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Regio- and Chemoselective Metalations of N-Heterocycles. Applications to the Synthesis of Biologically Active Compounds

von

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aus

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Erklärung

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Ehrenwörtliche Versicherung

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Marc Mosrin

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2. Gutachter: Prof. Dr. Thomas Carell

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

1) **Marc Mosrin**, Gabriel Monzon, Tomke Bresser and Paul Knochel. "Microwave-Accelerated Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl". *Chem. Commun.* **2009**, *manuscript submitted*.

2) **Marc Mosrin**, Tomke Bresser and Paul Knochel. "Regio- and Chemoselective Multiple Functionalizations of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine". *Org. Lett*. **2009**, *submitted*.

3) **Marc Mosrin** and Paul Knochel. "A New Active Selective Base for the Directed Zincation of Sensitive Aromatics and Heteroaromatics". *Org. Lett*. **2009**, *11*, 1837.

4) **Marc Mosrin** and Paul Knochel. "Regio- and Chemoselective Metalations of Chloropyrimidines Derivatives using TMPMgCl·LiCl and $TMP_2Zn·2MgCl_2·2LiCl$. Application to the Synthesis of Mepanipyrim". *Chem. Eur. J.* **2009**, *15*, 1468.

5) **Marc Mosrin**, Marilena Petrera and Paul Knochel. "Multiple Regio- and Chemoselective Functionalizations of Pyrimidine Derivatives using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$". *Synthesis* **2008**, 3697.

6) **Marc Mosrin**, Nadège Boudet and Paul Knochel. "Regio- and Chemoselective Magnesiation of Protected Uracils and Thiouracils using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$". *Org. Biomol. Chem.* **2008**, *6*, 3237.

7) **Marc Mosrin** and Paul Knochel. "Regio- and Chemoselective Multiple Functionalization of Pyrimidine Derivatives by Selective Magnesiations using TMPMgCl·LiCl". *Org. Lett*. **2008**, *10*, 2497.

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Table of Contents

Table of Contents

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
aq	aqueous
Ar	aryl
Bn	benzyl
bs	broad singlet
d	doublet
dba	*trans*,*trans*-dibenzylideneacetone
DMF	*N*,*N*-dimethylformamide
DMGs	directing metalation groups
DMSO	dimethyl sulfoxide
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
i-Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
JNK	Jun *N*-terminal kinase
LDA	lithium diisopropylamide
LTMP	lithium tetramethylpiperidyl
M	molarity
m	meta
m	multiplet
Me	methyl
Met	metal
min	minute
mol	mole
mp.	melting point
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
o	ortho
p	para
PG	protecting group
Ph	phenyl

q	quartet
quint	quintet
RNA	ribonucleic acid
rt	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
Tf	triflate
tfp	*tri*-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TMPH	2,2,6,6-tetramethylpiperidine
TP	typical procedure

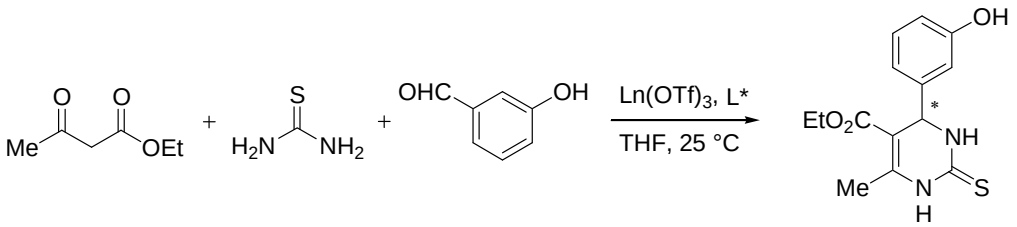
A: General Introduction

1. Overview

Heterocycles form one of the most important classes of organic molecules both in view of their economic importance and their mere production quantity. Pyrimidines, pyrazines, pyrazoles, indoles and purines are well-known *N*-heterocycles displaying a large spectrum of interesting properties in many fields, for instance medicinal chemistry, or increasingly gaining relevance in disciplines such as chemical biology and material science.

The discovery of new active compounds often starts with the identification of a particular class of heterocycles showing a desired biological activity. The second part of the process deals with the functionalization of these heterocycles in order to create several libraries allowing an easy access to the preparation of several potential active drugs.

The traditional methods available for the construction of polysubstituted aromatics and heteroaromatics can rapidly become very involved and can make the synthesis not only challenging to perform (e.g., through a growing number of steps), but also complicate since the sequence of steps must often be repeated to modify structures. Two different synthetic approaches for the functionalization of polysubstituted heterocycles can be highlighted. The first method corresponds to the construction of the heterocyclic scaffold when the substituents have been installed and properly functionalized. The reaction below illustrates an example of this methodology for the synthesis of the dihydropyrimidine derivative monastrol, [1] considered as a lead for the development of new anticancer drugs (Scheme 1).



1: Monastrol

Scheme 1: Modern asymmetric Biginelli three-component synthesis of monastrol (**1**).

The second approach consists in directly using the heterocyclic scaffold to which different substituents are successively added. This methodology is very flexible concerning the choice

[1] (a) Lampson, M. A.; Kapoor, T. M. *Nat. Chem. Biol.* **2006**, *2*, 19. (b) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386. (c) Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett.* **2002**, *43*, 5913. (c) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971.

of the substituents and allows a fast creation of numerous libraries. Organometallic chemistry turned out to be here an excellent tool with a broad applicability.[2] Over the years, considerable progress has been achieved in organometallic chemistry, especially with Grignard, copper and zinc reagents, which favoured the development of a considerable number of new synthetic methods for efficient and selective reactions and found powerful applications in industrial processes. However, the need to discover new more efficient organometallic methods and reagents in heterocyclic chemistry still exists and represents an exciting challenge.[3]

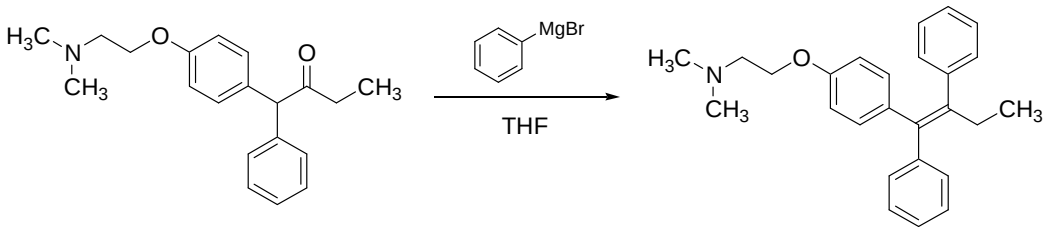
[2] For general review, see: (a) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F in *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH, Weinheim **2005**: p. 251. (b) Knochel, P.; Millot, P.; Rodriguez, A. L.; Tucker, C. E. in *Organic reactions*; Overman, L. E.,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

[3] Boudet , N. PhD Thesis, LMU München, **2007**.

2. Direct Preparation and Applications of Magnesiated Aryl and Heteroaryl Compounds

2.1. Introduction

Since their first discovery at the beginning of the last century by *Victor Grignard*,[4] organomagnesium reagents have occupied a privileged position in organic synthesis. In 1912, this pioneering work was honored with the Nobel Price "*for the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress in organic chemistry*" and this statement still holds true today.[3] Their easy preparation, good stability and their high reactivity make Grignard reagents one of the most powerful tools for carbon-carbon bond formation used in industry[5] and academic laboratories. An illustration of the Grignard reaction is a key step in the industrial production of *Tamoxifen*[6] (**2**), an antagonist of the estrogen receptor in breast tissue used in the treatment of breast cancer (Scheme 2). In 2004, it was the world's largest selling drug for that purpose.



2: Tamoxifen

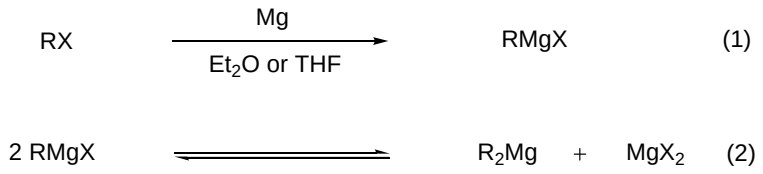
Scheme 2: Key step of the industrial production of the drug Tamoxifen (**2**).

Another considerable advantage of the use of Grignard reagents is their capability to undergo transmetalation reactions with a variety of main group- and transition- metal salts, like copper[7] or zinc providing a better control in terms of stability and chemoselectivity.

[4] (a) Grignard, V. *C. R. Acad. Sci*. **1900**, *130*, 1322. (b) Grignard, V. *Ann. Chim*. **1901**, *24*, 433.
[5] Bush, F. R.; De Antonis, D. M. Grignard Reagents - New Developments; Richey, H. G., Jr., Ed.; Wiley, New York, **2000**, pp.165-183.
[6] (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.
[7] Lipshutz B. H.; Sengupta S. *Org. Reactions* **1992**, *41*, 135.

2.2. Preparation of Grignard reagents by direct oxidative addition of magnesium to organic halides

A useful method for their preparation consists in the direct oxidative addition of magnesium metal (turnings or powder) to organic halides in an aprotic solvent like THF or diethyl ether under inert atmosphere since Grignard reagents are sensitive to air and moisture. (Scheme 3, Eq. 1).



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

Although the detailed mechanism of this reaction is not yet fully clarified, a radical pathway is generally accepted.[8] In solution, a Grignard reagent (RMgX) is in equilibrium (Schlenk equilibrium) with R_2Mg and MgX_2 (Scheme 3, Eq. 2), depending on temperature, solvent and the anion X^-.[9]

Such a direct insertion reaction has several advantages. It is atom economical and magnesium turnings are one of the cheapest reagents for the formation of organometallic species. Moreover, the low toxicity of magnesium makes organomagnesium reagents particularly environmentally friendly.

However, the presence of sensitive functional groups like cyano-, nitro-, esters or keto-groups makes this insertion complicated. In pioneering studies, *Rieke* prepared (Mg*)[10] highly activated magnesium powder using lithium in the presence of naphthalene with $MgCl_2$.

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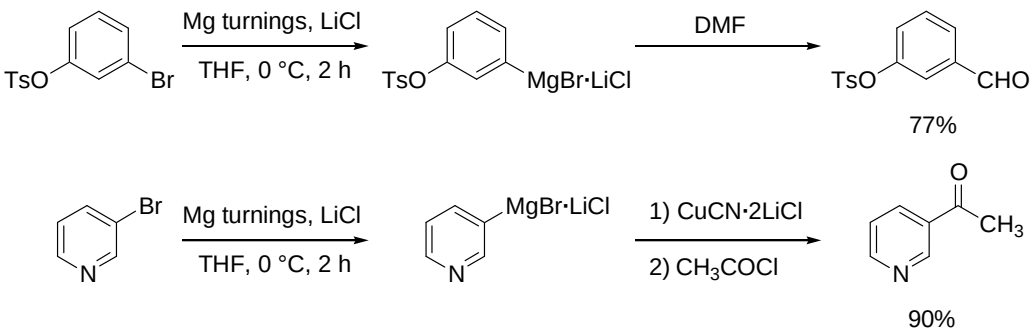
[8] (a) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286. (b) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95. (c) Rogers, H. R.; Hill, C. L.; Fujuwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217. (d) Garst, J. F.; Ungvary, F. *Grignard Reagents* (Ed.: H. G. Richey, Jr.), Wiley, Chichester, **2000**, p. 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**, p. 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] (a) Lee, J.; Velarde-Ortiz, R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428. (b) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (c) Rieke, R. D. *Aldrichim. Acta* **2000**, *33*, 52. (d) 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.

The highly activated generated magnesium species was used for the preparation of different functionalized aryl magnesium reagents at very low temperatures.

Recently, *Knochel et al.* reported that aryl and heteroaryl magnesium halides can be readily obtained from aryl and heteroaryl halides by using magnesium powder in the presence of LiCl.[11] This salt has a fundamental role and displays several functions. Firstly, it solubilizes the resulting organomagnesium compound and thus furnishes a constantly clean metal surface. Secondly, it promotes the initial electron transfert by the electrophilic activation of the aromatic ring through complexation. Finally, the high ionic strength of LiCl solutions facilitates charge separation and accelerates the metal insertion.[12] This new methodology presents the advantage to prepare several aryl and heteroaryl magnesium reagents under milder conditions, even bearing sensitive functional groups (Scheme 4).



Scheme 4: Preparation of functionalized Grignard reagents using magnesium powder in the presence of LiCl.

2.3. Preparation of Grignard reagents by halogen/magnesium exchange reaction

The halogen-lithium exchange reaction discovered by Wittig[13] and Gilman[14] allows the preparation of a broad range of organolithium derivatives and has become of great importance for the preparation of aromatics and heteroaromatics, using commercially available alkyllithium reagents and the corresponding organic halides, mainly bromides and iodides.[15]

[11] Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[12] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, Wiley-VCH, Weinheim, **2003**, p. 46.
[13] Wittig, G.; Pockels, U.; Dröge, H. *Chem. Ber.* **1938**, *71*, 1903.
[14] (a) Jones, R. G.; Gilman, H. *Org. Reactions* **1951**, *6*, 339. (b) Gilman, H.; Langham, W.; Jacoby, Y. *J. Am. Chem. Soc.* **1939**, *61*, 106.
[15] (a) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187. (b) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394. (c) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 2704. (d) Parham, W. E.; Boykin, D. W. *J. Org. Chem.* **1977**, *42*, 260. (e) Parham, W. E.; Boykin, D. W. *J. Org. Chem.* **1977**, *42*, 257. (f) Tucker, C. E.; Majid T. N.; Knochel, P. *J. Am. Chem. Soc*. **1992**, *114*, 3983.

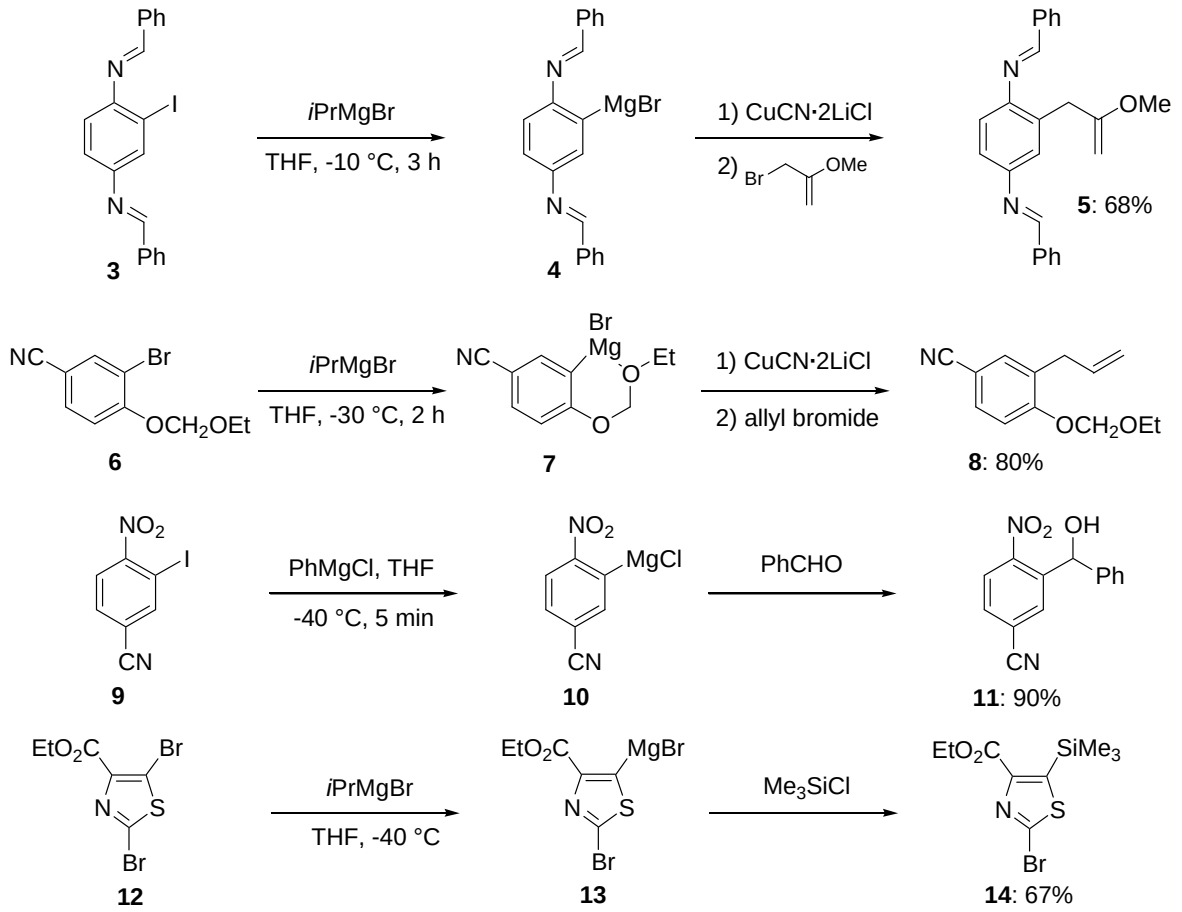
Although the reaction proceeds very fast, the main drawbacks with the use of lithium reagents are the very low temperatures required and the moderate functional groups tolerance. In contrast, the halogen-magnesium exchange turned out to be a very efficient method for the preparation of new functionalized reagents of great synthetic utility.[16]

The halogen/magnesium exchange favors the formation of the more stable organomagnesium species (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,[17 d] in contrast to the halogen-lithium exchange that goes *via* the formation of a halogenate complex.

In 1971, *Tamborski* demonstrated the fundamental role of the electronic properties of both the halogen atom and the organic molecule in the formation rate of the new Grignard reagent.[18] The reactivity order (I > Br > Cl >> F) is also influenced by the halogen-carbon bond strength, by the electronegativity and polarizability of the halide.

In 1998, *Knochel* reported the possibility to carry out I/Mg exchange reactions at low temperatures with aromatics and heteroaromatics, even bearing sensitive functional groups, for the preparation of functionalized aromatic Grignard reagents (Scheme 5).[16, 19] Thus, the bis-imine **3** underwent an iodine-magnesium exchange with *i*-PrMgBr at –10 °C in 3 h providing the magnesium species **4**. Transmetalation with CuCN·2LiCl and allylation with 2-methoxyallyl bromide gave the bis-imine **5** in 68% yield. An oxygen-chelating functional group such as an ethoxymethoxy group in the aryl bromide **6** enhances the Br/Mg exchange rate, allowing the preparation of the magnesium derivative **7** at –30 °C within 2 h. Trapping with allyl bromide in the presence of CuCN·2LiCl furnished the aromatic nitrile **8** in 80% yield. *Ortho*-nitro groups can also be tolerated. Thus, the nitro-substituted aromatic **9** underwent a smooth I/Mg exchange with phenylmagnesium chloride within 5 min at –40 °C, leading to the expected Grignard reagent **10**. Quenching with benzaldehyde allowed the formation of the corresponding alcohol **11** in 90% yield.

[16] 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.
[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] (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701. (b) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Knochel, P. *Synlett* **2001**, 477.

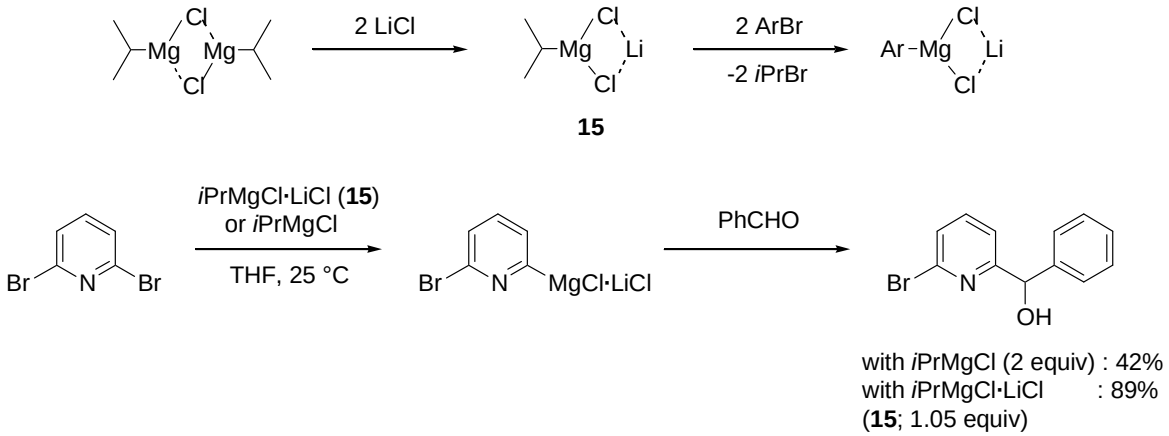


Scheme 5: Halogen-magnesium exchange reactions and trapping with electrophiles.

This methodology could also be readily applied to heteroaromatics.[20] The selective exchange at the position C5 of the dibromothiazole **12** using *i*-PrMgBr at –40 °C led to the magnesium species **13**. Trapping with trimethylsilyl chloride provided the silylated thiazole **14** in 67% yield.

However, some unactivated aryl bromides or electron rich substrates do not react at a sufficient rate even at room temperature. A considerable improvement of this reaction was recently developed by *Knochel* and *Krasovskiy* using a stochiometric amount of LiCl, which dramatically enhances the reactivity of the Grignard reagent by breaking the aggregates of *i*-PrMgCl.[21] The new mixed organometallic *i*-PrMgCl·LiCl (**15**) allows a faster Br/Mg exchange leading to the desired Grignard reagents in high yields under mild conditions (Scheme 6).

[20] For review concerning the halogen/magnesium exchange on heterocycles, see: Hiriyakkanavar, I.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583.
[21] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.



Scheme 6: Br/Mg-exchange reaction with LiCl.

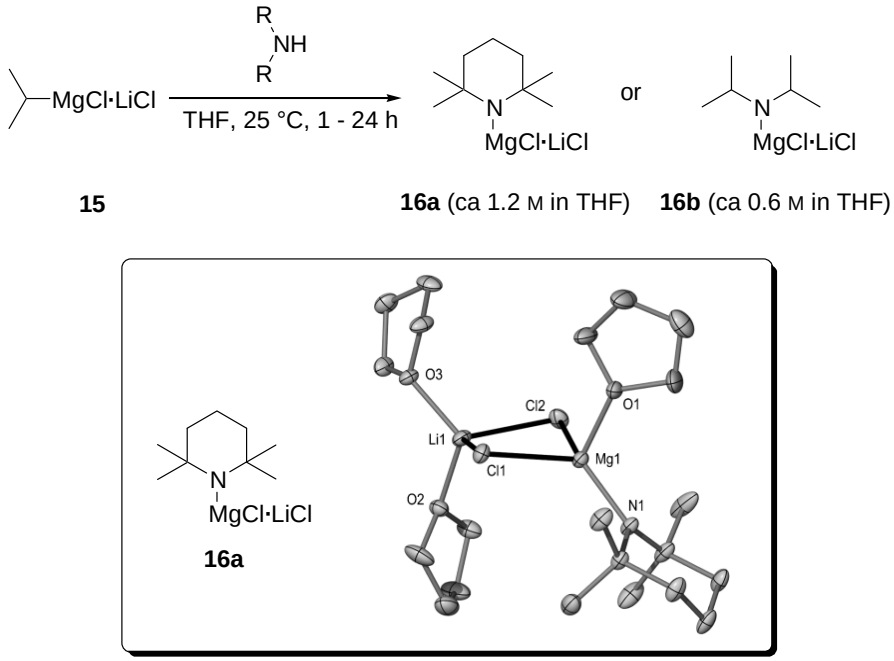
2.4. Preparation of Grignard reagents by metalation reactions with magnesium amide bases

The metalation of arenes and heteroarenes is one of the most useful transformations in organic synthesis since it allows the regioselective functionalization of various aryl and heteroaryl derivatives. Traditionally, strong bases such as alkyllithium reagents (RLi like *sec*-BuLi) and lithium amides (R_2NLi) such as lithium 2,2,6,6-tetramethylpiperidyl (LTMP) have been extensively used for this kind of metalations, especially for the directed *ortho*-lithiation.[22] However, such bases are often complicated to handle since they often lead to undesirable side reactions as a result of their high reactivity, their strong nucleophilicity (e.g. Chichibabin addition) and their low functional group tolerance. Another serious drawback is the low stability of lithium amides in THF solutions at 25 °C. Furthermore, such deprotonation reactions have to be carried out at very low temperatures (–78 to –100 °C), which is not convenient for the reaction upscaling. Alternative methods have been developed using magnesium amides of type R_2NMgCl, R_2NMgR or $(R_2N)_2Mg$ [23] to overcome these

[22] (a) Schlosser, M. *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. 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.

[23] (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.

limitations. However, low kinetic basicity and low solubility were observed and it was usually necessary to use large amounts of bases to obtain high conversion rates. Recently, our group reported very efficient mixed Mg/Li-bases of type $R_2NMgCl{\cdot}LiCl$ (**16a** and **16b**, Scheme 7).[24]



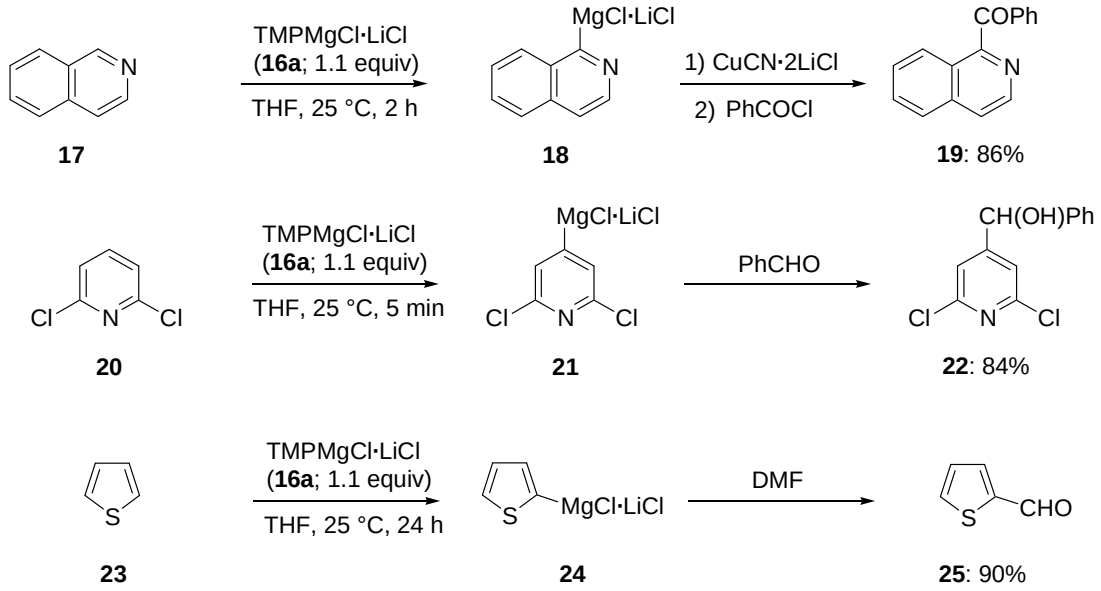
Scheme 7: Preparation of Mg/Li amide bases of type $R_2NMgCl{\cdot}LiCl$ and molecular structure of TMPMgCl·LiCl (**16a**) (hydrogen atoms ommited for clarity).

The considerable advantages of these new bases are their excellent kinetic basicity, their very good solubility and excellent thermal stability in THF solution, and their long term storage. TMPMgCl·LiCl (**16a**) showed a better kinetic basicity than *i*-$Pr_2NMgCl{\cdot}LiCl$ (**16b**) and afforded the magnesiation of numerous aromatics and heteroaromatics in high conversion rates with excellent regio- and chemoselectivity at convenient temperatures (Scheme 8). Thus, the metalation using TMPMgCl·LiCl (**16a**) of the isoquinoline **17** was readily achieved at 25 °C within 2 h. Transmetalation of **18** with CuCN·2LiCl and quenching with benzoyl chloride furnished the keto-derivative **19** in 86% yield. 2,6-Dichloropyridine (**20**) underwent smooth deprotonation at 25 °C for 5 min to give the Grignard reagent **21**. Trapping with benzaldehyde provided the corresponding alcohol **22** in 84% yield. Thiophene (**23**) could also be metalated

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, S., 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.

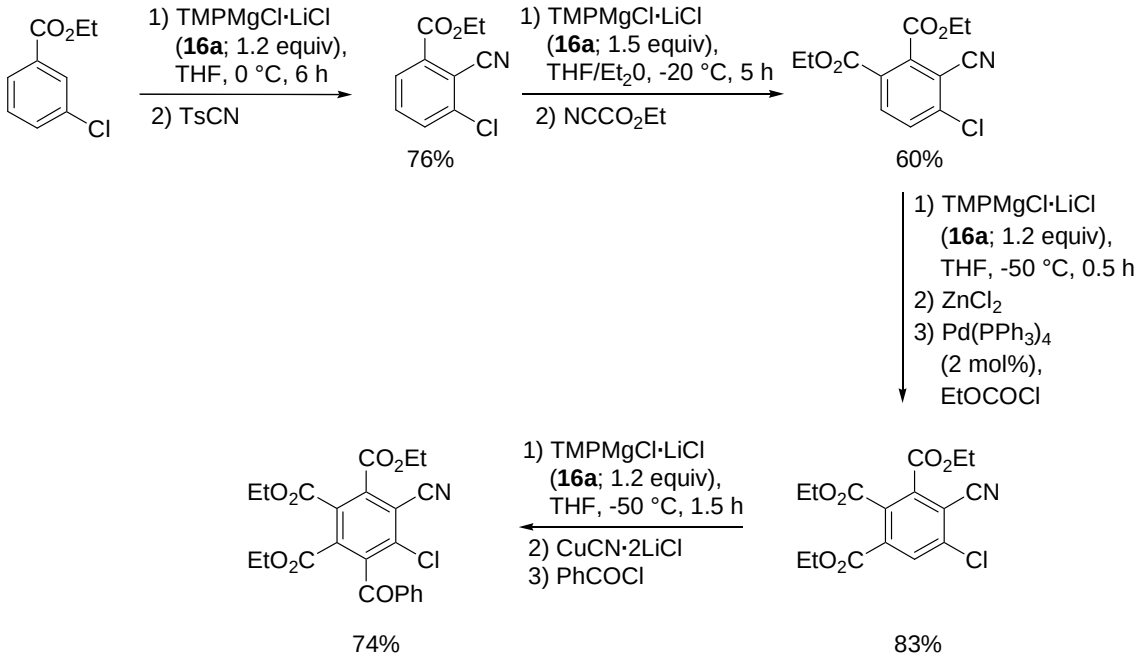
[24] (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. (b) Garcia-Alvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.

at 25 °C for 24 h allowing the magnesium species **24**. Quenching with DMF gave the aldehyde derivative **25** in 90% yield.



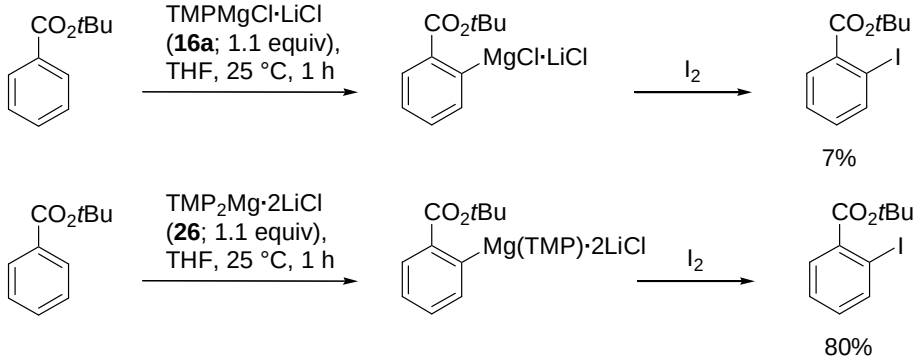
Scheme 8: Magnesiation of arenes and heteroarenes using TMPMgCl·LiCl (**16a**) and trapping with electrophiles.

This methodology has been successfully extended to arenes through successive direct magnesiations of highly functionalized aromatics bearing an ester, a nitrile or a ketone.



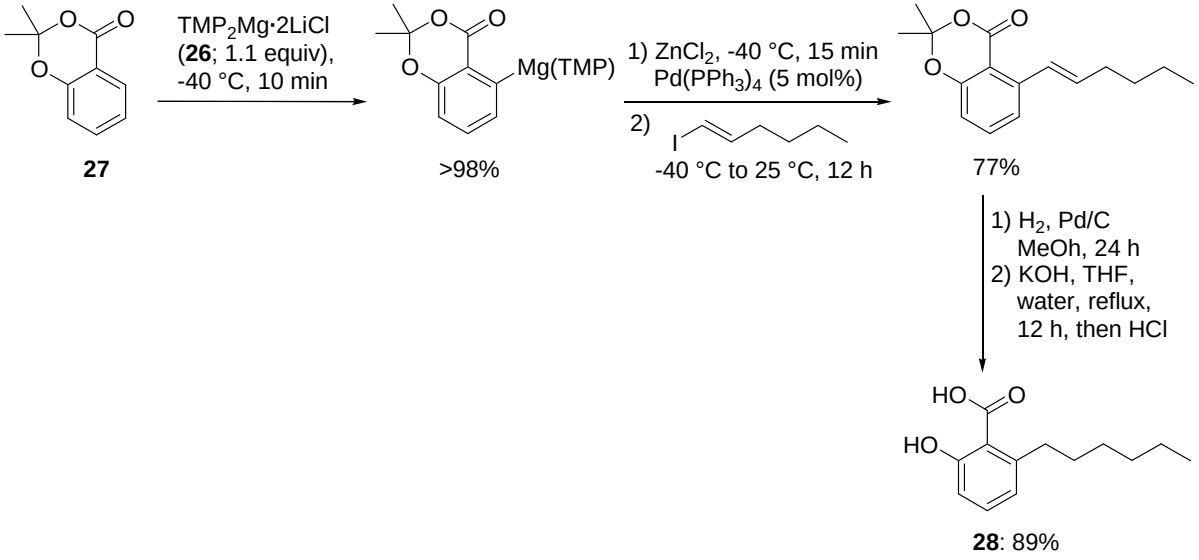
Scheme 9: Succesive regio- and chemoselective magnesiations of 3-chlorobenzoate.

Trapping the magnesium species with electrophiles provided highly functionalized benzene derivatives in good to excellent yields (Scheme 9).[25] However, some moderatery activated arenes such as *tert*-butyl benzoate gave unsatisfactory results (Scheme 10).



Scheme 10: Comparison between TMPMgCl·LiCl (**16a**) and TMP_2Mg·2LiCl (**26**).

Our group recently reported a new class of mixed Li/Mg bases: magnesium bisamides complexed with lithium chloride of type ($(R_2N)_2Mg$·2LiCl) such as TMP_2Mg·2LiCl (**26**) (Scheme 11).[26]



Scheme 11: Preparation of 6-hexylsalicylic acid (**28**) *via* regio- and chemoselective magnesiation using TMP_2Mg·2LiCl (**26**).

[25] Lin, W.; Baron, O. *Org. Lett*. **2006**, *8*, 5673.
[26] (a) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. (b) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.

These new bases display a superior magnesiation capability affording an easy access to new polyfunctional aromatic or heteroaromatic reagents even bearing sensitive functional groups such as esters, nitriles or ketones. This methodology could readily be used for the synthesis of natural products as shown in the example above with the metalation of dimethyl-1,3-benzodioxan-4-one (**27**) using $TMP_2Mg{\cdot}2LiCl$ (**26**) (Scheme 11). A transmetalation with $ZnCl_2$ allowing a Negishi cross-coupling, an hydrogenation and a deprotection led to 6-hexylsalicylic acid (**28**), a natural product found in essential oil of *Pelargonium sidoides* DC.

3. Direct Preparation and Applications of Zincated Aryl and Heteroaryl Compounds

3.1 Introduction

Organozinc reagents have been known since the preparation of diethylzinc by *Frankland* in 1849 in Marburg.[27] These organometallic reagents were often used to form new carbon-carbon bonds until *Grignard*[4] discovered in 1900 a convenient preparation of organomagnesium compounds. These reagents turned out to be more reactive species toward electrophiles and generally gave higher yields in comparison to zinc reagents. However, some reactions were still carried out using zinc organometallics like the Reformatsky reaction[28] or the Simmons-Smith cyclopropanation.[29] The intermediate organometallics (zinc enolate and zinc carbenoid) were easier to handle and more selective than the corresponding magnesium organometallics. In 1943, *Hunsdiecker* reported that the preparation of organozinc reagents bearing a long carbon chain terminated by an ester is possible,[30] but it was only recently that *Knochel* proved that these reagents represent a powerful synthetic tool.[31] A considerable advantage with the use of organozincs is their excellent group tolerance and their ability to undergo a broad range of transmetalations due to the presence of empty low-lying *p*-orbitals which readily interact with the *d*-orbitals of many transition metal salts, leading to more reactive species such as organocopper[32] or palladium intermediates[33] (Scheme 12).

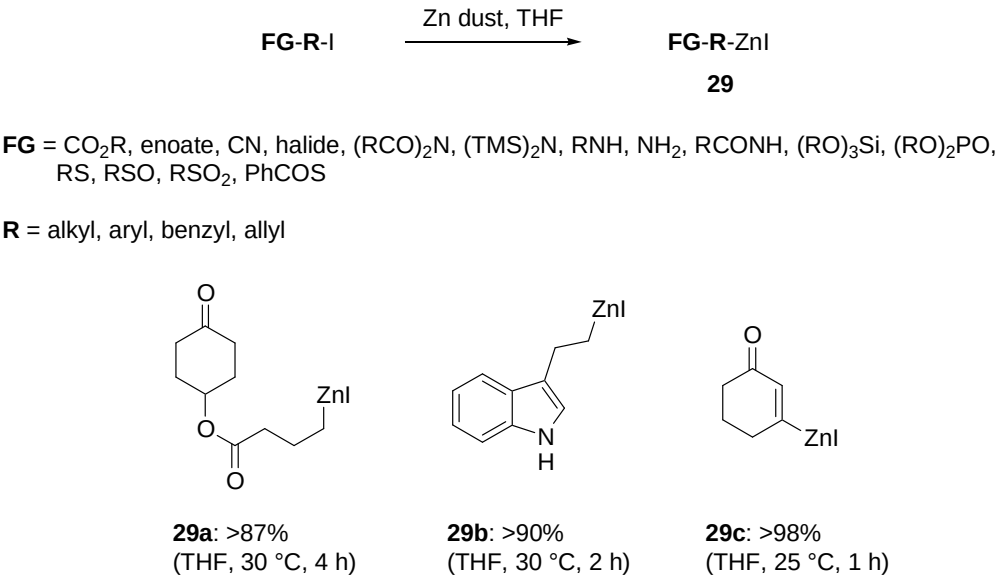
Scheme 12: Transmetalation of organozincs reagents.

[27] Frankland, E. *Liebigs Ann. Chem*. **1849**, *71*, 171 and 173.
[28] (a) Reformatsky, S. *Chem. Ber*. **1887**, *20*, 1210; **1895**, *28*, 2842. (b) Fürstner, A. *Angew. Chem. Int. Ed*. **1993**, *32*, 164.
[29] 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.
[30] Hunsdiecker, H.; Erlbach, H., Vogt, E. **1942**, German patent 722467; *Chem. Abstr*. **1943**, *37*, 5080.
[31] (a) Knochel, P.; Singer, R. D. *Chem. Rev*. **1993**, *93*, 2117. (b) Knochel, P.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
[32] (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.
[33] (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.

Another advantage of great importance is the highly covalent character of the carbon-zinc bond which makes organozinc species stable at temperatures which would lead to decomposition for the corresponding organomagnesiums and organolithiums. These typical features make organozincs extremely interesting reagents for organic synthesis. The reactivity order 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. Different ways to prepare organozinc reagents are possible by an insertion of zinc dust into organic halides, by an I/Zn exchange of iodinated alkyl and aryl substrates, or by direct deprotonation reactions using Zn bases.

3.2 Preparation of zinc reagents by direct oxidative addition of zinc to aryl and heteroaryl halides

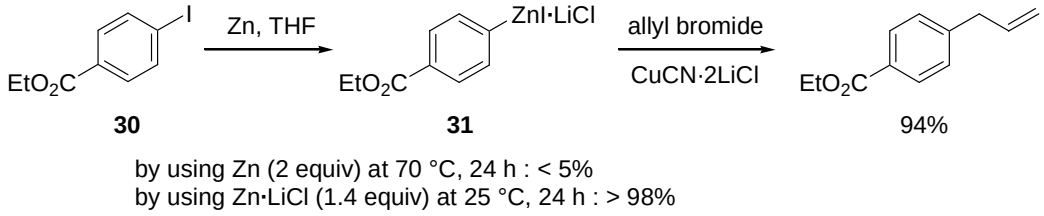
The oxidative addition of zinc dust to functionalized organic halides allows the preparation of a broad range of polyfunctional organozinc iodides of type **29** (Scheme 13). This method of preparation tolerates several functionalities and is sensitive to the reaction conditions (solvent, concentration, temperature), the nature of the halide and the method of zinc activation.



Scheme 13: Functionalized organozinc compounds of type **29** prepared by oxidative addition.

A specific feature of zinc is the slow oxidation in air and the resulting oxide layer on its surface. To activate zinc, it is possible to employ 1,2-dibromoethane in THF (reflux, 1-2 min),

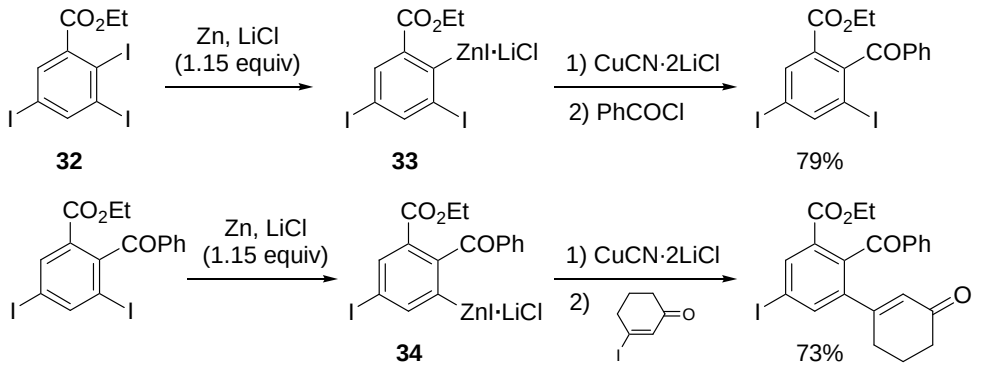
followed by the addition of TMSCl (1-2 mol%; reflux, 1 min).[2a, 31a, 32d] Another possibility is the use of *Rieke* zinc (Zn*)[34] prepared by the direct reduction of zinc chloride with lithium naphthalenide in THF. These methods allowed the preparation of a wide range of functionalized organozinc iodides.[2] 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[35] or the use of *Rieke* zinc (Zn*). However, the use of Zn* has the drawback that the activity decreases with time. Our group has recently reported a new convenient procedure for the zinc insertion, which allows, in the presence of LiCl, a considerable improvement for the preparation of highly functionalized zinc compounds as shown by the example of ethyl 4-iodobenzoate (**30**) furnishing the corresponding zinc derivative (**31**) (Scheme 14).[36]



Scheme 14: Insertion of Zn in the presence and absence of LiCl.

The scope of this method was extended to a new approach for the preparation of highly functionalized aryl and heteroaryl zinc reagents using directed *ortho* insertion[37] (DoI) and highly benzylic zinc chlorides (Scheme 15).[38] Thus, the tri- iodo-substituted aromatic **32** readily reacts with Zn dust in the presence of LiCl in THF at 0 °C and furnishes after 30 min the ortho-zincated intermediate **33**. Trapping with benzoyl chloride after transmetalation with CuCN·2LiCl gives the corresponding ketoester in 79% yield. A further insertion is possible affording in the same conditions the zinc reagent **34**. The ketone group plays now the role of an ortho-directing group. Quenching with 3-iodocyclohexenone provides the substitution product in 73% yield.

[34] (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.
[35] (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.
[36] Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed*. **2006**, *45*, 6040.
[37] Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc*. **2008**, *129*, 12358.
[38] Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett*. **2008**, *10*, 1107.



Scheme 15: Insertion of Zn in the presence and absence of LiCl.

3.3 Preparation of zinc reagents by metalation reactions with zinc amide bases

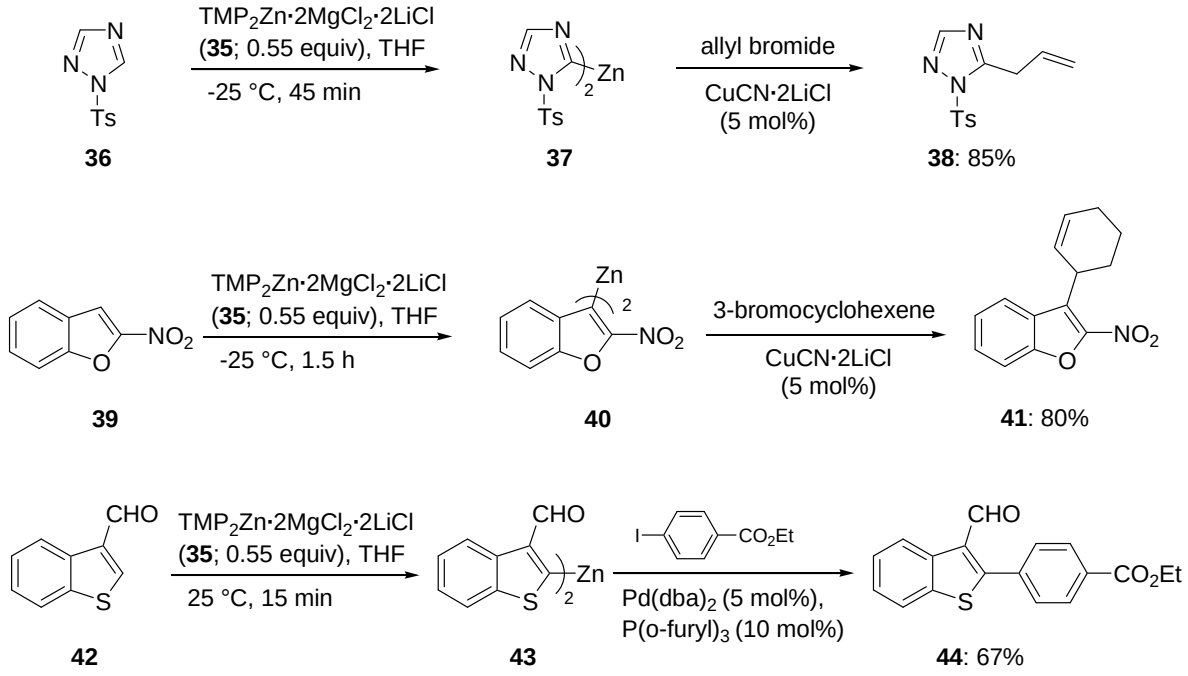
The directed metalation of arenes and heteroarenes is one of the most useful methods for the functionalization of these scaffolds. Lithium bases have been extensively used to *ortho*-metalate various unsaturated systems.[22] The use of magnesium bases such as mixed bases Mg/Li of the type $R_2NMgCl \cdot LiCl$[24] like TMPMgCl·LiCl (**16a**) proved to be especially effective and is compatible with functional groups such as esters, aryl ketones and nitriles.[25] However, more sensitive functionalities such as aldehydes or nitro- groups are not tolerated. Also some classes of heterocycles, for example 1,3- and 1,2-oxazoles and 1,2,5- and 1,3,4-oxadiazoles, provide unstable lithiated or magnesiated intermediates, which are prone to ring opening.[39] Therefore, a range of zinc amides have been reported that provide after metalation organozinc reagents compatible with most functionalities. In a pioneer work, lithium di-*tert*-butyl-(2,2,6,6-tetramethylpiperidino)zincate (t-Bu_2Zn(TMP)Li) was reported by *Kondo* to be an excellent base for the zincation of sensitive aromatics and heteroaromatics.[40] The use of highly reactive zincates or relative ate-bases is sometimes not compatible with sensitive functions such as an aldehyde or a nitro group.[41] Recently, *Wunderlich* and *Knochel* reported

[39] (a) Micetich, R. G. *Can. J. Chem.* **1970**, *48*, 2006. (b) Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1974**, *95*, 3408. (c) Knaus, G. N.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1189. (d) Miller, R. A.; Smith, M. R.; Marcune, B. *J. Org. Chem.* **2005**, *70*, 9074. (e) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber. Rec.* **1997**, *130*, 1213.

[40] (a) Kondo, Y.; Shilai, H.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) Imahori, T.; Uchiyama, M.; Kondo, Y. *Chem. Commun.* **2001**, 2450. (c) Schwab, P. F. H.; Fleischer, F.; Michl, J. *J. Org. Chem.* **2002**, *67*, 443. (d) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514.

[41] (a) Uchiyama, M.; Matsumoto, Y.; Nobuto, D.; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc.* **2006**, *128*, 8748. (b) Clegg, W.; Dale, S. H.; Drummond, A. M.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2006**, *128*, 7434. (c) Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2005**, *127*, 13106. (d) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 3775. (e) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.;

the preparation of the highly chemoselective base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[42] (**35**) for the direct zincation of sensitive aromatics and heteroaromatics (LiCl[21] leads to a high solubility and $MgCl_2$[43] enhances the base reactivity) (Scheme 16). The presence of these Lewis salts with TMP_2Zn[44] turned out to be very effective for the metalation of sensitive arenes and heteroarenes like *N*-tosyl-1,2,4-triazole (**36**), that underwent a smooth deprotonation providing the zincated compound **37**. Trapping with allyl bromide led to the allylated pyridine **38** in 85%. A considerable advantage of the zinc base **35** is that very sensitive functional groups such as nitro groups can also be tolerated as shown in the example of nitrobenzofuran **39**.[45] Quenching the zinc species **40** with 3-bromocyclohexene in the presence of CuCN·2LiCl provided the new substituted benzofuran **41** in 80% yield. Aldehydes can be metalated as well.[45,46] The formylbenzothiophene **42** was zincated at 25 °C furnishing the intermediate **43**, that could then undergo a Negishi cross-coupling to afford the benzothiophene derivative **44** in 67% yield.



Scheme 16: Zincation of sensitive arenes and heteroarenes using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) and trapping with electrophiles.

Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2374. (f) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921.

[42] Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

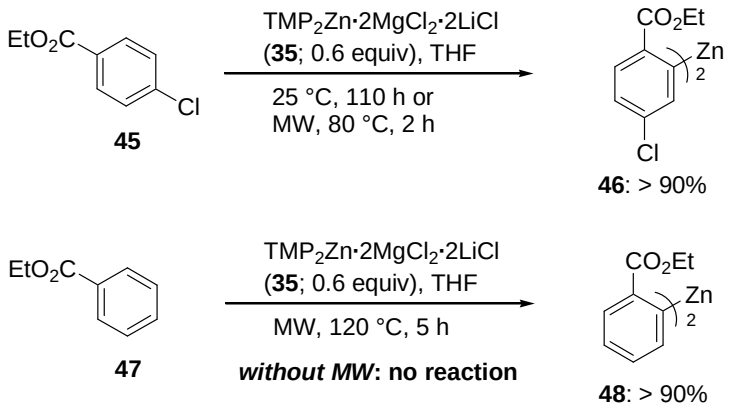
[43] Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 1017.

[44] (a) Hlavinka, M. L.; Hagadorn J. R. *Tetrahedron Lett.* **2006**, *47*, 5049. (b) Hlavinka, M. L.; Hagadorn J. R. *Organometallics* **2007**, *26*, 4105.

[45] Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.

[48] Gong, L.-Z.; Knochel, P. *Synlett* **2005**, 267.

Over the last decades, microwave irradiation has been used to accelerate numerous organic reactions[47] including organometallic reactions.[48] Since organozinc reagents of the type RZnX display a good thermal stability and tolerate functional groups even at elevated temperatures,[49] *Wunderlich* and *Knochel* extended the scope of metalations by forcing TMP_2Zn-mediated zincations using microwave irradiation.[50] For example, the direct zincation of ethyl 4-chlorobenzoate (**45**) at 25 °C usually requires 110 h for completion. By applying microwave irradiation, a complete metalation was achieved within 2 h at 80 °C leading to the expected *bis*-aryl zinc species **46** in >90% yield (Scheme 17). Additionally, ethyl benzoate (**47**), which could not be metalated at 25 °C, reacted with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) under microwave irradiation leading to the corresponding zinc reagent **48** in > 90% yield (Scheme 17).



Scheme 17: Zincation of **45** and **47** with and without microwave irradiation.

[47] (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, R. *Tetrahedron Lett.* **1986**, *27*, 279. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945. (c) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, **2002**. (d) *Microwave-Assisted Organic Synthesis*; Lidström, P.; Tierney, J. P. Eds.; Blackwell Publishing: Oxford, **2005**. (e) *Microwaves in Organic Synthesis,* 2nd ed.; Loupy, A. Ed.; Wiley-VCH: Weinheim, **2006**. (f) *Microwave Methods in Organic Synthesis*; Larhed, M.; Olofsson, K. Eds.; Springer: Berlin, **2006**.

[48] (a) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107* , 2563. (b) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. (c) Tsukamoto, H.; Matsumoto, T.; Kondo, Y. *J. Am. Chem. Soc*. **2008**, *130,* 388. (d) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2761. (e) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1589. (f) Fustero, S.; Jimenez, D.; Sanchez-Rosello, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129,* 6700. (g) Constant, S.; Tortoioli, S. ; Müller, J. ; Linder, D.; Buron, F.; Lacour, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8979.

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

[50] Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705.

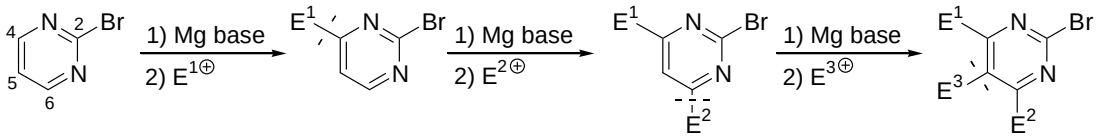
4. Objectives

We envision in this work to apply the newly developed methods of preparation of organo-magnesium and zinc reagents for the synthesis of various *N*-heterocyclic magnesium and zinc intermediates. Our goal was to carry out selective functionalizations of *N*-heterocycles, and apply our methodology to the synthesis of biologically active compounds.

In a first project, our work dealt with the total functionalization of the pyrimidine scaffold and was then mainly focused on two important pyrimidine families: protected uracils and thiouracils, and chloropyrimidines. Both represent two main classes of biological importance and where metalation and subsequent functionalization are still unexplored.

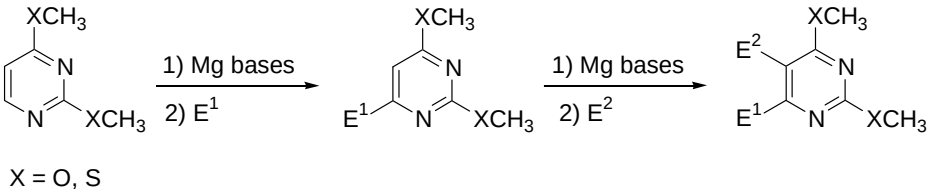
More precisely, our objectives were:

- The total functionalization of the pyrimidine core using successive sequences (regio- and chemoselective magnesiations and trapping with different electrophiles) at positions 4, 5 and 6 using Mg bases (Scheme 18).



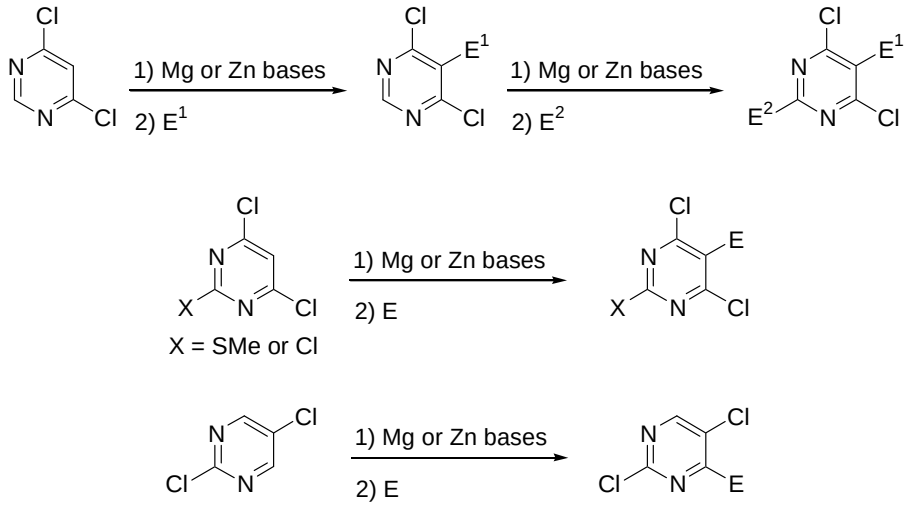
Scheme 18: Multiple regio- and chemoselective functionalizations of pyrimidine derivatives *via* magnesiations.

- The selective magnesiation of 2,4-dimethoxypyrimidine and 2,4-bis(methylthio)pyrimidine as a synthetic route to polyfunctionalized protected uracils and thiouracils using magnesium bases (Scheme 19).



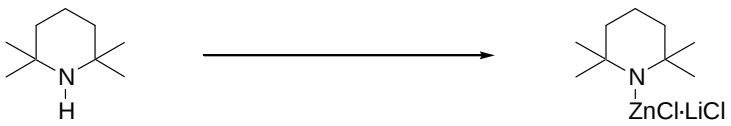
Scheme 19: Regio- and chemoselective functionalization of uracil and thiouracil derivatives.

- The regio- and chemoselective metalation of chloropyrimidine derivatives at all positions (2, 4, 5 and 6) at convenient temperatures and applications to the synthesis of biologically active compounds using zinc and magnesium bases (Scheme 20).



Scheme 20: Regio- and chemoselective functionalization of chloropyrimidine derivatives.

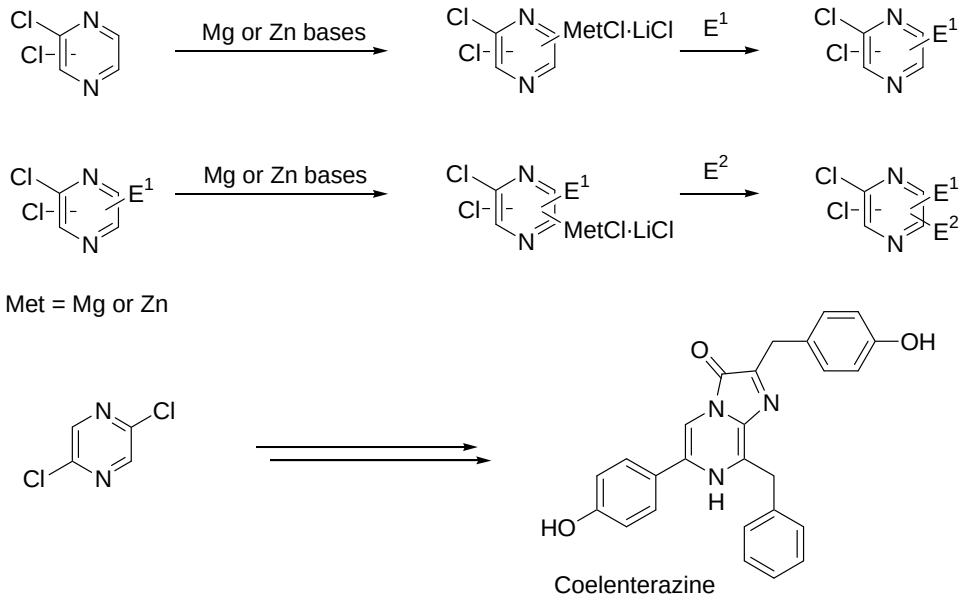
In the second project, we planned to prepare a more active chemoselective Zn base of type TMPZnCl·LiCl for the directed zincation of sensitive arenes and heteroarenes (Scheme 21).



Scheme 21: Preparation of a new active chemoselective Zn base of type TMPZnCl·LiCl.

In the third project, we envisioned to perform the functionalization of the pyrazine ring toward regio- and chemoselective multiple functionalizations of chloropyrazine derivatives

using Mg and Zn bases with a direct application to the total synthesis of the bioluminescent natural product Coelenterazine isolated from the jellyfish *Aequorea victoria* (Scheme 22).



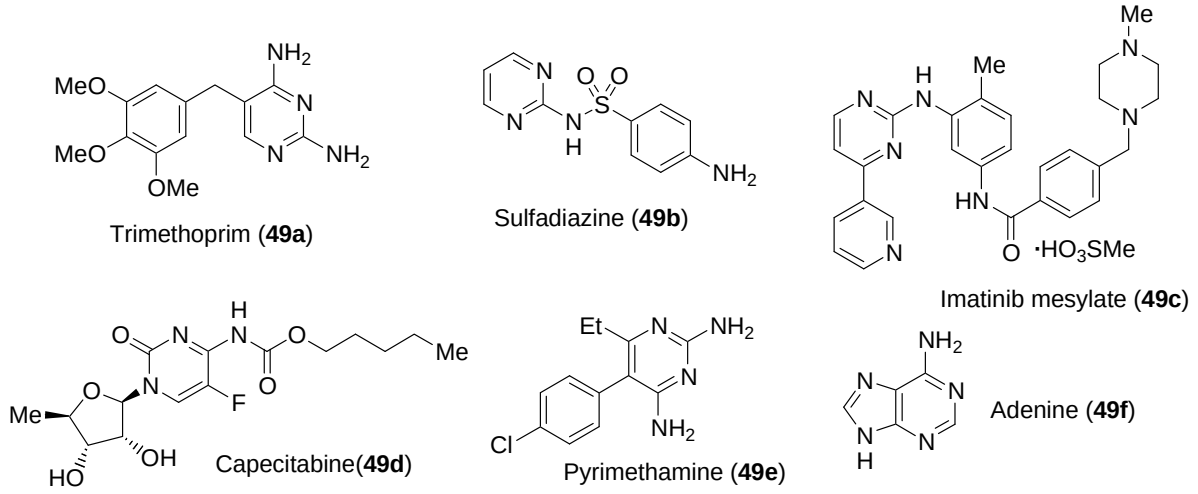
Scheme 22: Regio- and chemoselective multiple functionalizations of chloropyrazine derivatives and application to the synthesis of Coelenterazine.

B: Results and Discussion

1. Functionalization of Pyrimidine Derivatives *via* Regio- and Chemoselective Magnesiations

1.1 Introduction

Azaheterocycles constitute a very important class of biologically active compounds. In particular, pyrimidine derivatives are present in a large number of natural products, pharmaceuticals, and functional materials.[51] The functionalization of pyrimidines and its derivatives is therefore of great interest since many examples of pharmaceutically important compounds include trimethoprim[52] (**49a**, antibiotic), sulfadiazine[53] (**49b**, antibiotic), Gleevec[54] (**49c**, imatinib mesylate, anti-cancer), Xeloda[55] (**49d**, capecitabine, anti-cancer) and pyrimethamine[56] (**49e**, antimalarial) as well as other natural (**49f**, adenine)[51] and unnatural compounds[57] (Scheme 23).



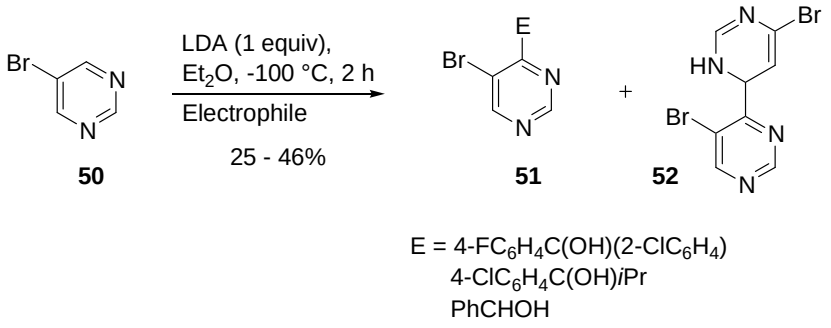
Scheme 23: Biologically active compounds containing a pyrimidine scaffold.

[51] (a) Hurst, D. T. *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; Wiley: Chichester, **1980**. (b) Brown, D. J. *The Pyrimidines*; Wiley: New York, **1994**. (c) Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, **1996**. (d) Gribble, G.; Joule, J. *Progress in Heterocyclic Chemistry, 18*; Elsevier: Oxford, **2007**. (e) Lagoja, I. M. *Chem. Biodiversity* **2005**, *2*, 1. (f) Michael, J. P. *Nat. Prop. Rep.* **2005**, *22*, 627.
[52] Joffe, A. M.; Farley, J. D.; Linden, D.; Goldsand, G. *Am. J. Med.* **1989**, *87*, 332.
[53] Petersen, E.; Schmidt, D. R. *Expert Rev. Anti-Infect. Ther.* **2003**, *1*, 175.
[54] Nadal, E.; Olavarria, E. *Int. J. Clin. Pract.* **2004**, *58*, 511.
[55] Blum, J. L. *Oncologist* **2001**, *6*, 56.
[56] Roper, C.; Pearce, R.; Nair, S.; Sharp, B.; Nosten F.; Anderson, T. *Science* **2004**, *305*, 1124.
[57] Köytepe, S.; Pasahan, A.; Ekinci, E.; Seçkin, T. *Eur. Polym. J.* **2005**, *41*, 121.

1.2 Total functionalization of the pyrimidine scaffold using successive regio- and chemoselective magnesiations

1.2.1 Functionalization of 5-bromopyrimidine (50) and 2-chloropyrimidine (53) using lithium bases

The direct functionalization of pyrimidines by lithiation is difficult due to the electrophilic character of the ring, which readily undergoes the addition of various organometallics at the positions 4 and 6.[58] This also implies that very low temperatures are mandatory for the metalation of pyrimidines.[59] Thus, the metalation of 5-bromopyrimidine (**50**) using LDA as metalating agent in Et_2O at –100 °C for 2 h furnishes the lithium species that can be then trapped with aldehydes to give 4-substituted pyrimidines **51** in moderate yields. In the absence of electrophile, the dihydropyrimidylpyrimidine **52** was isolated in 32% yield (Scheme 24).[60]



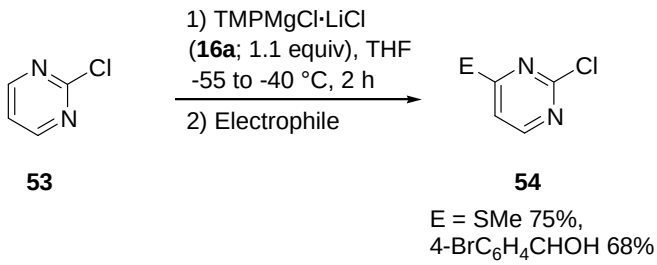
Scheme 24: Deprotonative functionalization of 5-bromopyrimidine using LDA (**34**).

Similar results were observed with 2-chloropyrimidine (**53**) using LTMP as metalating agent.[61]

1.2.2 Successive regio- and chemoselective functionalizations of 2-bromopyrimidine (55) using mixed Mg/Li amide bases

[58] (a) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley: Weinheim, **2003**. (b) Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *Synthesis* **1996**, 838. (c) Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *Tetrahedron* **1998**, *54*, 9701. (d) Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1997**, *34*, 551.
[59] (a) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron Lett.* **2001**, *57*, 4489. (b) Schlosser, M.; Lefebvre, O.; Ondi, L. *Eur. J. Org. Chem.* **2006**, *6*, 1593.
[60] Kress, T. J. *J. Org. Chem.* **1979**, *44*, 2081.
[61] Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *J. Org. Chem.* **1995**, *60*, 3781.

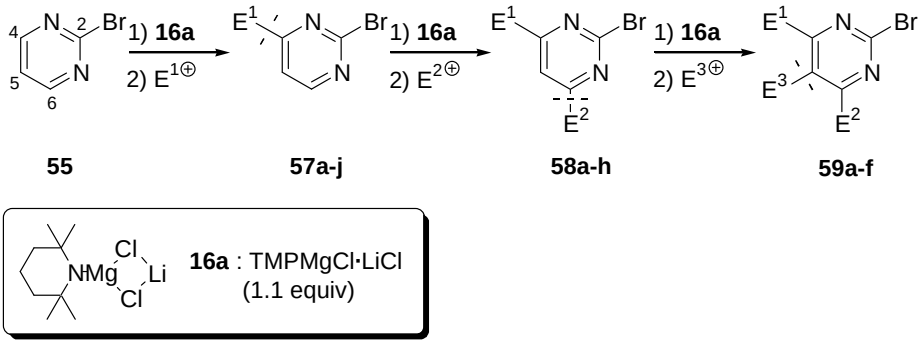
The use of the mixed Mg/Li amide TMPMgCl·LiCl (**16a**; 1.1 equiv) can solve the above mentionned problems; thus, the metalation of the chloropyrimidine **53** becomes possible at temperatures between –55 and –40 °C and subsequent trapping with typical electrophiles leads to 4-substituted pyrimidines **54** without any traces of dihydropyrimidylpyrimidine (Scheme 25).[26]



53 **54**

Scheme 25: Magnesiation of 2-chloropyrimidine (**53**) using TMPMgCl·LiCl (**16a**) and trapping with electrophiles.

Since the functionalization of pyrimidines is of great importance, we focused our attention on the total functionalization of this scaffold, starting from commercially available 2-bromopyrimidine (**55**), by performing successive regio- and chemoselective magnesiations using TMPMgCl·LiCl (**16a**) (Scheme 26).

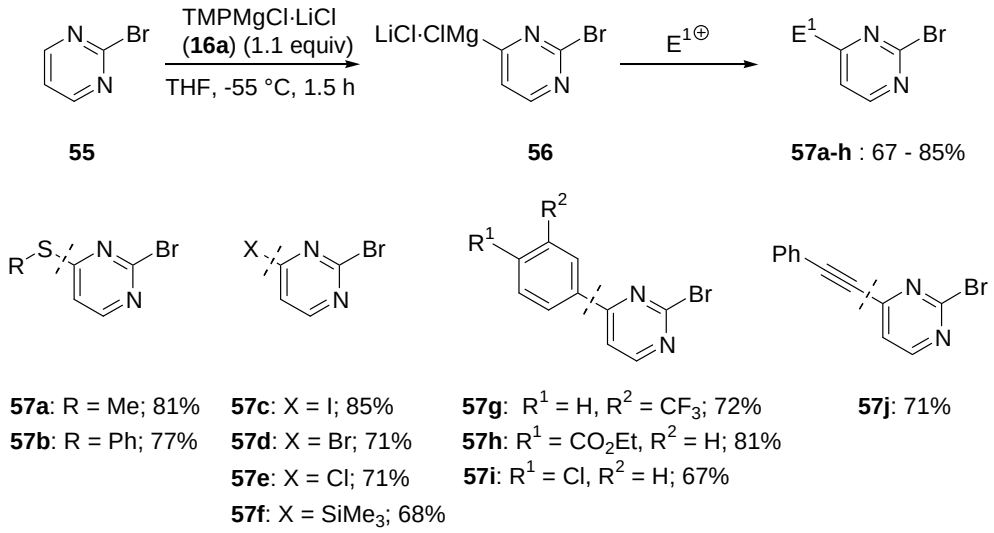


55 **57a-j** **58a-h** **59a-f**

Scheme 26: Successive regio- and chemoselective magnesiations of 2-bromopyrimidine (**55**) using TMPMgCl·LiCl (**16a**).

Thus, the treatment of 2-bromopyrimidine (**55**) with TMPMgCl·LiCl (**16a**; 1.1 equiv, –55 °C, 1.5 h) leads to the 4-magnesiated pyrimidine (**56**) which can be trapped by various electrophiles such as $MeSO_2SMe$, $PhSO_2SPh$, I_2, $BrCCl_2CCl_2Br$, $FCCl_2CClF_2$ and TMSCN leading to the expected products of type **57a-f** in 68 - 85% (Scheme 27). The formation of a

new carbon-carbon bond is readily performed by a Negishi [62] cross-coupling or a Sonogashira[63] reaction of *in situ* generated 2-bromo-4-iodopyrimidine (**57c**) providing the 4-substituted heterocycles **57g-j** in 67 - 81% (Scheme 27).



Scheme 27: Magnesiation of 2-bromopyrimidine (**55**) at position 4 using TMPMgCl·LiCl (**16a**; 1.1 equiv) and trapping with electrophiles.

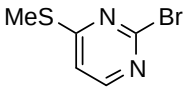
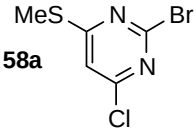
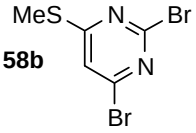
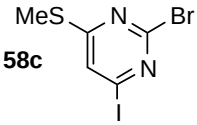
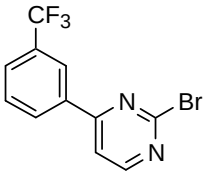
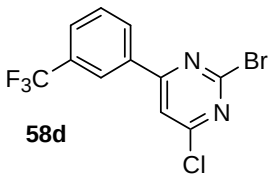
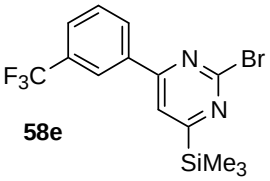
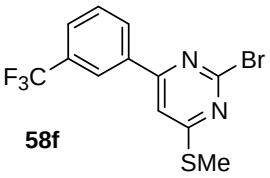
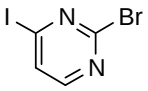
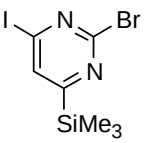
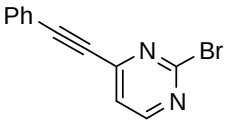
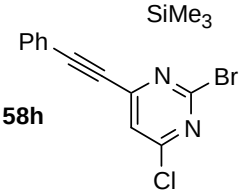
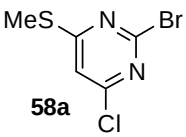
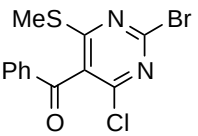
A subsequent magnesiation is readily achieved at position 6 by the addition of TMPMgCl·LiCl (**16a**) to various 4-substituted 2-bromopyrimidines. Thus, the 2-bromo-4-(methylthio)pyrimidine[64] **57a** is converted within 5 min at 20 °C to the 6-magnesiated species which is chlorinated by reaction with FCl_2CCF_2Cl leading to the chloropyrimidine **58a** in 76% yield (entry 1 of Table 1). Reaction with $BrCl_2CCCl_2Br$ furnishes the bromo-pyrimidine **58b** in 81% yield (entry 2). An iodolysis using I_2 leads to the 2-bromo-4-iodopyrimidine derivative **58c** in 78% yield (entry 3). Similarly, the 4-arylated-2-bromopyrimidine **57g** is magnesiated quantitatively with TMPMgCl·LiCl (**16a**; 1.1 equiv, –40 °C, 45 min) and reacted with FCl_2CCF_2Cl, TMSCN or $MeSO_2SMe$ affording the expected 4,6-disubstituted 2-bromopyrimidines **58d-f** in 72 - 91% yield (entries 4-6).

[62] (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E.; Kobayashi, M. *J. Org. Chem.* **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (d) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

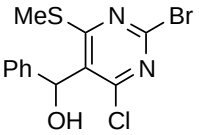
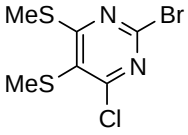
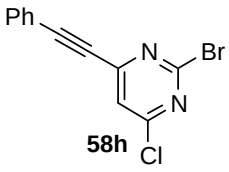
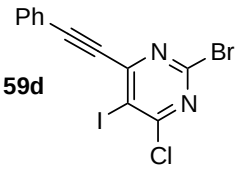
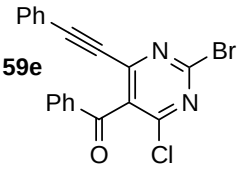
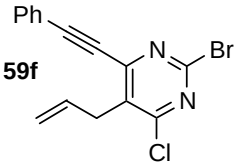
[63] (a) Benderitter, P.; de Araujo, J. X. Jr.; Schmitt, M.; Bourguignon, J.-J. *Tetrahedron* **2007**, *63*, 12465. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. (d) Sonogashira, K. *Comprehensive Organic Synthesis* Pergamon Press: New York, **1991**, Vol. 3.

[64] The thiomethyl group can serve as a leaving group in cross-coupling reactions: Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

Table 1: Products obtained by regioselective magnesiation of pyrimidines of type **57** and **58** with TMPMgCl·LiCl (**16a**) and quenching with electrophiles.

entry	substrate of type **57** and **58**	electrophile	product	yield, %[a]
1	 **57a**	FCl_2CCF_2Cl	 **58a**	76
2	**57a**	$(BrCl_2C)_2$	 **58b**	81
3	**57a**	I_2	 **58c**	78
4	 **57g**	FCl_2CCF_2Cl	 **58d**	91
5	**57g**	Me_3SiCN	 **58e**	72
6	**57g**	$MeSO_2SMe$	 **58f**	76
7	 **57c**	Me_3SiCN	 **58g**	93
8	 **57j**	FCl_2CCF_2Cl	 **58h**	84
9	 **58a**	PhCOCl[b]	 **59a**	81

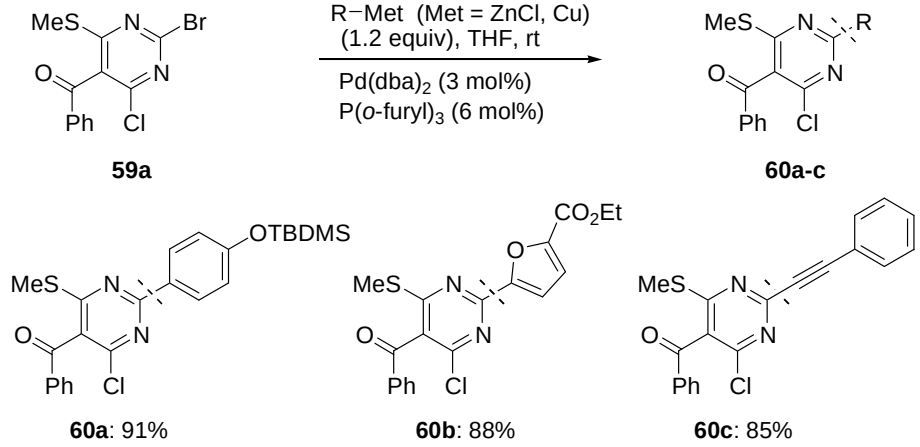
a Isolated, analytically pure product. *b* Transmetalation with 1.1 equiv of CuCN·2LiCl.

entry	substrate of type **57** and **58**	electrophile	product	yield, %[a]
10	**58a**	PhCHO	**59b** 	75
11	**58a**	$MeSO_2SMe$	**59c** 	92
12	 **58h**	I_2	**59d** 	71
13	**58h**	PhCOCl[b]	**59e** 	69
14	**58h**	allyl bromide[c]	**59f** 	67

a Isolated, analytically pure product. *b* Transmetalation with 1.1 equiv of CuCN·2LiCl. *c* Catalyzed with 5 mol% of CuCN·2LiCl.

Other 2-bromopyrimidines substituted at position 4 with an alkynyl group or an iodine (**57c**, **57j**) are magnesiated under mild conditions. Quenching with typical electrophiles furnishes the polyfunctional pyrimidines **58g** and **58h** in 84% and 93% yields (entries 7 and 8). The last position (position 5) can be magnesiated as well between –5 °C and 20 °C within 20 - 30 min with TMPMgCl·LiCl (**16a**; 1.1 equiv). Trapping with iodine, PhCOCl (after transmetalation with CuCN·2LiCl[65] (1.1 equiv)), allyl bromide, PhCHO or $MeSO_2SMe$ provides the fully substituted pyrimidines **59a-f** in 67 - 92% yields (entries 9-14). The bromine attached at position 2 can be readily substituted using a Negishi[62] or a Sonogashira[63] reaction giving the 2-substituted pyrimidines **60a-c** in 85 - 91% yields (Scheme 28).

[65] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

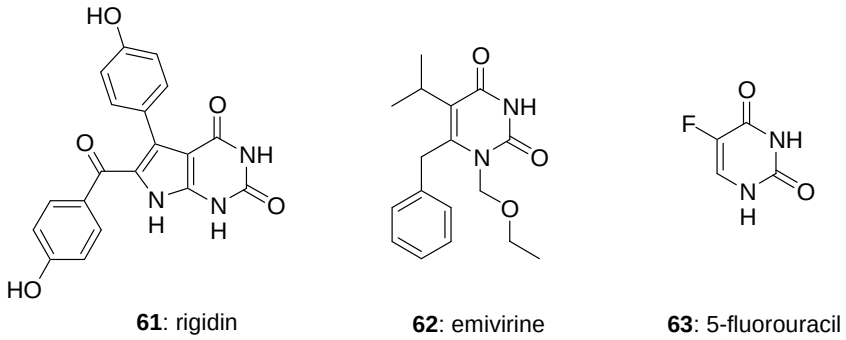


Scheme 28: Negishi and Sonogashira cross-coupling reactions at position 2 leading to fully substituted pyrimidines **60a-c**.

1.3 Total functionalization of protected uracils and thiouracils using successive regio- and chemoselective magnesiations

1.3.1 Functionalization of protected uracils and thiouracils using lithium bases

Uracil derivatives are present in many natural products, for instance the marine alkaloid rigidin[66] (**61**), and represent a priviledge structure in drug discovery[51] (Scheme 29).



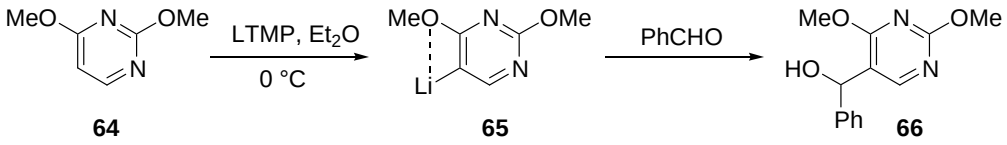
Scheme 29: Biologically relevant uracil derivatives.

The functionalization of these heterocycles is therefore of great interest for the preparation of bio-relevant molecules, especially with antiviral properties.[58a] For example, emivirine[67] (**62**),

[66] 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.

a non-nucleoside reverse transcriptase inhibitors (NNRTIs), targets the retrovirus HIV-1. 5-Fluorouracil[68] (**63**), an anti-cancer agent has been in use for about more than 40 years.

Wada[69] and *Quéguiner*[70] have investigated the lithiation of 2,4-dimethoxypyrimidine (**64**) using LTMP in Et_2O at 0 °C and observed a regioselective lithiation at the position 5 furnishing the lithium species **65.** The chelating effect of the methoxy- group in the intermediate species **65** led to the thermodynamically most stable species[71] (Scheme 30). The main limitation with the use of lithium reagents is their very high reactivity due to the ionic character of the C-Li bond. For this reason, the choice of potential electrophiles is strongly limited and the 5-functionalized uracil derivatives were obtained in low to moderate yields (4 - 65%). The lithiation of the pyrimidine **64** using LDA as metalating agent led to very low yields and with recovery of the starting materials.[70]



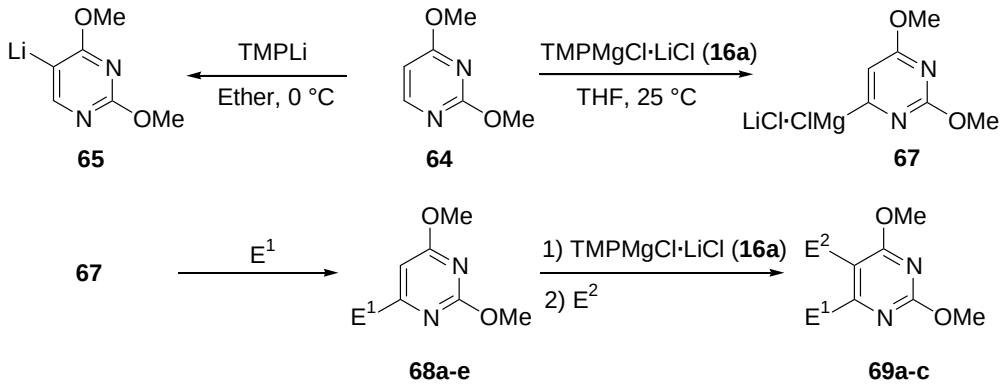
Scheme 30: *Ortho*-directed lithiation of 2,4-dimethoxypyrimidine (**64**) using LTMP.

1.3.2 Successive regio- and chemoselective functionalizations of protected uracils and thiouracils using Mg/Li bases

Whereas the lithiation of dimethoxyuracil (**64**) with LTMP (Et_2O, 0 °C, 10 min) produces exclusively the 5-lithiated pyrimidine **65**, we have found that the treatment of **64** with TMPMgCl·LiCl (**16a**; 1.1 equiv, THF, 25 °C, 15 min) furnishes exclusively the 6-magnesiated uracil derivative **67** (Scheme 31). No trace of 5-magnesiated uracil could be detected after 1 h at 25 °C. Thus, the quenching of **67** with various electrophiles such as I_2, Me_3SiCN, 4-ethyl iodobenzoate[62] (after transmetalation with $ZnCl_2$ followed by the addition of $Pd(dba)_2$ and P(*o*-furyl)$_3$), *t*-BuCOCl (after transmetalation with CuCN·2LiCl)[65] and ethyl cyanoformate provides a range of polyfunctional uracil derivatives (**68a-e**) in 70 - 75% yields

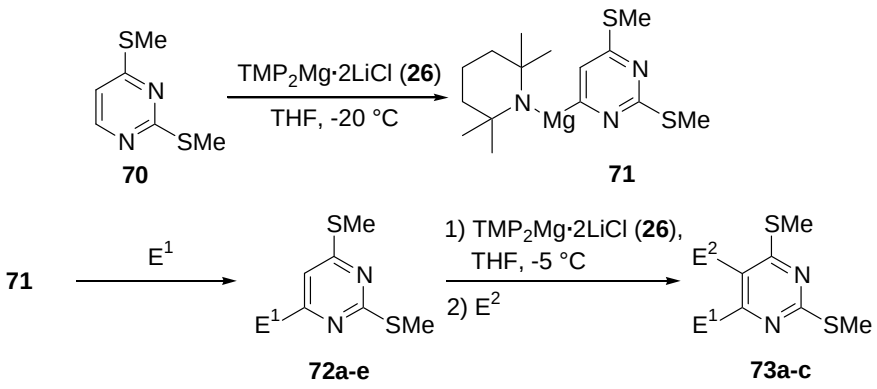
[67] (a) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem*. **1995**, *38*, 2860. (b) Pedersen, O. S.; Pedersen, E. B. *Antiviral Chem. Chemother*. **1999**, *10*, 2860.
[68] Cai, T. B.; Tang, X.; Nagorski, J.; Brauschweiger, P. G.; Wang, P. G. *Bioorg. & Med. Chem.* **2003**, *11*, 4971.
[69] Wada, A.; Yamamoto, J.; Kanatomo, S. *Heterocycles* **1987**, *26*, 585.
[70] Plé, N. ; Turck, A. ; Fiquet, E. ; Quéguiner, G. *J. Heterocyclic Chem.* **1991**, *28*, 283.
[71] Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1994**, *3*, 2149.

(Scheme 31 and Table 2, entries 1-5). Subsequent magnesiation of selected uracils **68** allows a further functionalization in position 5 leading to the 5,6-disubstituted uracils **69a** and **69b** in 81% and 74% (entries 6 and 7).



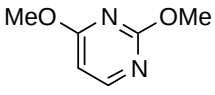
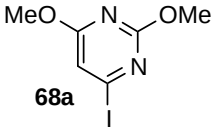
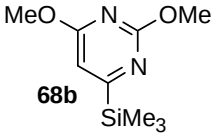
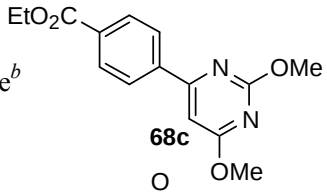
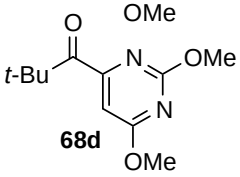
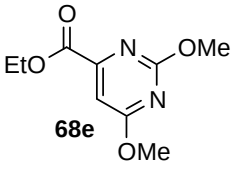
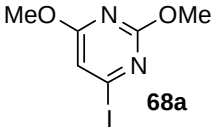
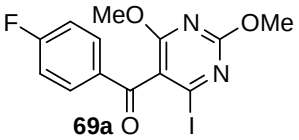
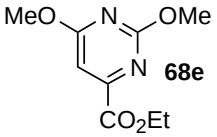
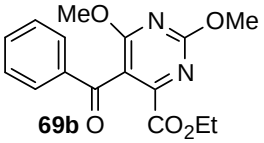
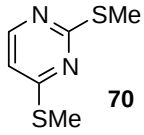
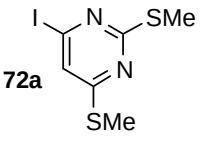
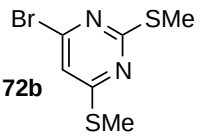
Scheme 31: Successive regio- and chemoselective magnesiations of 2,4-dimethoxypyrimidine (**64**) at the positions 6 and 5 using TMPMgCl·LiCl (**16a**; 1.1 equiv) and trapping with electrophiles.

We have extended our approach to the thiouracil derivatives, and have treated 2,4 bis(methylthio)pyrimidine (**70**) with $TMP_2Mg{\cdot}2LiCl$ (**26**; 1.1 equiv, THF, –20 °C, 1 h) which provides the 6-magnesiated pyrimidine derivative **71** (Scheme 32).

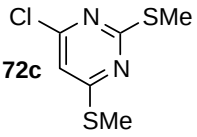
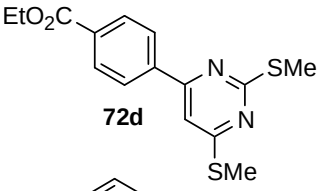
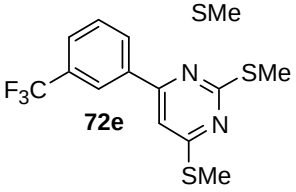
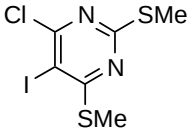
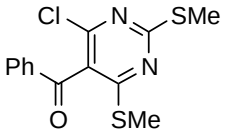
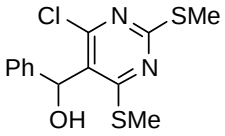


Scheme 32: Successive regio- and chemoselective magnesiations of bis(methylthio)pyrimidine (**70**) at the positions 6 and 5 with $TMP_2Mg{\cdot}2LiCl$ (**26**; 1.1 equiv) and trapping with electrophiles.

Table 2: Products obtained by regioselective magnesiation of pyrimidines of type **64** and **70** with TMPMgCl·LiCl (**16a**) and with $TMP_2Mg·2LiCl$ (**26**) quenching with electrophiles.

entry	substrate	electrophile	product	yield, %[a]
1	 **64**	I_2	 **68a**	74
2	**64**	Me_3SiCN	 **68b**	70
3	**64**	ethyl 4-iodobenzoate[b]	 **68c**	75
4	**64**	*t*-BuCOCl[c]	 **68d**	72
5	**64**	$NCCO_2Et$	 **68e**	70
6	 **68a**	4-fluorobenzoyl chloride[c]	 **69a**	81
7	 **68e**	PhCOCl[c]	 **69b**	74
8	 **70**	I_2	 **72a**	76
9	**70**	$(BrCCl_2)_2$	 **72b**	81

a Isolated, analytically pure product. *b* The Grignard reagent was transmetalated with 1.1 or 2.2 equiv of $ZnCl_2$ in THF and then undergoes a Negishi cross-coupling using $Pd(dba)_2$ and P(*o*-furyl)$_3$. *c* Transmetalation with 1.1 equiv of CuCN·2LiCl.

entry	substrate	electrophile	product	yield, %[a]
10	**70**	ClF_2CCCl_2F	 **72c**	78
11	**70**	ethyl 4-iodobenzoate[b]	 **72d**	71
12	**70**	3-iodobenzotrifluoride[b]	 **72e**	80
13	**72c**	I_2	**73a** 	61
14	**72c**	PhCOCl[c]	**73b** 	65
15	**72c**	PhCHO	**73c** 	66

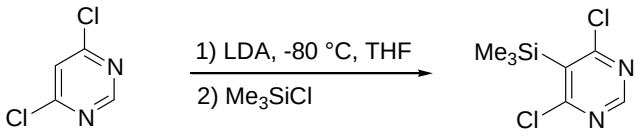
a Isolated, analytically pure product. *b* The Grignard reagent was transmetalated with 1.1 or 2.2 equiv of $ZnCl_2$ in THF and then undergoes a Negishi cross-coupling using $Pd(dba)_2$ and P(*o*-furyl)$_3$. *c* Transmetalation with 1.1 equiv of CuCN·2LiCl.

No trace of 5-magnesiated thiouracil could be detected. Thus, trapping of **71** with typical electrophiles furnishes the new 6-substituted thiouracils **72a-c** in 76 - 81% yields (Scheme 32 and Table 2, entries 8-10). The formation of a new carbon-carbon bond is also readily performed by a Negishi[62] cross-coupling providing the 6-arylpyrimidines **72d** and **72e** in 71 and 80% (Table 1, entries 11 and 12). A further metalation with TMP_2Mg·2LiCl (**26**, 1.1 equiv, THF, –5 °C, 45 min) can be performed at the position 5. Quenching with electrophiles such as I_2, PhCOCl (after transmetalation with CuCN·2LiCl (1.1 equiv))[65] or PhCHO provides the fully substituted pyrimidines **73a-c** in 61 - 66% yield (entries 13-15).

1.4 Functionalization of chloropyrimidine derivatives using successive regio- and chemoselective metalations.

1.4.1 Functionalizations of chloropyrimidine derivatives using lithium bases

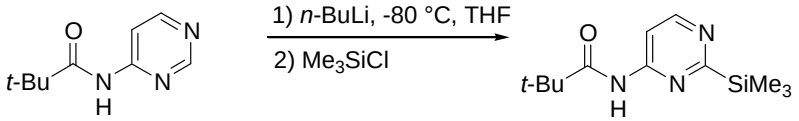
Chloropyrimidines are important heterocyclic scaffolds and their derivatives occupy a priviledge position among substances with pharmaceutical or agrochemical applications.[51] *Quéguiner* and *Radinov*[72] have reported the regioselective lithiation of polychloropyrimidines using classical lithium amide bases (Scheme 33). 4,6-Dichloropyrimidine (**74**) was metalated in THF at –80 °C for 30 min using LDA. The addition order is very important (substrates to metalating agents in order to secure thereby an excess of the latter in the reaction mixture) to avoid decomposition. Trapping with typical electrophiles furnished the new substituted pyrimidines **75** in moderate yields (44 - 66%).



74 **75a**: 44%

Scheme 33: Lithiation of 4,6-dichloropyrimidine (**74**) using LDA and trapping with Me_3SiCl.

The sole example of a pyrimidine deprotonation at the C2 position was reported by Kanamoto;[73] 4-(*tert*-butoxycarbonyl)amino-2-(trimethylsilyl)-pyrimidine (**76**) was obtained in 14% yield after deprotonation with *n*-BuLi and trapping with TMSCl (Scheme 34).



76: 14%

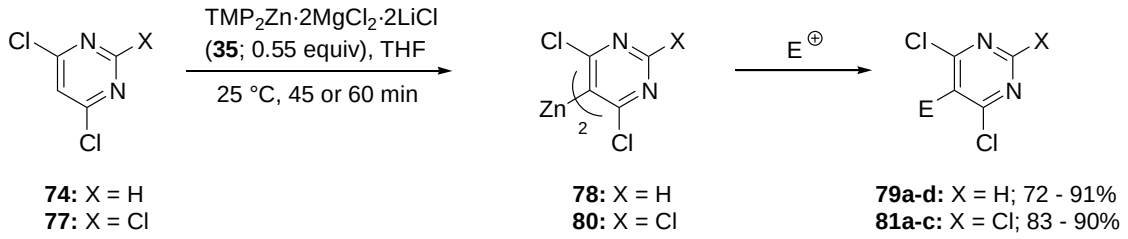
Scheme 34: Lithiation at position 2 using *n*-BuLi and trapping with Me_3SiCl.

[72] (a) Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1994**, *37*, 2149. (b) Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793.
[73] Wada, A.; Yamamoto, J.; Hamaoka, Y.; Ohki, K.; Nagai, S.; Kanatomo, S. *J. Heterocycl. Chem.* **1990**, *27*, 1831.

1.4.2 Regio- and chemoselective functionalizations of chloropyrimide derivatives using mixed Mg/Li bases

Recently, our group reported a new neutral mixed-metal base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[42] (**35**), which turned out to be very efficient for the metalation of aromatics and heteroaromatics bearing sensitive functionalities under mild conditions.

We first investigated the direct zincation of inexpensive starting materials such as 4,6-dichloropyrimidine (**74**) and 2,4,6-trichloropyrimidine (**77**) using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**; 0.55 equiv, 25 °C) (Scheme 35).

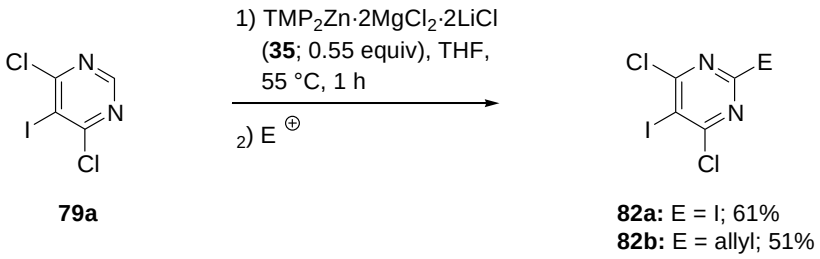


Scheme 35: Regio- and chemoselective metalation of 4,6-dichloropyrimidine (**74**) and 2,4,6-trichloropyrimidine (**77**) at the C5 position using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**; 0.55 equiv) and trapping with electrophiles.

Treatment of 4,6-dichloropyrimidine (**74**) with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**; 0.55 equiv) provides the corresponding zinc reagent (**78**) after 45 min at 25 °C. Trapping with I_2, PhCOCl (after transmetalation with CuCN·2LiCl),[65] 3-bromocyclohexene (after the addition of a catalytic amount of CuCN·2LiCl) and chloranil[74] affords the 5-functionalized pyrimidines **79a-d** in 72 - 91% (entries 1-4 of Table 3). Smooth deprotonation of 2,4,6-trichloropyrimidine (**77**) can also be carried out under mild conditions using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**; 0.55 equiv) and gives the zinc species (**80**) at 25 °C within 60 min. Quenching with typical electrophiles (I_2, allyl bromide (after the addition of a catalytic amount of CuCN·2LiCl) and propionyl chloride (after transmetalation with CuCN·2LiCl)[65]) furnishes 5-substituted pyrimidines **81a-c** in 83 - 90% yields (entries 5-7). A further metalation is also achieved at the position C2 by the addition of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**; 0.55 equiv) to 5-substituted pyrimidines (Scheme 36). Thus, 4,6-dichloro-5-iodopyrimidine (**79a**) was converted at 55 °C

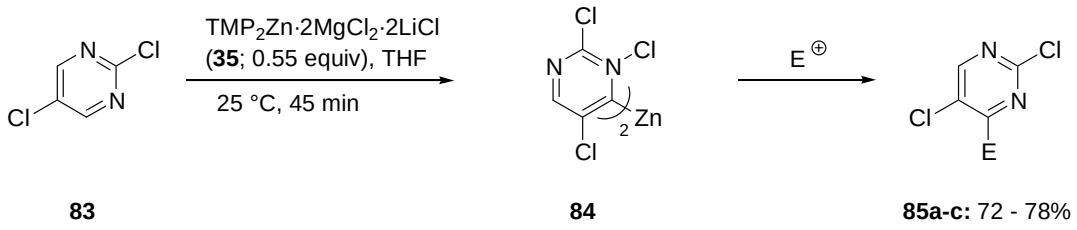
[74] (a) Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5010. (b) Iwanaga, H. U.S. Pat. Appl. US 20040062950, **2004**; *Chem Abstr*. **2004**, *140*, 312117.

within 1 h to the 2-zincated species and was iodinated by reaction with I_2 leading to the 2-iodopyrimidine **82a** in 61% yield (entry 8). Reaction with allyl bromide (after the addition of a catalytic amount of CuCN·2LiCl) furnishes the allyl derivative **82b** in 51% yield (entry 9) (Scheme 36).



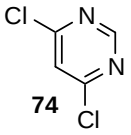
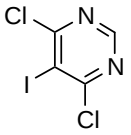
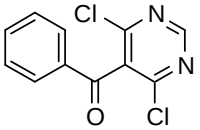
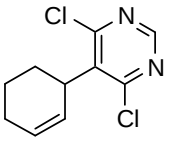
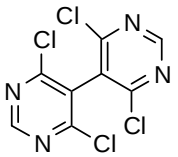
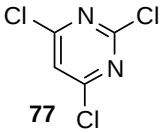
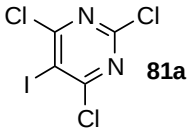
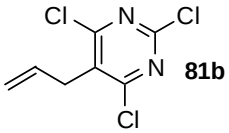
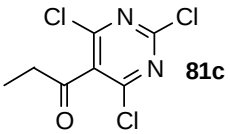
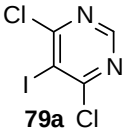
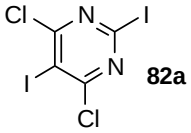
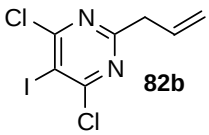
Scheme 36: Chemoselective metalation and trapping of 5-iodo-4,6-dichloropyrimidine (**79a**) at the C2 position using $TMP_2Zn·2MgCl_2·2LiCl$ (**35**; 0.55 equiv).

The metalation of 2,5-dichloropyrimidine (**83**) can also be easily performed. Thus, treatment of **83** with $TMP_2Zn·2MgCl_2·2LiCl$ (**35**; 0.55 equiv) provides the corresponding zinc reagent **84** after 45 min at 25 °C. Trapping with I_2 provides the iodopyrimidine **85a** in 72% (entry 10). The formation of a new C-C bond is readily achieved by the Negishi[62] cross-coupling giving the 4-aryled pyrimidines **85b** and **85c** in 78% and 73% (entries 11 and 12) (Scheme 37).

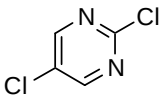
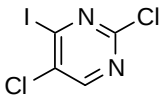
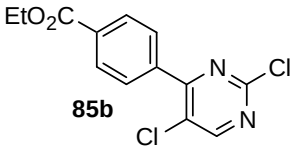
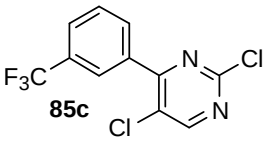


Scheme 37: Chemoselective metalation of 2,5-dichloropyrimidine (**83**) at the C4 position using $TMP_2Zn·2MgCl_2·2LiCl$ (**35**; 0.55 equiv) and trapping with electrophiles.

Table 3: Products obtained by regio- and chemoselective zincation of chloropyrimidines of type **74**, **77** and **83** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) and quenching with electrophiles.

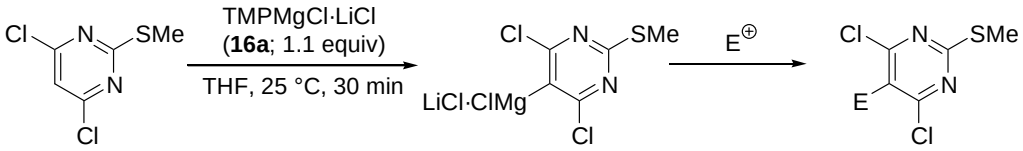
entry	substrate	electrophile	product	yield, %[a]
1	 **74**	I_2	 **79a**	91
2	**74**	PhCOCl[b]	 **79b**	86
3	**74**	bromocyclohexene[c]	 **79c**	72
4	**74**	chloranil	 **79d**	82
5	 **77**	I_2	 **81a**	83
6	**77**	allyl bromide[c]	 **81b**	90
7	**77**	EtCOCl[b]	 **81c**	86
8	 **79a**	I_2	 **82a**	61
9	**79a**	allyl bromide[c]	 **82b**	51

a Isolated, analytically pure product. *b* Transmetalation with 1.1 equiv of CuCN·2LiCl. *c* Catalyzed with 5 mol% of CuCN·2LiCl.

entry	substrate	electrophile	product	yield, %[a]
10	 **83**	I_2	 **85a**	72
11	**83**	ethyl 4-iodobenzoate[b]	 **85b**	78
12	**83**	3-iodobenzotrifluoride[b]	 **85c**	73

a Isolated, analytically pure product. *b* Negishi cross-coupling using $Pd(dba)_2$ (3 mol%) and P(*o*-furyl)$_3$ (6 mol%) .

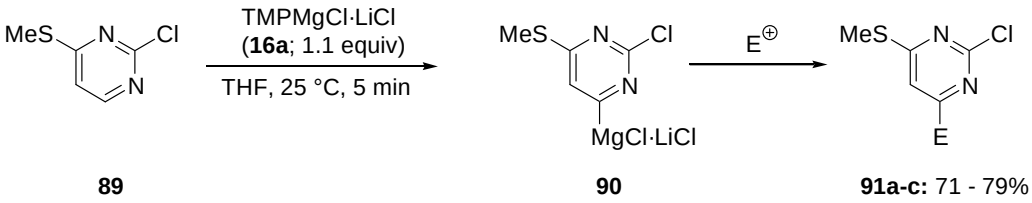
We have then extended this approach to the functionalization of other polychloropyrimidines and have investigated the metalation of 4,6-dichloro-2-(methylthio)pyrimidine (**86**). Thus, the treatment of (**86**) with TMPMgCl·LiCl (**16a**; 1.1 equiv, 25 °C, 30 min) leads to the 5-magnesiated pyrimidine (**87**) (Scheme 38). Trapping with various electrophiles such as I_2, PhCHO, $NCCO_2Et$, CH_3I, Me_3SiCN or iodomethyl pivalate leads to the 5-substituted pyrimidines **88a-f** in 76 - 92% yields (entries 1-6 of Table 4). Acylations can also be readily performed after transmetalation with CuCN·2LiCl.[65] Quenching of the metalated species with 4-fluorobenzoyl chloride, 3,3-dimethylbutanoyl chloride, PhCOCl and furan-2-carbonyl chloride furnishes 5-ketopyrimidine derivatives **88g-j** in 84 - 93% yields (entries 7-10).



86 **87** **88a-j:** 76 - 93%

Scheme 38: Chemoselective magnesiation of 4,6-dichloro-2-(methylthio)pyrimidine (**86**) at the C5 position using TMPMgCl·LiCl (**16a**; 1.1 equiv) and trapping with electrophiles.

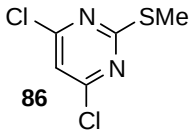
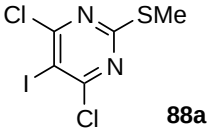
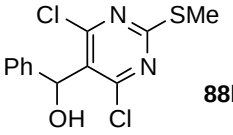
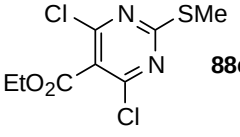
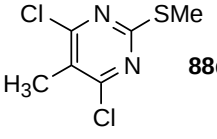
The metalation of 2-chloro-4-(methylthio)pyrimidine (**89**) can also be selectively achieved at the position 6 with TMPMgCl·LiCl (**16a**; 1.1 equiv, 25 °C, 5 min) providing the magnesium reagent **90** (Scheme 39).



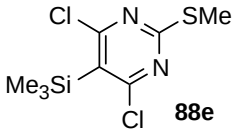
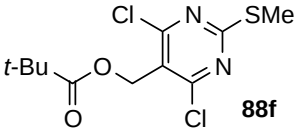
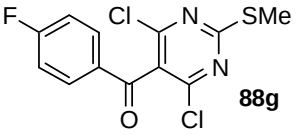
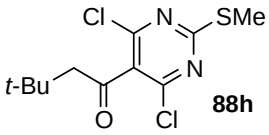
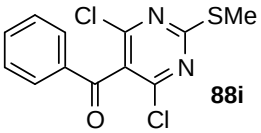
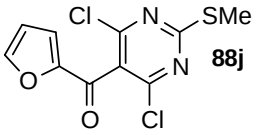
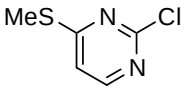
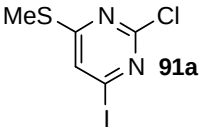
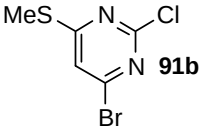
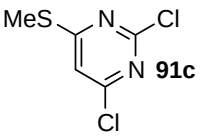
Scheme 39: Chemoselective magnesiation of 2-chloro-4-(methylthio)pyrimidine (**89**) at the C6 position using TMPMgCl·LiCl (**16a**; 1.1 equiv) and trapping with electrophiles.

Iodination by reaction with I_2 leads to the iodopyrimidine derivative **91a** in 71% yield (entry 11). Reaction with $(BrCCl_2)_2$ furnishes the bromopyrimidine **91b** in 79% yield (entry 12). A chlorination using $F_2ClCCCl_2F$ gives the chloropyrimidine **91c** in 72% yield (entry 13).

Table 4: Products obtained by the magnesiation of 4,6-dichloro-2-(methylthio)pyrimidine (**86**) and 2-chloro-4-(methylthio)pyrimidine (**89**) with TMPMgCl·LiCl (**16a**) and reactions with electrophiles.

entry	substrate	electrophile	product	yield, %[a]
1	 **86**	I_2	 **88a**	90
2	**86**	PhCHO	 **88b**	90
3	**86**	$NCCO_2Et$	 **88c**	86
4	**86**	CH_3I	 **88d**	92

a Isolated, analytically pure product.

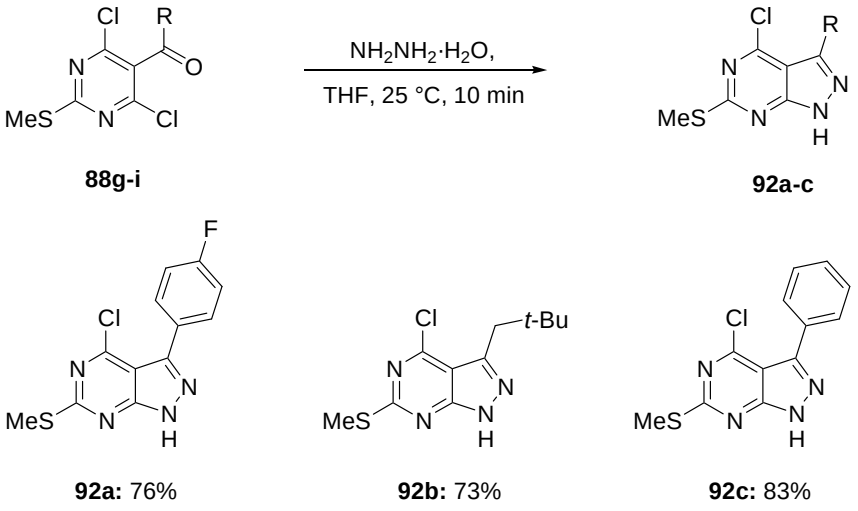
entry	substrate	electrophile	product	yield, %[a]
5	**86**	Me_3SiCN	 **88e**	79
6	**86**	iodomethyl pivalate	 **88f**	76
7	**86**	4-fluorobenzoyl chloride[b]	 **88g**	93
8	**86**	3,3-dimethylbutyryl chloride[b]	 **88h**	84
9	**86**	$PhCOCl$[b]	 **88i**	90
10	**86**	furan-2-carbonyl chloride[b]	 **88j**	86
11	 **89**	I_2	 **91a**	71
12	**89**	$(BrCCl_2)_2$	 **91b**	79
13	**89**	FCl_2CCClF_2	 **91c**	72

a Isolated, analytically pure product. *b* Transmetalation with 1.1 equiv of CuCN·2LiCl.

1.5 Application to the synthesis of biologically active compounds

1.5.1 Preparation of pyrazolopyrimidines. Synthesis of the antiviral p38 kinase inhibitor (92d)

This method is of great utility for the preparation of pharmaceutically active heterocycles such as pyrazolopyrimidines.[75] The treatment of 5-ketopyrimidine derivatives **88g-i** with $NH_2NH_2 \cdot H_2O$ at 25 °C allows the formation of the pyrazolopyrimidines **92a-c** in 73 - 83% yields (Scheme 40).

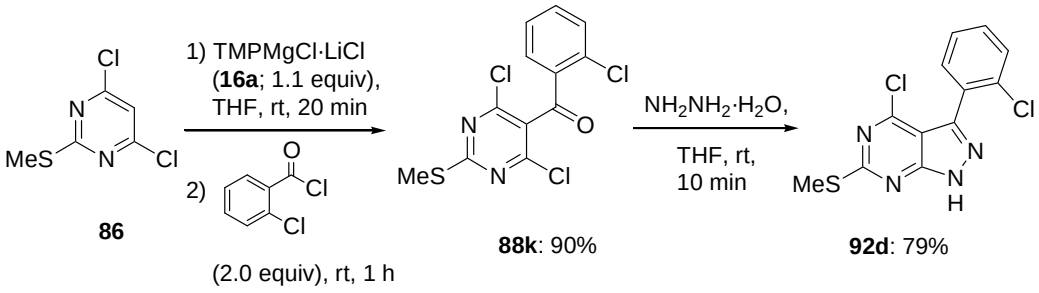


Scheme 40: Synthesis of the pyrazolopyrimidines **92a-c**.

As an application, we have prepared a p38 kinase inhibitor (useful as antiviral agent), recently patented by Roche,[76] starting from 4,6-dichloro-2-(methylthio)pyrimidine (**86**). The magnesiation of **86** with TMPMgCl·LiCl (**16a**) is complete within 30 min at 25 °C. Transmetalation with CuCN·2LiCl[65] (1.1 equiv) and acylation with 2-chlorobenzoyl chloride (2 equiv, 25 °C, 1 h) provides the tetrasubstituted pyrimidine **88k** in 90% yield. Subsequent treatment with $NH_2NH_2 \cdot H_2O$ furnished the p38 kinase inhibitor **92d** in 79% yield (Scheme 41).

[75] (a) Smith, C. J.; Iglesias-Sigüenza, F. J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 2758. (b) Gomtsyan, A.; Didomenico, S.; Lee, C.; Stewart, A. O.; Bhagwat, S. S.; Kowaluk, E. A.; Jarvis, M. F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4165. (c) Revesz, L.; Blum, E.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Neumann, U.; Rucklin, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 262.

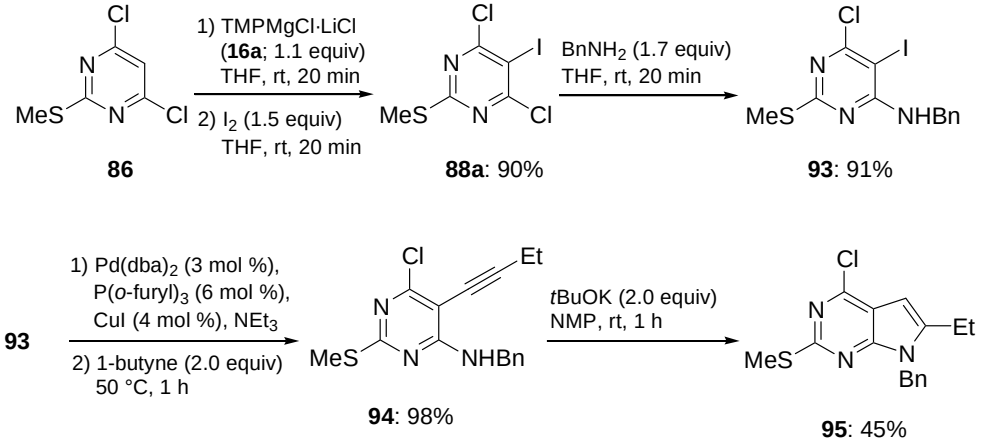
[76] (a) Dewdney, N. J.; Gabriel, T.; McCaleb, K. L. WO 2007023115, **2007**. (b) Arora, N.; Billedeau, R. J.; Dewdney, N. J.; Gabriel, T.; Goldstein, D. M.; O'Yang, C.; Soth, M.; Trejo-Martin, T. A. WO 2007023105, **2007**. (c) Arora, N.; Billedeau, R. J.; Dewdney, N. J.; Gabriel, T.; Goldstein, D. M.; O'Yang, C.; Soth, M. US 2005197340, **2005**.



Scheme 41: Application to the synthesis of a p38 kinase inhibitor (**92d**).

1.5.2 Synthesis of the anti-inflammatory pyrrolopyrimidine sPLA2 (95)

Similarly, we performed the synthesis of an sPLA2 inhibitor **95** having anti-inflammatory properties reported by Eli Lilly.[77] Iodination of the dichloropyrimidine **86** gives the iodopyrimidine derivative **88a** in 90% yield. The substitution of the chlorine at position 6 with benzylamine[78] (1.7 equiv, THF, 25 °C, 20 min) leads to the aminopyrimidine **93** in 91% yield. The Sonogashira[63] cross-coupling of the pyrimidine **93** with 1-butyne affords the 5-alkynyl-6-aminopyrimidine **94** in 98% yield. Smooth cyclization with KO*t*Bu[79] (2 equiv, NMP, 25 °C, 1 h) finally provides the sPLA2 inhibitor **95** in 45% yield (Scheme 42).

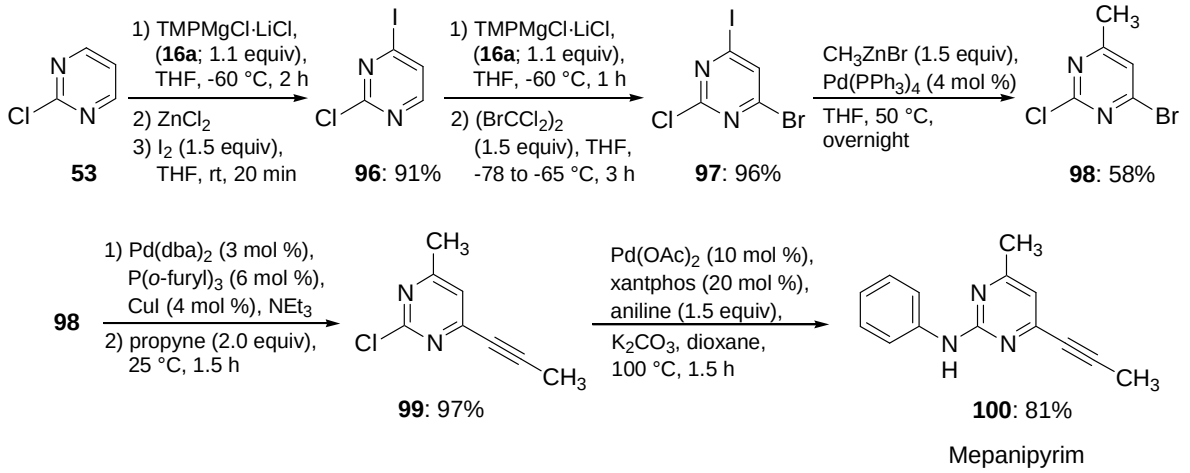


Scheme 42: Synthesis of an sPLA2 inhibitor (**95**) by chemoselective magnesiation.

[77] Hutchison, D. R.; Martinelli, M. J.; Wilson, T. M. WO 2000000201, **2000**.
[78] Baindur, N.; Chadha, N.; Player, M. R. *J. Comb. Chem.* **2003**, *5*, 653.
[79] (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488. (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.

1.5.3 Synthesis of the fungicide Mepanipyrim (100)

To demonstrate the robustness of our metalation method, we also performed the synthesis of fungicide Mepanipyrim[80] (**100**) (Scheme 43).



Scheme 43: Synthesis of the fungicide Mepanipyrim (**100**).

Treatment of commercially available 2-chloropyrimidine (**53**) with TMPMgCl·LiCl (**16a**; 1.1 equiv, –60 °C, 2 h) leads after transmetalation with $ZnCl_2$ and quenching with I_2 to 4-iodopyrimidine (**96**) in 91% yield. A subsequent magnesiation of **96** at the position 6 can be readily achieved using TMPMgCl·LiCl (**16a**; 1.1 equiv, –60 °C, 1 h) and provides after trapping with $(BrCCl_2)_2$ 2-chloro-4-bromo-6-iodopyrimidine (**97**) in 96%. The Negishi[62] cross-coupling furnishes the 4-methylpyrimidine derivative **98** in 58% yield. The Sonogashira[63] reaction of **98** then affords the 6-alkynylpyrimidine **99** in 97%. Finally, a Buchwald-Hartwig Pd-catalyzed amination[81] allows the substitution of the chlorine at the position 2 to give Mepanipyrim (**100**) in 81% yield.

[80] (a) Nishide, H.; Nishimura, S.; Mitani, S.; Minamida, K.; Kanamori, F.; Ogawa, M.; Kanbayashi, S.; Tanimura, T.; Higuchi, K.; Kominami, H.; Okomoto, T.; Nishimura, A. PCT Int. Appl. WO 2005041663, **2005**. (b) Nagata, T.; Masuda, K.; Maeno, S.; Miura, I. *Pest Manag. Sci.* **2004**, *60*, 399. (c) Nakamura, M.; Kono, Y.; Takatsuki, A. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 139. (d) Ito, S.; Masuda, K.; Kusano, S.; Nagata, T.; Kojima, Y.; Sawai, N.; Maeno, S. Eur. Pat. Appl. EP 224339, **1987**.

[81] (a) Garnier, E.; Audoux, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Lebret, B.; Guillaumet, G. *J. Org. Chem.* **2004**, *69*, 7809. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *67*, 805. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

2. Preparation of a New Active Selective Base for the Functionalization of Sensitive Aromatics and Heteroaromatics

2.1. Introduction

Directed metalation of aromatic and heterocyclic compounds is an important method for the functionalization of these scaffolds. Lithium bases have been extensively used for performing the *ortho*-metalation of various unsaturated systems.[22] The use of magnesium bases, pioneered by Eaton,[82] has found a renewed interest.[83] Recently, lithium magnesiates[24b,84,85] have found useful synthetic applications. Mixed Mg/Li-bases of type $R_2NMgCl \cdot LiCl$ such as 2,2,6,6-tetramethylpiperidyl magnesium chloride - lithium chloride (TMPMgCl·LiCl; Turbo-Hauser base) proved to be an especially effective metalating agent, compatible with functional groups such as an ester, a nitrile or an aryl ketone.[24,25,26] However, more sensitive functionalities such as an aldehyde or a nitro group are not tolerated. Also, sensitive heterocycles may undergo fragmentation.[39] Therefore, a range of zinc amides have been reported which provide after metalation organozinc reagents compatible with most functionalities. In a pioneer work, lithium di-*tert*-butyl-(2,2,6,6-tetra-methylpiperidino)zincate (*t*-Bu_2Zn(TMP)Li) was reported by *Kondo* to be an excellent base for the zincation of various aromatics.[40] However, the use of highly reactive zincates or related ate-bases[41] is sometimes not compatible with sensitive functions such as an aldehyde or a nitro group.

[82] (a) Eaton, P. E.; Martin, R. M. *J. Org. Chem.* **1988**, *53*, 2728. (b) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11370. (d) Zhang, M.-X.; Eaton, P. E. *Angew. Chem. Int. Ed.* **2002**, *41*, 2169.

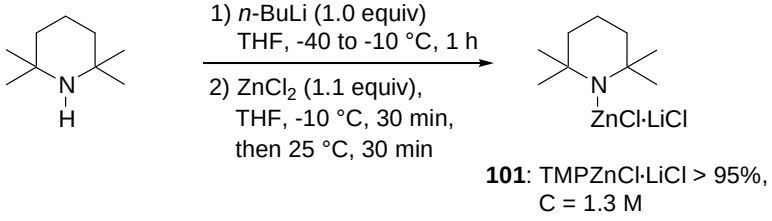
[83] (a) Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E.; Sherrington, D. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 68. (b) Andrikopolous, P. C.; Armstrong, D. R.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T.; Talmard, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 3459. (c) Kondo, Y.; Akihiro, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331. (d) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442. (e) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190. (f) Eaton, P. E.; Zhang, M.-X.; Komiya, N.; Yang, C.-G.; Steele, I.; Gilardi, R. *Synlett* **2003**, 1275.

[84] (a) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2481. (b) Farkas, J.; Stoudt, S. J.; Hannawalt, E. M.; Pajeski, A. D.; Richey, H. G. *Organometallics* **2004**, *23*, 423. (c) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron Lett.* **2004**, *45*, 6697.

[85] (a) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (b) Mulvey, R. E. *Chem. Commun.* **2001**, 1049. (c) Westerhausen, M. *Dalton Trans.* **2006**, 4755. (e) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.

2.2. Preparation of the active selective base TMPZnCl·LiCl (101)

Recently, we have reported the preparation of a highly chemoselective base $TMP_2Zn·2MgCl_2·2LiCl$ (**35**) for the directed zincation of sensitive aromatics and heteroaromatics, with a great tolerance for functionalities such as aldehydes or nitro groups.[42] However, some electron-poor functionalized arenes and heteroarenes still give with this reagent, unsatisfactory results in terms of yields and reaction selectivity. Moreover, several activated aromatics or heteroaromatics like nitro derivatives or pyridazines require metalations below –50 °C, which is not convenient for the reaction upscaling.[42,86] Thus, we have explored the preparation of a more selective zinc base, which would allow chemoselective metalations at 25 °C, for the directed zincation of sensitive aryl and heteroaryl substrates. The treatment of 2,2,6,6-tetramethylpiperidine (TMPH) with *n*-BuLi (1.0 equiv, –40 to –10 °C, 1 h) followed by the addition of $ZnCl_2$ (1.1 equiv, –10 °C, 30 min) provides a ca. 1.3 M solution of TMPZnCl·LiCl (**101**) in THF, stable at room temperature (Scheme 44).[87] In contrast to $TMP_2Zn·2MgCl_2·2LiCl$ (**35**), this complex base showed a very good chemoselectivity for the zincation at 25 °C of various sensitive aromatics and heteroaromatics.

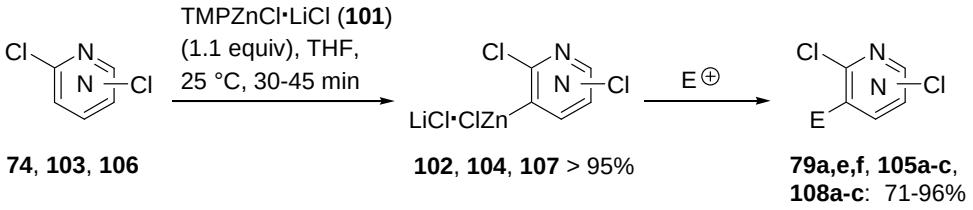


Scheme 44: Preparation of 2,2,6,6-tetramethylpiperidyl zinc chloride lithium chloride (TMPZnCl·LiCl) (**101**).

[86] Wunderlich, S. H.; Knochel, P. *Chem. Commun.* **2008**, *47*, 6387.
[87] In the absence of LiCl, the zinc base was much less soluble.

2.3. Regio- and chemoselective zincations of chlorodiazines and purines

Several sensitive heteroarenes such as pyrimidines,[72] pyridazines[86] and pyrazines[88] are cleanly zincated at 25 °C using the base TMPZnCl·LiCl (**101**; Scheme 45 and Table 5).

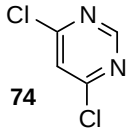
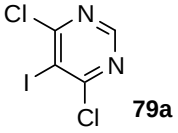
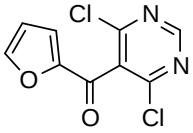
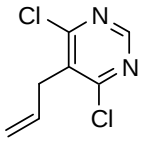
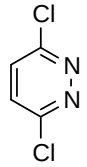
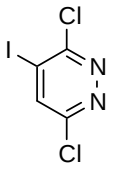
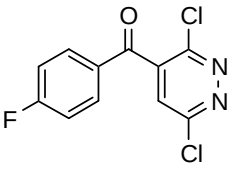
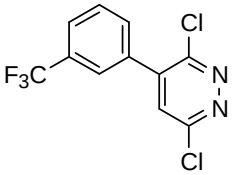
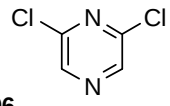
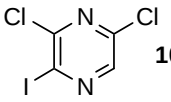
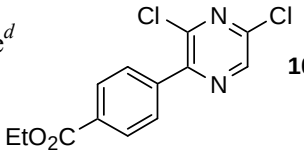
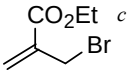
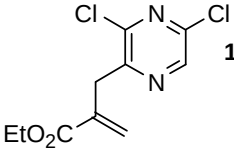


Scheme 45: Zincation of 4,6-dichloropyrimidine (**74**), 3,6-dichloropyridazine (**103**) and 2,6-dichloropyrazine (**106**) using TMPZnCl·LiCl (**101**; 1.1 equiv; 25 °C) and trapping with electrophiles.

Thus, the treatment of 4,6-dichloropyrimidine (**74**) with **101** converted it within 30 min at 25 °C to the 5-zincated species **102**. Trapping with I_2 furnishes the iodopyrimidine **79a** in 83% yield (entry 1 of Table 5). Reaction with furoyl chloride (after transmetalation with CuCN·2LiCl)[65] provides the 5-ketopyrimidine **79e** in 71% (entry 2). An allylation (after addition of CuCN·2LiCl) leads to the allylated derivative **79f** in 89% (entry 3). Zincations of other sensitive heteroaromatics can be readily achieved by the addition of TMPZnCl·LiCl (**101**). Deprotonation of 3,6-dichloropyridazine (**103**) with TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C, 45 min) gives the zincated species (**104**), which can be trapped with I_2, 4-fluorobenzoyl chloride (after transmetalation with CuCN·2LiCl)[65] or undergoes a Negishi[62] cross-coupling leading to the expected products **105a-c** in 83-96% yield (entries 4-6). Similarly, 2,6-dichloropyrazine (**106**) is zincated quantitatively with TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C, 30 min) and reacted with iodine or is subjected to the Negishi[62] cross-coupling or an allylation with ethyl 2-(bromomethyl)acrylate[89] (after addition of CuCN·2LiCl) affording the expected products **108a-c** in 72 - 90% yields (entries 7-9).

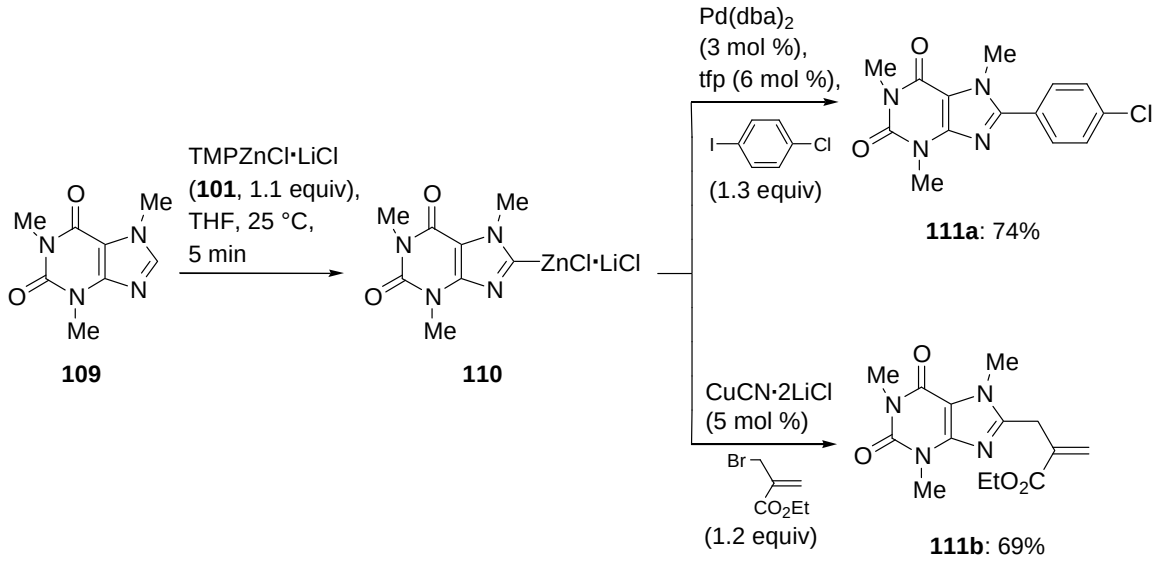
[88] Turck A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, *412*, 301.
[89] Villiéras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

Table 5: Products obtained by regio- and chemoselective zincation of diazines of type **74**, **103** and **106** with TMPZnCl·LiCl (**101**; 1.1 equiv; 25 °C) and quenching with electrophiles.

entry	substrate	electrophile	product	yield, %[a]
1	 **74**	I_2	 **79a**	83
2	**74**	furoyl chloride[b]	 **79e**	71
3	**74**	allyl bromide[c]	 **79f**	89
4	 **103**	I_2	 **105a**	84
5	**103**	4-fluorobenzoyl chloride[b]	 **105b**	96
6	**103**	3-iodobenzotrifluoride[d]	 **105c**	83
7	 **106**	I_2	 **108a**	90
8	**106**	ethyl 4-iodobenzoate[d]	 **108b**	87
9	**106**	 [c]	 **108c**	72

a Isolated, analytically pure product. *b* Transmetalation with 1.1 equiv of CuCN·2LiCl. *c* Catalyzed with 5 mol% of CuCN·2LiCl. *d* Negishi cross-coupling using $Pd(dba)_2$ and P(*o*-furyl)$_3$.

Other sensitive heterocycles such as purines[90] can be metalated as well under mild conditions (Scheme 46). Caffeine (**109**)[91] undergoes a smooth zincation using TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C, 5 min) furnishing the zinc species **110**. Negishi[62] cross-coupling provides the arylated caffeine **111a** in 74% yield. Trapping with ethyl 2-(bromomethyl)acrylate[89] (after addition of a catalytic amount of CuCN·2LiCl) leads to the purine derivative **111b** in 69% yield.

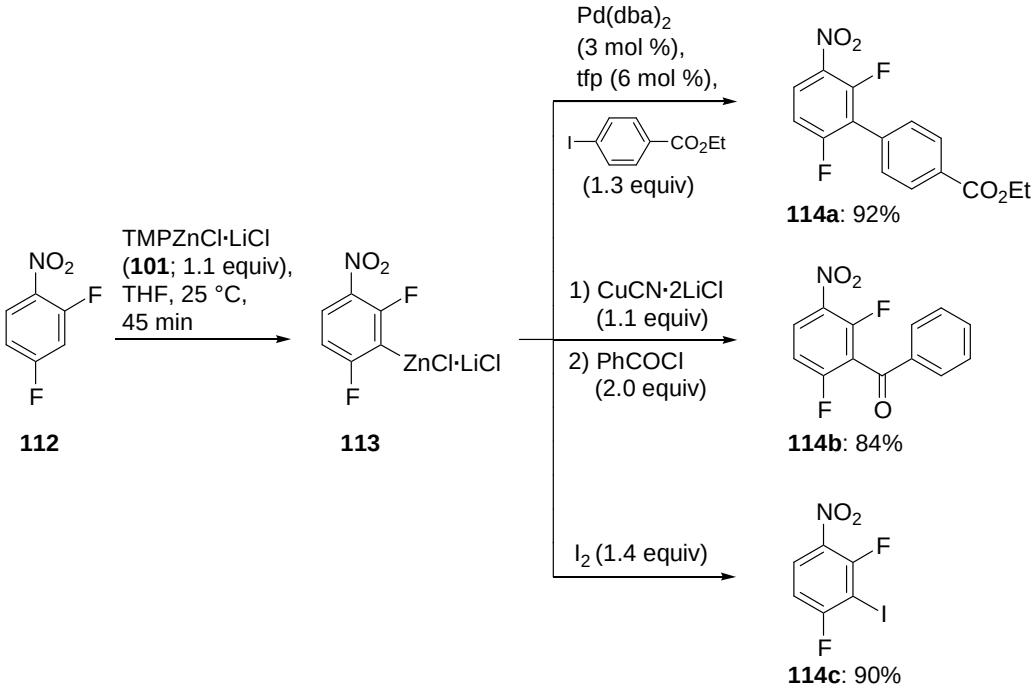


Scheme 46: Zincation of caffeine (**109**) using TMPZnCl·LiCl (**101**; 1.1 equiv; 25 °C) and trapping with electrophiles.

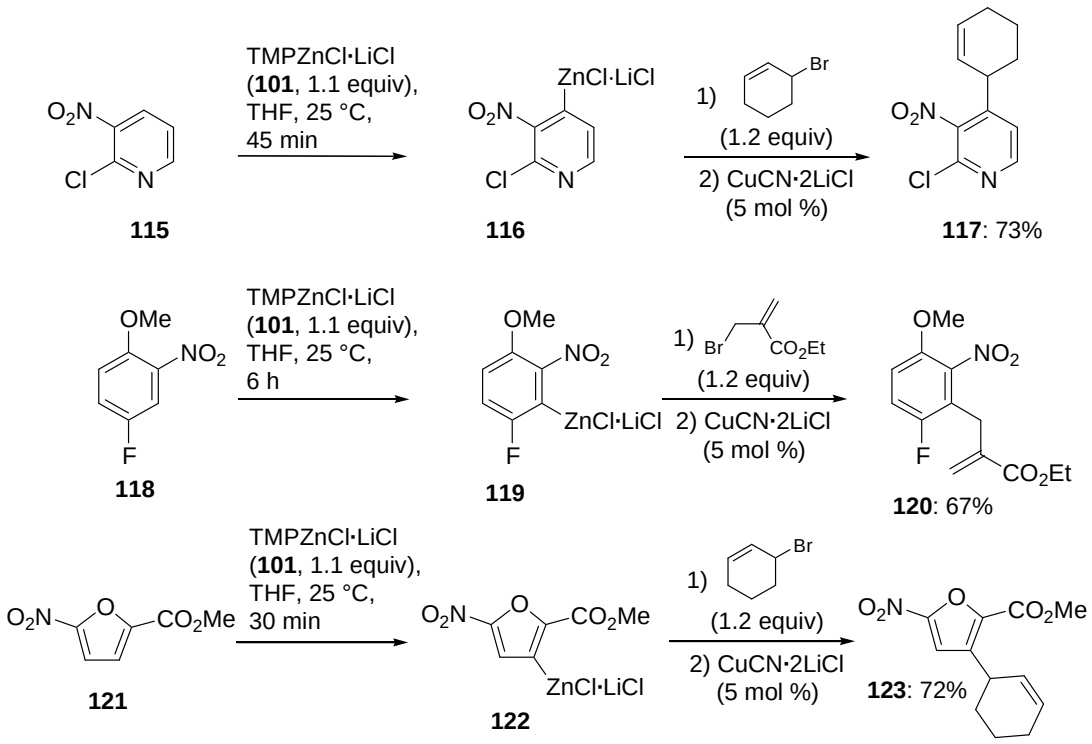
2.4. Regio- and chemoselective zincations of sensitive aromatics and heteroaromatics bearing aldehydes and nitro groups

A unique advantage of the zinc base **101** is that very sensitive functional groups such as a nitro group can be tolerated at 25 °C (Schemes 47 and 48).[45] Thus, 2,4-difluoronitrobenzene (**112**) was converted to the corresponding zinc reagent **113** by treatment with TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C, 45 min). The Negishi[62] cross-coupling can be readily performed to furnish the aryl derivative **114a** in 92% yield (Scheme 47). Trapping with benzoyl chloride (after transmetalation with CuCN·2LiCl)[65] provides the ketone **114b** in 84% yield. After quenching with I_2, the iodobenzene derivative **114c** was obtained in 90% yield.

[90] (a) Boudet, N; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2007**, *10*, 1715. (b) Tobrman, T.; Dvořák, D. *Org. Lett.* **2006**, *8*, 1291.
[91] Do, H.-Q.; Kashif-Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.



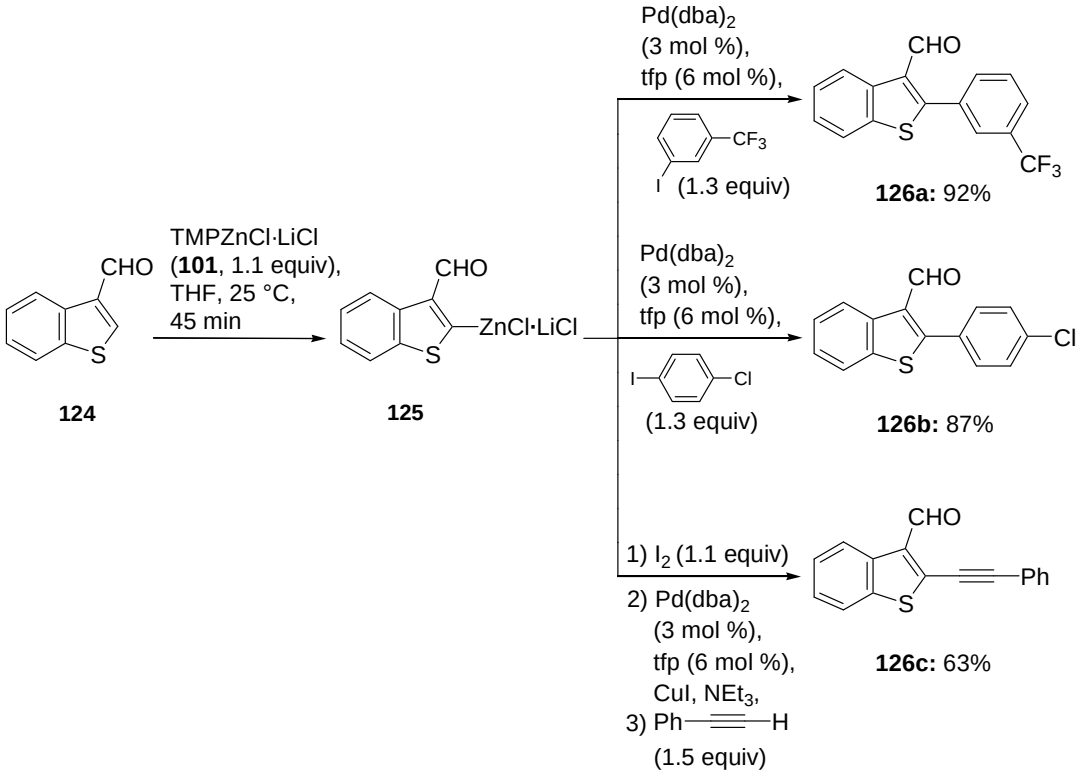
Scheme 47: Zincation of 2,4-difluoronitrobenzene (**112**) using TMPZnCl·LiCl (**101**; 1.1 equiv; 25 °C) and trapping with electrophiles.



Scheme 48: Zincation of 2-chloro-3-nitropyridine (**115**), 4-fluoro-1-methoxy-2-nitrobenzene (**118**) and methyl 5-nitrofuran-2-carboxylate (**121**) using TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C) and trapping with electrophiles.

Other sensitive electron-poor arenes and heteroarenes are metalated as well using the new base **101**. Accordingly, 2-chloro-3-nitropyridine (**115**) undergoes a smooth metalation with TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C, 45 min) furnishing the zinc species **116**. Trapping with 3-bromocyclohexene (after addition of CuCN·2LiCl) provides the pyridine **117** in 73% yield. Similarly, 4-fluoro-1-methoxy-2-nitrobenzene (**118**) was converted within 6 h at 25 °C to the corresponding zinc reagent **119**. Quenching with ethyl 2-(bromomethyl)acrylate[89] (after addition of CuCN·2LiCl) leads to the allyled derivative **120** in 67% yield. Zincation of methyl 5-nitrofuran-2-carboxylate (**121**) can also be readily carried out using **101** (1.1 equiv) and furnishes the zinc species **122** in 30 min at 25 °C. Allylation with 3-bromocyclohexene (after addition of CuCN·2LiCl) gives the furan **123** in 72% yield (Scheme 48).

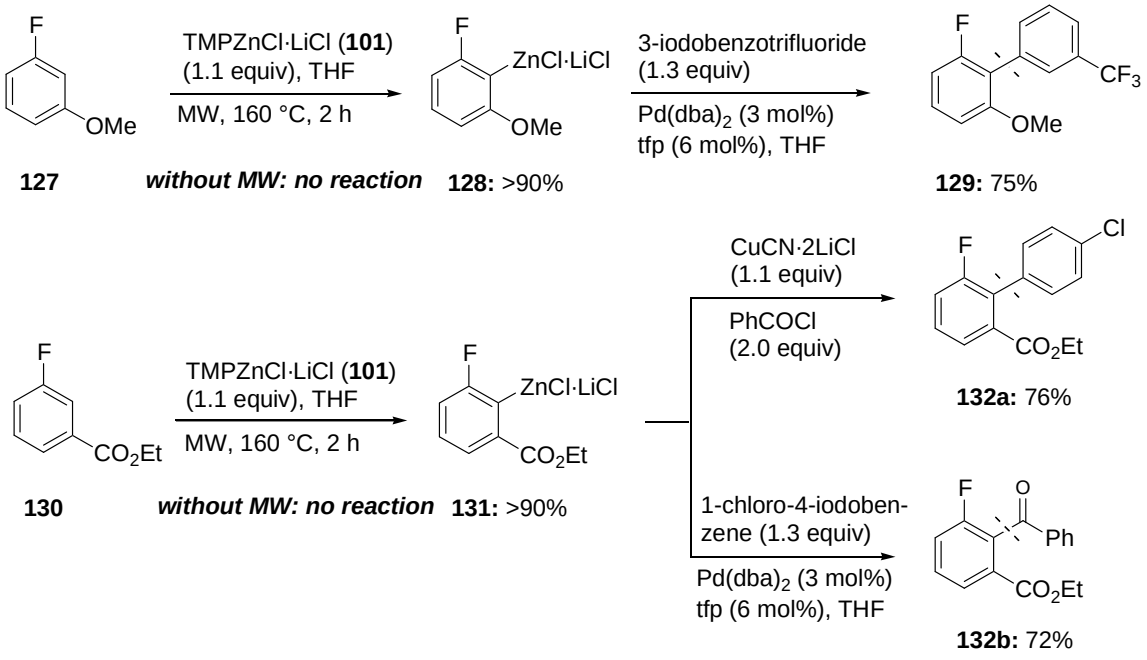
An aldehyde is also well tolerated.[43,46] Thus, benzo[*b*]thiophene-3-carbaldehyde (**124**) was converted to the zinc species **125** at 25 °C using TMPZnCl·LiCl (**101**; 1.1 equiv) within 30 min reaction time (Scheme 49). The formation of a subsequent carbon-carbon bond is also easily carried out by a Negishi[62] cross-coupling or after iodination, by a Sonogashira[63] reaction giving the arylated heterocycles **126a-c** in 63 - 92% yield.



Scheme 49: Zincation of benzo[*b*]thiophene-3-carbaldehyde (**124**) using TMPZnCl·LiCl (**101**; 1.1 equiv; 25 °C) and trapping with electrophiles.

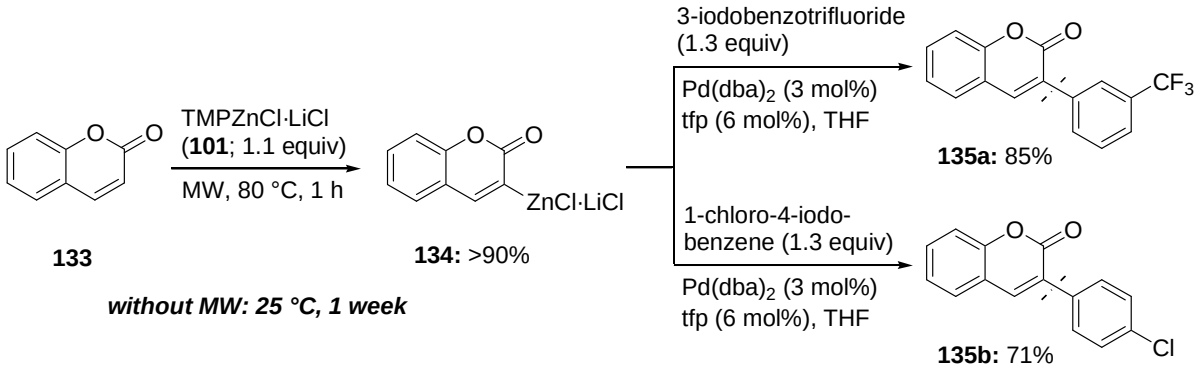
2.5. High temperature metalation of functionalized aromatics and heteroaromatics using TMPZnCl·LiCl (101) under microwave irradiation

Over the last decades, microwave irradiation has been used to accelerate numerous organic reactions[47] including organometallic reactions.[48] Since organozinc reagents of the type RZnX display a good thermal stability and tolerate functional groups even at elevated temperatures,[49] *Wunderlich* and *Knochel* extended the scope of metalations by forcing TMP_2Zn-mediated zincations using microwave irradiation.[50] We also applied microwave irradiation using TMPZnCl·LiCl (**101**) for the functionalization of arenes and heteroarenes. Thus, the direct zincation of the weakly activated arene 3-fluoroanisole (**127**) with TMPZnCl·LiCl (**101**; 1.1 equiv, 160 °C, 2 h) leads to the expected zinc species **128** in > 90% yield (Scheme 50). Negishi[62] cross-coupling then furnishes the new substituted aromatic **129** in 75% yield. The metalation of aromatics bearing sensitive functionalities such as an ester is also possible at high temperatures. Ethyl 3-fluorobenzoate (**130**) is zincated using TMPZnCl·LiCl (**101**; 1.1 equiv) at 160 °C within 2 h. The zinc intermediate **131** then undergoes a Negishi[62] cross-coupling or an acylation using benzoyl chloride (after addition of CuCN·2LiCl)[65] giving the substituted aromatics **132a** and **132b** in 76% and 72% respectively.

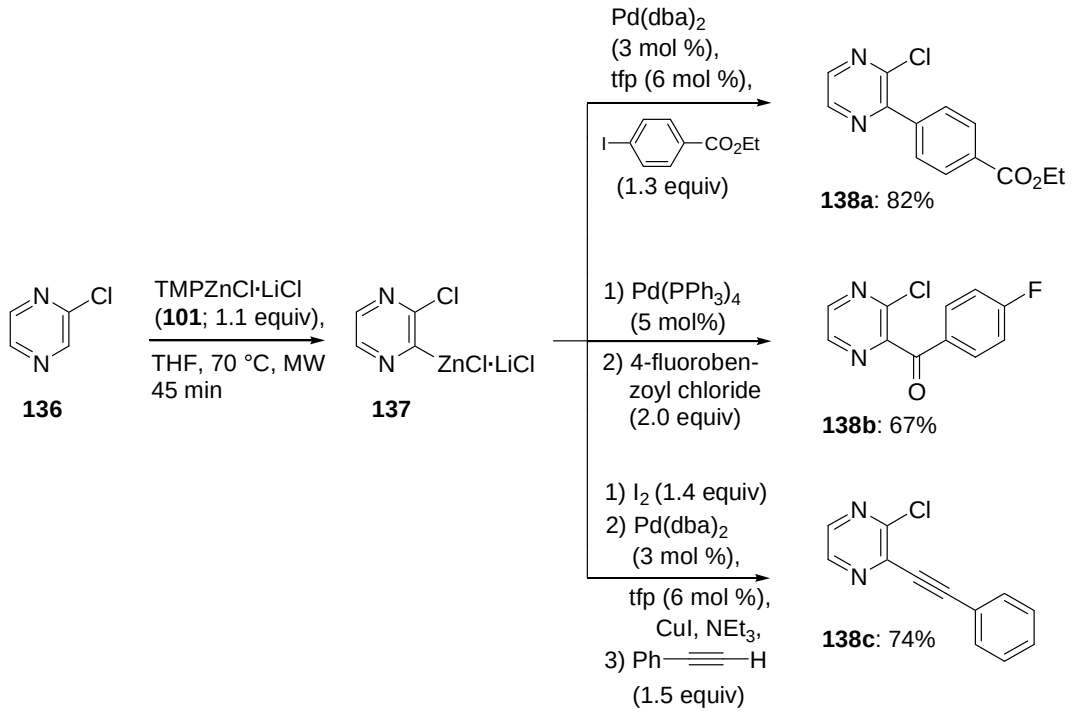


Scheme 50: Zincation of 3-fluoroanisole (**127**) and ethyl 3-fluorobenzoate (**130**) using TMPZnCl·LiCl (**101**; 1.1 equiv; 160 °C) with and without microwave and trapping with electrophiles.

Microwave irradiation is essential since heating of **127** and **130** using an oil bath at 160 °C provides only low conversions after 5 h of the zinc reagents **128** and **131**. The metalation of sensitive heteroarenes can also be performed. Thus, coumarin (**133**) is zincated using TMPZnCl·LiCl (**101**; 1.1 equiv) and microwave irradiation at 80 °C within 1 h (Scheme 51). Negishi[62] cross-couplings then provide the arylated coumarins **135a** and **135b** in 85% and 71% respectively.



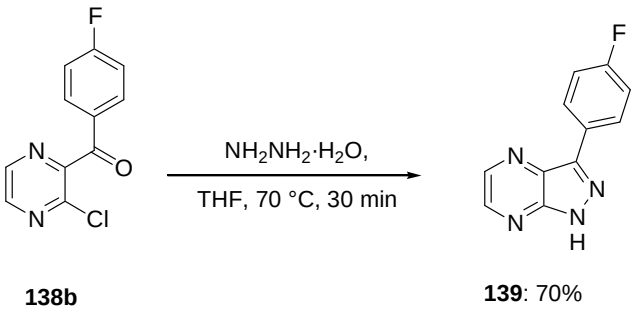
Scheme 51: Zincation of coumarin (**133**) using TMPZnCl·LiCl (**101**; 1.1 equiv) with and without microwave and trapping with electrophiles.



Scheme 52: Zincation of 2-chloropyrazine (**136**) using TMPZnCl·LiCl (**101**; 1.1 equiv; 70 °C) and microwave irradiation and trapping with electrophiles.

2-Chloropyrazine (**136**) also undergoes a zincation using TMPZnCl·LiCl (**101**; 1.1 equiv) under microwave irradiation at 80 °C affording the zinc species **137**. Negishi cross-couplings,[62, 92] and Sonogashira[63] cross-coupling leads to the new pyrazine derivatives **138a-c** in 67 - 82% yields (Scheme 52).

As an application, we also prepared a JNK kinase inhibitor (**139**; JNK (Jun *N*-terminal kinase)) which is a stress-activated protein kinase that modulates pathways implicated in a variety of disease states).[93, 94] Thus, the treatment of **138b** with hydrazine in THF at 70 °C is complete within 30 min and furnishes the pyrazolopyrazine **139** in 70% yield (Scheme 53).



138b **139**: 70%

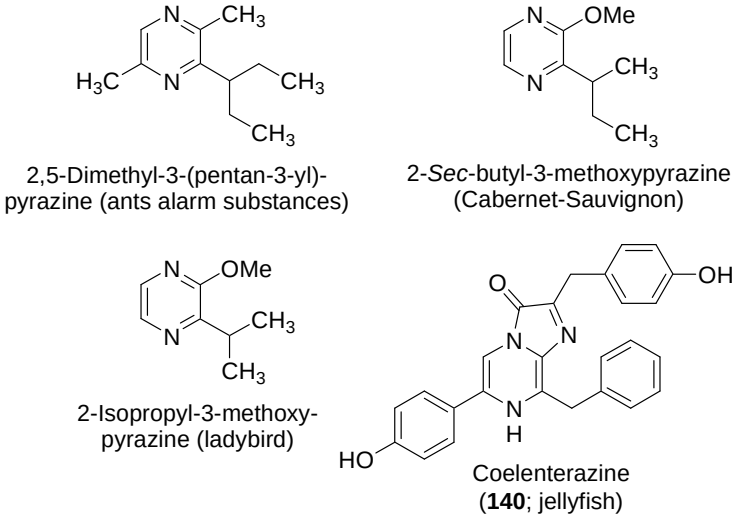
Scheme 53: Preparation of the JNK kinase inhibitor **139**.

[92] Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.
[93] (a) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021. (b) Bhagwat, S. S.; Satoh, Y.; Sakata, S. T. WO 2002010137, **2002**.
[94] Stebbins, J. L.; De, S. K.; Machleidt, T.; Becattini, B.; Vazquez, J.; Kuntzen, C.; Chen, L.-H.; Cellitti, J. F.; Riel-Mehan, M.; Emdadi, A.; Solinas, G.; Karin, M.; Pellecchia, M. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 16809.

3. Functionalization of Chloropyrazine Derivatives *via* Regio- and Chemoselective Metalations

3.1. Introduction

Pyrazines are important scaffolds that are highly active and widely distributed flavour compounds, formed either thermally like alkylpyrazines present in coffee, meat and potatoes or biosynthetically like 2-alkyl-3-methoxypyrazines present in wines such as Cabernet-Sauvignon or like some other natural products such as Coelenterazine (**140**), a naturally occurring bioluminescent imidazolopyrazine of a marine origin bearing a trisubstituted pyrazine unit, isolated from the jellyfish *Aequorea Victoria* (Scheme 54).[95]



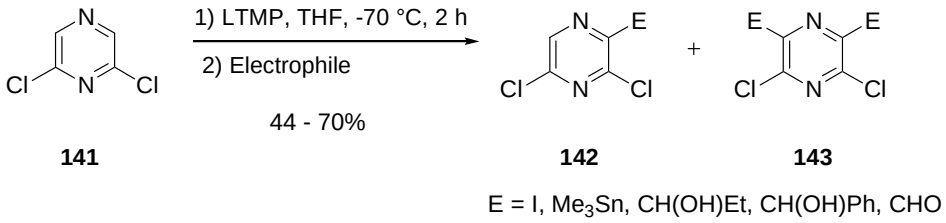
Scheme 54: Natural products containing a pyrazine scaffold.

3.2. Functionalization of chloropyrazines using lithium bases

The direct functionalization of these heterocycles by lithiation is difficult due to the electrophilic character of the ring, which readily undergoes the addition of various organometallics. This implies that low temperatures are quite often required for the metalation of pyrazines.[96] The metalation/functionalization sequence was already applied to a few

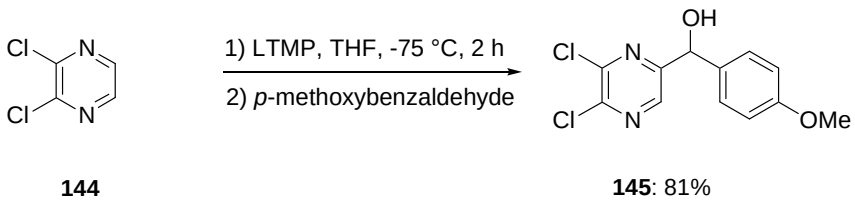
[95] (a) Steglich, W.; Fugmann, B.; Lang-Fugmann, S. *RÖMPP Encyclopedia Natural Products;* Stuttgart; New York: Thieme **2000**. (b) Vance, E. *Nature* **2008**, *455*, 726. (c) Knight, M. R.; Campbell, A. K.; Smith, S. M.; Trewavas, A. J. *Nature* **1991**, *352*, 524.
[96] (a) Zhang, C. Y.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 8783. (b) Liu W.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **2001**, *66*, 4783. (c) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595.

dichloropyrazines such as 2,6-dichloropyrazine (**141**) to obtain the compounds of type **142** in moderate to good yields. Nevertheless, the outcome of the reaction depends on the amount of base used since the formation of 3,5-difunctionalized products of type **143** could not be avoided using an excess of metalating agent and electrophiles, compatible with *in situ* trapping such as benzaldehyde, iodine or chlorotributylstannane (Scheme 55).[97, 98]



Scheme 55: Lithiation of 2,6-dichloropyrazine (**144**) and trapping with electrophiles.

Turck also reported as a key step the metalation of 2,3-dichloropyrazine (**144**) using LTMP for the synthesis of natural products such as compounds from *Botryllus leachi*.[99] Thus, **144** was metalated with LTMP at –75 °C and the lithium species was then trapped with *p*-methoxybenzaldehyde to afford the corresponding alcohol **145** in 81% yield.



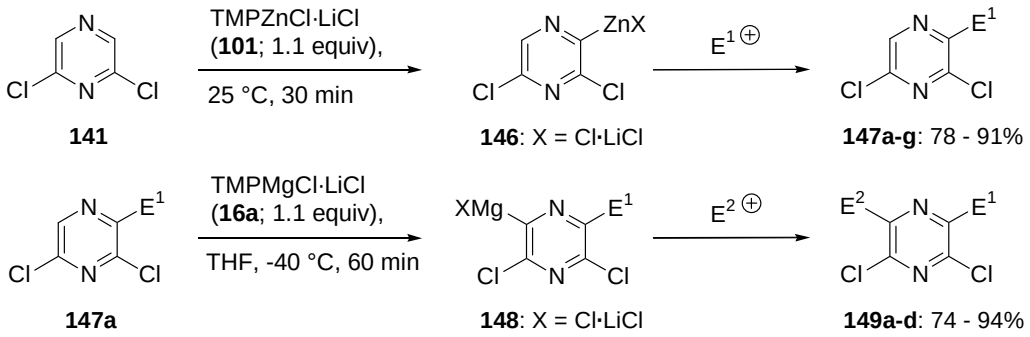
Scheme 56: Lithiation of 2,3-dichloropyrazine (**144**) and trapping with electrophiles.

3.3. Total functionalization of the pyrazine scaffold using regio- and chemoselective metalations

TMPMgCl·LiCl (**16a**) and TMPZnCl·LiCl (**101**) allow an easy access for the metalation of simple dichloropyrazines in good to excellent yields under mild conditions. Thus, 2,6-

[97] (a) Turck, A.; Mojovic L.; Quéguiner, G. *Synthesis* **1988**, 881. (b) Turck, A.; Plé, N.; Dognon, D.; Harmoy, C.; Quéguiner, G. *J. Heterocycl. Chem.* **1994**, *31*, 1449. (c) Liu, W.; Walker, J. A.; Chen, J. J.; Wise D. S.; Townsend, B. L. *Tetrahedron Lett.* **1996**, *37*, 5325.
[98] (a) Ward J. S.; Merritt, L. *J. Heterocycl. Chem.* **1991**, *28*, 765. (b) Turck, A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, *412*, 301.
[99] Buron, F.; Plé, N.; Turck, A.; Quéguiner, G. *J. Org. Chem.* **2004**, *70*, 2616.

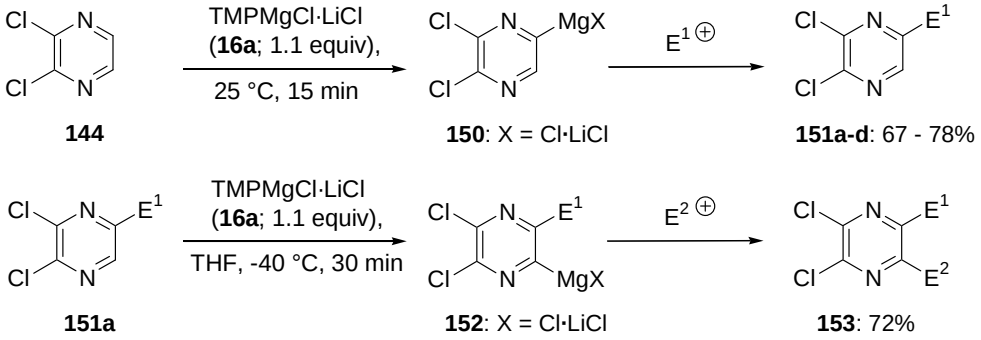
dichloropyrazine (**141**) is zincated quantitatively with TMPZnCl·LiCl (**101**; 1.1 equiv, 25 °C, 30 min) giving the zinc species **146**, which undergoes Negishi[62] cross-couplings providing the 3-substituted heterocycles **147a-d** in 81 - 86% yields (Scheme 57, entries 1-4 of Table 6). An allylation with allyl bromide (after the addition of a catalytic amount of CuCN·2LiCl) gives the allylated pyrazine **147e** in 78% (entry 5). Trapping with iodine provides the iodopyrazine **147f** in 91% (entry 6). Sonogashira[63] cross-coupling of *in situ* generated **147f** allows the pyrazine derivative **148g** in 83% yield (entry 7). Subsequent metalation of the arylpyrazine **147a** using TMPMgCl·LiCl (**16a**; 1.1 equiv, –40 °C, 60 min) provides the magnesium reagent **148**, which affords after transmetalation with CuCN·2LiCl[65] and trapping with benzoyl chloride or furoyl chloride, the ketopyrazines **149a** and **149b** in 94% and 84% yields (entries 8 and 9). Quenching with 3-bromocyclohexene gives the fully substituted pyrazine **149c** in 93% yield (entry 10). Negishi[62] cross-coupling using ethyl 4-iodobenzoate provides the substituted heterocycle **149d** in 94% yield (entry 11).



Scheme 57: Successive metalation of 2,6-dichloropyrazine (**141**) at positions 3 and 5 using TMPZnCl·LiCl (**101**) and TMPMgCl·LiCl (**16a**) and trapping with electrophiles.

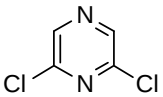
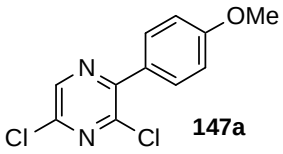
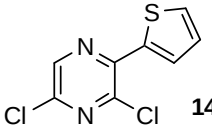
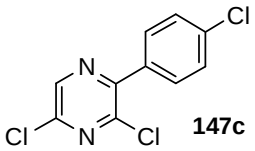
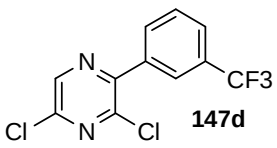
Other dichloropyrazines are metalated as well under mild conditions. Thus, the treatment of 2,3-dichloropyrazine (**144**) with TMPMgCl·LiCl (**16a**; 1.1 equiv, 25 °C, 15 min) leads to the 5-magnesiated pyrazine (**150**), which is trapped by electrophiles such as $MeSO_2SMe$ and 3-bromocyclohexene (after transmetalation with $ZnCl_2$ and addition of a catalytic amount of CuCN·2LiCl) leading to the expected pyrazines of type **151a** and **151b** in 67% and 72% (Scheme 58, entries 12 and 13 of Table 6). The formation of a new carbon-carbon bond is readily performed by a Negishi[62] cross-coupling or a Sonogashira[63] reaction of *in situ* generated 2,3-dichloro-5-iodopyrazine providing the 5-substituted heterocycles **151c** and **151d** in 78% and 77% yields (entries 14 and 15). A further magnesiation was achieved at the last position by the addition of TMPMgCl·LiCl (**16a**; 1.1 equiv). Thus, 2,3-dichloro-5-

(methylthio)pyrazine **151a** is converted within 30 min at –40 °C to the 6-magnesiated species **152**. Reaction with 4-fluorobenzoyl chloride (after transmetalation with CuCN·2LiCl)[65] furnishes the ketopyrazine **153** in 72% yield (entry 16).

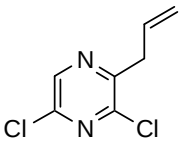
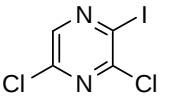
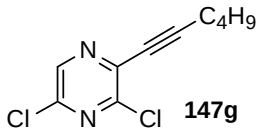
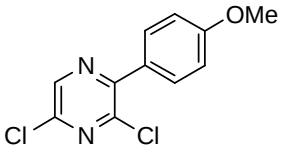
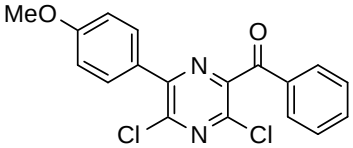
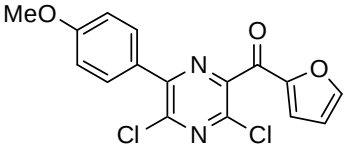
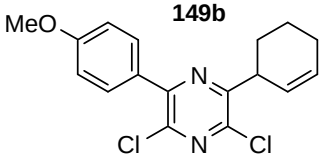
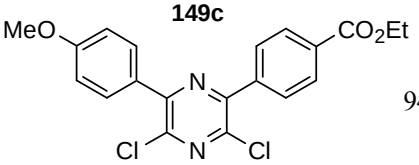
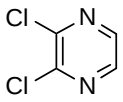
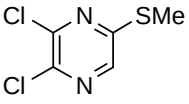
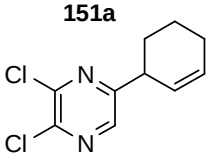
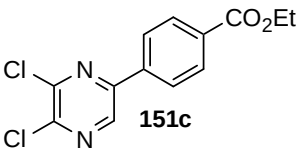


Scheme 58: Successive metalation of 2,3-dichloropyrazine (**144**) at positions 5 and 6 using TMPMgCl·LiCl (**16a**) and trapping with electrophiles.

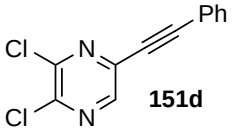
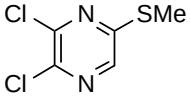
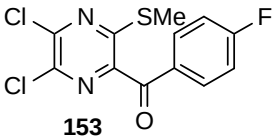
Table 6: Products obtained by regio- and chemoselective metalation of chloropyrazines of type **141** and **144** with TMPZnCl·LiCl (**101**; 1.1 equiv) and TMPMgCl·LiCl (**16a**; 1.1 equiv) and trapping with electophiles.

entry	substrate	electrophile	product	yield, %[a]
1	 **141**	4-iodoanisole[b]	 **147a**	86
2	**141**	2-iodothiophene[b]	 **147b**	83
3	**141**	1-chloro-4-iodo -benzene[b]	 **147c**	81
4	**141**	3-iodo-benzotrifluoride[b]	 **147d**	83

a Isolated, analytically pure product. *b* Negishi cross-coupling using $Pd(dba)_2$ and P(*o*-furyl)$_3$.

entry	substrate	electrophile	product	yield, %[a]
5	**141**	allyl bromide[b]	 **147e**	78
6	**141**	I_2	 **147f**	91
7	**141**	I_2 then hexan-1-yl[c]	 **147g**	83
8	 **147a**	benzoyl chloride[d]	 **149a**	94
9		2-furoyl chloride[d]	 **149b**	84
10	**147a**	3-bromo-cyclohexene[b]	 **149c**	93
11	**147a**	ethyl 4-iodo benzoate[e]	 **149d**	94
12	 **144**	$MeSO_2SMe$	 **151a**	67
13	**144**	3-bromo-cyclohexene[b]	 **151b**	72
14	**144**	ethyl 4-iodo benzoate[e]	 **151c**	78

a Isolated, analytically pure product. *b* Catalyzed with 5 mol% of CuCN·2LiCl. *c* Obtained by Pd catalyzed cross- coupling using $Pd(dba)_2$, $(o\text{-furyl})_3P$, CuI and NEt_3. *d* Transmetalation with 1.1 equiv of CuCN·2LiCl. *e* Negishi cross-coupling with $Pd(dba)_2$ and $P(o\text{-furyl})_3$.

entry	substrate	electrophile	product	yield, %[a]
15	**144**	I_2 then phenylacetylene[b]	 **151d**	77
16	 **151a**	4-fluorobenzoyl chloride[c]	 **153**	72

a Isolated, analytically pure product. *b* Obtained by Pd- catalyzed cross-coupling using $Pd(dba)_2$, $(o\text{-furyl})_3P$, CuI and NEt_3. *c* Transmetalation with 1.1 equiv of CuCN·2LiCl.

3.4. Application to the synthesis of the marine bioluminescent natural product Coelenterazine

As an application, we have carried out the total synthesis of Coelenterazine (**140**) [95a,100] in 9 steps using a metalation step in 7% overall yield. Thus, a Negishi[62] cross-coupling using 2,5-dichloropyrazine[101] (**154**) as electrophile provides the arylpyrazine **155** in 64% yield (Scheme 60). A magnesiation using TMPMgCl·LiCl (**16a**; 1.1 equiv, –45 °C, 1 h) gives after transmetalation with $ZnCl_2$ and acylation[92] with benzoyl chloride the ketopyrazine **156** in 71% yield. The chlorine substitution is then achieved using NH_3 in BuOH[102] furnishing the aminopyrazine **157** in 94% yield. Cleavage of the methyl ether with sodium thioethanolate in DMF[103] yields the corresponding alcohol **158** in 72%. The reduction of the ketone is finally carried out using a Wolff-Kishner[104] reduction affording Coelenteramine (**159**) in 93% yield.

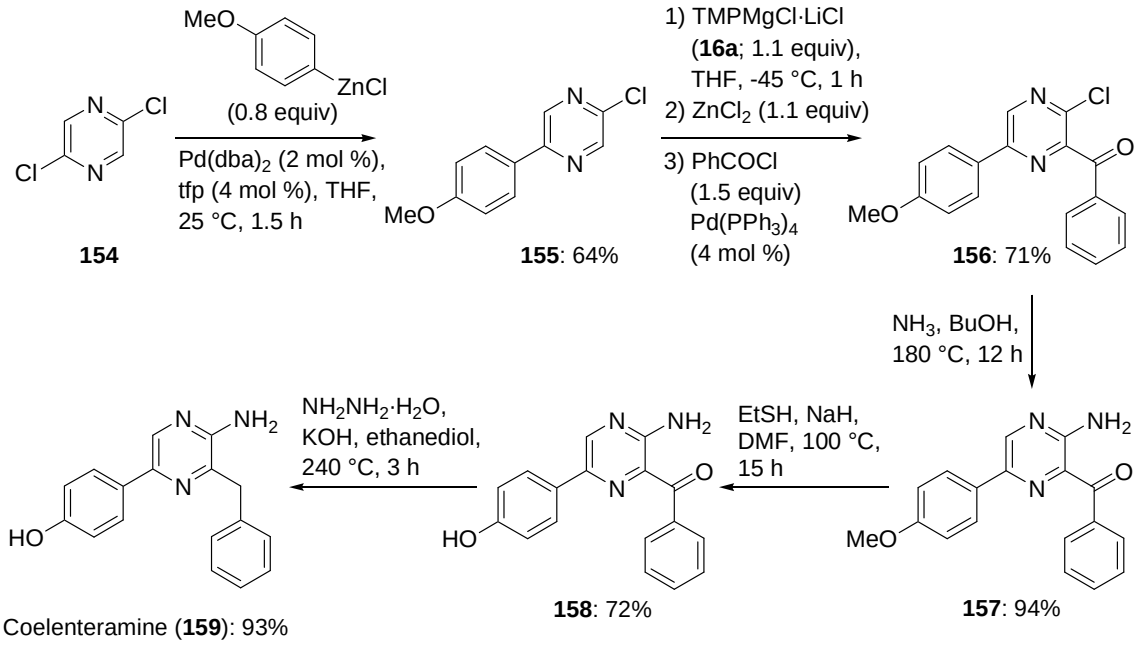
[100] (a) Kishi, Y.; Tanino, H.; Goto, T. *Tetrahedron Lett.* **1972**, *27*, 2747. (b) Inoue, S.; Sugiura, S.; Kakoi, H.; Hashizume, K.; Goto, T.; Iio, H. *Chem. Lett.* **1975**, 141. (c) Inoue, S.; Kakoi, H.; Murata, M.; Goto, T.; Shimomura, O. *Chem. Lett.* **1979**, 249. (d) Shimomura, O.; Johnson, F. H.; Morise, H. *Biochemistry* **1974**, *13*, 3278. (e) Shimomura, O.; Musicki, B.; Kishi, Y. *Biochem. J.* **1989**, *261*, 913. (f) Gonzalez-Trueba, G.; Paradisi, C.; Zoratti, M. *Anal. Biochem.* **1996**, *240*, 308. (g) Jones, K.; Keenan, M.; Hibbert, F. *Synlett* **1996**, 509. (h) Keenan, M.; Jones, K.; Hibbert, F. *Chem. Commun.* **1997**, *3*, 323. (i) Kakoi, H *Chem. Pharm. Bull.* **2002**, *50*, 301.

[101] For the preparation of 2,5-dichloropyrazine, see: Klein, B.; Hetman, N. E.; O'Donnell, M. E. *J. Org. Chem.* **1963**, *28*, 1682.

[102] Turck, A.; Mojovic, L.; Quéguiner, G. *Synthesis* **1988**, 881.

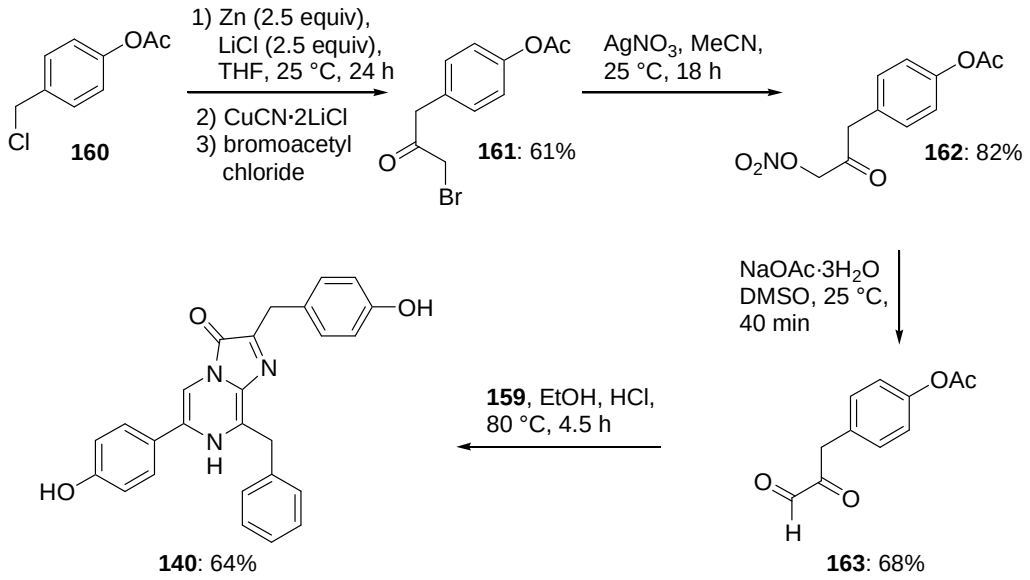
[103] Burton, M.; De Tollenaere, C.; Dussart, F.; Marchand, C.; Rees, J. F.; Marchand-Brynaert, J. *Synthesis* **2001**, 768.

[104] Lehr, M. *J. Med. Chem*. **1997**, *40*, 3381.



Scheme 60: Synthesis of Coelenteramine (**159**).

The preparation of the second moiety is presented as followed (Scheme 61).



Scheme 61: Synthesis of Coelenterazine (**140**).

The addition of 4-(chloromethyl)phenyl acetate (**160**) to commercial Zn dust (2.5 equiv) in the presence of LiCl (2.5 equiv) at 25 °C is complete within 24 h.[105] Trapping with bromoacetyl chloride (after transmetalation with CuCN·2LiCl)[65] furnishes the acylated

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

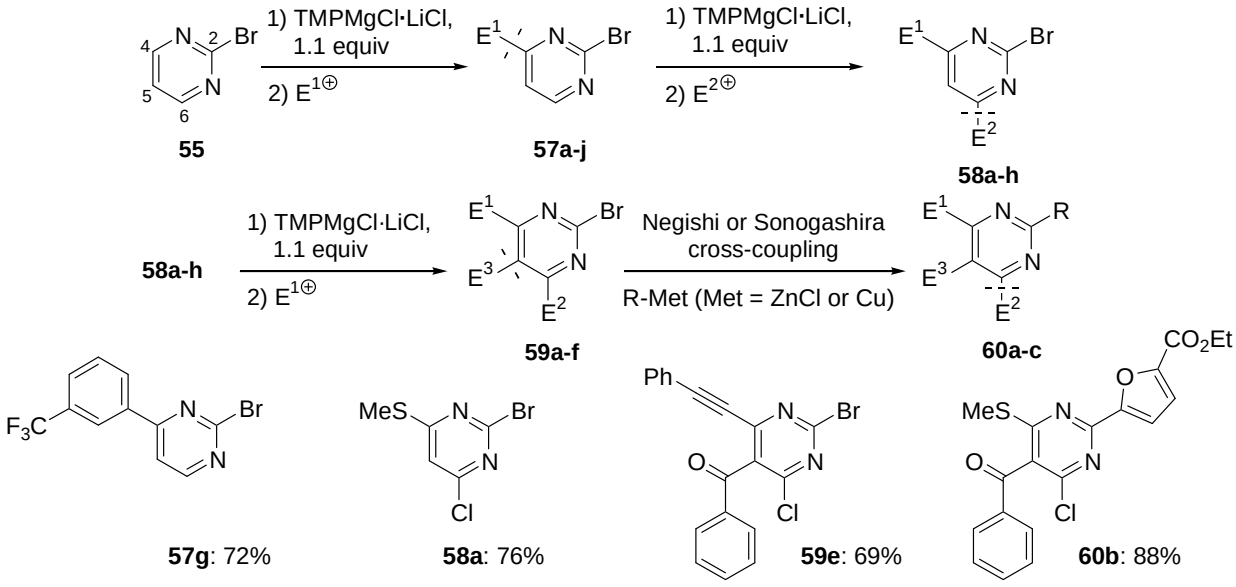
derivative **161** in 61% yield. Addition of silver nitrate at 25 °C gives after 18 h the new substituted aromatic **162** in 82% yield. [106] Subsequent reaction of **162** with NaOAc in DMSO affords the corresponding acetoxy α–keto aldehyde **163** in 68%.[106] Finally, the condensation of **163** with Coelenteramine (**159**) provides the bioluminescent natural product Coelenterazine (**140**) in 64%.[100h,106]

[106] Chen, F.-Q.; Zheng, J.-L.; Hirano, T.; Niwa, H.; Ohmiya, Y.; Ohashi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *17*, 2129.

4. Summary and Outlook.

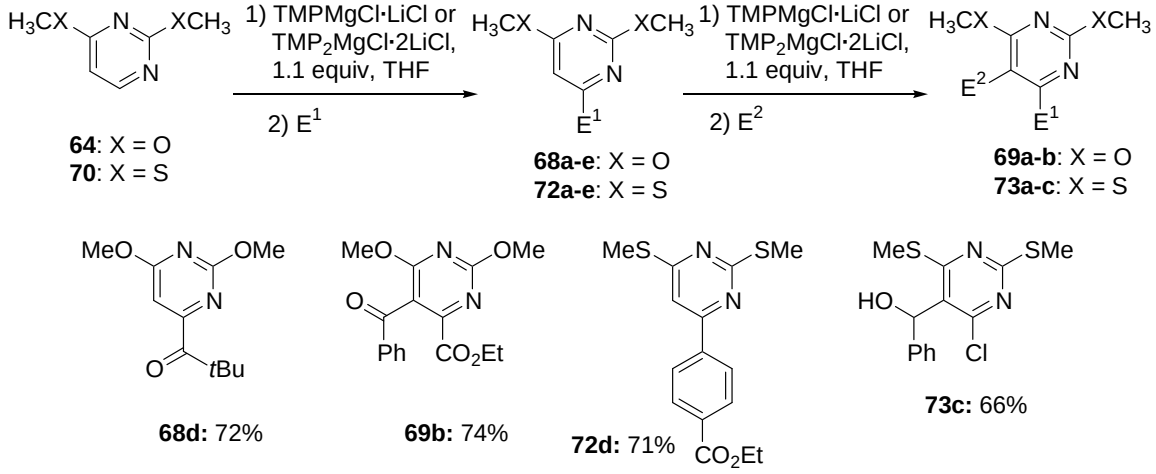
4.1. Functionalizations of Pyrimidine Derivatives *via* Regio- and Chemoselective Metalations

In summary, we have described the full functionalization of the pyrimidine scaffold *via* successive regio- and chemoselective magnesiations using TMPMgCl·LiCl starting from simple commercially available starting materials (Scheme 61).



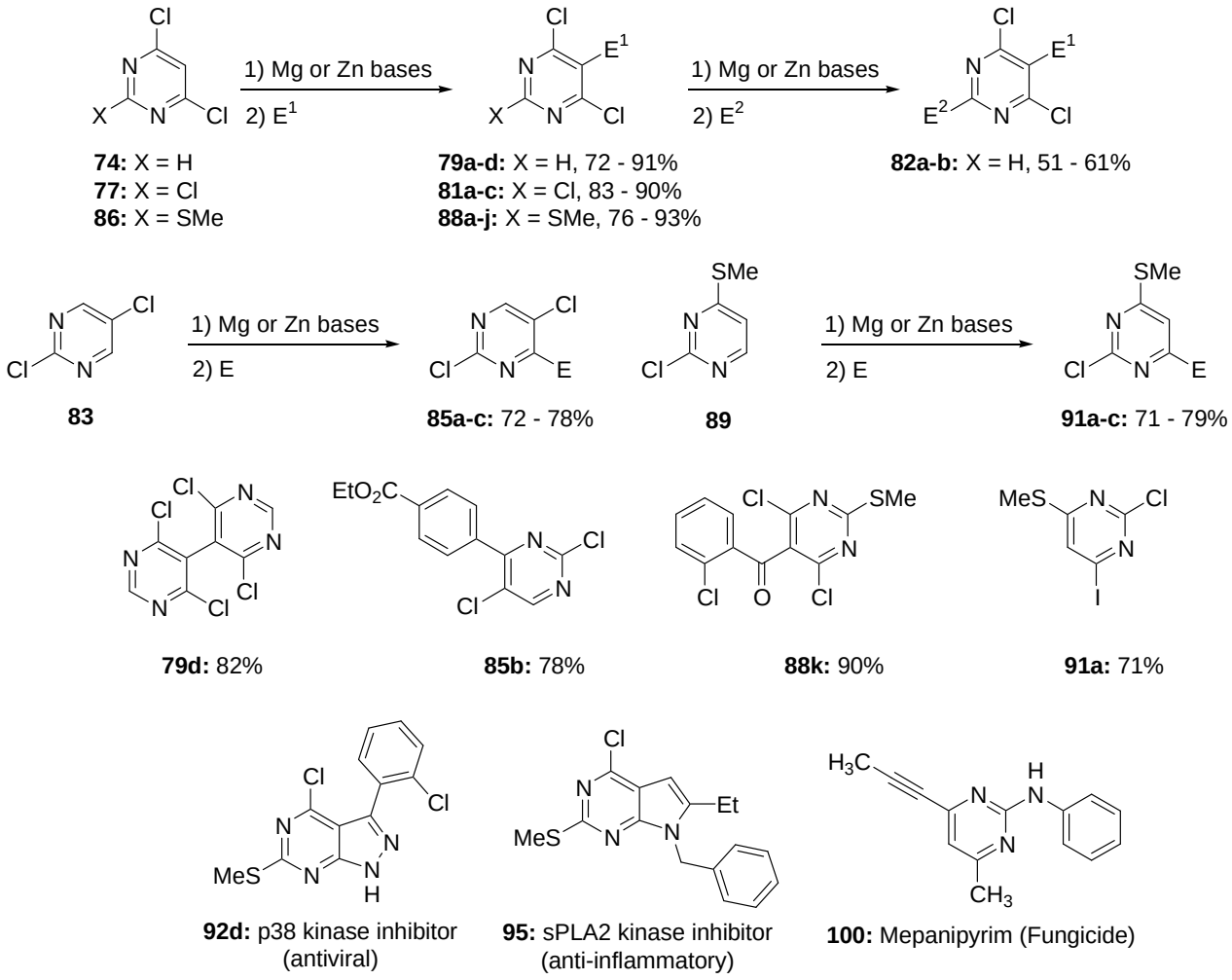
Scheme 61: Total functionalization of the pyrimidine scaffold.

We then performed successive magnesiations of protected uracils and thiouracils using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ (Scheme 62).



Scheme 62: Total functionalization of the protected uracils and thiouracils.

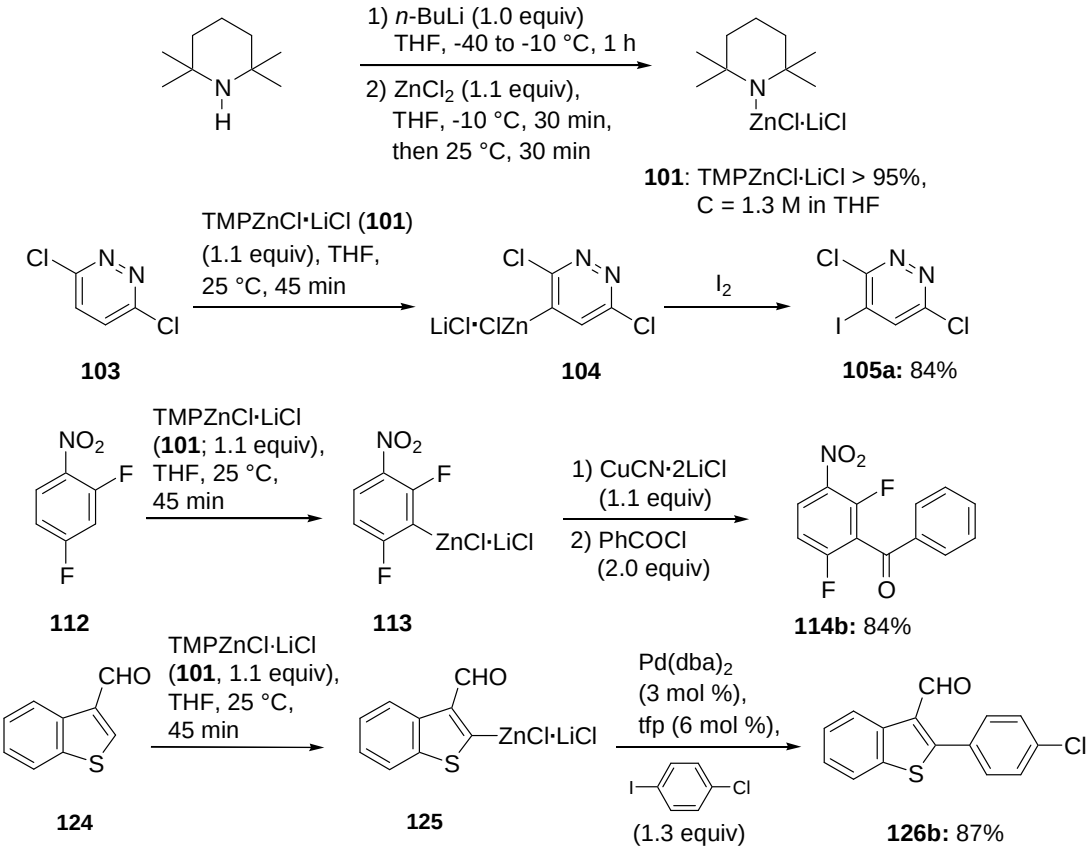
We finally extended our methodology to the functionalization under mild conditions of polychloropyrimidines for the preparation of kinase inhibitors such as pyrrolo- and pyrazolopyrimidines and the fungicide Mepanipyrim (5 steps, 40%) (Scheme 63).



Scheme 63: Regio- and chemoselective functionalization of chloropyrimidine derivatives.

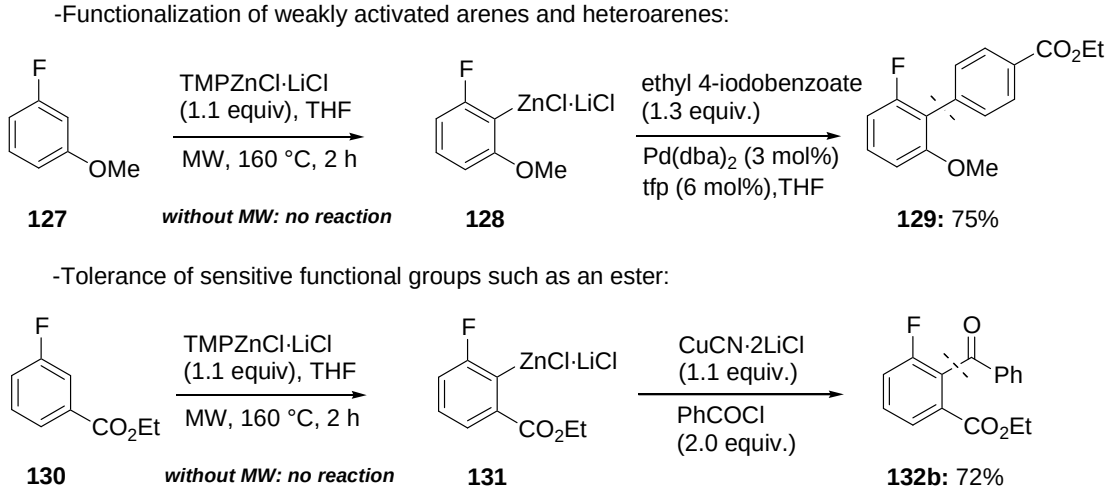
4.2. Preparation of a New Active Selective Base for the Direct Zincation of Sensitive Aromatics and Heteroaromatics

We have developed a new active selective base, which allows chemoselective zincations of sensitive heterocycles (pyridazines, pyrimidines, pyrazines and purines) at room temperature and tolerating sensitive functions such as an aldehyde or a nitro group. Especially, the compatibility with nitro groups opens new avenues in metalations of aromatic and heterocyclic substrates (Scheme 64).



Scheme 64: Regio- and chemoselective zincation of sensitive arenes and heteroarenes using TMPZnCl·LiCl (**101**).

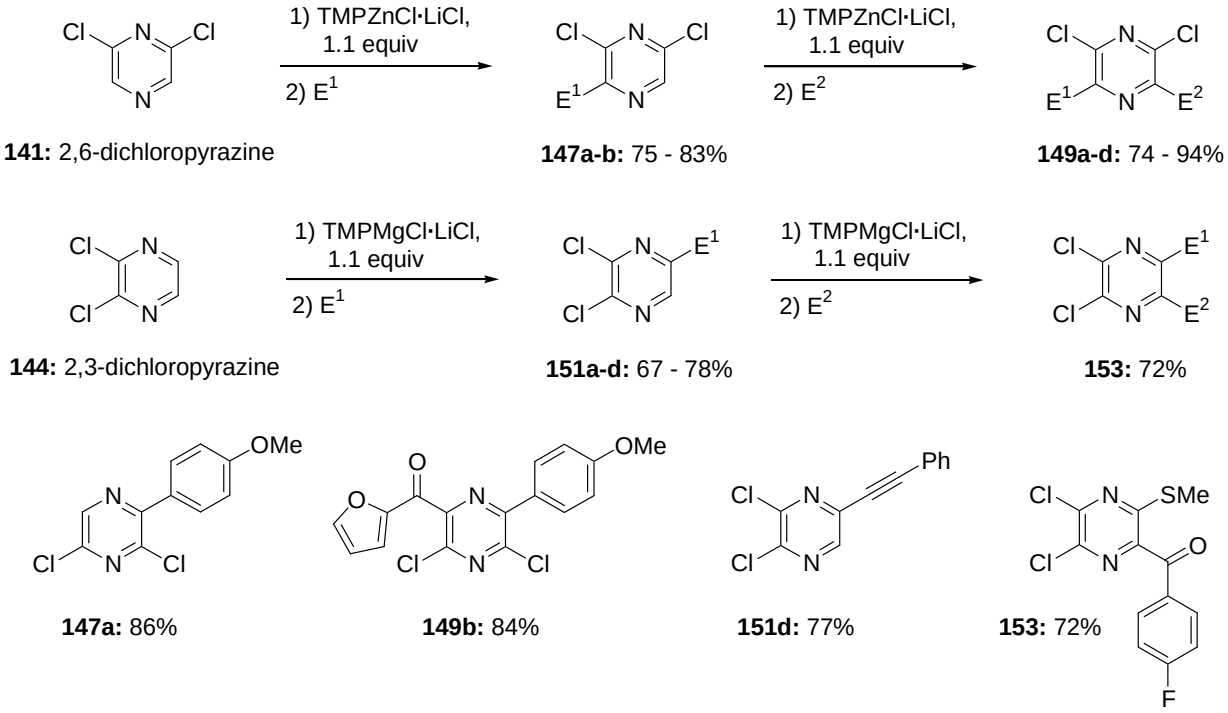
We have also extended the scope of our methodology with TMPZnCl·LiCl (**101**) by using microwave irradiation with unactivated substrates (Scheme 65).



Scheme 65: Zincation of arenes and heteroarenes using TMPZnCl·LiCl (**101**) under microwave irradiation.

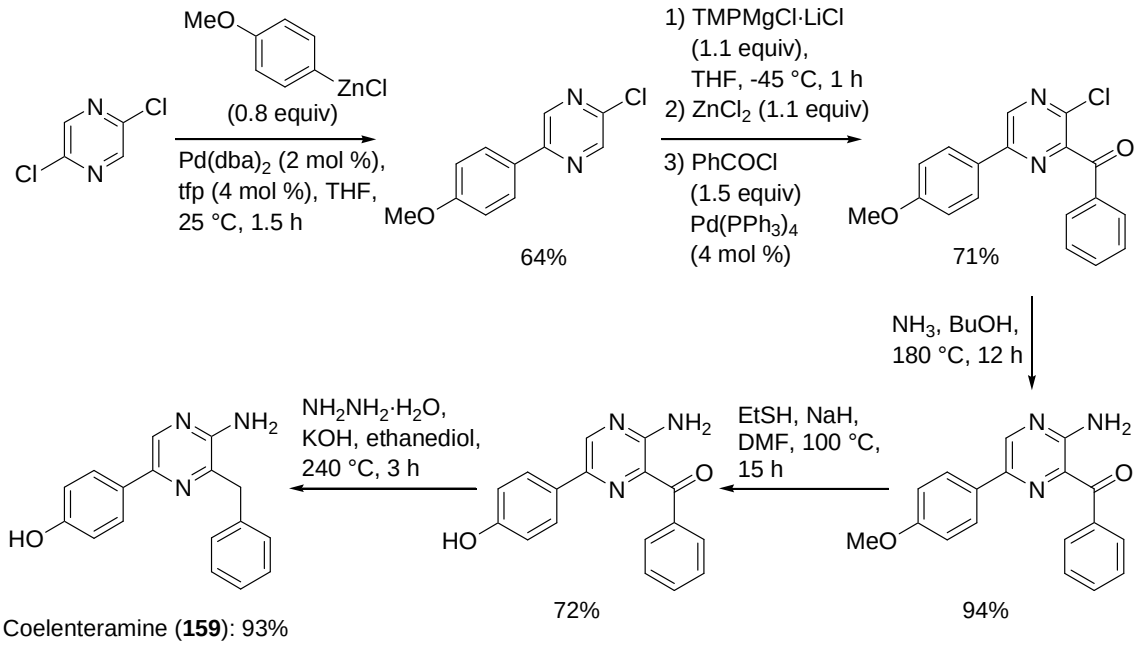
4.3. Functionalizations of Pyrazine Derivatives *via* Regio- and Chemoselective Metalations

We have described the multiple regio- and chemoselective functionalization of the pyrazine scaffold using TMPMgCl·LiCl and TMPZnCl·LiCl as effective bases (Scheme 66).



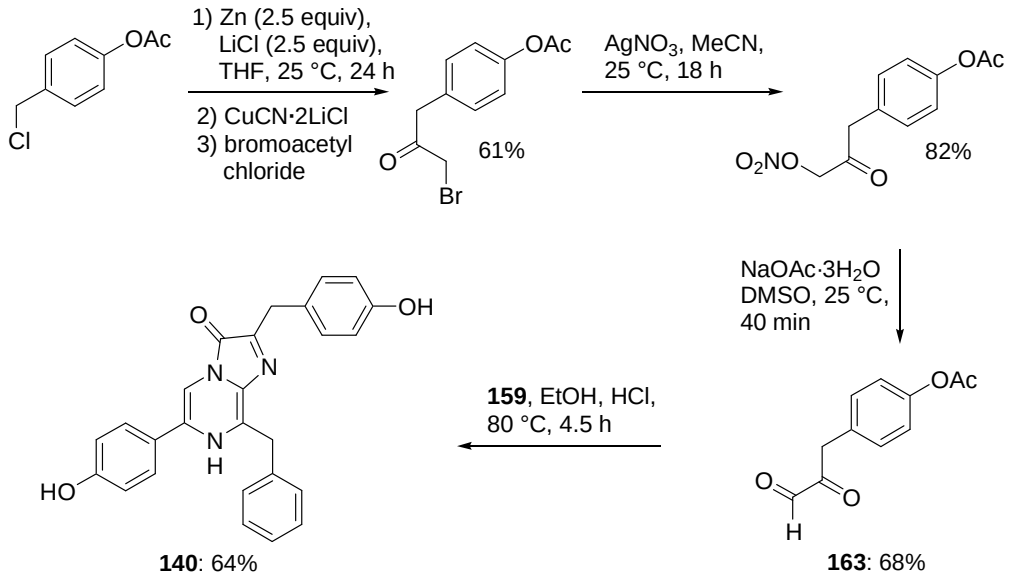
Scheme 66: Regio- and chemoselective successive metalations of chloropyrazine derivatives.

We reported as a direct application the synthesis of Coelenteramine (**159**), the precursor of the bioluminescent natural product Coelenterazine (**140**) (Scheme 67).



Scheme 67: Synthesis of Coelenteramine (**159**).

We finally performed the preparation of the 1,2-ketoaldehyde **163** to afford the synthesis of Coelenterazine (**140**) (Scheme 68).



Scheme 68: Synthesis of Coelenterazine (**140**).

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 (25 g/L) and sodium, heated to reflux for 6 h and distilled.

Methanol was treated with magnesium turnings (20 g/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.

$ZnCl_2$ 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.

Lithiated reagents

***n*-Butyllithium** was used as a 1.5 M solution in hexane purchased from Chemetall.

Magnesiated reagents

***i*-PrMgCl·LiCl**: 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 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.[107]

TMPMgCl·LiCl (16a): 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) (17.8 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. 48 h).[24] The solution of TMPMgCl·LiCl was titrated by using benzoic acid in dry THF and 4-(phenylazo)diphenylamine as an indicator.

$TMP_2Mg·2LiCl$ (26): was prepared according to the known procedure.[26]

Zincated reagents

$TMP_2Zn·2MgCl_2·2LiCl$ (35): was prepared according to the known procedure.[42]

TMPZnCl·LiCl (101): A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with freshly 2,2,6,6-tetramethylpiperidine (10.22 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to –40 °C and *n*-BuLi (2.4 M in hexane, 25 mL, 60 mmol) was dropwise added. After the addition was complete, the reaction mixture was allowed to warm up slowly to –10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was dropwise added and the resulting solution was stirred for 30 min at –10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the

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

salts were completely dissolved.[108] The freshly prepared TMPZnCl·LiCl (**101**) solution was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Others reagents

The following reagents were prepared according to literature procedures: palladium(II)bis(dibenzylidenacetone),[109] tri-(2-furyl)phosphine,[110] ethyl 2-(bromomethyl)-acrylate,[89] and *S*-phenyl benzenesulfonothioate.[111]

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,[112] 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.[113]

[108] Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837.
[109] Takahashi, Y.; Ito, T.; Sakai, S. *Chem. Commun.* **1970**, 1065.
[110] Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc. Perkin Trans. II* **1972**, 63.
[111] Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.
[112] Brockmann, H.; Schodder, H. *Ber. Deut. Chem. Ges*. **1941**, *74*, 73.
[113] Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

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).
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), q (quartet), 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 Pyrimidine Derivatives *via* Regio- and Chemoselective Magnesiations

2.1. General procedure for the deprotonation using TMPMgCl·LiCl (16a), TMP_2Mg·2LiCl (26) or TMP_2Zn·2$MgCl_2$·2LiCl (35) as metalating agents (GP1)

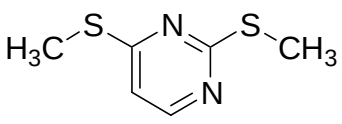
A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with TMPMgCl·LiCl (**16a**) (1.1 equiv) or TMP_2Mg·2LiCl (**26**) (1.1 equiv) or TMP_2Zn·2$MgCl_2$·2LiCl (**35**) (1.1 equiv). The pyrimidine substrate (1.0 equiv) in THF was dropwise added at the temperature T1. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at the temperature T2. 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 solution . The aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by filter column chromatography.

2.2. General procedure for the reaction with acyl chlorides (GP2)

According to **GP1**, the freshly prepared magnesium or zinc reagent was cooled to −30 °C, and CuCN·2LiCl[65] (1.1 equiv, 1.00 M in THF) was added and stirred for 30 min. Thereafter, acyl chloride (2.0 equiv) was added at −30 °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 extracted with Et_2O and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude residue was purified by filter column chromatography.

2.3. Starting material synthesis

Synthesis of 2,4-bis(dimethylthio)pyrimidine (70):



A solution of sodium methanethiolate (5.05 g, 72 mmol, 3 equiv) and 2,4-dichloropyrimidine (3.58 g, 24 mmol) in 50 mL THF was heated at 80 °C for 4 h. A sat. aq. NH_4Cl solution (100 mL) was added and the crude was then extracted with ether (3 x 150 ml), dried over Na_2SO_4, filtrated and concentrated *in vacuo* to furnish the pure colourless oil **70** in a quantitative yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.07 (d, 1 H, *J* = 5.6 Hz), 6.78 (d, 1 H, *J* = 5.6 Hz), 2.51 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 171.9, 170.4, 153.9, 113.7, 13.9, 12.2.

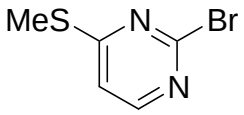
MS (EI, 70 eV) *m/z* (%): 172 (M^+, 100), 157 (43), 139 (44), 125 (31), 111 (50), 47 (13).

IR (neat) ν (cm^{-1}): 3087 (w), 3003 (w), 2929 (w), 1523 (s), 1478 (s), 1431 (m), 1407 (m), 1354 (m), 1312 (w), 1288 (w), 1251 (s), 1170 (m), 1098 (m), 977 (w), 964 (w), 832 (w), 816 (w), 769 (s), 750 (w), 603 (w).

HRMS (EI) for $C_6H_8N_2S_2$ (172.0129): 172.0122.

2.4. Preparation of polyfunctionalized pyrimidines

Synthesis of 2-bromo-4-(methylthio)pyrimidine (57a):



2-Bromopyrimidine (**55**) (960 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.00 M in THF, 6.6 mL, 6.6 mmol) at −55 °C for 1.5 h according to **GP1**. S-Methyl methanethiolsulfonate (1.136 g, 9.0 mmol) was added dropwise at −55 °C, the resulting mixture was allowed to warm up fast at −30 °C and then slowly to room temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), then extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **57a** as a colourless solid (981 mg, 81%).

m.p.: 50.8 – 53.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.09 (d, *J* = 5.3 Hz, 1 H), 7.09 (d, *J* = 5.3 Hz, 1 H), 2.54 (s, 3 H).

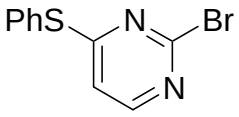
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 173.6, 155.7, 152.5, 117.4, 12.7.

MS (EI, 70 eV) m/z (%): 206 (97), 204 (100) [^{79}Br-M^+], 158 (8), 124 (19), 79 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3002, 2925, 1546, 1499, 1396, 1318, 1199, 1171, 1150, 1083, 972, 830, 791, 752, 721, 672.

HRMS (EI) for $C_5H_5BrN_2S$ (203.9357): 203.9351.

Synthesis of 2-bromo-4-(phenylthio)pyrimidine (57b):



2-Bromopyrimidine (**55**) (960 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.00 M in THF, 6.6 mL, 6.6 mmol) at −55 °C for 1.5 h according to **GP1**. S-Phenyl benzenethiolsulfonate (2.253 g, 9.0 mmol) dissolved in 9 mL THF was added dropwise at −55 °C, the resulting mixture was allowed to warm up fast at -30 °C and then slowly to room temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), then extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **57b** as a colourless solid (1.232 g, 77%).

m.p.: 83.7 – 85.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.09 (d, *J* = 5.4 Hz, 1 H), 7.45 − 7.60 (m, 5 H), 6.64 (d, *J* = 5.4 Hz, 1 H).

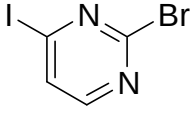
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 172.6, 157.3, 151.9, 135.4, 130.5, 130.1, 126.7, 115.5.

MS (EI, 70 eV) m/z (%): 267 (100), 265 (96) [^{79}Br-M$^+$], 187 (79), 109 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3021, 1542, 1509, 1473, 1443, 1396, 1314, 1158, 1144, 1092, 1067, 1020, 1001, 974, 828, 790, 757, 691, 675.

HRMS (EI) for $C_{10}H_7BrN_2S$ (265.9513): 265.9505.

Synthesis of 2-bromo-4-iodopyrimidine (57c):



2-Bromopyrimidine (**55**) (960 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.00 M in THF, 6.6 mL, 6.6 mmol) at −55 °C for 1.5 h according to **GP1**. A transmetalation using $ZnCl_2$ (1.00 M in THF, 6.6 mL, 6.6 mmol) was performed and the resulting mixture was allowed to warm up slowly to rt. Iodine (2.284 g, 9.0 mmol) dissolved in dry THF (9 mL) was then added dropwise and the resulting mixture was stirred for 45 min at rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL) and sat. aq. $Na_2S_2O_3$ (30 mL) was added, extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography on silica (CH_2Cl_2/pentane 1:4) furnished the compound **57c** as a coulourless solid (1.327 g, 85%).

m.p.: 103.5 – 104.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 5.1 Hz, 1 H), 7.74 (d, *J* = 5.1 Hz, 1 H).

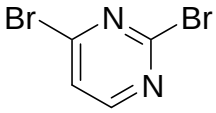
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.7, 151.2, 131.5, 129.9.

MS (70 eV, EI) m/z (%): 286 (73), 284 (73) [^{79}Br-M$^+$], 157 (100), 127 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 3006, 1513, 1388, 1312, 1180, 1150, 976, 832, 750, 662.

HRMS (EI) for $C_4H_2BrIN_2$ (283.8446): 283.8438.

Synthesis of 2,4-dibromopyrimidine (57d):



2-Bromopyrimidine (**55**) (960 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.00 M in THF, 6.6 mL, 6.6 mmol) at −55 °C for 1.5 h according to **GP1**. 1,2-Dibromotetrachloroethane (2.931 g, 9.0 mmol) dissolved in dry THF (9 mL) was then added dropwise at −55 °C, the resulting mixture was stirred for 1 h at −30 °C and then allowed to warm up slowly to rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **57d** as a colourless solid (1.008 g, 71%).

m.p.: 67.7 – 68.9°C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 5.3 Hz, 1 H), 7.50 (d, *J* = 5.3 Hz, 1 H).

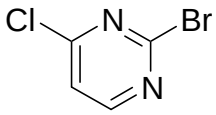
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 159.0, 153.2, 151.7, 124.6.

MS (70 eV, EI) m/z (%): 238 (97), 236 (48) [^{79}Br-M^{+}], 157 (100), 124 (19), 79 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3101, 3020, 1522, 1397, 1317, 1191, 1160, 1135, 978, 826, 752, 670.

HRMS (EI) for $C_4H_2Br_2N_2$ (235.8585): 235.8576.

Synthesis of 2-bromo-4-chloropyrimidine (57e):



2-Bromopyrimidine (**55**) (1.60 g, 10 mmol) dissolved in THF (10 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF; 10 mL, 11 mmol) at −55 °C for 1.5 h according to **GP1**. FCl_2CCClF_2 (2.81 g, 15 mmol) was dropwise added at −60 °C, then the mixture was allowed to warm up slowly to −45 °C and was stirred overnight at the same temperature. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/CH_2Cl_2 1:1) afforded the pyrimidine **57e** (1.381 g, 71%) as a yellowish solid.

m.p.: 46.5 – 47.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.44 (d, *J* = 5.3 Hz, 1 H), 7.35 (d, *J* = 5.3 Hz, 1 H).

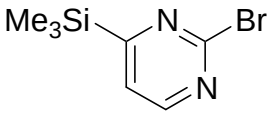
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 162.1, 159.7, 152.2, 120.7.

MS (EI, 70 eV) m/z (%): 194 (62), 192 (49) [^{79}Br-M^{+}], 157 (10), 115 (37).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3090, 3048, 1720, 1526, 1404, 1318, 1189, 1161, 1092, 979, 859, 815, 789, 755, 680.

HRMS (EI) for $C_4H_2BrClN_2$ (191.9090): 191.9075.

Synthesis of 2-bromo-4-trimethylsilanyl-pyrimidine (57f):



2-Bromopyrimidine (**55**) (480 mg, 3.0 mmol) dissolved in THF (3 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.20 M in THF, 2.75 mL, 3.3 mmol) at −55 °C for 1.5 h according to **GP1**. Trimethylsilyl cyanide (893 mg, 9.0 mmol) was then slowly added dropwise at −78 °C, the resulting mixture was stirred for 1 h at –55 °C. The reaction mixture

was quenched with a sat. aq. NH_4Cl solution (25 mL), extracted with diethyl ether (5 × 25 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **57f** as a yellow oil (471 mg, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.41 (d, *J* = 4.8 Hz, 1 H), 7.41 (d, *J* = 4.8 Hz, 1 H), 0.32 (s, 9 H).

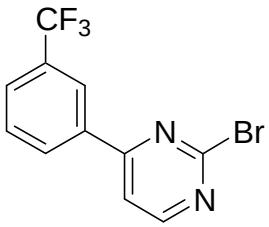
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 183.5, 157.2, 153.8, 124.8, -2.5.

MS (70 eV, EI) m/z (%): 232 (20), 230 (20) [^{79}Br-M$^+$], 215 (41), 151 (100), 137 (56), 73 (73).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 2895, 1550, 1503, 1396, 1317, 1251, 1152, 837, 771, 749, 667.

HRMS (EI) for $C_7H_{11}BrN_2Si$ (229.9875): 229.9851.

Synthesis of 2-bromo-4-(3-(trifluoromethyl)phenyl)pyrimidine (57g):



2-Bromopyrimidine (**55**) (960 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.00 M in THF, 6.6 mL, 6.6 mmol) at −55 °C for 1.5 h according to **GP1**. A transmetalation using $ZnCl_2$ (1.00 M in THF, 6.6 mL, 6.6 mmol) was performed and the resulting mixture was allowed to warm up slowly to rt. $Pd(dba)_2$ (102 mg, 3 mol%) and P(o-furyl)$_3$ (84 mg, 6 mol%) dissolved in THF (6 mL), and mixed with the addition of 3-iodobenzotrifluoride (2.122 g, 7.8 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **57g** (1.309 g, 72%) as a colourless solid.

m.p.: 92.9 – 94.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.58 (d, *J* = 5.1 Hz, 1 H), 8.19 – 8.26 (m, 2 H), 7.69 (d, *J* = 5.1 Hz, 1 H), 7.57 – 7.74 (m, 2 H).

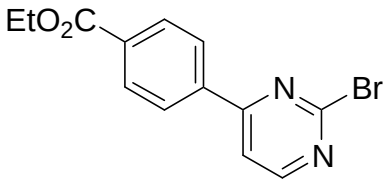
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.1, 159.9, 153.6, 135.6, 131.5 (q, *J* (C-F) = 32.6 Hz), 130.4, 129.6, 128.2 (q, *J* (C-F) = 3.6 Hz), 124.0 (q, *J* (C-F) = 3.6 Hz), 123.6 (q, *J* (C-F) = 272.6 Hz), 115.5.

MS (70 eV, EI) m/z (%): 304 (50), 302 (56) [^{79}Br-M^+], 223 (100), 203 (45), 171 (17), 151 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3040, 1615, 1560, 1533, 1419, 1335, 1271, 1156, 1110, 1092, 1064, 999, 924, 848, 840, 808, 761, 703.

HRMS (EI) for $C_{11}H_6BrF_3N_2$ (301.9666): 301.9659.

Synthesis of ethyl 4-(2-bromopyrimidin-4-yl)benzoate (57h):



2-Bromopyrimidine (**55**) (960 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.00 M in THF, 6.6 mL, 6.6 mmol) at −55 °C for 1.5 h according to **GP1**. A transmetalation using $ZnCl_2$ (1.00 M in THF, 6.6 mL, 6.6 mmol) was performed and the resulting mixture was allowed to warm up slowly to rt. $Pd(dba)_2$ (102 mg, 3 mol%) and P(o-furyl)$_3$ (84 mg, 6 mol%) dissolved in THF (6 mL), followed by the addition of ethyl 4-iodobenzoate (2.386 g, 7.8 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane, 1:3) furnished the compound **57h** (1.492 g, 81%) as a colourless solid.

m.p.: 128.9 – 130.1 °C.

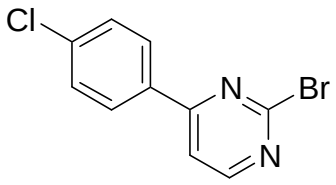
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.60 (d, *J* = 5.3 Hz, 1 H), 8.15 (d, *J* = 6.2 Hz, 2 H), 8.11 (d, *J* = 6.2 Hz, 2 H), 7.71 (d, *J* = 5.3 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.7, 159.9, 153.7, 138.7, 133.3 130.2, 127.3, 116.0, 61.4, 14.3.

MS (70 eV, EI) m/z (%): 308 (31), 306 (25) [^{79}Br-M^+], 280 (48), 278 (49), 263 (84), 261 (100), 235 (19), 233 (20), 199 (29), 154 (20), 127 (17).

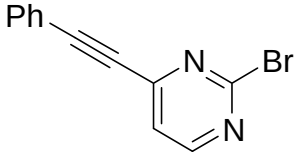
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3135, 3083, 2992, 2903, 1711, 1612, 1563, 1531, 1503, 1476, 1430, 1364, 1347, 1277, 1164, 1129, 1117, 1102, 1062, 1019, 984, 874, 850, 800, 780, 754, 712.
HRMS (EI) for $C_{13}H_{11}BrN_2O_2$ (306.0004): 305.9975.

Synthesis of 2-bromo-4-(4-chloro-phenyl)pyrimidine (57i):



2-Bromopyrimidine (**55**) (1.60 g, 10 mmol) dissolved in THF (10 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF; 10 mL, 11 mmol) at −55 °C for 1.5 h according to **GP1**. $ZnCl_2$ (1.0 M in THF; 12 mL, 12 mmol) was dropwise added at −60 °C and the resulting mixture was allowed to warm up slowly to 25 °C for 3 h. $Pd(dba)_2$ (115 mg, 2 mol %) and P(o-furyl)$_3$ (93 mg, 4 mol %) dissolved in THF (10 mL) and mixed with 1-chloro-4-iodobenzene (2.86 g, 12 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 50 °C for 1 h. Purification by flash chromatography (pentane/CH_2Cl_2 2:1) furnished the pyrimidine **57i** (1.810 g, 67%) as a yellowish solid.
m.p.: 130.9 – 132.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.56 (d, *J* = 5.3 Hz, 2 H), 8.02 (d, *J* = 8.6 Hz, 1 H), 7.63 (d, *J* = 5.3 Hz, 1 H), 7.47 (d, *J* = 8.6 Hz, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.6, 159.7, 153.6, 138.3, 133.4, 129.6, 128.7, 115.2.
MS (70 eV, EI) m/z (%): 270 (100), 268 (73) [^{79}Br-M$^+$], 191 (50), 137 (17).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 1594, 1561, 1523, 1488, 1423, 1397, 1337, 1167, 1088, 1060, 1010, 982, 817, 802, 763, 723, 660, 628.
HRMS (EI) for $C_{10}H_6BrClN_2$ (267.9403): 267.9412.

Synthesis of 2-bromo-4-(phenylethynyl)pyrimidine (57j):



To the solution of generated *in situ* 2-bromo-4-iodopyrimidine **57c** (starting from 2-bromopyrimidine (**55**) for 2 mmol scale), NEt_3 (14 mL), CuI (16 mg, 4 mol%), $Pd(dba)_2$ (34 mg, 3 mol%) and P(o-furyl)$_3$ (28 mg, 6 mol%) in THF (2 mL) and phenylacetylene (205 mg, 2.00 mol, 1.0 equiv) were successively slowly added. The reaction mixture was stirred at rt for 0.5 h. The resulting mixture was quenched with a sat. aq. NH_4Cl solution (25 mL), extracted with diethyl ether (5 × 25 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **57j** as a colourless solid (366 mg, 71%).

m.p.: 109.5 – 110.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 4.9 Hz, 1 H), 7.58 – 7.61 (m, 2 H), 7.38 – 7.44 (m, 3 H), 7.40 (d, *J* = 4.9 Hz, 1 H).

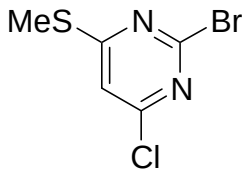
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 159.0, 153.1, 153.0, 132.5, 130.4, 128.6, 122.0, 120.6, 96.3, 88.8.

MS (70 eV, EI) m/z (%): 260 (68), 258 (70) [^{79}Br-M^+], 180 (16), 179 (100), 152 (14), 127 (39), 77 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3050, 2923, 2227, 2195, 1549, 1512, 1489, 1325, 1170, 1156, 1083, 1072, 1025, 974, 916, 890, 916, 890, 848, 748, 684, 553.

HRMS (EI) for $C_{12}H_7BrN_2$ (257.9793): 257.9795.

Synthesis of 2-bromo-4-chloro-6-(methylthio)pyrimidine (58a):



2-Bromo-4-(methylthio)pyrimidine (**57a**) (205 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 1.24 mL, 1.1 mmol) at rt for 5 min according to **GP1**. 1,2,2-Trichlorotrifluoroethane (281 mg, 1.5 mmol) was added dropwise at rt and the resulting mixture was stirred at this temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **58a** as a colourless solid (181 mg, 76%).

m.p.: 89.0 – 91.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.13 (s, 1 H), 2.56 (s, 3 H).

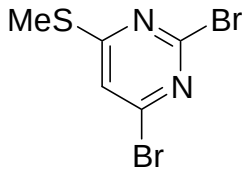
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 175.0, 159.2, 151.2, 116.4, 13.0.

MS (EI, 70 eV) m/z (%): 240 (100), 238 (75) [^{79}Br-M^+], 115 (16), 113 (53), 44 (32).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 3003, 2927, 1531, 1483, 1371, 1323, 1268, 1210, 1101, 970, 849, 809, 745.

HRMS (EI) for $C_5H_4BrClN_2S$ (237.8967): 237.9023.

Synthesis of 2,4-dibromo-6-(methylthio)pyrimidine (58b):



2-Bromo-4-(methylthio)pyrimidine (**57a**) (205 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 1.24 mL, 1.1 mmol) at rt for 5 min according to **GP1**. 1,2-Dibromotetrachloroethane (489 mg, 1.5 mmol) dissolved in THF (2 mL) was added dropwise at rt and the resulting mixture was stirred at this temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **58b** as a colourless solid (230 mg, 81%).

m.p.: 101.3 – 102.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.31 (s, 1 H), 2.56 (s, 3 H).

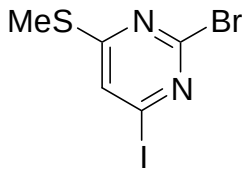
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.8, 151.2, 150.5, 120.7, 13.3.

MS (EI, 70 eV) m/z (%): 284 (100), 282 (47) [^{79}Br-M^+], 238 (7), 159 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3085, 3003, 2925, 1522, 1468, 1359, 1248, 1197, 1093, 964, 843, 804, 768.

HRMS (EI) for $C_5H_4Br_2N_2S$ (281.8462): 281.8437.

Synthesis of 2-bromo-4-iodo-6-(methylthio)pyrimidine (58c):



2-Bromo-4-(methylthio)pyrimidine (**57a**) (205 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 1.24 mL, 1.1 mmol) at rt for 5 min according to **GP1**. Iodine (381 mg, 1.5 mmol) dissolved in THF (2 mL) was added dropwise at rt and the resulting mixture was stirred at this temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL) and sat. aq. $Na_2S_2O_3$ solution (10 mL) was added, extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **58c** as a colourless solid (254 mg, 78%).

m.p.: 122.5 – 124.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.56 (s, 1 H), 2.53 (s, 3 H).

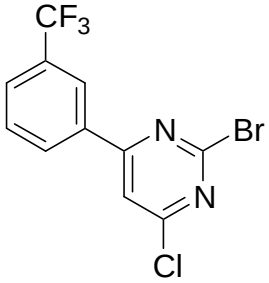
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.0, 150.5, 127.9, 126.3, 13.1.

MS (EI, 70 eV) m/z (%): 332 (97), 330 (100) [^{79}Br-M^+], 206 (54), 178 (22), 127 (61), 98 (65), 83 (41).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3121, 3075, 3013, 2930, 1553, 1484, 1290, 1230, 1194, 1117, 964, 868, 827, 804, 747.

HRMS (EI) for $C_5H_4BrIN_2S$ (329.8323): 329.8321.

Synthesis of 2-bromo-4-chloro-6-(3-(trifluoromethyl)-phenyl)pyrimidine (58d):



2-Bromo-4-(3-(trifluoromethyl)phenyl)pyrimidine (**57g**) (1.213 g, 4.0 mmol) dissolved in THF (8 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 4 mL, 4.4 mmol) at −40 °C for 45 min according to **GP1**. 1,1,2-Trichlorotrifluoroethane (1.124 g, 6.0 mmol) was then slowly added dropwise at −40 °C, the resulting mixture was then allowed to warm up slowly to rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **58d** as a colourless solid (1.221 g, 91%).

m.p.: 93.9 – 96.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.23 – 8.30 (m, 2 H), 8.80 – 8.83 (m, 1 H), 7.73 (s, 1 H), 7.63 – 7.69 (m, 1 H).

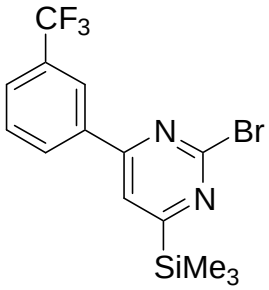
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.2, 162.9, 152.5, 134.9, 131.9 (q, *J* (C-F) = 33 Hz), 130.7, 129.9, 128.8 (q, *J* (C-F) = 3.6 Hz), 124.4 (q, *J* (C-F) = 3.6 Hz), 123.6 (q, *J* (C-F) = 272.7 Hz), 115.9.

MS (70 eV, EI) m/z (%): 338 (48), 336 (37) [^{79}Br-M^+], 259 (35), 257 (100), 196 (21), 176 (19), 145 (21), 87 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3131, 3070, 2961, 2930, 2868, 1724, 1615, 1551, 1517, 1478, 1452, 1437, 1383, 1336, 1307, 1295, 1277, 1241, 1161, 1122, 1096, 1070, 998, 977, 926, 895, 861, 807, 755, 690, 667, 636.

HRMS (EI) for $C_{11}H_5BrClF_3N_2$ (335.9277): 335.9273.

Synthesis of 2-bromo-4-(3-(trifluoromethyl)phenyl)-6-(trimethylsilyl)pyrimidine (58e):



2-Bromo-4-(3-(trifluoromethyl)phenyl)pyrimidine (**57g**) (304 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1 mL, 1.1 mmol) at −40 °C for 45 min according to **GP1**. Trimethylsilyl cyanide (149 mg, 1.5 mmol) was then slowly added dropwise at −40 °C, the resulting mixture was then allowed to warm up slowly to rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL),

extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **58e** as a colourless solid (271 mg, 72%).

m.p.: 82.2 – 83.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.23 – 8.29 (m, 2 H), 7.81 (s, 1 H), 7.75 – 7.77 (m, 1 H), 7.60 – 7.65 (m, 1 H), 0.38 (s, 9 H).

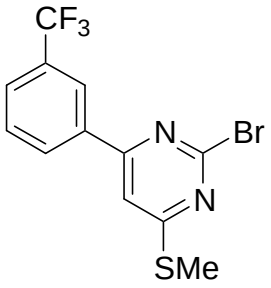
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 184.0, 163.1, 154.2, 136.5, 131.6 (q, *J* (C-F) = 32.5 Hz), 130.6, 129.6, 129.2, 127.9 (q, *J* (C-F) = 4.1 Hz), 124.4 (q, *J* (C-F) = 4.1 Hz), 123.8 (q, *J* (C-F) = 272.7 Hz), -2.4.

MS (70 eV, EI) m/z (%): 376 (36), 374 (33) [^{79}Br-M$^+$], 361 (35), 359 (32), 295 (100), 285 (24), 283 (21), 139 (29), 137 (28), 73 (64).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961, 2899, 1553, 1499, 1473, 1437, 1341, 1313, 1272, 1251, 1220, 1661, 1119, 1096, 1068, 838, 807, 789, 752, 688, 665, 623.

HRMS (EI) for $C_{14}H_{14}BrF_3N_2Si$ (374.0062): 374.0049.

Synthesis of 2-bromo-4-(methylthio)-6-(3-(trifluoromethyl)-phenyl)pyrimidine (58f):



2-Bromo-4-(3-(trifluoromethyl)phenyl)pyrimidine (**57g**) (304 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1 mL, 1.1 mmol) at −40 °C for 45 min according to **GP1**. S-Methyl methanethiol sulfonate (189 mg, 1.5 mmol) was then slowly added dropwise at −40 °C, the resulting mixture was then allowed to warm up slowly to rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:8) furnished the compound **58f** as a colourless solid (265 mg, 76%).

m.p.: 85.9 – 87.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.14 – 8.22 (m, 2 H), 7.71 – 7.74 (m, 1 H), 7.55 – 7.61 (m, 1 H), 7.47 (s, 1 H), 2.60 (s, 3 H).

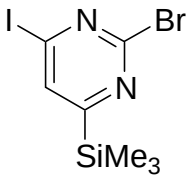
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.3, 162.0, 152.8, 135.8, 131.4 (q, *J* (C-F) = 32.4 Hz), 130.4, 129.5, 127.8 (q, *J* (C-F) = 3.6 Hz), 124.0 (q, *J* (C-F) = 3.6 Hz), 123.7 (q, *J* (C-F) = 272.7 Hz), 112.8, 12.9.

MS (70 eV, ESI) m/z (%): 351 (100), 349 (99) [^{79}Br-M^+], 317 (22), 241 (9), 239 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1615, 1558, 1504, 1491, 1476, 1447, 1429, 1385, 1339, 1313, 1292, 1230, 1184, 1168, 1117, 1096, 1070, 969, 923, 897, 853, 807, 758, 716, 690, 665, 636.

HRMS (ESI) for $C_{12}H_8BrF_3N_2S$ (348.9622 (M^+ + H)): 348.9621.

Synthesis of 2-bromo-4-iodo-6-(trimethylsilyl)pyrimidine (58g):



2–Bromo-4-iodopyrimidine (**57c**) (285 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1.0 mL, 1.1 mmol) at −55 °C for 1 h according to **GP1**. Trimethylsilyl cyanide (149 mg, 1.5 mmol) was then slowly added dropwise at −55 °C, the resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **58g** as a colourless solid (330 mg, 93%).

m.p.: 64.3 – 66.6 °C.

^{1}H-NMR (400 MHz, THF-d_8) δ: 8.03 (s, 1 H), 0.31 (s, 9 H).

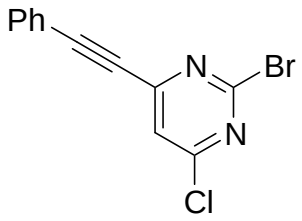
^{13}C-NMR (100 MHz, THF-d_8) δ: 182.8, 151.9, 137.1, 131.0, –2.7.

MS (70 eV, EI) m/z (%): 358 (13), 356 (11) [^{79}Br-M^+], 340 (22), 338 (15), 276 (62), 231 (100), 229 (98), 139 (41), 137 (39).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957, 2898, 1518, 1449, 1250, 1218, 1168, 1134, 1120, 1078, 970, 837, 776, 744, 728, 625.

HRMS (EI) for $C_7H_{10}BrIN_2Si$ (355.8841): 355.8829.

Synthesis of 2-bromo-4-chloro-6-(phenylethynyl)pyrimidine (58h):



2-Bromo-4-(phenylethynyl)pyrimidine (**57j**) (1.554 g, 6.0 mmol) dissolved in THF (12 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 6.00 mL, 6.6 mmol) THF at -20 °C for 30 min according to **GP1**. 1,1,2-Trichlorotrifluoroethane (1.686 g, 9.0 mmol) was then slowly added at -20 °C, the resulting mixture was then allowed to warm up slowly to rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **58h** as a white solid (1.471 g, 84%).

m.p.: 105.7 – 106.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.58 – 7.61 (m, 2 H), 7.36 – 7.46 (m, 3 H), 7.44 (s, 1 H).

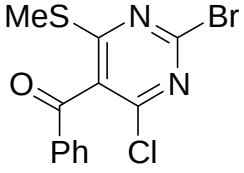
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.9, 153.5, 151.9, 132.6, 130.7, 128.7, 122.1, 120.2, 97.6, 85.1.

MS (70 eV, EI) m/z (%): 294 (100), 292 (64) [^{79}Br-M^+], 215 (23), 213 (80), 153 (17), 152 (43), 126 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062, 2209, 1539, 1494, 1483, 1442, 1394, 1346, 1324, 1244, 1226, 1180, 1172, 1008, 1069, 1026, 998, 973, 925, 912, 864, 812, 756, 741, 686, 590, 570.

HRMS (EI) for $C_{12}H_6BrClN_2$ (291.9403): 291.9391.

Synthesis of (2-bromo-4-chloro-6-(methylthio)pyrimidin-5-yl)(phenyl)methanone (59a):



2-Bromo-4-chloro-6-(methylthio)pyrimidine (**58a**) (240 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 1.24 mL, 1.1 mmol) at rt for 20 min according to **GP1**. The reaction mixture was cooled to –30 °C,

CuCN·2LiCl (1.00 M solution in THF, 1.1 mL, 1.1 mmol) was added and the reaction mixture was stirred for 30 min according to **GP2**. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at –30 °C and the resulting mixture was stirred at rt for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **59a** as a colourless solid (276 mg, 81%).

m.p.: 120.5 – 121.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.79 – 7.82 (m, 2 H), 7.62 – 7.68 (m, 1 H), 7.47 – 7.52 (m, 2 H), 2.55 (s, 3 H).

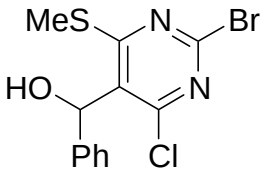
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 190.4, 172.2, 155.4, 150.5, 135.0, 134.5, 129.4, 129.2, 127.8, 13.5.

MS (EI, 70 eV) m/z (%): 344 (99), 342 (71) [^{79}Br-M^+], 329 (16), 327 (16), 311 (90), 309 (71), 267 (24), 265 (20), 253 (47), 251 (35), 105 (94), 77 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3018, 2922, 2851, 1674, 1596, 1485, 1450, 1284, 1233, 1204, 1177, 1101, 922, 829, 710, 687.

HRMS (EI) for $C_{12}H_8BrClN_2OS$ (341.9229): 341.9182.

Synthesis of (2-bromo-4-chloro-6-(methylthio)pyrimidin-5-yl)(phenyl)methanol (59b):



2-Bromo-4-chloro-6-(methylthio)pyrimidine (**58a**) (240 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 1.24 mL, 1.1 mmol) at rt for 20 min according to **GP1**. Benzaldehyde (159 mg, 1.5 mmol) was added dropwise at rt and the resulting mixture was stirred at this temperature for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **59b** as a colourless solid (257 mg, 75%).

m.p.: 116.8 – 118.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.30 – 7.36 (m, 5 H), 6.41 (d, *J* = 6.8 Hz, 1 H), 3.12 (d, *J* = 7.1 Hz, 1 H), 2.52 (s, 3 H).

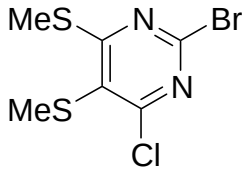
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.0, 158.2, 148.9, 138.8, 129.3, 128.5, 128.0, 125.6, 70.4, 14.4.

MS (EI, 70 eV) m/z (%): 346 (100), 344 (75) [^{79}Br-M^+], 331 (85), 329 (67), 281 (54), 279 (40), 255 (23), 253 (53).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3327, 3027, 2906, 1526, 1475, 1311, 1255, 1210, 1127, 1053, 882, 844, 814, 768, 713.

HRMS (EI) for $C_{12}H_{10}BrClN_2OS$ (343.9386): 343.9375.

Synthesis of 2-bromo-4-chloro-5,6-bis(methylthio)pyrimidine (59c):



2-Bromo-4-chloro-6-(methylthio)pyrimidine (**58a**) (240 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 1.24 mL, 1.1 mmol) at rt for 20 min according to **GP1**. Then, S-methyl methanethiol sulfonate (252 mg, 2.0 mmol) was added dropwise at rt and the resulting mixture was stirred at the same temperature for 45 min and was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:9) furnished the compound **59c** as a colourless solid (260 mg, 92%).

m.p.: 90.3 – 92.2°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3 H), 2.37 (s, 3 H).

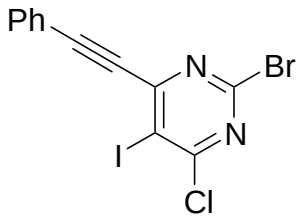
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 179.6, 163.4, 149.6, 125.5, 16.8, 14,9.

MS (EI, 70 eV) m/z (%): 286 (28), 284 (21) [^{79}Br-M^+], 269 (74), 251 (12), 189 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3200, 3018, 2927, 1498, 1465, 1321, 1283, 1258, 1202, 1043, 968, 834, 816, 798, 761.

HRMS (EI) for $C_6H_6BrClN_2S_2$ (283.8844): 283.8816.

Synthesis of 2-bromo-4-chloro-5-iodo-6-(phenylethynyl)-pyrimidine (59d):



2-Bromo-4-chloro-6-(phenylethynyl)pyrimidine (**58h**) (294 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1 mL, 1.1 mmol) at –5 °C for 30 min according to **GP1**. Iodine (381 mg, 1.5 mmol) dissolved in THF (2 mL) was then slowly added dropwise at the same temperature, the resulting mixture was then allowed to warm up slowly to rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL) was added, extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished the compound **59d** as a colourless solid (297 mg, 71%).

m.p.: 194.6 – 196.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.66 – 7.68 (m, 2 H), 7.46 – 7.49 (m, 1 H), 7.40 – 7.42 (m, 2 H).

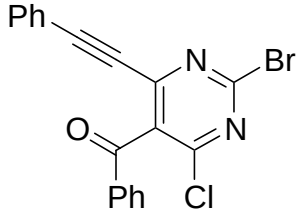
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 165.8, 158.5, 150.5, 132.7, 131.0, 128.7, 120.2, 100.9, 98.9, 88.9.

MS (70 eV, EI) m/z (%): 420 (100), 418 (78) [^{79}Br-M^+], 341 (10), 339 (31), 212 (21), 177 (43), 151 (36).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3055, 2923, 2206, 1496, 1483, 1452, 1441, 1380, 1267, 1227, 1183, 1167, 1011, 924, 911, 816, 753, 684, 553.

HRMS (EI) for $C_{12}H_5BrClIN_2$ (417.8369): 417.8348.

Synthesis of (2-bromo-4-chloro-6-(phenylethynyl)pyrimidin-5-yl)(phenyl)methanone (59e):



2-Bromo-4-chloro-6-(phenylethynyl)pyrimidine (**58h**) (294 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1 mL, 1.1 mmol) at –5 °C for 30 min according to **GP1**. The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.00 M solution in THF, 1.1 mL, 1.1 mmol) was added and the reaction mixture was stirred for 30 min according to **GP2**. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at –30 °C and the resulting mixture was stirred at rt for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **59e** as a colourless solid (274 mg, 69%).

m.p.: 155.6 – 157.9 °C.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.88 (m, 2 H), 7.66 – 7.69 (m, 1 H), 7.52 – 7.55 (m, 2 H), 7.34 – 7.36 (m, 1 H), 7.22 – 7.25 (m, 2 H), 7.13 – 7.15 (m, 2 H).

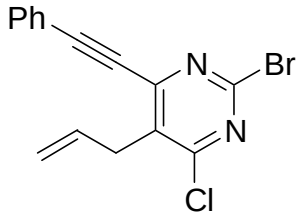
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 190.0, 158.4, 151.5, 150.6, 135.0, 134.8, 132.7, 132.5, 130.9, 129.6, 129.3, 128.5, 119.6, 102.6, 84.1.

MS (EI, 70 eV) m/z (%): 397 (100), 396 (75) [^{79}Br-M$^+$], 369 (40), 367 (25), 361 (19), 359 (16), 281 (63), 254 (90), 252 (46), 227 (39), 151 (36), 105 (45), 77 (95).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3330, 3055, 2918, 2850, 2211, 1670, 1594, 1581, 1520, 1491, 1475, 1438, 1378, 1338, 1307, 1264, 1222, 1167, 1098, 1069, 1024, 995, 940, 914, 829, 800, 779, 756, 708, 687, 579.

HRMS (EI) for $C_{19}H_{10}BrClN_2O$ (395.9665): 395.9650.

Synthesis of 5-allyl-2-bromo-4-chloro-6-(phenylethynyl)-pyrimidine (59f):



2-Bromo-4-chloro-6-(phenylethynyl)pyrimidine (**58h**) (294 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1 mL, 1.1 mmol) at –5 °C for 30 min according to **GP1**. The reaction mixture was cooled to –78 °C, CuCN·2LiCl (1.00 M solution in THF, 5 drops) was added and the reaction mixture was stirred for 5 min. Then, allyl bromide (242 mg, 2.0 mmol) was added dropwise at –78 °C and

the resulting mixture was allowed to warm up slowly at –30 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **59f** as a colourless solid (230 mg, 67%).

m.p.: 112.5 – 114.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.57 – 7.61 (m, 2 H), 7.36 – 7.47 (m, 3 H), 5.83 – 5.96 (m, 1 H), 5.13 – 5.20 (m, 2 H), 3.67 (dt, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 2 H).

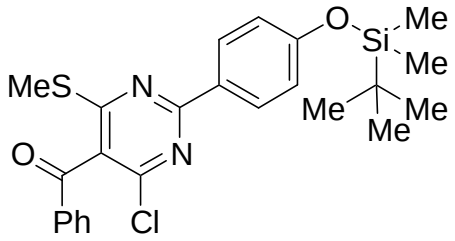
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 162.0, 153.1, 148.6, 132.4, 131.8, 131.3, 130.6, 128.7, 120.4, 118.1, 99.9, 84.5, 34.0.

MS (EI, 70 eV) m/z (%): 333 (100), 332 (29) [^{79}Br-M$^+$], 331 (90), 253 (21), 252 (12), 251 (21), 218 (18), 217 (23), 216 (38), 191 (15), 190 (38), 165 (21), 103 (17), 44 (33), 43 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 2908, 2844, 2211, 1636, 1525, 1486, 1444, 1431, 1383, 1320, 1262, 1212, 1180, 1170, 1114, 1088, 1069, 1025, 990, 938, 924, 880, 845, 787, 758, 687, 616, 603, 574.

HRMS (EI) for $C_{15}H_{10}BrClN_2$ (331.9716): 331.9722.

Synthesis of (2-(4-(*tert*-butyldimethylsilyloxy)phenyl)-4-chloro-6-(methylthio)pyrimidin-5-yl)-(phenyl)methanone (60a):



This compound was prepared from 2-bromo-4-chloro-6-(methylthio)pyrimidin-5-yl)(phenyl)methanone (**59a**). *Tert*-butyl(4-iodophenoxy)dimethylsilane (401 mg, 1.2 mmol, 1.2 equiv) was charged with freshly titrated *i*-PrMgCl·LiCl (1.20 M in THF, 1 mL, 1.2 mmol). The reaction mixture was stirred at –20 °C for 45 min. After completion of the reaction, a solution of zinc chloride (1.2 mL, 1.00 M, 1.2 mmol) was added and the resulting mixture was stirred at –20 °C until –10 °C and finally warmed up to rt for 15 min. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of **59a** (344 mg, 1.0 mmol) dissolved in THF (2 mL), were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 45 min and

then quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane, 1:5) furnished the compound **60a** (425 mg, 91%) as a colourless solid.

m.p.: 124.3 – 126.2 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.40 (d, *J* = 8.8 Hz, 2 H), 7.86 – 7.89 (m, 2 H), 7.61 – 7.67 (m, 1 H), 7.47 – 7.52 (m, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 2.66 (s, 3 H), 1.01 (s, 9 H), 0.25 (s, 6 H).

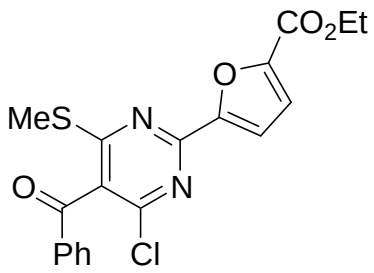
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.1, 169.5, 163.3, 159.5, 155.6, 135.4, 134.5, 130.6, 129.5, 129.0, 128.9, 125.9, 120.3, 25.6, 18.3, 13.2, –4.4.

MS (70 eV, EI) m/z (%): 470 (18) [M^+], 413 (100), 105 (55), 77 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3068, 2952, 2922, 2886, 2851, 1662, 1599, 1578, 1533, 1483, 1394, 1316, 1260, 1233, 1162, 1119, 1005, 922, 904, 859, 826, 781, 712, 687.

HRMS (ESI) for $C_{24}H_{27}ClN_2O_2SSi$ (471.1329 (M^+ + H)): 471.1328.

Synthesis of ethyl 5-(5-benzoyl-4-chloro-6-(methylthio)-pyrimidin-2-yl)furan-2-carboxylate (60b):



This compound was prepared from 2-bromo-4-chloro-6-(methylthio)pyrimidin-5-yl)(phenyl)methanone (**59a**). 5-Bromofuran-2-carboxylic acid ethyl ester (263 mg, 1.2 mmol, 1.2 equiv) was treated with freshly titrated *i*-PrMgCl·LiCl (1.20 M in THF, 1 mL, 1.2 mmol). The reaction mixture was stirred at –30 °C for 45 min. After completion of the reaction, a solution of zinc chloride (1.2 mL, 1.00 M, 1.2 mmol) was added and the resulting mixture was stirred at –20 °C until –10 °C and finally warmed up to rt for 15 min. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of **59a** (344 mg, 1.0 mmol) dissolved in THF (2 mL) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 3 h and then quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over

anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane, 1:2) furnished the compound **60b** (351 mg, 88%) as a colourless solid.

m.p.: 101.3 – 104.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.82 – 7.85 (m, 2 H), 7.62 – 7.67 (m, 1 H), 7.47 – 7.52 (m, 2 H), 7.44 (d, *J* = 3.8 Hz, 1 H), 7.30 (d, *J* = 3.8 Hz, 1 H), 4.41 (q, *J* = 7.3 Hz, 2 H), 2.64 (s, 3 H), 1.40 (t, *J* = 7.3 Hz, 3 H).

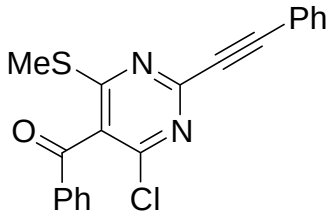
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 191.3, 170.5, 158.2, 155.7, 155.4, 152.8, 146.7, 135.0, 134.8, 129.5, 129.1, 127.2, 119.2, 116.4, 61.4, 14.3, 13.2.

MS (70 eV, EI) m/z (%): 402 (43) [M^+], 294 (81), 369 (98), 311 (100), 105 (63), 77 (65).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3124, 3058, 3003, 2982, 1702, 1669, 1584, 1530, 1490, 1450, 1397, 1366, 1288, 1240, 1152, 1016, 922, 829, 763, 710, 685.

HRMS (EI) for $C_{19}H_{15}ClN_2O_4S$ (402.0441): 402.0428.

Synthesis of (4-chloro-6-(methylthio)-2-(phenylethynyl)-pyrimidin-5-yl)(phenyl)-methanone (60c):



This compound was prepared from 2-bromo-4-chloro-6-(methylthio)pyrimidin-5-yl)(phenyl)methanone (**59a**). To a solution of NEt_3 (6 mL) and CuI (8 mg, 4 mol%) were added $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) in THF (2 mL), followed by **59a** (344 mg, 1.0 mmol) dissolved in THF (2 mL) and phenylacetylene (123 mg, 1.2 mol, 1.2 equiv). The reaction mixture was stirred at rt for 3 h and then quenched with a sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane, 1:3) furnished the compound **60c** (310 mg, 85%) as a colourless solid.

m.p.: 133.0 – 134.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.85 (m, 10 H), 2.59 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 191.1, 170.2, 155.0, 151.5, 134.8, 134.7, 132.7, 130.1, 129.4, 129.1, 128.4, 127.6, 120.7, 89.8, 87.3, 13.3.

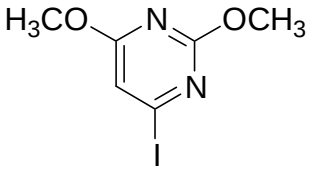
MS (70 eV, EI) m/z (%): 364 (19) [M^+], 331 (41), 273 (44), 128 (27), 105 (44), 87 (16), 77 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2931, 2213, 1669, 1599, 1518, 1475, 1397, 1321, 1270, 1233, 1175, 1111, 930, 831, 758, 715, 687.

HRMS (ESI) for $C_{20}H_{13}ClN_2OS$ (365.0515 (M^+ + H)): 365.0506.

2.5. Preparation of polyfunctionalized protected uracils and thiouracils

Synthesis of 4-iodo-2,6-dimethoxypyrimidine (68a):



2,4-Dimethoxypyrimidine (**64**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to **GP1**. Iodine (381 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –15 °C for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at –15 °C, followed by the addition of sat. aq. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) afforded **68a** (196 mg, 74%) as a colourless solid.

m.p.: 100.5 – 101.9 °C.

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

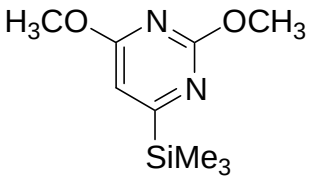
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.6, 163.6, 127.8, 112.5, 55.3, 54.1.

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

IR (ATR) $\tilde{\nu}$ (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).

HRMS for $C_6H_7IN_2O_2$ (265.9552): 265.9560.

Synthesis of 2,4-dimethoxy-6-(trimethylsilyl)pyrimidine (68b):



2,4-Dimethoxypyrimidine (**64**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to **GP1**. TMSCN (1.5 mmol, 149 mg, 1.5 equiv) was then added to the resulting mixture at 25 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) afforded **68b** (149 mg, 70%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.53 (s, 1 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 0.23 (s, 9 H).

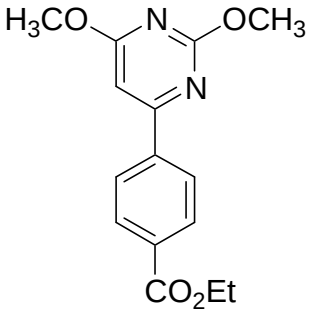
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 179.2, 170.5, 164.7, 107.2, 54.4, 53.3, –2.6.

MS (EI, 70 eV) m/z (%): 212 (10) [M^+], 197 (30), 92 (11), 80 (11), 44 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (m), 2899 (w), 1742 (s), 1570 (s), 1543 (s), 1470 (m), 1361 (m), 1327 (vs), 1247 (m), 1218 (w), 1200 (m), 1095 (m), 1030 (w), 881 (m), 835 (m), 820 (m), 755 (m).

HRMS for $C_9H_{16}N_2O_2Si$ (212.0981): 212.0969.

Synthesis of ethyl 4-(2,6-dimethoxypyrimidin-4-yl)benzoate (68c):



2,4-Dimethoxypyrimidine (**64**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to **GP1**. Transmetalation with $ZnCl_2$ (1.2 mL, 1.2 equiv, 1.00 M in THF) was then performed at 25 °C for 20 min. In another flame-dried round bottom flask, $Pd(dba)_2$ (17 mg, 3

mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min followed by the addition of ethyl 4-iodobenzoate (331 mg, 1.2 mmol, 1.2 equiv). The resulting solution was then transferred to the zinc reagent flask and refluxed for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 3:2) afforded **68c** (216 mg, 75%) as a colourless solid.

m.p.: 116.0 – 118.2 °C

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

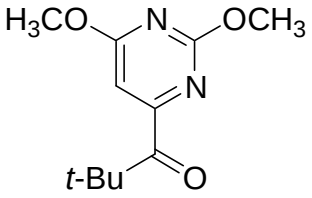
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.7, 166.1, 165.6, 164.8, 140.7, 132.2, 129.9, 126.9, 98.0, 61.2, 54.9, 54.1, 14.3.

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

IR (ATR) $\tilde{\nu}$ (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).

HRMS (EI) for $C_{15}H_{16}N_2O_4$ (288.1110): 288.1097.

Synthesis of 1-(2,6-dimethoxypyrimidin-4-yl)-2,2-dimethylpropan-1-one (68d):



2,4-Dimethoxypyrimidine (**64**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to **GP1**. Transmetalation with CuCN·2LiCl (1.0 mL, 1.0 equiv, 1.00 M in THF) was then performed at –30 °C and stirred at the same temperature for 30 min according to **GP2**. Pivaloyl chloride (241 mg, 2.0 mmol, 2.0 equiv) was added to the resulting mixture at –30 °C and stirred at the same temperature for 6 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane/ethyl acetate 9:1) afforded **68d** (161 mg, 72%) as a colourless solid.

m.p.: 67.8 – 69.0 °C.

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

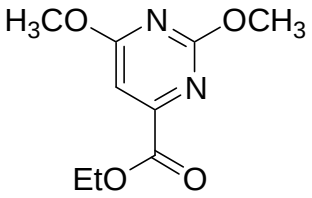
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 205.1, 172.7, 164.7, 163.4, 101.1, 55.1, 54.2, 44.0, 26.9.

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

IR (ATR) $\tilde{\nu}$ (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).

HRMS for $C_{11}H_{16}N_2O_3$ (224.1161): 224.1142.

Synthesis of ethyl 2,6-dimethoxypyrimidine-4-carboxylate (68e):



2,4-Dimethoxypyrimidine (**64**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to **GP1**. Ethyl cyanoformate (198 mg, 2 mmol, 2.0 equiv) was then added to the resulting mixture at –60 °C and stirred at the same temperature for 10 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane/ethyl acetate 4:1) afforded **68e** (147 mg, 70%) as a colourless solid.

m.p.: 67.2 – 68.9 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.03 (s, 1 H), 4.40 (q, J = 7.0 Hz, 2 H), 4.04 (s, 3 H), 4.00 (s, 3 H), 1.39 (t, J = 7.0 Hz, 3 H).

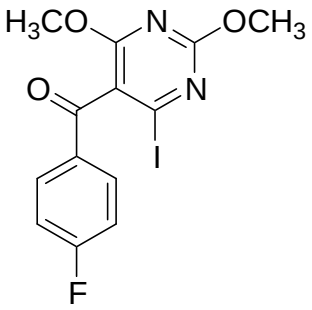
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.8, 165.9, 163.9, 157.2, 103.1, 62.2, 55.1, 54.1, 14.1.

MS (EI, 70 eV) m/z (%): 212 (21) [M^+], 211 (10), 182 (15), 167 (11), 140 (100), 139 (13), 125 (31), 82 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 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).

HRMS (EI) for $C_9H_{12}N_2O_4$ (212.0797): 212.0794.

Synthesis of (4-fluorophenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (69a):



4-Iodo-2,6-dimethoxypyrimidine (**68a**) (1.0 mmol, 266 mg, 1.0 equiv) dissolved in dry THF (2.0 mL) was added dropwise to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 0 °C according to **GP1**. CuCN·2LiCl (1 mL, 1 mmol, 1.00 M in THF) was added at –30 °C and stirred for 30 min according to **GP2**. Thereafter, 4-fluorobenzoyl chloride (316 mg, 2.0 mmol, 2.0 equiv) was added at –30 °C, and the reaction mixture was warmed to 25 °C within 5 h. The resulting mixture was quenched with sat. aq. NH_4Cl solution, extracted with EtOAc (3 x 30 ml), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pentane/Et_2O 1:1) afforded **69a** (313 mg, 81%) as a colourless solid.

m.p.: 151.9 – 157.1 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.83 – 7.77 (m, 2 H), 7.12 – 7.05 (m, 2 H), 3.98 (s, 3 H), 3.83 (s, 3 H).

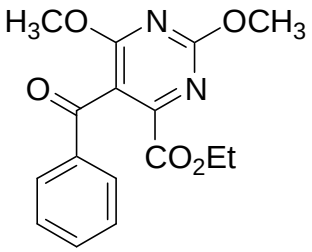
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 191.4, 166.4 (d, J = 257.1 Hz), 167.2, 163.5, 132.4 (d, J = 9.7 Hz), 132.1 (d, J = 2.8 Hz), 126.7, 120.9, 116.2 (d, J = 22.1 Hz), 55.7, 54.8.

MS (EI, 70 eV) m/z (%): 388 (66) [M^+], 358 (5), 293 (31), 261 (10), 136 (25), 123 (100), 95 (80), 75 (24).

IR (ATR) $\tilde{\nu}$ (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).

HRMS (EI) for $C_{13}H_{10}FIN_2O_3$ (387.9720): 387.9722.

Synthesis of ethyl 5-benzoyl-2,6-dimethoxypyrimidine-4-carboxylate (69b)



Ethyl 2,6-dimethoxypyrimidine-4-carboxylate (**68e**) (1.0 mmol, 212 mg, 1.0 equiv) dissolved in dry THF (2.0 mL) was added dropwise to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at –40 °C according to **GP1**. The reaction mixture was stirred for 2 h at this temperature. CuCN·2LiCl (1 mL, 1 mmol, 1.00 M in THF) was added at –40 °C and stirred for 1 h according to **GP2**. 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 vacuo*. Purification by flash chromatography (pentane/ Et_2O 1:1) afforded **69b** (233 mg, 74%) as a colourless solid.

m.p.: 98.4 – 100.4 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.80 – 7.77 (m, 2 H), 7.60 – 7.54 (m, 1 H), 7.47 – 7.41 (m, 2 H), 4.17 (q, *J* = 7.3 Hz, 2 H), 4.11 (s, 3 H), 3.95 (s, 3 H), 1.08 (t, *J* = 7.1 Hz, 3 H).

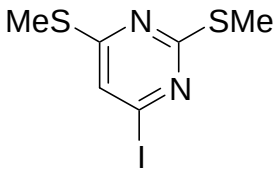
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.0, 169.9, 165.2, 163.3, 155.3, 137.0, 133.6, 128.9, 128.9, 128.7, 128.7, 116.1, 62.6, 55.5, 55.0, 13.5.

MS (EI, 70 eV) m/z (%): 316 (45) [M^+], 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).

IR (ATR) $\tilde{\nu}$ (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).

HRMS (EI): **for $C_{16}H_{16}N_2O_5$** (316.1059): 316.1036.

Synthesis of 4-iodo-2,6-bis(methylthio)pyrimidine (72a):



2,4-Bis(methylthio)pyrimidine (**70**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –20 °C for 1 h according to **GP1**. Iodine (381 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –20 °C for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at –20 °C, followed by the addition of sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) afforded **72a** (226 mg, 76%) as a colourless solid.

m.p.: 122.8 – 123.5 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25 (s, 1 H), 2.51 (s, 3 H), 2.50 (s, 3 H).

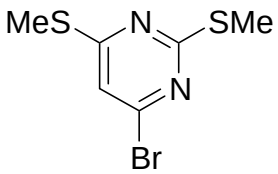
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 171.9, 170.5, 126.2, 123.5, 14.3, 12.5.

MS (EI, 70 eV) m/z (%): 298 (100) [M^+], 283 (14), 265 (26), 98 (50), 83 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2998 (w), 2921 (w), 1516 (s), 1505 (s), 1474 (m), 1434 (m), 1406 (s), 1348 (m), 1323 (w), 1283 (w), 1247 (s), 1205 (m), 1164 (m), 1096 (m), 975 (s), 961 (s), 821 (m), 754 (s), 748 (s).

HRMS (EI) for $C_6H_7IN_2S_2$ (297.9095): 297.9072.

Synthesis of 4-bromo-2,6-bis(methylthio)pyrimidine (72b):



2,4-Bis(methylthio)pyrimidine (**70**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –20 °C for 1 h according to **GP1**. $(BrCCl_2)_2$ (488 mg, 1.5 mmol, 1.5 equiv) dissolved in THF (2 mL) was then added to the resulting mixture at –20 °C for 1 h. The reaction mixture was quenched with

sat. aq. NH_4Cl solution at –20 °C and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) afforded **72b** (203 mg, 81%) as a colourless solid.

m.p.: 93.0 – 94.8 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.00 (s, 1 H), 2.53 (s, 6 H).

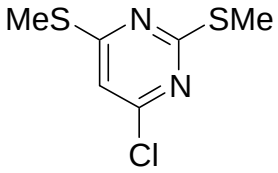
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.5, 171.6, 149.9, 116.4, 14.3, 12.6.

MS (EI, 70 eV) m/z (%): 250 (100) [^{79}Br-M^+], 235 (36), 217 (83), 149 (35), 98 (69).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3087 (w), 2997 (w), 2923 (w), 1520 (s), 1481 (s), 1430 (m), 1404 (w), 1357 (m), 1325 (w), 1291 (w), 1254 (s), 1170 (m), 1098 (s), 974 (w), 959 (s), 832 (m), 816 (w), 774 (s), 748 (m).

HRMS (EI) for $C_6H_7BrN_2S_2$ (249.9234): 249.9230.

Synthesis of 4-chloro-2,6-bis(methylthio)pyrimidine (72c):



2,4-Bis(methylthio)pyrimidine (**70**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –20 °C for 1 h according to **GP1**. ClF_2CCFCl_2 (281 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –35 to –20 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution at –20 °C and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) afforded **72c** (161 mg, 78%) as a colourless solid.

m.p.: 85.0 – 86.7 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.83 (s, 1 H), 2.54 (s, 6 H).

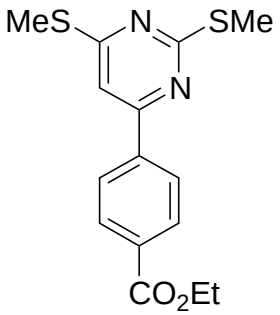
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.7, 172.1, 158.7, 112.5, 14.2, 12.7.

MS (EI, 70 eV) m/z (%): 206 (100) [M^+], 191 (21), 173 (40), 145 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3093 (w), 2998 (w), 2925 (w), 1530 (s), 1491 (s), 1433 (m), 1410 (w), 1360 (m), 1324 (w), 1312 (w), 1259 (s), 1175 (m), 1097 (s), 966 (w), 809 (s), 748 (m).

HRMS (EI) for $C_6H_7ClN_2S_2$ (205.9739): 205.9721.

Synthesis of 4-(2,6-bis(methylthio)pyrimidin-4-yl)-benzoic acid ethyl ester (72d):



2,4-Bis(methylthio)pyrimidine (**70**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –20 °C for 1 h according to **GP1**. Transmetalation with $ZnCl_2$ (1.2 mL, 1.2 equiv, 1.00 M in THF) was then performed at –60 to 25 °C for 3 h. In another flame-dried round bottom flask, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min followed by the addition of ethyl 4-iodobenzoate (331 mg, 1.2 mmol, 1.2 equiv). The resulting solution was then transferred to the zinc reagent flask and refluxed for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) afforded **72d** (227 mg, 71%) as a colourless solid.

m.p.: 108.7 – 110.2 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 8.7 Hz, 2 H), 8.05 (d, *J* = 8.7 Hz, 2 H), 7.22 (s, 1 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 2.61 (s, 3 H), 2.58 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

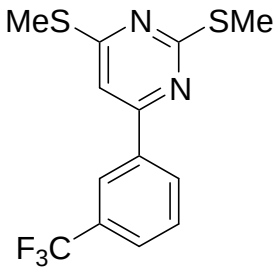
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.1, 171.1, 166.0, 160.1, 140.3, 132.2, 129.8, 127.0, 109.7, 61.1, 14.3, 14.1, 12.4.

MS (EI, 70 eV) m/z (%): 320 (100) [M^+], 305 (21), 287 (28), 275 (13), 213 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2981 (m), 2920 (w), 1709 (s), 1575 (w), 1544 (s), 1505 (s), 1491 (s), 1471 (m), 1427 (w), 1407 (w), 1363 (w), 1307 (m), 1268 (s), 1248 (s), 1148 (w), 1120 (w), 1100 (s), 1078 (w), 1013 (w), 969 (w), 868 (w), 837 (s), 815 (m), 779 (s), 756 (s), 700 (s).

HRMS (EI) for $C_{15}H_{16}N_2O_2S_2$ (320.0653): 320.0642.

Synthesis of 2,4-bis(methylthio-6-(3-trifluoromethyl-phenyl))pyrimidine (72e):



2,4-Bis(methylthio)pyrimidine (**70**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –20 °C for 1 h according to **GP1**. Transmetalation with $ZnCl_2$ (1.2 mL, 1.2 equiv, 1.00 M in THF) was then performed at –60 to 25 °C for 3 h. In another flame-dried round bottom flask, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min followed by the addition of 3-iodobenzotrifluoride (327 mg, 1.2 mmol, 1.2 equiv). The resulting solution was then transferred to the zinc reagent flask and refluxed for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) afforded **72e** (251 mg, 80%) as a colourless solid.

m.p.: 85.9 – 87.1 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1 H), 8.17 (d, 1 H, *J* = 7.7 Hz), 7.70 (d, 1 H, *J* = 7.7 Hz), 7.56 (t, 1 H, *J* = 7.7 Hz), 7.20 (s, 1 H), 2.62 (s, 3 H), 2.58 (s, 3 H).

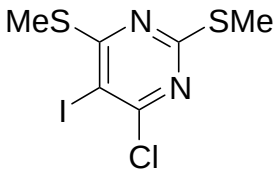
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.2, 171.3, 159.6, 137.1, 131.2 (q, *J* = 32.5 Hz), 130.2, 129.2, 127.2 (q, *J* = 3.6 Hz), 123.9 (q, *J* = 272.4 Hz), 123.8 (q, *J* = 3.9 Hz), 109.3, 14.1, 12.4.

MS (EI, 70 eV) m/z (%): 316 (100) [M^+], 301 (18), 283 (27), 269 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929 (w), 1559 (s), 1516 (s), 1492 (m), 1437 (m), 1336 (s), 1313 (m), 1291 (s), 1252 (s), 1197 (s), 1180 (s), 1142 (s), 1113 (s), 1090 (s), 1074 (s), 964 (m), 926 (m), 919 (w), 876 (w), 836 (m), 802 (s), 761 (w), 690 (s), 670 (s).

HRMS (EI) for $C_{13}H_{11}F_3N_2S_2$ (316.0316): 316.0305.

Synthesis of 4-chloro-5-iodo-2,6-bis(methylthio)pyrimidine (73a):



4-Chloro-2,6-bis(methylthio)pyrimidine (**72c**) (207 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –5 °C for 45 min according to **GP1**. Iodine (381 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –5 °C for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at –5 °C, followed by the addition of sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:8) afforded **73a** (202 mg, 61%) as a colourless solid.

m.p.: 100.9 – 102.5 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.54 (s, 3 H), 2.53 (s, 3 H).

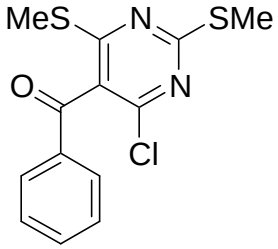
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 175.7, 171.0, 162.0, 86.8, 16.4, 14.5.

MS (EI, 70 eV) m/z (%): 332 (100) [M^+], 205 (38), 159 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2919 (m), 1486 (s), 1461 (s), 1405 (m), 1321 (m), 1273 (s), 1257 (s), 1187 (s), 994 (m), 966 (m), 843 (m), 801 (s), 742 (m).

HRMS (EI) for $C_6H_6ClIN_2S_2$ (331.8706): 331.8709.

Synthesis of (4-chloro-2,6-bis(methylthio)pyrimidin-5-yl)-phenyl-methanone (73b):



4-Chloro-2,6-bis(methylthio)pyrimidine (**72c**) (207 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –5 °C for 45 min according to **GP1**. Transmetalation with CuCN·2LiCl (1.0 mL, 1.0 equiv, 1.00 M in THF) was then performed at –30 °C for 30 min according to **GP2**. Benzoyl chloride (282

mg, 2.0 mmol, 2.0 equiv) was added to the resulting mixture at –30 °C to 25 °C for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) afforded **73b** (201 mg, 65%) as a colourless solid.

m.p.: 108.0 – 109.6 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.84 (m, 5 H), 2.60 (s, 3 H), 2.53 (s, 3 H).

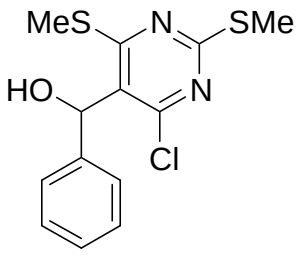
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 191.7, 172.5, 169.6, 154.9, 135.3, 134.6, 129.5, 129.0, 123.9, 14.3, 13.2.

MS (EI, 70 eV) m/z (%): 310 (100) [M^+], 295 (24), 277 (63), 241 (14), 233 (38), 219 (57), 105 (77), 77 (87).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061 (w), 3003 (w), 2929 (w), 1665 (s), 1594 (m), 1576 (w), 1533 (s), 1470 (s), 1446 (m), 1417 (m), 1346 (m), 1307 (m), 1278 (s), 1225 (s), 1188 (m), 1172 (m), 1101 (m), 1072 (w), 961 (w), 916 (s), 845 (w), 821 (s), 769 (w), 706 (m), 684 (m).

HRMS (EI) for $C_{13}H_{11}ClN_2OS_2$ (310.0001): 310.0002.

Synthesis of (4-chloro-2,6-bis-methylsulfanyl-pyrimidin-5-yl)-phenyl-methanol (73c):



4-Chloro-2,6-bis(methylthio)pyrimidine (**72c**) (207 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg{\cdot}2LiCl$ (**26**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at –5 °C for 45 min according to **GP1**. PhCHO (212 mg, 2.0 mmol, 2.0 equiv) was then added to the resulting mixture at –5 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) afforded **73c** (206 mg, 66%) as a colourless solid.

m.p.: 117.0 – 119.3 °C

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29 – 7.41 (m, 5 H), 6.40 (s, 1 H), 3.02 (bs, 1 H), 2.57 (s, 3 H), 2.52 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 171.0, 170.3, 157.7, 139.8, 128.3, 127.6, 125.5, 125.1, 70.4, 14.2, 13.9.

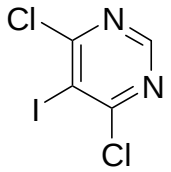
MS (EI, 70 eV) m/z (%): 312 (82) [M^+], 297 (100), 247 (49), 219 (35), 105 (65), 77 (47).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3303 (bs), 3061 (w), 2997 (w), 2923 (w), 1602 (w), 1525 (s), 1470 (s), 1449 (m), 1415 (m), 1328 (w), 1304 (s), 1259 (s), 1220 (w), 1185 (w), 1117 (m), 1043 (m), 1027 (m), 964 (w), 919 (w), 882 (m), 837 (w), 814 (m), 776 (w), 719 (m), 695 (m).

HRMS (EI) for $C_{13}H_{13}ClN_2OS_2$ (312.0158): 312.0156.

2.6. Preparation of polyfunctionalized chloropyrimidines

Synthesis of 4,6-dichloro-5-iodo-pyrimidine (79a):



4,6-Dichloropyrimidine (**74**) (745 mg, 5.0 mmol) dissolved in dry THF (10 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 6.96 mL, 5.5 mmol) and stirred at the same temperature for 45 min according to **GP1**. Iodine (1.78 g, 7.0 mmol) dissolved in dry THF (5 mL) was then slowly added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL) and a sat. aq. $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **79a** as a colourless solid (1.25 g, 91%).

m.p : 134.9 – 136.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (s, 1 H).

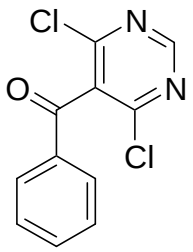
^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 156.8, 98.9.

MS (70 eV, EI) *m/z* (%): 274 [^{35}Cl-M^+] (100), 239 (27), 97 (12), 83 (12), 57 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 2855, 1900, 1499, 1386, 11341, 1296, 1214, 1080, 1014, 790, 763, 745.

HRMS (EI) for $C_4H^{35}Cl_2IN_2$ (273.8561): 273.8565.

Synthesis of (4,6-dichloropyrimidin-5-yl)(phenyl)methanone (79b):



4,6-Dichloropyrimidine (**74**) (149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 1.1 mmol) and stirred at the same temperature for 45 min according to **GP1**. CuCN·2LiCl (1.0 M in THF; 1.1 mL, 1.1 mmol) was then slowly added at –20 °C and the mixture was stirred at the same temperature for 30 min according to **GP2**. Benzoyl chloride was then slowly added at –20 °C and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **79b** as a colourless solid (215 mg, 86%).

m.p.: 106.0 – 108.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.90 (s, 1 H), 7.51 – 7.82 (m, 5 H).

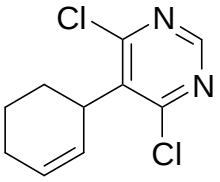
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 188.7, 158.6, 158.3, 135.2, 134.3, 132.0, 129.5, 129.4.

MS (70 eV, EI) *m/z* (%)**:** 252 [^{35}Cl-M^+] (21), 167 (11), 149 (100), 105 (40), 77 (39).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3329, 3061, 2957, 1726, 1668, 1593, 1581, 1531, 1511, 1453, 1404, 1386, 1348, 1317, 1256, 1242, 1236, 1184, 1162, 1071, 999, 924, 826, 794, 766, 698, 681, 674, 605.

HRMS (EI) for $C_{11}H_6{}^{35}Cl_2N_2O$ (251.9857): 251.9850.

Synthesis of 4,6-dichloro-5-(cyclohex-2-enyl)pyrimidine (79c):



4,6-Dichloropyrimidine (**74**) (149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 1.1 mmol) and stirred at the same temperature for 45 min according to **GP1**. CuCN·2LiCl (1 M in THF; 0.05 mL, 5 mol %) was then slowly added at -20 °C. 3-Bromocyclohexene (322 mg, 2.0 mmol) was then slowly added at –30 °C. The resulting mixture was then allowed to warm up slowly to 0 °C for 4 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **79c** as a colourless oil (165 mg, 72%).

^{1}H NMR (600 MHz, $CDCl_3$) δ**:** 8.59 (s, 1 H), 5.85 – 5.87 (m, 1 H), 5.50 – 5.52 (m, 1 H), 5.15 – 5.19 (m, 1 H), 4.14 – 4.20 (m, 2 H), 2.13 – 2.09 (m, 3 H), 1.85 – 1.97 (m, 1 H).

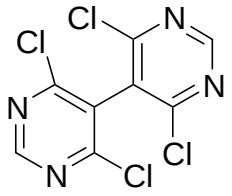
^{13}C NMR (150 MHz, $CDCl_3$) δ**:** 155.3, 135.4, 128.6, 126.2, 38.4, 25.7, 24.2, 22.5.

MS (70 eV, EI) *m/z* (%)**:** 230 (55), 228 [^{35}Cl-M^+] (81), 215 (26), 213 (44), 202 (19), 200 (29), 193 (20), 139 (31), 112 (21), 54 (100).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3025, 2933, 2861, 2836, 2363, 2340, 1531, 1509, 1447, 1408, 1377, 1351, 1329, 1307, 1214, 1162, 1127, 1046, 980, 882, 848, 809, 779, 721, 617, 560.

HRMS (EI) for $C_{10}H_{10}{}^{35}Cl_2N_2$ (228.0221): 228.0226.

Synthesis of 4,4',6,6'-tetrachloro-5,5'-bipyrimidine (79d):



4,6-Dichloropyrimidine (**74**) (149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 1.1 mmol) and stirred at the same temperature for 45 min according to **GP1**. Chloranil (295 mg, 1.2 mmol) dissolved in dry THF (7 mL) was then slowly added at –40 °C. The resulting mixture was then allowed to warm up slowly to 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished **79d** as a colourless solid (121 mg, 82%).

m.p.: 149.0 – 150.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.93 (s, 2 H).

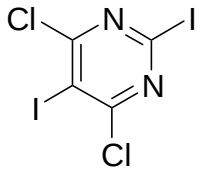
^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.4, 158.9, 126.6.

MS (70 eV, EI) *m/z* (%)**:** 296 (100), 294 [^{35}Cl-M$^+$] (86), 207 (19), 205 (18), 149 (35), 57 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3382, 3303, 2928, 1692, 1531, 1507, 1402, 1370, 1288, 1228, 1164, 988, 811, 771, 727, 571.

HRMS (EI) for $C_8H_2{}^{35}Cl_4N_4$ (293.9034): 293.9045.

Synthesis of 4,6-dichloro-2,5-diiodo-pyrimidine (82a):



4,6-Dichloro-5-iodo-pyrimidine (**79a**) (275 mg, 1.0 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at 55 °C for 1 h according to **GP1**. Iodine (508 mg, 2.0 mmol) dissolved in dry THF (4 mL) was then slowly added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL) and a sat. aq. $Na_2S_2O_3$ solution (20 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **82a** as a colourless solid (241 mg, 61%).

m.p.: 148.4 – 150.0 °C.

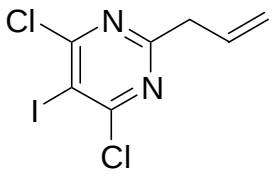
^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 123.6, 98.7.

MS (70 eV, EI) *m/z* (%)**:** 400 [^{35}Cl-M$^+$] (100), 273 (71), 127 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 2913, 2850, 2628, 2417, 1739, 1460, 1344, 1264, 1249, 1196, 1172, 1001, 806, 745.

HRMS (EI) for $C_4{}^{35}Cl_2I_2N_2$ (399.7528): 399.7529.

Synthesis of 5-allyl-4,6-dichloro-2-iodopyrimidine (82b):



4,6-Dichloro-5-iodo-pyrimidine (**79a**) (275 mg, 1.0 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at 55 °C for 1 h according to **GP1**. CuCN·2LiCl (1.0 M solution in THF, 5 drops) was added at –20 °C, followed by the slow addition of allyl bromide (242 mg, 2.0 mmol) at –78 °C and the resulting mixture was allowed to slowly warm up to –10 °C and stirred for 4 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished **82b** as a colourless solid (160 mg, 51%).

m.p.: 74.3 – 75.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 5.75 – 5.88 (m, 1 H), 5.08 – 5.18 (m, 2 H), 3.56 (dt, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 2 H).

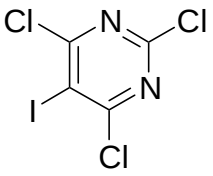
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 161.2, 130.1, 130.0, 121.8, 118.5, 33.7.

MS (70 eV, EI) *m/z* (%)**:** 314 [^{35}Cl-M^+] (100), 187 (59), 151 (13), 99 (12), 58 (30), 43 (69).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3087, 3018, 2971, 2923, 2855, 1739, 1726, 1636, 1528, 1478, 1433, 1370, 1341, 1325, 1283, 1228, 1206, 1185, 1156, 1114, 1093, 985, 922, 904, 853, 808, 785, 777, 558.

HRMS (EI) for $C_7H_5{}^{35}Cl_2IN_2$ (313.8874): 313.8869.

Synthesis of 2,4,6-trichloro-5-iodo-pyrimidine (81a):



2,4,6-Trichloropyrimidine (**77**) (186 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL,

0.55 mmol) and stirred at the same temperature for 1 h according to **GP1**. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL) and a sat. aq. $Na_2S_2O_3$ solution (10 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:7) furnished **81a** as a colourless solid (256 mg, 83%).

m.p.: 97.0 – 98.0 °C.

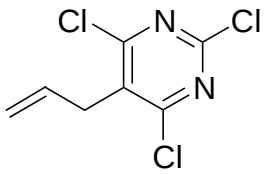
^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 159.3, 96.5.

MS (70 eV, EI) *m/z* (%)**:** 308 [^{35}Cl-M$^+$] (100), 273 (25), 127 (18), 85 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1477, 1270, 1208, 1182, 1009, 851, 806, 752.

HRMS (EI) for $C_4{}^{35}Cl_3IN_2$ (307.8172): 307.8162.

Synthesis of 5-allyl-2,4,6-trichloro-pyrimidine (81b):



2,4,6-Trichloropyrimidine (**77**) (186 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at the same temperature for 1 h according to **GP1**. CuCN·2LiCl (1.0 M solution in THF, 5 drops) was added at –20 °C, followed by the slow addition of allyl bromide (242 mg, 2.0 mmol) at –60 °C and the resulting mixture was allowed to warm up slowly to –20 °C. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:6) furnished **81b** as a colourless solid (201 mg, 90%).

m.p.: 39.2 – 40.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.75 – 5.88 (m, 1 H), 5.08 – 5.18 (m, 2 H), 3.61 (dt, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 2 H).

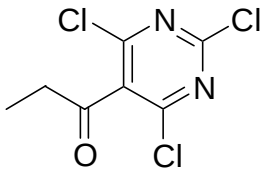
^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.0, 157.1, 130.2, 129.3, 118.5, 33.5.

MS (70 eV, EI) *m/z* (%)**:** 222 [^{35}Cl-M$^+$] (100), 187 (33), 151 (62), 125 (35), 90 (43).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3087, 2934, 1635, 1533, 1501, 1435, 1330, 1287, 1215, 1185, 1123, 1095, 993, 930, 907, 875, 790.

HRMS (EI) for $C_7H_5{}^{35}Cl_3N_2$ (221.9518): 221.9494.

Synthesis of 1-(2,4,6-trichloro-pyrimidin-5-yl)-propan-1-one (81c):



2,4,6-Trichloropyrimidine (**77**) (186 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at the same temperature for 1 h according to **GP1**. CuCN·2LiCl (1.0 M solution in THF; 1.2 mL, 1.2 mmol) was added at –20 °C and the reaction mixture was stirred for 30 min at the same temperature according to **GP2**. Then, propionyl chloride (0.231 g, 2.5 mmol) was added dropwise at –20 °C and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished **81c** as a colourless solid (205 mg, 86%).

m.p.: 74.3 – 75.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) *δ:* 2.83 (q, 2 H, *J* = 7.2 Hz), 1.19 (t, 3 H, *J* = 7.2 Hz).

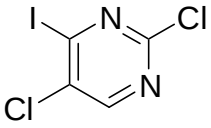
^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 198.2, 159.2, 158.3, 131.7, 36.8, 7.2.

MS (70 eV, EI) *m/z* (%): 238 [^{35}Cl-M$^+$] (2), 209 (100), 120 (8).

IR IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2987, 2941, 2894, 1718, 1538, 1501, 1403, 1305, 1210, 1155, 1065, 946, 835, 657.

HRMS (EI) for $C_7H_5{}^{35}Cl_3N_2O$ (237.9467): 237.9482.

Synthesis of 2,5-dichloro-4-iodopyrimidine (85a):



2,5-Dichloropyrimidine **83** (149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at the same temperature for 45 min according to **GP1**. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added at 25 °C and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL) and a sat. aq. $Na_2S_2O_3$ solution (10 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished **85a** as a colourless solid (203 mg, 72%).

m.p.: 118.8 – 120.2 °C.

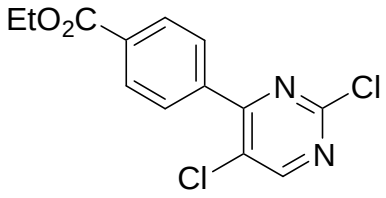
^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.39 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 156.8, 155.4, 137.5, 134.0.

MS (70 eV, EI) *m/z* (%)**:** 274 [^{35}Cl-M$^+$] (100), 149 (61), 147 (90), 120 (31), 43 (30). **IR IR (ATR)** $\tilde{\nu}$ **(cm^{-1}):** 3075, 3018, 2992, 1883, 1721, 1537, 1514, 1494, 1470, 1362, 1336, 1284, 1192, 1171, 1135, 1034, 944, 812, 752, 659.

HRMS (EI) for $C_4H^{35}Cl_2IN_2$ (273.8561): 273.8554.

Synthesis of ethyl 4-(2,5-dichloropyrimidin-4-yl)benzoate (85b):



2,5-Dichloropyrimidine **83** (149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at the same temperature for 45 min according to **GP1**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of ethyl 4-iodobenzoate (359 mg, 1.3 mmol, 1.3 equiv) were then transferred *via* cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 45 min and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished **85b** as a yellowish solid (232 mg, 78%).

m.p.: 86.4 – 87.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.67 (s, 1 H), 8.16 (d, J = 8.2 Hz, 2 H), 7.94 (d, J = 8.2 Hz, 2 H), 4.41 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.1 Hz, 3 H).

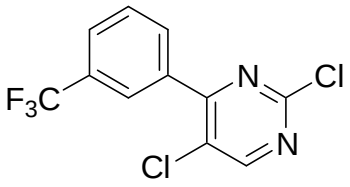
^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 164.1, 160.0, 159.0, 138.1, 132.6, 129.5 (2), 127.9, 61.4, 14.3.

MS (70 eV, EI) *m/z* (%)**:** 296 [^{35}Cl-M^+] (29), 268 (64), 253 (100), 223 (34), 126 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3033, 2992, 2935, 2915, 1718, 1610, 1574, 1545, 1520, 1499, 1486, 1463, 1442, 1401, 1362, 1336, 1315, 1272, 1194, 1170, 1130, 1106, 1095, 1037, 1016, 944, 861, 840, 786, 763, 724, 701, 652.

HRMS (EI) for $C_{13}H_{10}{}^{35}Cl_2N_2O_2$ (296.0119): 296.0117.

Synthesis of 2,5-dichloro-4-(3-(trifluoromethyl)phenyl)pyrimidine (85c):



2,5-Dichloropyrimidine **83** (149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**35**) (0.79 M in THF; 1.39 mL, 0.55 mmol) and stirred at the same temperature for 45 min according to **GP1**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of 3-iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred *via* cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 45 min and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **85c** as a colourless solid (232 mg, 73%).

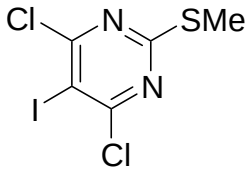
m.p.: 45.2 – 46.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.69 (d, J = 5.1 Hz, 1 H), 7.62 – 8.16 (m, 4 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.4, 160.1, 159.1, 135.0, 132.7 (2), 131.1 (q, J(C-F) = 32.3 Hz), 129.1, 127.8 (q, J(C-F) = 3.7 Hz), 126.4 (q, J(C-F) = 3.7 Hz), 123.7 (q, J(C-F) = 272.5 Hz).

MS (70 eV, EI) *m/z* (%)**:** 292 [^{35}Cl-M^{+}] (84), 257 (100), 231 (24), 204 (15), 149 (15), 44 (24).
IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3090, 3048, 1616, 1547, 1524, 1486, 1449, 1401, 1336, 1324, 1310, 1252, 1198, 1166, 1103, 1071, 1036, 1000, 946, 909, 882, 810, 791, 776, 699, 656, 630.
HRMS (EI) for $C_{11}H_5{}^{35}Cl_2F_3N_2$ (291.9782): 291.9786.

Synthesis of 4,6-dichloro-5-iodo-2-(methylthio)pyrimidine (88a):



4,6-Dichloro-2-(methylthio)pyrimidine (**86**) (195 mg, 1.0 mmol) dissolved in THF (2 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.10 M in THF, 1.0 mL, 1.1 mmol) at rt for 20 min according to **GP1**. Then, iodine (381 mg, 1.5 mmol) dissolved in THF (2 mL) was added dropwise at rt and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL) and a sat. aq. $Na_2S_2O_3$ (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:7) furnished the compound **88a** as a colourless solid (289 mg, 90%).

m.p.: 104.4 – 105.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.51 (s, 3 H).

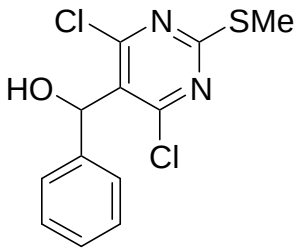
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 172.5, 165.4, 90.1, 14.6.

MS (EI, 70 eV) m/z (%): 322 (68), 320 (100) [^{35}Cl-M^{+}], 276 (74), 274 (21), 239 (14).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3003, 2930, 2636, 2450, 1501, 1463, 1326, 1264, 1176, 1000, 997, 848, 804, 747.

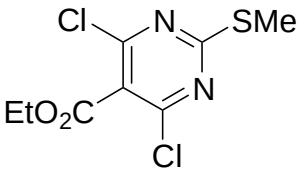
HRMS (EI) for $C_5H_3{}^{35}Cl_2IN_2{}^{32}S$ (319.8439): 319.8429.

Synthesis of 4,6-dichloro-2-(methylthio)pyrimidin-5-yl)-phenyl-methanol (88b):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.14 M in THF; 1.45 mL, 1.65 mmol) and stirred at the same temperature for 30 min according to **GP1**. Benzaldehyde (239 mg, 2.25 mmol) dissolved in dry THF (3 mL) was then slowly added at 25 °C and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished **88b** as a colourless solid (405 mg, 90%).
m.p.: 83.9 – 84.6 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 – 7.36 (m, 5 H), 6.52 (s, 1 H), 3.48 (bs, 1 H), 2.57 (s, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.0, 160.8, 139.5, 128.2, 127.5, 126.7, 125.0, 70.2, 14.2.
MS (70 eV, EI) *m/z* (%): 300 [^{35}Cl-M$^+$] (100), 223 (29).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3561, 3447, 2925, 1538, 1478, 1339, 1308, 1259, 1171, 1111, 1021, 876, 814, 727, 711, 639.
HRMS (EI) for $C_{12}H_{10}{}^{35}Cl_2N_2O^{32}S$ (299.9891): 299.9878.

Synthesis of 4,6-dichloro-2-(methylthio)pyrimidine-5-carboxylic acid ethyl ester (88c):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.14 M in THF; 1.45 mL, 1.65 mmol) and stirred at the same temperature for 30 min according to **GP1**. Ethyl

cyanoformate (298 mg, 3 mmol) was then slowly added at 25 °C and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by fast flash chromatography (CH_2Cl_2/pentane 1:5) furnished **88c** as a colourless solid (345 mg, 86%).

m.p.: 63.6 – 65.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 4.42 (q, 2 H, J = 6 Hz), 2.56 (s, 3 H), 1.38 (t, 3 H, J = 6 Hz).

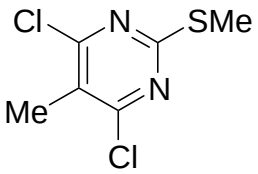
^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.3, 162.5, 157.9, 121.9, 62.9, 14.5, 13.9.

MS (70 eV, EI) *m/z* (%)**:** 266 [^{35}Cl-M$^+$] (100), 238 (55), 221 (53).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2982, 2932, 1735, 1550, 1479, 1374, 1346, 1320, 1293, 1217, 1067, 1008, 860, 825, 780.

HRMS (EI) for $C_8H_8{}^{35}Cl_2N_2O_2{}^{32}S$ (265.9684): 265.9689.

Synthesis of 4,6-dichloro-5-methyl-2-(methylthio)pyrimidine (88d):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.14 M in THF; 1.45 mL, 1.65 mmol) and stirred at the same temperature for 30 min according to **GP1**. Iodomethane (426 mg, 3 mmol) was then slowly added at 25 °C and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished **88d** as a colourless solid (287 mg, 92%).

m.p.: 60.2 – 62.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 2.48 (s, 3 H), 2.32 (s, 3 H).

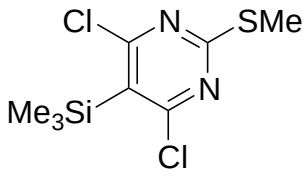
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 169.8, 161.1, 122.7, 15.4, 14.2.

MS (70 eV, EI) *m/z* (%)**:** 208 [^{35}Cl-M$^+$] (100), 162 (31), 127 (20).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2930, 2480, 1545, 1480, 1383, 1343, 1316, 1292, 1222, 1190, 1116, 1010, 973, 862, 792, 756, 694.

HRMS (EI) for $C_6H_6{}^{35}Cl_2N_2O_2{}^{32}S$ (207.9629): 207.9620.

Synthesis of 4,6-dichloro-2-(methylthio)-5-trimethylsilanyl-pyrimidine (88e):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.14 M in THF; 1.45 mL, 1.65 mmol) and stirred at the same temperature for 30 min according to **GP1**. Trimethylsilyl cyanide (179 mg, 1.8 mmol) was then slowly added at 25 °C and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished **88e** as a colourless solid (317 mg, 79%).

m.p.: 82.5 – 84.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 2.52 (s, 3 H), 0.46 (s, 9 H).

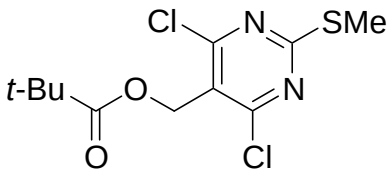
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 173.4, 166.9, 124.0, 14.0, 1.8.

MS (70 eV, EI) *m/z* (%)**:** 266 [^{35}Cl-M$^+$] (56), 251 (100), 178 (18), 166 (23), 95 (24).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2956, 2930, 2894, 1509, 1455, 1323, 1284, 1246, 1163, 1034, 845, 799, 778, 701, 636.

HRMS (EI) for $C_8H_{12}{}^{35}Cl_2N_2{}^{32}SSi$ (265.9867): 265.9825.

Synthesis of (4,6-dichloro-2-(methylthio)pyrimidin-5-yl)methyl pivalate (88f):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (195 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF; 1.0 mL, 1.1 mmol) and stirred at the same temperature for 30 min according to **GP1**. Iodomethyl pivalate (339 mg, 1.4 mmol) was then slowly added at –15 °C and the resulting mixture was then allowed to warm up slowly to 25 °C for 3 h. The reaction mixture was quenched with a

sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished **88f** as a colourless solid (235 mg, 76%).

m.p.: 58.3 – 60.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.20 (s, 2 H), 2.56 (s, 3 H), 1.19 (s, 9 H).

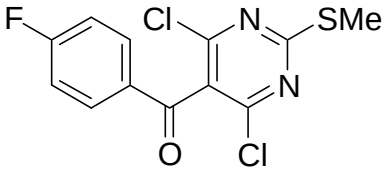
^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.9, 173.6, 162.5, 120.8, 60.1, 39.0, 27.1, 14.5.

MS (70 eV, EI) *m/z* (%)**:** 308 [^{35}Cl-M$^+$] (100), 210 (62), 208 (53), 57 (76).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976, 2928, 2873, 1723, 1552, 1481, 1458, 1426, 1397, 1382, 1369, 1339, 1317, 1302, 1280, 1227, 1189, 1142, 1122, 1032, 993, 974, 916, 868, 793, 770.

HRMS (EI) for $C_{11}H_{14}{}^{35}Cl_2N_2O_2{}^{28}S$ (308.0153): 308.0135.

Synthesis of (4,6-dichloro-2-(methylthio)pyrimidin-5-yl)(4-fluorophenyl)methanone (88g):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.14 M in THF; 1.45 mL, 1.65 mmol) and stirred at the same temperature for 30 min according to **GP1**. CuCN·2LiCl (1.0 M solution in THF, 1.7 mL, 1.7 mmol) was slowly added at –20 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, 4-fluorobenzoyl chloride (476 mg, 3 mmol) was added dropwise at –20 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished **88g** as a colourless solid (441 mg, 93%).

m.p.: 133.5 – 135.0 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.85 – 7.88 (m, 2 H), 7.18 – 7.20 (m, 2 H), 2.61 (s, 3 H).

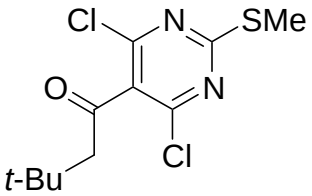
^{13}C NMR (150 MHz, $CDCl_3$) δ: 187.7, 174.6, 166.8(d, *J* (C-F) = 258.6 Hz), 157.9, 132.4 (d, *J* (C-F) = 9.7 Hz), 131.4 (d, *J* (C-F) = 3.0 Hz), 125.4, 116.7 (d, *J* (C-F) = 22.2 Hz), 14.4.

MS (70 eV, EI) *m/z* (%)**:** 316 [^{35}Cl-M$^+$] (68), 221 (10), 123 (100), 95 (36), 75 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3071, 2929, 2469, 2359, 1668, 1591, 1547, 1502, 1475, 1409, 1351, 1320, 1291, 1233, 1220, 1185, 1154, 1104, 1093, 969, 919, 848, 814, 774, 750, 684, 663, 637, 624.

HRMS (EI) for $C_{12}H_7{}^{35}Cl_2FN_2O^{32}S$ (315.9640): 315.9632.

Synthesis of 1-(4,6-dichloro-2-(methylthio)pyrimidin-5-yl)-3,3-dimethylbutan-1-one (88h):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (975 mg, 5 mmol) dissolved in dry THF (5 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF; 5.0 mL, 5.5 mmol) and stirred at the same temperature for 30 min according to **GP1**. CuCN·2LiCl (1.0 M solution in THF, 5.5 mL, 5.5 mmol) was slowly added at –20 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, 3,3-dimethylbutanoyl chloride (1.35 g, 10 mmol) was added dropwise at –20 °C and the resulting mixture was stirred at 25 °C for 60 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:7) furnished **88h** as a colourless solid (1.23 g, 84%).

m.p.: 95.0 – 96.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.75 (s, 2 H), 2.57 (s, 3 H), 1.12 (s, 9 H).

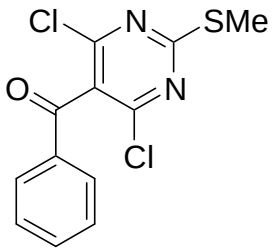
^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.6, 173.7, 156.6, 128.0, 55.9, 31.0, 29.3, 14.4.

MS (70 eV, EI) *m/z* (%)**:** 292 [^{35}Cl-M$^+$] (7), 238 (23), 236 (35), 223 (66), 221 (100), 57 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2929, 2897, 2871, 1715, 1541, 1475, 1425, 1380, 1359, 1327, 1304, 1275, 1249, 1217, 1180, 1154, 1127, 996, 906, 853, 806, 777.

HRMS (EI) for $C_{11}H_{14}{}^{35}Cl_2N_2O^{32}S$ (292.0204): 292.0201.

Synthesis of 4,6-dichloro-2-methyl(thiopyrimidin-5-yl)-phenyl-methanone (88i):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.14 M in THF; 1.45 mL, 1.65 mmol) and stirred at the same temperature for 30 min according to **GP1**. CuCN·2LiCl (1.0 M solution in THF, 1.6 mL, 1.6 mmol) was slowly added at –20 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, benzoyl chloride (421 mg, 3 mmol) was dropwise added at –20 °C and the resulting mixture was stirred at 25 °C for 60 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:6) furnished **88i** as a colourless solid (402 mg, 90%).

m.p.: 135.1 – 136.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 7.81 – 7.83 (m, 2 H), 7.62 – 7.66 (m, 1 H), 7.46 – 7.52 (m, 2 H), 2.59 (s, 3 H).

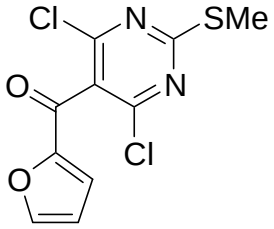
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 189.2, 174.2, 157.8, 134.8, 129.5, 129.1, 125.7, 14.4.

MS (70 eV, EI) *m/z* (%)**:** 298 [^{35}Cl-M^+] (100), 221 (26), 105 (78), 77 (33).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3318, 3060, 2925, 1667, 1594, 1535, 1473, 1450, 1344, 1308, 1284, 1230, 1173, 1096, 915, 848, 822, 771, 706, 680.

HRMS (EI) for $C_{12}H_8{}^{35}Cl_2N_2O^{32}S$ (297.9734): 297.9739.

Synthesis of (4,6-dichloro-2-(methylthio)pyrimidin-5-yl)(furan-2-yl)methanone (88j):



4,6-Dichloro-2-(methylthio)pyrimidine **86** (390 mg, 2.0 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF; 2.0 mL, 2.2 mmol) and stirred at the same temperature for 30 min according to **GP1**. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was slowly added at –20 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, furan-2-carbonyl chloride (522 mg, 4 mmol) was dropwise added at –20 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **88j** as a colourless solid (498 mg, 86%).

m.p.: 122.8 – 124.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 7.71 (m, 1 H), 7.28 (m, 1 H), 7.65 – 7.67 (m, 1 H), 2.63 (s, 3 H).

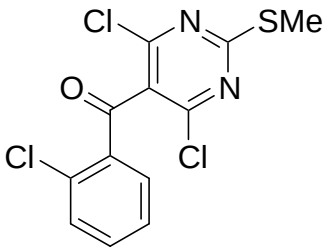
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 176.2, 174.6, 158.1, 151.3, 148.7, 124.9, 121.2, 113.3, 14.5.

MS (70 eV, EI) *m/z* (%)**:** 290 (62), 288 [^{35}Cl-M^+] (100), 221 (12), 95 (55).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3140, 3119, 2929, 2464, 1649, 1562, 1536, 1475, 1454, 1446, 1394, 1344, 1320, 1265, 1264, 1222, 1183, 1154, 1122, 1109, 1075, 1030, 1014, 945, 887, 874, 832, 819, 790, 766, 740, 661, 619, 584.

HRMS (EI) for $C_{10}H_6{}^{35}Cl_2N_2O_2{}^{32}S$ (287.9527): 287.9530.

Synthesis of (2-chlorophenyl)(4,6-dichloro-2-(methylthio)-pyrimidin-5-yl)methanone (88k):



4,6-Dichloro-2-(methylthio)pyrimidine (**86**) (585 mg, 3.0 mmol) dissolved in THF (3 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (0.89 M in THF, 3.72 mL, 3.3 mmol) at rt for 20 min according to **GP1**. The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1.00 M solution in THF, 3.3 mL, 3.3 mmol) was added and the reaction mixture was stirred

for 30 min. Then, 2-chlorobenzoyl chloride (1.050 g, 6.0 mmol) was added dropwise at –30 °C and the resulting mixture was stirred at rt for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), then extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **88k** as a colourless solid (897 mg, 90%).

m.p.: 130.0 – 132.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.77 – 7.80 (m, 1 H), 7.36 – 7.54 (m, 3 H), 2.59 (s, 3 H).

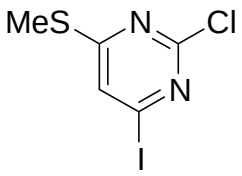
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 188.1, 174.1, 157.8, 134.6, 134.4, 133.8, 132.1, 131.4, 127.3, 127.0, 14.5.

MS (EI, 70 eV) m/z (%): 334 (89), 332 (87) [^{35}Cl-M^+], 223 (27), 221 (31), 141 (28), 139 (100), 111 (31), 75 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3354, 3064, 3013, 2930, 1682, 1587, 1538, 1473, 1429, 1344, 1321, 1290, 1228, 1132, 1109, 1055, 1037, 964, 920, 845, 822, 786, 768, 745, 703, 654.

HRMS (EI) for $C_{12}H_7Cl_3N_2OS$ (331.9345): 331.9336.

Synthesis of 2-chloro-4-iodo-6-(methylthio)pyrimidine (91a):



2-Chloro-4-(methylthio)pyrimidine **89** (161 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF; 1.0 mL, 1.1 mmol) and stirred at the same temperature for 5 min according to **GP1**. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added at 25 °C and the resulting mixture was stirred for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL) and a sat. aq. $Na_2S_2O_3$ solution (10 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished **91a** as a colourless solid (203 mg, 71%).

m.p.: 97.9 – 99.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 7.53 (s, 1 H), 2.53 (s, 3 H).

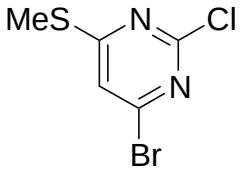
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 173.8, 158.7, 127.1, 126.4, 12.8.

MS (70 eV, EI) *m/z* (%)**:** 286 [^{35}Cl-M^{+}] (100), 123 (13), 98 (53), 83 (16).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3080, 3008, 2930, 1517, 1496, 1468, 1414, 1359, 1336, 1320, 1287, 1241, 1194, 1117, 1098, 1031, 964, 946, 838, 822, 809, 750, 708, 659, 602.

HRMS (EI) for $C_5H_4{}^{35}ClIN_2S$ (285.8828): 285.8812.

Synthesis of 4-bromo-2-chloro-6-(methylthio)pyrimidine (91b):



2-Chloro-4-(methylthio)pyrimidine **89** (161 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF; 1.0 mL, 1.1 mmol) and stirred at the same temperature for 5 min according to **GP1**. $(BrCl_2C)_2$ (429 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added at 25 °C and the resulting mixture was stirred for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **91b** as a colourless solid (189 mg, 79%).

m.p.: 86.8 – 88.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 7.28 (s, 1 H), 2.56 (s, 3 H).

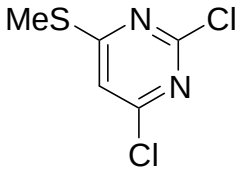
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 174.9, 159.5, 150.7, 120.0, 13.0.

MS (70 eV, EI) *m/z* (%)**:** 238 [^{35}Cl-M^{+}] (28), 194 (11), 58 (69), 44 (12), 43 (100).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3090, 2997, 2925, 1529, 1481, 1416, 1367, 1321, 1261, 1207, 1189, 1101, 967, 905, 848, 832, 778, 747, 708, 605.

HRMS (EI) for $C_5H_4{}^{79}Br{}^{35}ClN_2S$ (237.8967): 237.8958.

Synthesis of 2,4-dichloro-6-(methylthio)pyrimidine (91c):



2-Chloro-4-(methylthio)pyrimidine **89** (161 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of TMPMgCl·LiCl (**16a**) (1.1 M in THF; 1.0 mL, 1.1 mmol) and stirred at the same temperature for 5 min according to **GP1**. FCl_2CCFCl_2 (281 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added at 25 °C and the resulting mixture was stirred for 45 min. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished **91c** as a colourless solid (140 mg, 72%).

m.p.: 80.1 – 81.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 7.11 (s, 1 H), 2.57 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 175.3, 160.0, 159.8, 116.1, 13.0.

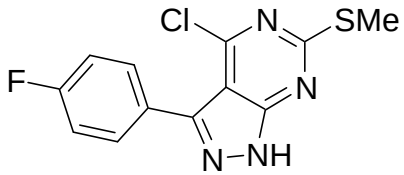
MS (70 eV, EI) *m/z* (%)**:** 194 [^{35}Cl-M$^+$] (100), 148 (36), 113 (26), 87 (32).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3090, 3002, 2930, 1532, 1483, 1414, 1372, 1321, 1261, 1215, 1197, 1099, 969, 889, 851, 820, 809, 750, 716, 683, 603.

HRMS (EI) for $C_5H_4{}^{35}Cl_2N_2S$ (193.9472): 193.9467.

2.7. Preparation of pyrazolopyrimidines and application to the synthesis of the antiviral p38 kinase inhibitor 92d

Synthesis of 4-chloro-3-(4-fluorophenyl)-6-(methylthio)-1H-pyrazolo[3,4-*d*]pyrimidine (92a):



Hydrazine (64% in water; 0.12 mL, 2.4 mmol) was added to a solution of **88g** (0.317 g, 1.0 mmol) dissolved in 2 mL THF at 25 °C. The resulting mixture was stirred at the same temperature for 10 min and was quenched with a sat. aq. Na_2CO_3 solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished **92a** as a colourless solid (224 mg, 76%).

m.p.: 225.7 – 227.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ**:** 7.77 (m, 2 H), 7.32-7.36 (m, 2 H), 2.58 (s, 3 H).

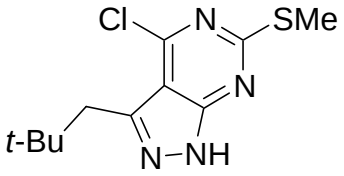
^{13}C NMR (100 MHz, DMSO-d$_6$) *δ:* 168.6, 162.6 (d, *J*(C-F) = 246.2 Hz), 156.3, 153.0, 144.0, 131.9 (d, *J* (C-F) = 8.6 Hz), 127.8, 115.2 (d, *J* (C-F) = 31.7 Hz), 106.9, 13.8.

MS (70 eV, EI) *m/z* (%)**:** 294 [^{35}Cl-M$^+$] (100), 213 (35).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3187, 3156, 3076, 3029, 2982, 2918, 1739, 1597, 1531, 1520, 1467, 1420, 1399, 1367, 1322, 1304, 1267, 1217, 1156, 1151, 1098, 1069, 1022, 982, 972, 956, 869, 832, 816, 806, 785, 740, 692, 645, 602, 561.

HRMS (EI) for $C_{12}H_8{}^{35}ClFN_4{}^{32}S$ (294.0142): 294.0130.

Synthesis of 4-chloro-6-(methylthio)-3-neopentyl-1H-pyrazolo[3,4-*d*]pyrimidine (92b):



Hydrazine (64% in water; 0.17 mL, 3.4 mmol) was added to a solution of **88h** (0.294 g, 1.0 mmol) dissolved in 2 mL THF at 25 °C. The resulting mixture was stirred at the same temperature for 10 min and was quenched with a sat. aq. Na_2CO_3 solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished **92b** as a colourless solid (199 mg, 73%).

m.p.: 130.9 – 132.4 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) *δ***:** 2.88 (s, 2 H), 2.55 (s, 3 H), 0.94 (s, 9 H).

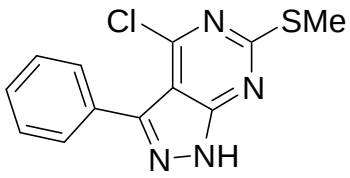
^{13}C NMR (100 MHz, DMSO-d$_6$) *δ***:** 168.1, 155.6, 152.9, 143.5, 108.5, 31.9, 29.3, 13.8.

MS (70 eV, EI) *m/z* (%)**:** 270 [^{35}Cl-M$^+$] (12), 214 (100), 57 (24).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3203, 3156, 3119, 2960, 2929, 2902, 2860, 2359, 2332, 1739, 1594, 1533, 1483, 1462, 1449, 1412, 1362, 1330, 1291, 1267, 1238, 1209, 1199, 1143, 1101, 1069, 1006, 969, 890, 856, 811, 774, 750, 632, 616, 553.

HRMS (EI) for $C_{11}H_{15}{}^{35}ClN_4{}^{32}S$ (270.0706): 270.0703.

Synthesis of 4-chloro-6-(methylthio)-3-phenyl-1H-pyrazolo[3,4-*d*]pyrimidine (92c):



Hydrazine (64% in water; 0.17 mL, 3.4 mmol) was added to a solution of **88i** (0.298 g, 1.0 mmol) dissolved in 2 mL THF at 25 °C. The resulting mixture was stirred at the same temperature for 10 min and was quenched with a sat. aq. Na_2CO_3 solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished **92c** as a colourless solid (229 mg, 83%).

m.p.: 201.0–202.3 °C.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ**:** 7.70-7.72 (m, 2 H), 7.46-7.50 (m, 3 H), 2.57 (s, 3 H).

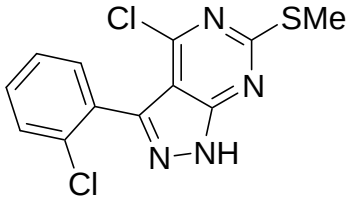
^{13}C NMR (100 MHz, DMSO-d$_6$) δ**:** 168.5, 156.4, 153.1, 144.9, 131.3, 129.8, 129.0, 128.1, 106.9, 13.9.

MS (70 eV, EI) *m/z* (%)**:** 276 [^{35}Cl-M$^+$] (100), 195 (40), 77 (11).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3101, 3023, 2977, 2853, 1612, 1532, 1509, 1463, 1408, 1367, 1321, 1253, 1228, 1155, 1083, 1018, 977, 876, 863, 786, 765, 701, 636.

HRMS (EI) for $C_{12}H_9{}^{35}ClN_4{}^{32}S$ (276.0236): 276.0215.

Synthesis of 4-chloro-3-(2-chlorophenyl)-6-(methylthio)-1H-pyrazolo[3,4-d]pyrimidine (92d):



Hydrazine 64% in water (169 mg, 3.4 mmol) was slowly added to a solution of (2-chlorophenyl)(4,6-dichloro-2-(methylthio)-pyrimidin-5-yl)-methanone (**88k**) (334 mg, 1.0 mmol) dissolved in THF (2 mL) at rt. The resulting mixture was stirred at the same temperature for 10 min and was quenched with a sat. aq. Na_2CO_3 solution (10 mL), then extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration,

the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **92d** as a colourless solid (246 mg, 79%).

m.p.: 188.9 – 190.1 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.45 – 7.63 (m, 4 H), 2.59 (s, 3 H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ: 169.0, 155.8, 153.2, 142.4, 133.5, 132.3, 131.1, 130.7, 129.3, 127.1, 108.1, 13.9.

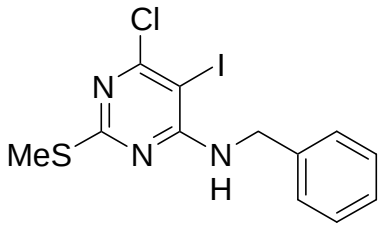
MS (EI, 70 eV) m/z (%): 312 (62), 310 (100) [^{35}Cl-M$^+$], 266 (11), 264 (17), 231 (13), 229 (46), 193 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3173, 2930, 1605, 1582, 1532, 1509, 1450, 1401, 1334, 1300, 1277, 1189, 1161, 1132, 1073, 1013, 980, 951, 858, 786, 752, 729, 714, 631.

HRMS (EI) for $C_{12}H_8Cl_2N_4S$ (309.9847): 309.9824.

2.8. Preparation of the anti-inflammatory sPLA2 kinase inhibitor 95

Synthesis of N-benzyl-6-chloro-5-iodo-2-(methylthio)-pyrimidin-4-amine (93):



Benzylamine (980 mg, 9.1 mmol, 1.7 equiv) was added slowly to a solution of 4,6-dichloro-5-iodo-2-(methylthio)-pyrimidine (**88a**) (1.765 g, 5.5 mmol) dissolved in THF (15 mL) at rt. The resulting mixture was stirred at the same temperature for 10 min and was quenched with a sat. aq. Na_2CO_3 solution (50 mL), then extracted with diethyl ether (5 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **93** as a white solid (1.960 g, 91%).

m.p.: 111.0 – 112.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.27 – 7.39 (m, 5 H), 5.87 (s, 1 H), 4.69 (d, J = 5.6 Hz, 2 H), 2.45 (s, 3 H).

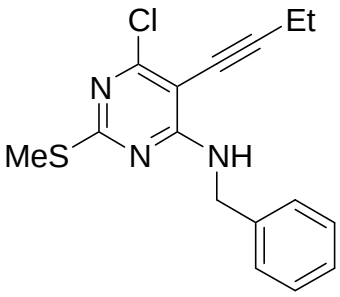
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 171.6, 161.7, 161.2, 137.7, 128.8, 127.7, 127.5, 72.7, 46.2, 14.4.

MS (ESI, 70 eV) m/z (%): 394 (32), 392 (100) [^{35}Cl-M$^+$].

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3261, 2925, 1587, 1551, 1517, 1465, 1414, 1336, 1308, 1264, 1235, 1192, 1104, 1073, 1024, 998, 928, 827, 760, 732, 690, 641.

HRMS (ESI) for $C_{12}H_8Cl_2N_4S$ (391.9485 (M^+ + H)): 391.9481.

Synthesis of N-benzyl-5-(but-1-ynyl)-6-chloro-2-(methylthio)-pyrimidin-4-amine (94):



To a solution of NEt_3 (52.5 mL) and CuI (60 mg, 4 mol%) were added $Pd(dba)_2$ (127 mg, 3 mol%) and P(o-furyl)$_3$ (105 mg, 6 mol%) in THF (15 mL), followed by N-benzyl-6-chloro-5-iodo-2-(methylthio)-pyrimidin-4-amine (**93**) (2.940 g, 7.5 mmol) and recondensed 1-butyne (811 mg, 15.0 mol, 2.0 equiv). The reaction mixture was stirred at 55 °C for 1.5 h and then quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **94** (2.334 g, 98%) as a colourless solid.

m.p.: 97.5 – 99.2 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.27 – 7.37 (m, 5 H), 5.94 (s, 1 H), 4.71 (d, *J* = 5.9 Hz, 2 H), 2.48 (q, *J* = 7.4 Hz, 2 H), 2.46 (s, 3 H), 1.23 (t, *J* = 7.4 Hz, 3 H).

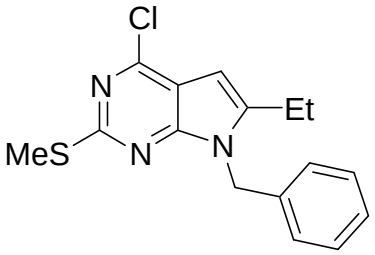
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 169.7, 161.7, 158.4, 138.1, 128.7, 127.5, 127.4, 104.6, 96.5, 70.7, 45.1, 14.2, 13.7, 13.6.

MS (EI, 70 eV) m/z (%): 318 (21), 317 (49) [^{35}Cl-M^+], 303 (15), 302 (100), 288 (15), 266 (20), 106 (12), 91 (96), 65 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3267, 2984, 2926, 1547, 1454, 1428, 1370, 1346, 1314, 1255, 1166, 1077, 1000, 963, 911, 833, 775, 754, 698, 615.

HRMS (EI) for $C_{16}H_{16}ClN_3S$ (317.0753): 317.0748.

Synthesis of 7-benzyl-4-chloro-6-ethyl-2-methylsulfanyl-7H-pyrrolo[2,3-d]pyrimidine (95):



This compound was prepared from **94**. To a stirred solution of potassium *tert*-butoxide (224 mg, 2.0 mmol) in 8 mL NMP, was added under argon *N*-benzyl-5-(but-1-ynyl)-6-chloro-2-(methylthio)pyrimidin-4-amine (**94**) (317 mg, 1.0 mmol) in 2 mL NMP. The resulting mixture was then vigorously stirred at rt for 1.25 h. The reaction mixture was then quenched with water (1 mL), dichloromethane (100 mL) was added, washed with a sat. aq. NaCl solution (20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **95** as a colourless solid (142 mg, 45%).

m.p.: 118.0 – 119.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.27 - 7.34 (m, 3 H), 7.11 - 7.08 (m, 2 H), 6.28 (s, 1 H), 5.42 (s, 2 H), 2.63 (d, J = 7.5 Hz, 2 H), 2.61 (s, 3 H), 1.30 (t, J = 7.5 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 163.1, 153.2, 150.2, 143.6, 136.7, 128.7, 127.6, 126.7, 113.6, 95.9, 45.4, 20.0, 14.4, 11.5.

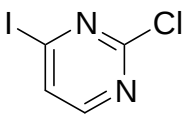
MS (EI, 70 eV) m/z (%): 319 (27), 317 (85) [^{35}Cl-M$^+$], 284 (16), 226 (25), 91 (100), 65 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3134, 3066, 3036, 2967, 2925, 2875, 1727, 1582, 1557, 1526, 1496, 1470, 1453, 1438, 1378, 1369, 1355, 1312, 1288, 1260, 1226, 1204, 1190, 1168, 1116, 1031, 967, 937, 871, 795, 750, 735, 699, 654.

HRMS (EI) for $C_{16}H_{16}ClN_3S$ (317.0753): 317.0748.

2.9. Preparation of the fungicide Mepanipyrim (100)

Synthesis 2-chloro-4-iodopyrimidine (96):



2-Chloropyrimidine (**53**) (684 mg, 6.0 mmol) dissolved in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (**1**) (1.1 M in THF, 6.0 mL, 6.6 mmol) at –60 °C for 2 h. A transmetalation using $ZnCl_2$ (1.0 M in THF, 6.6 mL, 6.6 mmol) was performed and the resulting mixture was allowed to warm up slowly to rt. Iodine (2.284 g, 9.0 mmol) dissolved in dry THF (9 mL) was then dropwise added and the resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (50 mL) and sat. aq. $Na_2S_2O_3$ (30 mL) was added, extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography on silica (CH_2Cl_2/pentane 1:4) furnished the compound **96** as a colourless solid (1.31 g, 91%).

m.p.: 111.3 – 112.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 5.1 Hz, 1 H), 7.72 (d, *J* = 5.1 Hz, 1 H).

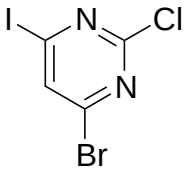
^{13}C-NMR (75 MHz, $CDCl_3$) δ**:** 160.1, 158.0, 131.2, 130.2.

MS (70 eV, EI) m/z (%)**:** 240 (47) [^{35}Cl-M$^+$], 127 (17), 115 (22), 113 (64), 86 (16), 58 (39), 52 (15), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3094, 1511, 1395, 1342, 1318, 1227, 1192, 1165, 1133, 979, 834, 776, 758, 666, 578.

HRMS (EI) for $C_4H_2{}^{35}Cl^{127}IN_2$ (239.8951): 239.8950.

Synthesis of 4-bromo-2-chloro-4-iodopyrimidine (97):



2-Chloro-4-iodopyrimidine **96** (1.21 g, 5.0 mmol) dissolved in THF (10 mL) was slowly added at –60 °C to a solution of TMPMgCl·LiCl (1; 1.1 M in THF; 5.5 mL, 5 mmol) and the mixture was stirred at the same temperature for 1 h. $(BrCl_2C)_2$ (2.442 g, 7.5 mmol) was added dropwise at –78 °C and the resulting mixture was then allowed to warm up slowly to –65 °C for 3 h. Purification by flash chromatography (pentane/CH_2Cl_2 3:1) afforded the pyrimidine **97** (1.53 g, 96%) as a colourless solid.

m.p.: 145.9 – 147.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.94 (s, 1 H).

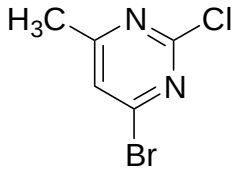
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 159.0, 152.6, 134.5, 129.6.

MS (EI, 70 eV) m/z (%): 320 (44), 318 (33) [^{79}Br-M^{+}], 193 (67), 191 (51), 130 (20), 127 (20), 86 (10), 14 (62), 62 (13), 58 (77), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3108, 1486, 1357, 1338, 1267, 1241, 1098, 977, 845, 806, 745, 587.

HRMS (EI) for $C_4H^{79}Br^{35}Cl^{127}IN_2$ (317.8056): 317.8058.

Synthesis of 4-bromo-2-chloro-6-methylpyrimidine (98):



$ZnCl_2$ (1.0 M in THF, 6 mL, 6 mmol) was dropwise added to a stirred solution of CH_3MgCl (2.93 M in THF, 1.95 mL, 5.65 mmol) at –20 °C. After 15 min stirring at this temperature, the mixture was allowed to warm up slowly to 25 °C. Then, a solution of **97** (1.28 g, 4.0 mmol) and $Pd(PPh_3)_4$ (200 mg, 4 mol %) in THF (8 mL) was added, and the resulting mixture was stirred at 50 °C overnight. The resulting mixture was cooled to 25 °C and quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (5 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/CH_2Cl_2 4:1) afforded the pyrimidine **98** (483 mg, 58%) as a colourless solid.

m.p.: 80.6 – 82.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (s, 1 H), 2.50 (s, 3 H).

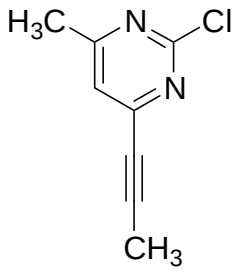
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 171.1, 160.0, 153.5, 123.5, 23.6.

MS (EI, 70 eV) m/z (%): 208 (29), 206 (24) [^{79}Br-M^{+}], 129 (29), 127 (81), 86 (28), 66 (100), 64 (15), 62 (28), 55 (16), 51 (21), 43 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3124, 3082, 2955, 2918, 2850, 1721, 1552, 1515, 1462, 1430, 1404, 1370, 1354, 1296, 1251, 1228, 1188, 1130, 1040, 1011, 974, 911, 893, 861, 795, 750, 692, 600.

HRMS (EI) for $C_5H_4^{79}Br^{35}ClN_2$ (205.9246): 205.9240.

Synthesis of 2-chloro-4-methyl-6-(prop-1-ynyl)pyrimidine (99):



To a solution of recondensed propyne (81 mg, 2.0 mol) were added a mixture of NEt_3 (7 mL), CuI (12 mg, 4 mol %), $Pd(dba)_2$ (25 mg, 2 mol %) and $P(o\text{-furyl})_3$ (21 mg, 4 mol %) in THF (2 mL) and **98** (312 mg, 1.5 mmol). The reaction mixture was stirred at 25 °C for 1.5 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/CH_2Cl_2 3:1) afforded the pyrimidine **99** (241 mg, 97%) as a colourless solid.

m.p.: 127.4 – 128.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.07 (s, 1 H), 2.47 (s, 3 H), 2.08 (s, 3 H).

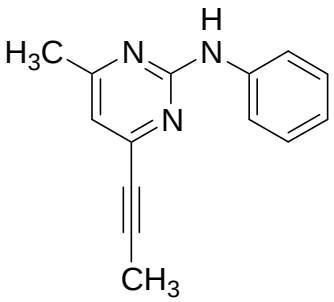
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.5, 160.9, 153.0, 121.0, 93.8, 77.3, 23.8, 4.5.

MS (EI, 70 eV) m/z (%): 168 (17), 166 (50) [^{35}Cl-M^+], 58 (37), 44 (17), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3066, 2971, 2923, 2248, 2227, 1562, 1502, 1417, 1386, 1351, 1246, 1193, 1185, 1051, 982, 916, 893, 811, 764, 568.

HRMS (EI) for $C_8H_7{}^{35}ClN_2$ (166.0298): 166.0297.

Synthesis of 4-methyl-*N*-phenyl-6-(prop-1-ynyl)pyrimidin-2-amine (100; Mepanipyrim):



A Schlenk flask was flushed with nitrogen and charged with xantphos (11 mg, 20 mol %) and dry dioxane (3 mL). After purging the flask with dry argon, $Pd(OAc)_2$ (58 mg, 10 mol %) was charged, and the mixture was stirred under nitrogen for 10 min. In another Schlenk flask, **99** (84 mg, 0.5 mmol), aniline (70 mg, 0.75 mmol), and K_2CO_3 (1.38 g, 10 mmol) were mixed with dry dioxane (4 mL). Then, the $Pd(OAc)_2$/Xantphos solution was added via cannula. The resulting mixture was subsequently heated to 100 °C under argon with vigorous stirring for 1.5 h. After cooling, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated, and the crude residue purified by flash chromatography (CH_2Cl_2) affording the pyrimidine **100** (91 mg, 81%) as a colourless solid.

m.p.: 125.5 – 127.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.61 – 7.64 (m, 2 H), 7.30 – 7.33 (m, 2 H), 7.21 (bs, 1 H), 6.98 – 7.03 (m, 1 H), 6.63 (s, 1 H), 2.38 (s, 3 H), 2.07 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.1, 159.7, 151.3, 139.5, 128.8, 122.3, 119.0, 114.1, 89.9, 78.5, 24.0, 4.4.

MS (EI, 70 eV) m/z (%): 223 (53) [^{35}Cl-M^+], 222 (100), 77 (8), 43 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3266, 3193, 3124, 3066, 2960, 2908, 2850, 2237, 1602, 1576, 1539, 1494, 1457, 1136, 1380, 1365, 1338, 1246, 1199, 1183, 1069, 1030, 996, 969, 890, 864, 824, 787, 750, 692, 621, 608, 590.

HRMS (EI) for $C_{14}H_{13}N_3$ (223.1109): 223.1109.

3. Functionalizations of Sensitive Aromatics and Heteroaromatics *via* Regio- and Chemoselective Zincations using Mixed Zn/Li Bases

3.1 General procedure for the deprotonation of sensitive arenes and heteroarenes using TMPZnCl·LiCl (100) (GP3)

A dry argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with TMPZnCl·LiCl (**101**) (1.1 equiv). The substrate (1.0 equiv) in THF was dropwise added at 25 °C. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at the temperature T1. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with a sat. aqueous NH_4Cl solution), the reaction mixture was quenched with a sat. aqueous NH_4Cl solution . The aqueous layer was extracted with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

3.2 General procedure for the reaction with acyl chlorides (GP4)

According to **GP3**, the freshly prepared magnesium or zinc reagent was cooled to −30 °C, and CuCN·2LiCl[65] (1.1 equiv, 1.00 M in THF) was added and stirred for 30 min. Thereafter, an acyl chloride (2.0 equiv) was added at −30 °C, 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 extracted with Et_2O and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude residue was purified by flash column chromatography.

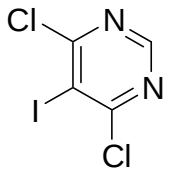
3.3 General procedure for the deprotonation of sensitive arenes and heteroarenes using TMPZnCl·LiCl (100) under microwave irradiations (GP5)

A dry argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with TMPZnCl·LiCl (**101**) (1.1 equiv). The substrate (1.0 equiv) in THF was dropwise added at 25 °C and submitted to microwave irradiation at the temperature T1. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at the temperature

T2. 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 solution . The aqueous layer was extracted with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

3.4 Functionalization of pyrimidines, pyridazines, pyrazines and purines

Synthesis of 4,6-dichloro-5-iodo-pyrimidine (79a):



4,6-Dichloropyrimidine **74** (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **GP3**. I_2 (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution (10 mL) and with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:4) furnished compound **79a** (227 mg, 83%) as a colourless solid.

m.p.: 134.9 – 136.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.65 (s, 1 H).

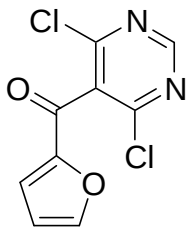
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 166.6, 156.8, 98.9.

MS (70 eV, EI) *m/z* (%)**:** 274 (100) [M^+], 239 (27), 97 (12), 83 (12), 57 (21).

IR (ATR) $\tilde{\nu}$ (cm^{-1})**:** 2923, 2855, 1900, 1499, 1386, 11341, 1296, 1214, 1080, 1014, 790, 763, 745.

HRMS (EI) for $C_4HCl_2IN_2$ (273.8561): 273.8565.

Synthesis of (4,6-dichloropyrimidin-5-yl)(furan-2-yl)methanone (79e):



4,6-Dichloropyrimidine **74** (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **GP3**. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at –30 °C and the reaction mixture was stirred at the same temperature for 30 min according to **GP4**. Then, furan-2-carbonyl chloride (261 mg, 2.0 mmol) was dropwise added at –30 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished **79e** as a colourless solid (172 mg, 71%).

m.p.: 143.6 – 145.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 8.88 (s, 1 H), 7.70 (m, 1 H), 7.28 (m, 1 H), 6.66 (m, 1 H).

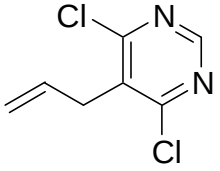
^{13}C NMR (100 MHz, $CDCl_3$) δ**:** 175.6, 158.8, 158.4, 150.8, 149.0, 130.9, 121.5, 113.5.

MS (70 eV, EI) *m/z* (%)**:** 242 (48) [M^+], 167 (49), 95 (100), 58 (21), 43 (33).

IR (ATR) $\tilde{\nu}$ (cm^{-1})**:** 3133, 2969, 2359, 2340, 1738, 1636, 1558, 1540, 1512, 1450, 1403, 1375, 1361, 1297, 1230, 1216, 1168, 1123, 1083, 1032, 956, 904, 888, 878, 815, 789, 781, 746, 738, 668, 626, 615, 609.

HRMS (EI) for $C_9H_4Cl_2N_2O_2$ (241.9650): 241.9653.

Synthesis of 5-allyl-4,6-dichloropyrimidine (79f):



4,6-Dichloropyrimidine **74** (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **GP3**. CuCN·2LiCl (1 M in THF; 0.05 mL, 5 mol %) was then slowly added at –30 °C. Allyl bromide (242 mg, 2.0 mmol) was then slowly added at –60 °C. The resulting mixture was then allowed to warm up slowly to 0 °C within 4 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished **79f** as a colourless oil (215 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64 (s, 1 H), 5.80 – 5.90 (m, 1 H), 5.09 – 5.18 (m, 2 H), 3.64 (dt, ^3J = 6.4 Hz, ^4J = 1.4 Hz, 2 H).

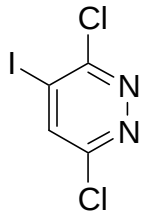
^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 155.8, 130.9, 130.6, 118.2, 34.0.

MS (70 eV, EI) *m/z* (%)**:** 188 (70) [M^+], 125 (22), 117 (44), 90 (59), 64 (35), 49 (43), 41 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1})**:** 2969, 2360, 1739, 1639, 1539, 1513, 1435, 1406, 1375, 1348, 1313, 1290, 1200, 1162, 1129, 1090, 989, 929, 906, 839, 777, 687, 668, 627, 621, 616.

HRMS (EI) for $C_7H_6Cl_2N_2$ (187.9908): 187.9913.

Synthesis of 3,6-dichloro-4-iodopyridazine (105a):



3,6-Dichloropyridazine (**103**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. I_2 (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution (10 mL) and with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by

flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **105a** (231 mg, 84%) as a colourless solid.

m.p.: 145.1 – 146.6 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.06 (s, 1 H).

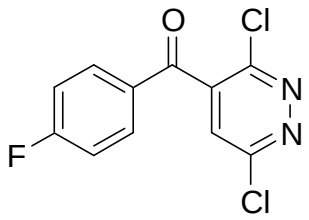
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 159.7, 153.9, 139.7, 105.4.

MS (70 eV, EI) *m/z* (%): 274 (95) [M^+], 127 (23), 123 (10), 121 (10), 119 (100), 86 (15), 84 (43), 49 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3092, 3020, 1796, 1516, 1488, 1464, 1332, 1296, 1276, 1236, 1152, 1136, 1060, 1044, 992, 956, 900, 812, 764, 728, 672, 660, 628, 608, 588, 564.

HRMS (EI) for $C_4HCl_2IN_2$ (273.8561): 273.8538.

Synthesis of (3,6-dichloropyridazin-4-yl)(4-fluorophenyl)methanone (105b):



3,6-Dichloropyridazine (**103**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. After cooling to –30 °C, CuCN·2LiCl (1.0 M in THF, 1.1 mmol, 1.1 equiv) was added and the resulting mixture was stirred for 30 min at this temperature according to **GP4**. 4-Fluorobenzoyl chloride (317 mg, 2.0 mmol) was then slowly added and the resulting mixture was allowed to warm up slowly to 10 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished compound **105b** (259 mg, 96%) as a white solid.

m.p.: 71.1 – 72.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.79 – 7.83 (m, 2 H), 7.51 (s, 1 H), 7.19 – 7.24 (m, 2 H).

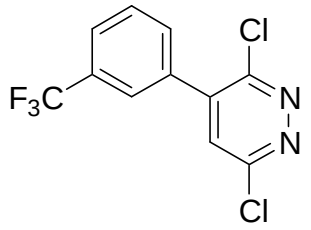
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 187.4, 167.0 (d, *J* (C-F) = 259.9 Hz), 156.3, 151.5, 139.6, 132.8 (d, *J* (C-F) = 9.9 Hz), 130.4 (d, *J* (C-F) = 3.1 Hz), 127.7, 116.8 (d, *J* (C-F) = 22.6 Hz).

MS (70 eV, EI) *m/z* (%): 270 (11) [M^+], 123 (100), 95 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3067, 2927, 2358, 1917, 1673, 1590, 1504, 1414, 1344, 1319, 1256, 1237, 1178, 1157, 1140, 1103, 1041, 1009, 967, 955, 909, 849, 841, 818, 795, 760, 753, 683, 659, 650, 645, 638, 633, 625, 620, 614, 606, 602.

HRMS (EI) for $C_{11}H_5Cl_2FN_2O$ (269.9763): 269.9762.

Synthesis of 3,6-dichloro-4-(3-(trifluoromethyl)phenyl)pyridazine (105c):



3,6-Dichloropyridazine (**103**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. $Pd(dba)_2$ (17 mg, 3 mol%) and $P(o\text{-furyl})_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzomethyltrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **105c** (243 mg, 83%) as a colourless solid.

m.p.: 93.0 – 94.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 – 7.81 (m, 4 H), 7.53 (s, 1 H).

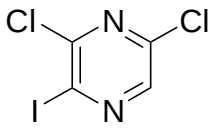
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.1, 154.4, 143.3, 141.2, 133.9, 131.5 (q, J (C-F) = 33.0 Hz), 129.6 (2), 128.3, 127.0 (q, J (C-F) = 3.8 Hz), 125.7 (q, J (C-F) = 3.8 Hz), 123.4 (q, J (C-F) = 272.5 Hz).

MS (70 eV, EI) *m/z* (%): 294 (60), 292 (100) [M^+], 266 (17), 264 (25), 229 (28), 206 (16), 204 (49), 194 (21), 169 (13), 138 (10), 136 (24), 113 (25), 59 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3048, 2359, 1743, 1614, 1558, 1485, 1435, 1361, 1323, 1309, 1281, 1241, 1226, 1214, 1167, 1144, 1109, 1097, 1078, 1060, 1042, 1001, 933, 917, 903, 884, 803, 782, 755, 709, 697, 660, 645, 639, 632, 625, 620, 614, 606, 601.

HRMS (EI) for $C_{11}H_5Cl_2F_3N_2$ (291.9782): 291.9785.

Synthesis of 3,5-dichloro-2-iodopyrazine (108a):



2,6-Dichloropyrazine (**106**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. I_2 (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution (10 mL) and with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **108a** (251 mg, 90%) as a colourless solid.

m.p.: 101.3 – 103.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.30 (s, 1 H).

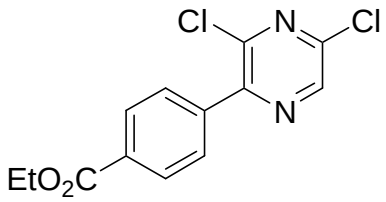
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.1, 146.9, 142.4, 115.7.

MS (70 eV, EI) *m/z* (%): 274 (100) [M^+], 147 (75), 127 (18), 86 (32), 57 (21), 44 (94).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 2633, 2281, 1784, 1738, 1510, 1491, 1379, 1353, 1323, 1274, 1230, 1217, 1205, 1175, 1162, 1143, 1018, 893, 843, 655, 634, 618, 611, 604.

HRMS (EI) for $C_4HCl_2IN_2$ (273.8561): 273.8555.

Synthesis of ethyl 4-(3,5-dichloropyrazin-2-yl)benzoate (108b):



2,6-Dichloropyrazine (**106**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of ethyl 4-iodobenzoate (359 mg, 1.3 mmol), were then transferred *via* cannula to the reaction mixture.

The reaction mixture was stirred at 25 °C for 1.5 h. with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **108b** (251 mg, 87%) as a colourless solid.

m.p.: 88.5 – 90.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.59 (s, 1 H), 8.14 (d, J = 8.6 Hz, 2 H), 7.84 (d, J = 8.6 Hz, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 1.40 (t, J = 7.0 Hz, 3 H).

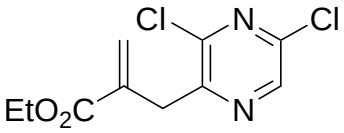
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.8, 150.1, 145.9, 142.0, 139.0, 131.6, 129.4 (2), 61.2, 14.3.

MS (70 eV, EI) *m/z* (%): 296 (32) [M^+], 270 (24), 268 (38), 251 (100), 223 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3086, 3005, 2985, 2359, 1966, 1708, 1611, 1569, 1537, 1507, 1482, 1466, 1446, 1423, 1408, 1366, 1310, 1283, 1263, 1190, 1175, 1140, 1131, 1114, 1098, 1028, 1021, 1009, 915, 858, 843, 786, 758, 719, 698, 657, 634, 621, 616, 610, 602.

HRMS (EI) for $C_{13}H_{10}Cl_2N_2O_2$ (296.0119): 296.0119.

Synthesis of ethyl 2-((3,5-dichloropyrazin-2-yl)methyl)acrylate (108c):



2,6-Dichloropyrazine (**106**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. After cooling to –50 °C, ethyl (2-bromomethyl)acrylate (230 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added and the resulting mixture was allowed to warm up slowly to –20 °C. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished compound **108c** (187 mg, 72%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.38 (s, 1 H), 6.34 (s, 1 H), 5.56 (s, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.92 (s, 2 H), 1.21 (t, J = 7.1 Hz, 3 H).

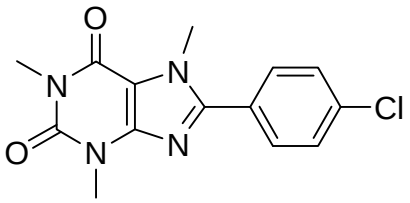
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.0, 151.5, 146.8, 145.0, 141.5, 136.0, 127.6, 60.9, 36.7, 14.0.

MS (70 eV, EI) *m/z* (%): 261 (100) [M^+-H], 163 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 2359, 1738, 1503, 1385, 1342, 1294, 1226, 1215, 1084, 1013, 987, 954, 795, 764, 749, 667, 621, 615, 608, 603.

HRMS (ESI) for $C_{10}H_{10}Cl_2N_2O_2$ (260.0119 (M^+-H)): 261.0196.

Synthesis of 8-(4-chlorophenyl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (111a):



TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) was added to a solution of 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (**109**) (194 mg, 1.0 mmol) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for max. 5 min. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (310 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/ether 1:1) furnished compound **111a** (226 mg, 74%) as a colourless solid.

m.p.: 199.4 – 201.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H), 4.03 (s, 3 H), 3.59 (s, 3 H), 3.39 (s, 3 H).

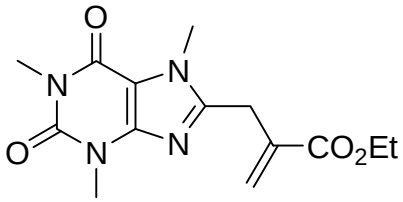
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 155.4, 151.5, 150.7, 148.1, 136.7, 130.4, 129.2, 126.7, 108.6, 33.9, 29.8, 28.0.

MS (70 eV, EI) *m/z* (%): 304 (100) [M^+], 82 (23), 67 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 1738, 1694, 1646, 1605, 1569, 1538, 1473, 1454, 1430, 1408, 1374, 1288, 1229, 1216, 1180, 1108, 1090, 1074, 1030, 1008, 977, 835, 803, 759, 749, 739, 730, 708, 685, 671, 650, 645, 639, 632, 625, 620, 614, 606. 601.

HRMS (ESI) for $C_{14}H_{13}ClN_4O_2$ (304.0727): 304.0722.

Synthesis of ethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)methyl)acrylate (111b):



TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) was added to a solution of 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (**109**) (194 mg, 1.0 mmol) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for max. 5 min. After cooling to –50 °C, ethyl 2-(bromomethyl)acrylate (230 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added and the resulting mixture was allowed to warm up slowly overnight. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/ether, 1:1) furnished compound **111b** (211 mg, 69%) as a colourless solid.

m.p.: 113.5 – 115.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.28 (s, 1 H), 5.49 (s, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 3.70 (s, 2 H), 3.45 (s, 3 H), 3.29 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.7, 155.1, 151.4, 150.8, 147.7, 135.0, 127.3, 107.4, 61.1, 31.8, 29.6, 29.3, 27.7, 14.0.

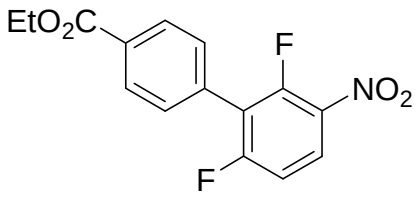
MS (70 eV, EI) *m/z* (%): 306 (78) [M^+], 260 (28), 232 (100), 219 (11), 67 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2998, 2956, 2358, 1719, 1697, 1658, 1548, 1497, 1448, 1426, 1402, 1362, 1340, 1293, 1253, 1215, 1162, 1112, 1033, 978, 960, 939, 894, 858, 831, 812, 759, 743, 718, 693, 663, 641, 630, 602.

HRMS (ESI) for $C_{14}H_{18}N_4O_4$ (306.1328): 306.1320.

3.5 Functionalization of arenes and heteroarenes bearing a nitro group:

Synthesis of ethyl 2',6'-difluoro-3'-nitrobiphenyl-4-carboxylate (114a):



2,4-Difluoro-1-nitrobenzene **112** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **GP3**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of ethyl 4-iodobenzoate (359 g, 1.3 mmol), were then transferred *via* cannula at -20°C. The resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **114a** (281 mg, 92%) as a colourless solid.

m.p.: 85.0 – 86.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.09 – 8.18 (m, 1 H), 8.15 (d, J = 8.8 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.11 – 7.18 (m, 1 H), 4.40 (q, J = 7.0 Hz, 3 H), 1.40 (d, J = 7.0 Hz, 2 H).

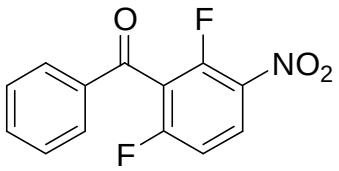
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 165.8, 162.5 (dd, J = 6.0 Hz, J = 260.1 Hz), 153.7 (dd, J = 6.0 Hz, J = 260.1 Hz), 131.2 (dd, J = 0.5 Hz, J = 3.9 Hz), 130.2 (dd, J = 1.8 Hz, J = 2.0 Hz), 129.7, 126.6 (dd, J = 1.8 Hz, J = 21.4 Hz), 120.2 (dd, J = 28.1 Hz, J = 1.8 Hz), 112.1 (dd, J = 4.3 Hz, J = 24.7 Hz), 61.3, 14.3.

MS (70 eV, EI) *m/z* (%)**:** 307 (23) [M^+], 279 (48), 262 (100), 216 (43), 188 (34), 44 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1})**:** 3101, 2969, 2359, 1712, 1621, 1589, 1567, 1535, 1510, 1472, 1404, 1368, 1341, 1304, 1286, 1269, 1215, 1185, 1170, 1148, 1127, 1103, 1070, 1020, 1011, 948, 879, 857, 824, 778, 756, 714, 702, 667, 636, 620, 607, 602.

HRMS (EI) for **$C_{15}H_{11}F_2NO_4$** (307.0656): 307.0651.

Synthesis of (2,6-difluoro-3-nitrophenyl)(phenyl)methanone (114b):



2,4-Difluoro-1-nitrobenzene **112** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **GP3**. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at –40 °C and the reaction mixture was stirred at the same temperature for 30 min according to **GP4**. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at –40 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane, 1:2) furnished compound **114b** (221 mg, 84%) as a colourless solid.

m.p.: 75.8 – 77.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 7.14 – 8.31 (m, 7 H).

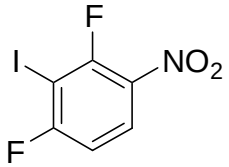
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 186.2, 162.2 (dd, J = 4.2 Hz, J = 262.4 Hz), 153.7 (dd, J = 9.0 Hz, J = 269.9 Hz), 135.7, 135.1, 133.8, 130.2, 129.6, 129.1, 128.7 (dd, J = 2.1 Hz, J = 10.9 Hz), 128.5, 119.3 (dd, J = 21.9 Hz, J = 2.1 Hz).

MS (70 eV, EI) *m/z* (%)**:** 263 (52) [M^+], 105 (100), 33 (77).

IR (ATR) $\tilde{\nu}$ (cm^{-1})**:** 3100, 1912, 1738, 1675, 1619, 1594, 1530, 1496, 1469, 1450, 1351, 1320, 1311, 1280, 1266, 1217, 1180, 1159, 1128, 1100, 1073, 1034, 1027, 1000, 970, 934, 862, 834, 828, 797, 774, 759, 731, 705, 692, 683, 668, 645, 638, 630, 626, 620, 614, 606, 601.

HRMS (EI) for **$C_{13}H_7F_2NO_3$** (263.0394): 263.0393.

Synthesis of 2,4-difluoro-3-iodonitrobenzene (114c):



2,4-Difluoro-1-nitrobenzene **112** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **GP3**. I_2 (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution (10 mL) and with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished compound **114c** (256 mg, 90%) as a colourless solid.

m.p.: 46.1 – 47.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.12 – 8.17 (m, 1 H), 7.04 – 7.08 (m, 1 H).

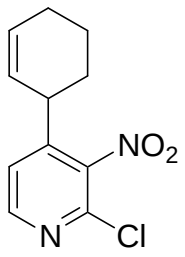
^{13}C NMR (75 MHz, $CDCl_3$) δ**:** 165.6 (dd, J = 5.0 Hz, J = 252.6 Hz), 156.4 (dd, J = 6.9 Hz, J = 264.1 Hz), 127.7 (dd, J = 2.3 Hz, J = 10.3 Hz), 111.6 (dd, J = 4.2 Hz, J = 26.1 Hz), 74.3 (dd, J = 29.2 Hz, J = 1.9 Hz).

MS (70 eV, EI) *m/z* (%)**:** 285 (100) [M^+], 258 (17), 239 (19), 227 (17), 167 (25), 149 (66), 112 (58), 71 (11), 57 (12), 44 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1})**:** 3098, 2926, 2855, 2359, 1916, 1739, 1602, 1584, 1529, 1463, 1425, 1336, 1301, 1277, 1218, 1147, 1105, 1011, 860, 827, 751, 698, 669, 621, 616.

HRMS (EI) for **$C_6H_2F_2INO_2$** (284.9098): 284.9094.

Synthesis of 2-chloro-4-cyclohex-2-enyl-3-nitro-pyridine (117):



2-Chloro-3-nitropyridine (**115**) (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. After cooling to –50 °C, 3-bromocyclohexene (192 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.05 mL, 0.05 mmol) were added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with

diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished 2-chloro-4-(cyclohex-2-enyl)-3-nitro-pyridine (**117**) (173 mg, 73%) as a colourless solid.

m.p.: 54.5 – 55.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (d, ^3J = 5.1 Hz, 1 H), 7.32 (d, ^3J = 5.1 Hz, 1 H), 6.07 (ddd, ^3J = 10.0 Hz, ^3J = 6.1 Hz, ^4J = 3.7 Hz, 1 H), 5.54 (dd, ^3J = 10.0, ^4J = 1.9 Hz, 1 H), 3.46 (m, 1 H), 2.09 (m, 3 H), 1.76 (m, 1 H), 1.64 (m, 1 H), 1.51 (m, 1 H).

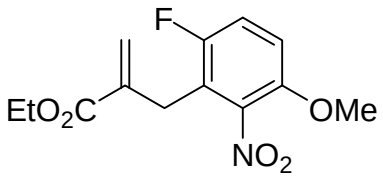
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.2, 150.0, 146.5, 141.8, 131.9, 125.9, 123.3, 37.4, 31.3, 24.7, 20.8.

MS (70 eV, EI) *m/z* (%): 237 (3) [M^+-H], 223 (31), 221 (100), 203 (48), 193 (48), 185 (20), 181 (45), 167 (32), 165 (31), 157 (21), 129 (29), 128 (31), 115 (21), 77 (35), 51 (22), 41 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2939, 1589, 1539, 1446, 1361, 1347, 1231, 1137, 1041, 973, 918, 890, 855, 845, 757, 723, 691, 616.

HRMS (EI) for **$C_{11}H_{11}ClN_2O_2$** (237.0431 [M^+-H]): 237.0424.

Synthesis of ethyl 2-(6-fluoro-3-methoxy-2-nitrobenzyl)acrylate (120):



4-Fluoro-2-nitrobenzene (**118**) (171 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 6 h according to **GP3**. After cooling to –50 °C, ethyl 2-(bromomethyl)acrylate (230 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added at -40 °C and the resulting mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished compound **120** (189 mg, 67%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.15 (m, 1 H), 8.89 – 8.93 (m, 1 H), 6.24 (s, 1 H), 5.31 (s, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 3.63 (bs, 2 H), 1.27 (t, J = 7.1 Hz, 3 H).

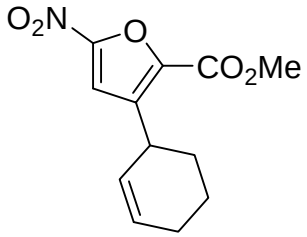
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.9, 154.3 (d, J = 243.6 Hz), 147.1 (d, J = 2.8 Hz), 136.2 (d, J = 0.8 Hz), 126.3 (d, J = 0.8 Hz), 120.0 (d, J = 21.9 Hz), 117.6, 117.3, 111.7 (d, J = 8.3 Hz), 61.1, 56.7, 26.9 (d, J = 2.9 Hz), 14.1.

MS (70 eV, EI) *m/z* (%): 283 (1) [M^+], 237 (100), 209 (88), 192 (58), 166 (20), 149 (21), 133 (16), 121 (13), 99 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 2359, 1738, 1503, 1385, 1342, 1294, 1226, 1215, 1084, 1013, 987, 954, 795, 764, 749, 667, 621, 615, 608, 603.

HRMS (ESI) for **$C_{13}H_{14}FNO_5$** (283.0856): 283.0845.

Synthesis of methyl 3-(cyclohex-2-enyl)-5-nitrofuran-2-carboxylate (123):



Methyl 5-nitrofuran-2-carboxylate (**121**) (171 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. After cooling to –50 °C, 3-bromocyclohexene (209 mg, 1.3 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added and the resulting mixture was stirred for 1 h at this temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **123** (179 mg, 72%) as a yellowish oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.20 (s, 1 H), 5.94 (m, 1 H), 5.56 (m, 1 H), 4.10 (m, 1 H), 3.92 (s, 3 H), 2.07 (m, 3 H), 1.50 – 1.69 (m, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.5, 142.6, 133.9, 130.4, 126.2, 120.1, 52.8, 32.2, 29.0, 24.6, 20.5.

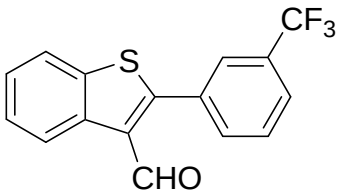
MS (70 eV, EI) *m/z* (%): 252 (2) [M^+], 234 (100), 217 (55), 146 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2936, 2356, 1729.35, 1629, 1594, 1532, 1502, 1435, 1398, 1338, 1288, 1226, 1206, 1110, 1091, 985, 925, 880, 848, 819, 799, 763, 725, 668, 634, 622.

HRMS (EI) for **$C_{12}H_{13}NO_5$** (251.0794): 251.0794.

3.6 Functionalization of heteroarenes bearing an aldehyde

Synthesis of 2-(3-(trifluoromethyl)phenyl)benzo[b]thiophene-3-carbaldehyde (126a):



Benzo[b]thiophene-3-carbaldehyde (**124**) (162 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. $Pd(dba)_2$ (17 mg, 3 mol%) and $P(o\text{-furyl})_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzomethyltrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished compound **126a** (281 mg, 92%) as a colourless solid.

m.p.: 102.8 – 104.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.02 (s, 1 H), 8.79 (m, 1 H), 7.45 – 7.87 (m, 7 H).

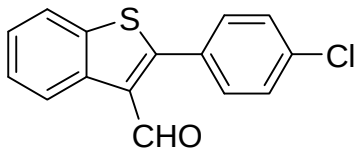
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 185.9, 158.0, 138.0, 136.8, 133.7, 132.4, 131.5 (q, *J* (C-F) = 33.0 Hz), 130.7, 129.5, 127.0 (q, *J* (C-F) = 3.8 Hz), 126.6 (q, *J* (C-F) = 3.8 Hz), 126.5, 126.2, 123.5 (q, *J* (C-F) = 272.5 Hz), 121.7.

MS (70 eV, EI) *m/z* (%): 306 (97) [M^+], 305 (100), 278 (12), 257 (13), 237 (28), 233 (18), 208 (29), 160 (13), 44 (40).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3068, 2866, 2359, 1926, 1745, 1669, 1590, 1520, 1483, 1459, 1438, 1421, 1392, 1351, 1325, 1310, 1288, 1265, 1217, 1178, 1156, 1118, 1097, 1092, 1073, 1051, 1018, 1000, 994, 966, 947, 933, 907, 868, 863, 812, 773, 754, 733, 703, 679, 653, 641, 633, 620, 608, 603.

HRMS (EI) for **$C_{16}H_9F_3OS$** (306.0326): 306.0326.

Synthesis of 2-(4-chlorophenyl)benzo[b]thiophene-3-carbaldehyde (126b):



Benzo[b]thiophene-3-carbaldehyde (**124**) (162 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (310 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished compound **126b** (236 mg, 87%) as a colourless solid.

m.p.: 99.7 – 101.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.02 (s, 1 H), 8.76 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.42 – 7.54 (m, 6 H).

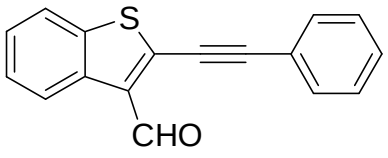
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 186.2, 158.9, 137.8, 136.9, 136.4, 131.6, 130.3, 130.0, 129.2, 126.4, 126.0, 125.2, 121.6.

MS (70 eV, EI) *m/z* (%): 272 (100) [M^+], 237 (54), 208 (34), 165 (12), 118 (20), 104 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 2969, 2867, 2362, 1947, 1739, 1671, 1590, 1562, 1517, 1482, 1457, 1431, 1407, 1397, 1346, 1265, 1218, 1187, 1161, 1135, 1109, 1091, 1050, 1020, 1012, 971, 952, 938, 846, 830, 813, 748, 723, 716, 710, 698, 667, 638, 616, 610, 603.

HRMS (EI) for **$C_{15}H_9ClOS$** (272.0063): 272.0057.

Synthesis of 2-(phenylethynyl)benzo[b]thiophene-3-carbaldehyde (126c):



Benzo[b]thiophene-3-carbaldehyde (**124**) (162 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP3**. I_2 (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 0.5 h. To the solution of freshly generated *in situ* 2-iodobenzo[b]thiophene-3-carbaldehyde, NEt_3 (7 mL), CuI (8 mg, 4 mol%), $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) in THF (2 mL) and phenylacetylene (254 mg, 1.5 mol, 1.5 equiv) were successively slowly added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$ solution (10 mL) and with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished compound **126c** (165 mg, 63%) as a yellowish solid.

m.p.: 104.9 – 106.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.47 (s, 1 H), 8.69 (m, 1 H), 7.77 (m, 1 H), 7.60 (m, 2 H), 7.38 – 7.51 (m, 5 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 185.6, 138.9, 138.5, 135.9, 135.2, 131.8, 129.8, 128.6, 126.8, 126.5, 124.9, 121.6, 121.3, 102.9, 80.0.

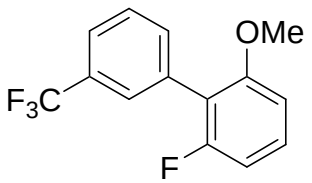
MS (70 eV, EI) *m/z* (%): 262 (100) [M^+], 234 (38), 232 (13), 202 (11), 189 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 2832, 2359, 2340, 2203, 1739, 1661, 1587, 1569, 1507, 1481, 1458, 1442, 1427, 1361, 1316, 1293, 1250, 1229, 1216, 1177, 1162, 1141, 1119, 1070, 1059, 1043, 1015, 997, 953, 918, 868, 748, 737, 697, 687, 668, 630, 621, 616, 610.

HRMS (EI) for **$C_{17}H_{10}OS$** (262.0452): 262.0459.

3.7 Functionalization of arenes and heteroarenes using TMPZnCl·LiCl (100) under microwave irradiation (GP5)

Synthesis of 2-fluoro-6-methoxy-3'-trifluoromethyl-biphenyl (129):



3-Fluoroanisole (**127**) (126 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting

mixture was heated at 160 °C (250 W) for 2 h according to **GP5**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:8) furnished the compound **129** (194 mg, 72%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.73 (s, 1 H), 7.54 – 7.66 (m, 3 H), 7.28 – 7.38 (m, 1 H), 6.81 – 6.88 (m, 2 H), 3.82 (s, 3 H).

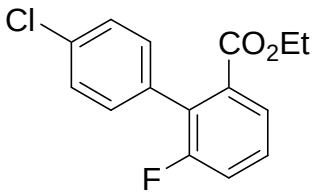
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.3 (d, J = 245.7 Hz), 157.7 (d, J = 6.7 Hz), 134.1 (quint., J = 1.6 Hz), 132.4 (d, J = 0.8 Hz), 130.3 (q, J = 32.3 Hz), 129.6 (d, J = 10.8 Hz), 128.3, 127.6 (dddd, J = 1.5 Hz), 124.3 (q, J = 3.7 Hz), 124.2 (q, J = 272.4 Hz), 117.2 (d, J = 17.6 Hz), 108.4 (d, J = 23.2 Hz), 106.8 (d, J = 2.8 Hz), 56.1.

MS (EI, 70 eV) m/z (%): 270 (100) [M^+], 255 (14), 235 (36), 201 (13), 186 (37), 157 (11), 136 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941, 2848, 1616, 1580, 1499, 1471, 1431, 1331, 1285, 1271, 1251, 1238, 1163, 1120, 1098, 1072, 1027, 942, 904, 825, 803, 780, 752, 728, 700, 655.

HRMS (EI) for $C_{14}H_{10}F_4O$ (270.0668): 270.0657.

Synthesis of ethyl 4'-chloro-6-fluorobiphenyl-2-carboxylate (132a):



Ethyl 3-fluorobenzoate (**130**) (168 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (200 W) for 1.5 h according to **GP5**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (308 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over

anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **132a** (209 mg, 76%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65 – 7.68 (m, 1 H), 7.36 – 7.43 (m, 3 H), 7.21 – 7.30 (m, 3 H), 4.07 (q, J = 7.2 Hz, 2 H), 1.02 (t, J = 7.2 Hz, 3 H).

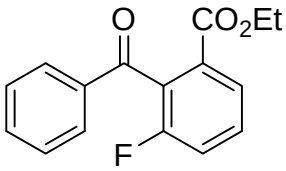
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.0 (d, J (C-F) = 3.3 Hz), 159.6 (d, J (C-F) = 246.4 Hz), 133.8, 133.5 (d, J (C-F) = 2.5 Hz), 132.6, 130.6 (d, J (C-F) = 1.3 Hz), 129.0 (d, J (C-F) = 8.5 Hz), 128.7 (d, J (C-F) = 17.5 Hz), 128.2, 125.5 (d, J (C-F) = 3.7 Hz), 118.8 (d, J (C-F) = 23.4 Hz), 61.2, 13.6.

MS (70 eV, EI) *m/z* (%): 278 (52) [M^+], 270 (37), 250 (20), 233 (100), 199 (19), 186 (22), 170 (72), 149 (14), 85 (14), 44 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3070, 2987, 1716, 1675, 1607, 1594, 1579, 1476, 1449, 1366, 1292, 1273, 1194, 1152, 1114, 1027, 963, 928, 811, 762, 709, 660.

HRMS (EI) for **$C_{15}H_{12}ClFO_2$** (278.0510): 278.0506.

Synthesis of ethyl 2-benzoyl-3-fluorobenzoate (132b):



Ethyl 3-fluorobenzoate (**130**) (168 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (200 W) for 1.5 h according to **GP5**. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at –30 °C and the reaction mixture was stirred at the same temperature for 30 min according to **GP4**. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at –30 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished compound **132b** (196 mg, 72%) as a colourless solid.

m.p.: 101.6 – 103.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.90 – 7.93 (m, 1 H), 7.79 – 7.82 (m, 2 H), 7.31 – 7.59 (m, 5 H), 4.13 (q, J = 7.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H).

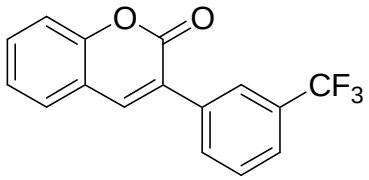
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.5, 164.6 (d, *J* (C-F) = 3.1 Hz), 159.1 (d, *J* (C-F) = 248.0 Hz), 137.0, 133.5, 130.9 (d, *J* (C-F) = 3.8 Hz), 130.5 (d, *J* (C-F) = 8.0 Hz), 129.5 (d, *J* (C-F) = 20.1 Hz), 129.0, 128.6, 126.2 (d, *J* (C-F) = 3.1 Hz), 120.2 (d, *J* (C-F) = 21.9 Hz), 61.8, 13.6.

MS (70 eV, EI) *m/z* (%): 272 (39) [M^+], 227 (35), 195 (46), 170 (15), 167 (100), 151 (13), 105 (71), 77 (44).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1716, 1597, 1577, 1498, 1454, 1397, 1367, 1284, 1242, 1177, 1140, 1090, 1073, 1020, 1006, 954, 938, 865, 824, 751, 685.

HRMS (EI) for **$C_{16}H_{13}FO_3$** (272.0849): 272.1014.

Synthesis of 3-(3-(trifluoromethyl)phenyl)-2H-chromen-2-one (135a):



Coumarin (**133**) (168 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 80 °C (100 W) for 1 h according to **GP5**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **135a** (182 mg, 71%) as a colourless solid.

m.p.: 124.0 – 125.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.91 – 7.94 (m, 2 H), 7.86 (s, 1 H), 7.63 – 7.66 (m, 1 H), 7.52 – 7.58 (m, 3 H), 7.28 – 7.37 (m, 2 H).

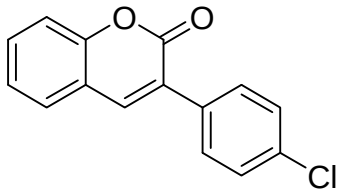
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.1, 153.6, 140.7, 135.4, 132.0, 130.9 (q, *J* = 32.4 Hz), 128.9, 128.1, 126.8, 125.4 (q, *J* = 3.9 Hz), 125.2 (q, *J* = 3.9 Hz), 124.7, 123.9 (d, *J* = 272.5 Hz), 119.3, 116.5.

MS (EI, 70 eV) m/z (%): 290 (85) [M^+], 262 (100), 233 (15), 183 (12), 165 (72).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925, 2853, 1711, 1608, 1562, 1491, 1458, 1429, 1339, 1331, 1290, 1259, 1166, 1148, 1109, 1076, 967, 956, 920, 904, 859, 808, 773, 759, 734, 692, 654, 644, 626.

HRMS (EI) for $C_{16}H_9F_3O_2$ (290.0555): 290.0550.

Synthesis of 3-(4-chlorophenyl)-2H-chromen-2-one (135b):



Coumarin (**133**) (168 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 80 °C (100 W) for 1 h according to **GP5**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (308 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **135b** (182 mg, 71%) as a colourless solid.

m.p.: 189.2 – 191.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.79 (s, 1 H), 7.65 (d, *J* = 8.9 Hz, 2 H), 7.50 – 7.56 (m, 2 H), 7.40 (d, *J* = 8.9 Hz, 2 H), 7.26 – 7.36 (m, 2 H).

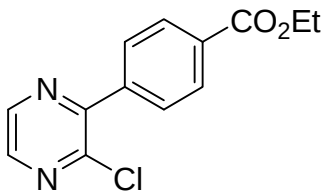
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.3, 153.5, 139.9, 134.9, 133.0, 131.6, 129.8, 128.6, 128.0, 127.1, 124.6, 119.4, 116.5.

MS (EI, 70 eV) m/z (%): 256 (100) [^{35}Cl-M$^+$], 228 (72), 165 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 1708, 1685, 1608, 1566, 1489, 1452, 1401, 1352, 1297, 1259, 1228, 1153, 1123, 1091, 1013, 952, 923, 838, 815, 776, 748, 742, 706, 633, 622.

HRMS (EI) for $C_{15}H_9ClO_2$ (256.0291): 256.0288.

Synthesis of ethyl 4-(3-chloropyrazin-2-yl)benzoate (138a):



2-Chloropyrazine (**136**) (115 mg, 1.0 mmol) dissolved in THF (1 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 70 °C (100 W) for 45 min according to **GP5**. $Pd(dba)_2$ (17 mg, 3 mol%) and $P(o\text{-furyl})_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with ethyl 4-iodobenzoate (359 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1.5 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **138a** (216 mg, 82%) as a brown solid.

m.p.: 90.1 – 91.7 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.56 (d, *J* = 2.4 Hz, 1 H), 8.33 (d, *J* = 2.4 Hz, 1 H), 8.12 (d, *J* = 8.8 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.37 (t, *J* = 7.1 Hz, 3 H).

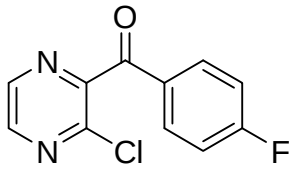
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 165.8, 152.2, 147.3, 142.5, 142.3, 140.1, 131.2, 129.3, 129.2, 61.1, 14,2.

MS (EI, 70 eV) m/z (%): 262 (97) [^{35}Cl-M^+], 234 (35), 217 (100), 199 (13), 189 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3053, 2983, 2918, 1704, 1611, 1573, 1510, 1486, 1464, 1436, 1364, 1312, 1284, 1267, 1187, 1157, 1129, 1108, 1053, 1023, 1010, 963, 872, 856, 841, 813, 789, 760, 699, 652, 642, 625, 604.

HRMS (EI) for $C_{13}H_{11}ClN_2O_2$ (262.0509): 262.0498.

Synthesis of (3-chloropyrazin-2-yl)(4-fluorophenyl)methanone (138b):



2-Chloropyrazine (**136**) (115 mg, 1.0 mmol) dissolved in THF (1 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 70 °C (100 W) for 45 min according to **GP5**. $Pd(PPh_3)_4$ (100 mg) dissolved in THF (1 mL) was then simultaneous added to the reaction mixture with 4-fluorobenzoyl chloride (317 mg, 2.0 mmol) at the same temperature. The resulting mixture was then stirred at 65 °C and quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was

evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **138b** (158 mg, 67%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.57 (d, *J* = 2.5 Hz, 1 H), 8.53 (d, *J* = 2.5 Hz, 1 H), 7.84 – 7.88 (m, 2 H), 7.12 – 7.18 (m, 2 H).

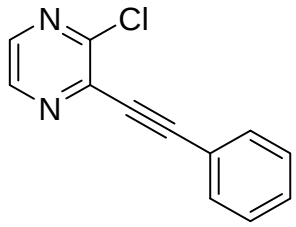
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 189.2, 166.5 (d, *J* = 257.8 Hz), 150.4, 146.6, 144.9, 141.6, 133.0 (d, *J* = 9.8 Hz), 131.0 (d, *J* = 2.9 Hz), 116.1 (d, *J* = 22.2 Hz).

MS (EI, 70 eV) m/z (%): 236 (8) [^{35}Cl-M^+], 123 (100), 95 (28).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2924, 1675, 1595, 1548, 1505, 1438, 1411, 1372, 1297, 1280, 1234, 1212, 1182, 1147, 1082, 1056, 1012, 936, 849, 820, 799, 769, 753, 723, 687, 652, 633, 622, 606.

HRMS (EI) for $C_{11}H_6ClFN_2O$ (236.0153): 236.0141.

Synthesis of 2-chloro-3-(phenylethynyl)pyrazine (138c):



2-Chloropyrazine (**136**) (115 mg, 1.0 mmol) dissolved in THF (1 mL) was added to a solution of TMPZnCl·LiCl (**101**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 70 °C (100 W) for 45 min according to **GP5**. After cooling down to 25 °C, iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was added dropwise and the resulting mixture was stirred for 1 h at rt. To the solution of generated *in situ* 2-chloro-3-iodopyrazine, NEt_3 (7 mL), CuI (8 mg, 4 mol%), $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) in THF (2 mL) and phenylacetylene (155 mg, 1.5 mol, 1.5 equiv) were slowly successively added. The reaction mixture was stirred at rt for 1 h. The resulting mixture was quenched with a sat. aq. NH_4Cl solution (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **138c** as a colourless solid (159 mg, 74%).

m.p.: 76.2 – 77.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 2.7 Hz, 1 H), 8.26 (d, *J* = 2.5 Hz, 1 H), 7.61 – 7.64 (m, 2 H), 7.34 – 7.40 (m, 3 H).

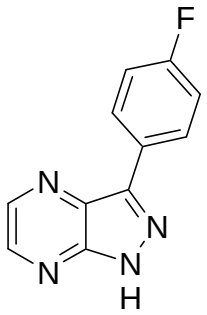
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.6, 142.2, 141.6, 139.4, 132.2, 129.9, 128.4, 121.1, 97.4, 84.4.

MS (70 eV, EI) m/z (%): 214 (100) [^{35}Cl-M^+], 179 (67), 128 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3045, 2919, 2262, 2217, 1937, 1595, 1548, 1507, 1491, 1442, 1435, 1381, 1335, 1304, 1211, 1185, 1168, 1153, 1078, 1054, 1024, 998, 926, 863, 772, 758, 692, 667, 657, 622, 611, 605.

HRMS (EI) for $C_{12}H_7ClN_2$ (214.0298): 214.0291.

Synthesis of 3-(4-fluoro-phenyl)-1H-pyrazolo[3,4-b]pyrazine (JNK kinase inhibitor (139)):



Hydrazine (64% in water; 0.17 mL, 3.4 mmol) was added to a solution of **138b** (236 mg, 1.0 mmol) dissolved in 2 mL THF at 70 °C. The resulting mixture was stirred at the same temperature for 30 min, then quenched with a sat. aq. Na_2CO_3 solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/Et_2O 19:1) furnished **139** as a colourless solid (150 mg, 70%).

m.p.: 249.1 – 251.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.68 (s, 1 H), 8.61 (s, 1 H), 8.42 – 8.45 (m, 2 H), 7.31 – 7.36 (m, 2 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 162.2 (d, J = 245.8 Hz), 145.3, 143.1, 140.9, 140.6, 130.6, 128.4 (d, J = 3.1 Hz), 128.1 (d, J = 8.4 Hz), 115.7 (d, J = 21.8 Hz).

MS (EI, 70 eV) m/z (%): 214 (100) [M^+], 187 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3202, 3157, 3035, 2911, 1598, 1552, 1530, 1494, 1460, 1411, 1379, 1332, 1258, 1215, 1193, 1162, 1098, 1042, 992, 931, 849, 814, 801, 770, 738, 690.

HRMS (EI) for $C_{11}H_7FN_4$ (214.0655): 214.0648.

4. Functionalization of Pyrazine Derivatives via Regio- and Chemoselective Metalations.

4.1 General procedure for the deprotonation using TMPMgCl·LiCl (16a) or TMPZnCl (101) (GP6)

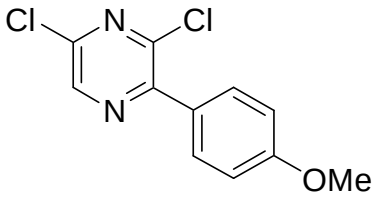
A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with TMPMgCl·LiCl (**16a**) or TMPZnCl·LiCl (**101**) (1.1 equiv). The substrate (1.0 equiv) in THF was dropwise added at the temperature T1. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at the temperature T2. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with a sat. aqueous NH_4Cl solution), the reaction mixture was quenched with a sat. aqueous NH_4Cl solution . The aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography.

4.2 General procedure for the reaction with acyl chlorides (GP7)

According to **GP6**, the freshly prepared magnesium or zinc reagent was cooled to −30 °C, and CuCN·2LiCl[65] (1.1 equiv, 1.00 M in THF) was added and stirred for 30 min. Thereafter, acyl chloride (2.0 equiv) was added at −30 °C, and the reaction mixture was warmed to 25 °C and stirred for the appropriate time. The reaction mixture was quenched with a sat. aq. NH_4Cl solution extracted with ether and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. The crude residue was purified by flash column chromatography.

4.3 Preparation of polyfunctionalized pyrazines

Synthesis of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (147a):



2,6-Dichloropyrazine (**141**) (1,49 g, 10.0 mmol) dissolved in THF (10 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 7.9 mL, 11.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. $Pd(dba)_2$ (113 mg, 2 mol%) and $P(o\text{-furyl})_3$ (93 mg, 4 mol%) dissolved in THF (5 mL), and mixed with 4-iodoanisole (3.04 g, 13 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (100 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **147a** (2.17 g, 86%) as a colourless solid.

m.p.: 95.7 – 97.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.54 (s, 1 H), 7.79 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 3.86 (s, 3 H).

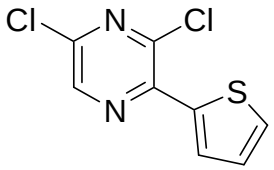
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.9, 150.8, 145.0, 144.4, 141.7, 131.0, 127.2, 113.7, 55.4.

MS (70 eV, EI) m/z (%): 254 (100) [^{35}Cl-M^+], 239 (12), 219 (35), 133 (11), 44 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3013, 2940, 2840, 1738, 1607, 1577, 1531, 1512, 1461, 1452, 1415, 1379, 1320, 1304, 1250, 1217, 1174, 1143, 1115, 1105, 1032, 1017, 1003, 953, 934, 920, 853, 842, 826, 804, 792, 774, 661, 641, 625, 618, 603.

HRMS (EI) for $C_{11}H_8Cl_2N_2O$ (254.0014): 254.0012.

Synthesis of 3,5-dichloro-2-thienylpyrazine (147b):



2,6-Dichloropyrazine (**141**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 0.79 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. $Pd(dba)_2$ (17 mg, 3 mol%) and $P(o\text{-furyl})_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 2-iodothiophene (273 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash

chromatography (CH_2Cl_2/pentane 1:6) furnished the compound **147b** (242 mg, 83%) as a colourless solid.

m.p.: 90.2 – 92.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (s, 1 H), 8.13 (dd, *J* = 3.8 Hz, *J* = 1.0 Hz, 1 H), 7.54 (dd, *J* = 5.1 Hz, *J* = 1.0 Hz, 1 H), 7.54 (dd, *J* = 5.1 Hz, *J* = 1.2 Hz, 1 H).

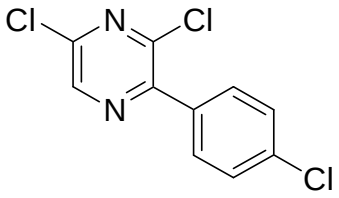
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 144.8, 143.3, 142.1, 141.4, 138.6, 130.7, 130.4, 128.3.

MS (70 eV, EI) m/z (%): 230 (100) [^{35}Cl-M$^+$], 195 (60), 165 (17), 109 (20), 44 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3078, 2969, 1738, 1524, 1515, 1500, 1433, 1426, 1397, 1359, 1328, 1309, 1295, 1282, 1267, 1228, 1215, 1179, 1163, 1136, 1100, 1085, 1070, 1055, 979, 960, 911, 892, 861, 855, 849, 824, 761, 750, 733, 696, 660, 635, 621, 601.

HRMS (EI) for $C_8H_4Cl_2N_2S$ (229.9472): 229.9463.

Synthesis of 3,5-dichloro-2-(4-chlorophenyl)pyrazine (147c):



2,6-Dichloropyrazine (**141**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 0.79 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (310 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **147c** (210 mg, 81%) as a colourless solid.

m.p.: 122.6 – 124.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.57 (s, 1 H), 7.75 (d, *J* = 9.0 Hz, 2 H), 7.47 (d, *J* = 9.0 Hz, 2 H).

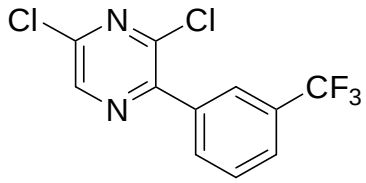
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.0, 145.6, 145.3, 142.0, 136.3, 133.4, 130.8, 128.6.

MS (70 eV, EI) m/z (%): 258 (100) [^{35}Cl-M$^+$], 223 (55), 137 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2924, 1903, 1656, 1597, 1536, 1500, 1416, 1401, 1312, 1289, 1258, 1173, 1143, 1113, 1103, 1088, 1021, 1007, 959, 912, 865, 834, 825, 772, 737, 712, 657, 631, 620, 615, 602.

HRMS (EI) for $C_{10}H_5Cl_3N_2$ (257.9518): 257.9353.

Synthesis of 3,5-dichloro-2-(3-(trifluoromethyl)phenyl)pyrazine (147d):



2,6-Dichloropyrazine (**141**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 0.79 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **147d** (242 mg, 83%) as colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.61 (s, 1 H), 8.07 (s, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H).

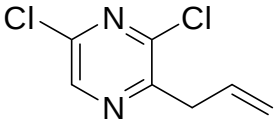
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 149.6, 146.1, 145.5, 142.2, 135.7, 132.6 (q, *J* = 2.7 Hz), 131.0 (q, *J* = 32.6 Hz), 128.9, 126.6 (q, *J* = 3.9 Hz), 126.5 (q, *J* = 3.9 Hz), 123.7 (q, *J* = 272.7 Hz).

MS (70 eV, EI) m/z (%): 292 (100) [^{35}Cl-M$^+$], 257 (66), 171 (18), 145 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2340, 1615, 1534, 1504, 1411, 1332, 1296, 1275, 1256, 1166, 1112, 1094, 1072, 1023, 1002, 903, 867, 807, 793, 772, 705, 697, 662, 653, 646, 620, 610, 604.

HRMS (EI) for $C_{11}H_5Cl_2F_3N_2$ (291.9782): 291.9782.

Synthesis of 2-allyl-3,5-dichloropyrazine (147e):



2,6-Dichloropyrazine (**141**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 0.79 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. After cooling to -30 °C, CuCN·2LiCl (1 M solution in THF, 5 drops) was added and the reaction mixture was then cooled to –78 °C. Allyl bromide (181 mg, 1.5 mmol) was added dropwise at –78 °C and the reaction mixture was allowed to warm up slowly to –50 °C for 1.5 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:6) furnished the compound **147e** (148 mg, 78%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (s, 1 H), 5.93 – 6.07 (m, 1 H), 5.14-5.22 (m, 2 H), 3.70 (dt, ^3J = 6.6 Hz, ^4J = 1.5 Hz, 2 H).

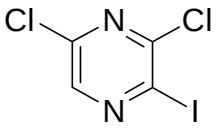
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 152.3, 146.8, 145.1, 141.8, 132.2, 118.3, 38.6.

MS (70 eV, EI) m/z (%): 188 (36) [^{35}Cl-M^+], 187 (100), 153 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2986, 2938, 1722, 1646, 1516, 1419, 1377, 1290, 1250, 1143, 1058, 894, 878.

HRMS (EI) for $C_7H_6Cl_2N_2$ (187.9908): 187.9888.

Synthesis of 3,5-dichloro-2-iodopyrazine (147f):



2,6-Dichloropyrazine (**141**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 0.79 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then added dropwise and the resulting mixture was stirred for 1 h at rt. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL) and sat. aq. $Na_2S_2O_3$ (20 mL) was added, extracted with diethyl ether (3 ×

30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography on silica (CH_2Cl_2/pentane 1:2) furnished the compound **147f** as a colourless solid (250 mg, 91%).

m.p.: 101.3 – 103.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.30 (s, 1 H).

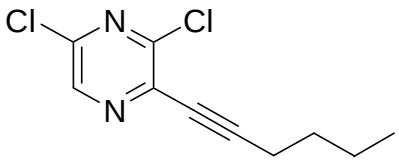
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.1, 146.9, 142.4, 115.7.

MS (70 eV, EI) m/z (%): 274 (100) [^{35}Cl-M$^+$], 147 (75), 86 (32), 57 (21), 44 (94).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 2633, 2281, 1784, 1738, 1510, 1491, 1379, 1353, 1323, 1274, 1230, 1217, 1205, 1175, 1162, 1143, 1018, 893, 843, 655, 634, 618, 611, 604.

HRMS (EI) for $C_4HCl_2IN_2$ (273.8561): 273.8555.

Synthesis of 3,5-dichloro-2-(hex-1-ynyl)pyrazine (147g):



2,6-Dichloropyrazine (**141**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**101**) (1.4 M in THF, 0.79 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **GP6**. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was added dropwise and the resulting mixture was stirred for 1 h at rt. To the solution of freshly generated *in situ* 2,3-chloro-5-iodopyrazine, NEt_3 (7 mL), CuI (8 mg, 4 mol%), $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) in THF (2 mL) and 1-hexyne (115 mg, 1.4 mol, 1.4 equiv) were successively slowly added. The reaction mixture was stirred at 20 °C for 1 h. The resulting mixture was quenched with a sat. aq. NH_4Cl solution (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **147g** as a colourless oil (189 mg, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) : 8.40 (s, 1 H), 2.51 (t, *J* = 7.1 Hz, 2 H), 1.40 – 1.68 (m, 4 H), 2.51 (t, *J* = 7.5 Hz, 3 H).

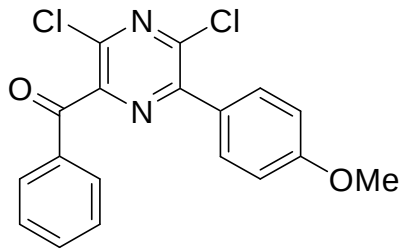
^{13}C-NMR (75 MHz, $CDCl_3$) : 148.7, 144.6, 141.7, 137.5, 101.6, 75.7, 29.9, 21.9, 19.4, 13.5.

MS (70 eV, EI) m/z (%): 228 (47) [^{35}Cl-M$^+$], 213 (92), 199 (100), 186 (39), 165 (31), 149 (72), 57 (44), 43 (50).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958, 2932, 2872, 2231, 1494, 1465, 1418, 1308, 1274, 1249, 1166, 1141, 1091, 1051, 1007, 948, 903, 875, 851, 829, 767, 743, 669, 654, 648, 638, 633, 628, 623, 618, 612, 601.

HRMS (EI) for $C_{10}H_{10}Cl_2N_2$ (228.0221): 228.0213.

Synthesis of (3,5-dichloro-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (149a):



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**147a**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at –40 °C for 1 h according to **GP6**. The reaction mixture was then cooled to –50 °C, CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added according to **GP7**. After 30 min stirring at the same temperature, benzoyl chloride (282 mg, 2.0 mmol) was added and the resulting mixture was then allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **149a** (342 mg, 96%) as a colourless solid.

m.p.: 98.6 – 100.4 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.84 – 7.90 (m, 2 H), 7.83 (d, *J* = 5.1 Hz, 2 H), 7.63 – 7.68 (m, 1 H), 7.48 – 7.53 (m, 2 H), 6.97 (d, *J* = 5.1 Hz, 2 H) , 3.85 (s, 3 H).

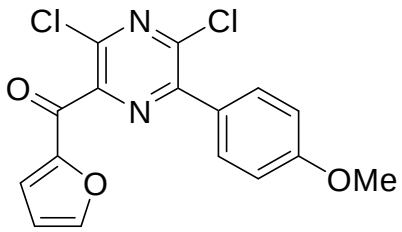
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 190.3, 161.3, 149.9, 147.6, 145.3, 141.4, 134.6 (2), 131.3, 130.3, 128.8, 126.4, 113.8, 55.4.

MS (70 eV, EI) m/z (%): 358 (16) [^{35}Cl-M$^+$], 105 (100), 77 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3004, 2841, 2049, 1665, 1604, 1594, 1579, 1512, 1501, 1463, 1449, 1442, 1421, 1361, 1308, 1298, 1253, 1216, 1178, 1152, 1120, 1086, 1028, 1011, 1000, 954, 863, 835, 809, 794, 778, 734, 711, 684, 660, 641, 615, 605.

HRMS (EI) for $C_{18}H_{12}Cl_2N_2O_2$ (358.0276): 358.0270.

Synthesis of (3,5-dichloro-6-(4-methoxyphenyl)pyrazin-2-yl)(furan-2-yl)methanone (149b):



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**147a**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at –40 °C for 1 h according to **GP6**. The reaction mixture was then cooled to –50 °C, CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added according to **GP7**. After 30 min stirring at the same temperature, furoyl chloride (261 mg, 2.0 mmol) was added and the resulting mixture was then allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **147b** (292 mg, 84%) as a colourless solid.

m.p.: 137.9 – 139.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 9.0 Hz, 2 H), 7.73 (m, 1 H), 7.31 (m, 1 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 6.60 (m, 1 H), 3.86 (s, 3 H).

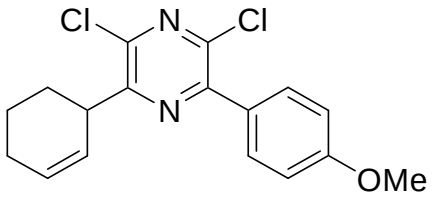
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 176.8, 161.3, 150.9, 149.6, 148.7, 145.7, 145.6, 142.0, 131.2, 126.3, 123.0, 113.9, 112.9, 55.4.

MS (70 eV, EI) m/z (%): 348 (36) [^{35}Cl-M^+], 320 (20), 95 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3141, 3113, 3000, 2918, 2848, 1647, 1604, 1558, 1511, 1486, 1459, 1421, 1396, 1367, 1349, 1304, 1255, 1183, 1157, 1125, 1115, 1093, 1019, 964, 918, 883, 838, 826, 797, 790, 773, 759, 717, 696, 663, 649, 635, 619, 614, 608.

HRMS (EI) for $C_{16}H_{10}Cl_2N_2O_3$ (348.0068): 348.0067.

Synthesis of 2,6-dichloro-3-(cyclohex-2-enyl)-5-(4-methoxyphenyl)pyrazine (149c):



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**147a**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at –40 °C for 1 h according to **GP6**. The reaction mixture was cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 5 drops) was added and the reaction mixture was then cooled to –60 °C. 3-Bromocyclohexene (242 mg, 1.5 mmol) was added dropwise at –60 °C and the reaction mixture was allowed to warm up slowly to –10 °C for 3 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **149c** (311 mg, 93%) as a colourless solid.

m.p.: 84.1 – 85.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 9.0 Hz, 2 H), 6.99 (d, *J* = 9.0 Hz, 2 H), 5.87 – 5.94 (m, 1 H), 5.73 (m, 1 H), 3.98 – 4.04 (m, 1 H), 3.86 (s, 3 H), 2.06 – 2.14 (m, 3 H), 1.68 – 1.96 (m, 3 H).

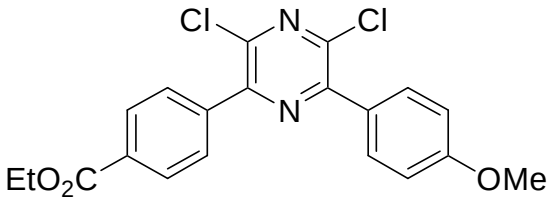
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.8, 155.7, 149.7, 143.1, 141.6, 131.2, 129.0, 127.7, 126.5, 113.6, 55.4, 39.4, 27.6, 24.6, 21.4.

MS (70 eV, EI) m/z (%): 334 (82) [^{35}Cl-M^+], 305 (38), 299 (68), 268 (100), 67 (33).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3006, 2969, 2931, 2856, 2837, 2044, 1738, 1605, 1577, 1520, 1503, 1461, 1454, 1443, 1419, 1373, 1341, 1297, 1249, 1217, 1172, 1155, 1135, 1124, 1082, 1028, 1013, 987, 962, 925, 895, 887, 869, 837, 808, 792, 776, 721, 686, 670, 664, 649, 637, 611.

HRMS (EI) for $C_{17}H_{16}Cl_2N_2O$ (334.0640): 334.0636.

Synthesis of ethyl 4-(3,5-dichloro-6-(4-methoxyphenyl)pyrazin-2-yl)benzoate (149d):



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**147a**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at –40 °C for 1 h according to **GP6**. A solution of $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol) was added and the resulting mixture was stirred at –40 °C for 1 h. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with ethyl 4-iodobenzoate (387 mg, 1.4 mmol, 1.4 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (100 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **149d** (382 mg, 95%) as a colourless solid.

m.p.: 118.1 – 119.8 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 8.7 Hz, 2 H), 7.94 (d, *J* = 8.7 Hz, 2 H) , 7.88 (d, *J* = 8.9 Hz, 2 H) , 7.01 (d, *J* = 8.9 Hz, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.87 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

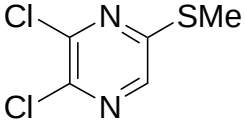
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.0, 161.1, 150.2, 149.1, 143.0, 141.9, 139.3, 131.5, 131.1, 129.5, 129.4, 127.1, 113.8, 61.2, 55.4, 14.3.

MS (70 eV, EI) m/z (%): 402 (100) [^{35}Cl-M$^+$], 357 (27), 178 (12), 157 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2986, 2902, 2046, 1719, 1607, 1577, 1523, 1507, 1489, 1442, 1410, 1354, 1311, 1296, 1280, 1257, 1176, 1137, 1126, 1103, 1023, 1015, 1005, 974, 948, 894, 879, 869, 858, 826, 795, 783, 767, 756, 731, 720, 701, 680, 666, 646, 629, 612.

HRMS (EI) for $C_{20}H_{16}Cl_2N_2O_3$ (402.0538): 402.0535.

Synthesis of 2,3-dichloro-5-methylsulfanyl-pyrazine (151a):



2,3-Dichloropyrazine (**144**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at 25 °C and the

reaction mixture was then stirred at this temperature for 15 min according to **GP6**. S-Methyl-methanethiosulfonate (151 mg, 1.2 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred for 1 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:6) furnished the compound **151a** (131 mg, 67 %) as a yellowish solid.

m.p.: 62.1 – 64.1 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.15 (s, 1 H), 2.56 (s, 3 H).

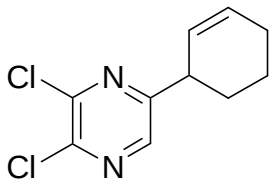
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 155.9, 146.7, 141.8, 139.8, 13.3.

MS (70 eV, EI) m/z (%): 193 (100) [^{35}Cl-M$^+$], 163 (54), 161 (80), 97 (13), 83 (11), 71 (14), 69 (16), 57 (26), 44 (53), 43 (19), 41 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3075, 2922, 2851, 1831, 1531, 1489, 1432, 1418, 1395, 1376, 1333, 1319, 1289, 1193, 1151, 1123, 1033, 960, 918, 860, 719, 658.

HRMS (EI) for $C_5H_4Cl_2N_2S$ (193.9472): 193.9458.

Synthesis of 2,3-dichloro-5-(3-cyclohex-2-enyl)pyrazine (151b):



2,3-Dichloropyrazine (**144**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **GP6**. A solution of $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol) was added at 25 °C and the resulting mixture was stirred at 25 °C for 15 min. The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 5 drops) was added and the resulting mixture was cooled to –60 °C. 3-Bromocyclohexene (242 mg, 1.5 mmol) was added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C overnight. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **151b** (160 mg, 72%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.18 (s, 1 H), 5.95 – 6.01 (m, 1 H), 5.69 – 5.74 (m, 1 H), 3.54 (m, 1 H), 2.01 – 2.14 (m, 3 H), 1.63 – 1.77 (m, 3 H).

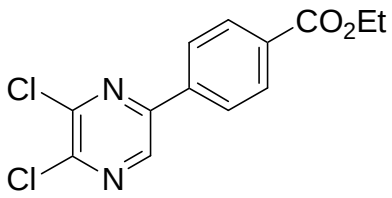
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 159.0, 146.5, 144.8, 140.5, 130.7, 126.0, 40.6, 29.8, 24.7, 20.5.

MS (EI, 70 eV) m/z (%): 228 (99) [^{35}Cl-M^+], 213 (43), 199 (100), 193 (62), 174 (26), 162 (36).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3313, 2933, 2862, 1649, 1544, 1506, 1447, 1411, 1316, 1283, 1244, 1191, 1148, 1041, 998, 909, 887, 854, 822, 751, 724, 661, 633, 616, 608, 604.

HRMS (EI) for $C_{10}H_{10}Cl_2N_2$ (228.0221): 228.0220.

Synthesis of ethyl 4-(5,6-dichloropyrazin-2-yl)benzoate (151c):



2,3-Dichloropyrazine (**144**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **GP6**. A solution of $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol) was added at 25 °C and the resulting mixture was stirred at 25 °C for 15 min. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with ethyl 4-iodobenzoate (387 mg, 1.4 mmol, 1.4 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1.5 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **151c** (231 mg, 78%) as a colourless solid.

m.p.: 114.9 – 116.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.76 (s, 1 H), 8.17 (d, J = 8.8 Hz, 2 H), 8.06 (d, J = 8.8 Hz, 2 H), 4.41 (q, J = 7.0 Hz, 2 H), 1.42 (t, J = 7.0 Hz, 3 H).

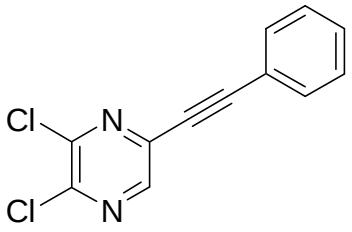
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.8, 149.6, 147.1, 146.3, 138.7, 137.6, 132.3, 130.3, 126.9, 61.4, 14.3.

MS (EI, 70 eV) m/z (%): 296 (33) [^{35}Cl-M^{+}], 268 (44), 251 (100), 223 (25), 188 (11), 69 (10), 44 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2986, 2905, 1943, 1706, 1610, 1577, 1552, 1540, 1515, 1479, 1454, 1443, 1425, 1400, 1364, 1315, 1267, 1238, 1213, 1199, 1180, 1160, 1126, 1107, 1060, 1038, 1017, 965, 925, 881, 860, 840, 777, 748, 696, 663, 633, 621, 614, 604.

HRMS (EI) for $C_{13}H_{10}Cl_2N_2O_2$ (296.0119): 296.0109.

Synthesis of 2,3-dichloro-5-(phenylethynyl)pyrazine (151d):



2,3-Dichloropyrazine (**144**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **GP6**. A solution of $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol) was added at 25 °C and the resulting mixture was stirred at 25 °C for 15 min. Iodine (280 mg, 1.1 mmol) dissolved in dry THF (1 mL) was then added dropwise and the resulting mixture was stirred for 1 h at rt. To the solution of freshly generated *in situ* 2,3-chloro-5-iodopyrazine, NEt_3 (7 mL), CuI (8 mg, 4 mol%), $Pd(dba)_2$ (17 mg, 3 mol%) and $P(o\text{-furyl})_3$ (14 mg, 6 mol%) in THF (2 mL) and phenylacetylene (134 mg, 1.3 mol, 1.3 equiv) were successively slowly added. The reaction mixture was stirred at 20 °C for 1 h. The resulting mixture was quenched with a sat. aq. NH_4Cl solution (25 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **151d** as a yellowish solid (183 mg, 77%).

m.p.: 103.2 – 104.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.43 (s, 1 H), 7.58 – 7.61 (m, 2 H), 7.35 – 7.44 (m, 3 H).

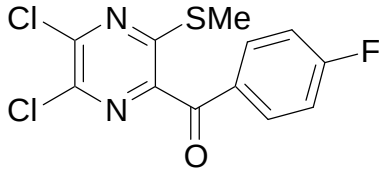
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 146.9, 145.8, 144.2, 137.3, 132.2, 130.0, 128.6, 120.8, 95.5, 83.9.

MS (EI, 70 eV) m/z (%): 248 (100) [^{35}Cl-M^{+}], 127 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3078, 3034, 2994, 2204, 1989, 1903, 1825, 1688, 1569, 1534, 1489, 1441, 1409, 1337, 1315, 1291, 1215, 1194, 1159, 1073, 1037, 996, 977, 927, 916, 902, 854, 833, 776, 759, 750, 690, 667, 620, 603.

HRMS (EI) for $C_{12}H_6Cl_2N_2$ (247.9908): 247.9907.

Synthesis of (5,6-dichloro-3-methylsulfanyl-pyrazin-2-yl)-(4-fluoro-phenyl)-methanone (153):



2,3-Dichloro-5-methylsulfanylpyrazine (**151a**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**16a**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **GP6**. A solution of $ZnCl_2$ (1 M in THF, 1.2 mL, 1.2 mmol) was added and the resulting mixture was stirred at –40 °C for 30 min. CuCN·2LiCl (1.0 M in THF, 1.1 mL) was then added and the resulting mixture was stirred at –40 °C for 30 min according to **GP7**. Then, 4-fluorobenzoyl chloride (317 mg, 2 mmol) was added at –40 °C and the mixture was allowed to warm up to –10 °C for 2 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:7) furnished the compound **153** (228 mg, 72 %) as a yellowish solid.

m.p.: 144.3 – 146.4 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.10 – 8.03 (m, 2 H), 7.20 – 7.10 (m, 2 H), 2.55 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 188.7, 166.0 (d, J = 256.2 Hz), 159.0, 147.9, 142.0, 138.9, 133.5 (d, J = 9.5 Hz), 131.9 (d, J = 2.8 Hz), 115.6 (d, J = 21.9 Hz), 14.5.

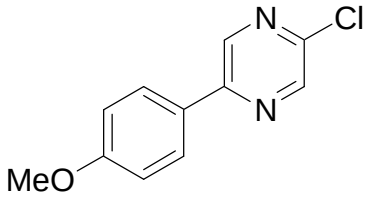
MS (70 eV, EI) m/z (%): 316 (18) [^{35}Cl-M$^+$], 301 (16), 283 (13), 123 (100), 95 (48), 75 (16), 46 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3063, 1905, 1770, 1734, 1660, 1599, 1507, 1467, 1432, 1408, 1360, 1332, 1297, 1264, 1239, 1185, 1157, 1098, 1016, 977, 965, 943, 870, 846, 807, 788, 737, 703, 670.

HRMS (EI) for $C_{12}H_7Cl_2FN_2OS$ (315.9640): 315.9647.

4.4 Total Synthesis of Coelenterazine (140)

Synthesis of 2-chloro-5-(4-methoxyphenyl)pyrazine (155):



This compound was prepared from 2,5-dichloropyrazine (**154**). 4-Iodoanisole (10.8 g, 46 mmol) was charged with freshly titrated *i*-PrMgCl·LiCl (1.3 M in THF, 38.6 mL, 50.6 mmol) and the reaction mixture was stirred at 25 °C for 1 h. After completion of the reaction, a solution of zinc chloride (1.0 M in THF, 55 mL, 55 mmol) was added and the resulting mixture was stirred at 25 °C for 30 min. $Pd(dba)_2$ (519 mg, 2 mol%) and $P(o\text{-furyl})_3$ (395 mg, 4 mol%) were then introduced, the resulting mixture was then transferred dropwise at 25 °C via cannula to a solution of **154** (8.9 g, 60 mmol) dissolved in THF (60 mL) and stirred for 1 h at the same temperature. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (100 mL), extracted with diethyl ether (5 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **155** (6.47 g, 64%) as a yellowish solid.

m.p.: 79.1 – 81.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.85 (s, 1 H), 8.42 (s, 1 H), 7.98 (d, J = 9.0 Hz, 2 H), 7.00 (d, J = 9.0 Hz, 2 H), 3.86 (s, 3 H).

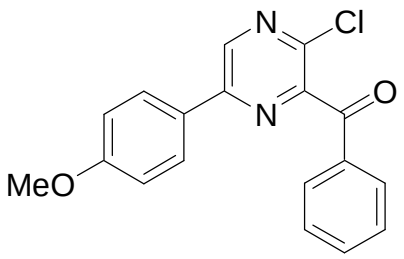
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.6, 141.3, 138.6, 128.6, 127.2, 114.5, 55.4.

MS (70 eV, EI) m/z (%): 220 (100) [^{35}Cl-M^+], 205 (16), 177 (12), 167 (21), 149 (57).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 1724, 1604, 1516, 1501, 1440, 1415, 1382, 1292, 1257, 1176, 1162, 1148, 1073, 1073, 1026, 1006, 870, 827, 657, 610.

HRMS (ESI) for $C_{11}H_9ClN_2O$ (220.0403): 220.0396.

Synthesis of (3-chloro-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (156):



2-Chloro-5-(4-methoxyphenyl)pyrazine (**155**) (5.8 g, 26.7 mmol) dissolved in THF (25 mL) was reacted with a solution of TMPMgCl·LiCl (**2a**) (1.2 M in THF, 25 mL, 29.4 mmol) at –45 °C and the reaction mixture was then stirred at this temperature for 1 h according to **GP6**. A solution of $ZnCl_2$ (1 M in THF, 30 mL, 30 mmol) was added at –50 °C and the resulting mixture was stirred at this temperature for 1 h and then at 25 °C for 15 min. $Pd(PPh_3)_4$ (925 mg, 3 mol%) and benzoyl chloride (5.69 g, 40.5 mmol, 1.5 equiv) dissolved in THF (20 mL) were then transferred via cannula very slowly to the reaction mixture. The resulting mixture was stirred at 25 °C overnight and then quenched with a sat. aq. NH_4Cl solution (50 mL), extracted with diethyl ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 2:1) furnished the compound **156** (6.14 g, 71%) as a yellowish solid.

m.p.: 103.8 – 105.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.91 (s, 1 H), 8.05 (d, J = 8.9 Hz, 2 H), 7.87 – 7.91 (m, 2 H), 7.59 – 7.66 (m, 1 H), 7.46 – 7.51 (m, 2 H), 7.03 (d, J = 8.9 Hz, 2 H), 3.87 (s, 3 H).

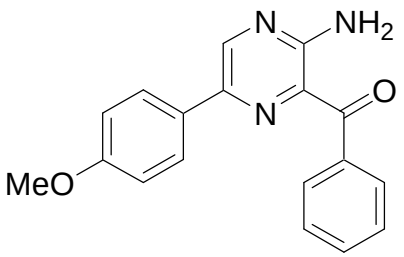
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 191.3, 162.1, 152.9, 146.6, 145.9, 137.4, 135.1, 134.1, 130.2, 128.9, 128.6, 126.4, 114.6, 55.4.

MS (EI, 70 eV) m/z (%): 324 (54) [^{35}Cl-M^+], 296 (21), 105 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2923, 1669, 1607, 1544, 1517, 1458, 1432, 1338, 1315, 1288, 1256, 1200, 1166, 1117, 1070, 1019, 942, 922, 914, 832, 807, 772, 702, 689, 658, 631.

HRMS (EI) for $C_{18}H_{13}ClN_2O_2$ (324.0666): 324.0658.

Synthesis of (3-amino-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (157):



(3-Chloro-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (**156**) (324 mg, 1.0 mmol) dissolved in *n*-BuOH (2 mL) and 25% aq. NH_3 (2 mL) was heated in a sealed tube at 180 °C for 12 h. The resulting mixture was then quenched with a sat. aq. Na_2CO_3 solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **157** (287 mg, 94%) as a fluorescent yellowish solid.

m.p.: 147.9 – 149.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.44 (s, 1 H), 8.04 (d, J = 8.9 Hz, 2 H), 7.95 – 7.98 (m, 2 H), 7.45 – 7.56 (m, 3 H), 7.01 (d, J = 8.9 Hz, 2 H), 3.87 (s, 3 H).

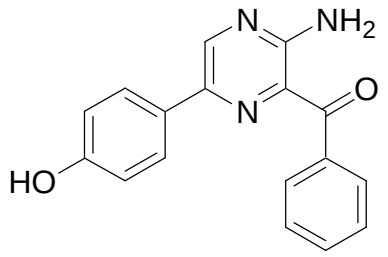
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 195.1, 161.9, 155.5, 153.7, 138.4, 131.8, 130.4, 129.7, 129.1, 128.0, 127.9, 127.8, 114.4, 55.4.

MS (EI, 70 eV) m/z (%): 305 (100) [M^+], 276 (23), 105 (27), 77 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3427, 3286, 1618, 1593, 1533, 1502, 1454, 1442, 1335, 1299, 1247, 1209, 1173, 1149, 1112, 1026, 1000, 960, 890, 853, 810, 774, 706, 695, 670.

HRMS (EI) for $C_{18}H_{15}N_3O_2$ (305.1164): 305.1166.

Synthesis of (3-amino-6-(4-hydroxyphenyl)pyrazin-2-yl)(phenyl)methanone (158):



(3-Amino-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (**157**) (305 mg, 1.0 mmol) and sodium ethanethiolate (494 mg, 5 mmol) in DMF (5 mL) were heated at 100 °C for 20 h

under argon atmosphere. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), and extracted with AcOEt (5 × 50 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/Et_2O 1:1) furnished the compound **158** (209 mg, 72%) as a yellowish solid.

m.p.: 204.5 – 206.2 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1 H), 8.49 (s, 1 H), 8.06 (d, *J* = 8.8 Hz, 2 H), 7.83 – 7.86 (m, 4 H), 7.53 – 7.56 (m, 1 H), 7.45 – 7.49 (m, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H).

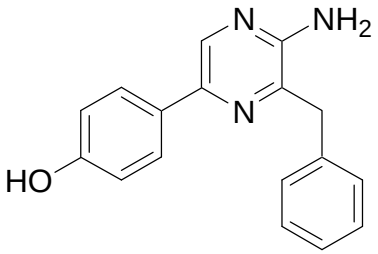
^{13}C-NMR (100 MHz, DMSO-d_6) δ: 194.4, 160.3, 155.6, 153.5, 138.7, 131.3, 130.1, 129.3, 128.7, 127.6, 126.6, 126.0, 115.8.

MS (EI, 70 eV) m/z (%): 291 (100) [M^+], 290 (95), 263 (12), 262 (24), 105 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3457, 3364, 3332, 1608, 1588, 1540, 1521, 1504, 1446, 1340, 1324, 1294, 1278, 1254, 1219, 1208, 1171, 962, 930, 889, 838, 815, 805, 772, 702, 690, 673, 625.

HRMS (EI) for $C_{17}H_{13}N_3O_2$ (291.1008): 291.1001.

Synthesis of 4-(5-amino-6-benzylpyrazin-2-yl)phenol Coelenteramine (159):



A stirred solution of (3-amino-6-(4-hydroxyphenyl)pyrazin-2-yl)(phenyl)methanone (**158**) (291 mg, 1.0 mmol), ethylene glycol (2 mL) and hydrazine hydrate (0.5 mL) were heated at 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature. Then, KOH pellets (500 mg) were added, the resulting mixture was heated in a sand bath at 240 °C. After cooling to room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed with dilute HCl and dried over Na_2SO_4. Purification by flash chromatography (CH_2Cl_2/Et_2O 1.5:1) furnished Coelenteramine (**159**) (257 mg, 93%) as a colourless solid.

m.p.: 201.6 – 203.1 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.70 (s, 1 H), 8.18 (s, 1 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 7.24 – 7.31 (m, 4 H), 7.15 – 7.19 (m, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.21 (bs, 2 H), 4.03 (s, 2 H).

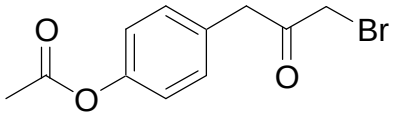
^{13}C-NMR (100 MHz, DMSO-d_6) δ: 158.3, 152.7, 147.3, 138.5, 128.9, 128.2, 127.6, 127.4, 126.0, 115.4, 38.3.

MS (EI, 70 eV) m/z (%): 277 (100) [M^+], 276 (83), 130 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3487, 3298, 1624, 1610, 1588, 1537, 1519, 1493, 1448, 1422, 1367, 1347, 1324, 1279, 1228, 1203, 1166, 1139, 1105, 959, 865, 833, 821, 763, 736, 728, 702, 675.

HRMS (EI) for $C_{17}H_{15}N_3O$ (277.1215): 277.1201.

Synthesis of acetic acid 4-(3-bromo-2-oxo-propyl)phenyl ester (161):

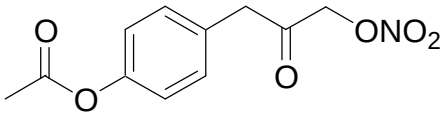


A Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (42 g, 48.9 mmol, 2.5 equiv). The flask was heated with a heat gun (400 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Zinc dust (3.18 g, 48.9 mmol, 2.5 equiv) was added followed by THF. 1,2-Dibromethane was added (5 mol %) and the reaction mixture was heated until ebullition occurs. After cooling to 25 °C, trimethylsilyl chloride (1 mol %) was added and the mixture was heated again until ebullition occurs. Acetic acid 4-chloromethylphenyl ester (**160**; 3.6 g, 19.56 mmol) was added at 25 °C as a solution in THF. After the reaction mixture was allowed to settle down for some hours, the yield of the resulting benzylic zinc chloride was determined by iodiometric titration (C = 0.77 M). To a CuCN·2LiCl solution (1.0 M in THF, 1.1 mL) at –40 °C was added dropwise the freshly prepared benzylic zinc chloride solution (1.27 mL, 1 mmol). The resulting reaction mixture was stirred for 30 min at this temperature. Then, the solution was cooled to –80 °C and the bromoacetyl chloride (234 mg, 1.5 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred overnight and allowed to warm to 25 °C. Then, a mixture of a sat. aqueous NH_4Cl was added, the layers were separated and the aqueous layer was extracted with Et2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash chromatography (pentane/Et_2O 3:1) afforded the expected ketone **161** as a colourless solid (184 mg, 61%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (d, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 3.94 (s, 2 H), 3.90 (s, 2 H), 2.29 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 199.1, 169.3, 150.0, 130.6, 130.5, 122.0, 45.9, 33.4, 21.1.

Synthesis of acetic acid 4-(3-nitrooxy-2-oxo-propyl)phenyl ester (162):

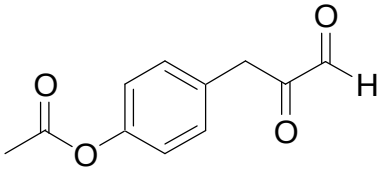


This compound was prepared according to the known procedure.[100h,106] A solution of $AgNO_3$ (195 mg, 1.15 mmol, 2.3 equiv) in MeCN (1 mL) was added to a solution of **161** (137 mg, 0.5 mmol) in MeCN (0.5 mL). The resulting mixture was then stirred for 18 h at 25 °C, filtrated, quenched with a sat. aq. NH_4Cl solution (2 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents *in vacuo* afforded the pure expected derivative **162** as a colourless solid (102 mg, 82%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.19 (d, *J* = 8.5 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 4.94 (s, 2 H), 3.72 (s, 2 H), 2.27 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 198.6, 169.3, 150.1, 130.4, 129.3, 122.1, 73.3, 45.3, 21.0.

Synthesis of Acetic acid 4-(2,3-dioxo-propyl)phenyl ester (163):

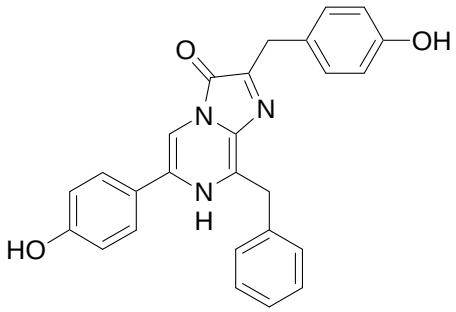


This compound was prepared according to the known procedure.[100h,106] $NaOAc{\cdot}3H_2O$ (68 mg, 0.5 mmol) was slowly added to a solution of **162** (126 mg, 0.5 mmol)in DMSO (2 mL). The reaction mixture was stirred at 25 °C for 40 min and then poured inti ice-water. The resulting mixture was saturated with sodium chloride and then extracted with. The organic phase was washed with water, aqueous sodium hydrogen carbonate and then again with water. Removal of the solvent by distillation under reduced pressure followed by drying *in vacuo* afforded the pure expected derivative **163** as a colourless solid (70 mg, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.22 (s, 1 H), 7.84 (d, *J* = 8.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 6.67 (bs, 1 H), 6.14 (s, 1 H), 2.30 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 188.2, 169.2, 151.1, 148.6, 131.6, 131.3, 121.9, 121.7, 21.1.

Synthesis of Coelenterazine (140):



This compound was prepared according to the known procedure.[100h,106] A mixture of **163** (145 mg, 0.7 mmol), Coelenteramine **159** (138 mg, 0.5 mmol), ethanol (5 mL), 36% aqueous HCl (0.2 mL)and water (0.7 mL) was heated at 80 °C for 4.5 h under argon. After cooling the mixture to room temperature, the solvent was removed by evaporation and the residue further dried *in vacuo*. Purification by flash chromatography (CH_2Cl_2/MeOH 9:1) furnished Coelenterazine (**140**) (134 mg, 64%) as a yellowish solid.

m.p.: 175.2 – 178.5 °C.

^{1}H-NMR (600 MHz, DMSO-d_6) : 10.98 (bs, 1 H), 9.55 (bs, 1 H), 9.13 (s, 1 H), 7.37 (d, 2 H, *J* = 7.7 Hz), 7.17 – 7.30 (m, 5 H), 7.08 (d, 2 H, *J* = 8.5 Hz), 6.71 (d, 2 H, *J* = 8.1 Hz), 6.64 (d, 2 H, *J* = 8.6 Hz), 6.44 (bs, 1 H), 4.15 (s, 2 H), 3.84 (s, 2 H).

^{13}C-NMR (DMSO-d_6, 150 MHz) δ: 157.3, 155.5, 137.5, 130.9, 129.9, 129.6, 129.3, 128.8, 128.4, 128.2, 126.7, 121.6, 114.9, 114.7, 113.6, 109.5, 56.0, 48.6.

MS (EI, 70 eV) m/z (%): 423 (24) [M^+], 393 (23), 317 (24), 277 (55), 261 (100), 107 (32), 91 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3164, 3043, 3028, 1612, 1512, 1440, 1373, 1229, 1152, 826, 697.

HRMS (EI) for $C_{26}H_{21}N_3O_3$ (423.1583): 423.1570.

D: **Appendix**

Lebenslauf aus Gründen des Datenschutzes entfernt