical pathways.[120] Organocopper intermediates, due to their exceptional functional group tolerance, would be ideal reagents for DNA and RNA modification. [121, 122]



93a: uracil **93b**: thymine **93c**: cytosine **93d**: adenine **93e**: guanine

Scheme 71: DNA and RNA bases of type **93**.

Recently, we have reported an efficient oxidative amination procedure of lithium amidocuprates using chloranil.[46a] We have applied this method to the amination of various pyrimidine and purine derivatives.

[120] For recent advance in DNA modifications: (a) Leumann, C. J. *Bioorg. Med. Chem.* **2002**, *10*, 841; (b) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc*. **2006**, *128*, 1398; (c) Wilson, J. N.; Kool, E. T. *Org. Biomol. Chem*. **2006**, *4*, 4265; (c) Matsuda, S.; Fillo, J. D.; Henry, A. A.; Rai, P.; Wilkens, S. J.; Dwyer, T. J.; Geierstanger, B. H.; Wemmer, D. E.; Schultz, P. G.; Spraggon, G.; Romesberg, F. E. *J. Am. Chem. Soc*. **2007**, *129*, 10466; (d) McCulloch, S. D.; Kokoska, R. J.; Masutani, C.; Iwai, S.; Hanaoka, F.; Kunkel, T. A. *Nature*. **2004**, *428*, 97.

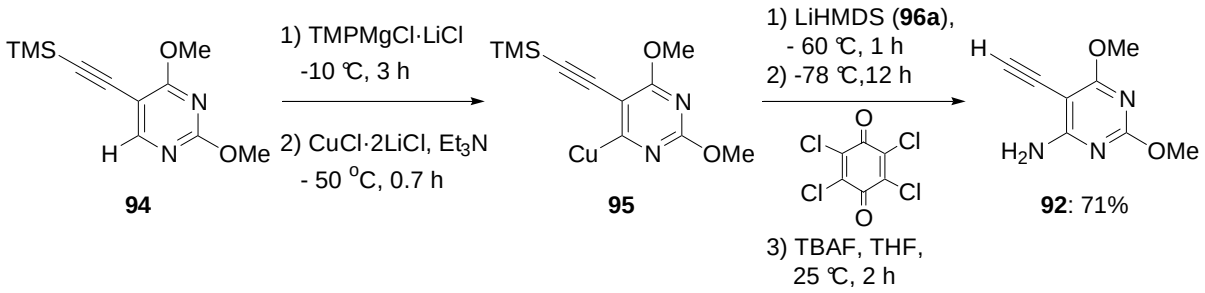
[121] (a) Yang, X.; Althammer, A.; Knochel, P. *Org. Lett*. **2004**, *6*, 1665. (b) Yang, X.; Knochel, P. *Synthesis* **2006**, *15*, 2618; (c) Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed*. **2002**, *41*, 3263.

[122] For a recent contribution in organocopper chemistry: (a) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem. Int. Ed*. **2007**, *46*, 1650; (b) Krause, N.; Morita, N. *Application of Copper, Silver and Gold in Preparative Organic Chemistry in*: "Comprehensive Organometallic Chemistry III" (Crabtree, R. H.; Mingos, D. M. P. Eds.), Elsevier, Oxford. **2007**, *9*, 501-586. (c) Lipshutz, B. H.; Taft, B. R. *Angew. Chem. Int. Ed*. **2006**, *45*, 8235; (d) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc*. **2006**, *128*, 15572; (e) Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2005**, *44*, 2752; (f) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem. Int. Ed*. **2007**, *46*, 7462; (g) Sulzer-Mosse, S.; Tissot, M.; Alexakis, A. *Org. Lett*. **2007**, *9*, 3749; (h) Isobe, H. ; Cho, K.; Solin, N.; Werz, D. B.; Seeberger, P. H.; Nakamura, E. *Org. Lett*. **2007**, *9*, 4611.

3.2. Selective aminations of pyrimidine derivatives

3.2.1 Preliminary studies

Thus, in preliminary experiments, we magnesiated the 5-alkynyl pyrimidine **94** with TMPMgCl·LiCl (**18a**, THF, -10 °C, 3 h)[37] and performed transmetalation to the copper derivative **95** using CuCl·2LiCl (Et_3N, -50 °C, 45 min)[123] (Scheme 72). After the additions of LiHMDS (**96a**, 2 equiv, -60 °C, 1 h) and chloranil (**22**, 1.2 equiv, -78 °C, 12 h), followed by a deprotection using TBAF (25 °C, 2 h), the desired 2,4-dimethoxypyrimidine **92** was obtained in 71% yield. Compared with the previous method for the synthesis of the compound **90** (Scheme 70), this method afforded a better overall yield of compound **92** under milder conditions.



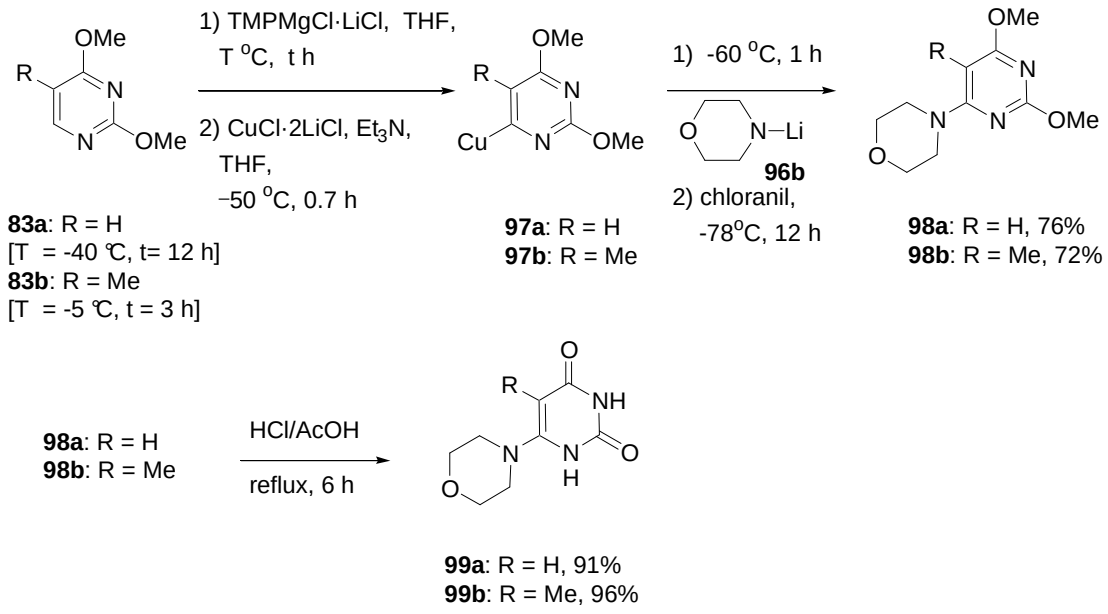
Scheme 72: Synthesis of **92**, a precursor for the synthesis of rigidin (**58**).

3.2.2 Synthesis of aminated uracil and thymine

We have examined the reaction scope of this oxidative amination. By using the regioselective C6-magnesiation of the 2,4-dimethoxypyrimidine **83a** (TMPMgCl·LiCl (1.1 equiv), -40 °C, 12 h) followed by the transmetalation (CuCl·2LiCl) to the corresponding copper derivative (**97a**), we could obtained after the successive additions of N-lithiomorpholine **96b** and chloranil the expected aminated product **98a** in 76 % yield (Scheme 73). Similarly, starting from the 5-methyl-2,4-dimethoxypyrimidine (**83b**), the direct magnesiation using TMPMgCl·LiCl (1.1 equiv, -5 °C, 3 h) led after transmetalation with CuCl·2LiCl to the cuprated protected thymine **97b** (Scheme 73). The successive additions of **96b** (2 equiv, -60 °C, 0.7 h) and chloranil (1.2 equiv, -78 °C, 12 h) furnished the corresponding aminated pyrimidine **98b** in 72% yield. The treatment of the functionalized pyrimidines **98a-b** under

[123] 1.2 equivalents of Et_3N improved the yield of the amination reaction.

acidic conditions provided the 6-N-morpholino-uracil (**99a**) and 6-N-morpholino-thymine (**99b**) in excellent yields (91-96%; Scheme 73).



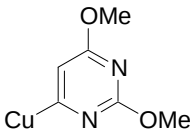
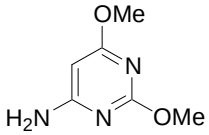
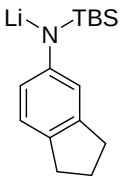
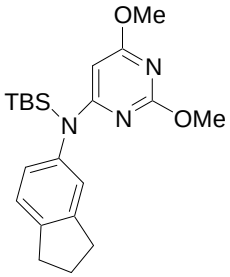
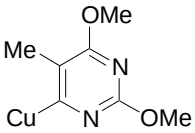
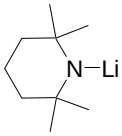
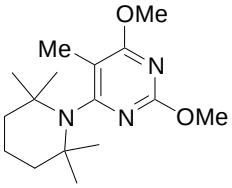
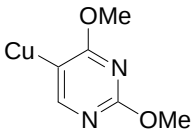
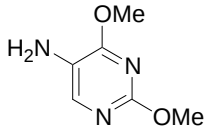
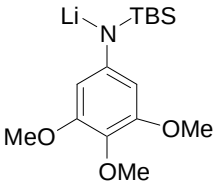
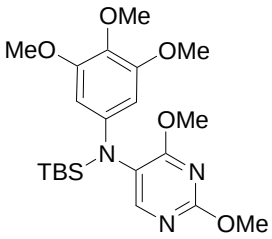
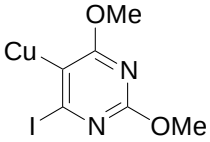
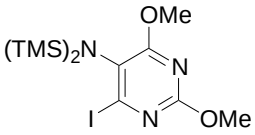
Scheme 73: Amination of 2,4-dimethoxypyrimidine (**83a**) and 5-methyl-2,4-dimethoxypyrimidine (**83b**). An access to 6-aminated uracil and thymine.

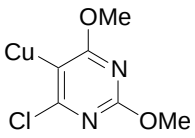
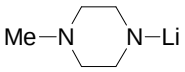
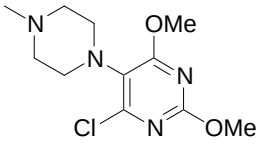
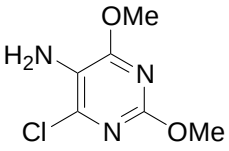
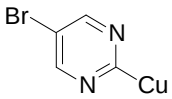
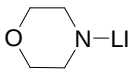
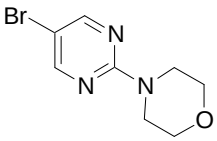
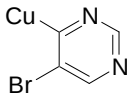
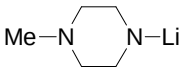
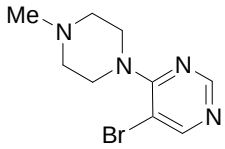
3.2.3 Selective aminations of functionalized pyrimidines

We have applied this method to the amination of several functionalized protected uracils and halogenated pyrimidines (Table 6). Thus, the reaction of the copper derivative **97a** with LiHMDS (**96a**) furnished after the addition of chloranil and a deprotection using TBAF 6-amino-2,4-dimethoxypyrimidine **98c** (81%, entry 1 of Table 6). Similarly, starting from **97a**, the additions of the lithiated N-TBS aniline derivative (**96c**) and chloranil gave the TBS-protected 6-aminated pyrimidine **98d** (76%, entry 2), a derivative of the antibacterial TMAU, developed by Bayer AG.[124] The cuprated pyrimidine **97b** reacted with the sterically hindered TMP-Li (**96d**, -50 °C, 1 h) providing after the treatment with chloranil the thymine **98e** in 70% yield (entry 3). Starting from 5-bromo-2,4-dimethoxypyrimidine, a Br/Mg exchange using *i*-PrMgCl·LiCl (1.1 equiv, -20 °C, 2 h)[31] followed by a transmetalation with CuCl·2LiCl gave the C5-cuprated 2,4-dimethoxypyrimidine **97c**. The addition of LiHMDS (**96a**) followed by chloranil, furnished the 5-amino-2,4-dimethoxypyrimidine (**98f**) after N-desilylation (79%, entry 4). Similarly, the N-TBS pyrimidine derivative **98g** was obtained (68% yield, entry 5).

[124] Kuhl, A.; Svenstrup, N.; Ladel, C.; Otteneder, M.; Binas, A.; Schiffer, G.; Brands, M.; Lampe, T.; Ziegelbauer, K.; Ruebsamen-Waigmann, H.; Haebich, D.; Ehlert, K. *Antimicrob. Agents Chemother*. **2005**, *49*, 987.

Table 6: Amination of cuprated pyrimidines derivatives of type **97**.

entry	copper reagent	lithium amide	product	yield [%][a]
1	 **97a**[b]	LiHMDS **96a**	 **98c**	81
2	**97a**[b]	 **96c**	 **98d**	76
3	 **97b**[c]	 **96d**	 **98e**	70
4	 **97c**[b]	LiHMDS **96a**	 **98f**	79
5	**97c**[b]	 **96e**	 **98g**	68
6	 **97d**[c]	LiHMDS **96a**	 **98h**	65

7	 **97e**[c]	 **96f**	 **98i**	78
8	**97e**[c]	LiHMDS **96a**	 **98j**	60
9	 **97f**[c]	 **96b**	 **98k**	70
10	 **97g**[c]	 **96f**	 **98l**	66

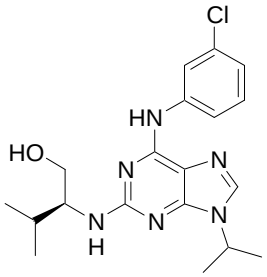
[a] Isolated yield of analytically pure product. [b]1.2 equiv of $(Et_2NCH_2CH_2)_2O$ was added. [c]1.2 equiv of Et_3N was added.

Commercially available 4-chloro-2,6-dimethoxypyrimidine (**70a**) and readily prepared 4-iodo-2,6-dimethoxypyrimidine (**87b**) could be deprotonated at C5 position using TMPMgCl·LiCl (**18a**, 1.1 equiv, 0-25 °C, 1 h) and transmetalated using CuCl·2LiCl (1.2 equiv, -50 °C, 0.7 h) affording the corresponding organocoppers **97d-e**. Their reaction with LiHMDS (**96a**) or N-lithium amide **96f**, in the presence of chloranil, provided 5-amino-2,4-dimethoxypyrimidine derivatives (**98h-i**, 65-78%, entries 6-7) and 5-amino-6-chloro-2,4-dimethoxypyrimidine (**98j**, 60%, entry 8), after deprotection using TBAF. Similarly, the polyfunctionalized cuprated pyrimidines **97f-g** were oxidatively aminated by the secondary lithium amides **96b** and **96f** giving the bromo-aminated pyrimidines (**98k-l**, 66-70%, entries 9-10).

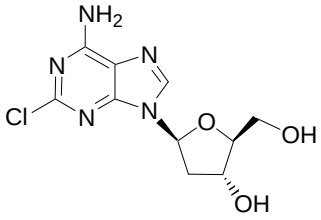
3.3 Selective aminations of purine derivatives

3.3.1 Introduction

Purines are ubiquitous molecules that exist at relatively high (millimolar) concentrations in living organisms. More than 10% of the proteins encoded by the yeast genome evidently depend on a purine-containing ligand for their function. Purines libraries might be expected to have a high probability of yielding bioactive compounds. It seemed likely that structural variation at the 2, 6, 8, or 9 positions might impact specificity towards a variety of target proteins.[125] Several candidates, containing purine skeleton, include amines as substituents and are DNA analogs,[120] such as purvalanol A (**100**),[125a, 126] a CDK inhibitor, and cladribine (**101**),[127] a drug commercialized to treat hairy cell leukemia (Scheme 74).



100: purvalanol A



101: cladribine

Scheme 74: Drugs containing purine skeleton.

The amination of purines in positions 8 and 2 are especially troublesome[128] and involve harsh reaction conditions for the substitution (Scheme 75)[129] or cross-coupling.[130] Therefore, we have developed a selective cupration of purines (via magnesium intermediates) and subsequent oxidative Cu-mediated amination.

---

[125] (a) Chang, Y.-T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Shultz. P. G. *Chem. Biol.* **1999**, *6*, 361; (b) For a review on the synthesis of C-substituted purines using organometallic intermediates, see: M. Hocek. *Eur. J. Org. Chem.* **2003**, 245.

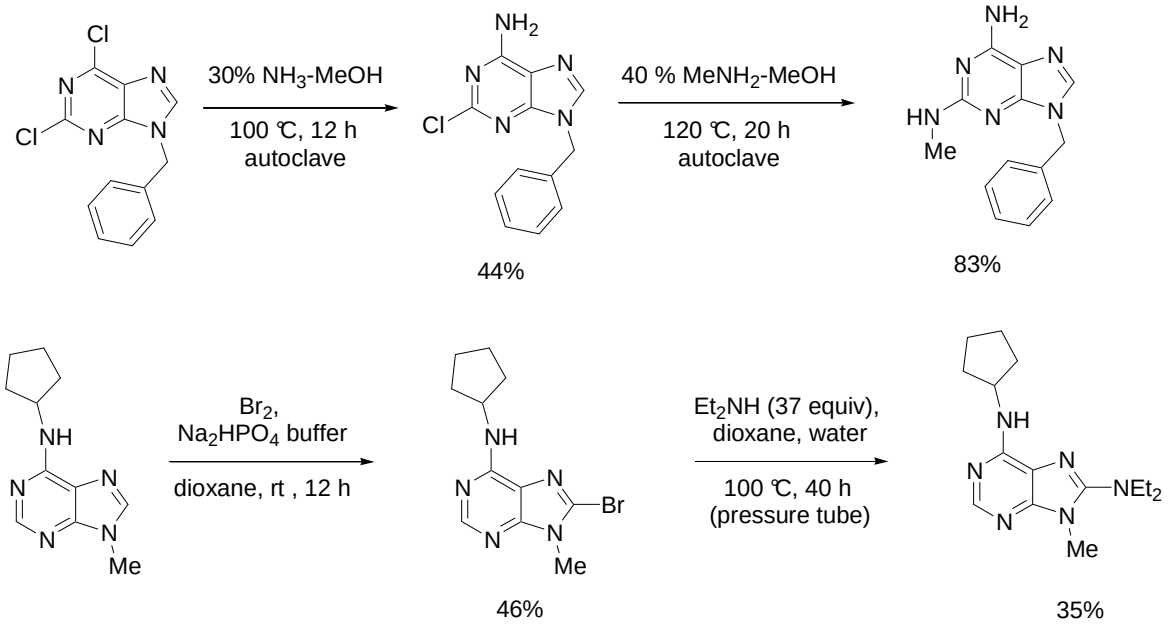
[126] For a preparation of purvalanol A: Taddei, D.; Slawin, A. M. Z.; Woollins, J. D. *Eur. J. Org. Chem.* **2005**, *5*, 939.

[127] (a) Cottam, H. B.; Carson, D. A. *Drug Discovery Research*. **2007**, 393; (b) Janeba, Z.; Francom, P.; Robins M. J. *J. Org. Chem*. **2003**, *68*, 989.

[128] For a recent method of C8-arylamino substitution on purines see: (a) Bookser, B. C.; Matelich, M. C.; Ollis, K., Ugarkar, B. G. *J. Med. Chem*. **2005**, *48*, 3389.

[129] (a) A. Kurimito, T. Ogino, S. Ichii, Y. Isobe, M. Tobe, H. Ogita, H. Takaku, H. Sajiki, K. Hirota, H. Kawakami. *Bioorg. Med. Chem*. **2003**, *11*, 5501; (b) de Ligt, R. A. F.; van der Klein, P. A. M.; Frijtag Drabbe Künzel, J. K.; Lorenzen, A.; El Maate, F. A.; Fujikawa, S.; van Westhoven, R.; van den Hoven, T.; Brussee, J.; IJzerman, Ad. P. *Bioorg. Med. Chem*. **2004**, *12*, 139.

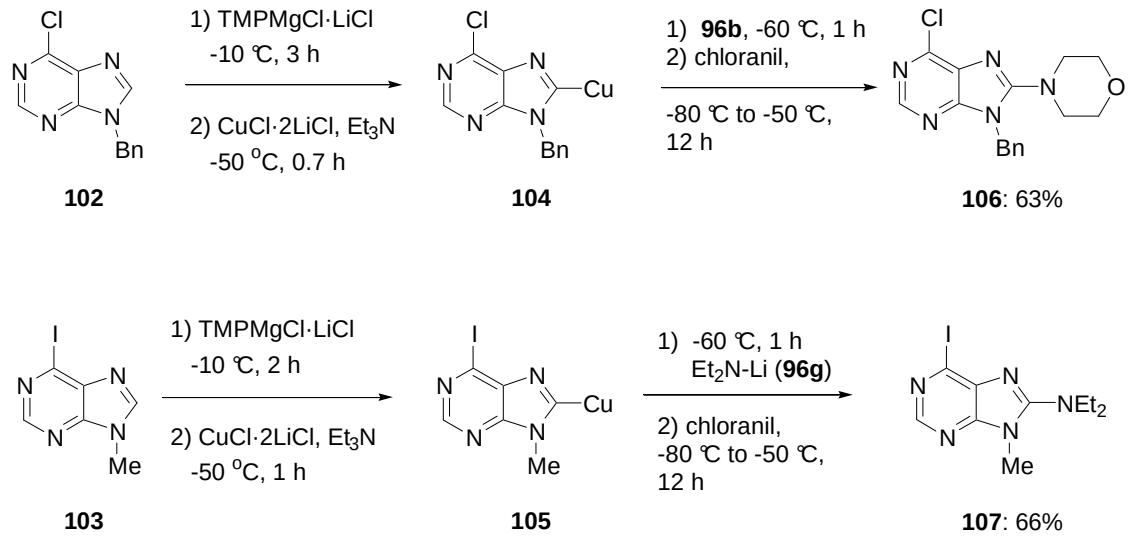
[130] Dai, Q.; Ran, C.; Harvey, R. G. *Org. Lett*. **2005**, *7*, 999.



Scheme 75: Aminations of purines in positions 8 and 2.

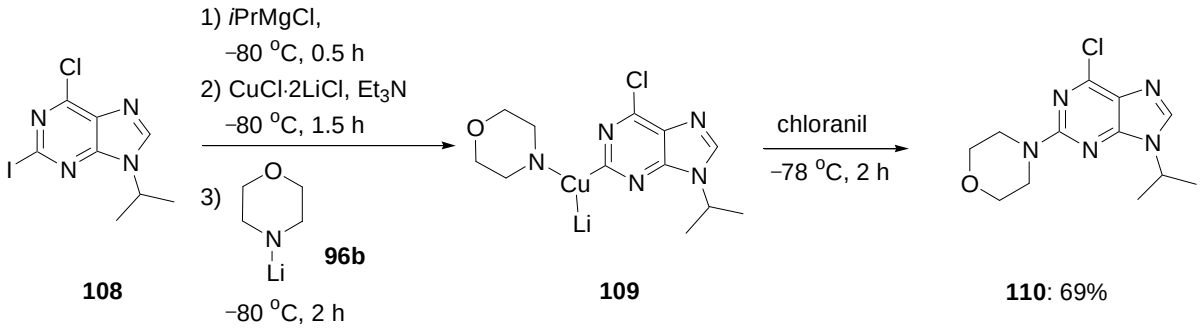
3.3.2 Selective C8 and C2-aminations of purine derivatives

We have first concentrated our efforts on the aminations of positions 8 and 2 starting from readily available purines. Thus, a selective magnesiation in position 8 could be achieved by the reaction of the halogenated purine **102** and **103** (Scheme 76) with TMPMgCl·LiCl (**18a**) under convenient reaction conditions (THF, -10 °C, 2-3 h) giving after Cu-transmetalation the 8-cuprated purines **104** and **105**, which by oxidative amination with lithium N-morpholide (**96b**) or Et_2NLi (**96g**) provided the expected 8-aminated purines (**106** and **107**) in 63-66% yield (Scheme 76).



Scheme 76: Amination at C8 position of protected purines **102** and **103**.

Using *Dvořák´*s conditions[131] for the selective magnesiation in position 2 of the iodopurine **108** and a copper transmetalation (CuCl·2LiCl, Et_3N, -80 °C, 1.5 h) we obtained after the addition of the amide **96b** the amidocuprate **109**. Its treatment with chloranil (-78 °C, 2 h), gave the desired 2-aminated purine **110** in 69% yield (Scheme 77).

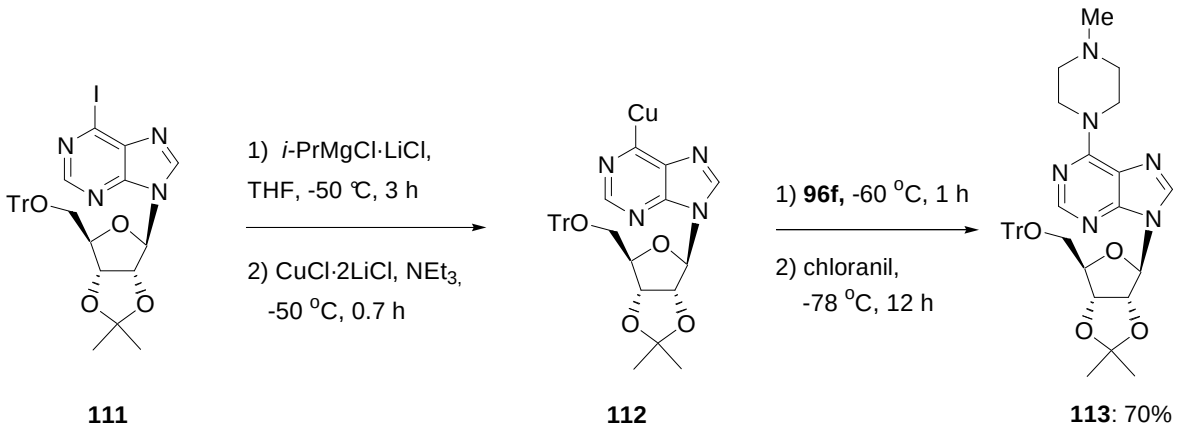


Scheme 77: Amination at C2 position of protected purine **108**.

[131] Tobrman, T.; Dvořák. D. *Org. Lett.* **2006**, *8*, 1291.

3.3.3 Selective C6-amination of purines derivatives. An access to adenine, adenosine units and to the CDK inhibitor purvalanol A.

The mild amination conditions tolerated the presence of a protected ribose unit. Thus, the 6-iodopurine nucleoside **111** was successively magnesiated (*i*PrMgCl·LiCl (**13**), -50 °C, 3 h),[132] and finally aminated via the Cu intermediate **112** with the lithiated N-methylpiperazide (**96f**), furnishing the adenosine derivatives **113** (70%, Scheme 78).

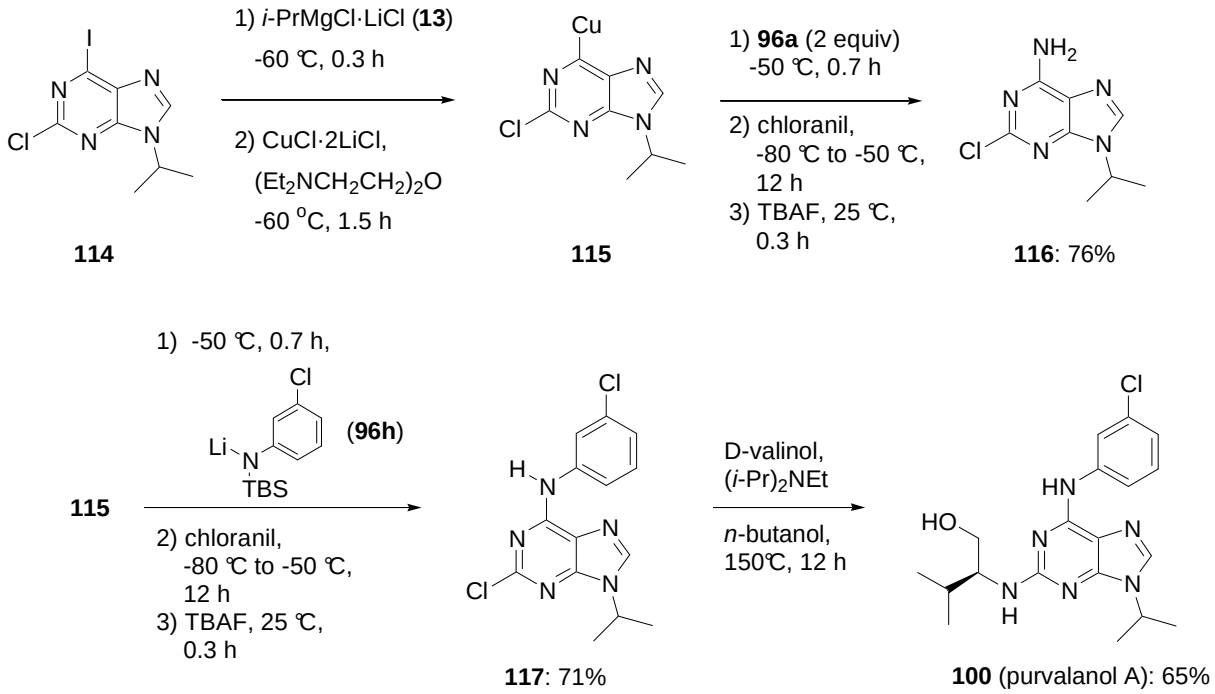


111 **112** **113**: 70%

Scheme 78: Synthesis of an adenosine derivative.

Similarly, adenine analogs were prepared via this oxidative amination. The magnesiation of the iodopurine **114**, transmetalation to **115** provided after an oxidative amination with LiHMDS (**96a**) and chloranil the adenine **116** in 76% yield (Scheme 79). This encouraging result led us to apply the new amination procedure to the synthesis of the CDK inhibitor purvalanol A (**100**).[126] Thus, the amination of the 6-cuprated purine **115** with the lithiated N-TBS-aniline derivative (**96h**) gave the expected adenine derivative **117** in 71% yield. We have completed the synthesis by the reaction of **117** in a sealed tube with D-valinol in the presence of *Hunig´*s base in *n*-butanol (150 °C, 2 h), and obtained purvalanol A (**100**) in 65% yield (Scheme 79).

[132] For the magnesiation of 6-purine nucleoside see: Tobrman, T.; Dvořák. D. *Org. Lett.* **2003**, *5*, 4289.

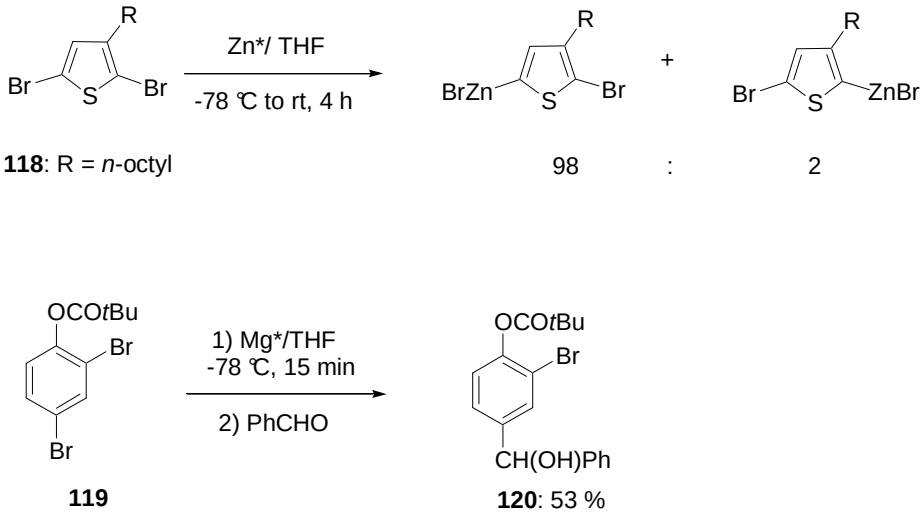


Scheme 79: Amination at C6 position of the iodopurine **114**. Application of to the synthesis of adenine derivative (**116**) and purvalanol A (**100**).

4. Direct Chemo- and Regioselective Zinc Insertions into Polyhalogenated Aryl and N-Heteroaryl Compounds.

4.1. Introduction

The preparation of polyfunctional organozincs is an important synthetic task since they are versatile organometallic reagents.[2,52] Recently, we have found that the addition of LiCl to zinc powder considerably facilitates its insertion into various aryl and heteroaryl iodides and bromides.[62] It is well known, that metalation-directing groups (DMGs) are essential for the regioselective functionalization of aromatics and heterocycles with Li- or Mg-bases.[133] DMGs have also been used to perform regioselective halogen/metal exchanges[19, 134] and metalations[34b, 35a, 37, 135] but rarely direct metal insertion. By the best of our knowledge, the only selective metal insertions described in the literature were made by *Rieke* (Scheme 80).[136] These two examples showed a regiocontrol of the zinc and the magnesium insertions using bulky alkyl groups as directing groups. Rieke zinc (Zn*) underwent a direct oxidative addition to the C-Br bond primarly at the 5-position of **118** at -78 °C (Scheme 80).[136a]

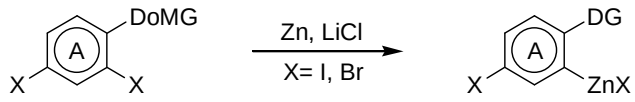


Scheme 80: Regioselective zinc and magnesium insertions.

[133] (a) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Wagner, F. F.; Comins, D. L. *Eur. J. Org. Chem.* **2006**, 3562. (d) Katritzky, A. R.; Xu, Y.-J.; Jain, R. *J. Org. Chem.* **2002**, *67*, 8234.
[134] (a) Rieke, R. D. *Science* **1989**, *246*, 1260. (b) Wu, X.; Rieke, R. D. *J. Org. Chem*. **1995**, *60*, 6658.
[135] (a) Schlosser, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 376.
[136] (a) For a regioselective Zn/Br-insertion, see: Chen, T.-A.; Wu, X.; Rieke, R. D. *J. Am. Chem. Soc*. **1995**, *117*, 233. (b) For a regioselective Mg/Br insertion, see: Lee, J.-S.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

Rieke demonstrated that highly reactive magnesium displayed unusual selectivity in the insertion into bulky ester **119**. He postulated that the sterically hindered ester prevented the coordination of the ester to the magnesium surface and led to the corresponding *para*-product (**120**, Scheme 80) after quenching with benzaldehyde.[136b]

We decided to focus our attention on the regioselectivity of the zinc insertion in the presence of LiCl into poly-iodo and -bromo aryls and N-heteroaryls of type **121** (Scheme 81). We studied the control of the insertion by DoMGs (Directing *ortho*-Metalation Groups) such as an ester or a tosylate, or by the presence of an appropriate heteroatom which should lead selectively to zincated intermediates of type **122** (Scheme 81).



121: A: aryl or N-heteroaryl **122**

Scheme 81: LiCl-mediated regioselective zinc insertion of aryls and heteroaryl compound of type **121**.

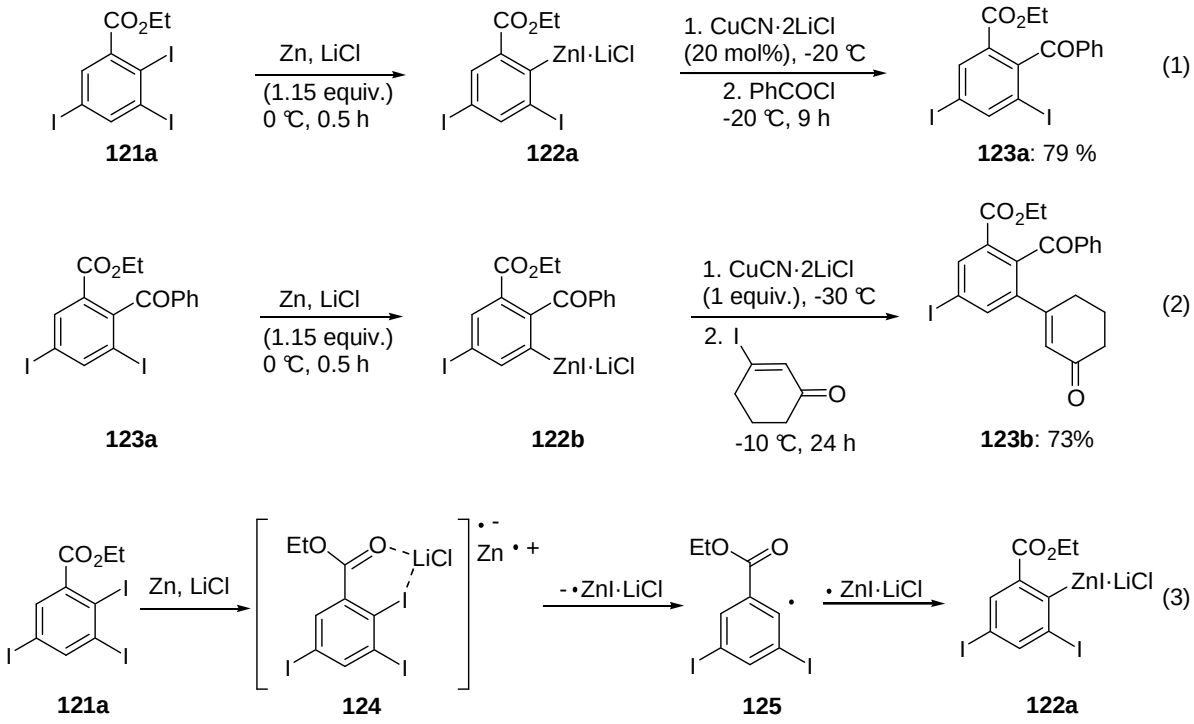
4.2. DoI (Directed *ortho*-Insertion): a new access to aryl functionalized zinc reagents

4.2.1 Successive zinc insertion into triiodobenzoate and a proposed mechanism

We first studied the triiodobenzoate **121a**[137] and showed that it reacted readily with zinc dust[7] (1.15 equiv) and LiCl (1.15 equiv) in THF at 0 °C, furnishing after 0.5 h the *ortho*-zincated intermediate **122a** (Scheme 82). After the addition of CuCN·2LiCl (20 mol%), a smooth benzoylation with PhCOCl provided the aromatic ketoester **123a** in 79% yield (Eq. 1). Interestingly, the diiodide **123a** further underwent a selective zinc insertion giving the polyfunctional zinc reagent **122b** which after transmetalation with CuCN·2LiCl reacted with 3-iodocyclohexenone affording the substitution product **123b** in 73% yield (Eq. 2). In the absence of LiCl no zinc insertion was observed and higher reaction temperature led to unselective reactions. The origin of this unprecedented regioselectivity for a direct metal insertion is certainly due to the presence of an *ortho*-directing group. LiCl may chelate to this directing group and to the *ortho*-iodide, leading after an electron transfer from the zinc surface, the intermediate radical anion **124** (Scheme 82). The departure of the radical •ZnI

[137] This example was studied by the co-authors (Sase, S. and Sinha, P.) of the publication: *J. Am. Chem. Soc.* **2007**, *129*, 12358.

(facilitated by the presence of LiCl) provides the radical **125**, which gives after the recombination with •ZnI the zinc reagent **122a**. This directing effect explains also the regioselectivity of the second zinc insertion leading to the zinc reagent **122b**.



Scheme 82: Regioselective and successive zinc insertions to the triiodobenzoate **121a**.

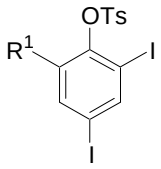
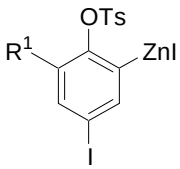
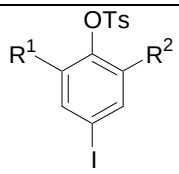
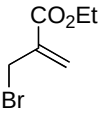
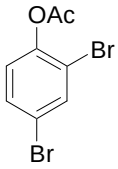
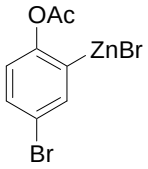
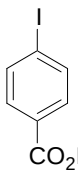
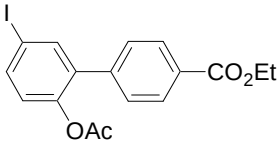
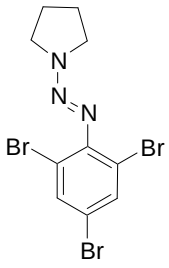
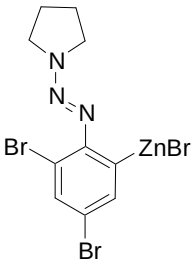
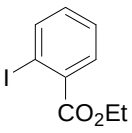
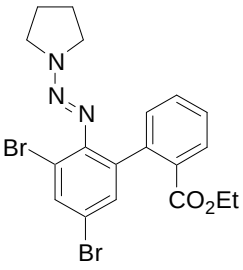
4.2.2 Regioselective zinc insertions into diiodo-and dibromo-aryl compounds

We have found that other chelating groups such as an aryl sulfonate,[138] an acetate, or a triazene,[139] display the similar directing abilities. Thus, the 3,5-diiodobenzonitrile **121c** reacts regioselectively with zinc dust in the presence of LiCl (1.15 equiv) at 0 °C, furnishing the *ortho*-zincated product **122c** (Table 7). After a copper(I)-catalyzed allylation, the aryl iodide **123c** was obtained in 82% yield (entry 1). Similarly, the diiodobenzoate **121d** underwent a selective zinc insertion providing the arylzinc **122d**, which after a reaction with ethyl (2-bromomethyl)acrylate[83] gave the polyfunctional diester **123d** in 85 % yield (entry 2). The dibromoarene **121e**, bearing an acetate as DoI group, is sufficiently reactive toward a zinc insertion and afforded the desired zinc reagent **122e** (entry 3; 50 °C, 20 h). In the absence of LiCl, only starting material decomposition is observed. The zinc reagent **122e** underwent a

[138] (a) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4364. (b) Lin, W.; Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *44*, 4258.
[139] (a) Liu, C. J.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543. (b) Saeki, T.; Son, E.-C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617.

Pd-catalyzed Negishi cross-coupling reaction[54] with methyl 4-iodobenzoate furnishing the biphenyl **123e** in 73 % yield.

Table 7: Preparation and reaction of aryl functionalized zinc reagents of type **122**.[140]

entry	aryl halide	zinc reagent[a] (conditions)	electrophile	product of type **123**, yield (%)[b]
1	 **121c**: R^1 = CN	 (0 ˚C, 12 h) **122c**: R^1 = CN	CH_2=CH-CH_2Br	 **123c**: R^1 = CN, R^2 = C_3H_5, 82[c]
2	**121d**: R^1 = CO_2Et	(0 ˚C, 12 h) **122d**: R^1 = CO_2Et		**123d**: R^1 = CO_2Et, R^2 = $CH_2C(CO_2Et)CH_2$, 85[c]
3	 **121e**	 **122e** (50 ˚C, 20 h)		 **123e**: 73[e]
4	 **121f**	 **122f** (50 ˚C, 20 h)		 **123f**: 76[e]

[a] X = I·LiCl or Br·LiCl [b] Isolated yield of analytically pure product. [c] Catalytic amount of CuCN·2LiCl was added. [d] 1 equiv of CuCN·2LiCl was added. [e] 1 mol % of $Pd(Ph_3P)_4$ was added.

Remarkably, the mild conditions of the lithium chloride-mediated zinc insertion tolerate also a triazene moiety which is an important synthetic equivalent of a diazonium function.[141] Thus, the readily available tribromoaryltriazene **121**[142] was converted with Zn/LiCl (2 equiv) to the zinc reagent **122f** (50 °C, 20 h) and provided after the Negishi cross-coupling reaction with

[140] These products were prepared by the co-authors (Sase, S.; Sinha, P.; Liu, C;-Y.) of the publication: *J. Am. Chem. Soc*. **2007**, *129*, 12358.
[141] Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805.
[142] For the preparation of tribromoaryltriazene **1h**, see: Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T. Y.; Natarajan, S.; Chu, X. J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584.

methyl 2-iodobenzoate the polyfunctionalized dibromoaryltriazene **123f** in 76 % yield (entry 4).

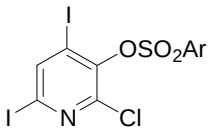
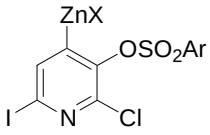
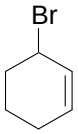
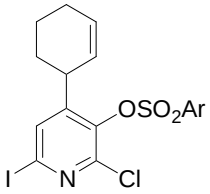
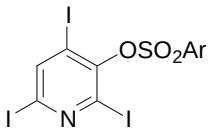
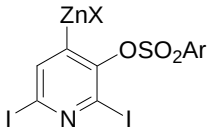
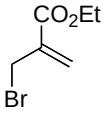
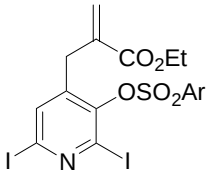
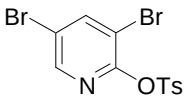
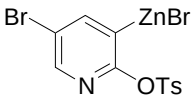
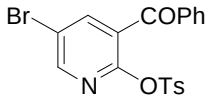
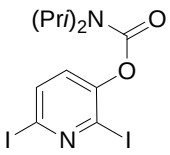
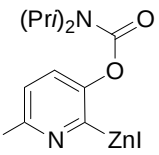
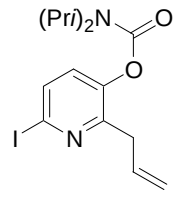
4.3. DoI (Directed *ortho*-Insertion): a new access to N-heteroaryl functionalized zinc reagents

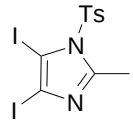
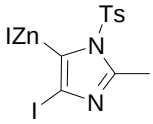
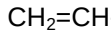
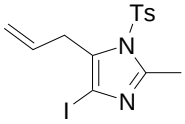
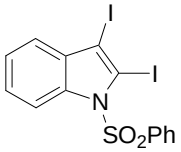
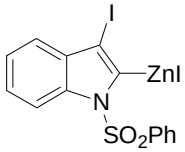
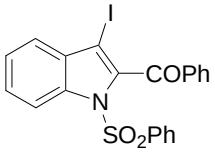
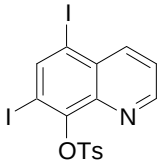
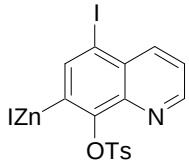
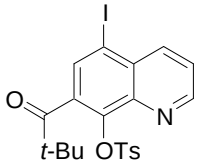
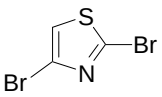
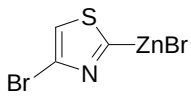
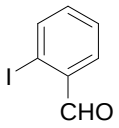
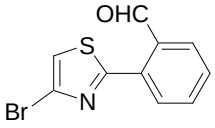
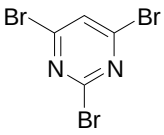
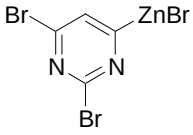
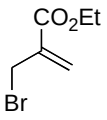
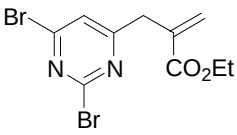
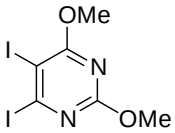
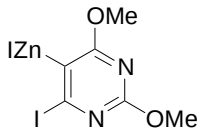
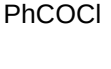
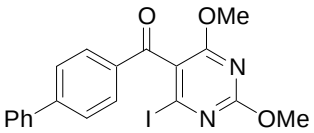
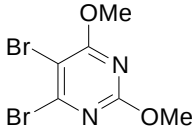
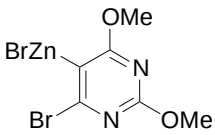
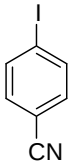
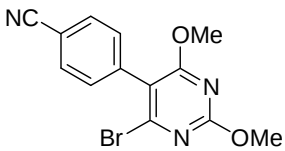
We have examined the scope of this regioselective insertion on various N-heterocycles. Interestingly, various di- or tri- iodo- or bromo-pyridines **121g-i** bearing a sulfonate functionality[138] could be chemo- and regioselectively converted to the *ortho*-zincated pyridyl-sulfonates **122g-i** (Table 8). Their copper(I)-catalyzed allylation or benzoylation afforded the polyfunctional pyridines **123g-i** in 80-83 % yield (Table 8, entries 1-3). Interestingly, the carbamate group[143] smoothly directed the zinc insertion of the diiodopyridine **121j** with complete regioselectively leading to the zinc derivative **122j** (entry 4). After allylation, the polyfunctional pyridine **123j** was obtained in 83% yield. Various other diiodo- N-heterocyclic compounds such as the 4,5-diiodoimidazole[144] **121k** and the 2,3-diiodoindole **121l** were converted at 50 °C within 2 h to the zinc reagents **122k** and **122l** (entries 5 and 6). In the presence of CuCN·2LiCl,[57] the addition of allyl bromide and benzoyl chloride led to the corresponding allylated iodoimidazole (**123k**) and the indole derivative **123l** in 80-83% yield (entries 5 and 6). A tosylate is also an excellent DoI group. Thus, the 5,7-diiodoquinoline **121m** inserts selectively zinc in the presence of LiCl at 25 ˚C and led, after transmetalation with CuCN·2LiCl and quenching with pivaloyl chloride to the polyfunctional quinoline **123m** in 78% yield (entry 7). The mild conditions of the Zn/LiCl insertion allow performing regioselective zinc insertion on heterocycles, having well differentiated reactivity sites. Thus, 2,5-dibromothiazole[145] **121n** underwent a selective zincation at 25 ˚C and gave the heteroarylzinc bromide **122n** (entry 8). The Pd-catalyzed Negishi cross-coupling with 2-iodobenzaldehyde furnished the corresponding aldehyde **123n** in 85 % yield. A selective zinc insertion occured with the tribromopyrimidine **121o** at 25 ˚C within 4 h, leading to the zincated dibromopyrimidine **122o** (entry 9). Addition of ethyl (2-bromomethyl)acrylate[83] in the presence of catalytic amount of CuCN·2LiCl led to the substituted dibromopyrimidine **123o** in 63% yield. The zinc insertion into the 4,5-diiodo- and 4,5-dibromo-2,6-dimethoxypyrimidine (**89a** and **69b**) was found to be regioselective. Thus, treatment of 4,5-diiodo-2,6-dimethoxy-pyrimidine (**89a**) with Zn/LiCl (1.5 equiv, 50 ^{o}C, 3 h, entry 10) resulted

[143] Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem*. **2005**, *70*, 7149.
[144] (a) For the preparation of 4,5-diiodo-2-methyl-1H-imidazole, see: Bell, A.S.; Campbell, S. F.; Morris, D. S.; Roberts, D. A.; Stefaniak, M. H. *J. Med. Chem*. **1989**, *32*, 1552. (b) Lipshutz, B. H.; Hagen, W. *Tetrahedron Lett*. **1992**, *33*, 5865.
[145] Delgado, O.; Heckmann, G.; Mueller, H. M.; Bach, T. *J. Org. Chem*. **2006**, *71*, 4599.

only in the insertion into the C–I bond at position 5 to give the zinc reagent **122p**. Treatment of **122p** with benzoyl chloride in the presence of CuCN·2LiCl (0.5 equiv) provided the product **123p** in 83% yield. A regioselective zinc insertion at position C5 into 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) was also achieved under mild reaction conditions (12 h, 25 ^{o}C, entry 11). The corresponding zinc reagent **122q** reacted in the Negishi cross-coupling with 4-iodobenzonitrile to give the polyfunctional 4-bromo-2,6-dimethoxypyrimidine **123q** in 86% yield.

Table 8: Preparations and reactions of unsaturated organozinc reagents of type **121** leading to products of type **122**.

entry	aryl halide	zinc reagent (conditions)	electrophile	product of type **123**, yield (%)[b]
1[f]	 **121g**	 **122g** (0 ˚C, 2.5 h)		 **123g**: 83[c]
2[f]	 **121h**	 **122h** (0j ˚C, 2.5 h)		 **123h**: 80[c]
3	 **121i**	 **122i** (25 ˚C, 20 h)	PhCOCl	 **123i**: 81[d]
4	 **121j**	 **122j** (25 ˚C, 5 h)	CH_2=CH-CH_2Br	 **123j**: 83[c]

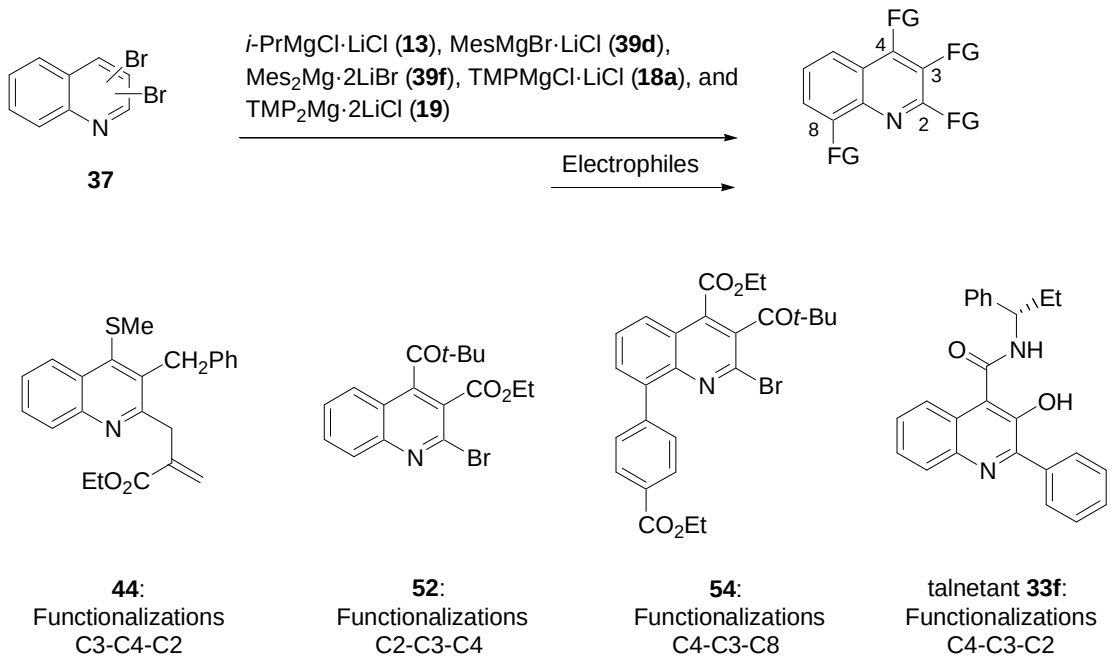
				
5	**121k**	**122k** (50 ˚C, 2 h)		**123k**: 80[c]
				
6	**121l**	**122l** (50 ˚C, 2 h)		**123l**: 83[d]
				
7	**121m**	**122m** (25 ˚C, 12 h)		**123m**: 78[d]
				
8	**121n**	**122n** (25 ˚C, 0.5 h)		**123n**: 85[e]
				
9	**121o**	**122o** (0 ˚C, 12 h)		**123o**: 63[c]
				
10	**89a**	**122p** (50 ˚C, 3 h)		**123p**: 83[g]
				
11	**69b**	**122q** (25 ˚C, 12 h)		**123q**: 86[h]

[a] X = I·LiCl or Br·LiCl [b] Isolated yield of analytically pure product. [c] Catalytic amount of CuCN·2LiCl was added. [d] 1 equiv of CuCN·2LiCl was added. [e] 1 mol % of $Pd(Ph_3P)_4$ was added. [f] Ar = 4-ClC_6H_4. [g] 0.5 equiv of CuCN·2LiCl was added. [h] $Pd(dba)_2$ (5 mol%) and P(o-furyl)$_3$ (10 mol%) were added.

5. Summary and Outlook

5.1. Functionalizations of Quinoline Moieties *via* Chemo- and Regioselective Magnesiations.

In summary, we have described various versatile regioselective functionalizations of quinolines *via* chemo- and regioselective magnesiation reactions using appropriate Mg-reagents such as *i*-PrMgCl·LiCl, MesMgBr·LiCl, Mes_2Mg·2LiBr, TMPMgCl·LiCl, and TMP_2Mg·2LiCl (Scheme 83). Several sensitive functionalities such as an ester and a ketone were tolerated. This approach opened a new route for the direct preparation of drug analogs, containing the quinoline skeleton. An application to the total synthesis of the biologically active compound talnetant was performed (6 steps, 28%).

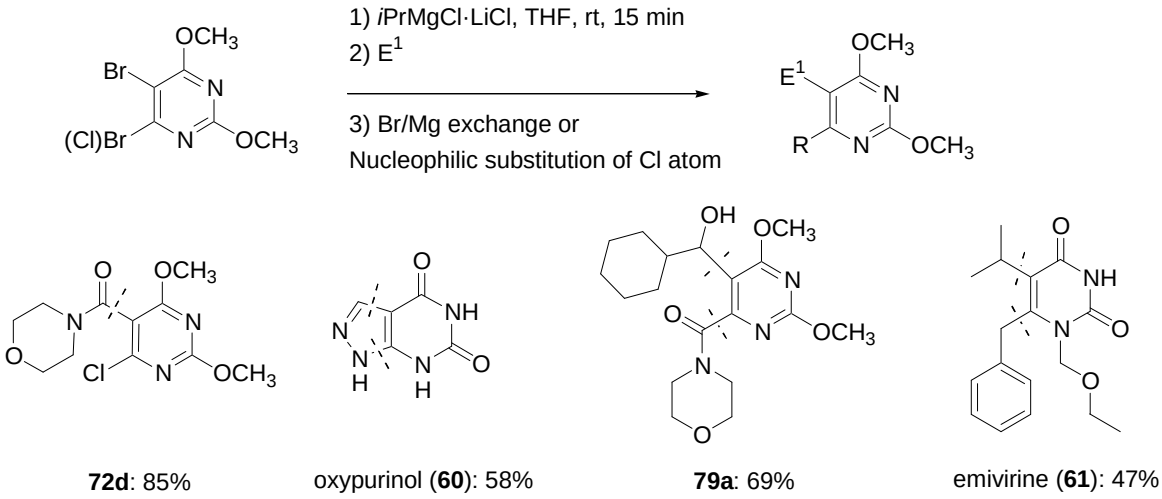


Scheme 83: Sequences of selective functionalizations of quinoline cores.

An extension of this study would be the regioselective magnesiation of quinolines at C5, C6 and C7 positions inducing by DoM groups, and the regioselective functionalizations of isoquinoline moiety.

5.2. Functionalizations of Protected Uracils *via* Chemo- and Regioselective Magnesiations.

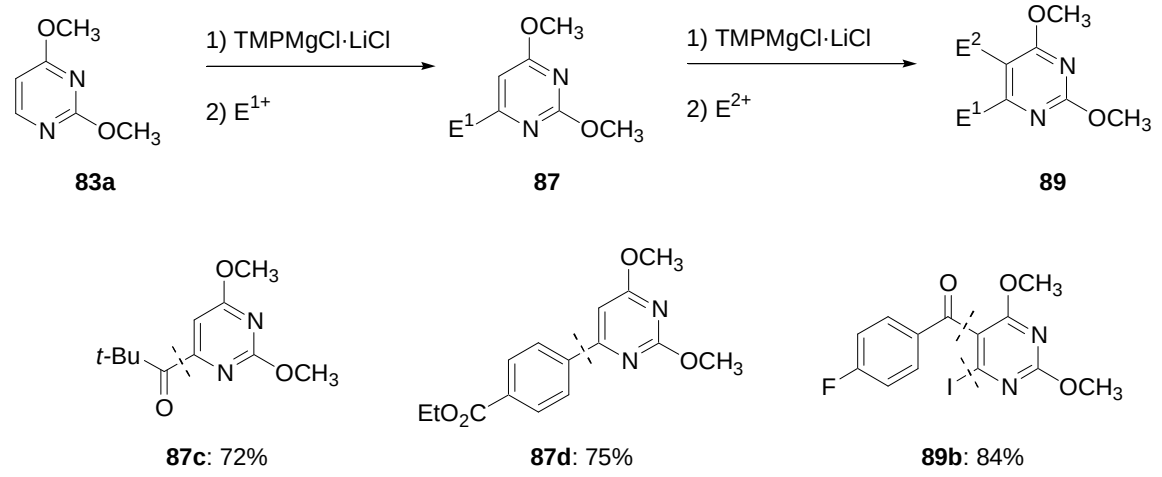
We have developed a chemo- and regioselective functionalization method of uracils *via* successive Br/Mg-exchanges using *i*-PrMgCl·LiCl (**13**). We applied this method to the synthesis of biologically active uracils like oxypurinol (**60**) and emivirine (**61**) and opened a new route to synthesis of their analogs (Scheme 84).



72d: 85% oxypurinol (**60**): 58% **79a**: 69% emivirine (**61**): 47%

Scheme 84: Polyfunctionalization of protected uracils via Br/Mg exchange.

By using the mixed Mg/Li amide base TMPMgCl·LiCl (**18a**), the successive direct deprotonations and functionalizations at 6-position (**87**) and 5-position (**89**) of 2,4-dimethoxypyrimidine (**83a**) has been achieved, opening a novel route for the synthesis of 5,6-difunctionalized protected uracils (Scheme 85).



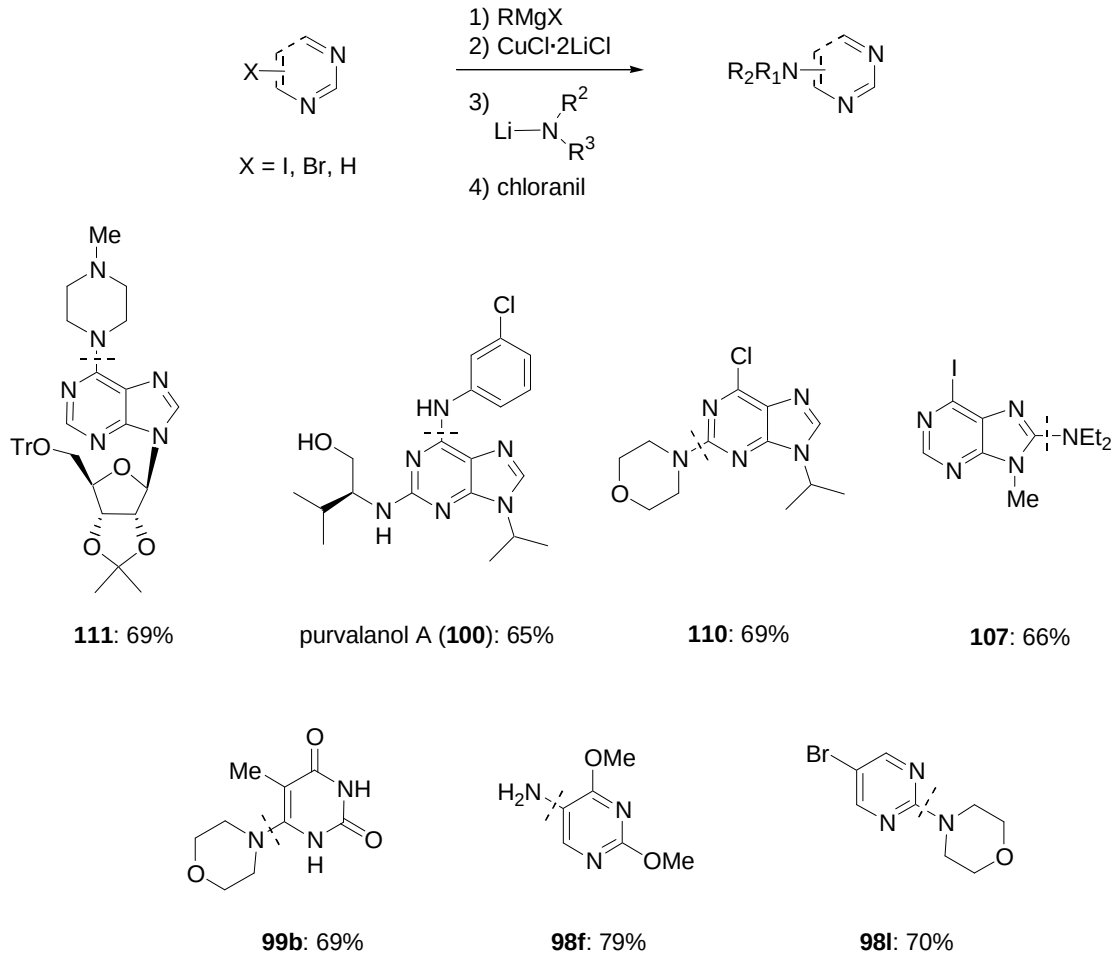
83a **87** **89**

87c: 72% **87d**: 75% **89b**: 84%

Scheme 85: Polyfunctionalization of protected uracils via direct magnesiation using **18a**.

5.3. Amination of DNA and RNA units via cuprated pyrimidines and purines

Recently, we have found a new amination procedure via the oxidative coupling of aryl and heteroaryl amidocuprates using chloranil. We have achieved using this method, the preparation of primary, secondary and tertiary amino-pyrimidines and purines (Scheme 86). We believe that this method gives an alternative to common amination procedures, usually involving harsh reactions conditions. This practical amination protocol led to aminated pyrimidine (**98l**) and uracil derivatives (**98f**), 6-aminated thymine (**99b**), adenine and adenosine derivatives (**100**, **111**) and to challenging C2 and C8 aminated purines **110** and **107**.

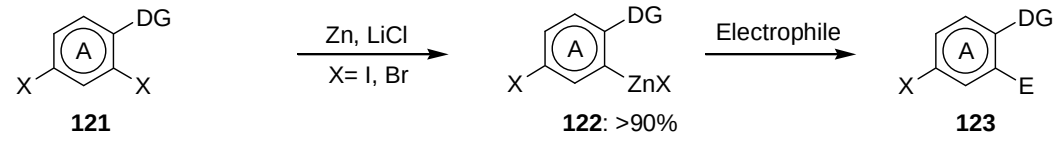


Scheme 86: Aminated DNA and RNA units via an oxidative coupling method.

As this method tolerates the ribose unit, it may have a real potential for preparing DNA and RNA nucleoside analogs. Moreover, one extension of this method could be the use of lithiated diprotected amino-alcohols. Amino-alcohols, as amines, are present in several drug candidates and are often implemented under harsh conditions (cf the synthesis of purvalanol A with D-valinol).

5.4. Direct chemo- and regioselective zinc insertions into polyhalogenated N-heteroaryl compounds

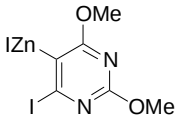
We have demonstrated that in the presence of LiCl, a regioselective insertion of zinc powder occurred into various poly- iodo- and bromo- aryls and heteroaryls. This exceptional regioselectivity was obtained starting from substrates bearing various "*ortho*-directing group" possessing chelating properties such as an ester, a ketone, an aryl sulfonate, an acetate, a triazene or a carbamate, or/and the presence of an appropriate heteroatom in the case of polyhalogenated heterocycles. By this new concept DoI (Directed *ortho*-Insertion), we have prepared a wide range of polyfunctional N-heterocyclic zinc reagents of type **122** (Scheme 87).



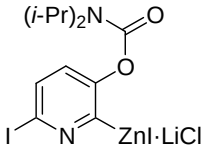
121 **122**: >90% **123**

A: aryl or N-heteroaryl

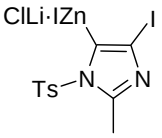
Directing group (DG) = -CO_2R, -COR, -OAc, -N=N-NR_2, -OCON(*i*-Pr)$_2$, -OSO_2Ar



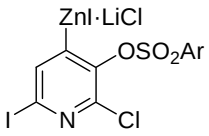
122p



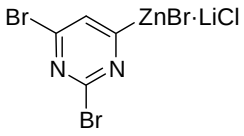
122j



122k



122h: (Ar= 4-ClC_6H_4)



122o

Scheme 87: Regioselective zinc insertion into polyhalogenated N-heteroaryl compounds.

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C: Experimental Section

1. General Considerations

All reactions were carried out with magnetic stirring and, if air or moisture sensitive, in flame-dried glassware under argon. Syringes were used to transfer reagents, and solvents were purged with argon prior to use.

Solvents

Solvents were dried according to standard methods by distillation from drying agents as stated below and were stored under argon.

CH_2Cl_2 and **toluene** were predried over $CaCl_{2(s)}$ and distilled from $CaH_{2(s)}$.

Diethyl ether and **THF** were continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Dimethylformamide (DMF) was heated to reflux for 14 h over $CaH_{2(s)}$ and distilled from $CaH_{2(s)}$.

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

Methanol was treated with magnesium turnings (20g/L) and sodium, heated to reflux for 6 h and distilled.

Triethylamine was dried over $KOH_{(s)}$ and distilled from $KOH_{(s)}$.

Reagents*: *Metal salts solution

CuCN·2LiCl solution (1.0 M/THF) was prepared by drying CuCN (869 mg, 10 mmol) and LiCl (848 mg, 20 mmol) in a Schlenk flask under vacuum for 5 h at 140 °C. After cooling to 25 °C, dry THF (10 mL) was added and stirred continuously until the salts were dissolved.

CuCl·2LiCl solution (1.0 M in THF): A dry and argon-flushed 50 mL Schlenk-flask, equipped with a magnetic stirrer and a glass stopper, was charged with LiCl (1.7 g, 40 mmol) and heated up to 130 °C under high vacuum for 1 h. After cooling to 25 °C under argon, CuCl (1.98 g, 20 mmol, 99.5% Cu) was added under inert atmosphere inside a glove-box. The Schlenk-flask was further heated to 130 °C for 5 h under high vacuum, cooled to 25 °C, charged with freshly distilled THF (20 mL) under argon flush and wrapped with an aluminium foil to protect it from light. The mixture was vigorously stirred until all solid goes in solution (ca. 6 h.). The reagent CuCl·2LiCl (1 M in THF) appears as a colourless or slightly yellow solution.

$ZnBr_2$ solution (1.0 M/THF) was prepared by drying $ZnBr_2$ (33.78 g, 150 mmol) under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (150 mmol) was added and stirred continuously until the salts were dissolved.

$ZnCl_2$ solution (1.0 M/THF) was prepared by drying $ZnCl_2$ (20.45 g, 150 mmol) under vacuum for 5 h at 150 °C. After cooling to 25 °C, dry THF (150 mmol) was added and stirred continuously until the salts were dissolved.

$LaCl_3 \cdot 2LiCl$ solution in THF (0.33 M) was prepared following the literature.[108]

Lithiated reagents

***n*-Butyllithium** was used as a 1.5 M solution in hexane purchased by Chemetall.
***t*-Butyllithium** was used as a 1.5 M solution in pentane purchased by Chemetall.
Methyllithium was used as a 1.7 M solution in Et_2O purchased by Chemetall.

Magnesiated reagents

***i*-PrMgCl**: A dry three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (110 mmol). A small amount of THF was added to cover the magnesium, and a solution of isopropyl chloride (100 mmol) in THF (50 mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete, the reaction mixture was stirred for 12 h at 25 °C. The grey solution of *i*-PrMgCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98 % of *i*-PrMgCl was obtained and the *i*-PrMgCl-solution was titrated prior to use according to reported literature.[146]

PhMgCl was used as a 2.0 M solution in THF purchased by Chemetall.

***i*-PrMgCl·LiCl (13)**: A dry three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol). A small amount of THF was added to cover the magnesium, and a solution of isopropyl chloride (100 mmol) in THF (50 mL) was added dropwise, keeping the

[146] (a) H. S. Lin, L. Paquette, *Synth. Commun.* **1994**, *24*, 2503; (b) A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

temperature of the mixture below 30 °C (water bath). After the addition was complete, the reaction mixture was stirred for 12 h at 25 °C. The grey solution of *i*-PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98 % of *i*-PrMgCl·LiCl was obtained and the *i*-PrMgCl·LiCl-solution was titrated prior to use according to reported literature.[146]

s-BuMgBr·LiCl (39a), PhMgBr·LiCl (39b), 1-naphtylmagnesium chloride (39c), MesMgBr·LiCl (39d), and **1,3,5-triisopropylphenylmagnesium bromide (39e)**, were prepared according to the procedure of ***i*-PrMgCl·LiCl** (**13**) from the corresponding bromides.

Mes_2Mg·2LiBr (39f): A solution of *t*-BuLi in pentane (190 mmol, 1.70 M) was added dropwise at -78 °C to a solution of mesitylbromide (100 mmol) in Et_2O (25 mL) for 15 min. The resulting mixture was first warmed to -20 °C, and stirred for 1 h, and then warmed to 25 °C. The solvents were evaporated under vacuum for 1 h. To the obtained lithium salt, a solution of MesMgBr[147] in THF (105 mmol, 0.65 M) was added at -50 °C and stirred for 1 h. Thereafter, the mixture is allowed to warm to 25 °C and stirred for 12 h. A clear solution of Mes_2Mg·LiBr is obtained and the concentration (0.61 M of [Mg] in THF) was checked by titration of iodine (1mmol).

TMPMgCl·LiCl (18a): A dry and nitrogen-flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*-PrMgCl·LiCl(100 mL, 1.2 M in THF, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH) (19.8 g, 126 mmol, 1.05 equiv.) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C until gas evolution was completed (ca. 24 h).[37] The concentration of the solution of TMPMgCl·LiCl was titrated by using benzoic acid in dry THF and 4-(phenylazo)diphenylamine as an indicator.

TMP_2Mg·2LiCl (19): was prepared according to the known procedure.[40]

[147] This reagent was directly used from commercial sources such as Aldrich.

Other reagents

The following reagents were prepared according to literature procedures: Palladium(II)bis(dibenzylidenacetone),[148] tri-(2-furyl)phosphine[149], ethyl 2-(bromomethyl)-acrylate,[83] *S*-phenyl benzenesulfonothioate[81] and *S*-phenyl benzenesulfonothioate.[82]

Chromatography

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

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

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh ASTM) from Merck or aluminium oxide 90 active neutral (0.063-0.200 mm, 70-230 mesh ASTM), grade III,[150] from Merck.

Preparative TLC were performed using PSC-Plates 20 x 20 cm, Kieselgel 60 F_{254}, 2 mm, from Merck.

The diameters of the columns and the amount of silicagel were calculated according to the recommendation of W. C. Still.[151]

Analytical Data

NMR-spectra were recorded on *Bruker* ARX 200, AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ–values in ppm relative to the deuterated solvent peak: $CDCl_3$ (δ 3 H = 7.25; δ C (ppm) = 77.0), DMSO-d_6 (δ 6 H = 2.49; δ C(ppm) = 39.5).

[148] Y. Takahashi, T. Ito, S. Sakai, *Chem. Comm.* **1970**, 1065.
[149] D. W. Allen, B. G. Hutley, M. T. J. Mellor, *J. Chem. Soc. Perkin Trans. II* **1972**, 63.
[150] Brockmann, H.; Schodder, H. *Ber. Deut. Chem. Ges*. **1941**, *74*, 73.
[151] W. C. Still, M. Khan, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

For the characterization of the observed signal multiplicities, the following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (doublet of triplets), quint (quintet), sext (sextet), sept (septet), br (broad). If not otherwise noted, the coupling constants given are (CH)- coupling constants.

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

Infrared spectra were recorded from 4000-400 cm^{-1} on a *Nicolet* 510 FT-IR or a *Perkin-Elmer* 281 IR spectrometer. Samples were measured either as film between potassium bromide plates (film), as potassium bromide tablets (KBr), or neat (*Smiths Detection* DuraSampl *IR* II Diamond ATR).
The absorption bands are reported in wavenumbers (cm^{-1}). For the band characterization, the following abbreviations were used: br (broad), vs (very strong), s (strong), m (medium), w (weak).

Gas chromatography (GC) was performed with machines of the types *Hewlett-Packard* 6890 or 5890 Series II, using a column of the type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). The detection was accomplished using a flame ionization detector. Depending on the retention time of the substrate, decane or tetradecane were used as internal standards.
Mass Spectra were recorded on a *Finnigan* MAT 95Q or *Finnigan* MAT90 instrument for electron impact ionization (EI). High resolution mass spectra (HRMS) were recorded on the same instrument.
For the combination of gas chromatography with mass spectroscopic detection, a GC-MS of the type *Hewlett-Packard* 6890 / MSD 5793 networking was used (column: HP 5-MS, *Hewlett-Packard*; 5% phenylmethylpolysiloxane; length: 15 m, diameter 0.25 mm; film thickness: 0.25 μm).

2. Functionalizations of Quinoline Moieties *via* Chemo- and Regioselective Magnesiations

2.1. General procedure for the Br/Mg exchange reaction using *i*-PrMgCl·LiCl (13) or MesMgBr·LiCl (39d) as magnesiation reagent (GP1).

A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with the quinoline derivative (1 equiv) dissolved in dry THF (1.0 M solution). The magnesiation reagent *i*-PrMgCl·LiCl (**13**) or MesMgBr·LiCl (**39d**) (1.1 equiv) was added slowly, dropwise, at appropriate temperature (as stated in the experiment). The reaction mixture was stirred at the same temperature, and the completion of the Br/Mg exchange was checked by GC-analysis using decane as internal standard or by TLC. The freshly prepared magnesium reagent was cooled to the corresponding temperature or used at 25 °C and the corresponding electrophile (1.1-1.5 equiv) or its solution in THF was added. The mixture was stirred for a time depending on the reactivity of the electrophile. The consumption of the magnesium reagent was checked by GC-analysis, using decane as internal standard. After the reaction was completed, sat. NH_4Cl solution was added, the mixture was extracted three times with Et_2O or EtOAc and dried over anhydrous Na_2SO_4. The solvent was evaporated and the product was purified by *flash*-chromatography (SiO_2).

2.2. General procedure for the deprotonation using TMPMg·LiCl (18a) as magnesiation reagent (GP2).

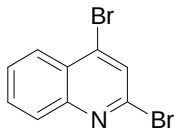
A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with the quinoline derivative (1 equiv) dissolved in dry THF (1.0 M solution) and 1.1 equivalents of TMPMg·LiCl (**18a**) were added dropwise at the given temperature. The reaction mixture was stirred at the same temperature, and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. The freshly prepared magnesium reagent was cooled to the corresponding temperature or used at 25 °C and the corresponding electrophile (1.2 equiv) or its solution in THF was added. The mixture was stirred for a time depending on the reactivity of the electrophile. The consumption of the magnesium reagent was checked by GC-analysis, using decane as internal standard. After the reaction was completed, sat. NH_4Cl solution was added, the mixture was extracted three times with Et_2O or EtOAc and dried over anhydrous Na_2SO_4. The solvent was evaporated and the product was purified by *flash*-chromatography (SiO_2).

2.3. General procedure for the reaction with acyl chlorides (GP 3)

According to **GP1** or **GP2**, the freshly prepared magnesium reagent was cooled to −40 °C, and CuCN·2LiCl[57] (1 equiv, 1.00 M in THF) was added and stirred for 30 min. Thereafter, acyl chloride (1.5 equiv) was added at −40 °C, and the reaction mixture was warmed to 25 °C and stirred for the appropriate time. The reaction mixture was quenched with sat. aq. NH_4Cl solution or NH_4OH (2M aq.) extracted with Et_2O or EtOAc and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuum*. Purification by *flash*-chromatography furnished the desired product.

2.4 Starting material synthesis

Synthesis of 2,4-dibromoquinoline (37a) [77]



A mixture of commercially available quinoline-2,4-diol (4.835 g, 30 mmol) and phosphorus oxybromide (34 g,120 mmol) was refluxed for 5 h in dry toluene (300 mL). After cooling in an ice bath, the reaction mixture was hydrolyzed carefully by addition of ice (200 mL) and neutralized using a 6N solution of sodium hydroxide. The insoluble product was collected by filtration, washed with water (3 x 100 mL) and dried under vacuum. 2,4-dibromoquinoline (**37a**) was obtained as a pale yellow solid (6.4 g, 75%).

mp.: 93.8-95.0 °C.

IR (ATR): ν (cm^{-1}) = 3088 (s), 3060 (vs), 1652 (s), 1562 (s), 1552 (s), 1486 (s), 1452 (m), 1390 (s), 1262 (m), 1140 (s), 1086 (m), 844 (m), 808 (m), 756 (s), 680 (m).

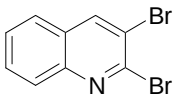
^{1}H-NMR (DMSO-d_6, 300 MHz): δ (ppm) = 8.17 (s, 1 H), 8.12 (d, ^3J = 7.8 Hz, 1 H), 7.99 (d, ^3J = 8.2 Hz, 1 H), 7.89 (m, 1 H), 7.79 (m, 1 H).

^{13}C-NMR (DMSO-d_6, 75 MHz): δ (ppm) = 148.6, 141.2, 135.6, 132.7, 129.7, 129.4, 129.3, 127.3, 126.8.

MS (EI, 70 eV): *m/z* (%) = 288 (41), 287 (10), 286 (100), 284 (46), 207 (67), 205 (76), 126 (60).

HRMS (EI) ($C_9H_5Br_2N$): calculated $[M]^+$: 284.8789 found: 284.8762

Synthesis of 2,3-dibromoquinoline (37b)[152]



Prepared according to **GP2** from 3-bromoquinoline (**34**) (1.24 g, 6 mmol, 1 equiv), TMPMgCl·LiCl (**18a**) [reaction condition: -20 °C for 2 h], and 1,2-dibromo-1,1,2,2-tetrachloroethane (2.14 g, 6.6 mmol, in 6 mL of THF) [reaction condition: -20 °C to 25 °C for 12 h]. Purification by *flash*-chromatography (SiO_2, pentane/ether = 19:1) afforded 2,3-dibromoquinoline (**37b**, 1.11 g, 65%) as a white solid.

mp.: 110.2-112.0 °C.

IR (ATR): ν (cm^{-1}) = 3046 (s), 1614 (m), 1572 (m), 1558 (m), 1546 (s), 1484 (s), 1360 (s), 1318 (s), 1292 (m), 1200 (m), 1150 (m), 1132 (m), 1110 (vs), 950 (s), 916 (s), 772 (s), 746 (vs), 662 (m), 626 (m).

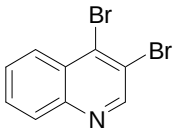
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.36 (s, 1 H), 8.01 (d, ^3J = 8.8 Hz, 1 H), 7.76 – 7.71 (m, 2 H), 7.58 (t, ^3J = 7.5 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 146.7, 142.8, 140.4, 130.8, 130.8, 128.6, 128.0, 126.7, 119.7.

MS (EI, 70 eV): *m/z* (%) = 288 (31) [M^+, ^{81}Br], 286 (100) [M^+, ^{81}Br, ^{79}Br], 284 (37) [M^+, ^{79}Br], 207 (68), 205 (56), 127 (73), 74 (11).

HRMS (EI) ($C_9H_5{}^{79}Br_2N$): calculated $[M]^+$: 284.8789 found: 284.8765

Synthesis of 3,4-dibromoquinoline (37c)



To a stirred solution of 4-quinolinol (2.08 g, 14.3 mmol, 1.0 equiv) in glacial acetic acid (40 mL), bromine (0.81 mL, 1.1 equiv) was slowly added. The mixture was refluxed for 24 h, cooled to 25 °C and the 3-bromo-4-quinolinol hydrobromide was collected by filtration, washed with water and dried *in vacuum*. 3-bromo-4-quinolinol (3.01 g, 94%) was obtained as a colourless solid.

[152] Steck, E. A.; Hallock, L. L.; Holland, A. J. *J. Am. Chem. Soc.* **1946**, *68*, 1241.

mp.: 81.8-83.6 °C.

IR (ATR): ν (cm^{-1}) = 3050 (m), 2968 (m), 2894 (s), 2860 (s), 2792 (s), 1626 (m), 1580 (m), 1552 (vs), 1504 (vs), 1470 (vs), 1440 (s), 1386 (m), 1354 (s), 1298 (m), 1188 (s), 1136 (m), 836 (m), 754 (m), 744 (m), 688 (m), 600 (m).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) = 12.24 (s, 1 H), 8.44 (s, 1 H), 8.11 (d, ^{3}J = 8.0 Hz, 1 H), 7.68 – 7.63 (m, 1 H), 7.57 (d, ^{3}J = 8.2 Hz, 1 H), 7.36 (t, ^{3}J = 7.4 Hz, 1 H).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) = 149.1, 134.4, 127.9, 127.7, 126.5, 126.5, 125.1, 122.7, 105.0.

MS (EI, 70 eV): *m/z* (%) = 224 (98) [M^+, ^{81}Br], 222 (100) [M^+, ^{79}Br], 144 (11), 116 (27), 115 (12), 104 (17), 89 (14).

HRMS (EI) (C_9H_6BrNO): calculated [M]$^+$: 222.9633 found: 222.9636

A mixture of 3-bromo-4-quinolinol (3.01 g, 13.4 mmol, 1.0 equiv) and phosphorous tribromide (12 mL) was refluxed for 5 h. After cooling the reaction mixture was hydrolyzed by pouring onto crushed ice (100 mL) and the resulting aq. suspension made strongly alkaline with a solution of sodium hydroxide (32 %). The insoluble product was collected by filtration, washed with water, and dried *in vacuum.* 3,4-dibromoquinoline was afforded (**37c**) (3.11 g, 76%) as a colourless solid.

mp.: 236.9-239.9 °C.

IR (ATR): ν (cm^{-1}) = 3108 (s), 3062 (s), 2924 (s), 1818 (m), 1552 (s), 1484 (vs), 1340 (s), 1246 (m), 1166 (m), 1106 (m), 964 (m), 848 (m), 808 (m), 750 (s), 662 (m), 628 (w), 594 (w).

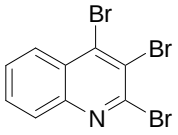
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.89 (s, 1 H), 8.21 (d, ^{3}J = 8.4 Hz, 1 H), 8.07 (d, ^{3}J = 8.4 Hz, 1 H), 7.75 (t, ^{3}J = 7.5 Hz, 1 H), 7.64 (t, ^{3}J = 7.7 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 151.3, 146.7, 135.2, 130.3, 129.9, 129.1, 128.9, 127.4, 121.3.

MS (EI, 70 eV): *m/z* (%) = 288 (54) [M^+, ^{81}Br], 287 (13), 286 (100) [M^+, ^{81}Br, ^{79}Br], 284 (63) [M^+, ^{79}Br], 207 (26), 205 (23), 180 (12), 127 (29), 100 (14).

HRMS (EI) ($C_9H_5Br_2N$): calculated [M]$^+$: 284.8789 found: 284.8769

Synthesis of 2,3,4-tribromoquinoline (37d)



Prepared according to **GP2** from 3,4-dibromoquinoline (**37c**) (288 mg, 1.0 mmol, 1.0 equiv), TMPMgCl·LiCl (**18a**) [reaction condition: -78 °C for 2 h], and 1,2-dibromo-1,1,2,2-tetrachloroethane in THF (310 mg, 1.3 mmol, 1.3 equiv) [reaction condition: – 78 °C to 25 °C for 12 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 8:2) afforded 2,3,4-tribromoquinoline (**37d**) (280 mg, 76 %) as a colourless solid.

mp.: 132.6-134.2 °C.

IR (ATR): ν (cm^{-1}) = 2358 (m), 2338 (w), 1552 (s), 1484 (m), 1452 (m), 1354 (m), 1338 (s), 1326 (m), 1290 (m), 1246 (m), 1166 (m), 1140 (w), 1106 (s), 964 (m), 910 (w), 848 (m), 808 (m), 752 (s), 662 (m).

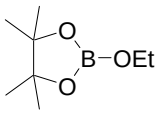
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.20 (d, ^3J = 8.4 Hz, 1 H), 8.03 (d, ^3J = 8.4 Hz, 1 H), 7.78 (t, ^3J = 7.6 Hz, 1 H), 7.68 (t, ^3J = 7.7 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 146.6, 142.8, 137.5, 131.5, 129.5, 129.4, 128.4, 128.2, 124.2.

MS (EI, 70 eV): *m/z* (%) = 368 (29) [M^+, ^{81}Br], 366 (97) [M^+, ^{81}Br, ^{81}Br, ^{79}Br], 364 (100) [M^+, ^{79}Br, ^{79}Br, ^{81}Br], 362 (31) [M^+, ^{79}Br], 287 (26), 285 (56), 283 (27), 206 (47), 204 (46), 126 (19), 100 (10), 99 (12).

HRMS (EI) ($C_9H_4Br_3N$): calculated: 362.7894 found: 362.7887

Synthesis of 2-ethoxy-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (ethyl pinacol borate)

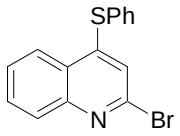


Boric acid (1.24 g, 20 mmol, 1 equiv), dry ethanol (4.40 g, 95.4 mmol, 4.77 equiv), and pinacol (2.36 g, 20 mmol, 1 equiv) were mixed in 15 mL of dry benzene. After stirring 30 min at 25 °C, the ethanol/water/benzene ternary azeotrope was distilled off for 10 h, and most of the residual benzene was removed *in vacuum* at 30 °C. The crude product was distilled (32 °C, 7 mbar) to give the title compound as a colourless liquid (V= 1.5 mL, 41%) containing no traces of benzene.

^{1}H-NMR ($CDCl_3$, 200MHz): δ (ppm) = 3.84 (q, J = 7.1 Hz, 2H), 1.20 (s, 12H and t "overlapped", 3H).

2.5 Preparation of polyfunctionalized quinolines

Synthesis of 2-bromo-4-phenylsulfanyl-quinoline (43a)



Prepared according to **GP1** from 2,4-dibromoquinoline (**37a**) in THF (287 mg, 1.0 mmol, 1.0 equiv), *i*-PrMgCl·LiCl (**13**) [reaction condition: -78 °C for 2 h], and benzenethiosulfonic acid *S*-phenyl ester[81] (300 mg, 1.2 mmol, 1.2 equiv) [reaction condition: -50 °C to 25 °C for 12 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 4:1) afforded 2-bromo-4-phenylsulfanyl-quinoline (**43a**) (286 mg, 91%) as a yellow solid.

mp.: 89.0-91.7 °C.

IR (ATR): ν (cm^{-1}) = 3056 (w), 3044 (w), 1956 (w), 1724 (w), 1544 (m), 1488 (m), 1440 (m), 1384 (m), 1252 (m), 1140 (s), 1100 (m), 976 (m), 852 (m), 824 (s), 780 (m), 752 (vs), 688 (s).

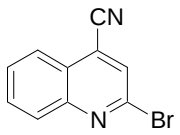
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.17 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.74 (td, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 1H), 7.63-7.49 (m, 6H), 6.77 (s, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 151.8, 147.6, 141.5, 135.5, 135.5, 130.9, 130.3, 130.3, 129.1, 128.2, 126.9, 124.6, 123.5, 120.8.

MS (EI, 70 eV): *m/z* (%) = 316 (81) [M^+, ^{81}Br], 314 (81) [M^+, ^{79}Br], 236 (100), 208 (11), 204(13), 190 (10), 166 (20), 159 (10), 127 (18), 117 (14), 108 (30), 104 (14), 101(14), 77 (17), 75 (21), 68 (15), 65 (26), 51 (28).

HRMS (EI) ($C_{15}H_{10}BrNS$): calculated for $[M+H]^+$ 315.9791 found: 315.9796

Synthesis of 2-bromoquinoline-4-carbonitrile (43b)



Prepared according to **GP1** from 2,4-dibromoquinoline (**37a**) in THF (1 mL) (287 mg, 1.0 mmol, 1.0 equiv), *i*-PrMgCl·LiCl (**13**) [reaction condition: -78 °C for 2 h], and tosyl cyanide

(220 mg, 1.2 mmol, 1.2 equiv) [reaction condition: -50 °C for 30 min and warmed to 25 °C for 6 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 2:3) afforded 2-bromoquinoline-4-carbonitrile (**43b**) (196 mg, 85%) as a colourless solid.

mp.: 153.0-155.5 °C.

IR (ATR): ν (cm^{-1}) = 3055 (w), 2235 (w), 1571 (w), 1539 (m), 1495 (w), 1408 (w), 1279 (m), 1223 (w), 1146 (m), 1088 (s), 891 (m), 866 (s), 853 (m), 762 (s).

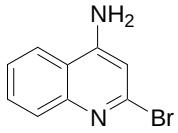
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.15 (t, J = 8.8 Hz, 2H), 7.88 (td, J = 8.4 Hz, J = 1.3 Hz, 1H), 7.85 (s, 1H), 7.78 (td, J = 8.2 Hz, J = 1.3 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 148.4, 140.1, 132.3, 129.5, 129.5, 129.4, 125.1, 124.6, 120.8, 114.2.

MS (EI, 70 eV): *m/z* (%) = 233 (71) [M^+, ^{81}Br], 231 (74) [M^+, ^{79}Br], 152 (100), 125 (14), 99 (2), 76 (1).

HRMS (EI) ($C_{10}H_5BrN_2$): calculated $[M]^+$: 231.9636 found: 231.9614

Synthesis of 2-bromoquinolin-4-ylamine (43c)



Prepared according to **GP1** from 2,4-dibromoquinoline (**37a**) in THF (1 mL) (287 mg, 1.0 mmol, 1.0 equiv), *i*-PrMgCl·LiCl (**13**) [reaction condition: -78 °C for 2 h]. To the freshly prepared magnesium reagent, CuCl·2LiCl (1.2 mL, 1.0 M in THF, 1.2 mmol) was added dropwise at -50 °C under argon and the mixture was stirred for 1 h. To the formed aryl copper reagent, commercially available LiHMDS (1M in THF/ethylbenzene) (2 mL, 2 mmol, 2 equiv) was added dropwise and the mixture was further stirred for 1 h at -60 ^{o}C. The reaction mixture was cooled to -78 ^{o}C, then a solution of chloranil (**22**, 298 mg, 1.2 mmol) in dry THF (7 mL) was added slowly over a period of 1 h at -78 ^{o}C. The reaction mixture was then stirred for further 12 h. Et_2O (10 mL) was poured into the crude reaction mixture. The resulting mixture was then filtered through celite and the residue washed with Et_2O (ca. 100 mL). The organic phase was washed with 2 x 10 mL portions of aqueous NH_4OH (2.0 M) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material obtained was redissolved in THF (3 mL) before TBAF (1.0 m in THF) (2 mL, 2 mmol) was added in one portion and the mixture was stirred at 25 °C

for 15 min, poured over EtOAc (10 mL) and washed with deionised water (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by *flash*-chromatography (SiO_2, pentane/ether = 9:1 with 0.5 % NEt_3) afforded 2-bromoquinolin-4-ylamine (**43c**) (166 mg, 75%) as a pale yellowish solid.

mp.: 191.9-193.3 °C.

IR (ATR): ν (cm^{-1}) = 3456 (m), 3310 (m), 3195 (br), 2923 (w), 1685 (s), 1574 (s), 1549 (s), 1511 (s), 1439 (s), 1351 (m), 1322 (m), 1143 (m), 1106 (m), 907 (s), 816 (m), 808 (m), 752 (s).

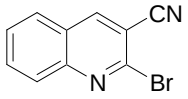
^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) = 8.13 (d, J = 9.1 Hz, 1H), 7.68-7.61 (m, 2H), 7.45-7.41 (m, 1H), 7.14 (s, 2H), 6.64 (s, 1H).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) = 153.7, 148.4, 142.2, 130.2, 127.8, 124.4, 122.6, 117.8, 104.1.

MS (EI, 70 eV): *m/z* (%) = 223 (73) [M^+, ^{81}Br], 221 (82) [M^+, ^{79}Br], 143 (47), 116 (100), 115 (12), 89 (22), 76 (5), 63 (5), 50 (5).

HRMS (EI) ($C_9H_7{}^{79}BrN_2$): calculated [M]$^+$: 221.9793 found: 221.9786

Synthesis of 2-bromo-3-cyanoquinoline (43d)



Prepared according to **GP1** from 2,3-dibromoquinoline (**37b**) (1.23 g, 4.3 mmol, 1.0 equiv), *i*-PrMgCl·LiCl (**13**) [reaction condition: -50 °C for 2 h], and tosyl cyanide (1.02 g, 5.6 mmol, 1.3 equiv) [reaction condition: -50 °C to 25 °C for 12 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded 2-bromo-3-cyanoquinoline (**43d**) (837 mg, 84 %) as a colourless solid.

mp.: 176.6-177.4 °C.

IR (ATR): ν (cm^{-1}) = 3052 (s), 2230 (m), 1612 (m), 1576 (s), 1556 (s), 1486 (s), 1456 (m), 1392 (m), 1370 (s), 1358 (m), 1334 (m), 1132 (s), 1020 (vs), 1010 (s), 970 (m), 936 (s), 774 (m), 760 (vs), 678 (m).

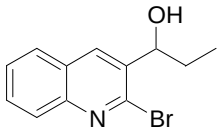
^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.50 (s, 1H), 8.10 (d, ^3J = 8.60 Hz, 1 H), 7.93-7.88 (m, 2 H), 7.72-7.70 (m, 1 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 149.1, 144.5, 139.7, 134.1, 129.3, 129.0, 128.4, 125.5, 116.4, 111.1.

MS (EI, 70 eV): *m/z* (%) = 233 (47) [M^+, ^{81}Br], 231 (50) [M^+, ^{79}Br], 153 (10), 152 (100), 125 (21).

HRMS (EI) ($C_{10}H_5BrN_2$): calculated $[M]^+$: 231.9636 found: 231.9640

Synthesis of 1-(2-bromo-quinolin-3-yl)-propan-1-ol (43e)



Prepared according to **GP1** from 2,3-dibromoquinoline (**37b**) (287 mg, 1.0 mmol, 1.0 equiv), *i*-PrMgCl·LiCl (**13**) [reaction condition: -50 °C for 2 h], and propionaldehyde (70 mg, 1.2 mmol, 1.2 equiv) [reaction condition: -50 °C to 25 °C for 12 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded 1-(2-bromo-quinolin-3-yl)-propan-1-ol (**43e**) (202 mg, 76%) as a colourless solid.

mp.: 85.5-86.7 °C.

IR (ATR): ν (cm^{-1}) = 3273 (s), 2964 (w), 2928 (w), 1587 (m), 1489 (m), 1330 (s), 1172 (m), 1128 (m), 1101 (s), 1019 (m), 1008 (m), 976 (s), 776 (s), 750 (s).

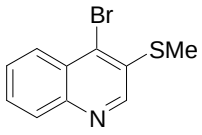
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.21 (s, 1H), 7.95 (d, 7.9 Hz, 1H), 7.72 (d, 7.9 Hz ,1H), 7.64 (td, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1 H), 7.50 (td, ^3J = 7.1 Hz, ^4J = 1.3 Hz, 1 H), 5.07-5.03 (dd, *J* = 3.8 Hz, *J* = 8.0 Hz, 1H), 2.98 (s, 1H), 1.98-1.97 (m, 1H), 1.77-1.62 (m, 1H), 1.03 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 193.5, 147.4, 141.9, 138.2, 135.3, 130.1, 128.0, 127.7, 127.4, 73.1, 30.7, 10.0.

MS (EI, 70 eV): *m/z* (%) = 267 (8) [M^+, ^{81}Br], 265 (8) [M^+, ^{79}Br], 238 (97), 236 (100), 156 (62), 128 (61), 101 (15), 77 (4).

HRMS (EI) ($C_{12}H_{12}BrNO$): calculated $[M]^+$: 265.0102 found: 265.0103

Synthesis of 4-bromo-3-methylsulfanylquinoline (43f)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with $Mes_2Mg \cdot 2LiBr$ (**39f**) (1.80 mL, 1.1 mmol, 1.1 equiv, 0.62M of [Mg] in THF) and TMEDA (0.18 mL, 1.1 mmol, 1.1 equiv) and stirred at -10 °C for 10 min. Thereafter, a solution of 3,4-dibromoquinoline (**37c**) (287 mg, 1.0 mmol, 1.0 equiv) in dry THF (1 mL) was added slowly, dropwise, at -10 °C and stirred for 6 h. The completion of the Br/Mg exchange was checked by GC-analysis using decane as internal standard. To the freshly prepared red magnesium reagent was added benzenethiosulfonic acid *S*-methyl ester[82] (244 mg, 1.3 mmol, 1.3 equiv) at -10 °C and the mixture was then stirred and warmed to 25 °C for 6 h. After the reaction was completed, sat. NH_4Cl solution was added and the mixture was extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by *flash*-chromatography (SiO_2, pentane/ether = 1:1) afforded 4-bromo-3-methylsulfanylquinoline (**43f**) (199 mg, 79%) as a colourless solid.

mp.: 108.0-109.2 °C.

IR (ATR): ν (cm^{-1}) = 2921 (w), 1612 (w), 1545 (m), 1483 (s), 1473 (s), 1432 (m), 1331 (s), 1320 (s), 1253 (m), 1163 (m), 1111 (s), 952 (m), 931 (m), 871 (m), 810 (s), 750 (s), 667 (s).

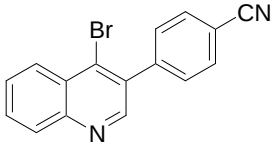
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.69 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.71-7.59 (m, 2H), 2.56 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 147.1, 146.2, 133.7, 132.3, 129.7, 129.2, 128.4, 127.8, 126.1, 16.3.

MS (EI, 70 eV): *m/z* (%) = 254 (100) [M^+, ^{81}Br], 252 (98) [M^+, ^{79}Br], 239 (10), 237 (9), 173 (10), 159 (34), 132 (8), 87 (7).

HRMS (EI) ($C_{10}H_8BrNS$): calculated $[M]^+$: 252.9561 found: 252.9540

Synthesis of 4-(4-bromoquinolin-3-yl)-benzonitrile (43g)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with $Mes_2Mg \cdot 2LiBr$ (**39f**) (1.80 mL, 1.1 mmol, 1.8 mL, 1.1 equiv, 0.62M of [Mg] in THF) and TMEDA (0.18 mL, 1.1 mmol, 1.1 equiv) and stirred at -10 °C for 10 min. Thereafter, a solution of 3,4-dibromoquinoline (**37c**) (287 mg, 1.0 mmol, 1.0 equiv) in dry THF (1 mL) was added slowly dropwise at -10 °C and stirred for 6 h. The completion of the Br/Mg exchange was checked by GC-analysis using decane as internal standard. The corresponding freshly prepared red magnesium reagent was transmetalated with $ZnCl_2$ (1.1 mL, 1.1 equiv, 1 M in dry THF) and the mixture was warmed to 25 °C for 1 h. 4-Iodobenzonitrile (297 mg, 1.3 mmol, 1.3 equiv) was then added neat to the reaction mixture. A flame-dried round bottom flask was charged with $Pd(dba)_2$ (30 mg, 5 mol%), P(*o*-furyl)$_3$ (24 mg, 10 mol%) and THF (1 mL). The mixture was stirred at 25 ^oC for 10 min, and then transferred to the reaction flask which was charged with the organozinc solution. The resulting mixture was stirred 12 h at 25 °C, quenched with sat. aq. NH_4Cl and extracted three times with AcOEt. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by *flash*-chromatography (SiO_2, pentane/ether = 1:1) afforded 4-(4-bromoquinolin-3-yl)-benzonitrile (**43g**) (219 mg, 71%) as a colourless solid.

mp.: 160.0-162.7 °C.

IR (ATR): ν (cm^{-1}) = 2978 (w), 2230 (w), 1724 (m), 1690 (w), 1603 (w), 1548 (m), 1476 (s), 1337 (m), 1077 (m), 1022 (w), 958 (w), 871 (w), 839 (s), 759 (s), 671 (s).

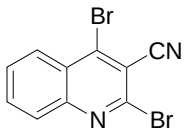
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.71 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 8.16 (d, 7.9 Hz, 1H), 7.84-7.60 (m, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 149.9, 148.1, 142.8, 134.3, 133.6, 132.2 (2carbons), 130.7 (2 carbons), 129.8, 128.7, 127.5 (2carbons), 118.4, 112.4.

MS (EI, 70 eV): *m/z* (%) = 309 (100) [M^+, ^{81}Br], 307 (94) [M^+, ^{79}Br], 230 (17), 229 (86), 228 (14), 201 (38), 175 (22), 114 (14), 101 (16), 88 (5), 75 (4).

HRMS (EI) ($C_{16}H_9{}^{81}BrN_2$): calculated $[M]^+$: 309.9949 found: 309.9911

Synthesis of 2,4-dibromo-quinoline-3-carbonitrile (43h)



Prepared according to **GP1** from 2,3,4-tribromoquinoline (**37d**) in THF (1 mL) (365 mg, 1.0 mmol, 1.0 equiv), MesMgBr·LiCl (**39d**) [reaction condition: -10 °C for 3 h], and tosyl cyanide (220 mg, 1.2 mmol, 1.2 equiv) [reaction condition: -50 °C for 30 min and warmed to 25 °C for 6 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 9:1) afforded 2,4-dibromoquinoline-3-carbonitrile (**43h**) (274 mg, 88%) as colourless needles (recrystallization ether/AcOEt 1:1).

mp.: 207.1-208.1 °C.

IR (ATR): ν (cm^{-1}) = 3059 (w), 3038 (w), 2226 (w), 1544 (m), 1474 (m), 1376 (w), 1354 (w), 1298 (m), 1203 (w), 1136 (w), 1033 (m), 912 (m), 871 (m), 757 (s), 731 (s).

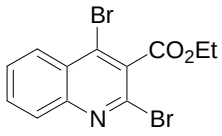
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.22 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.93 (t, J = 8.2 Hz, 1H), 7.78 (t, J = 8.2 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 75MHz): δ (ppm) = 148.3, 141.7, 139.3, 134.3, 129.8, 129.5, 128.1, 125.8, 115.6, 114.4.

MS (EI, 70 eV): *m/z* (%) = 313 (28), 311 (57), 309 (28), 232 (50), 230 (48), 152 (100), 125 (15), 99 (30), 75 (19), 51 (11).

HRMS (EI) ($C_{10}H_4Br_2N_2$): calculated $[M+H]^+$ 310.8820 found: 310.8818

Synthesis of 2,4-dibromo-quinoline-3-carboxylic acid ethyl ester (43i)



Prepared according to **GP1** from 2,3,4-tribromoquinoline (**37d**) in THF (1 mL) (365 mg, 1.0 mmol, 1.0 equiv), MesMgBr·LiCl (**39d**) [reaction condition: -10 °C for 3 h], and ethyl cyanoformate (119 mg, 1.2 mmol, 1.2 equiv) [reaction condition: -50 °C for 30 min and warmed to 25 °C for 6 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 9:1) afforded 2,4-dibromo-quinoline-3-carboxylic acid ethyl ester (**43i**) (320 mg, 90%) as a colourless solid.

mp.: 109.8-111.8 °C.

IR (ATR): ν (cm^{-1}) = 2983 (w), 1731 (s), 1692 (w), 1552 (s), 1476 (m), 1377 (m), 1354 (m), 1319 (m), 1295 (m), 1243 (m), 1230 (s), 1179 (s), 1130 (m), 1018 (m), 919 (m), 857 (w), 808 (m), 746 (s), 679 (s).

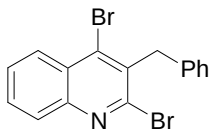
^{1}H-NMR (CDCl$_3$, 300 MHz): δ (ppm) = 8.19 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.80 (td, *J* = 7.1 Hz, *J* = 1.5 Hz, 1H), 7.69 (td, *J* = 7.2 Hz, *J* = 1.5 Hz ,1H), 4.53 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (CDCl$_3$, 75 MHz): δ (ppm) = 165.1, 147.9, 136.2, 132.5, 132.2, 132.1, 129.1, 129.0, 127.3, 126.1, 62.9, 14.0.

MS (EI, 70 eV): *m/z* (%) = 317 (80), 236 (100), 204 (13), 190 (10), 165 (19), 127 (18), 117 (14), 109 (14), 77 (17), 75 (20), 65 826), 51 (28).

HRMS (EI) ($C_{12}H_9Br_2NO_2$): calculated $[M+H]^+$ 357.9079 found: 357.9078

Synthesis of 3-benzyl-2,4-dibromoquinoline (43j)



Prepared according to **GP1** from 2,3,4-tribromoquinoline (**37d**) (1.82 g, 5.0 mmol, 1.0 equiv) dissolved in dry THF (5 mL), MesMgBr·LiCl (**39d**) [reaction condition: -10 °C for 3 h], and benzyl bromide (1.19 g, 1.4 mmol, 1.4 equiv) [reaction condition: -50 °C for 30 min and warmed to 25 °C for 10 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 3:2) afforded 3-benzyl-2,4-dibromoquinoline (**43j**) (1.67 mg, 89%) as a colourless solid.

mp.: 99.2-100.6 °C.

IR (ATR): ν (cm^{-1}) = 3028 (w), 2924 (w), 1600 (w), 1552 (s), 1491 (w), 1475 (s), 1451 (m), 1354 (m), 1299 (m), 1135 (m), 1027 (m), 1016 (m), 908 (m), 879 (m), 762 (s), 722 (s), 693 (s).

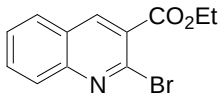
^{1}H-NMR (CDCl$_3$, 300 MHz): δ (ppm) = 8.22 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.74 (td, *J* = 7.1 Hz, *J* = 1.5 Hz, 1H), 7.66 (td, *J* = 7.0 Hz, *J* = 1.5 Hz, 1H), 7.30-7.17 (m, 5H), 4.65 (s, 2H).

^{13}C-NMR (CDCl$_3$, 75 MHz): δ (ppm) = 147.2, 144.6, 137.2, 137.0, 134.5, 130.7, 128.9, 128.5, 128.5, 128.4, 128.3, 128.3, 127.6, 127.5, 126.5, 42.1.

MS (EI, 70 eV): *m/z* (%) = 376 (14), 295 (10), 217 (37), 216 (100), 215 (11), 189 (12), 140 (7), 107 (14), 94 (10), 63 (7), 51 (7).

HRMS (EI) ($C_{16}H_{11}Br_2N$): calculated $[M+H]^+$: 375.9337 found: 375.9333

Synthesis of 2-bromo-quinoline-3-carboxylic acid ethyl ester (43k)



Prepared according to **GP1** from 2,3-dibromoquinoline (**37b**) (1.15 g, 4.0 mmol, 1.0 equiv), *i*-PrMgCl·LiCl (**13**) [reaction condition: -50 °C for 2 h], and ethyl cyanoformate (475 mg, 4.8 mmol, 1.2 equiv) [reaction condition: -50 °C to 25 °C for 5 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded 2-bromoquinoline-3-carboxylic acid ethyl ester (**43k**) (1.03 g, 92 %) as a colourless solid.

mp.: 104.1-107.2 °C.

IR (ATR): ν (cm^{-1}) = 3056 (w), 2980 (w), 2928 (w), 1724 (s), 1480 (m), 1388 (m), 1368 (m), 1268 (m), 1264 (m), 1244 (s), 1228 (s), 1196 (s), 1124 (s), 1112 (s), 1028 (s), 996 (s), 936 (s), 876 (s), 816 (m), 780 (vs), 752 (vs).

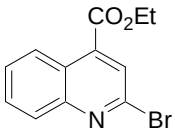
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.55 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.81 (td, J = 7.1 Hz, J = 1.5 Hz ,1H), 7.62 (td, J = 8.1 Hz, J = 1.1 Hz ,1H), 4.47 (q, J = 7.3 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 165.1, 148.8, 140.4, 138.5, 132.4, 128.6, 128.4, 127.9, 126.9, 25.9, 62.2, 14.2.

MS (EI, 70 eV): *m/z* (%) = 281 (12), 279 (13), 278 (100), 252 (24), 250 (25), 235 (73), 233 (74), 207 (17), 205 (17), 172 (20), 128 (12).

HRMS (EI) ($C_{12}H_{10}BrNO_2$): calculated $[M]^+$: 278.9895 found: 278.9956

Synthesis of ethyl 2-bromoquinoline-4-carboxylate (43l)



Prepared according to **GP1** from 2,4-dibromoquinoline (**37a**) (8 mmol, 2.3 g, 1.0 equiv) dissolved in THF (10 mL), *i*-PrMgCl·LiCl (**13**) [reaction condition: -78 °C for 2 h], and ethyl cyanoformate (9.6 mmol, 950 mg, 1.2 equiv) [reaction condition: -78 °C to 25 °C for 12 h].

The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 4:1) afforded ethyl 2-bromoquinoline-4-carboxylate (**43l**) (2.06 g, 92%) as a colourless solid.

mp.: 74.3-76.9 °C.

IR (ATR): ν (cm^{-1}) = 3102 (s), 2992 (s), 1724 (s), 1550 (vs), 1480 (s), 1454 (m), 1440 (m), 1338 (m), 1264 (s), 1238 (s), 1196 (m), 1146 (s), 1100 (s), 1028 (m), 894 (m), 798 (s), 774 (s), 750 (s), 662 (m), 594 (w).

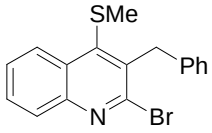
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.71 (d, ^3J = 8.4 Hz, 1 H), 8.07 (d, ^3J = 8.4 Hz, 1 H), 8.00 (s, 1 H), 7.77 (td, ^3J = 7.1 Hz, ^4J = 1.3 Hz ,1 H), 7.65 (td, ^3J = 7.1 Hz, ^4J = 1.3 Hz ,1 H), 4.50 (q, ^3J = 7.2 Hz, 2 H), 1.47 (t, ^3J = 7.1 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.7, 149.5, 141.0, 137.5, 130.8, 129.2, 128.4, 126.9, 125.8, 124.1, 62.3, 14.2.

MS (EI, 70 eV): *m/z* (%) = 281 (16), 280 (96) [M^+, ^{79}Br], 279 (15), 278 (100) [M^+, ^{81}Br], 251 (11), 236 (29), 234 (29), 207 (23), 205 (22), 200 (40), 172 (29), 128 (35), 126 (42), 116 (12), 101 (19), 75 (12).

HRMS (EI) ($C_{12}H_{10}BrNO_2$): calculated $[M]^+$: 278.9895 found: 278.9903

Synthesis of 3-benzyl-2-bromo-4-methylsulfanylquinoline (44)



Prepared according to **GP1** from 3-benzyl-2,4-dibromoquinoline (**43j**) (1.13 g, 3.0 mmol, 1.0 equiv) dissolved in THF (3 mL), *i*PrMgCl·LiCl (**13**) [reaction condition: -50 °C for 12 h], and benzenethiosulfonic acid *S*-methyl ester (675 mg, 3.6 mmol, 1.2 equiv) [reaction condition: -50 °C to 25 °C for 12 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether) afforded 3-benzyl-2-bromo-4-methylsulfanylquinoline (**44**) (897 mg, 87%) as a colourless oil.

IR (ATR): ν (cm^{-1}) = 3028 (w), 2924 (vw), 1708 (vs), 1476 (m), 1356 (s), 1220 (s), 1136 (m), 1028 (s), 916 (m), 884 (m), 764 (s), 744 (m), 724 (s), 712 (m).

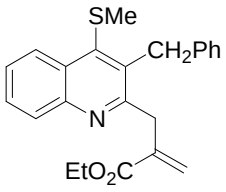
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.51 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.78-7.66 (m, 2H), 7.31-7.16 (m, 5H), 4.82 (s, 2H), 2.28 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 147.6, 147.0, 145.6, 138.8, 138.4, 130.1, 130.1, 129.4, 129.4, 128.8, 128.4, 128.4, 127.9, 126.6, 126.2, 40.3, 20.0.

MS (EI, 70 eV): *m/z* (%) = 345 (100) [M^+, ^{81}Br], 343 (94) [M^+, ^{79}Br], 329 (5), 327 (6), 264 (31), 217 (24), 216 (88), 189 (5), 91 (4).

HRMS (EI) ($C_{17}H_{14}BrNS$): calculated $[M]^+$: 343.0030 found: 343.0016

Synthesis of 2-(3-benzyl-4-methylsulfanylquinolin-2-ylmethyl)-acrylic acid ethyl ester (45)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with $Mes_2Mg{\cdot}LiBr$ (**39f**) (1.1 mmol, 1.1 equiv, 0.62M of [Mg] in THF) and stirred at 0 °C for 10 min. Therefore, a solution of 3-benzyl-2-bromo-4-methylsulfanyl-quinoline (**44**) (1 mmol, 344 mg, 1.0 equiv) dissolved in THF (1 mL) was added slowly, dropwise, at 0 °C and stirred for 12 h. The completion of the Br/Mg exchange was checked by GC-analysis using decane as internal standard. Ethyl (2-bromomethyl)acrylate[83] was then added to the mixture at -20 °C, followed by 2 drops of CuCN·2LiCl (cat., 1M in THF) and the reaction mixture was warmed to 25 °C over 12 h. Sat. NH_4Cl solution was added and the mixture was extracted three times with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded 2-(3-benzyl-4-methylsulfanyl-quinolin-2-ylmethyl)-acrylic acid ethyl ester (**45**) (263 mg, 70%) as a colourless oil.

IR (ATR): ν (cm^{-1}) = 3060 (w), 2984 (w), 1716 (vs), 1636 (m), 1604 (w), 1556 (m), 1480 (w), 1380 (m), 1308 (m), 1264 (m), 1176 (m), 1124 (m), 976 (w), 952 (w), 820 (w), 746 (m).

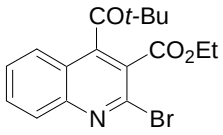
^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.52 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.70-7.63 (m, 2H), 7.07-7.02 (m, 3H), 6.85-6.83 (m, 2H), 6.25 (d, *J* = 1.8 Hz, 1H), 5.87 (d, *J* = 1.8 Hz, 1H), 4.19 (q, *J* = 7.3 Hz, 2H), 4.03 (s, 2H), 2.22 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 166.7, 158.8, 146.6, 145.4, 140.0, 138.0, 137.4, 130.4, 129.2, 129.1, 129.0, 129.0, 127.8, 127.8, 127.6, 126.2, 125.7, 125.7, 60.6, 54.5, 37.2, 19.6, 14.2.

MS (EI, 70 eV): *m/z* (%) = 324 (1), 308 (5), 254 (28), 240 (100), 193 (15), 68 (11).

HRMS (EI) ($C_{23}H_{23}NO_2{}^{32}S$): calculated $[M]^+$: 377.1449 found: 377.1444

Synthesis of ethyl 2-bromo-4-pivaloylquinoline-3-carboxylate (52)



Prepared according to **GP2** and **GP3** from 2-bromoquinoline-3-carboxylic acid ethyl ester (**43k**) (560 mg, 2.0 mmol, 1.0 equiv), TMPMgCl·LiCl (**18a**) [reaction condition: 0 °C for 3 h], CuCN·2LiCl [reaction condition: -40 °C for 10 min], and pivaloyl chloride (240 mg, 2.2 mmol, 1.2 equiv) [reaction condition: -40 °C to 25 °C for 6 h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded ethyl 2-bromo-4-pivaloylquinoline-3-carboxylate (**52**) (612 mg, 84 %) as a colourless solid.

mp.: 120.2 - 121.9 °C.

IR (ATR): ν (cm^{-1}) = 2976 (w), 1725 (vs), 1691 (s), 1558 (m), 1267 (m), 1231 (s), 1182 (s), 1152 (m), 1086 (m), 1012 (m), 977 (m), 771 (s), 756 (m).

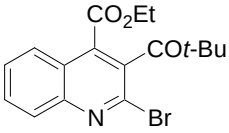
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.08 (d, *J* = 8.4 Hz, 1H), 7.80 (td, *J* = 6.2 Hz, *J* = 1.9 Hz, 1H), 7.64-7.55 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 211.4, 165.6, 149.3, 148.2, 137.7, 132.1, 129.3, 128.2, 126.1, 124.3, 122.4, 62.9, 45.3, 27.7, 27.7, 27.7, 13.9.

MS (EI, 70 eV): *m/z* (%) = 320 (4), 318 (4), 309 (40), 308 (29), 307 (41), 280 (98), 278 (100), 208 (9), 198 (12), 154 (22), 126 (8), 57 (7).

HRMS (EI) ($C_{17}H_{18}BrNO_4$): calculated $[M+H]^+$ 364.0549 found: 364.0540

Synthesis of ethyl 2-bromo-3-pivaloylquinoline-4-carboxylate (53)



Prepared according to **GP2** and **GP3** from ethyl 2-bromoquinoline-4-carboxylate (**43l**) (1.59 g, 5.7 mmol, 1.0 equiv) dissolved in dry THF (5 mL), TMPMgCl·LiCl (**18a**) [reaction condition: -10 °C for 3 h], CuCN·2LiCl [reaction condition: -40 °C for 30 min], and pivaloyl chloride (748 mg, 6.8 mmol, 1.2 equiv) [reaction condition: -40 °C warmed to 25 °C for 12

h]. The crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 8:2) afforded ethyl 2-bromo-3-pivaloylquinoline-4-carboxylate (**53**) (1.67 g, 81%) as a colourless crystalline solid.

mp.: 70.8-72.0 °C.

IR (ATR): ν (cm^{-1}) = 2976 (m), 1724 (vs), 1690 (s), 1552 (s), 1482 (m), 1456 (m), 1270 (m), 1220 (vs), 1186 (m), 1142 (m), 1078 (s), 1014 (m), 978 (m), 890 (m), 762 (s), 682 (w), 580 (w).

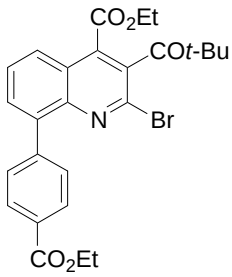
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.08 (d, ^3J = 8.4 Hz, 1 H), 7.98 (d, ^3J = 8.4 Hz, 1 H), 7.80 (t, ^3J = 7.1 Hz, 1H), 7.65 (t, ^3J = 7.1 Hz, 1H), 4.46 (q, ^3J = 7.1 Hz, 2H), 1.41 (t, ^3J = 7.1 Hz, 3 H), 1.33 (s, 9 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 210.0, 165.4, 147.9, 137.0, 136.2, 134.6, 131.4, 129.0, 128.7, 125.5, 122.6, 63.0, 45.4, 28.2, 28.2, 28.2, 14.0.

MS (EI, 70 eV): *m/z* (%) = 364 [M^+] not found, 308 (37), 307 (16), 306 (47), 305 (11), 280 (13), 279 (98), 278 (14), 277 (100), 153 (18).

HRMS (EI) ($C_{17}H_{18}BrNO_3$): calculated $[M+H]^+$ 364.0549 found: 364.0573

Synthesis of 2-bromo-3-pivaloyl-8-(4-ethoxycarbonyl-phenyl)-quinoline-4-carboxylic acid ethyl ester (54)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with ethyl 2-bromo-3-pivaloylquinoline-4-carboxylate (**53**) (365 mg, 1 mmol, 1.0 equiv) dissolved in dry THF (1 mL). $TMP_2Mg{\cdot}2LiCl$ (**19**, 2 mL, 1.1 mmol, 0.55 M in THF) was added dropwise to the mixture at 0 °C and the resulting mixture was stirred at this temperature for 20 h. The freshly prepared magnesium reagent was then transmetalated with $ZnCl_2$ (1.1 mL, 1.1 equiv, 1 M in dry THF) at 0 °C and the mixture was warmed to 25 °C for 1 h. 4-Iodo-benzoic acid ethyl ester (358 mg, 1.3 mmol, 1.3 equiv) was added to the reaction mixture at 25 °C. A flame-dried round bottom flask was charged with $Pd(dba)_2$ (30 mg, 5 mol%), P(*o*-furyl)$_3$ (24 mg, 10 mol%) and THF (1 mL). The mixture was stirred at 25 °C for

10 min then transferred to the reaction flask which was charged with the organozinc solution. The resulting mixture was stirred and refluxed for 4 h, quenched with sat. aq. NH_4Cl and extracted three times with AcOEt. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded 2-bromo-3-(2,2-dimethyl-propionyl)-8-(4-ethoxycarbonyl-phenyl)-quinoline-4-carboxylic acid ethyl ester (**54**) (363 mg, 71%) as a colourless solid.

mp.: 126.0 - 129.1 °C.

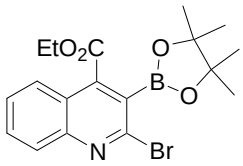
IR (ATR): ν (cm^{-1}) =2968 (w), 2908 (w), 1732 (s), 1718 (vs), 1556 (s), 1478 (m), 1459 (m), 1364 (m), 1275 (s), 1235 (vs), 1177 (s), 1082 (s), 991 (s), 894 (m), 767 (vs), 699 (m).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.16 (d, ^3J = 8.3 Hz, 2H), 7.98 (d, ^3J = 8.3 Hz, 1H), 7.85 (d, ^3J = 7.3 Hz, 1H), 7.76-7.71 (m, 3H), 4.48 (q, ^3J = 7.2 Hz, 2H), 4.42 (q, ^3J = 7.2 Hz, 2H), 1.45-1.41 (m, 6H), 1.33 (s, 9H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 210.1, 166.6, 165.5, 145.2, 142.4, 139.3, 137.4, 135.8, 134.7, 132.0, 130.7 (2carbons), 129.7, 129.2 (2 carbons), 128.4, 125.5, 123.1, 63.1, 61.0, 45.3, 28.2 (2 carbons), 14.4, 14.0.

HRMS (ESI) ($C_{26}H_{26}BrNO_5$): calculated $[M+H]^+$ 512.1070 found: 512.1062

Synthesis of 2-bromo-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoline-4-carboxylic acid ethyl ester (55).



According to **GP2** from ethyl 2-bromoquinoline-4-carboxylate (**43l**) (1.39 g, 5.0 mmol, 1.0 equiv) dissolved in dry THF (5 mL), TMPMgCl·LiCl (**18a**) [reaction condition: -10 °C for 3 h]. To the corresponding obtained 2-bromo-3-magnesiated-4-carboethoxyquinoline was added at -10 °C freshly prepared ethyl pinacol borate (1.03 g, 6 mmol, 1.2 equiv) and the resulting mixture was stirred and warmed to 25 °C for 12 h. The reaction mixture was cooled to -50 °C after which anhydrous HCl (3 mL, 6 mmol, 1.2 equiv, 2M in Et_2O) was added. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C. After removal of the precipitated MgCl by filtration and removal of the volatiles under reduced pressure, the crude residue was purified by *flash*-chromatography (SiO_2, pentane/ether = 9:1) afforded 2-

bromo-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoline-4-carboxylic acid ethyl ester (**55**) (1.44 g, 71%) as a colourless solid.

mp.: 85.9-88.6 °C.

IR (ATR): ν (cm^{-1}) = 2996 (w), 2976 (w), 1692 (m), 1552 (m), 1368 (m), 1312 (m), 1291 (s), 1235 (s), 1140 (s), 1119 (s), 1016 (m), 850 (m), 771 (s).

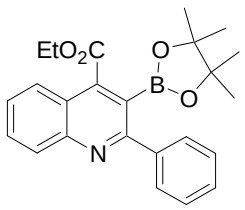
^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.30 (d, ^{3}J = 7.3 Hz, 1H), 8.05 (d, ^{3}J = 7.3 Hz, 1H), 7.74 (t, ^{3}J = 7.0 Hz, 1H), 4.55 (q, ^{3}J = 7.3 Hz, 2H), 1.48 (t, ^{3}J = 7.1 Hz, 3H), 1.45 (s, 12H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 167.9, 149.3, 144.0, 143.7, 131.0, 129.1, 128.0, 125.6, 122.9, 85.0 (2 carbons), 62.8, 25.1 (4C), 14.3. [C from C-B bond, not visible].

MS (EI, 70 eV): *m/z* (%) = 390 (13), 347 (67), 317 (100), 277 (69), 233 (21), 154 (25), 127 (21), 43 (32).

HRMS (EI) ($C_{18}H_{21}B^{79}BrNO_4$): calculated $[M]^+$: 405.0747 found: 405.0746

Synthesis of 2-phenyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoline-4-carboxylic acid ethyl ester (56)



To a solution of commercially available phenyl magnesium chloride in THF (1.51 mL, 2.2 mmol, 1.45 M in THF) at 0 °C was added dropwise $ZnCl_2$ (2.1 mL, 2.2 mmol, 1.1 equiv, 1.0 M in THF). After 30 min of stirring, a solution of the boronic ester **55** (812 mg, 2 mmol, 1.0 equiv) in dry THF (1 mL) was added dropwise, followed by the addition of 5 mol% of $Pd(Ph_3)_4$. The resulting mixture was stirred at 25 °C for 1 h and then quenched with sat. aq. NH_4Cl and extracted three times with AcOEt. The solvent was evaporated and the product was purified by *flash*-chromatography (SiO_2, pentane/ether = 7:3) afforded 2-phenyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoline-4-carboxylic acid ethyl ester (**56**) (612 mg, 76%) as a colourless solid.

mp.: 237.5-239.9 °C.

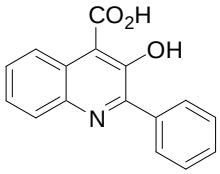
IR (ATR): ν (cm^{-1}) = 2981 (m), 2928 (w), 1694 (vs), 1665 (m), 1560 (m), 1373 (s), 1323 (vs), 1252 (m), 1220 (m), 1139 (vs), 1096 (vs), 1039 (m), 854 (w), 773 (m), 702 (m).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.27 (d, ^{3}J = 7.9 Hz, 1H), 8.20 (d, ^{3}J = 8.1 Hz, 1H), 7.78-7.69 (m, 3H), 7.59 (t, ^{3}J = 8.1 Hz, 1H), 7.48-7.42 (m, 3H), 4.58 (q, ^{3}J = 7.1 Hz, 2H), 1.51 (t, ^{3}J = 8.1 Hz, 3H), 1.18 (s, 12H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.9, 162.2, 148.4, 143.2, 142.1, 130.2, 130.1, 129.3 (2 carbons), 128.6, 128.1 (2 carbons), 127.4, 125.0, 122.4, 84.4 (2 carbons), 62.4, 25.0 (4C), 14.4. [C from C-B bond, not visible].

HRMS (ESI) ($C_{24}H_{26}BNO_4$): calculated $[M+H]^+$: 404.2034 found: 404.2025

Synthesis of 3-hydroxy-2-phenyl-quinoline-4-carboxylic acid (57)



To a heterogeneous solution of 2-phenyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinoline-4-carboxylic acid ethyl ester (**56**) (806 mg, 1.2 mmol, 1. equiv) in MeOH (2 mL) at 25 °C, was added neat LiOH (172 mg, 6 equiv) and aq. solution of H_2O_2 (0.45 mL, 3 equiv, 32% in water). The resulting mixture became rapidly yellow and heterogeneous and was stirred at 25 °C for 15 h. A precipitate was obtained and was filtrated and dried over vacuum. The crude residue was purified by *flash*-chromatography (SiO_2, EtOAc/CH_3CN/MeOH/H_2O, 7:1:0.25:0.25 with 0.5% NEt_3) giving the corresponding ammonium salt which was dissolved in CH_3CN/H_2O 1:1 and then acidified with HCl conc. to obtain a pH of 2. A precipitate was collected by filtration and dried over vacuum. A yellow fluffy solid is obtained (**57**, 283 mg, 89%).

mp.: 183.0-185.9 °C.

IR (ATR): ν (cm^{-1}) = 3395 (mbroad), 2923 (w), 2596 (mbroad), 1632 (m), 1527 (m), 1500 (m), 1400 (s), 1322 (s), 1241 (s), 1160 (m), 1027 (m), 877 (m), 755 (s), 696 (s).

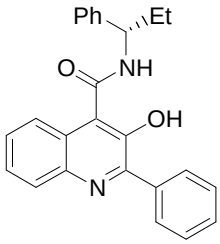
^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) = 8.76 (d, J = 7.8 Hz, 1H), 8.04-7.99 (m, 1H), 7.66-7.58 (m, 3H), 7.56-7.51 (m, 5H).

^{13}C-NMR (DMSO-d_6, 100 MHz): δ (ppm) = 171.0, 153.8, 151.5, 139.7, 135.7, 129.7 (2 carbons), 129.5, 128.4, 127.9 (2 carbons), 126.5, 125.3, 124.6 (2 carbons), 155.4.

MS (EI, 70 eV): *m/z* (%) = 265 [M^+] (50), 247 (39), 218 (100), 190 (31), 165 (18), 105 (23), 76 (15), 44 (22).

HRMS (EI) ($C_{16}H_{11}NO_3$): calculated $[M]^+$: 265.0739 found: 265.0729

Synthesis of 3-hydroxy-2-phenyl-quinoline-4-carboxylic acid (1-phenyl-propyl)-amide (talnetant, 33f).



This compound was prepared following the literature procedure starting from **57**.[90] A pale yellow solid is obtained (**33f**, 84%).

mp.: 125.1- 126.2 °C

IR (ATR): ν (cm^{-1}) = 3266 (wbroad), 3058 (wbroad), 2931 (w), 1646 (s), 1629 (s), 1532 (s), 1492 (m), 1312 (m), 1236 (m), 1198 (m), 1146 (m), 760 (s), 695 (s).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ (ppm) = 9.78 (s, 1H), 9.12 (d, *J* = 8.2 Hz, 1H), 7.98-7.94 (m, 3H), 7.69-7.43 (m, 8H), 7.38-7.34 (m, 2H), 7.28-7.25 (m, 1H), 5.08-5.02 (q, *J* = 7.0 Hz, 1H), 1.87-1.74 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (DMSO-d_6, 100MHz): δ (ppm) = 164.6, 152.3, 144.5, 143.4, 142.3, 137.8, 129.4 (2 carbons), 129.0, 128.7 (2 carbons), 128.1 (2 carbons), 127.9, 126.9, 126.7 (5 carbons), 125.4, 123.6, 54.8, 29.2, 11.1.

HRMS (ESI) ($C_{25}H_{22}N_2O_2$): calculated $[M+H]^+$: 383.1760 found: 383.1756

3. Functionalizations of Protected Uracils *via* Chemo- and Regioselective Magnesiations.

3.1 General procedure for the Br/Mg exchange reaction on 4-halogeno-2,6-dimethoxypyrimidines 69a and 69b (GP4):

A dry and argon flushed 10 mL flask, equipped with a magnetic stirring bar and a septum, was charged with the 5-bromo-4-halogeno-2,6-dimethoxypyrimidine **69a** or **69b** (1mmol, 1 equiv) dissolved in dry THF (1.0 M). *i*-PrMgCl·LiCl (**13**, 1 mL, 1.05 M in THF, 1.05 equiv) was added slowly at 25 °C and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). The freshly prepared magnesium reagent was cooled to the corresponding temperature or used at 25 °C and the corresponding electrophile (1.1-1.5 equiv.) was added. The mixture was stirred for time depending of the reactivity of the electrophile. The consumption of the magnesium reagent was checked by GC-analysis, using tetradecane as internal standard. After the reaction was completed, sat. NH_4Cl solution (10 mL) was added and the mixture was extracted with Et_2O or AcOEt (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. The product was purified by flash chromatography (SiO_2).

3.2 General procedure for the Br/Mg exchange reaction on 5-functionalized-2,6-dimethoxypyrimidines (GP5):

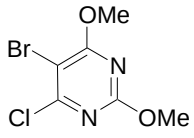
A dry and argon flushed 10 mL flask, equipped with a magnetic stirring bar and a septum, was charged with the halogenated 2,6-dimethoxypyrimidine (1 equiv) dissolved in dry THF (1.0 M). *i*-PrMgCl·LiCl (**13**, 1.05-1.1 equiv) was added slowly, dropwise, at appropriate temperature (as stated in the experiment). The reaction mixture was stirred at the same or plus 5°C temperature, and the completion of the Br/Mg exchange was checked by GC-analysis using tetradecane as internal standard or by TLC. The freshly prepared magnesium reagent was cooled to the corresponding temperature or used at 25 °C and the corresponding electrophile (1.1-1.5 equiv.) was added. The mixture was stirred for time depending of the reactivity of the electrophile. The consumption of the magnesium reagent was checked by GC-analysis, using tetradecane as internal standard. After the reaction was completed, sat. NH_4Cl solution (10 mL) was added and the mixture was extracted with Et_2O or AcOEt (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. The product was purified by flash chromatography (SiO_2).

3.3 General procedure for the direct magnesiation of 2,4-dimethoxypyrimidine derivatives using TMPMg·LiCl (18a) (GP6).

A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with the 2,6-dimethoxypyrimidine derivative (1 mmol, 1 equiv) dissolved in dry THF (1.0 M solution) and TMPMg·LiCl (**18a**, 1.1 mmol, 1.1 equiv) were added dropwise at the given temperature. The reaction mixture was stirred at the same temperature, and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. The freshly prepared magnesium reagent was cooled to the corresponding temperature or used at 25 °C and the corresponding electrophile (1.2 equiv) or its solution in THF was added. The mixture was stirred for a time depending on the reactivity of the electrophile. The consumption of the magnesium reagent was checked by GC-analysis, using decane as internal standard. After the reaction was completed, sat. NH_4Cl (10 mL) solution was added and the mixture was extracted with Et_2O or EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. The product was purified by *flash*-chromatography (SiO_2).

3.4 Starting material synthesis

Synthesis of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (69a)



This compound was prepared starting from 4-chloro-2,6-dimethoxypyrimidine (**70a**) according to the literature procedure.[103] The analytic data correspond to the analytic data from the literature. The product **69a** was obtained as a white solid.

mp.: 98.7-99.7 °C.

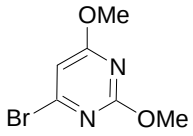
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 4.05 (s, 3H), 3.99 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.3, 162.8, 160.4, 97.1, 55.8.

MS (EI, 70 ev): *m/z* (%) = 254 (100), 253 (77), 252 (75), 251 (58), 239 (27), 224 (92), 221 (70), 209 (37), 143 (42).

HRMS (EI) $C_6H_6BrClN_2O_2$: calculated [M^+]: 251.9301 found: 251.9284.

Synthesis of 4-bromo-2,6-dimethoxypyrimidine (70b)



4-bromo-2,6-dimethoxypyrimidine (**70b**) was prepared starting from barbituric acid in two steps in 85% yield, according to the literature procedure.[104] The analytic data correspond to the analytic data from the literature. The product was obtained as a white solid.

mp.: 90.9-92.0 °C.

IR (KBr): 1589 (m), 1550 (s), 1463 (s), 1363 (m), 1199 (m), 819 (s).

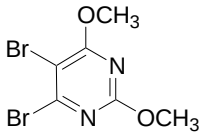
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.52 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.1, 164.9, 152.4, 105.4, 55.8, 54.8.

MS (EI, 70 ev): *m/z* (%) = 220 (79), 219 (67), 218 (78), 217 (75), 190 (90), 188 (100), 175 (37), 109 (51), 82 (65).

HRMS (EI) $C_6H_7BrN_2O_2$: calculated [M^+]: 217.9691 found: 217.9692.

Synthesis of 4,5-dibromo-2,6-dimethoxypyrimidine (69b)



This compound (**69b**) was prepared with the same procedure for the synthesis of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**), starting from 4-bromo-2,6-dimethoxypyrimidine (**70b**). 5,4-dibromo-2,6-dimethoxypyrimidine (**69b**) was isolated as a white solid in 96% yield.

mp.: 117.6-118.0 °C

IR (KBr): 2957 (w), 1526 (s), 1455 (m), 1343 (s), 1311 (m), 1008 (s).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.05 (s, 3H), 3.99 (s, 3H).

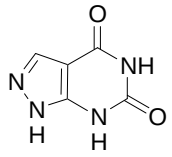
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 167.7, 162.54, 153.74, 100.8, 55.8 (2 carbons).

MS (EI, 70 ev): *m/z* (%) = 300 (46), 299 (47), 298 (100), 297 (71), 296 (48), 295 (31), 283 (20), 270 (31), 268 (64), 266 (30), 189 (19), 187 (21).

HRMS (EI) $C_6H_6Br_2N_2O_2$: calculated [M^+]: 295.8796 found: 295.8799.

3.5 Preparation of polyfunctionalized 2,4-dimethoxypyrimidines

Synthesis of 1*H*-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione, oxypurinol (60)



A mixture of 4,6-dimethoxy-1*H*-pyrazolo[3,4-d]pyrimidine (**75**) (0.54 g, 3 mmol) with concentrated hydrochloric acid (30 mL) was heated under reflux for 2 h. After the reaction was complete, the solution was treated with activated charcoal and evaporated under reduced pressure. The residue was recrystallized from water affording **60** (1.60 g, 81%) as a white solid.

mp.: > 300 °C.

IR (KBr): 3268 (m), 3124 (w), 3028 (m), 2804 (w), 1709(s), 1677 (s), 1616 (m), 1419 (m), 1244 (m), 1169 (s), 1025 (m), 810 (m), 748 (s), 700 (s).

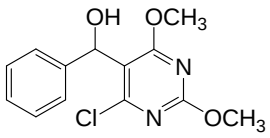
^{1}H-NMR (DMSO, 300 MHz): δ (ppm) = 13.27 (s, 1H), 11.30 (s, 1H), 10.63 (s, 1H), 8.33 (s, 1H).

^{13}C-NMR (DMSO, 75 MHz): δ (ppm) = 159.6, 151.6, 150.8, 128.9, 100.2.

MS (EI, 70 ev): *m/z* (%) = 152.0 (100), 109.0 (92), 52.0 (31), 44.0 (14).

HRMS (EI) $C_5H_4N_4O_2$: calculated [M^+]: 152.0334 found: 152.0324.

Synthesis of (4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanol (72a)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (254 mg, 1 mmol, 1.0 equiv) in dry THF (1 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), benzaldehyde (117 mg, 1.1 mmol, 1.1 equiv). Reaction conditions [5 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **72a** (255 mg, 91%) as a white solid.

mp.: 90,1- 91,4 °C.

IR (KBr): 3412 (s), 2955 (w), 1583 (s), 1553 (s), 1464 (m), 1375(s), 1242 (m), 1032 (s).

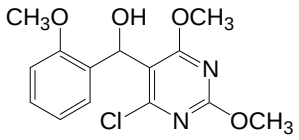
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.33-7.24 (m, 5H), 6.21 (d, *J* = 11 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.41 (d, *J* = 11 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 169.7, 163.2, 159.4, 141.7, 128.3 (2 carbons), 127.4, 125.3 (2 carbons), 114.0, 70.0, 55.4, 55.0.

MS (EI, 70 ev): *m/z* (%) = 282 (15), 280 (44), 262 (20), 205 (29), 203 (100), 105 (10), 77 (12).

HRMS (EI) $C_{13}H_{13}ClN_2O_3$: calculated [M^+]: 280.0615 found: 280.0612.

Synthesis of (4-chloro-2,6-dimethoxypyrimidin-5-yl)(2-methoxyphenyl)methanol (72b)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (254 mg, 1 mmol, 1.0 equiv) in dry THF (1 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), 2-methoxybenzaldehyde (150 mg, 1.1 mmol, 1.1 equiv). Reaction conditions [10 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **72b** (258 mg, 83%) as a white solid.

mp.: 106.0-107.3 °C

IR (KBr): 3472 (s), 3003 (m), 2963 (w), 1553 (s), 1455 (m), 1375 (s), 1241 (m), 1206 (m), 1021 (s).

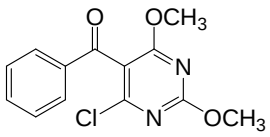
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.8 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.79 (s, 3H), 3.33 (d, *J* = 8.8 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 170.1, 163.1, 156.8 (2 carbons), 129.4, 128.9, 127.1, 120.2, 113.5, 110.6, 66.7, 55.5, 55.5, 55.0.

MS (EI, 70 ev): *m/z* (%) = 312 (22), 311 (15), 310 (58), 294 (38), 293 (23), 292 (100), 257 (57), 242 (12), 205 (13), 203 (51), 201 (53), 175 (29), 135 (16), 109 (17), 108 (19), 77 (10).

HRMS (EI) $C_{14}H_{15}ClN_2O_4$: calculated [M^+]: 310.0720 found: 310.0733.

Synthesis of (4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanone (72c)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (254 mg, 1 mmol, 1 equiv) in dry THF (1 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), benzoyl chloride (154 mg, 1.1mmol, 1.1 equiv). Reaction conditions [3 h, -20 °C to 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **72c** (231 mg, 86%) as a white solid.

mp.: 116.0-117.3 °C.

IR (KBr): 3436 (m), 3000 (w), 2952 (w), 1676 (s), 1589 (s), 1485 (s), 1485 (m), 1389 (s), 1200 (s), 1027 (m), 921 (m).

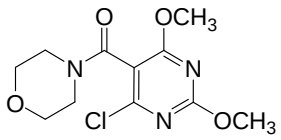
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.83 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.07 (s, 3H), 3.94 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 190.7, 169.5, 164.3, 158.1, 136.2, 134.2, 129.4 (2 carbons), 128.8 (2 carbons), 112.8, 55.7, 55.1.

MS (EI, 70 ev): *m/z* (%) = 280 (17), 278 (47), 203 (34), 201 (100), 105 (30), 77 (17), 76 (11).

HRMS (EI) $C_{13}H_{11}ClN_2O_3$: calculated [M^+]: 278.0458 found: 278.0441.

Synthesis of (4-chloro-2,6-dimethoxypyrimidin-5-yl)(morpholino)methanone (72d)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (254 mg, 1 mmol, 1 equiv) in dry THF (1 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), 4-morpholinecarbonyl chloride (165 mg, 1.1 mmol, 1.1 equiv). Reaction conditions [15 h, -20 °C to 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 2:3) afforded **72d** (244 mg, 85%) as a white solid.

mp.: 109.9-111.3 °C.

IR (KBr): 2960 (w), 2862 (w), 1634 (m), 1580 (s), 1534 (s), 1494 (m), 1370 (s), 1357 (m), 1275 (m), 1235 (s), 1111 (s), 1009 (s).

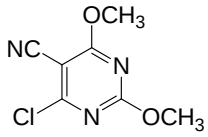
^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 4.01 (2 singulets, 6H), 3.86-3.61 (3 multiplets, 6H), 3.28 (m, 2H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 168.5, 164.1, 162.0, 157.9, 109.4, 66.7, 66.6, 55.6, 55.2, 46.9, 42.2.

MS (EI, 70 ev): *m/z* (%) = 287.0 (9), 252.1 (11), 203.0 (28), 201.0 (100), 75.9 (11).

HRMS (EI) $C_{11}H_{14}ClN_3O_4$: calculated [M^+]: 287.0673 found: 287.0664.

Synthesis of 4-chloro-2,6-dimethoxypyrimidine-5-carbonitrile (72e)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (254 mg, 1 mmol, 1 equiv) in dry THF (1 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), *p*-toluenesulfonyl cyanide (200 mg, 1.1 mmol, 1.1 equiv). Reaction conditions [12 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 1:4) afforded **72e** (178 mg, 89%) as a white solid.

mp.: 123.3-124.8 °C.

IR (KBr): 3021 (w), 2947 (w), 2233 (m), 1586 (m), 1529 (s), 1474 (m), 1378 (m), 1218 (m), 1071 (m), 1018 (s).

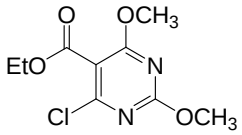
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.11 (s, 3H), 4.07 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.2, 165.1, 164.9, 117.7, 89.7, 56.4, 55.6.

MS (EI, 70 ev): *m/z* (%) = 201 (25), 199 (71), 198 (32), 171 (33), 169 (100), 154 (32), 106 (19), 70 (11).

HRMS (EI) $C_7H_6ClN_3O_2$: calculated [M^+]: 199.0149 found: 199.0131.

Synthesis of ethyl 4-chloro-2,6-dimethoxypyrimidine-5-carboxylate (72f)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (381 mg, 1.5 mmol, 1 equiv) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.58 mmol, 1.05 equiv), ethyl cyanoformate (164 mg, 1.1 equiv). Reaction conditions [8 h, -20 °C to 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 4:1) afforded **72f** (322 mg, 87%) as a yellow oil.

IR (film): 2957 (w), 1731 (s), 1585 (s), 1540 (s), 1488 (m), 1376 (m), 1218 (m), 1071 (m), 1018 (s).

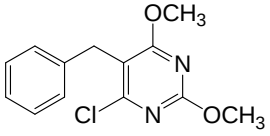
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.40 (q, *J* = 7.1 Hz, 2H), 4.02 (s, 6H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 169.2, 163.9, 163.4, 158.9, 108.7, 62.1, 55.7, 55.2, 14.0.

MS (EI, 70 ev): *m/z* (%) = 246 (15), 218 (13), 203 (30), 201 (100), 174 (13), 76 (14).

HRMS (EI) $C_9H_{11}ClN_2O_4$: calculated [M^+]: 246.0407 found: 246.0388.

Synthesis of 5-benzyl-4-chloro-2,6-dimethoxypyrimidine (72g)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (381 mg, 1.5 mmol, 1 equiv) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.58 mmol, 1.05 equiv), benzylbromide (360 mg, 2.1 mmol, 1.4 equiv). Reaction conditions [4 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 1:4) afforded **72g** (300 mg, 75%) as a colourless oil.

IR (film): 3028 (w), 2950 (w), 1586 (m), 1541 (s), 1453 (m), 1369 (s), 1213 (m), 1078 (m), 1026 (s).

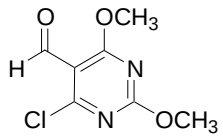
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.14 (m, 5H), 3.90-3.91 (m, 8H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 170.2, 162.6, 160.2, 138.6, 128.3 (3 carbons), 126.3 (2 carbons), 112.0, 55.1, 54.8, 31.2.

MS (EI, 70 ev): *m/z* (%) = 266 (31), 264 (100), 249 (33), 234 (19), 173 (17), 156 (10), 91 (18), 77 (8).

HRMS (EI) $C_{13}H_{13}ClN_2O_2$: calculated [M^+]: 264.0666 found: 264.0639.

Synthesis of 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (72h)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69a**) (1.27 g, 5 mmol, 1 equiv) in dry THF (5 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 5.25 mmol, 1.05 equiv), 4-formylmorpholine (0.635 g, 1.1 equiv). Reaction conditions [4 h, -35 °C]. The mixture was quenched with a mixture of a solution of acetic acid in water (≈ 1M; 3 mL) and saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with ether (3 × 20 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuum*. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **72h** (840 mg, 83%) as a white solid.

mp.: 97.8-99.1°C.

IR (KBr): 3008 (w), 2956 (w), 2882 (w), 2797 (w), 1686 (s), 1528 (s), 1449 (s), 1356 (s), 1324 (s), 1205 (m), 1014 (m), 789 (s).

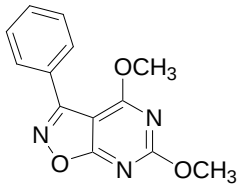
^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 10.30 (s, 1H), 4.12 (s, 3H), 4.08 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 169.6, 167.2, 164.3, 160.2, 106.9, 55.8, 55.5.

MS (EI, 70 ev): *m/z* (%) = 203 (40), 202 (76), 201 (100), 185 (22), 174 (17), 172 (43), 155 (17), 129 (10), 76 (23), 70 (10).

HRMS (EI) $C_7H_7ClN_2O_3$: calculated [M^+]: 202.0145 found: 202.0126.

Synthesis of 4,6-dimethoxy-3-phenylisoxazolo[5,4-d]pyrimidine (73)



To a stirring solution of 4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanone (**72c**) (1.39 mg, 5 mmol) in EtOH 50% (100 mL) at 25 °C was added hydroxylamine hydrochloride (1.04 g, 15 mmol) and sodium acetate (1.25 g, 15 mmol). The mixture was refluxing during 4 h. The product was collected by filtration and washed two times with H_2O (10 mL). Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **73** (1.88 g, 83%) as a white solid.

mp.: 210.1-211.9 °C.

IR (KBr): 3017 (w), 2951 (w), 1615 (s), 1539 (s), 1441 (s), 1385 (m), 1318 (s), 1138 (m).

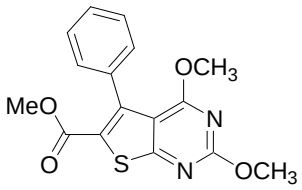
^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 8.20 (m, 2H), 7.60 (m, 3H), 4.14 (s, 3H), 4.00 (s, 3H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 166.8, 167.6, 166.8, 132.2, 132.2, 129.2 (2 carbons), 128.3 (2 carbons), 126.0, 96.3, 55.4, 55.1.

MS (EI, 70 ev): *m/z* (%) = 257.1 (100), 227.1 (57), 212.1 (36), 105.0 (65), 91.0 (8), 77.0 (41), 70.0 (12), 51.0 (11).

HRMS (EI) $C_{13}H_{11}N_3O_3$: calculated [M^+]: 257.0800 found: 257.0807.

Synthesis of methyl 2,4-dimethoxy-5-phenylthieno[2,3-d]pyrimidine-6-carboxylate (74)



Triethylamine (0.4 g, 4 mmol) was added dropwise to a mixture of 4-chloro-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanone (**72c**) (0.55 g, 2 mmol) and methyl mercapto-acetate (0.31 g, 2.6 mmol) in EtOH (10 mL). The reaction mixture was heated at reflux until the starting ketone **72c** disappeared according to gas chromatography (12 h). After cooling to 25 °C, the precipitate was filtered off and recrystallized in EtOH 95% affording **74** (456 mg, 69%) as a white powder.

mp.: 193.3-194.3 ° C.

IR (KBr): 3012 (w), 2951 (w), 1716 (s), 1577 (m), 1541 (s), 1473 (m), 1249 (s), 1168 (m), 1027 (m).

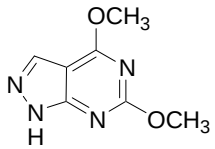
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.40 (m, 3H), 7.38 (m, 2H), 4.08 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 170.2, 167.2, 163.8, 162.2, 142.1, 134.9, 129.0 (2 carbons), 127.8, 127.2 (2 carbons), 122.5, 114.9, 55.3, 54.1, 52.2.

MS (EI, 70 ev): *m/z* (%) = 331 (16), 330 (100), 329 (15), 300 (11), 299 (26), 284 (11), 251 (7), 227 (8), 199 (7), 171 (6), 127 (8).

HRMS (EI) $C_{16}H_{14}N_2O_4S$: calculated [M^+]: 330.0674 found: 330.0660.

Synthesis of 4,6-dimethoxy-1H-pyrazolo[3,4-d]pyrimidine (75)



To a stirring solution of 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (**72h**) (1.01 mg, 5 mmol) in EtOH (80 mL) at 25 °C was added hydrazine monohydrate (0.9 g, 15 mmol). The mixture was refluxing during 30 min. After cooling to 25 °C, the precipitate was filtered off and recrystallized in EtOH 95% affording **75** (823 mg, 91%) as a white powder.

mp.: > 300 °C.

IR (KBr): 3252 (w), 2955 (w), 1608 (s), 1583 (m), 1503 (m), 1386 (m), 1320 (w), 1153 (m), 1081 (w), 942 (s), 788 (s).

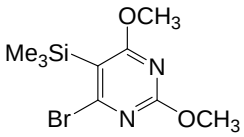
^{1}H-NMR (DMSO, 300 MHz): δ (ppm) = 8.05 (s, 1H), 4.04 (s, 3H), 3.93 (s, 3H).

^{13}C-NMR (DMSO, 75 MHz): δ (ppm) = 164.4, 163.9, 157.8, 97.8, 88.2, 54.5, 53.9.

MS (EI, 70 ev): *m/z* (%) = 180 (100), 179 (66), 165 (12), 150 (36), 135 (67), 109 (13), 70 (11).

HRMS (EI) $C_7H_8N_4O_4$: calculated [M^+]: 180.0647 found: 180.0643.

Synthesis of 4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (77a)



Prepared according to **GP4** starting from a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (596 mg, 2 mmol, 1 equiv) in dry THF (3 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv), trimethylsilyl chloride (240 mg, 2.2 mmol, 1.1 equiv). Reaction conditions [24 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 4:1) afforded **77a** (529 mg, 91%) as a white solid.

mp.: 71.1-72.2 °C.

IR (KBr): 2955 (w), 2899 (w), 1556 (m), 1524 (s), 1450 (m), 1344 (s), 1278 (m), 1114 (m), 1015 (m), 839 (s).

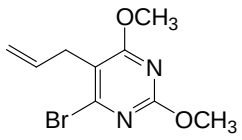
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.98 (s, 3H), 3.92 (s, 3H), 0.37 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 175. 5, 164.4, 159.9, 111.8, 55.0, 54.1, 1.2 (3 carbons).

MS (EI, 70 ev): *m/z* (%) = 292 (10), 290 (10), 277 (100), 275 (99), 247 (81), 220 (30), 194 (13), 137 (33), 72 (38).

HRMS (EI) $C_9H_{15}BrN_2O_2Si$: calculated [M^+]: 290.0086 found: 290.0062.

Synthesis of 5-allyl-4-bromo-2,6-dimethoxypyrimidine (77b)



Prepared according to **GP4** starting from a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (596 mg, 2 mmol, 1 equiv) in dry THF (3 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv), allyl bromide (266 mg, 2.2 mmol, 1.1 equiv). Reaction conditions [2 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 9:1) afforded **77b** (528 mg, 91%) as a colourless oil.

IR (film): 3081 (w), 2957 (w), 1639 (w), 1586 (m), 1542 (s), 1459 (m), 1370 (s), 1223 (m), 1079 (m), 1026 (s).

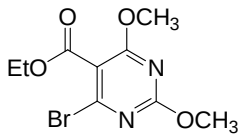
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.82 (m, 1H), 5.02 (2 dd, $^3J_{trans}$ = 13.2 Hz, J_{gem} and $^3J_{cis}$ = 1.7 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.35 (dt, ^3J = 6.1 Hz, ^4J = 1.5 Hz).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 170.1, 162.6, 160.0, 133.4, 115.9, 110.7, 55.1, 54.8, 29.6.

MS (EI, 70 ev): *m/z* (%) = 260 (98), 258 (100), 245 (23), 243 (22), 231 (41), 179 (25), 163 (14).

HRMS (EI) $C_9H_{11}BrN_2O_2$: calculated [M^+]: 258.0004 found: 258.0023.

Synthesis of ethyl 4-bromo-2,6-dimethoxypyrimidine-5-carboxylate (77c)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69b**) (298 mg, 1.0 mmol, 1 equiv) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), ethyl cyanoformate (164 mg, 1.1 equiv). Reaction conditions [12 h, -20 to 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 4:1) afforded **77c** (236 mg, 81%) as a white solid.

mp.: 42.5-43.8 °C.

IR (KBr): 2983 (w), 2960 (w), 1725 (s), 1570 (s), 1529 (s), 1491 (m), 1358 (m), 1265 (s), 1229 (s), 1048 (m), 1013 (s).

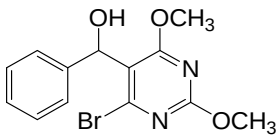
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.38 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 6H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 166.5, 164.0, 163.6, 149.9, 112.0, 62.2, 55.7, 55.1, 14.0.

MS (EI, 70 ev): *m/z* (%) = 292 (18), 290 (19), 247 (96), 245 (100), 218 (18), 151 (8), 122 (19), 70 (11).

HRMS (EI) $C_9H_{11}BrN_2O_4$: calculated [M^+]: 289.9902 found: 289.9902.

Synthesis of (4-bromo-2,6-dimethoxypyrimidin-5-yl)(phenyl)methanol (77d)



Prepared according to **GP4** starting from a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (298 mg, 1.0 mmol, 1 equiv) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), benzaldehyde (117 mg, 1.1 mmol, 1.1 equiv). Reaction conditions [4 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **77d** (308 mg, 95%) as a white solid.

mp.: 108.9-111.2°C.

IR (KBr): 3337 (s), 2953 (w), 2923 (w), 1572 (w), 1543 (s), 1488 (m), 1448 (m), 1368 (s), 1212 (m), 1016 (s).

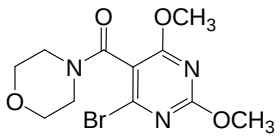
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.3 (m, 5H), 6.19 (d, *J* = 11.1 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.41 (d, *J* = 11.1 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 168.9, 162.9, 152.5, 141.7, 128.3 (2 carbons), 127.5, 125.3 (2 carbons), 116.6, 72.13, 55.4, 54.9.

MS (EI, 70 ev): *m/z* (%) = 326 (41), 324 (33), 308 (18), 306 (18), 249 (67), 247 (100), 227 (32), 105 (17), 77 (22).

HRMS (EI) $C_{13}H_{13}BrN_2O_3$: calculated [M^+]: 324.0110 found: 324.0092.

Synthesis of (4-bromo-2,6-dimethoxypyrimidin-5-yl)(morpholino)methanone (77e)



Prepared according to **GP4** starting from a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**69b**) (298 mg, 1 mmol, 1 equiv) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), 4-morpholinecarbonyl chloride (165 mg, 1.1 mmol, 1.1 equiv). Reaction conditions [12 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 2:3) afforded **77e** (210 mg, 70%) as a white solid.

mp: 112.0-113.6 °C.

IR (KBr): 2960 (w), 2862 (w), 1634 (m), 1580 (s), 1534 (s), 1494 (m), 1370 (s), 1357 (m), 1275 (m), 1235 (s), 1111 (s), 1009 (s).

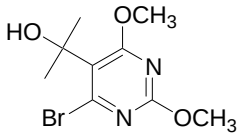
^{1}H-NMR (DMSO, 400 MHz): δ (ppm) = 3.95 (s, 3H), 3.94 (s, 3H), 3.57 (m, 6H), 3.27 (m, 2H).

^{13}C-NMR (DMSO, 100 MHz): δ (ppm) = 167.2, 163.1, 161.6, 148.6, 112.5, 66.7, 66.2, 55.3, 54.9, 46.3, 41.6.

MS (EI, 70 ev): *m/z* (%) = 333 (8), 331 (9), 252 (30), 247 (98), 245 (100), 167 (12), 122 (11), 120 (11), 70 (6).

HRMS (EI) $C_{11}H_{14}BrN_3O_4$: calculated [M^+]: 331.0168 found: 331.0177.

Synthesis of 2-(4-bromo-2,6-dimethoxypyrimidin-5-yl)propan-2-ol (77f)



In a flame dried, argon-flushed 50 mL Schlenk-flask equipped with a septum and a magnetic stirring bar was placed $LaCl_3$·2LiCl in THF (0.33 M; 30 mL, 10.00 mmol, 1.00 equiv). Dried acetone (580 mg, 10.0 mmol) was added and the resulting mixture was stirred for 2 h at 25 °C. A second dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (2.98 g, 10 mmol) in dry THF (10 mL). *i*-PrMgCl·LiCl (**13**, 1.0 M/THF, 10.5 mmol, 1.05 equiv) was

added very slowly (within 5 min) at 25 °C and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots) and obtain the Grignard reagent **76**. To the mixture of acetone with $LaCl_3 \cdot 2LiCl$ in THF cooled to 0 °C, was added dropwise the solution of the Grignard reagent **76**. The resulting mixture was allowed to stir at the same temperature for 4 h and was quenched with sat. aq. NH_4Cl (20 mL) and water (20 mL) was added. The aqueous layer was extracted with ethyl acetate (4 × 30 mL), the combined extracts were dried (Na_2SO_4) and evaporated *in vacuum*. The crude residue was purified by flash column chromatography (SiO_2, *n*-pentane/diethyl ether = 4:1) afforded **77f** (2.40 g, 81%) as a colourless oil.

IR (film): 3563 (m), 2950 (w), 1562 (m), 1527 (s), 1481 (m), 1383 (m), 1352 (m), 1215 (m), 1013 (s).

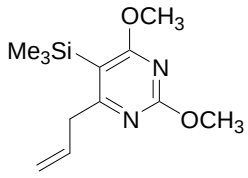
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.03 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H), 1.70 (s, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 168.9, 161.2, 149.0, 120.7, 72.4, 55.2, 55.0, 30.2 (2 carbons).

MS (EI, 70 ev): *m/z* (%) = 279 (3), 277 (3), 263 (100), 261 (97), 245 (29), 221 (5), 167 (7).

HRMS (EI) $C_9H_{13}BrN_2O_3$: calculated $[M+H]^+$: 277.0110 found: 277.0200.

Synthesis of 4-allyl-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (78)



Prepared according to **GP5** starting from a solution of 4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (**77a**) (291 mg, 1.0 mmol) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv), reaction conditions [-15 °C, 12 h]. Allyl bromide (145 mg, 1.2 mmol, 1.2 equiv), reaction conditions [-15 °C, 30 min]. CuCN·2LiCl (cat. (3 drops), 1M in THF), reaction conditions [-15 to 25 °C, 6 h]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 3:2) afforded **78** (204mg, 81%) as a colourless oil.

IR (film): 3081 (w), 2980 (w), 2960 (w), 2870 (w), 1638 (w), 1571 (s), 1457 (m), 1370 (s), 1362 (s), 1210 (m), 1084 (w).

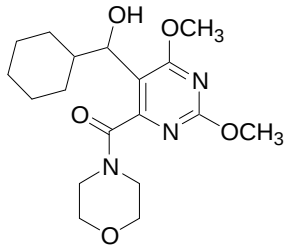
^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 6.03 (m, 0.8H), 5.08 (dd, *J* = 9.5 Hz, 0.8H), 5.02 (dd, *J* = 17.1 Hz, 0.8H), 3.96–3.93 (2s, 6H), 3.47 (d, *J* = 6.2 Hz, 2H), 0.31 (s, 9H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 176.0, 175.3, 135.8, 116.2, 107.0, 54.3, 53.4, 42.07, 29.7, 1.41 (3 carbons from TMS group).

MS (EI, 70 ev): *m/z* (%) = 253 (11), 252 (56), 251 (100), 237 (19), 207 (23), 89 (25).

HRMS (EI) $C_{12}H_{20}N_2O_2Si$: calculated [M^+]: 252.1294 found: 252.1266.

Synthesis of (5-(cyclohexyl(hydroxy)methyl)-2,6-dimethoxypyrimidin-4-yl)(morpholino)-methanone (79a)



A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (596 mg, 2 mmol, 1 equiv) in dry THF (3 mL). *i*-PrMgCl·LiCl (**13**, 1.0 M/THF, 2.1 mmol, 1.05 equiv) was added very slowly (within 5 min) at 25 °C and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Cyclohexanecarboxaldehyde (266 mg, 2.2 mmol, 1.2 equiv) was added at 25 °C and the mixture was stirred at 25 °C for12 h. *i*-PrMgCl·LiCl (**13**, 1.0 M/THF, 2.0 mmol, 1.5 equiv) was added at 25 °C to the mixture which was stirred for 24 h to complete the second bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). 4-morpholinecarbonyl chloride (597 mg, 2 equiv) was added and the resulting mixture was stirred at 25 °C for 12 h. Then, the mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuum*. Purification by flash chromatography (SiO_2, diethyl ether) afforded **79a** (503 mg, 69) as a colourless oil.

IR (film): 2924 (m), 2852 (m), 1700 (s), 1599 (m), 1567 (m), 1399 (m), 1218 (s), 1069 (m).

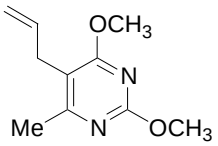
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.09 (s, 1H), 5.64 (d, *J* = 6.7 Hz), 3.99 (s, 3H), 3.97 (s, 3H), 1.88-0.88 (m, 11H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.3, 164.6, 156.2, 154.6, 114.1, 74.0, 66.6 (3 carbons), 54.0, 44.1, 42.1, 28.8, 28.4.

MS (EI, 70 ev): *m/z* (%) = 365 (1), 282 (2), 235 (24), 153 (100), 114 (12), 70 (6).

HRMS (EI) $C_{18}H_{27}N_3O_5$: calculated [M^+]: 365.1951 found: 365.1935.

Synthesis of 5-allyl-2,4-dimethoxy-6-methylpyrimidine (79b)



A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (596 mg, 2 mmol, 1 equiv) in dry THF (3 mL). *i*-PrMgCl·LiCl (**13**, 1.0 M/THF, 2.1 mmol, 1.05 equiv) was added very slowly (within 5 min) at 25 °C and the resulting mixture was stirred for 15 min to complete the bromine-magnesium exchange (checked by GC-MS analysis of reaction aliquots). Allyl bromide (266 mg, 2.2 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at 25 °C for 2 h. Then, the mixture was cooled down to -5 °C and *i*-PrMgCl·LiCl (**13**, 1.0 M/THF, 3.0 mmol, 1.5 equiv) was added slowly. After 8 h, the Br/Mg-exchange was complete (checked by GC-MS analysis of reaction aliquots) and methylene iodide (850 mg, 3 equiv) was added to the mixture at -5 °C following by the addition of 3 drops of CuCN·2LiCl (cat., 1M in THF). The mixture was warmed up to 25 °C for 4 h and quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated *in vacuum*. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 4:1) afforded **79b** (408 mg, 81%) as a colourless oil.

IR (film): 2980 (w), 2955 (w), 2871 (w), 1638 (w), 1571 (s), 1457 (m), 1369 (s), 1358 (s), 1203 (m), 1090 (w).

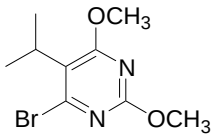
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.8 (m, 1H), 4.97 (dq, *J* = 10.2 Hz, 1H), 4.90 (dq, *J* = 17.1 Hz, 1H), 3.94 (s, 6H), 3.25 (dt, *J* = 5.9 Hz, 2H), 2.33 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 169.3, 166.6, 163.0, 134.7, 114.9, 109.7, 54.3, 53.9, 28.7, 21.2.

MS (EI, 70 ev): *m/z* (%) = 196 (45), 194 (100), 193 (49), 179 (28), 164 (29), 138 (11), 122 (5), 94 (6), 56 (21).

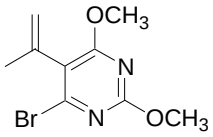
HRMS (EI) $C_{10}H_{14}N_2O_2$: calculated [M^+]: 194.1055 found: 194.1036.

Synthesis of 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine (80)



To an ice-cooled, rapidly stirred slurry of **77f** (1.38 g, 5mmol) dissolved in dry dichloromethane (20 mL) and triethylsilane (1.74 g, 3 equiv) was slowly added trifluoroacetic acid (1.99 g, 3.5 equiv). When the addition was complete, the mixture was warmed to 25 °C and stirred overnight (12 h). At the end of this period, the mixture was poured into 30 mL of saturated $NaHCO_3$ and extracted with dichloromethane (3 × 20 mL). Extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 40 °C (oil bath) to give 1.28 g (95 %) of colourless oil. The product was identified as a mixture of 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine **77f** (17%) and the corresponding unsaturated product (83%) (4-bromo-2,6-dimethoxy-5-(prop-1-en-2-yl)pyrimidine). The mixture was used for the next step without purification.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) = 5.34 (s, 1.0H), 4.95 (t, 1.0H), 3.95 (m, 7.1H), 3.40 (q, 0.37H), 1.96 (m, 3.03H) *, 1.26-1.23 (d, 1.17H)*.



unsaturated product from **80**

*These integrations give respectively the yield of **80** (17%) and the corresponding unsaturated product (83%)

The mixture (1.27 g) is directly used and solved in dry ethanol (10 mL). Platinium oxide (87 mg) is added to the solution and the resulting mixture is stirred at atmospheric pressure in a hydrogen atmosphere for 30 min. The catalyst was removed by filtration and the filtrate was concentrated *in vacuum*. The crude residue was purified by flash column chromatography (SiO_2, *n*-pentane/diethyl ether = 4:1) afforded **80** (1.17 g, 91%) as a colourless oil.
IR (film): 2986 (w), 2959 (w), 2874 (w), 1575 (m), 1534 (s), 1451 (m), 1362 (s), 1215 (m), 1017 (s).

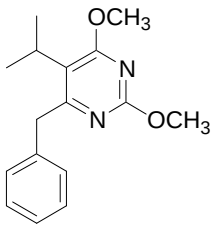
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.98 (s, 3H), 3.95 (s, 3H), 3.39 (sept, ^{3}J = 7.1 Hz), 1.24 (d, ^{3}J = 7.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 169.5, 161.7, 152.2, 120.2, 55.1, 54.3, 30.5, 19.7 (2 carbons).

MS (EI, 70 ev): *m/z* (%) = 262 (13), 260 (13), 247 (95), 245 (100), 165 (8), 151 (6).

HRMS (EI) $C_9H_{13}BrN_2O_2$: calculated [M^+]: 260.0160 found: 260.0171.

Synthesis of 4-benzyl-5-isopropyl-2,6-dimethoxypyrimidine (81)



Preparing according to **GP5** starting from a solution of 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine (**80**) (783 mg, 3.0 mmol) in dry THF (2 mL), *i*-PrMgCl·LiCl (1.0 M/THF, 3.15 mmol, 1.05 equiv), reaction conditions [5 h, 25 °C]. Benzyl bromide (1.03 g, 6 mmol, 2 equiv) followed by two drops of CuCN·2LiCl (1 M in THF), reaction conditions [20 h, 25 °C]. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 1:1) afforded **81** (709 mg, 87%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.22 (m, 5H), 4.06 (s, 2H), 3.95 (2 singulets, 6H), 3.16 (sept, ^{3}J = 7.0 Hz, 1H), 1.11 (d, ^{3}J = 7.0 Hz, 6H).

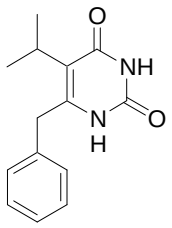
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 170.2, 166.3, 162.5, 138.8, 128.5 (2 carbons), 128.3 (2 carbons), 126.2, 117.8, 54.3, 53.4, 41.4, 26.7, 20.1 (2 carbons).

MS (EI, 70 ev): *m/z* (%) = 272 (80), 271 (100), 257 (93), 244 (29), 243 (23), 241 (16), 227 (10), 167 (14), 91 (14).

IR (film): 2956 (w), 2872 (w), 1562 (s), 1475 (w), 1451 (m), 1366 (s), 1217 (m), 1035 (w).

HRMS (EI) $C_{16}H_{20}N_2O_2$: calculated [M^+]: 272.1525 found: 272.1534.

Synthesis of 6-benzyl-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione (82)



A solution of 4-benzyl-5-isopropyl-2,6-dimethoxypyrimidine (**81**) (0.544 g, 2mmol) in MeOH (10 mL) with concentrated hydrochloric acid (30 mL) was heated under reflux for 4 h. After the reaction was complete, the solution was treated with activated charcoal and evaporated under reduced pressure. The residue was recrystallized from MeOH/ H_2O (4:1) to afford **82** (450 mg, 92%) as a white solid.

mp.: 103.1.-104.2.

IR (KBr): 2957 (w), 2869 (w), 1724 (s), 1640 (S), 1461 (m), 1411 (w), 1358 (w), 1193 (w).

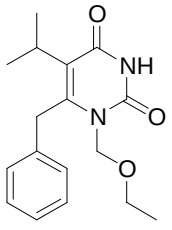
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.18 (s, 1H), 7.94 (s, 1H), 7.38-7.29 (m, 3H), 7.19 (dd, 2H), 3.82 (s, 2H), 3.03 (septuplet, ^3J = 7.0 Hz, 1H), 1.30 (d, ^3J = 7.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 163.7, 150.8, 148.3, 137.0, 128.5 (2 carbons), 127.9 (2 carbons), 126.5, 113.8, 35.1, 26.3, 20.0 (2 carbons).

MS (EI, 70 ev): *m/z* (%) = 244 (72), 230 (17), 215 (5), 229 (100), 186 (14), 153 (7), 91 (17), 69 (7).

HRMS (EI) $C_{14}H_{16}N_2O_2$: calculated [M^+]: 244.1212 found: 244.1225.

Synthesis of 6-benzyl-1-(ethoxymethyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione, emivirine (61)



6-Benzyl-5-isopropylpyrimidine-2,4(1H,3H)-dione (**82**) (366 mg, 1.5 mmol) was suspended in dry acetonitrile (10 mL) under nitrogen and BSA (1.33 ml, 5.2 mmol) was added. The reaction mixture was stirred for 10 min at 25 °C and then cooled to -45 °C. Diethoxymethane

(218 mg, 3 mmol) in dry acetonitrile (1 mL) and TMS-triflate (350 mg, 1.6 mmol) in dry acetonitrile (1 mL) were added to the reaction mixture, which was slowly warmed to 25 °C for 3.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) followed by evaporation under reduced pressure. Water (20 mL) was added followed by the extraction with diethyl acetate (3 × 20 mL). The combined organic phases were dried and evaporated under reduce pressure. Purification by recristallization from EtOH/ H_2O (4:1) to afford **61** (407 mg, 90%) as a white solid.

mp.: 109.1-110.7 °C.

IR (KBr): 3188 (w), 2968 (w), 1710 (s), 1673 (s), 1445 (m), 1100 (m), 1025 (m), 719 (m).

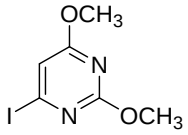
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.2 (s, 1H), 7.34-7.27 (m, 3H), 7.11-7.12 (m, 2H), 5.12 (s, 2H), 4.18 (s, 2H), 3.62 (q, ^3J = 6.9 Hz, 2H), 2.86 (septuplet, ^3J = 6.9 Hz, 1H), 1.28 (d, ^3J = 6.9 Hz, 6H), 1.18 (t, J = 6.9 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.3, 151.9, 148.6, 135.3, 129.2, 127.2 (3 carbons), 127.2, 119.7, 72.9, 65.0, 33.4, 28.3, 20.4 (2 carbons), 15.0.

MS (EI, 70 ev): *m/z* (%) = 303 (19), 302 (60), 287 (16), 273 (39), 257 (100), 241 (80), 229 (64), 135 (34), 91 (21), 59 (29).

HRMS (EI) $C_{17}H_{22}N_2O_3$: calculated [M^+]: 302.1630 found:[M^+]: 302.1641.

Synthesis of 4-iodo-2,6-dimethoxypyrimidine (87b)



Prepared according to **GP6** starting from a solution of 2,4-dimethoxypyrimidine (**83a**) (10.0 mmol, 1.40 g, 1.0 equiv) dissolved in dry THF (5 mL), TMPMgCl·LiCl (11.0 mmol, 1.12 M, 9.8 mL, 1.1 equiv), reaction conditions [–40 °C, 12 h]. Iodine (11.0 mmol, 2.80 g, 1.1 equiv), reaction conditions [–30 °C, 1 h]. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at 0 °C, extracted with EtOAc (3 x 50 ml). Purification by flash chromatography (SiO_2, CH_2Cl_2) afforded **87b** (3.78 g, 87 %) as a colourless solid.

mp.: 100.5-101.9 °C.

IR (film): ν (cm^{-1}) = 3108 (m), 3020 (m), 2956 (m), 1542 (vs), 1458 (vs), 1392 (m), 1360 (vs), 1336 (s), 1232 (s), 1198 (s), 1116 (m), 1088 (s), 1006 (m), 972 (s), 926 (m), 830 (m), 808 (m), 776 (m).

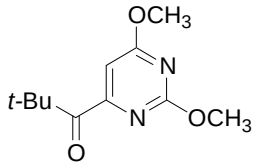
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): δ = 6.85 (s, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): δ = 170.6, 163.6, 127.8, 112.5, 55.3, 54.1.

MS (EI, 70 eV): *m/z* (%) = 265 (100) [M^+], 264 (26), 235 (23), 139 (19), 124 (10), 82 (9).

HRMS $C_6H_7IN_2O_2$: calculated [M^+]: 265.9552 found.265.9560

Synthesis of 1-(2,6-dimethoxypyrimidin-4-yl)-2,2-dimethylpropan-1-one (87c)



Prepared according to **GP6** starting from a solution of 2,4-dimethoxypyrimidine (**83a**) (5.0 mmol, 700 mg, 1.0 equiv) dissolved in dry THF (2.5 mL), TMPMgCl·LiCl (5.5 mmol, 1.12 M, 4.9 mL, 1.1 equiv), reaction conditions [–40 °C, 12 h]. Transmetalation with CuCN·2LiCl (5 mL, 1 equiv, 1.00 M in THF), reaction conditions [–40 °C, 15 min]. Pivaloyl chloride (900 mg, 1.5 equiv), reaction conditions [–40 °C, 5 h]. Purification by flash chromatography (SiO_2, *n*-pentane/ethyl acetate = 9:1) afforded **87c** (806 mg, 72%) as a colourless solid.

mp.: 67.8-69.0 °C.

IR (film): ν (cm^{-1}) = 2962 (w), 1689 (m), 1578 (s), 1560 (s), 1476 (s), 1459 (s), 1372 (s), 1344 (s), 1253 (w), 1196 (m), 1096 (m), 1030 (m), 978 (s), 939 (s), 857 (m), 772 (m), 679 (w).

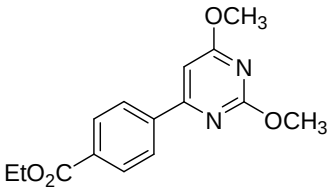
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.76 (s, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 1.39 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 205.1, 172.7, 164.7, 163.4, 101.1, 55.1, 54.2, 44.0, 26.9 (3 carbons).

MS (EI, 70 eV): *m/z* (%) = 224.1 [M^+] (7), 209.0 (7), 140.0 (100), 82.0 (9), 57.0 (23), 41.1 (18).

HRMS $C_{11}H_{16}N_2O_3$: calculated [M^+]: 224.1161 found. 224.1142

Synthesis of ethyl 4-(2,6-dimethoxypyrimidin-4-yl)benzoate (87d)



Prepared according to **GP6** starting from a solution of 2,4-dimethoxypyrimidine (**83a**) (5.0 mmol, 700 mg, 1.0 equiv) dissolved in dry THF (2.5 mL), TMPMgCl·LiCl (5.5 mmol, 1.12 M, 4.9 mL, 1.1 equiv), reaction conditions [–40 °C, 12 h]. Transmetalation with $ZnCl_2$ (5 mL, 1 equiv, 1.00 M in THF), reaction conditions [–40 to 25 °C, 30 min]. Ethyl iodobenzoate (1.93 mg, 7 mmol, 1.4 equiv). In another flame-dried round bottom flask, $Pd(dba)_2$ (135 mg, 5 mol%) and P(*o*-furyl)$_3$ (110 mg, 10 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min. The resulting solution was then transferred to the zinc reagent flask, reaction conditions [reflux, 4 h]. Purification by flash chromatography (SiO_2, *n*-pentane/ethyl acetate = 3:2) afforded **87d** (1.080 g, 75%) as a colourless solid.

mp. = 116.0-118.2 °C

IR (neat): ν (cm^{-1}) = 1714 (m), 1597 (m), 1578 (m), 1559 (s), 1467 (m), 1350 (s), 1274 (s), 1217 (m), 1104 (s), 1013 (m), 825 (s), 771 (s), 703 (s) .

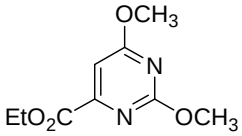
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.11 (m, 4H), 6.82 (s, 1H), 4.41 (q, *J* = 7.50 Hz, 2H), 4.09 (s, 3H), 4.02 (s, 3H), 1.41 (t, *J* = 7.05, 3H) .

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.7, 166.1, 165.6, 164.8, 140.7, 132.2, 129.9 (2 carbons), 126.9 (2 carbons), 98.0, 61.2, 54.9, 54.1, 14.3 ppm.

MS (EI, 70 eV): *m/z* (%) = 288 (M^+, 100), 258 (49), 243 (30), 143 (10), 99 (10).

HRMS (EI) $C_{15}H_{16}N_2O_4$ calculated [M^+]: 288.1110 found: 288.1097.

Synthesis of ethyl 2,6-dimethoxypyrimidine-4-carboxylate (87e)



Prepared according to **GP6** starting from a solution of 2,4-dimethoxypyrimidine (**83a**) (5.0 mmol, 700 mg, 1.0 equiv) dissolved in dry THF (2.5 mL), TMPMgCl·LiCl (5.5 mmol, 1.12

M, 4.9 mL, 1.1 equiv), reaction conditions [–40 °C, 12 h]. Ethyl cyanoformate (10 mmol, 990 mg, 2.0 equiv), reaction conditions [–60 °C, 10 h]. Purification by flash chromatography (SiO_2, *n*-pentane/ethyl acetate = 4:1) afforded **87e** (752 mg, 71%) as a colourless solid.

mp.: 67.2-68.9 °C

IR (ATR): 3104 (w), 2988 (w), 2956 (w), 2940 (w), 2868 (w), 1720 (m), 1600 (s), 1564 (s), 1484 (s), 1404 (s), 1352 (vs), 1264 (s), 1200 (s), 1100 (s), 1028 (vs), 880 (s), 776 (vs).

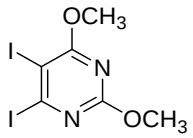
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.03 (s, 1H), 4.44-4.37 (q, 2H, *J* = 7.0 Hz), 4.04 (s, 3H), 4.00 (s, 3 H), 1.41-1.37 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 172.8, 165.9, 163.9, 157.2, 103.1, 62.2, 55.1, 54.1, 14.1.

MS (EI, 70 eV): *m/z* (%) = 212 (21) [M^+], 211 (10), 182 (15), 167 (11), 140 (100), 139 (13), 125 (31), 82 (9).

HRMS (EI) $C_9H_{12}N_2O_4$: calculated [M^+]: 212.0797 found: 212.0794

Synthesis of 4,5-diiodo-2,6-dimethoxypyrimidine (89a)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**18a**, 11.0 mmol, 1.12 M, 9.8 mL, 1.1 equiv) and 2,4-dimethoxypyrimidine (**83a**) (10.0 mmol, 1.40 g, 1.0 equiv) dissolved in dry THF (10 mL) was added dropwise at –40 °C. The reaction mixture was stirred for 12 h at this temperature and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. Iodine (11.0 mmol, 2.80 g, 1.2 equiv) was added and the reaction mixture was stirred for 2 h at –30 °C. The mixture was warmed to –30 °C and TMPMgCl·LiCl (**18a**, 15.0 mmol, 1.12 M, 13.4 mL, 1.5 equiv) was added dropwise. The mixture was warmed to 0 °C and stirred for 2 h. Iodine (20 mmol, 5.14 g, 2 equiv) was added at 25 °C and the mixture was stirred for 3 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (60 mL) solution at 0 °C, extracted with EtOAc (3 x 50 ml), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuum*.

Purification by flash chromatography (SiO_2, CH_2Cl_2) afforded **89a** (3.74 g, 87%) as a colourless solid.

mp.: 144.1-145.4 °C.

IR (ATR): ν (cm^{-1}) = 2996 (m), 2948 (m), 2864 (m), 1516 (vs), 1476 (s), 1450 (s), 1376 (s), 1336 (s), 1292 (s), 1222 (m), 1196 (s), 1102 (m), 1020 (m), 996 (s), 930 (m), 806 (m), 772 (m).

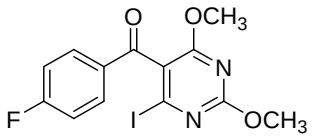
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 3.98 (s, 3 H), 3.96 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.9, 163.6, 141.8, 84.1, 55.8, 55.6

MS (EI, 70 eV): *m/z* (%) = 391 (100) [M^+], 390 (23), 361 (16), 249 (20), 192 (10).

HRMS (EI) ($C_6H_6I_2N_2O_2$): calculated [M^+]: 391.8519 found: 391.8498

Synthesis of (4-fluorophenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (89b)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**18a**, 1.1 mmol, 1.16 M, 0.96 mL, 1.1 equiv) and 4-iodo-2,6-dimethoxypyrimidine (**87b**) (1.0 mmol, 266 mg, 1.0 equiv) dissolved in dry THF (1.0 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at this temperature and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. CuCN·2LiCl (1 mL, 1 equiv, 1.00 M in THF) was added at –20 °C and stirred for 15 min. Thereafter, 4-fluorobenzoyl chloride (190 mg, 1.2 mmol, 1.2 equiv) was added at –20 °C, and the reaction mixture was warmed to 25 °C for 5 h. The resulting mixture was quenched with sat. aq. NH_4Cl solution, extracted with EtOAc (3 x 10 ml), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuum*. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether, 1:1) afforded **89b** (325 mg, 84%) as a colourless solid.

mp. = 151.9-157.1 °C

IR (neat): ν (cm^{-1}) = 1669 (m), 1595 (m), 1566 (s), 1525 (s), 1506 (m), 1475 (m), 1455 (m), 1381 (s), 1364 (s), 1312 (s), 1255 (s), 1245 (s), 1225 (s), 1158 (s), 1076 (s), 1015 (s), 920 (s).

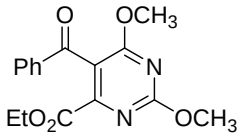
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.83-7.77 (m, 2H), 7.12-7.05 (m, 2H), 3.98 (s, 3H), 3.83 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 191.4, 168.1, 167.2, 164.7, 163.5, 132.5, 132.1, 126.6, 120.1, 116.3, 116.1, 55.7, 54.8 ppm.

MS (EI, 70 eV), *m/z* (%): 388 (M^+, 66), 358 (5), 293 (31), 261 (10), 136 (25), 123 (100), 95 (80), 75 (24).

HRMS (EI) $C_{13}H_{10}FIN_2O_3$: calculated [M^+]:387.9720 found: 387.9722.

Synthesis of ethyl 5-benzoyl-2,6-dimethoxypyrimidine-4-carboxylate (89c)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**18a**, 1.1 mmol, 1.16 M, 0.96 mL, 1.1 equiv) and ethyl 2,6-dimethoxypyrimidine-4-carboxylate (**87e**) (1.0 mmol, 212 mg, 1.0 equiv) dissolved in dry THF (1.0 mL) was added dropwise at -40 °C. The reaction mixture was stirred for 2 h at this temperature and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. CuCN·2LiCl (1 mL, 1 equiv, 1.00 M in THF) was added at –40 °C and stirred for 1 h. Thereafter, benzoyl chloride (210 mg, 1.5 mmol, 1.5 equiv) was added at –40 °C, and the reaction mixture was warmed to 25 °C for 12 h. The resulting mixture was quenched with sat. aq. NH_4Cl solution, extracted with EtOAc (3 x 10 ml), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuum*. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether, 1:1) afforded **89c** (246 mg, 78%) as a colourless solid.

mp. = 98.4-100.4 ^oC

IR (neat): ν (cm^{-1}) = 3067 (w), 2962 (w), 2925 (w), 1727 (s), 1668 (s), 1571 (s), 1556 (s), 1463 (m), 1447 (m), 1380 (s),1254 (s), 1229 (s), 1176 (m), 1082 (s), 1035 (s), 929 (m), 903 (s), 776 (s), 691 (s).

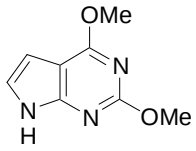
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.80-7.77 (m, 2H), 7.60-7.54 (m, 1H), 7.47-7.41 (m, 2H), 4.21-4.13 (q, 2H, *J* = 7.3 Hz), 4.11 (s, 3H),3.95 (s, 3H), 1.11-1.06 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 192.0, 169.9, 165.2, 163.3, 155.3, 137.0, 133.6, 128.9, 128.9, 128.7, 128.7, 116.1, 62.6, 55.5, 55.0, 13.5.

MS (EI, 70 eV): *m/z* (%): 316 (M^+, 45), 272 (67), 243 (55), 239 (54), 215 (19), 211 (27), 186 (12), 167 (62), 139 (24), 118 (12), 109 (12), 105 (100), 82 (17), 77 (83), 51 (14).

HRMS (EI): $C_{16}H_{16}N_2O_5$ calculated [M^+]: 316.1059 found: 316.1036.

Synthesis of 2,4-dimethoxy-7H-pyrrolo[2,3-d]pyrimidine (90)



To a stirred solution of KH (126 mg, 3 mmol, 3 equiv) in NMP (6 mL), was added at 25 °C, a solution of **92** (179 mg, 1 mmol, 1 equiv) in NMP (2 mL). The resulting mixture was vigorously stirred at 60 °C for 8 h and quenched with water (2 mL). The aqueous layer was extracted CH_2Cl_2 (3 x 80 mL) and Et_2O (2 x 50 mL) and the combined organic layer were washed with brine (2 x 80 mL) and dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **90** (144 mg, 81%) as a colorless solid.

mp.: 202.4-204.8 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 3212 (m), 3156 (m), 3004 (m), 2944 (m), 1604 (s), 1584 (s), 1472 (s), 1404 (s), 1316 (s), 1216 (s), 1192 (s), 1152 (s), 1088 (vs), 1076 (vs), 1052 (s), 944 (s), 896 (s), 744 (vs), 724 (s).

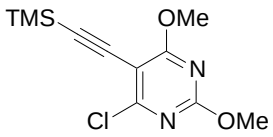
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.71 (s, 1H), 7.08 (dd, *Jcis* = 3.0 Hz, 1H), 6.34 (dd, *Jcis* = 3.0 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 163.4, 161.1, 153.7, 121.8, 99.6, 98.1, 54.0, 53.2.

MS (70 eV, EI): ***m/z* (%)** = 179 (100) $[M]^+$, 150 (15), 134 (21), 108 (5), 78 (5).

HRMS (EI) $C_8H_9N_3O_2$: calculated $[M]^+$: 179.0695 found: 179.0690.

Synthesis of 4-chloro-2,6-dimethoxy-5-trimethylsilanylethynyl-pyrimidine (91)



A dry and argon flushed 50 mL flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of commercially available 4-chloro-2,6-dimethoxypyrimidine (**70a**) (6.16 g, 28 mmol, 1.4 equiv) in dry THF (15 mL). TMPMgCl·LiCl (**18a**, 27.5 mL, 1.09 M in THF, 30 mmol, 1.5 equiv) was added dropwise at 25 °C. The reaction mixture was stirred at this same temperature for 1 h. The completion of the metalation was checked by GC-analysis. At -20 °C, $ZnCl_2$ (30 mL, 1 m in THF, 1.5 equiv) was then added to the freshly prepared magnesium reagent and allowed to warm to 25 °C for 1 h. Iodoethynyl-trimethyl-silane[4] (3.1 mL, 20 mmol, 1 equiv) was added to the reaction mixture at 25 °C. A round bottom flask was charged with $Pd(dba)_2$ (230 mg, 2 mol%), P(*o*-furyl)$_3$ (185 mg, 4 mol%) and THF (5 mL). The mixture was stirred at 25 ^oC for 10 min then transferred to the reaction flask which was charged with the organozinc solution. The resulting mixture was stirred 2 h at 40 °C, cooled to 25 ^oC, and quenched with sat. NH_4Cl solution (40 mL). The aqueous layer was extracted with AcOEt (3 x 40 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuum*. The solvent was evaporated and the product was purified by flash chromatography (SiO_2, *n*-pentane/Et_2O =7:3). 4-Chloro-2,6-dimethoxy-5-trimethylsilanyl-ethynyl-pyrimidine (**91**) was afforded (3.31 g, 64 %) as a pale yellowish solid.

mp.: 62.4-64.2 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 3024 (vw), 2957 (w), 2156 (m), 1584 (m), 1528 (s), 1473 (s), 1456 (s), 1379 (s), 1328 (s), 1247 (s), 1215 (m), 1184 (m), 1084 (s), 1028 (s), 944 (m), 840 (vs), 788 (s), 758 (s), 639 (m).

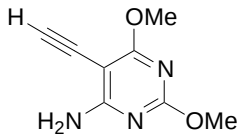
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.03 (s, 3H), 3.99 (s, 3H), 0.26 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.7, 163.1, 162.3, 106.0, 99.1, 94.1, 55.6, 55.3, -0.2 (3 CH_3 of TMS group).

MS (70 eV, EI): ***m/z* (%)** = 245 (21), 236 (34) $[M]^+$, 221 (100), 191 (28), 71 (10), 57 (13).

HRMS (EI) $C_{11}H_{16}N_2O_2Si$: calculated $[M]^+$: 236.0981 found: 236.0977.

Synthesis of 5-ethynyl-2,6-dimethoxy-pyrimidin-4-ylamine (92) starting from 91



A solution of **91** (135 mg, 0.5 mmol) dissolved in NH_3 sat. in MeOH (3 mL, 3 M in MeOH, 6 equiv) was introduced in a 25cm^3 autoclave and was heated 2 days at 90 °C. The consumption of the starting material was checked by TLC. The solvent was evaporated under vacuum. The crude oily residue was purified by flash chromatography (SiO_2) using pentane/Et_2O (95:5, with NEt_3 0.5 %). A colourless solid was obtained (56 mg, 31%) afforded to 5-ethynyl-2,6-dimethoxy-pyrimidin-4-ylamine (**92**). Analytic data matched data from the preparation of **9a** starting from **6a**.

mp.: 166.5-168.4 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 2956 (w), 2900 (w), 2153 (w), 1568 (m), 1535 (s), 1364 (vs), 1247 (s), 1109 (s), 1086 (s), 837 (broad vs), 680 (m).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.86 (broad s, NH_2), 4.33 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 171.1, 166.7, 163.2, 89.0, 76.2, 75.1, 54.0, 53.6.

MS (70 eV, EI): *m/z* (%) = 179 (79) $[M]^+$, 149 (26), 121 (23), 111 (35), 97 (51), 83 (50), 71 (74), 57 (100), 43 (75).

HRMS (EI) $C_8H_9N_3O_2$: calculated $[M]^+$: 179.0695 found: 179.0699.

4. Amination of DNA and RNA units via cuprated pyrimidines and purines intermediates.

4.1 General procedure for the amination via magnesiation using Br/Mg exchange reaction (GP7):

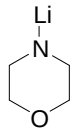
A dry and argon-flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with the aromatic or heteroaromatic halide (1.0 mmol) in THF (1 mL). *i*-PrMgCl·LiCl (**13**) or *i*-PrMgCl (Solution in THF, 1.1 equiv) was added dropwise and stirred at the indicated temperature for the indicated time [reaction conditions: temperature, time] to afford the corresponding Grignard reagent. The completion of the halogen/Mg-exchange was checked by GC analysis of reaction aliquots quenched with sat. aqueous NH_4Cl solution using decane as internal standard. This reagent was added dropwise to a solution of CuCl·2LiCl (1.0 m in THF; 1.2 mL, 1.2 mmol, 1.2 equiv) and the indicated ligand (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol, 1.2 equiv), or NEt_3 (121 mg, 1.2 mmol, 1.2 equiv) at -50 °C and the mixture was stirred for 0.7 h leading to the cuprated reagent. To the so formed aryl copper reagent, the indicated lithium amide (2.0 mmol, 2 equiv) was added dropwise and the mixture was further stirred for 1 h at -60 °C. The reaction mixture was cooled to -78 ^oC, then chloranil (**22**, 298 mg, 1.2 mmol), in dry THF (7 mL), was added slowly over a period of 1 h. The reaction mixture was stirred for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture and it was filtered through *Celite*, washed with Et_2O thoroughly, and the liquors washed with 2 x 10 mL portions of NH_4OH (aq., 2.0 m) and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuum*. The crude residue was purified by column chromatography (SiO_2 or Al_2O_3 neutral deactivated) or by preparative TLC (SiO_2).

4.2 General procedure for the amination via magnesiation using TMPMg·LiCl (GP8):

A dry and argon-flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with the aromatic or heteroaromatic halide (1.0 mmol) in THF (1 mL). TMPMgCl·LiCl (**18a**, solution in THF, 1.1 equiv) was added dropwise and stirred at the indicated temperature for the indicated time [reaction conditions: temperature, time] to afford the corresponding Grignard reagent. The completion of the metalation was checked by GC analysis of reaction aliquots quenched iodine using decane as internal standard. This reagent was added dropwise to a solution of CuCl·2LiCl (1.0 m in THF; 1.2 mL, 1.2 mmol, 1.2 equiv) and the indicated ligand (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol, 1.2

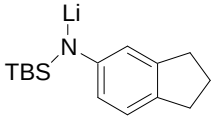
equiv), or NEt_3 (121 mg, 1.2 mmol, 1.2 equiv) at -50 °C and the mixture was stirred for 0.7 h leading to the cuprated reagent. To the so formed aryl copper reagent, the indicated lithium amide (2.0 mmol, 2 equiv) was added dropwise and the mixture was further stirred for 1 h at -60 °C. The reaction mixture was cooled to -78 °C, then chloranil (**22**, 298 mg, 1.2 mmol), in dry THF (7 mL), was added slowly over a period of 1 h. The reaction mixture was stirred for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture and it was filtered through *Celite*, washed with Et_2O thoroughly, and the liquors washed with 2 x 10 mL portions of NH_4OH (aq., 2.0 m) and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuum*. The crude residue was purified by column chromatography (SiO_2 or Al_2O_3 neutral deactivated) or by preparative TLC (SiO_2).

4.3 **Typical procedure (TP1)**: Preparation of the *N*-lithium morpholide (**96b**).



In a dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum, morpholine (174 mg, 2 mmol) was dissolved in 4 mL of dry THF. *n*-BuLi (2 mmol, solution in hexane) was added dropwise at -40 °C and stirred for 30 min and then 5 min at 20 °C.

4.4 **Typical procedure (TP2)**: Preparation of the lithium silinamide **96c**.

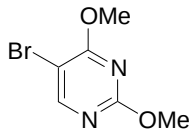


In a dry and argon flushed *Schlenk*-flask equipped with a magnetic stirrer and a septum, 5-aminoindane (266 mg, 2 mmol) was dissolved in dry THF (1 mL) and cooled to -50 °C. MeLi (1.70 M in Et_2O; 1.21 mL, 2.05 mmol) was added dropwise and the mixture was stirred for 10 min. Then, TBDMSCl (315 mg, 2.1 mmol), dissolved in dry THF (1 mL), was added dropwise. The reaction mixture was allowed to reach 25 °C and was further stirred for 30 min. The solvent and volatiles were removed under high vacuum for 1 h. The residue was redissolved in dry THF (1 mL) and was again cooled to -50 °C. MeLi (1.70 M in Et_2O; 1.21

mL, 2.05 mmol) was added dropwise and the mixture was stirred for 10 min, affording the lithium silanamide **8c**.

4.5 Starting material synthesis

Synthesis of 2,4-dimethoxy-5-bromo-pyrimidine (starting material of compounds 83b and 94)



Commercially available 2,4-dimethoxpyrimidine (**83a**) (4.20 g, 30 mmol, 1.0 equiv) was slurried with $NaHCO_3$ (4.0 g) in 90 mL of 50% aq. MeOH. Bromine (8.63 g, 2.70 mL, 1.8 equiv) was added dropwise with an efficient stirring over a period of 1 h. After 30 min of bromine addition, an additional 7.0 g of sodium bicarbonate was added and the mixture was stirred at 25 °C for a total of 2 h. The white precipitated obtained was collected by filtration, washed with MeOH (1 x 20 mL) and water (2 x 30 mL). The obtained solid was dried under reduced pressure. 2,4-Dimethoxy-5-bromopyrimidine was afforded as colourless crystalline plates (5.51 g, 84%).

mp.: 68.0-69.2 °C.

IR (ATR): ν (cm^{-1}) = 3024 (m), 2958 (m), 1556 (vs), 1486 (m), 1442 (m), 1394 (s), 1366 (s), 14 (m), 1272 (m), 1232 (m), 1192 (m), 1094 (s), 1032 (m), 1000 (s), 974 (m), 932 (m), 0 (m), 762 (m), 662 (w).

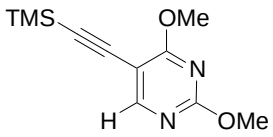
^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.29 (s, 1 H), 4.04 (s, 3 H), 3.97 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 166.8, 164.3, 159.2, 96.1, 55.3, 54.9.

MS (EI, 70 eV): *m/z* (%) = 219 (100) [M^+, ^{81}Br], 219 (65), 218 (79), 217 (78) [M^+], 204 (34), 202 (27), 190 (20), 189 (76), 188 (24), 187 (81), 174 (28), 172 (25), 109 (16), 82 (11), 69 (12).

HRMS (EI) $C_6H_7{}^{79}BrN_2O_2$: calculated [M^+, ^{81}Br]: 217.9691 found: 219.9650

Synthesis of 2,6-dimethoxy-5-trimethylsilanylethynyl-pyrimi-dine (94)



A dry and argon flushed 50 mL flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 5-bromo-4-chloro-2,6-dimethoxypyrimidine (6.57 g, 37 mmol, 1.4 equiv) in dry THF (25 mL). *i*-PrMgCl·LiCl (**13**, 38 mL, 1.05 M in THF, 40 mmol, 1.5 equiv) was added dropwise at -20 °C. The reaction mixture was stirred at this temperature for 2 h. The completion of the Br/Mg exchange was checked by GC-analysis of quenching reaction aliquots. At 25 °C, $ZnCl_2$ (30 mL, 1 m in THF, 1.5 equiv) was then added to the freshly prepared magnesium reagent and stirred for 1 h. Iodoethynyl-trimethylsilane[118] (4.2 mL, 27 mmol, 1 equiv) was added to the reaction mixture at 25 °C. A round bottom flask was charged with $Pd(dba)_2$ (342 mg, 2 mol%), P(*o*-furyl)$_3$ (280 mg, 4 mol%) and THF (6 mL). The mixture was stirred at 25 ^oC for 10 min then transferred to the reaction flask which was charged with the organozinc solution. The resulting mixture was stirred 12 h at 25 ^oC, and quenched with sat. NH_4Cl solution (60 mL). The aqueous layer was extracted with AcOEt (3 x 60 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuum*. Purification by flash chromatography (SiO_2, *n*-pentane/AcOEt = 95:5) afforded 2,6-dimethoxy-5-trimethylsilanylethynyl-pyrimidine (**94**) (5.54 g, 76 %) as a colourless solid.

mp.: 51.5-53.0 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 2956 (m), 2160 (m), 1600 (m), 1544 (s), 1472 (s), 1380 (s), 1248 (s), 1215 (m), 1183 (m), 1083 (m), 1030 (s), 943 (w), 829 (vs), 787 (s), 759 (s).

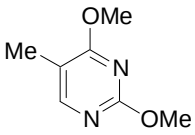
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.31 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 0.24 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.7, 164.0, 162.0, 101.2, 100.0, 96.1, 55.1, 54.5, -0.1(3 CH_3 of TMS group).

MS (70 eV, EI): *m/z* (%) = 270 (27) $[M]^+$, 255 (100), 240 (59), 225 (15), 168 (6), 43 (9).

HRMS (EI) $C_{11}H_{15}ClN_2O_2Si$: calculated $[M]^+$: 270.0591 found: 270.0581.

Synthesis of 2,4-dimethoxy-5-methyl-pyrimidine (83b)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with 5-bromo-2,6-dimethoxypyrimidine (2.74 g, 12.5 mmol, 1 equiv.) dissolved in dry THF (10 mL). *i*-PrMgCl·LiCl (**13**, 11 mL, 1.25 M in THF, 1.1 equiv) was added dropwise at -20°C. CuCN·2LiCl[57] (12.5 mL, 1.0 m in THF, 1.0 equiv) was added dropwise to the corresponding Grignard reagent at -30 °C and the mixture was stirred for 30 min. Methyl iodide (2.3 g, 1.3 equiv) was added dropwise and the reaction mixture allowed to warm to 25 °C and stirred for 12 h. The reaction was quenched with sat aq. NH_4Cl (20 mL) and extracted with EtOAc (5x 20 ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **83b** (1.69 g, 88%) as a colourless crystalline solid.

mp.: 61.9-63.2 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 3020 (w), 2952 (w), 1604 (s), 1572 (s), 1464 (s), 1444 (vs), 1388 (vs), 1348 (s), 1288 (s), 1200 (vs), 1068 (s), 1016 (vs), 1004 (vs), 784 (vs).

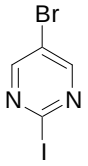
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.90 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 1.97 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.5, 163.9, 156.7, 110.9, 54.4, 53.6, 11.7.

MS (70 eV, EI): ***m/z* (%)** = 154 (100)[M^+], 139 (32), 124 (59), 109 (24), 96 (6), 82 (5).

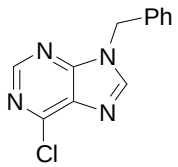
HRMS (EI) $C_7H_{10}N_2O_2$: calculated [M]$^+$: 154.0742 found: 154.0747.

Synthesis of 5-bromo-2-iodo-pyrimidine



This compound was prepared following the literature procedure.[153]

Synthesis of 9-benzyl-6-chloro-9H-purine (102)

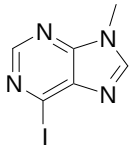


[153] F. Lutz, T. Kawasaki, K., Soai. *Tetrahedron Asymmetry* **2006**, *17*, 486.

This compound was prepared from commercially available 6-chloropurine using the literature procedure.[154] The analytic data were found to match literature data.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.76 (s, 1H), 8.10 (s, 1H), 7.39-7.27 (m, 5H), 5.44 (s, 2H).

Synthesis of 6-iodo-9-methyl-9H-purine (103)



This compound was prepared from 6-iodopurine[155] by the method used for the preparation of 6-chloro-9-methyl-9H-purine.[156]

6-Iodo-9-methyl-9H-purine **103** was afforded as a pale yellowish solid in 55% yield.

mp.: 210.0-212.2 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 3064 (w), 2952 (w), 1668 (w), 1552 (s), 1436 (s), 1388 (m), 1324 (s), 1228 (s), 1132 (s), 904 (s), 836 (s), 732 (s), 636 (vs).

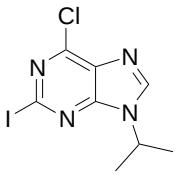
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.59 (s, 1H), 8.59 (s, 1H), 3.81 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 151.6, 148.3, 147.0, 137.8, 122.2, 30.0.

MS (70 eV, EI): ***m/z* (%)** = 260 (100), 133 (44), 16 (17), 79 (24), 52 (9).

HRMS (EI) $C_6H_5IN_4$: calculated $[M]^+$: 259.9559 found: 259.9563.

Synthesis of 6-chloro-2-iodo-9-isopropyl-9H-purine (108)



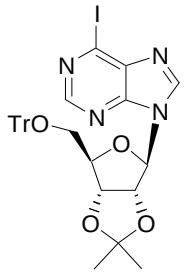
This compound was prepared following the literature procedure.[157]

[154] Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. Bull. Chem. Soc. Jpn. **1998**, *71*, 1973.

[155] 6-Iodopurine was prepared according to literature procedure: Elion, G. B.; Hitchings, G. H. *J. Am. Chem. Soc*. **1956**,*78*,3508.

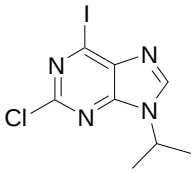
[156] K. Bok Young, A. Joong Bok, L. Hong Woo, K. Sung Kwon, L. Jung Hwa,; S. Jae Soo, A. Soon Kil, H. Chung Il, Y. Seung Soo. *Eur. J. Med. Chem*. **2004**, *39*, 433.

Synthesis of 9-(2,2-dimethyl-6-trityloxymethyl-tetrahydro-furo[3,4 d][1,3]dioxol-4-yl)-6-iodo-9H-purine (111)



This compound was prepared following the literature procedure.[158]

Synthesis of 2-chloro-6-iodo-9-isopropyl-9H-purine (114)



This compound was prepared from 2-chloro-6-iodo-9H-purine[155]by the Mitsonobu reaction procedure described in the literature.[159] Purification by flash chromatography (SiO_2, *n*-pentane/acetonitrile = 1:1) afforded **114** (8.55 g, 83%) as a colorless solid.

mp.: 148.8-151.5 ^{o}C.

IR (Diamond ATR): ν (cm^{-1}) = 3112 (w), 2980 (w), 2936 (w), 1572 (m), 1560 (w), 1540 (s), 1352 (s), 1208 (s), 1148 (s), 1136 (s), 936 (s), 836 (vs), 764 (s), 636 (s).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.79 (s, 1H), 4.77 (sept, *J* = 6.9 Hz), 1.53 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 150.4, 148.8, 145.7, 138.0, 123.4, 47.8, 21.7, 21.7.

MS (70 eV, EI): ***m/z* (%)** = 324 (25) [^{37}Cl], 322 (100) [^{35}Cl], 279 (32), 195 (10), 159 (13), 153 (17), 134 (7).

HRMS (EI) $C_8H_8{}^{35}Cl{}^{127}IN_4$: calculated $[M]^+$: 321.9482 found: 321.9486.

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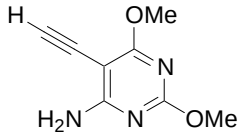
[157] M. Legraverend, O. Ludwig, E. Bisagni, S. Leclerc, L. Meijer, N. Giocanti, R. Sadri, V. Favaudon. *Bioorg. Med. Chem*. **1999**, *7*, 1281.
[158] M. Hocek, A. Holy. *Collect.Czech. Chem. Commun*. **1999**, *64*, 229.
[159] A. Toyota, N. Katagari, C. Kanebo. *Synth. Commun*. **1993**, *23*, 1295.

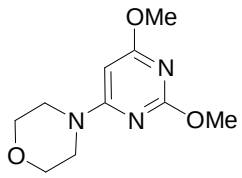
4.6 Preparation of aminated pyrimidines

Synthesis of 5-ethynyl-2,6-dimethoxy-pyrimidin-4-ylamine (92) starting from 94



According to **GP8**, starting from **94** (236 mg, 1 mmol, 1 equiv) dissolved in 1 mL dry THF; TMPMg·LiCl (0.91 mL, 1.1 equiv, 1.20 M in THF)[reaction conditions: -10 °C, 3 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **95**; LiHMDS (2 mL, 2 mmol, 1 M in THF/Ethylbenzene); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. The crude material obtained was redissolved in THF (3 mL) before TBAF (1.0 m in THF) (2 mL, 2 mmol) was added in one portion and the mixture was stirred at 25 °C for 2 h, poured over EtOAc (10 mL) and washed with deionised water (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **92** (127 mg, 71 %) as a colourless solid. The analytical data matched the data for the preparation of **92** starting from **91**.

Synthesis of 4-(2,6-dimethoxy-pyrimidin-4-yl)-morpholine (98a)



Prepared according to **GP8** from 2,4-dimethoxypyrimidine (**83a**) (280 mg, 2 mmol, 1 equiv), and TMPMgCl·LiCl (1.8 mL, 1.23 M in THF, 1.1 equiv) [reaction conditions: -40 °C, 12 h]; CuCl·2LiCl (2.4 mL, 1.2 equiv) and *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (284 mg, 2.4 mmol, 1.2 equiv) to afford the corresponding cuprated reagent **97a**; *N*-lithium morpholide (**96b,** 4 mmol, 2 equiv); chloranil (595 mg, 1.2 equiv) in 14 mL of THF. Purification by flash chromatography (SiO_2, pentane/ Et_2O = 4:1) afforded **98a** (341 mg, 76%) as a grey solid.

mp.: 93.9-95.7 °C.

IR (Diamond ATR): ν (cm^{-1}) = 2984 (w), 2972 (w), 2940 (w), 2876 (w), 1596 (vs), 1568 (vs), 1460 (s), 1368 (vs), 1264 (s), 1220 (s), 1200 (vs), 1100 (vs), 1036 (vs), 1000 (s), 868 (s), 788 (vs).

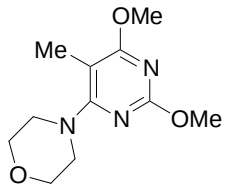
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.46 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.73 (t, *J* = 4.5 Hz, 4H), 3.53 (t, *J* = 5.0 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.5, 165.3, 164.8, 79.2, 66.4, 66.4, 54.2, 53.6, 44.6, 44.6.

MS (70 eV, EI): *m/z* (%) = 225 (66) $[M]^+$, 194 (84), 180 (51), 168 (100), 140 (49), 125 (23), 86 (7), 82 (8).

HRMS (EI): $C_{10}H_{15}N_3O$: calculated $[M]^+$: 225.1113, found: 225.1101.

Synthesis of 4-(2,6-dimethoxy-5-methyl-pyrimidin-4-yl)-morpholine (98b)



Prepared according to **GP8** from 2,4-dimethoxy-5-methyl-pyrimidine **83b** (175 mg, 1.0 mmol) in dry THF (0.5 mL), and TMPMgCl·LiCl (1.20 m in THF; 0.92 mL, 1.1 mmol) [reaction conditions: -5 °C, 3 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97b**; *N*-lithium morpholide (**96b**) (2 mmol, preparation described in **TP1**); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, pentane/Et_2O = 9:1) afforded **98b** (171 mg, 72 %) as a colourless oil.

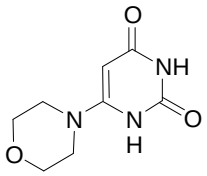
IR (Diamond ATR): ν (cm^{-1}) = 2956 (w), 2924 (w), 2852 (w), 1584 (s), 1564 (vs), 1456 (s), 1372 (vs), 1360 (vs), 1260 (m), 1212 (s), 1188 (m), 1148 (s), 1112 (s), 1084 (m), 1044 (s), 988 (m), 860 (w), 792 (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.92 (s, 3H), 3.89 (s, 3H), 3.77 (t, *J* = 4.7 Hz, 4H), 3.31 (t, *J* = 4.8 Hz, 4H), 1.95 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.3, 167.3, 162.2, 95.3, 66.8, 66.8, 54.1, 53.9, 49.0, 49.0, 11.1.

HRMS (ESI) $C_{11}H_{17}N_3O_3$: calculated $[M]^+$: 239.1270, found: 239.1235.

Synthesis of 6-morpholin-4-yl-1H-pyrimidine-2,4-dione (99a)



A solution of 4-(2,6-dimethoxy-pyrimidin-4-yl)-morpholine (**98a**, 113 mg, 0.5 mmol) in acetyl chloride (1 mL) was stirred at reflux overnight in the presence of a few drops of water. The reagent was removed under vacuum. Methanol (3 x 15 mL) was added and distilled off. The residue was dissolved in 2-propanol/methanol (3:2) at reflux, and the solution was then cooled and the precipitate collected by filtration. The solid was dissolved in deionised water, and the clear solution was lyophilized to result in a white solid, which was dried under vacuum to afford **99a** (88 mg, 91%).

mp.: 290-300 ^oC (decomposed).

IR (Diamond ATR): ν (cm^{-1}) = 3160 (m), 3080 (w), 3020 (w), 2920 (w), 2872 (w), 1708 (m), 1628 (s), 1596 (s), 1444 (s), 1376 (s), 1240 (s), 1112 (s), 1012 (s), 884 (s), 820 (s), 732 (m), 700 (vs), 600 (vs).

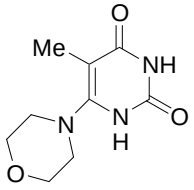
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 9.76 (broads, 2H), 4.56 (s, 1H), 3.59 (t, *J* = 4.7 Hz, 4H), 3.21 (t, *J* = 4.7 Hz, 4H)

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 165.1, 159.8, 154.4, 76.5, 65.8, 65.8, 45.7, 45.7.

MS (70 eV, EI): ***m/z* (%)** = 197 (100) $[M]^+$, 182 (31), 167 (21), 153 (17), 140 (41), 97 (18), 68 (78), 56 (12).

HRMS (ESI) $C_8H_{11}N_3O_3$ calculated $[M]^+$:197.0800 found: 197.0796.

Synthesis of 5-methyl-6-morpholin-4-yl-1H-pyrimidine-2,4-dione (99b)



A solution of 4-(2,6-dimethoxy-5-methyl-pyrimidin-4-yl)-morpholine (**98b**, 119 mg, 0.5 mmol) in acetyl chloride (1 mL) was stirred at reflux overnight in the presence of a few drops of water. The reagent was removed under vacuum. Methanol (3 x 15 mL) was added and distilled off. The residue was dissolved in 2-propanol/methanol (3:2) at reflux. The solution was then cooled and the precipitate collected by filtration. The solid was dissolved in deionised water, and the clear solution was lyophilized to result in a white solid, which was dried under vacuum to afford **99b** (106 mg, 96%).

mp.: 230-240 ^{o}C (decomposed).

IR (Diamond ATR): ν (cm^{-1}) = 3140 (broad w), 3040 (broad m), 2964 (m), 2860 (m), 2804 (m), 1700 (s), 1628 (s), 1588 (vs), 1500 (s), 1408 (s), 1360 (s), 1196 (s), 1108 (s), 1024 (s), 864 (s), 780 (s), 756 (s).

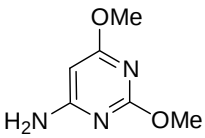
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 10.71 (broad s, 2H), 3.62 (t, *J* = 4.1 Hz, 4H), 3.09 (t, *J* = 4.1 Hz, 4H), 1.71 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 165.5, 153.5, 150.7, 92.2, 66.2, 66.2, 48.2, 10.3.

MS (70 eV, EI): ***m/z* (%)** = 211 (29) $[M]^+$, 166 (16), 142 (79), 126 (15), 99 (25), 86 (21), 56 (100), 44 (65).

HRMS (ESI) $C_9H_{13}N_3O_2$: calculated $[M]^+$: 211.0957 found: 211.0954.

Synthesis of 2,6-dimethoxypyrimidin-4-ylamine (98c)



Prepared according to **GP8** from 2,4-dimethoxypyrimidine (**83a**)(140 mg, 1 mmol, 1 equiv); TMPMgCl·LiCl (0.9 mL, 1.23 M in THF, 1.1 equiv)[reaction conditions: -40 °C, 12 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol, 1.2 equiv) to afford the corresponding cuprated reagent **97a**; LiHMDS (**96a**, 2 mL, 2.0 mmol, 1 M in THF/Ethylbenzene); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. For the workup of this reaction, the organic layer was only washed one time with brine (50 mL). The crude material obtained was redissolved in THF (3 mL) before TBAF (1.0 M in THF) (2 mL, 2 mmol) was added in one portion and the mixture was stirred at 25 °C for 10 min, poured over EtOAc (10 mL) and washed with deionised water (3 x 10 mL). The combined organic

extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by flash chromatography (Al_2O_3, CH_2Cl_2/MeOH 4%) afforded **98c** (125 mg, 81%) as a colourless solid.

mp.: 150.9-153.7 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 3452 (m), 3140 8m), 2952 (w), 1640 (s), 1572 (vs), 1452 (s), 1352 (s), 1204 (vs), 1048 (s), 956 (s).

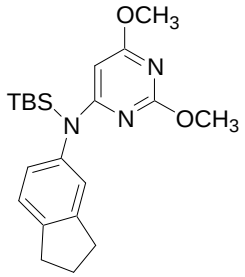
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.58 (broad s, NH_2), 5.36 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 171.0, 166.0, 164.9, 79.1, 53.5, 53.0.

MS (70 eV, EI): ***m/z* (%)** = 155 (100) $[M]^+$, 152 (68), 125 (18), 110 (11), 67 (6).

HRMS (EI) $C_6H_9N_3O_2$: calculated $[M]^+$: 155.0695 found: 155.0667.

Synthesis of (*tert*-butyl-dimethyl-silanyl)-(2,6-dimethoxy-pyrimidin-4-yl)-indan-5-yl-amine (98d)



Prepared according to **GP8** from 2,4-dimethoxypyrimidine (**83a**)(140 mg, 1 mmol, 1 equiv), and TMPMgClLiCl (0.89 mL, 1.23 M in THF, 1.1 equiv)[reaction conditions: -40 °C, 12 h]; CuCl·2LiCl (2.4 mL, 1.2 equiv) and (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97a**; lithium-(*t*-butyl-dimethyl-silanyl)-indan-5-yl-amine **96c** (2.0 mmol, preparation described in **TP2**); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 95:5) afforded **98d** (296 mg, 76%) as a pale yellowish solid.

mp.: 90.0-92.4 ^oC (brown).

IR (Diamond ATR): ν (cm^{-1}) = 2956 (w), 2928 (w), 2892 (w), 2856 (w), 1584 (s), 1552 (vs), 1440 (s), 1352 (vs), 1256 (s), 1196 (vs), 1172 (s), 1064 (s), 976 (m), 836 (s), 800 (vs), 780 (s), 680 (s), 672 (s).

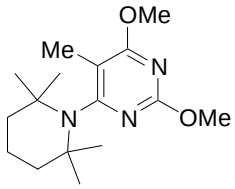
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.18 (d, *J* = 7.7 Hz, 1H), 6.88 (s, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 4.86 (s, 1H), 3.97 (s, 3H), 3.78 (s, 3H), 2.89 (q, *J* = 7.9 Hz, 4H), 2.09 (q, *J* = 7.5 Hz, 2H), 1.03 (s, 9H), 0.15 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 171.5, 170.6, 164.3, 145.8, 124.6, 141.4, 127.5, 125.6, 125.1, 83.6, 54.6, 53.3, 32.8, 32.4, 23.4 (2 carbons from Si-(*t*-Bu) group), 25.8, 20.0, -1.6 (2 carbons from $SiMe_2$ group).

MS (70 eV, EI): ***m/z* (%)** = 385 (7) $[M]^+$, 370 (5), 328 (100), 189 (3), 164 (4), 115 (2), 89 (3), 73 (2), 59 (2).

HRMS (EI) $C_{21}H_{31}N_3O_2Si$: calculated $[M]^+$: 385.2186 found: 385.2161.

Synthesis of 2,4-dimethoxy-5-methyl-6-(2,2,6,6-tetramethyl-piperidin-1-yl)-pyrimidine (98e)



Prepared according to **GP8** from 2,4-dimethoxy-5-methyl-pyrimidine (**83b**) (175 mg, 1.0 mmol, 1 equiv) in dry THF (0.5 mL), and TMPMgCl·LiCl (1.20 m in THF; 0.92 mL, 1.1 mmol) [reaction conditions: -5 °C, 3 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97b**; TMPLi (**96d**) (2 mmol in Et_2O, prepared according to the literature[160]); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **98e** (205 mg, 70%) as a colourless solid.

mp.: 77.5-78.7 °C

IR (Diamond ATR) 2980 (m), 2920 (s), 2872 (m), 2840 (m), 1560 (s), 1476 (m), 1448 (s), 1372 (vs), 1356 (vs), 1200 (s), 1132 (s), 1076 (s), 1044 (s), 776 (s), 696 (m).

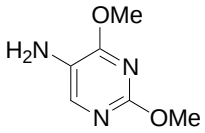
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.94 (s, 3H), 3.92 (s, 3H), 2.05 (s, 3H), 1.98-1.57 (m, 6H), 1.40 (s, 6H), 0.74 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.2, 166.7, 161.9, 111.9, 55.0, 55.0, 54.2, 53.9, 41.2, 41.2, 31.5, 31.5, 24.9, 24.9, 18.3, 11.9.

[160] Salman, H.; .Abraham, Y.; Tal, S.; Meltzman, S.; Kapon, M.; Tessler, N., Speiser, S.; Eichen, Y. *Eur. J. Org. Chem.* **2005**, 2207.

HRMS (ESI) $C_{16}H_{27}N_3O_2$: calculated $[M+H]^+$: 294.2182 found: 294.2176.

Synthesis of 2,4-dimethoxypyrimidin-5-ylamine (98f)



Prepared according to **GP7** from 5-bromo-2,4-dimethoxypyrimidine (214 mg, 1 mmol, 1 equiv), and *i*-PrMgCl·LiCl (1.17M in THF, 0.94 mL, 1.1 equiv)[reaction conditions: - 20°C, 2 h]; CuCl·2LiCl (2.4 mL, 1.2 equiv) and (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97c**; LiHMDS (**96a**, 2 mL, 2.0 mmol 1 M in THF/Ethylbenzene); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. For the workup of this reaction, the organic layer was only washed one time with water (50 mL). The crude material obtained was redissolved in THF (3 mL) before TBAF (1.0 m in THF) (2 mL, 2 mmol) was added in one portion and the mixture was stirred at 25 °C for 10 min, poured over EtOAc (10 mL) and washed with deionised water (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by flash chromatography (Al_2O_3, CH_2Cl_2/MeOH 3%) afforded **98f** (122 mg, 79%) as a colourless solid.

mp.: 76.9-77.9 ^oC.

IR (Diamond ATR): ν (cm^{-1}) = 3404 (m), 3320 (m), 2960 (w), 1580 (s), 1484 (s), 1456 (s), 1416 (s), 1376 (vs), 1284 (s), 1240 (s), 1200 (s), 1072 (s), 1016 (s), 936 (m), 904 (m), 776 (m), 648 (s).

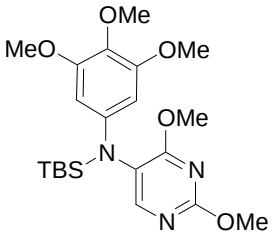
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.72 (s, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 3.21 (broad s, NH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 161.0, 158.2, 140.0, 123.6, 54.6, 54.1.

MS (70 eV, EI): ***m/z* (%)** = 155 (100) $[M]^+$, 140 (14), 126 (25), 110 (7), 83 (7), 70 (6), 58 (5), 55 (6), 42 (7).

HRMS (EI): *m/z* calc. for $[C_6H_9N_3O_2]$ 155.0695, found: 155.0694.

Synthesis of (*tert*-Butyl-dimethyl-silanyl)-(2,4-dimethoxy-pyrimidin-5-yl)-(3,4,5-trimethoxy-phenyl)-amine (98g)



Prepared according to **GP7** from 5-bromo-2,4-dimethoxypyrimidine (214 mg, 1 mmol, 1 equiv), and *i*-PrMgCl·LiCl (1.17M in THF, 0.94 mL, 1.1 equiv)[reaction conditions: - 20°C, 2 h]; CuCl·2LiCl (2.4 mL, 1.2 equiv) and *bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97c**; N-lithium-(tert-butyl-dimethyl-silanyl)-(3,4,5-trimethoxy-phenyl)-amide (**96e**, 2 mmol, 2 equiv; prepared according to **TP2** from 3,4,5-trimethoxyphenylamine); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 9:1) afforded **98g** (mg, 68%) as a yellow oil.

IR (Diamond ATR): ν (cm^{-1}) = 2956 (w), 2932 (w), 2856 (w), 1588 (m), 1556 (m), 1504 (m), 1460 (s), 1396 (s), 1376 (vs), 1280 (m), 1232 (s), 1184 (m), 1124 (s), 1076 (s), 1012 (s), 932 (m), 804 (s).

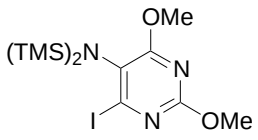
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.07 (s, 1H), 6.13 (s, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.75 (s, 3H), 3.73 (s, 6H), 0.92 (s, 9H), 0.14 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.8, 162.5, 158.6, 152.9, 152.9, 145.2, 133.2, 124.0, 100.5, 100.5, 60.9, 55.9, 55.9, 54.9, 53.9, 27.4 (2 carbons from Si-(*t*-Bu) group), 20.1, -2.6 (2 carbons from $SiMe_2$ group).

MS (70 eV, EI): ***m/z* (%)** = 435 (54) $[M]^+$, 378 (58), 363 (100), 348 (47), 332 (7), 318 (8), 233 (3), 181 (4), 167 (3), 89 (17), 73 (29).

HRMS (EI) $C_{21}H_{33}N_3O_5Si$: calculated $[M]^+$: 435.2189 found: 435.2170.

Synthesis of 5-(1,1,1,3,3,3-hexamethyl-disilazan-2-yl)-4-iodo-2,6-dimethoxy-pyrimidine (98h)



Prepared according to **GP8** from 4-iodo-2,6-dimethoxypyrimidine (**87b**) (1.33 g, 5 mmol, 1 equiv), and TMPMgCl·LiCl (1.16 M in THF, 4.75 mL, 1.1 equiv)[reaction conditions: -0 °C, 1 h]; CuCl·2LiCl (6.0 mL, 1.2 equiv) and NEt_3 (605 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97d**; and LiHMDS (**96a**, 10 mL, 10.0 mmol, 1 M in THF/Ethylbenzene); chloranil (1.47 g, 1.2 equiv) in 35 mL of THF. Purification by flash chromatography (Al_2O_3, *n*-pentane/ Et_2O = 9:1) afforded **98h** (276 mg, 65%) as a pale yellowish solid.

mp.: 85.1-87.2 °C.

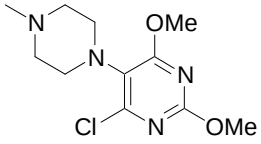
IR (Diamond ATR): ν (cm^{-1}) = 2956 (w), 2900 (w), 1560 (m), 1520 (s), 1456 (s), 1364 (s), 1304 (s), 1252 (s), 1180 (s), 1080 (s), 1020 8s), 896 (vs), 836 (vs), 816 (vs), 804 (vs), 780 (vs).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.94 (s, 3H), 3.90 (s, 3H), 0.12 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.6, 159.3, 137.8, 128.8, 55.2, 54.1, 2.3 (6C from two TMS group).

HRMS (ESI) $C_{12}H_{24}IN_3O_2Si_2$: calculated $[M-H]^+$: 426.0531 found: 426.0521.

Synthesis of 4-chloro-2,6-dimethoxy-5-(4-methyl-piperazin-1-yl)-pyrimidine (98i)



Prepared according to **GP8** from commercially available 4-chloro-2,6-dimethoxy pyrimidine (**70a**) (175 mg, 1.0 mmol) in dry THF (0.5 mL), and TMPMgCl·LiCl (1.20 m in THF; 0.92 mL, 1.1 mmol) [reaction conditions: 25 °C, 1 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97e**; *N*-lithium piperazide (**96f**, prepared according to **TP2** starting from N-methyl piperazine); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH; 95:5) afforded **98i** (213 mg, 78%) as a white crystalline solid.

mp.: 72.2-74.3 °C.

IR (Diamond ATR): ν (cm^{-1}) = 2931, 2840, 2792, 1586, 1533, 1459, 1452, 1385, 1334, 1283, 1240, 1218, 1187, 1180, 1089, 1023, 1009, 943, 859, 786, 739, 635.

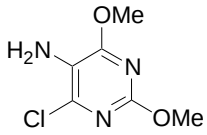
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.93 (s, 3H, OMe), 3.91 (s, 3H, OMe), 2.99 (br.s, 4H), 2.47 (br.s, 4H), 2.29 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.3, 160.3, 159.1, 123.5, 55.7, 55.2, 54.2, 49.5, 46.3.

MS (70 eV, EI): ***m/z* (%)** = 272 $[M]^+$ (100), 237 (20), 209 (12), 200 (17), 202 (14), 201 (15), 194 (9), 187 (20), 71 (34), 70 (11), 43 (20).

HRMS (EI) $C_{11}H_{17}O_2N_4{}^{35}Cl$: calculated $[M]^+$: 272.1040, found: 272.1039.

Synthesis of 4-chloro-2,6-dimethoxypyrimidin-5-amine (98j)



Prepared according to **GP8** from commercially available 4-chloro-2,6-dimethoxy pyrimidine (**70a**) (175 mg, 1.0 mmol) in dry THF (0.5 mL), and TMPMgCl·LiCl (1.20 m in THF; 0.92 mL, 1.1 mmol) [reaction conditions: 25 °C, 1 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97e**; LiHMDS (**96a**, 2.0 mmol); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. The crude residue was dissolved in Et_2O (3 mL) before TBAF (1.0 m in THF) (2 mL, 2 mmol) was added in one portion and the mixture was stirred at 25 °C for 10 min, poured over EtOAc (10 mL) washed with water (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by flash chromatography (SiO_2, *n*-pentane/EtOAc; 8:2; 0.5 mol% NEt_3) afforded **98j** (114 mg, 60%) as a light brown solid.

mp.: 76.0–77.5 °C.

IR (Diamond ATR): ν (cm^{-1}) = 3452, 3360, 2955, 1560, 1470, 1405, 1382, 1247, 1192, 1123, 1083, 1028, 941, 769.

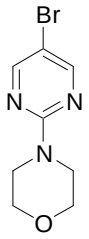
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.03 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.62 (br.s, 2H, NH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 160.0, 156.1, 145.5, 120.3, 55.0, 54.8.

MS (70 eV, EI): ***m/z* (%)** = 189 $[M]^+$ (100), 174 (13), 160 (20), 159 (22), 124 (7), 104 (10), 70 (10), 58 (7), 53 (9), 42 (10).

HRMS (EI) $C_6H_8O_2N_3{}^{35}Cl$: calculated $[M]^+$:189.0305 found: 189.0314.

Synthesis of 4-(5-bromo-pyrimidin-2-yl)-morpholine (98k)



Prepared according to **GP7** from 5-bromo-2-iodo-pyrimidine (284 mg, 1.0 mmol, 1 equiv) in dry THF (3.0 mL), and *i*-PrMgCl (0.92 mL, 1.20 m in THF, 1.1 mmol) [reaction conditions: -80 °C, 0.5 h]**;** CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv), [reaction conditions: -80 °C, 1.5 h], to afford the corresponding cuprated reagent **97f**; *N*-lithium morpholine (**96b,** 2.0 mmol, preparation described in **TP1**), [reaction conditions: -80 °C, 1.5 h]; chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, *n*-pentane/CH_2Cl_2 = 6:1) afforded **98k** (170 mg, 70%) as colourless needles.

mp.: 125.0-127.7 °C.

IR (Diamond ATR): ν (cm^{-1}) = 2960 (m), 2924 (m), 2868 (m), 1576 (s), 1496 (vs), 1452 (vs), 1356 (s), 1304 (s), 1248 (vs), 1112 (vs), 952 (vs), 848 (s), 788 (s).

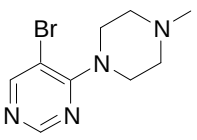
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.29 (s, 2H), 3.78-3.71 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.9, 157.9, 157.9, 106.2, 66.7, 66.7, 44.4, 44.4.

MS (70 eV, EI): ***m/z* (%)** = 245 (81)$[M]^+$, 243 (79), 228 (23), 214 (89), 212 (73), 200 (24), 188 (49), 186 (51), 160 (100), 158 (90), 107 (6), 79 (11), 53 (7).

HRMS (EI) $C_8H_{10}{}^{81}BrN_3O$: calculated $[M]^+$: 245.0001, found: 244.9971.

Synthesis of 5-bromo-4-(4-methyl-piperazin-1-yl)-pyrimidine (98l)



Prepared according to **GP8** from commercially available 5-bromopyrimidine (160 mg, 1.0 mmol) in dry THF (1.0 mL), and TMPMgCl·LiCl (1.31 m in THF; 0.92 mL, 1.2 mmol) [reaction conditions: -55 to -40 °C, 2 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **97g**; *N*-lithium 4-methylpiperazide

(**96f**, prepared according **TP1** starting from N-methylpiperazine); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 98:2) afforded **98l** (169 mg, 66%) as pale yellowish oil.

IR (Diamond ATR): ν (cm^{-1}) = 2936 (w), 2848 (w), 2796 (m), 1564 (vs), 1516 (m), 1444 (s), 1360 (m), 1252 (m), 1140 (s), 1008 (s), 956 (m), 764 (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.56 (s, 1H), 8.41 (s, 1H), 3.76 (t, *J* = 4.7 Hz, 4H), 2.58 (t, *J* = 4.9 Hz, 4H), 2.37 (s, 3H).

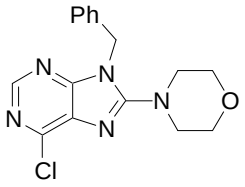
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 161.0, 159.6, 156.0, 104.7, 54.6, 54.6, 47.2, 47.2, 45.8.

MS (70 eV, EI): ***m/z* (%)** = 258 (12), 256 (14), 201 (10), 199 (15), 199 (10), 188 (35), 186 (37), 160 (18), 158 (20), 83 (72), 70 (100).

HRMS (EI) $C_9H_{13}{}^{79}BrN_4$: calculated $[M]^+$:256.0324 found: 256.0303.

4.7 Preparation of aminated purine

Synthesis of 9-benzyl-6-chloro-8-morpholin-4-yl-9H-purine (106)



Prepared according to **GP8** from 9-benzyl-6-chloro-9H-purine (**102**) (248 mg, 1 mmol, 1 equiv), and TMPMgCl·LiCl (0.89 ml,1.23 M in THF, 1.1 equiv)[reaction conditions: -10 °C, 3 h]; CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) to afford the corresponding cuprated reagent **104**; *N*-lithium morpholine (**96b,** 2.0 mmol); chloranil (298 mg, 1.2 equiv) in 7 mL of THF, [reaction conditions: -78 to 50 °C, 12 h]. For the workup of this reaction, the organic layer was only washed one time with brine (50 mL). Purification by flash chromatography (SiO_2, *n*-pentane/AcOEt = 1:1 with 0.5% NEt_3) afforded **106** (207 mg, 63%) as colourless oil.

IR (Diamond ATR): ν (cm^{-1}) = 2964 (w), 2920 (w), 2856 (w), 1596 (vs), 1572 (m), 1532 (s), 1452 (m), 1380 (m), 1344 (m), 1264 (m), 1152 (m), 1116 (m), 920 (m), 732 (m).

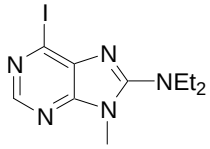
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.55 (s, 1H), 7.37-7.30 (m, 3H), 7.16-7.14 (m, 2H), 5.35 (s, 2H), 3.72 (t, *J* = 4.5 Hz, 4H), 3.37 (t, *J* = 4.9 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.1, 154.4, 150.2, 145.8, 134.9, 130.5, 129.1, 129.1, 128.2, 126.4, 126.4, 66.1, 66.1, 49.7, 49.7, 47.5.

MS (70 eV, EI): ***m/z* (%)** = 329 (15) [M^+], 301 (11), 272 (29), 238 (10), 111 (12), 97 (20), 91 (100), 83 (20), 69 826), 57 (32), 38 (21).

HRMS (EI) $C_{16}H_{16}ClN_5O$: calculated [M]$^+$: 329.1043 found: 329.1024.

Synthesis of diethyl-(6-iodo-9-methyl-9H-purin-8-yl)-amine (107)



Prepared according to **GP8** from 6-Iodo-9-methyl-9H-purine (**103**) (370 mg, 1.4 mmol, 1 equiv), and TMPMgClLiCl (1.25 ml,1.23 M in THF, 1.1 equiv)[reaction conditions: -10 °C, 2 h]; CuCl·2LiCl (1.7 mL, 1.2 equiv) and NEt_3 (170 mg, 1.2 equiv) to afford the corresponding cuprated reagent **105**; *N*-lithium diethylamide (**96g,** 2.8 mmol, 2 equiv, prepared according to **TP1** starting from dried diethyl amine); chloranil (417 mg, 1.2 equiv) in 10 mL of THF, [reaction conditions: -78 to 50 °C, 12 h]. Purification by preparative TLC (SiO_2, dichloromethane/Et_2O = 5:5 with 0.5% NEt_3) afforded **107** (219 mg, 66%) as colourless oil.

IR (Diamond ATR): ν (cm^{-1}) = 2936 (m), 2868 (w), 1592 (vs), 1536 (vs), 1476 (s), 1372 (s), 1324 (vs), 1252 (s), 1132 (s), 1068 (s), 1016 (s), 896 (s), 844 (vs), 784 (s), 704 (vs).

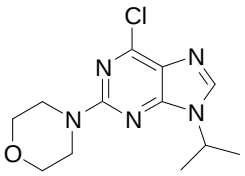
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.35 (s, 1H), 3.67 (s, 3H), 3.52 (q, *J* = 7.1 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 157.7, 150.7, 149.1, 138.2, 113.5, 44.9, 44.9, 30.8, 13.4, 13.4.

MS (70 eV, EI): ***m/z* (%)** = 331 (60), 303 (33), 288 (100), 42 (7).

HRMS (EI) $C_{10}H_4IN_4$: calculated [M]$^+$: 331.0294 found: 331.0286.

Synthesis of 6-chloro-9-isopropyl-2-morpholin-4-yl-9H-purine (110)



Prepared according to **GP7** from 6-chloro-2-iodo-9-isopropyl-9*H*-purine (**108**) (322 mg, 1.0 mmol) in dry THF (5.0 mL), and *i*-PrMgCl (0.92 mL, 1.20 m in THF, 1.1 mmol) [reaction conditions: -80 °C, 30 min]**;** The reaction mixture is added to CuCl·2LiCl (1.2 mL, 1.2 equiv) and NEt_3 (121 mg, 1.2 equiv) added at -80 °C and stirred for 1.5 h *N*-lithium morpholine (**96b,** 2.0 mmol, preparation described in **TP1**) is added at -80 °C and stirred for 2 h to afford the corresponding amidocuprated reagent **109**; chloranil (298 mg, 1.2 equiv) in 7 mL of THF, [reaction conditions: -78 °C, 2 h]. Purification by flash chromatography (SiO_2, *n*-pentane/Et_2O = 3:2) afforded **110** (170 mg, 69%) as colourless solid.

mp.: 155.4-157.3 °C (red).

IR (Diamond ATR): ν (cm^{-1}) = 3096 (w), 2968 (w), 2924 (w), 2872 (w), 2852 (w), 1612 (m), 1552 (s), 1528 (vs), 1440 (s), 1352 (s), 1224 (s), 1104 (vs), 932 (vs), 848 (s), 780 (s), 652 (s).

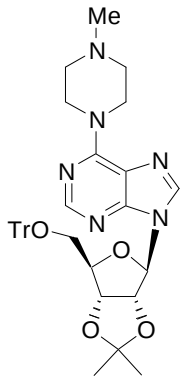
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78 (s, 1H), 4.68 (sept, *J* = 6.8 Hz, 1H), 3.85-3.74 (m, 8H), 1.56 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.1, 153.3, 150.8, 139.8, 124.8, 66.7, 66.7, 47.2, 45.0, 45.0, 22.3, 22.3.

MS (70 eV, EI): ***m/z* (%)** = 281 (81), 252 (31), 250 (100), 236 (21), 224 (50), 196 (44), 181 (32), 154 (25), 119 (16).

HRMS (EI) $C_{12}H_{16}ClN_5O$: calculated $[M]^+$: 281.1043 found: 281.1036.

Synthesis of 9-(2,2-dimethyl-6-trityloxymethyl-tetrahydro-furo[3,4-d] [1,3]dioxol-4-yl)-6-(4-methyl-piperazin-1-yl)-9H-purine (113)



Prepared according to **GP7** from 6-chloro-2-iodo-9-isopropyl-9*H*-purine (**111**) (330 mg, 0.5 mmol) in dry THF (1.0 mL), and *i*-PrMgCl (0.46 mL, 1.20 m in THF, 0.55 mmol) [reaction conditions: -50 °C, 3 h]**;** CuCl·2LiCl (0.6 mL, 1.2 equiv) and NEt_3 (61 mg, 1.2 equiv), to afford the corresponding cuprated reagent **112**; *N*-lithium 4-methylpiperazide (**96f**, 1.0 mmol, prepared according to **TP1** starting from N-methyl piperazine); chloranil (148 mg, 1.2 equiv) in 4 mL of THF. Purification by flash chromatography (SiO_2, chloroform/acetonitrile = 9:1) afforded **113** (221 mg, 70%) as pale yellowish crystalline oil.

mp.: 95.1-100.5 ^{o}C (black, decomposed).

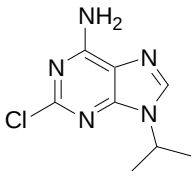
IR (Diamond ATR): ν (cm^{-1}) = 2936 (m), 2868 (m), 2792 (m), 1584 (vs), 1476 (s), 1448 (s), 1380 (s), 1288 (s), 1248 (s), 1208 (s), 1072 (vs), 1004 (s), 872 (s), 764 (s), 748 (s), 700 (vs), 632 (vs).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.51 (s, 1H), 8.30 (s, 1H), 7.49-7.38 (m, 15H), 6.45 (d, *J* = 1.5 Hz, 1H), 6.64 (dd, *J* = 6.3 Hz, *J* = 1.5 Hz, 1H), 5.18-5.16 (m, 1H), 4.55-4.52 (m, 1H), 4.44 (broad s, 3H), 3.43-3.28 (m, 2H), 2.73-2.70 (m, 8H), 1.73 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 153.1, 151.7, 149.7, 143.4, 139.1, 128.0, 128.0, 128.0, 128.0, 128.0, 128.0, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 126.9, 126.9, 126.9, 119.6, 113.2, 89.3, 86.0, 85.7, 83.2, 81.4, 64.0, 64.0, 54.3, 54.3, 54.3, 45.3, 26.9, 25.2.

HRMS (ESI) $C_{37}H_{40}N_6O_4$: calculated $[M]^+$: 633.3190 found: 633.3186

Synthesis of 2-chloro-9-isopropyl-9H-purin-6-ylamine (116)



Prepared according to **GP7** from 2-Chloro-6-iodo-9-isopropyl-9H-purine (**114**) (322 mg, 1.0 mmol, 1 equiv) in dry THF (1.0 mL), and *i*-PrMgCl·LiCl (0.89 mL, 1.23 M in THF, 1.1 mmol) [reaction conditions: -60 °C, 0.3 h]**;** CuCl·2LiCl (1.2 mL, 1.2 equiv) and (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol, 1.2 equiv), [reaction conditions: -60 °C, 1 h], to afford the corresponding cuprated reagent **115**; LiHMDS (**96a**, 1 M in THF/Ethylbenzene, 2 mL, 2.0 mmol) ; chloranil (298 mg, 1.2 equiv) in 7 mL of THF. Purification by flash chromatography (SiO_2, dichloromethane/methanol = 95:5) afforded **116** (160 mg, 76%) as a pale yellowish solid.

mp.: 253.5-254.9 ^{o}C (black).

IR (Diamond ATR): ν (cm^{-1}) = 3312 (m), 3140 (m), 2976 (w), 2936 (w), 1652 (s), 1596 (s), 1568 (s), 1464 (m), 1348 (s), 1304 (s), 1248 (s), 1216 (s), 1196 (s), 1020 (s), 928 (s), 788 (s), 680 (vs).

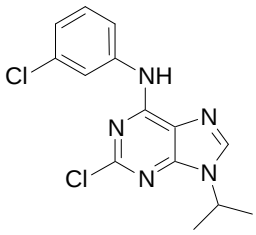
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.24 (s, 1H), 7.69 (broad s, NH2), 4.64 (sept, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 156.7, 152.6, 150.0, 139.3, 118.0, 46.6, 22.0, 22.0.

MS (70 eV, EI): ***m/z* (%)** = 211 (68) $[M]^+$, 196 (17), 171 (100), 134 (24), 108 (44), 80 (8), 53 (10), 41 (14).

HRMS (EI)$C_8H_{10}{}^{35}ClN_5$: calculated $[M]^+$: 211.0625 found: 211.0648.

Synthesis of (2-Chloro-9-isopropyl-9H-purin-6-yl)-(3-chloro-phenyl)-amine (117)



Prepared according to **GP7** from 2-chloro-6-iodo-9-isopropyl-9H-purine (**114**) (322 mg, 1.0 mmol, 1 equiv) in dry THF (1.0 mL), and *i*-PrMgCl·LiCl (0.92 mL, 1.20 M in THF, 1.1 mmol) [reaction conditions: -60 °C, 0.3 h]**;** CuCl·2LiCl (1.2 mL, 1.2 equiv) and (*bis*[2-(*N*,*N*-dimethylamino)ethyl] ether (192 mg, 1.2 mmol, 1.2 equiv), [reaction conditions: -60 °C, 1 h], to afford the corresponding cuprated reagent **115**; N-lithium (*tert*-butyl-dimethyl-silanyl)-(3-chloro-phenyl)-amide (**96h**, 2.0 mmol, prepared according to **TP2** starting from freshly distilled 3-chloro-phenylamine); chloranil (298 mg, 1.2 equiv) in 7 mL of THF. The crude residue was dissolved in Et_2O (3 mL) before TBAF (1.0 m in THF) (2 mL, 2 mmol) was added in one portion and the mixture was stirred at 25 °C for 10 min, poured over EtOAc (10 mL) washed with water (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuum. Purification by flash chromatography (SiO_2, dichloromethane/methanol = 95:5) afforded **117** (228 mg, 71%) as yellow solid.

mp.: 131.3-132.3 °C

IR (Diamond ATR): ν (cm^{-1}) = 3240 (w), 2980 (w), 2920 (w), 2870 (w), 1624 (vs), 1570 (vs), 1446 (s), 1423 (m), 1319 (m), 1218 (m), 1194 (m), 1076 (w), 1024 (s), 939 (m), 895 (m), 880 (s), 772 (s).

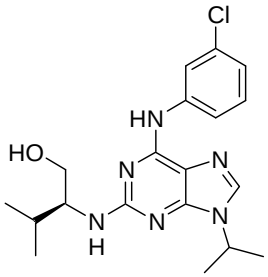
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.55 (s, 1H), 8.12 (s, 1H), 7.93 (t, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 4.90 (sept, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) = 153.7, 152.0, 150.5, 139.3, 138.7, 134.7, 130.1, 123.8, 120.0, 119.5, 118.1, 47.3, 22.8, 22.8.

MS (70 eV, EI): ***m/z* (%)** = 321 (100) $[M]^+$, 278 (67), 244 (87), 209 (9), 111 (10).

HRMS (EI) $C_{14}H_{13}{}^{35}Cl_2N_5$: calculated $[M]^+$: 321.0548 found: 321.0537.

Synthesis of 2-[6-(3-chloro-phenylamino)-9-isopropyl-9H-purin-2-ylamino]-3-methyl-butan-1-ol, purvalanol A (100)



To a solution of (2-chloro-9-isopropyl-9H-purin-6-yl)-(3-chloro-phenyl)-amine (**117**) (140 mg, 0.43 mmol, 1 equiv) in *n*-butanol (1 mL) was added *Hunig´*s base (75 µL, 1 equiv) and D-valinol (220 mg, 5 equiv). The resulting solution was heated in a sealed tube at 150 °C for 12 h. Following cooling down and evaporation to dryness, the resulting oil was purified by flash chromatography (SiO_2, dichloromethane/methanol = 97:3) afforded **100** (108 mg, 65 %) as a colourless solid.

mp.: 158.0-159.5 ^{o}C

IR (Diamond ATR): ν (cm^{-1}) = 3320 (w), 3240 (w), 2938 (m), 2924 (w), 2868 (w), 1636 (s), 1576 (vs), 1472 (vs), 1452 (s), 1408 (s), 1360 (s), 1308 (s), 1244 (s), 1152 (m), 1096 (s), 1068 (s), 1008 (vs), 876 (m), 848 (s), 768 (s), 700 (s), 636 (vs).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.99 (broad s, 1H), 7.96 (broad s, 1H), 7.58 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 5.16 (d, *J* = 5.8 Hz, 1H), 4.55 (sept, *J* = 6.8 Hz, 1H), 4.00-3.88 (m, 2H), 3.77-3.71 (m, 1H), 2.01 (m, 1H), 1.47 (dd, *J* = 6.1 Hz, *J* = 4.7 Hz, 6H), 1.03 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 159.5, 151.8, 151.8, 140.3, 135.1, 134.3, 129.7, 122.7, 119.7, 117.7, 114.8, 65.2, 59.7, 46.8, 30.1, 22.5, 22.4, 19.5, 19.0.

HRMS (ESI) $C_{19}H_{26}O^{35}ClN_6$: calculated $[M+H]^+$: 389.1857 found: 389.1852.

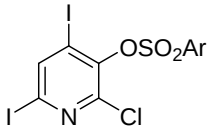
5. Direct chemo- and regioselective zinc insertions into polyhalogenated N-heteroaryl compounds

5.1 General procedure for the zinc insertion into polyiodo- and polybromo-heteroaryls compounds (GP9):

Anhydrous LiCl was placed in an Ar-flushed flask and dried additionally 10-20 min at 150-170 °C on high vacuum (1 mbar) or 2-3 min at 450 °C. Zinc powder was added under Ar, and heterogeneous mixture of Zn and LiCl was dried again 10-20 min at 150-170 °C on high vacuum (1 mbar). Afterwards flask was evacuated and refilled with argon three times. After the addition of THF, Zn was activated by treatment first with 1,2-dibromoethane (5 mol%) and then with chlorotrimethylsilane (2 mol%).[53d,62] The substrate was added neat or dissolved in THF at the temperature T_1. The completion of the insertion reaction was checked by GC analysis of reaction aliquots quenched with a solution of NH_4Cl in water (the conversion was more than 90 %). The organozinc solution in THF was carefully removed from the rest of zinc powder using syringe and was transferred to the new dry and Ar-flushed flask. The electrophile or its solution in THF was added at the temperature T_2. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with sat. aqueous NH_4Cl solution) the reaction mixture was quenched with sat. aqueous NH_4Cl (10 mL) solution. The aqueous layer was extracted with ethyl acetate or diethyl ether (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuum*. The crude residue was purified by flash column chromatography on silica gel.

5.2 Starting material synthesis

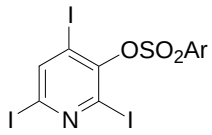
Synthesis of 4-chlorobenzenesulfonic acid 2-chloro-4,6-diiodo(pyridin-3-yl) ester (121g)



This material was prepared over two steps from commercially available 2-chloro-3-hydroxypyridine according to the procedure reported by Knochel et al.[161]

[161] Lin, W.; Ling, C.; Knochel, P. *Tetrahedron* **2007**, *63*, 2787.

Synthesis of 4-chlorobenzenesulfonic acid 2,4,6-triiodo(pyridin-3-yl) ester (121h)



To a solution of 3-hydroxypyridine (9.5 g, 100 mmol) and Na_2CO_3 (45.6 g, 430 mmol) in water was added iodine (76.2 g, 300 mmol) with stirring at 25 °C. After 24 h, the solid is filtered off and dried to give 2,4,6-triiodo-pyridin-3-ol as a yellow solid. A dry 250 mL round-bottomed flask, equipped with a magnetic stirrer and a septum, was charge with a solution of 2,4,6-triiodo-pyridin-3-ol in dry CH_2Cl_2 (100 mL). After cooling to 0 °C, Et_3N (18.8 mL, 135 mmol) was added, and then 4-chloro-benzenesulfonyl chloride (23.5 g, 108 mmol) was added portionwise. After the addition was completed, the reaction mixture was stirred at 25 °C overnight. This mixture was diluted with CH_2Cl_2 (100 mL). Saturated aqueous NH_4Cl solution (100 mL) was then added, and the resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (SiO_2, *n*-pentane/ether = 40:1) afforded **121h** (37.5 g, 58 %; overall yield of two steps) as a yellow solid.

mp.: 154.4-154.8 °C.

IR (KBr): ν (cm^{-1}) = 3078 (m), 1584 (m), 1511 (m), 1497 (s), 1474 (m), 1374 (vs), 1287 (s), 1182 (s), 1166 (m), 1083 (m), 1011 (w).

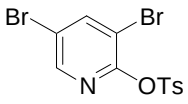
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.09 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 150.8, 144.6, 142.1, 135.9, 134.4, 129.9, 113.1, 113.0, 103.0;

MS (70 eV, EI): *m/z* (%): 646 (100, M^+), 518 (12), 471 (25), 344 (28), 253 (21), 189 (15), 175 (79), 127 (11), 111 (26).

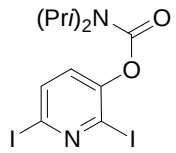
HRMS (EI) $C_{11}H_5ClI_3NO_3S$: calculated $[M]^+$: 646.6813 found: 646.6824.

Synthesis of *p*-toluenesulfonic acid 3,5-dibromo(pyridin-2-yl) ester (121i)



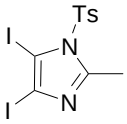
This material was prepared from commercially available 3,5-dibromo-2-hydroxypyridine according to the procedure reported by Knochel et al.[162]

Synthesis of diisopropylcarbamic acid 2,6-diiodo(pyridin-3-yl) ester (121j)



This material was prepared from commercially available 3-hydroxy-2,6-diiodopyridine according to the procedure from the literature.[163]

Synthesis of 4,5-diiodo-2-methyl-1-(*p*-toluenesulfonyl)-1*H*-imidazole (121k)



To a mixture of 4,5-diiodo-2-methyl-1*H*-imidazol[144] (10.0 g, 30 mmol) and *p*-toluenesulfonyl chloride (5.9 g, 31 mmol) in acetone (50 mL) at 25 °C was added Et_3N (90 mmol), and the resulting mixture was stirred at 25 °C for 12 h. The solvent was removed under vacuum, and the residue was purified by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 2/1) afforded **121k** (13.7 g, 94 %) as a light yellow solid

mp.:119.3-121.4 °C

IR (film): ν (cm^{-1}) = 2950 (w), 1593 (w), 1520 (m), 1385 (s), 1371 (s), 1280 (m), 1158 (s), 1093 (s), 995 (w), 814 (w), 665 (m), 578 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.86 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.37 (d, ^3J(H,H) = 8.5 Hz, 2H), 2.78 (s, 3H), 2.45 (s, 3H).

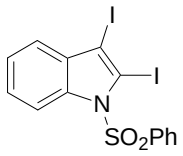
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 152.1, 146.7, 134.4, 130.2, 130.2, 128.0, 128.0, 127.9, 76.8, 21.8, 18.2.

MS (EI, 70 eV): m/z (%) = 487 (100), 154 (75), 90 (71), 65 (11).

HRMS (EI) $C_{11}H_{10}N_2O_2I_2$: calculated $[M]^+$: 487.8552 found: 487.8551.

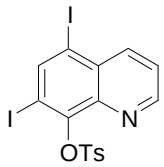
[162] Ren, H.; Knochel, P. *Chem. Commun*. **2006**, *7*, 726.
[163] Mongin, F.; Trecourt, F.; Gervais, B.; Mongin, O.; Queguiner, G. *J. Org. Chem*. **2002**, *67*, 3272.

Synthesis of 2,3-diiodo-1-(*p*-toluenesulfonyl)-1*H*-indole (121l)



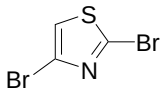
This material was prepared from commercially available 1*H*-indole according to the procedure from the literature.[164]

Synthesis of *p*-toluenesulfonic acid 5,7-diiodoquinolin-8-yl ester (121m)



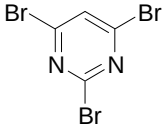
This material was prepared from commercially available 5,7-diiodo-8-quinolinol according to the procedure from the literature.[165]

Synthesis of 2,4-dibromothiazole (121n)



This material was prepared from commercially available 2,4-thiazolidinedione according to the procedure from the literature.[166]

Synthesis of 2,4,6-tribromopyrimidine (121o)

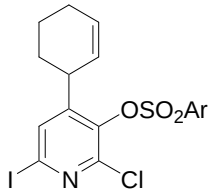


[164] (a) Witulski, B. ; Buschmann, N. ; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473; (b) Saulnier, M. G., Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.
[165] Baron, O.; Knochel, P. *Angew. Chem. Int. Ed*. **2005**, *44*, 3133.
[166] Ross, N. T.; Jagoe, G. T. Zhengxiang, G. *Tetrahedron Lett.* **1991**, *32*, 4263.

This material was prepared from commercially available barbituric acid according to the procedure from the literature.[104]

5.3 Preparation of halogenated functionalized N-heterocycles via direct zinc insertion

Synthesis of 4-chlorobenzenesulfonic acid 2-chloro-4-(2-cyclohexen-1-yl)- 6-iodo(pyridin-3-yl) ester (123g)



Prepared according to **GP9** from 4-chlorobenzenesulfonic acid 2-chloro-4,6-diiodo(pyridin-3-yl) ester[2] (**121g**) (1.112 g, 2 mmol), LiCl (172 mg, 4 mmol), zinc dust (260 mg, 4 mmol, 2.0 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion conditions*: 0 °C, 2.5 h; *reaction with electrophile*: transmetalation with CuCN·2LiCl (5 mol %) at –20 °C, followed by addition of 3-bromocyclohex-1-ene (2.3 mmol) at T_2 = –20 °C. The reaction mixture was allowed to warm gradually to 25 °C and stirred for 4 h. Purification by flash chromatography (SiO_2, *n*-pentane/ethyl acetate = 98:2) afforded **123g** (846 mg, 83%) as white solid.

mp.: 183.2-184.3 ˚C.

IR (): ν (cm^{-1}) = 2934 (w), 2910 (w), 1565 (m), 1403 (w), 1371 (s), 1335 (m), 1313 (w), 1187 (s), 1147 (s), 1084 (m), 865 (w), 773 (s), 708 (m).

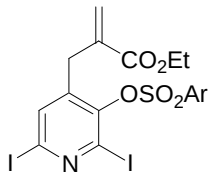
^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) = 7.97 (d, ^3J(H,H) = 7.9 Hz, 2H), 7.60 (d, ^3J(H,H) = 7.3 Hz, 3H), 6.02 (m, 1H), 5.54 (dd, ^3J(H,H) = 10.1 Hz, ^4J(H,H) = 2.0 Hz, 1H), 3.89 (m, 1H), 2.14 (m, 3H), 1.75-1.39 (m, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) = 154.6, 144.7, 141.8, 141.7, 134.9, 134.8, 130.9, 129.9, 129.8, 129.8, 129.7, 126.5, 111.9, 36.0, 30.5, 24.6, 20.8.

MS (70 eV, EI) *m/z* (%) = 511 (16), 509 (22), 336 (34), 335 (40), 334 (100), 333 (48), 292 (34), 207 (36), 175 (17), 115 (13), 111 (23), 77 (10).

HRMS (EI) $C_{17}H_{14}Cl_2INO_3S$: calculated [M^+]: 508.9116 found: 508.9130.

Synthesis of 2-{3-[(4-chlorobenzenesulfonyl)oxy]-2,6-diiodo(pyridin-4-yl)}methylacrylic acid ethyl ester (123h)



Prepared according to **GP9** from 4-chlorobenzenesulfonic acid 2,4,6-triiodopyridin-3-yl ester **121h** (647 mg, 1 mmol), LiCl (86 mg, 2 mmol), zinc dust (130 mg, 2 mmol, 2.0 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion conditions*: 0 °C, 3 h; *reaction with electrophile*: 2-bromomethyl acrylate (232 mg, 1.2 mmol) was added followed by the addition of CuCN·2LiCl(one drop of 1.0 M solution in THF, ca. 0.02 mmol, ca. 0.4 mol%) at -30 °C. The reaction mixture was afterwards warmed to 25 °C for 1h. Purification by flash chromatography (SiO_2, *n*-pentane/ether = 4:1) afforded **123h** (482 mg, 80%) as colourless liquid.

IR (Diamond ATR): ν (cm^{-1}) = 3092 (w), 2979 (w), 1709 (vs), 1632 (w), 1554 (m), 1516 (m), 1388 (vs), 1316 (s), 1237 (m), 1189 (s), 1134 (s), 1083 (s), 1014 (m), 955 (w).

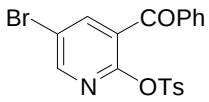
^{1}H-NMR (CDCl3, 300 MHz): δ (ppm) = 7.96 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.58 (d, ^3J(H,H) = 8.8 Hz, 2H), 7.47 (s, 1H), 6.40 (s, 1H), 5.74 (s, 1H), 4.14 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.77 (s, 2H), 1.22 (t, ^3J(H,H) = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 165.6, 147.8, 145.9, 142.0, 136.2, 135.8, 135.1, 130.3, 129.8, 129.4, 114.3, 113.2, 61.2, 33.4, 14.1.

MS (70 eV, EI): *m/z* (%) = 633 (62) $[M]^+$, 458 (54), 441 (63), 413 (100), 331 (84), 286 (49), 259 (30), 204 (35), 175 (43), 159 (27), 127 (43), 111 (45).

HRMS (EI) $C_{17}H_{14}ClI_2NO_5S$: calculated $[M]^+$: 632.8371 found: 632.8374.

Synthesis of *p*-toluenesulfonic acid 3-benzoyl-5-bromo(pyridin-2-yl) ester (123i)



Prepared according to **GP9** from *p*-toluenesulfonic acid 3,5-dibromo(pyridin-2-yl) ester **121i** (1.63 g, 4 mmol), LiCl (258 mg, 6 mmol), zinc dust (390 mg, 6 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion condition*: 25 °C, 12 h; *reaction with electrophile*: transmetalation with CuCN·2LiCl (1 equiv.) 10 min at 0°C, followed by addition of benzoyl chloride at T_2 = –78 °C. The reaction mixture was stirred afterwards for 1 h at –78 °C and warmed to 25 °C for 3 h. Purification by flash chromatography (SiO_2, *n*-pentane/ ether = 1:1) afforded **123i** (1.40 g, 81%) as a white solid.

mp.: 102.5-103.1 °C.

IR (KBr): ν (cm^{-1}) = 3060 (m), 1659 (vs), 1598 (s), 1572 (s), 1382 (vs), 1173 (vs), 689 (vs).

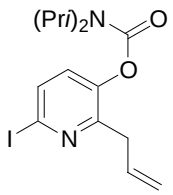
^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 8.43 (d, ^4J(H,H) = 2.7 Hz, 1H), 7.94 (d, ^4J(H,H) = 2.7 Hz, 1H), 7.54-7.71 (m, 5H), 7.43 (d, ^3J(H,H) = 8.0 Hz, 2H), 7.20 (d, ^3J(H,H) = 8.0 Hz, 2H), 2.35 (s, 3H).

^{13}C-NMR (CDCl3, 75 MHz) δ (ppm) =190.5, 152.4, 150.5, 145.4, 142.2, 135.6, 134.0, 133.1, 129.7, 129.4, 128.5, 128.3, 127.5, 117.9, 21.5.

MS (70 eV, EI) *m/z* (%) = 369 (M^+ (^{81}Br)-C_5H_4, 13), 367 (M^+ (^{79}Br)-C_5H_4, 13), 340 (14), 288(31), 155 (22), 91 (100).

HRMS (EI) $C_{19}H_{15}BrNO_4S$: calculated $[M+H]^+$: 431.9900 found: 431.9923.

Synthesis of diisopropylcarbamic acid 2-allyl-6-iodo(pyridin-3-yl) ester (123j)



Prepared according to **GP9** from diisopropylcarbamic acid 2,6-diiodo(pyridin-3-yl) ester **121j** (948 mg, 2 mmol), LiCl (129 mg, 3 mmol), zinc dust (216 mg, 3 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion conditions*: 25

°C, 5 h; *reaction with electrophile*: allyl bromide (1.3 equiv) was added, followed by the addition of one drop of CuCN·2LiCl (a 1.0 M solution in THF was used, ca. 0.02 mmol, ca. 0.5 mol %) at –20°C. The crude residue was purified by column chromatography (SiO_2, *n*-pentane/ ether = 3:2) afforded **123j** (645 mg, 83%) as colourless oil.

IR (KBr): ν (cm^{-1}) = 2970 (w), 1717 (s), 1575 (w), 1422 (s), 1314 (s), 1242 (s), 1172 (m), 1242 (m), 1153 (m), 1041 (w), 980 (w), 861 (w).

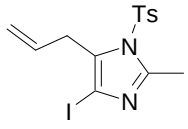
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55 (d, ^3J(H,H)J = 8.3 Hz, 1H), 7.08 (d, ^3J(H,H) = 8.3 Hz, 1 H), 6.04-5.91 (m, 1H), 5.09 (m, 1H), 5.05 (dd, ^3J(H,H) = 7.4 Hz, ^2J(H,H) = 1.5 Hz, 1H), 4.10 (broad m, 1H), 3.93 (broad m, 1H), 3.15 (m, 2H), 1.30 (d, ^3J(H,H) = 6.8 Hz, 12H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 154.9, 152.1, 146.4, 134.1, 133.2, 132.5, 116.6, 111.5, 46.8, 46.8, 37.5, 21.4, 20.4.

MS (70 eV, EI): *m/z* (%)= 387.3 (M^+), 259.5 (16), 127.9 (100), 69.9 (3), 42.9 (41).

HRMS (EI) $C_{15}H_{21}IN_2O_4$: calculated $[M]^+$: 388.0648 found: 388.0638.

Synthesis of 5-allyl-4-iodo-2-methyl-1-(*p*-toluenesulfonyl)-1*H*-imidazole (123k)



Prepared according to **GP9** from 4,5-diiodo-2-methyl-1*H*-imidazole **121k** (1.95 g, 4 mmol), LiCl (258 mg, 6 mmol), zinc dust (390 mg, 6 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion condition*: 50 °C, 1 h; *reaction with electrophile*: allyl bromide (1.1 equiv) was added, followed by the addition of one drop of CuCN·2LiCl (a 1.0 M solution in THF was used, ca. 0.02 mmol, ca. 0.5 mol %) at –20 °C. The crude residue was purified by column chromatography (SiO_2, *n*-pentane/ ether = 3:2) afforded **123k** (1.28 g, 80 %) as white needles.

mp.: 126.5-127.5 °C

IR (KBr): ν (cm^{-1}) = 3080 (w), 3018 (w), 2982 (w), 1642 (w), 1593 (w), 1524 (m), 1389 (m), 1373 (s), 1292 (s), 1193 (s), 1166 (s), 1114 (s), 1085 (m), 993 (m), 903 (m), 818 (w), 670 (m), 580 (m).

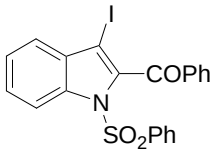
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.96 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.34 (d, ^3J(H,H) = 8.0 Hz, 2H), 5.80 (m, 1H), 5.06 (m, 1H), 5.02 (dd, ^3J(H,H) = 5.7 Hz and ^2J(H,H) = 1.4 Hz, 1H), 3.59 (d, ^3J(H,H) = 5.9 Hz, 2H), 2.58 (s, 3H), 2.45 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 148.5, 146.2, 135.4, 133.4, 132.3, 130.3, 130.3, 127.2, 127.2, 116.9, 88.0, 30.7, 21.7, 16.9.

MS (70 eV, EI): *m/z* (%) = 401.9 (M, 100), 246.9 (24), 154.9 (64), 119.9 (10), 94.0 (12), 90.9 (89), 65.0 (13).

HRMS (EI) $C_{14}H_{15}IN_2O_2S$: calculated [M^+]: 401.9894 found: 401.9894.

Synthesis of (1-benzenesulfonyl-3-iodo-1*H*-indol-2-yl) phenyl ketone (123l)



Prepared according to **GP9** from 2,3-diiodo-1-benzenesulfonyl-1*H*-indole (**121l**) (2.03 g, 4 mmol), LiCl (258 mg, 6 mmol), zinc dust (390 mg, 6 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion condition*: 50 °C, 2 h; *reaction with electrophile*: transmetalation with CuCN·2LiCl (1 equiv.) 10 min at 0°C, followed by addition of benzoyl chloride at T_2 = –78 °C. The reaction mixture was stirred afterwards for 1 h at –78 °C and warmed to 25 °C for 3 h. Purification by flash chromatography (SiO_2, *n*-pentane/ether = 1:1) afforded **123l** (1.63 g, 83%) as a white solid.

mp.: 144.9-147.0 °C

IR (KBr): ν (cm^{-1}) = 3067 (w), 1671 (m), 1595 (w), 1446 (m), 1372 (s), 1250 (m), 1174 (s), 1148 (s), 1186 (m), 1052 (w), 951 (m), 732 (s), 720 (m), 681 (m).

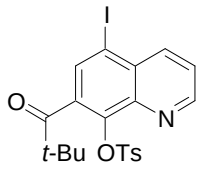
^{1}H NMR ($CDCl_3$, 300 MHz): *δ* (ppm) = 8.08-7.92 (m, 5H), 7.73-7.35 (m, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): *δ* (ppm) = 189.1, 137.5, 136.9, 136.7, 135.3, 134.3, 134.0, 131.8, 130.0, 129.2, 128.8, 127.5, 127.2, 124.9, 122.9, 114.5, 72.6.

MS (70 eV, EI) *m/z* (%) = 488.9 (M, 100), 345.9(64), 218.9 (80), 190.9 (31), 105.0 (11), 77.0 (33).

HRMS (EI) $C_{21}H_{14}INO_3S$: calculated [M^+]: 486.9739 found: 486.9721.

Synthesis of *p*-toluenesulfonic acid 7-(2,2-dimethylpropionyl)-5-iodo(quinolin-8-yl) ester (123m)



Prepared according to **GP9** from *p*-toluenesulfonic acid 5,7-diiodo(quinolin-8-yl) ester **121m** (1.10 g, 2 mmol), LiCl (172 mg, 3 mmol), zinc dust (260 mg, 3 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion conditions*: 25 °C, 24 h (**Note**: organozinc reagent has brown colour); *reaction with electrophile*: transmetalation with CuCN·2LiCl (1 equiv.) 10 min at 0°C, followed by addition of pivaloyl chloride at T_2 = –50 °C. The reaction mixture was stirred afterwards for 1 h at –50 °C and warmed to 25 °C for 6 h. Purification by flash chromatography (SiO_2, *n*-pentane/ dichloromethane = 1:1) afforded *p*-toluenesulfonic acid 7-(2,2-dimethylpropionyl)-5-iodo(quinolin-8-yl) ester **123m** (78%) as a pale yellow solid.

mp.: 119.5-124.0 °C.

IR (KBr): ν (cm^{-1}) = 2968 (w), 1997 (s), 1477 (w), 1451 (w), 1372 (s), 1341 (m), 1206 (m), 1177 (s), 1085 (s), 999 (m), 806 (m), 779 (s), 742 (s), 688 (m), 671 (s).

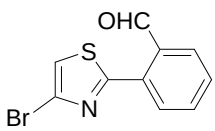
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.87 (dd, ^3J(H,H) = 4.1 Hz, ^3J(H,H) = 1.5 Hz, 1H), 8.34 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.90 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.84 (s, 1H), 7.53 (dd, ^3J(H,H) = 8.5 Hz, ^3J(H,H) = 4.1 Hz, 1H), 7.43 (d, ^3J(H,H) = 8.4 Hz, 2H), 2.46 (s, 3H), 1.12 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 208.4, 151.8., 145.1, 142.4, 142.3, 140.2, 136.0, 134.3, 133.8, 131.2, 129.3, 128.8, 123.9, 96.3, 45.4, 26.7, 21.7.

MS (70 eV, EI): *m/z* (%) = 451.9 ((M^+-*t*Bu); 100), 445.5 (47), 383.5 (21), 352.4 (12), 297.2 (73), 270.7 (23), 155.0 (51), 91.0 (37).

HRMS (EI) $C_{21}H_{20}INO_4S$: calculated [M^+]: 509.0158 found: 509.0164

Synthesis of 2-(2-bromothiazol-4-yl)benzaldehyde (123n)



Prepared according to **GP9** from 2,4-dibromothiazole **121n** (486 mg, 2 mmol), LiCl (172 mg, 3 mmol), zinc dust (260 mg, 3 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion conditions*: 25 °C, 0.5 h; *reaction with electrophile*: tetrakis(triphenylphosphine)palladium (104 mg, 0.09 mmol) was added at 25 °C followed by addition of 2-iodobenzaldehyde (925 mg, 4 mmol) and the mixture was heated at 50 °C for 20 h. Purification by flash chromatography (SiO_2, *n*-pentane/diethyl ether = 1:1) afforded 2-(2-bromothiazol-4-yl)benzaldehyde **123n** (455 mg, 85 %) as a colourless solid.

mp.: 121.1-123.5 °C.

IR (KBr): ν (cm^{-1}) = 3033 (w), 2790 (m), 2994 (w) 2741 (w), 1740 (s), 1452 (s), 1386 (m), 1233 (m), 1016 (s), 740 (m).

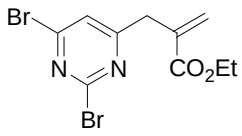
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 10.31 (s, 1H), 8.09 (s, 1H), 7.90 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.87 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.80 (td, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.1 Hz, 1H), 7.71 (tdd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.2 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 191.2, 165.7, 134.1, 133.9, 133.4, 130.7, 130.1, 128.2, 124.9, 120.8.

MS (70 eV, EI): *m/z* (%) = 268 (100), 266 (99), 192 (12), 105 (48), 77 (21), 51 (9).

HRMS (EI) $C_{10}H_6BrNOS$: calculated [M^+]: 266.9353 found: 266.9359.

Synthesis of [2-(2,6-dibromopyrimidin-4-yl)methyl]acrylic acid ethyl ester (123o)



Prepared according to **GP9** from 2,4,6-tribromopyrimidine **121o** (628 mg, 2 mmol), LiCl (172 mg, 3 mmol), zinc dust (260 mg, 3 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%).*Insertion condition*: 25 °C, 4 h (**Note**: organozinc reagent has brown colour); *reaction with electrophile*: ethyl (2-bromomethyl)acrylate (1.3 equiv) was added, followed by the addition of one drop of CuCN·2LiCl (a 1.0 M solution in THF was used, ca. 0.02 mmol, ca. 0.4 mol %) at –78°C. The reaction mixture was stirred afterwards for 2 h and warmed up to 25 °C for 4 h. Purification by flash chromatography (SiO_2, dichloromethane) afforded 2-[(2,6-dibromo-pyrimidin-4-yl)methyl]acrylic acid ethyl ester **123o** (438 mg, 63%) as a colorless oil.

IR (film): ν (cm^{-1}) = 2980 (w), 1711 (s), 1544 (s), 1510 (s), 1288 (w), 1223 (m), 1117 (w), 778 (m).

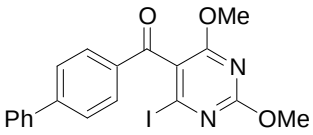
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.41 (s, 1H), 6.41 (s, 1H), 5.80 (s, 1H), 4.18 (q, ^3J(H,H) = 7.0 Hz, 2H), 3.72 (s, 2H), 1.20 (t, ^3J(H,H) = 7.0 Hz, 3H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 171.6, 165.8, 153.1, 151.4, 135.4, 129.5, 123.5, 61.2, 39.2, 14.1.

MS (EI, 70 ev): *m/z* (%) = 349.9 (M^+, 6), 320.8 (68), 304.9 (22), 276.9 (100), 195.7 (20), 43.8 (17).

HRMS (EI) $C_{10}H_{10}Br_2N_2O_2$: calculated [M^+]: 347.9109 found: 347.9100.

Synthesis of biphenyl-4-yl-(4-iodo-2,6-dimethoxy-pyrimidin-5-yl)methanone (123p)



Prepared according to **GP9** from 4,5-diiodo-2,6-dimethoxypyrimidine (**89a**) (266 mg, 1 mmol), LiCl (86 mg, 1.5 mmol), zinc dust (130 mg, 1.5 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion condition*: 50 °C, 3 h; *reaction with electrophile*: transmetalation with CuCN·2LiCl (0.5 equiv.) 10 min at 0°C, followed by addition of biphenyl-4-carbonyl chloride (260 mg, 1.3 equiv, 1.2 mmol) at T_2 = –30 °C. The reaction mixture was stirred afterwards for 1 h at –30 °C and slowly warmed to 25 °C for 14 h. Purification by flash chromatography (SiO_2, pentane/ Et_2O = 1:1) afforded **123p** (333 mg, 83%) as a white solid.

mp.:152.3-154.7 °C

IR (KBr): ν (cm^{-1}) =1664 (m), 1600 (m), 1570 (s), 1526 (s), 1460 (m), 1384 (s), 1369 (s), 1311 (s), 1261 (s), 1200 (m), 1075 (s), 1008 (s), 916 (s).

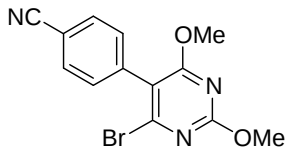
^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.85 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.42-7.37 (m, 2H), 7.36-7.31 (m, 1H), 3.99 (s, 3H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) = 190.2, 165.0, 161.1, 144.6, 137.3, 131.9, 128.0 (2 carbons), 126.7 (2 carbons), 126.1, 125.2 (2 carbons), 125.0 (2 carbons), 124.3, 118.9, 53.3, 52.5.

MS (EI, 70 eV): *m/z* (%) = 446 (M^+, 100), 345 (15), 293 (37), 181 (49), 152 (31).

HRMS (EI) $C_{19}H_{15}IN_2O_3$: calculated [M^+]: 446.0127 found: 446.0109.

Synthesis of 4-(4-bromo-2,6-dimethoxy-pyrimidin-5-yl)benzonitrile (123q)



Prepared according to **GP9** from 4,5-dibromo-2,6-dimethoxypyrimidine (**69b**) (253 mg, 0.85 mmol), LiCl (72 mg, 1.5 mmol), zinc dust (110 mg, 1.5 mmol, 1.5 equiv, <10 micron, 98+%, Aldrich), $BrCH_2CH_2Br$ (5 mol%), Me_3SiCl (2 mol%). *Insertion condition*: 25 °C, 12 h; *reaction with electrophile*: In a flame-dried round bottom flask was charged with $Pd(dba)_2$ (24 mg, 5 mol%), P(*o*-furyl)$_3$ (20 mg, 10 mol%) and THF (1 mL). The mixture was stirred at 25 ^oC for 10 min then transferred to the reaction flask which was charged with organozinc solution **122q**. 4-Iodobenzonitrile (234 mg, 1.2 equiv, 1.02 mmol). The reaction mixture was refluxed for 2 h. Purification by flash chromatography (SiO_2, pentane/ Et_2O = 3:2) afforded **123q** (234 mg, 86%) as a white solid.

mp.: 149.1-150.6 ^oC

IR (KBr): ν (cm^{-1}) = 2228 (w), 1587 (m), 1531 (m), 1460 (m), 1376 (s), 1324 (m), 1196 (m), 1094 (m), 1019 (m), 992 (m), 936 (m), 832 (m), 790 (m), 741 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.70 (d, *J*= 8.6 Hz, 2H), 7.40 (d, *J*= 8.6 Hz, 2H), 4.04 (s, 1H), 3.92 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.6, 163.4, 152.3, 138.4, 132.0, 131.3, 118.6, 115.6, 112.1, 104.7, 55.6, 55.1.

MS (EI, 70 eV): *m/z* (%): 321 (M^+, 100), 304 (12), 289 (28), 240 (18), 225 (24), 210 (29), 189 (23), 168 (16), 140 (38).

HRMS (EI): $C_{13}H_{10}N_3{}^{81}Br$: calculated [M^+]: 318.9936 found: 320.9911.

D: Appendix

1. Curriculum Vitae

Name: Nadège Boudet
Date of Birth: May, 18th 1981
Nationality: French
Place of birth: Toulouse
Marital Status: Single
Mother language: French. Other language: English, Spanish, German.

Education

Dec. 2004-Nov. 2007	**Ludwig-Maximilians-Universität** **Department Chemistry and Biochemistry** Ph.D. under the supervision of Prof. Dr. Paul Knochel	Munich, Germany
Sept. 2003-Sept. 2004	**National Polytechnic Institute of Chemistry** (**INP**, **ENSIACET)** Master Degree in Chemistry (DEA) with high honours Theme: "Reactivity of Natural Resources".	Toulouse, France
Sept. 2001-Sept. 2004	**National Polytechnic Institute of Chemistry** (**INP**, **ENSIACET,** Ecole Nationale Supérieure des Ingénieurs en Arts Chimiques et Technologiques, département CHIMIE) "Diplôme d' Ingénieur Chimiste"	Toulouse, France
Sept. 1999- June. 2001	**Technological Institute, University P. Sabatier** HND in Chemistry Technology "Diplôme de technicien chimiste supérieur"	Toulouse, France
Sept. 1998-Sept. 1999	**Lycée F. Mitterand** **Baccalaureate Degree Scientific**, obtained with high honours	Moissac, France
Languages	**French**: Native speaking. **Spanish**: Basic proficiency. **English**: Speaking and writing fluently. **German**: Basic proficiency.	

Research and work experience

Since Dec. 2004	**Ludwig-Maximilians-Universität** **Department Chemistry and Biochemistry** Ph.D. under the supervision of Prof. Dr. Paul Knochel Topic: Polyfunctionalizations of N-Heterocycles via chemo and regioselective metalations. Application to the synthesis of biologically active compounds. Teaching assistant in the organic chemistry practical courses for undergraduates students; Supervising of bachelor students; Education of a Chemical Technical Assistant for 2 years.	Munich, Germany
2004 (6 months)	**Sanofi-Aventis Research** Chemical Development Laboratory (Supervisor Dr. F. Brion) Master Degree work Topic: Cross-coupling reactions by organometallic catalysis on heterocycles.	Toulouse, France
2003 (3 months)	**D. R. T. ("Resin and Terpene Derivatives")** R&D Laboratory Training research work on Terpene Chemistry Topic: Synthesis of isobornyl acetate with ions exchange resins	Castets, France
2002 (1 month)	**Sanofi-Synthélabo Industry** Training technician work Topic: Industrial synthesis of Cordarone®.	Aramon, France

2001 (3 months) **Scientific National Research Center (CNRS)** Toulouse, France
Laboratory of "Synthesis and Physic-chemistry of Molecules with Biological Interest"
Topic: Synthesis of a new polyaminocarboxylic ligand as fluorescent marker cell.

Personal interests

Piano
Rowing, Canoe-Kayak, Hiking.

Publications

1) **Nadège Boudet**, Srinivas Reddy Dubbaka and Paul Knochel. "Amination of DNA and RNA units via Cuprated Pyrimidine and Purine Intermediates". *Org. Lett*. **2007**, *submitted*.

2) **Nadège Boudet**, Jennifer R. Lachs and Paul Knochel. "Multiple Regioselective Functionalization of Quinolines *via* Magnesiations". *Org. Lett.* **2007**, *9*, 5525-5528.

3) **Nadège Boudet**, Shohei Sase, Pradipta Sinha, Ching-Yuan Liu, Arkady Krasovskiy, and Paul Knochel. "Directed Ortho Insertion (DoI): a New Approach to Functionalized Aryl and Heteroaryl Zinc Reagents". *J. Am. Chem. Soc.* **2007**, 129, 12358-12359.

4) Darunee Soorukram, **Nadège Boudet**, Vladimir Malakhov and Paul Knochel. "Preparation of Polyfunctionalized 2,6-Dimethoxypyrimidine Derivatives *via* Chemo- and Regioselective Direct Zinc Insertion". *Synthesis*, **2007**, PSP, *24*, 3915-3922.

5) **Nadège Boudet** and Paul Knochel. "Chemo- and Regio-selective Functionalization of Uracil Derivatives. Application to the Synthesis of Oxipurinol and Emivirine". *Org. Lett*. **2006**. *8*, 3737-3741.

Posters and oral communications

1) **Nadège Boudet** and Paul Knochel." Chemo- and Regioselective Metalations on N-Heterocycles. Application to the Synthesis of Biologically Active Compounds" (Oral communication). **Sanofi-Aventis**, Mannheim, Germany, July, **2007**.

2) **Nadège Boudet** and Paul Knochel. "Synthesis of Functionalized Pyrimidine using a Selective Br/Mg Exchange Reaction: An Access to Uracil Derivatives" (Poster). **1st European Chemistry Congress**, Budapest, Hungary. August, **2006**.

3) **Nadège Boudet** and Paul Knochel. "Synthesis of Functionalized Pyrimidine using a Selective Br/Mg Exchange Reaction: An Access to Uracil Derivatives" (Poster). **3rd Industrie Tag**, Munich, Germany, October, **2006**.

4) **Nadège Boudet** and Paul Knochel. "Synthesis of Functionalized Pyrimidine using a Selective Br/Mg Exchange Reaction: An Access to Uracil Derivatives" (Oral communication). Work shop: **Graduiertenkolleg 1038 "Catalysts and Catalytic Reactions for Organic Synthesis**", Freiburg, Germany, 24th-25th, March **2006**.

5) **Nadège Boudet** and Paul Knochel, "Regioselective Functionalization of Quinolines *via* Bromine/Magnesium Exchange Reaction" (Poster). (Sanofi-Aventis [i]lab award 2005). 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (**OMCOS-13**), Geneva, Switzerland, 17th-21st, July **2005**.

München, den 29.11.2007