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Directed Magnesiation and Zincation of Highly Substituted Alkenes and N-Heterocycles Using 2,2,6,6-Tetramethylpiperidyl Bases. Application to the Total Synthesis of Coelenterazine

von

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aus

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Erklärung

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Ehrenwörtliche Versicherung

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Tomke Bresser

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1) Tomke Bresser, Paul Knochel, "Selective Magnesiation or Zincation of Highly Functionalized Alkenes and Cycloalkenes using 2,2,6,6,Tetramethylpiperidyl Bases", *Angew. Chem. Int. Ed.* **2011**, *50*, 1914. (*special issue in honor of Professor Carmen Najera on the occasion of her 60th birthday)*

2) Tomke Bresser, Marc Mosrin, Gabriel Monzon, Paul Knochel, "Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl•LiCl", *J. Org. Chem.* **2010**, *75*, 4686-4695.

3) Tomke Bresser, Gabriel Monzon, Marc Mosrin, Paul Knochel, "Scaleable Preparation of Sensitive Functionalized Aromatics and Heteroaromatics via Directed Metalation Using TMPZnCl•LiCl", *Org. Pro. Res. & Dev.* **2010**, *14*, 1299-1303.

4) Stefan Wunderlich, Tomke Bresser, Cora Dunst, Gabriel Monzon, Paul Knochel, "Efficient Preparation of Polyfunctional Organometallics via Directed *ortho*-Metalation", *Synthesis* **2010**, *15*, 2670-2678.

5) Marc Mosrin, Tomke Bresser, Paul Knochel, "Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine", *Org. Lett.* **2009**, *11*, 3406-3409.

6) Marc Mosrin, Gabriel Monzon, Tomke Bresser, Paul Knochel, "High Temperature Zincation of Functionalized Aromatics and Heteroaromatics using TMPZnCl•LiCl and Microwave Irradiation", *Chem. Commun.* **2009**, *37*, 5615-5617.

To Niki and my family

“On ne voit bien qu’avec le cœur, l’essentiel est invisible pour les yeux.”

- Antoine de Saint-Exupéry -

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Abbreviations

Ac	acetyl
acac	acetylacetonato
aq.	aqueous
Ar	aryl
Bu	butyl
conc.	concentrated
dba	*trans,trans*-dibenzylideneacetone
dist.	distilled
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
equiv	equivalent
E	electrophile
EI	electron ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
LDA	lithium diisopropylamide
M	mol/L
m	*meta*
Me	methyl
min	minute
mp.	melting point
MS	mass spectroscopy

MW	microwave irradiation
NMR	nuclear magnetic resonance
NMP	*N*-methyl-pyrrolidin-2-one
o	*ortho*
p	*para*
PG	protecting group
Ph	phenyl
R	organic substituent
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
*t*Bu	*tert*-butyl
TLC	thin layer chromatography
THF	tetrahydrofuran
tfp	tris-(2-furyl)phosphine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
TP	typical procedure

A. INTRODUCTION

1. Overview

We live in a world that is affected by organic substances. Thousands of new compounds are developed every year. In the process, synthetic methods should become more and more modern and efficient to optimize materials and active substances. The demand for new organic reagents is continuously rising. They should provide good selectivity and at the same time high reactivity and also tolerance towards functional groups. Furthermore they should preferably be cheap and environmentally benign. Organometallic reagents are excellent instruments to meet these requirements and are therefore indispensible nowadays. They play an important role in the production of different pharmaceuticals, food additives or agrochemicals.[1] The first example of an organometallic compound was given by *Frankland* in 1849 with the preparation of diethylzinc.[2] Thereby he established new ways in organic chemistry to form new carbon-carbon as well as carbon-heteroatom bonds. In the beginning of the 20th century, *Victor Grignard* synthesized the first organomagnesium compounds.[3] The diversity of organometallic substances lies in the different polarity of the carbon-metal bonds which depends on the electronegativity of the metal in question.[4] Nearly every metal in the periodic table has found useful applications in organometallic synthesis, either as catalyst or as reagent.[5] Organolithium compounds demonstrate high reactivity towards electrophiles as a consequence of the highly polar character of the carbon-lithium bond. However, organolithium species are less selective and tolerate only a small number of functional groups. Grignard reagents have an exceptional position in the reactivity chart of organometallic reagents, because of their high reactivity even at low temperatures and sufficient reactivity towards various electrophiles as well as high tolerance towards functional groups like nitriles or esters. By transmetallation of organomagnesiums to copper or zinc, they can be converted into new organometallics providing improved stability and selectivity. The reactivity of covalent organozinc, organotin and organoboron substances could be improved by catalysts

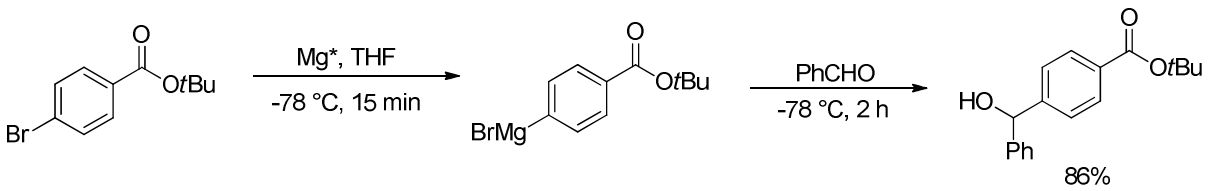
[1] Richey, H. G.; *Grignard-Reagents;* John Wiley and sons, Chichester **2000**.
[2] (a) Frankland, E. *Liebigs Ann. Chem.* **1848-49**, *71*, 171; (b) Frankland, E.; *J. Chem. Soc.* **1848-49**, *2*, 263.
[3] (a) Grignard, V. *Compt. Rend. Acad. Sci. Paris.* **1900**, *130*, 1322; (b) Grignard, V. *Ann. Chim.* **1901**, *24*, 433.
[4] Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem.* **2000**, *112*, 4585.
[5] For an overview, see: *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, Germany, **2005**.

like nickel, palladium or copper.[6] Because of their covalent character they show higher chemo- and regioselectivity and tolerate sensitive functions like nitro or aldehyde moieties. Organometallics can be prepared by three known pathways: The direct insertion of elemental metal into a carbon-halogen bond, a halogen-metal exchange reaction, or base-mediated direct C-H activation.

2. Preparation of Organometallic Reagents

2.1. Oxidative Insertion

The most common method for preparing organometal reagents is the direct oxidative insertion of elemental magnesium or zinc into a halogen-carbon bond. Because of the high temperatures required for such insertions, the tolerance towards functional groups is limited. Though, using highly active *Rieke*-magnesium (Mg^*), which is prepared by the reduction of $MgCl_2$ with lithium naphthalenide, the insertion reaction already proceeds at -78 °C.[7] Organomagnesium reagents bearing a nitrile or an ester could be obtained for the first time (Scheme 1).[8]



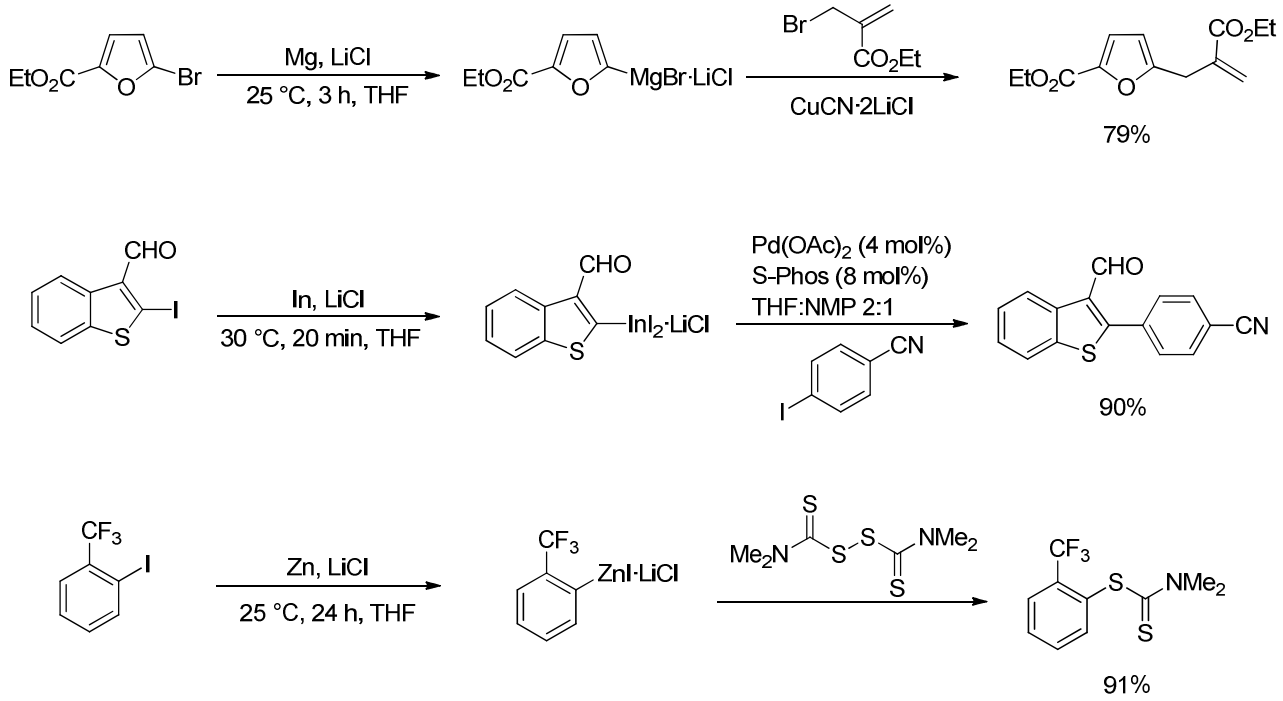
Scheme 1: Preparation of a functionalized magnesium reagent using highly reactive *Rieke*-magnesium.

[6] (a) *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed. (Eds.: A. de Meijere, F. Diederich) Wiley-VCH, Weinheim, **2004**; (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**; (c) *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH: Weinheim, Germany, **2002**.

[7] (a) Rieke, R. D. *Science* **1989**, *246*, 1260; (b) Rieke, R. D. *Aldrichim. Acta* **2000**, *33*, 52; (c) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674; (d) Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323; (e) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428; (f) Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197; (g) Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 2322; (h) Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445; (i) Ebert, G.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280; (j) Wu, T. C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5057.

[8] Lee, J. R.; Velarde-Ortiz, A.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

Recently, a more convenient way to insert metals into halogen-carbon bonds was reported by *Knochel* and co-workers, using Mg[9], Zn[10] and In[11] in the presence of LiCl in THF. This salt facilitates insertion reactions in several ways and allows them to proceed more selectively and under milder conditions (Scheme 2).



Scheme 2: Preparation of organomagnesium, organoindium and organozinc reagents by insertion in the presence of LiCl.

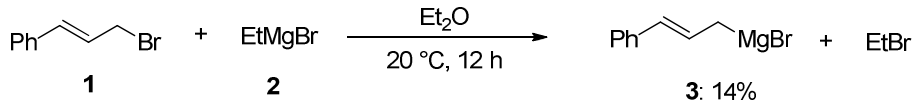
[9] (a) Piller, F. M.; Appukkuttan, P. ; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; (b) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 7192; (c) Metzger, A.; Piller, F. M.; Knochel, P. *Chem. Commun*. **2008**, 5824.

[10] (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; (b) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358; (c) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107.

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

2.2. Halogen-Metal Exchange

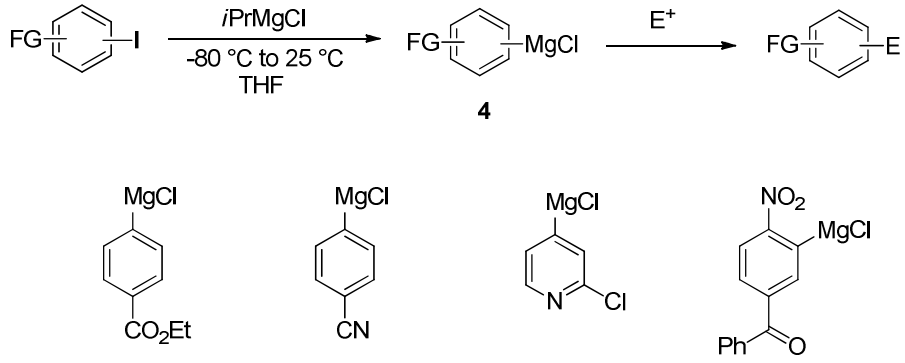
Besides the oxidative insertion, an alternative synthesis of organometallic reagents is the halogen-metal exchange reaction discovered by *Wittig* and *Gilman* in 1938, who prepared a range of organolithium compounds in that fashion.[12] Because of the low functional group tolerance of lithium reagents, the halogen-magnesium exchange became the method of choice for preparing new functionalized magnesium compounds of considerable synthetic utility. It was first decribed by *Prévost* in 1931.[13] Thus, the reaction of cinnamyl bromide (**1**) with EtMgBr (**2**) furnished cinnamylmagnesium bromide (**3**) in 14% yield (Scheme 3). The rate of the exchange is enhanced by the presence of electronegative substituents which leads to higher stability of the generated magnesium reagent compared to the exchange reagent.



Scheme 3: First example of a halogen-magnesium exchange.

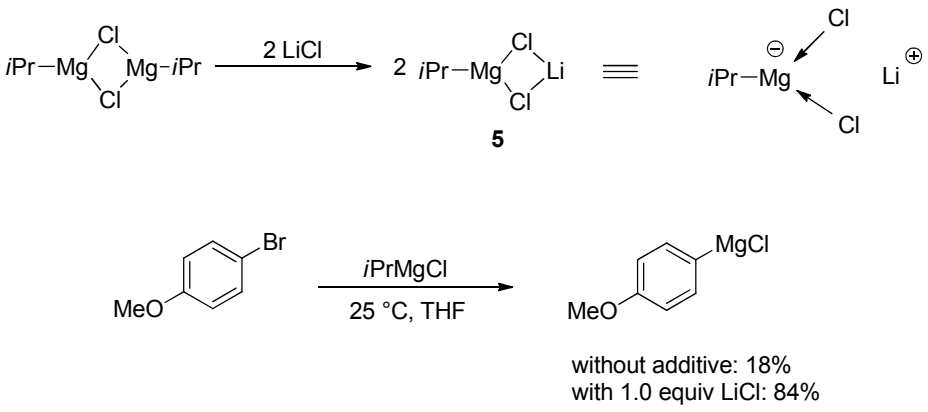
The low temperature iodine-magnesium exchange with *i*PrMgBr or *i*PrMgCl, first reported in 1998 by *Knochel* in cooperation with *Cahiez*, gives access to highly functionalized aromatic and heteroaromatic Mg compounds of type **4** in good yields under mild conditions, so that sensitive functions may be present (Scheme 4).[14]

[12] (a) Wittig, G.; Pockels, U.; Dröge, H. *Chem. Ber.* **1938**, *71*, 1903; (b) Jones, R.G.; Gilman, H. *Org. React.* **1951**, *6*, 339; (c) Gilman, H.; Langham, W.; Jacoby, A. L.; *J. Am. Chem. Soc.* **1939**, *61*, 106.
[13] Prévost, C. *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[14] (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; (c) Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapuntzis, I.; Vu, V. A.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302. (d) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Lett.* **2006**, *35*, 2.



Scheme 4: Preparation of highly functionalized aryl and heteroarylmagnesium compounds using *i*PrMgCl.

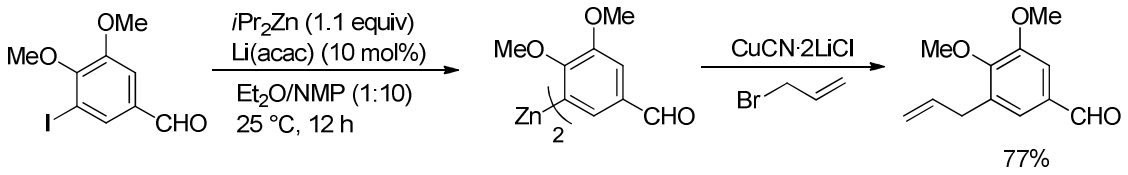
With the addition of 1.0 equivalents of LiCl to *i*PrMgCl by *Knochel* and *Krasovskiy* in 2004 the halogen-magnesium exchange could be expanded to organic bromides that are more stable and cheaper than iodides.[15] This was a huge improvement compared to earlier methods, since the formed *i*PrMgCl·LiCl (**5**) enables a faster exchange reaction at low temperatures between -15 °C and 25 °C and therefore reduces undesired side reactions with functional groups. The reason for the acceleration is the break-up of *i*PrMgCl aggregates by LiCl, which results in higher reactivity of the Mg species (Scheme 5).



Scheme 5: Rate acceleration of the bromine-magnesium exchange by LiCl.

[15] (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; (b) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 15.

Functionalized diorganozincs are efficiently obtained through an iodine-zinc exchange by reaction of polyfunctional alkyl iodides with diethylzinc and catalytic amounts of Cu(I) salt.[16] In 2004, the first iodine-zinc exchange on aromatic substrates was performed by *Knochel*, combining *i*Pr_2Zn and Li(acac) as catalyst (Scheme 6).[17]



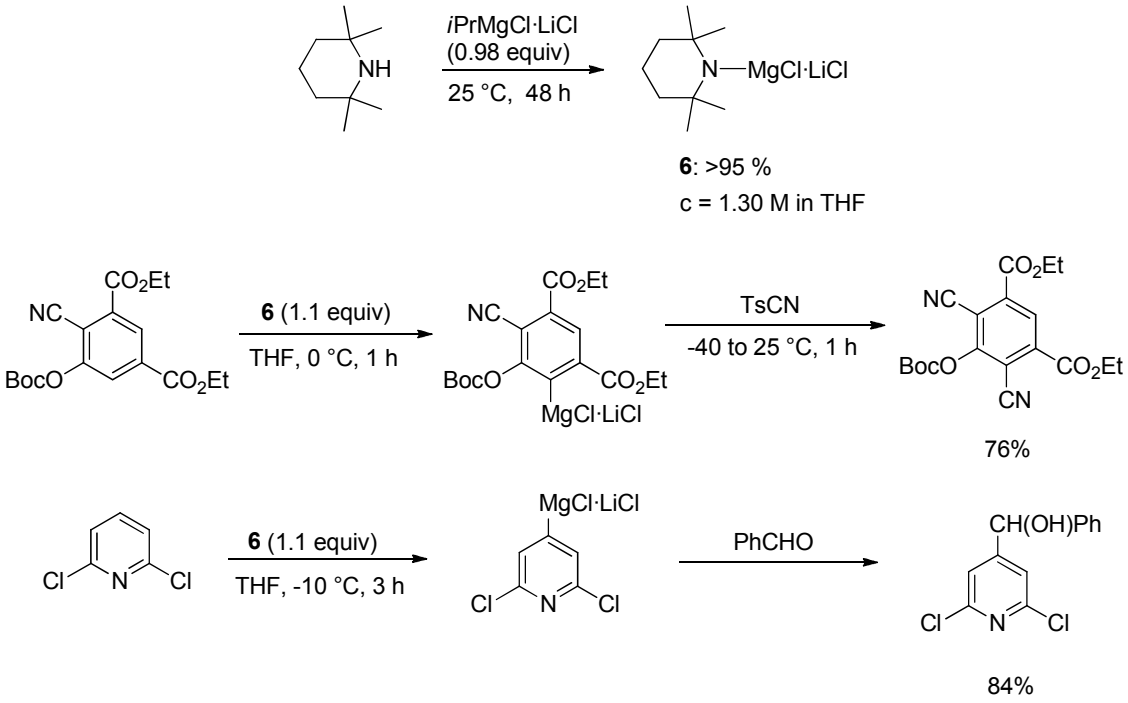
Scheme 6: Iodine-zinc exchange reaction on a functionalized aldehyde catalyzed by Li(acac).

2.3. Directed Metalation

One further possibility to generate organometallic reagents and the most convenient one is the directed metalation reaction using metal amide bases or alkyl organometallics. As a huge advantage, halogenated starting materials, which are often toxic, more expensive and difficult to dispose of, become dispensable in those kinds of reactions. Traditionally, strong bases such as alkyllithium reagents (RLi like *sec*-BuLi) as well as sterically demanding non-nucleophilic lithium amides like lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LiTMP) have been extensively used for this kind of reactions, especially for the directed *ortho*-lithiation.[18] The disadvantage of those reagents lies again in their high reactivity which often results in undesirable side reactions and attacks on functional groups. Furthermore, they have to be prepared *in situ* since their stability in solvents like THF and diethyl ether is limited and metalations have to be carried out at very low temperatures (-78 °C to -100 °C). Alternatively, magnesium amides pioneered by *Hauser* can be used to overcome these limitations.[19] Beyond that, *Eaton* demonstrated the use of the *bis*-amide TMP_2Mg and related reagents for the

[16] (a) Rozema, M. J.; Achyutha, R. S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956; (b) Rozema, M. J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115.
[17] Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[18] (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827. (c) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 93. (d) Yus, M.; Foubelo, F. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1.
[19] (a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; (b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.

functionalization of aromatic substrates.[20] In 1995, *Mulzer* reported the regioselective functionalization of pyridine carboxamides and carbamates using TMPMgCl as metalating agent.[21] However, because of their low solubility and kinetic basicity, a big excess of the metalation reagent is necessary to obtain good magnesiation rates which also hinders the subsequent reactions with electrophiles. In 2006 *Knochel* and co-workers succeeded in the development of the mixed lithium and magnesium amide base TMPMgCl·LiCl (**6**) by the simple reaction of *i*PrMgCl·LiCl with TMPH.[22] It shows a very good solubility and excellent thermal stability and is compatible with functional groups under convenient temperatures (Scheme 7).



Scheme 7: Preparation of TMPMgCl·LiCl (**6**) and its use in deprotonation reactions.

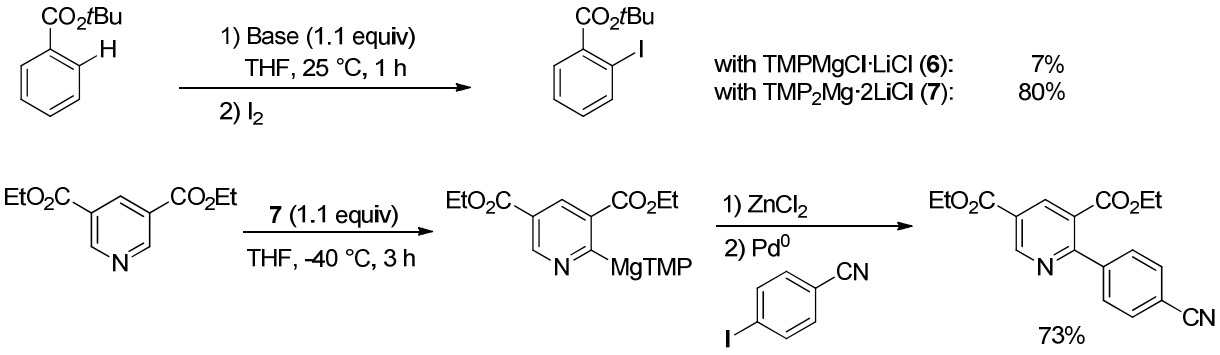
However, in the case of moderately activated aromatics and heteroaromatics, **6** turned out to be not sufficiently reactive. Recently, an extension of the directed magnesiation concept led to the development of the magnesium and lithium bisamide $TMP_2Mg·2LiCl$ (**7**) by the reaction of

[20] (a) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc*. **1989**, *111*, 8016; (b) Zhang, M.-X.; Eaton, P. E. *Angew. Chem. Int. Ed.* **2002**, *41*, 2169; (c) Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc*. **1993**, *115*, 11375; (d) Kondo, Y.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans 1*, **1996**, 2331.

[21] (a) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414; (b) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Liebigs Ann.* **1995**, 1441; (c) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Synthesis* **1995**, 1225.

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

TMPMgCl·LiCl (**6**) with LiTMP.[23] It shows an improved kinetic basicity and is able to metalate even moderately activated aromatics and heteroaromatics (Scheme 8).



Scheme 8: Reactivity comparison between TMPMgCl·LiCl (**6**) and $TMP_2Mg·2LiCl$ (**7**).

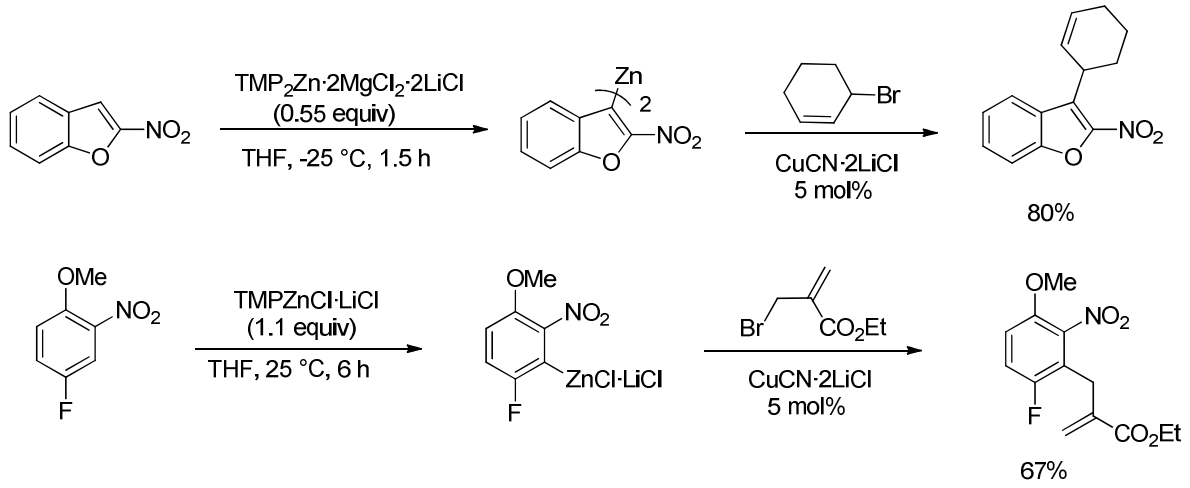
Beside this great progress in generating organometallic reagents under convenient conditions, there is still a need for more chemoselective metalation reagents. For example, molecules bearing aldehydes or nitro groups did not undergo directed magnesiations. Similarly, sensitive heterocycles which are subject to fragmentation could also not efficiently be converted into the corresponding magnesium reagents. Therefore a range of highly active zinc amides such as tBu$_2$Zn(TMP)Li have been reported by *Kondo* that can be used for directed *ortho*-metalation.[24] Moreover, the group of *Knochel* developed the highly chemoselective and chemosensitive zinc bases $TMP_2Zn·2MgCl_2·2LiCl$ (**8**)[25] and TMPZnCl·LiCl (**9**)[26] for the direct deprotonation of sensitive functionalized aromatics and heterocycles under mild conditions (Scheme 9).

[23] (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. (c) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem.* **2008**, *6*, 3237. (d) Mosrin, M.; Petrera, M.; Knochel, P. *Synthesis* **2008**, 3697. (e) Rohbogner, C. J.; Wirth, S.; Knochel, P. *Org. Lett.* **2010**, *12*, 1984.

[24] (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) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514; (d) Schwab, P. F. H.; Fleischer, F.; Michl, J.; *J. Org. Chem.* **2002**, *67*, 443.

[25] (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685. (b) Mosrin, M.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 1468. (c) Wunderlich, S.H.; Knochel, P. *Chem. Commun.* **2008**, *47*, 6387.

[26] Mosrin, M; Knochel, P. *Org. Lett.* **2009**, *11*, 1837; (b) Monzon, G.; Knochel, P. *Synlett*, **2010**, 304. (c) Crestey, F.; Knochel, P. *Synthesis*, **2010**, 1097.

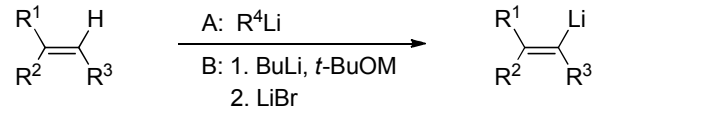


Scheme 9: TMP-derived zinc bases for the deprotonation of sensitive substrates.

2.4. Alkenylmetal Reagents

2.4.1. Alkenyllithium Reagents

The acess to a wide variety of alkenyllithium compounds is usually given by the removal of an vinylic proton using strong alkyllithium bases (Scheme 10).[27] Metalation-directing groups facilitate the deprotonation by chelatisation.



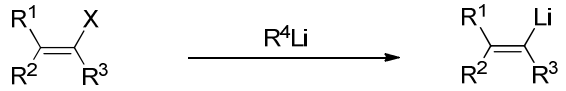
R^1, R^2 = F, OR, aryl, alkyl
R^3 = OR, Cl, CN, SO_2R, alkyl
R^4 = *n*Bu, *s*Bu, *t*Bu, NR_2
M = Na, K

Scheme 10: Preparation of alkenyllithium reagents by deprotonation with alkyllithium bases.

However, the metalation always competes with the addition of the base to the unsaturated system. Furthermore, the presence of functional groups requires very low temperatures for the deprotonation reactions to avoid elimination. A further synthetic route to alkyllithium reagents is

[27] (a) Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry*, Springer: Heidelberg, Germany, **1987**, Vol. 1; **1991**, Vol. 2.

the halogen-lithium exchange with alkyllithium bases or the metal-lithium exchange derived from alkenylboron, tin or mercury derivatives among others (Scheme 11).[27, 28]

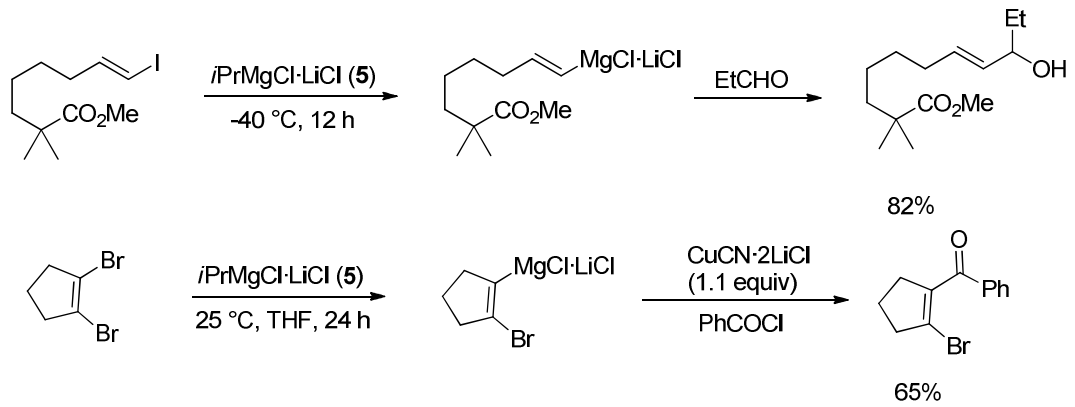


R^1, R^2 = F, OR,NR_2, aryl, alkyl, TMS
R^3 = alkyl, H,
R^4 = *n*Bu, *t*Bu
X = Cl, Br, I, SnR_3, PbR_3, BR_2, HgR_2, SeR_3, AlR_3

Scheme 11: Preparation of alkyllithium reagents by halogen-lithium and metal-lithium exchange reactions.

2.4.2. Alkenylmagnesium Reagents

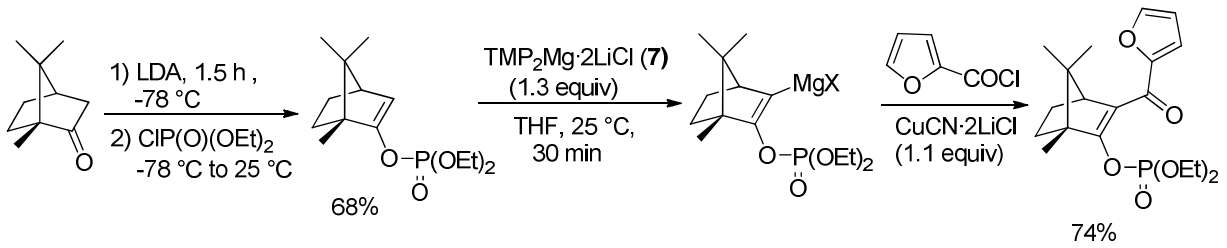
To date, alkenylmagnesium reagents can be prepared by halogen-magnesium exchange. In 2004 *Knochel et al.* demonstrated, that a range of cyclic and acyclic alkenyl- and dienyl-Grignard reagents can be available by halogen-magnesium exchange using *i*PrMgCl·LiCl (**5**).[29] The mild reaction conditions allow tolerating functions like esters, halides or nitriles (Scheme 12).



Scheme 12: Preparation of alkenylmagnesium reagents by halogen-magnesium exchange using *i*PrMgCl·LiCl (**5**).

[28] Perevre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*, Butterworth: London, **1987**.
[29] (a) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215; (b) Ren, H.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2005**, 543; (c) Despotopoulou, C.; Bauer, R. C.; Krasovskiy, A.; Mayer, P. ; Stryker, J. M.; Knochel, P. *Chem. Eur. J.* **2008**, *14*, 2499.

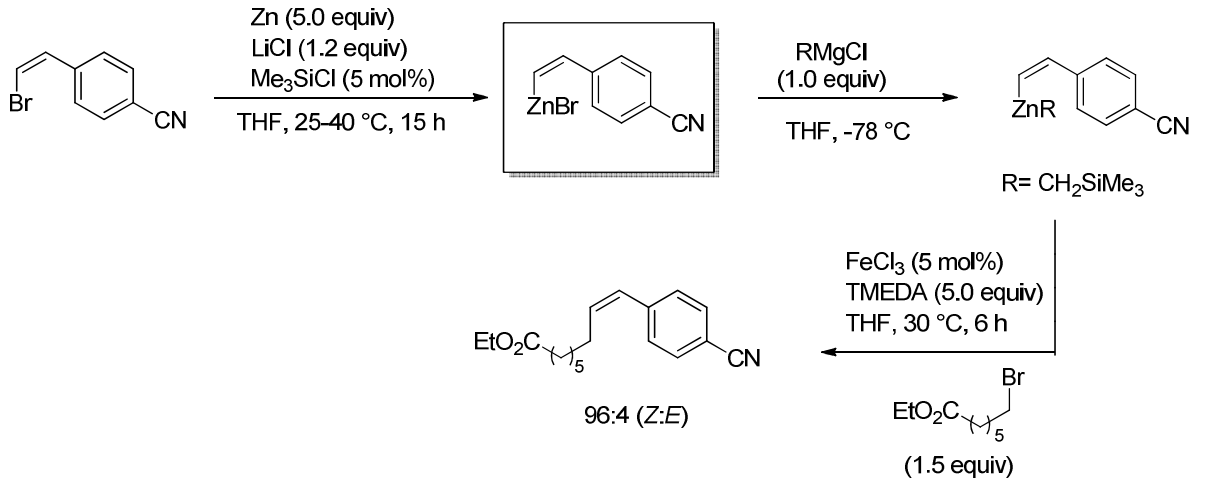
Recently, *Knochel* also reported the preparation of magnesiated enol phosphates derived from ketones using directed deprotonation reactions with $TMP_2Mg\cdot 2LiCl$ (**7**) (Scheme 13).[30]



Scheme 13: Preparation of magnesiated enol phosphates *via* directed deprotonation using $TMP_2Mg\cdot 2LiCl$ (**7**).

2.4.3. Alkenylzinc Reagents

So far, the only pathway to obtain alkenylzinc species is the direct insertion of zinc metal to an unsaturated halogen-carbon bond in the presence of LiCl.[10,31] In the following example the prepared organozinc species was involved in a selective iron-catalyzed cross-coupling reaction with an alkyl halide (Scheme 14).

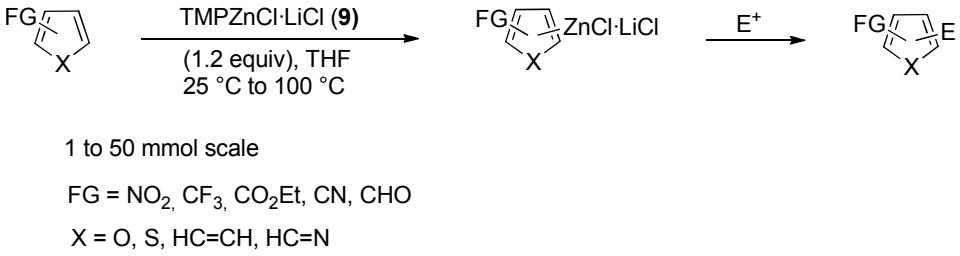


Scheme 14: Preparation of alkenylzinc reagents by oxidative insertion and subsequent cross coupling reaction.

[30] Piller, F.; Bresser, T.; Fischer, M.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4365.
[31] Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496.

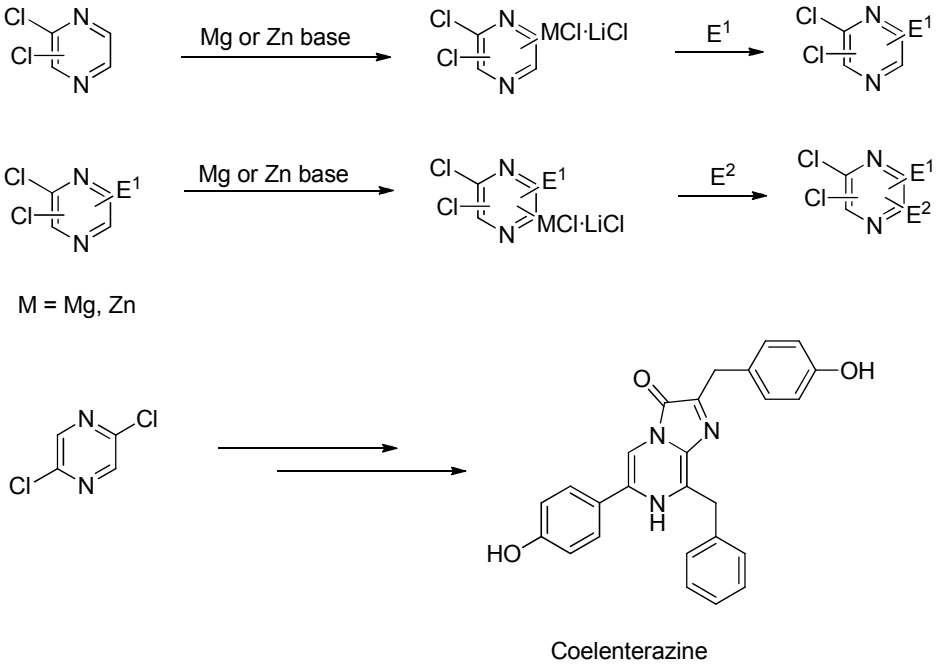
3. Objectives

In a first project, the recently developed active and chemoselective base TMPZnCl·LiCl (**9**) should be used for the metalation and functionalization of different highly substituted and sensitive aromatics and heteroaromatics under mild conditions. Another intention is to show that upscaling reactions with this base can be safely carried out with similar metalation rates as for small scales. Also the strength of this base and its tolerance towards functional groups even at elevated temperatures should be demonstrated by using conventional heating or microwave irradiation for the zincation of moderately activated substrates (Scheme 15).



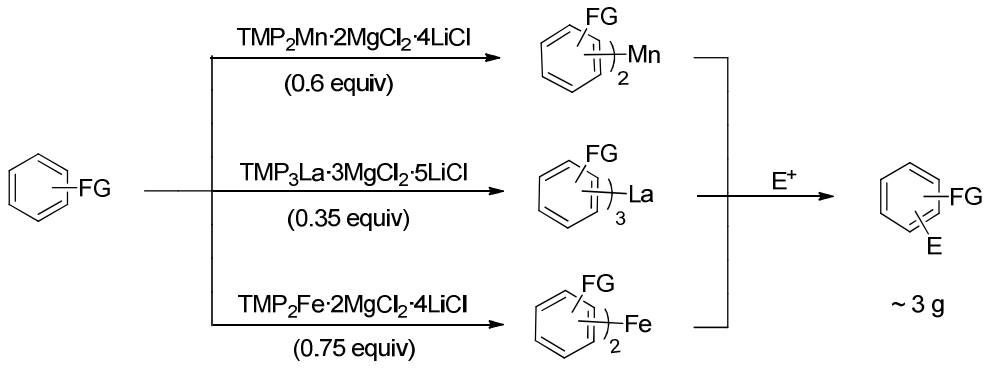
Scheme 15: Regio- and chemoselective zincation of sensitive and moderately activated aromatics and heteroaromatics using TMPZnCl·LiCl (**9**).

The second project was devoted to the functionalization of the pyrazine ring by metalation of chloropyrazine derivatives using magnesium and zinc bases with a direct application to the total synthesis of the natural product Coelenterazine found in *Aequorea Victoria* (Scheme 16).



Scheme 16: Regio- and chemoselective multiple functionalization of chloropyrazine derivatives. Application to the synthesis of Coelenterazine.

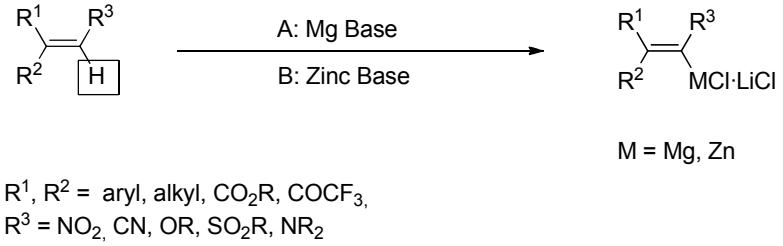
In a third project substituted aromatics should be functionalized on multigram scales using TMP-bases that were recently extended to other metals like manganese, lanthanum and iron (Scheme 17).



Scheme 17: Efficient preparation of polyfunctional organometallics *via* directed *ortho*-metalation using TMP bases of Mn, La and Fe.

Since the field of directed magnesiation and zincation of olefinic systems by deprotonation still remained to be explored, another project deals with the deprotonation and functionalization of

highly substituted alkenes under mild conditions using TMP-magnesium and zinc bases. Even the α-metalation of nitroolefins and the β-metalation of unsaturated trifluoromethyl ketones should be carried out, which was not reported so far (Scheme 18).



Scheme 18: Selective magnesiation or zincation of highly functionalized alkenes using TMP bases.

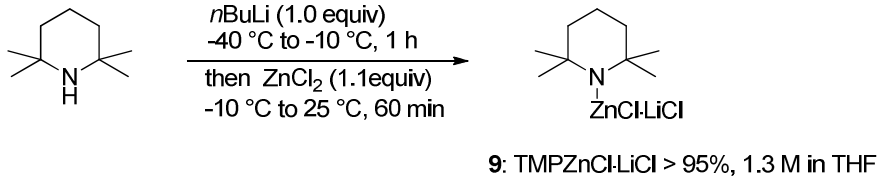
B. RESULTS AND DISCUSSION

1. Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl·LiCl

1.1. Introduction

The metalation of aromatics and heteroaromatics is an important tool since it allows a versatile functionalization of these molecules. A range of new bases for regio- and chemoselective metalation has already been developed.[18] Especially, mixed Zn/Li bases[24] and other ate reagents have found useful applications.[32] However, the use of highly reactive zincates or related ate bases is not always compatible with sensitive groups. Magnesium bases such as TMPMgCl·LiCl[22] (**6**) or $TMP_2Mg\cdot 2LiCl$[23](**7**) proved to be highly active and selective bases for the magnesiation of various aromatic ring systems. Remarkably, these bases are also compatible with several important functional groups such as an ester, a nitrile or an aryl ketone. However, more sensitive functionalities such as an aldehyde or a nitro group are not tolerated. Therefore, the chemoselective base $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$[25](**8**) was prepared for the direct zincation of sensitive aromatics and heteroaromatics. Nevertheless, with this reagent some electron-poor functionalized arenes and heteroarenes still give unsatisfactory results in terms of yields and reaction selectivity. Moreover, several activated aromatics bearing a nitro group or heterocycles like pyridazines require metalation temperatures below -50 °C, which is not convenient for reaction upscaling.[25c] Thus, a highly selective and mild base TMPZnCl·LiCl[26](**9**) was developed that allows chemoselective metalations at 25 °C for the directed zincation of molecules containing sensitive functional groups such as an aldehyde or a nitro group. Its higher selectivity is due to the absence of magnesium salts ($MgCl_2$) and to a different stoichiometry (TMPZnX instead of TMP_2ZnX). The mild base TMPZnCl·LiCl (**9**) is conveniently prepared in a one-pot procedure in quantitative yield as shown in Scheme 19.

[32] (a) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060; (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802; (c) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921; (d) Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E.; O'Hara, C. T.; Russo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 731; (e) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102.



Scheme 19: Preparation of TMPZnCl·LiCl (**9**).

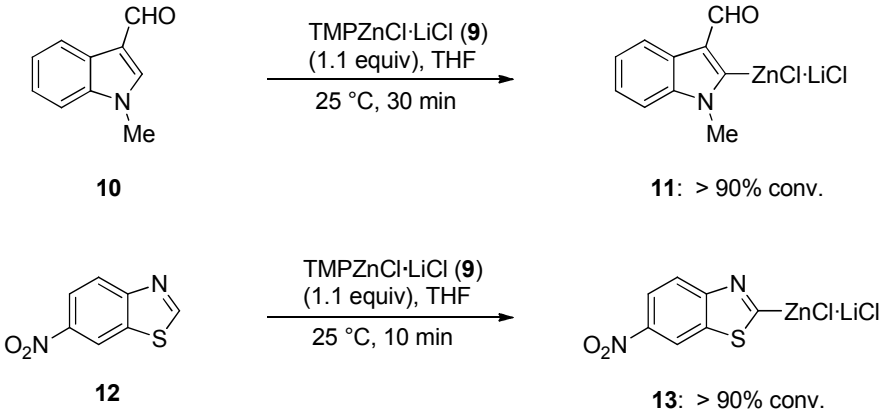
Whereas activated arenes and heteroarenes are smoothly metalated at 25 °C using TMPZnCl·LiCl (**9**), poorly activated systems bearing electron-donating groups or weakly electron-withdrawing substituents do not react at 25 °C with the base **9**. However, they undergo smooth metalation on heating (65-100°C) or on using microwave irradiation.

1.2. Results and Discussion

1.2.1. Metalation of Sensitive Substrates using TMPZnCl·LiCl (9) at 25 °C

Thus, the directed zincation of *N*-methylindole-3-carbaldehyde (**10**) provides the desired zinc species **11** at 25 °C within 30 min (Scheme 20). In the case of 6-nitro-1,3-benzothiazole (**12**) the metalation to **13** at 25 °C requires only 10 min (Scheme 20). The resulting zinc reagents **11** and **13** readily undergo an iodination, a copper-mediated allylation[33] as well as a Neghishi cross-coupling reaction[34] leading to new substituted heteroaromatics **14-15** and **16** which can be obtained in 66-84% yield (Table 1, entries 1-3).

[33] Knochel, P.; Yeh, M. C. P.; Berk S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
[34] 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.

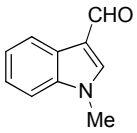
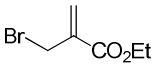
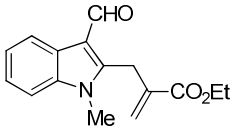
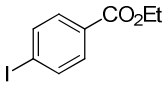
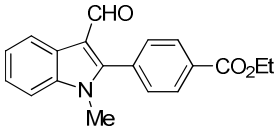
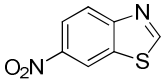
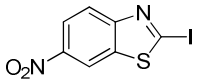
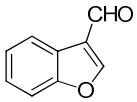
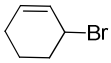
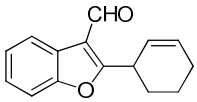
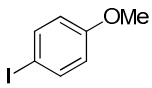
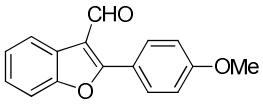
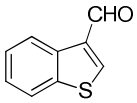
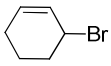
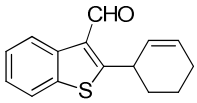
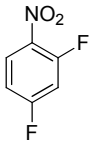
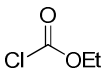
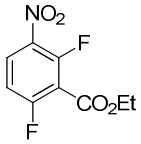


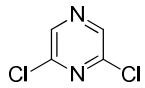
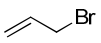
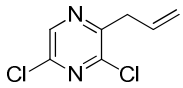
Scheme 20: Zincation of *N*-methylindole-3-carbaldehyde (**10**) and 6-nitro-1,3-benzothiazole (**12**) using TMPZnCl·LiCl (**9**) at 25 °C.

Similarly, benzofuran-3-carbaldehyde (**17**) was smoothly zincated at 25 °C within 30 min leading to a zinc reagent which undergoes an allylation with 3-bromocyclohexene (in the presence of a catalytic amount of CuCN·2LiCl)[33] leading to the allylated aldehyde **18** in 61% yield (entry 4). A Pd(0)-catalyzed cross-coupling reaction with 4-iodoanisole[34] gives the benzofuran derivative **19** in 65% yield (entry 5). Furthermore, benzothiophene-3-carbaldehyde (**20**) was converted to the coresponding zinc intermediate within 30 min at 25 °C. An allylation with 3-bromocyclohexene in the presence of copper[33] furnished the 2-allylated benzothiophene **21** in 62% (entry 6). 2,4-Difluoronitrobenzene (**22**) was reacted with **9** at 25 °C and fully metalated within 1 h. The resulting zinc species can be acylated with ethyl chloroformate[35] in the presence of catalytic amounts of $Pd(PPh_3)_4$ to give the nitroarene **23** in 63% yield (entry 7). Also, 2,6-dichloropyrazine (**24**) is smoothly zincated at 25 °C within 30 min. After quenching the reaction mixture with allyl bromide (in the presence of CuCN·2LiCl (5 mol%))[33] the resulting functionalized heteroarene **25** is obtained in 78% yield (entry 8).

[35] Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

Table 1: Products obtained by regio- and chemoselective zincation using TMPZnCl·LiCl (**9**) at 25 °C and quenching with electrophiles.

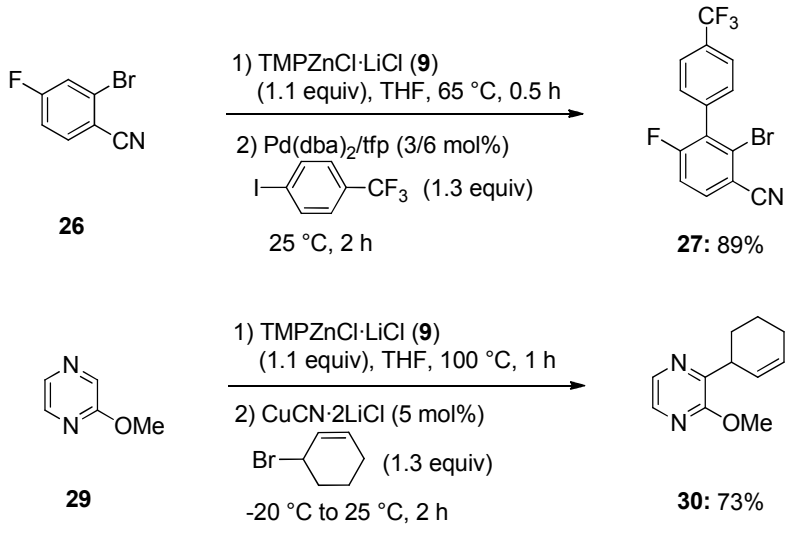
Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **10**		 **14**	66[b]
2	**10**		 **15**	73[c]
3	 **12**	I_2	 **16**	84
4	 **17**		 **18**	61[b]
5	**17**		 **19**	65[c]
6	 **20**		 **21**	62[b]
7	 **22**		 **23**	63[c]

8	 **24**		 **25**		78[b]

[a] Yield of analytically pure product; [b] In the presence of 5 mol% CuCN·2LiCl [c] In the presence of 5 mol% $Pd(PPh_3)_4$.

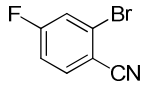
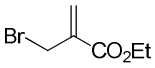
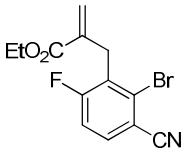
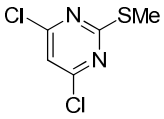
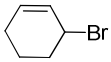
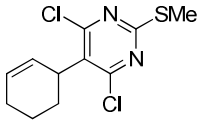
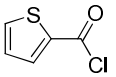
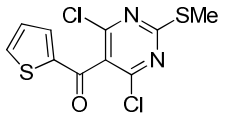
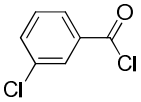
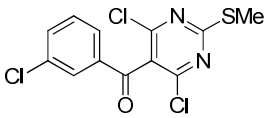
1.2.2. Zincation of less Activated Substrates Using TMPZnCl·LiCl and Conventional Heating

Aromatics and heteroaromatics which can not be fully metalated at 25 °C reacted with TMPZnCl·LiCl (**9**) on heating in an oil bath (65-100 °C). Thus, the treatment of 2-bromo-4-fluorobenzonitrile (**26**) with **9** (1.1 equiv, 65 °C, 30 min) leads to the zincated species which readily undergoes a Negishi cross-coupling[34] or a Cu-catalyzed allylation to the expected products **27** and **28** in 88-89% yield (Scheme 21 and Table 2, entry 1). Interestingly, 2-methoxypyrazine (**29**) can be converted to the corresponding Zn-compound with TMPZnCl·LiCl (**9**) at 100 °C within 60 min. Allylation with 3-bromocyclohexene affords the new pyrazine derivative **30** in 73% yield (Scheme 21). Similarly, 4,6-dichloro-2-(methylthio)pyrimidine (**31**) reacts with TMPZnCl·LiCl (**9**; 1.1 equiv, 65 °C, 30 min). An acylation or allylation,[33] give the functionalized pyrimidines **32**-**34** in 88-90 % yield (Table 2, entries 2-4).



Scheme 21: Zincation of 2-bromo-4-fluorobenzonitrile (**26**) and 2-methoxypyrazine (**29**) using TMPZnCl·LiCl (**9**) and conventional heating.

Table 2: Products obtained by regio- and chemoselective zincation using TMPZnCl·LiCl (**9**), conventional heating and quenching with electrophiles

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **26**		 **28**	88[b]
2	 **31**		 **32**	90[b]
3	**31**		 **33**	88[c]
4	**31**		 **34**	88[c]

[a] Yield of analytically pure product; [b] In the presence of 5 mol% CuCN·2LiCl; [c] 1.1 equiv of CuCN·2LiCl were added.

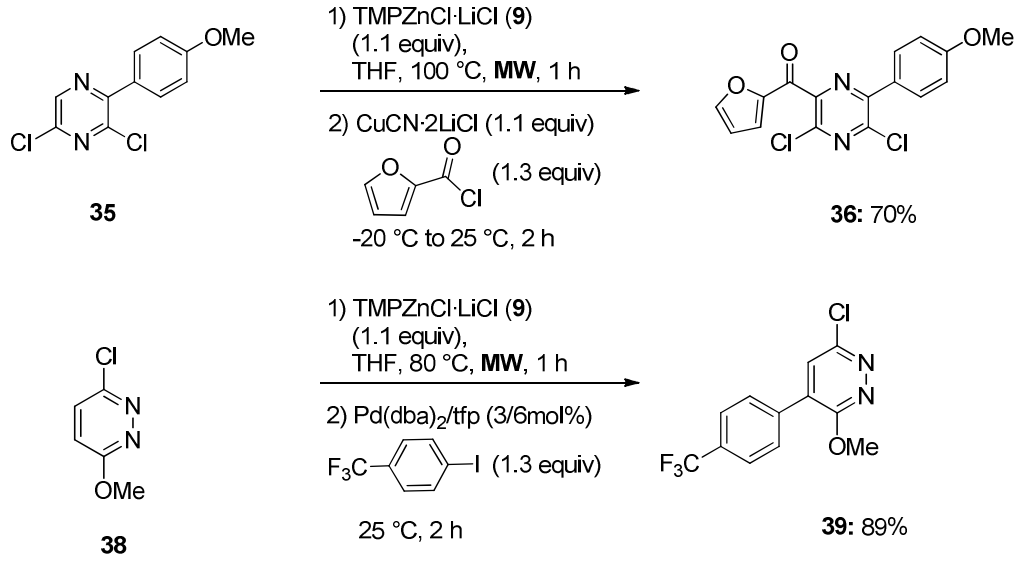
1.2.3. Zincation of less Activated Substrates Using TMPZnCl·LiCl and Microwave Irradiation

Over the last decades, microwave irradiation has been used to accelerate numerous organic reactions[36] including organometallic reactions.[37] Recently, it was shown that microwave irradiation allows an effective zincation of various arenes and heteroarenes using

[36] (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. ed. 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.; ed, Springer, Berlin, 2006.

[37] 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) Fustero, S.; Jimenez, D.; Sanchez-Rosello, M.; del Pozo,

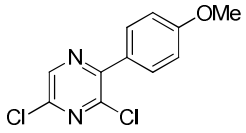
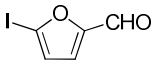
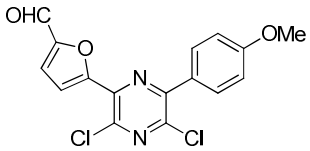
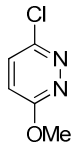
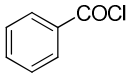
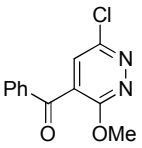
$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.[38] Organozinc reagents of the type RZnX possess a good thermal stability and tolerate functional groups even at elevated temperatures. In the case of less activated substrates, microwave irradiation turns out to be essential since conventional heating gives unsatisfactory conversions to the corresponding zinc reagents. Therefore, 3,5-dichloro-2-(4-methoxy-phenyl)pyrazine (**35**) is zincated at 100 °C within 1 h. Acylation with furoyl chloride (after transmetallation with $CuCN{\cdot}2LiCl$)[33] or Negishi cross-coupling[34] afforded the fully substituted pyrazines **36** and **37** in 65-70% yield (Scheme 22 and Table 3, entry 1). Interestingly, the use of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**8**) for the zincation of 3-chloro-6-methoxypyridazine (**38**) leads to a mixture of regioisomers (metalation in position 4 and 5). However, by using TMPZnCl·LiCl (**9**; 1.1 equiv, 80 °C, 100 W, 1 h), 3-chloro-6-methoxypyridazine (**38**) is regioselectively metalated in *ortho*-position to the methoxy group[39] (metalation in position 5). The resulting zinc species readily undergoes after transmetalation with $CuCN{\cdot}2LiCl$[33] an acylation with benzoyl chloride or a Pd(0)-catalyzed cross-coupling reaction leading to the new substituted pyridazines **39**-**40**[40] in 80-89% yield (Scheme 22 and Table 3, entry 2).



Scheme 22: Zincation of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**35**) and 5-bromo-2,4-dimethoxypyrimidine (**38**) using TMPZnCl·LiCl (**9**) and microwave irradiation.

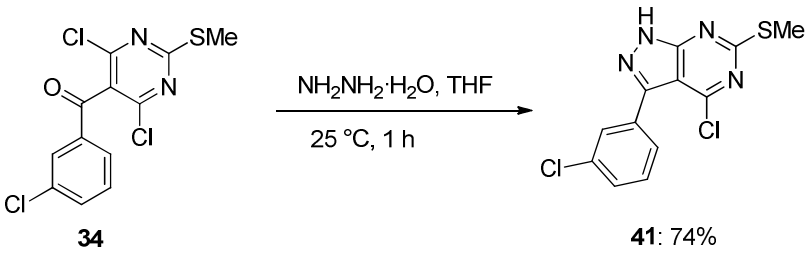
[38] Wunderlich, S. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705.
[39] The regioselectivity has been established by quenching the zinc organometallic with D_2O.
[40] Products prepared by Gabriel Monzon.

Table 3: Products obtained by regio- and chemoselective zincation using TMPZnCl·LiCl (**9**), microwave activation and quenching with electrophiles

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **35**		 **37**	65[b]
2	 **38**		 **40**	80[c]

[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] 1.1 equiv of CuCN·2LiCl were added.

Aa a further reaction, a ring closure was performed starting from the new functionalized pyrimidine **34**. Thus, the treatment of the ketone **34** with hydrazine in THF at 25°C for 1 h furnished the pyrazolopyrimidine **41** in 74% yield (Scheme 23).



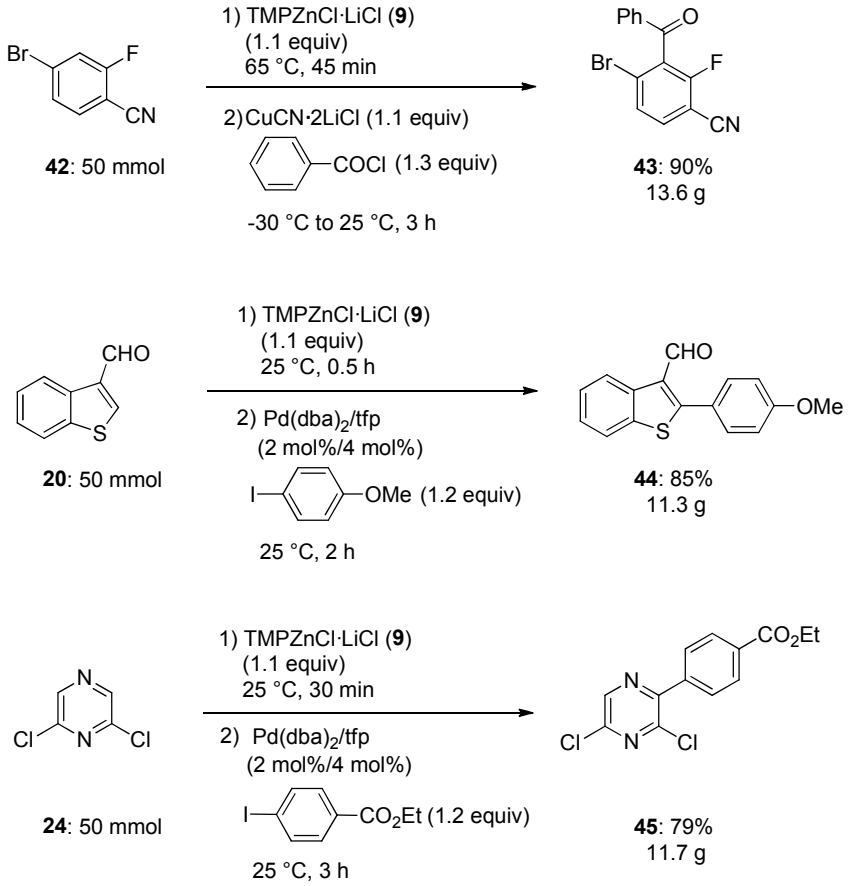
34 **41**: 74%

Scheme 23: Ring closure of dichlolopyrimidine **34** using hydrazine.

1.3. Scaleable Preparation of Sensitive Functionalized Aromatics and Heteroaromatics *via* Directed Metalation Using TMPZnCl·LiCl

Several experiments using TMPZnCl·LiCl[26] (**9**) and further reactions with electrophiles can safely be carried out on multigram scales with comparable yields as obtained for small scales (Scheme 24). Thus, 4-bromo-2-fluorobenzonitrile (**42**; 9.95 g, 50 mmol) dissolved in THF (50 mL) is reacted with TMPZnCl·LiCl (**9**; 40.7 mL, 1.1 equiv) at 25 °C and the resulting mixture is warmed to 65 °C for 45 min (same metalation rate as for reactions performed at 1 mmol scale; metalation progress checked by iodolysis of reaction aliquots and gas chromatographical analysis). Quenching with benzoyl chloride (9.1 g, 1.3 equiv) (after the addition of CuCN·2LiCl (55 mL, 1.1 equiv)[33] furnishes the new substituted benzonitrile **43** in 90% yield. Smooth zincations of arenes and heteroarenes bearing sensitive functionalities like aldehydes or nitro groups can also be tolerated on larger scales. Thus, the metalation of benzothiophene-3-carbaldehyde (**20**; 8.1 g, 50 mmol) is complete within 30 min at 25 °C using TMPZnCl·LiCl (**9**; 40.7 mL, 1.1 equiv). The corresponding zinc derivative undergoes a Pd-catalyzed cross-coupling reaction[34] with 4-iodoanisole (14.0 g, 1.2 equiv) using $Pd(dba)_2$ (565 mg, 2 mol%) and tfp (465 mg, 4 mol%)[41] to give after 2 h the corresponding functionalized aldehyde **44** in 85% yield. Similarly, 2,6-dichloropyrazine (**24**; 7.45 g, 50 mmol) is converted into the zincated species within 30 min at 25 °C (same metalation rate compared to 1 mmol scale reactions) using TMPZnCl·LiCl (**9**; 40.7 mL, 1.1 equiv). The trisubstituted pyrazine **45** is obtained in 79% yield after a Negishi cross-coupling reaction with ethyl 4-iodobenzoate[34] (16.5 g, 1.2 equiv) using $Pd(dba)_2$ (565 mg, 2 mol%) and tfp (465 mg, 4 mol%)[41].

[41] Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, 113, 9585. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, 59, 5905. (c) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, 52, 7201.

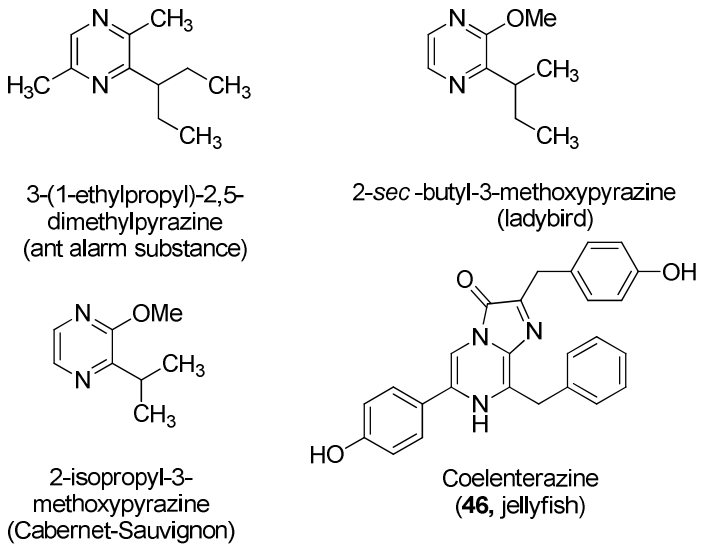


Scheme 24: Large scale zincations of aromatics and heteroaromatics **20**, **24** and **42** using TMPZnCl·LiCl (**9**) and subsequent reactions with electrophiles.

2. Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine

2.1. Introduction

Pyrazines are important biologically active metabolites. They are widely distributed in flavourings, formed either thermally such as alkylpyrazines present in coffee, meat and potatoes, or biosynthetically such as 2-alkyl-3-methoxypyrazines present in wines such as Cabernet-Sauvignon. Some pyrazine natural products like coelenterazine (**46**), a natural occurring bioluminescent imidazopyrazine of marine origin isolated from the jellyfish *Aequorea Victoria* bear a tetrasubstituted dihydropyrazine unit. Coelenterazine is used in new optical technologies for studying the complexity, diversity and *in vivo* behaviour of cancers (Scheme 25).[42]

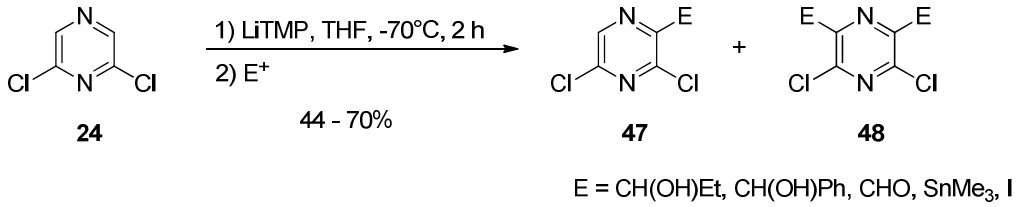


Scheme 25: Natural products containing a pyrazine scaffold.

[42] (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.

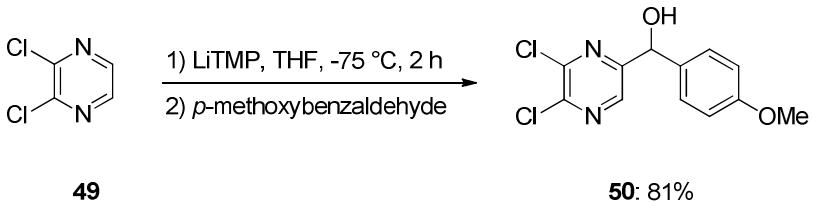
2.2. Functionalization of Chloropyrazines Using Lithium Bases

The direct functionalization of these heterocycles by lithiation is difficult due to the electrophilic character of the ring. Nucleophilic addition therefore becomes a very facile competitive reaction. For this reason, low temperatures are quite often required for the metalation of pyrazines.[43] The metalation and functionalization of dichloropyrazines such as 2,6-dichloropyrazine (**24**) has already been carried out to obtain products of type **47** in moderate to good yields (Scheme 26). However, using an excess of base and electrophile, compatible with *in situ* trapping such as iodine or aldehydes, results in mixtures of products containing 3,5-difunctionalized compounds of type **48**.[44]



Scheme 26: Lithiation of 2,6-dichloropyrzine (**24**) and reacting with electrophiles.

The metalation of 2,3-dichloropyrazine (**49**) was also reported by *Quéguiner* as an intermediate step for the synthesis of pyrazine alcaloids using LiTMP.[45] Therefore, **49** was reacted with LiTMP at -75 °C and the resulting lithium species was then converted with *p*-methoxybenzaldehyde to provide the corresponding alcohol **50** in 81 % yield (Scheme 27).



Scheme 27: Lithiation of 2,3-dichloropyrazine (**49**) and reaction with *p*-methoxybenzaldehyde.

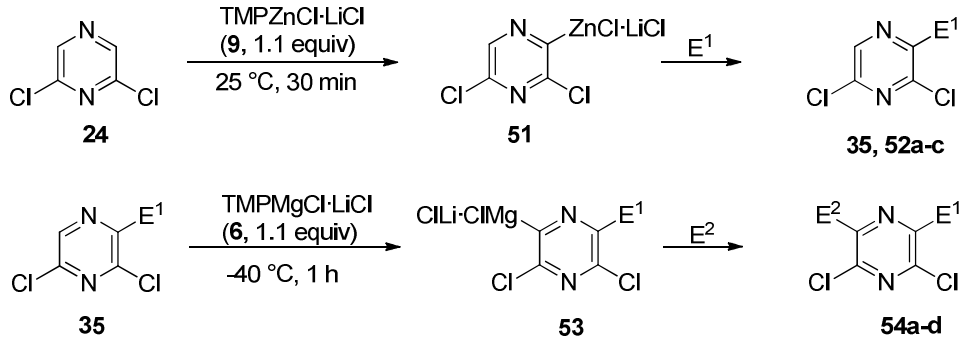
[43] (a) Zhang, C. Y.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 8783. (b) Liu W.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **2001**, *66*, 4783. (c) Chevallier, F. ; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595.

[44] (a) Turck, A.; Mojovic, L.; Quéguiner, G. *Synthesis* **1989**, 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. (d) Ward, J. S.; Merritt, L. *Heterocycl. Chem.* **1991**, *28*, 765. (e) Turck, A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, *412*, 301.

[45] Buron, F.; Plé, N.; Turck, A.; Quéguiner, G. *J. Org. Chem.* **2005**, *70*, 2616.

2.3. Total Functionalization of the Pyrazine Scaffold Using TMP-Bases

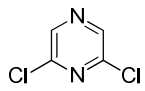
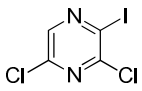
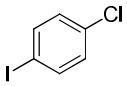
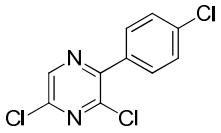
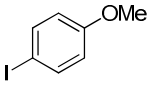
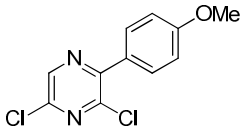
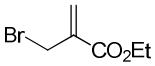
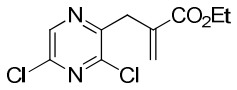
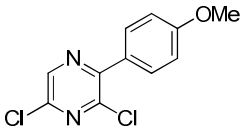
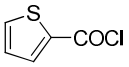
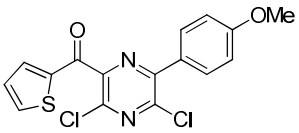
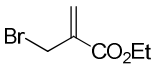
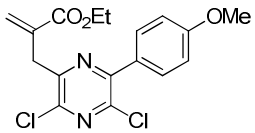
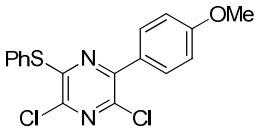
TMPMgCl·LiCl[22] (**6**) allows the direct magnesiation of a number of arenes and heteroarenes even bearing esters or ketones. TMPZnCl·LiCl[26] (**9**) permits a direct zincation of much more sensitive aromatics and heteroaromatics and tolerates aldehydes and nitro groups. Using these two bases enables the selective functionalization of all positions of the pyrazine ring starting from simple compounds such as dichloropyrazines by performing successive metalations (Scheme 28). Thus, the treatment of 2,6-dichloropyrazine (**24**) with TMPZnCl·LiCl (**9**; 1.1 equiv, 25 °C, 30 min) leads to the 3-zincated pyrazine (**51**), which is trapped with iodine to provide the iodopyrazine **52a** in 91% (Table 4, entry 1). The formation of a new carbon-carbon bond is readily performed by a Pd(0)-catalyzed Negishi cross-coupling reaction[34] of **51** with 4-iodoanisole or 1-chloro-4-iodobenzene giving the 3-substituted heterocycles **52b** and **35** in 86-91% (entries 2-3). An allylation with 2-(bromomethyl)acrylate[46] (after addition of a catalytic amount of CuCN·2LiCl)[33] affords the allylated pyrazine **52c** in 82% (entry 4). Subsequent metalation of the arylpyrazine **35** using TMPMgCl·LiCl (**6**; 1.1 equiv, -40 °C, 1 h) leads to the magnesium reagent **53**, which affords after transmetalation with CuCN·2LiCl[33] and trapping with thiophene-2-carbonyl chloride the ketopyrazine **54a** in 78% yield (entry 5). An allylation with 2-(bromomethyl)acrylate[46] gives the corresponding pyrazine **54b** in 74% (entry 6). Quenching with $PhSSO_2Ph$ or TosCN provides the new substituted pyrazines **54c-d** in 55-94% yield (entries 7-8).

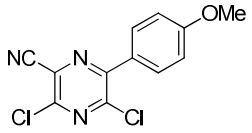


Scheme 28: Metalation of 2,6-dichloropyrazine (**24**) at positions 3 and 5 using TMPZnCl·LiCl (**9**) and TMPMgCl·LiCl (**6**) and trapping with electrophiles.

[46] Villiéras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

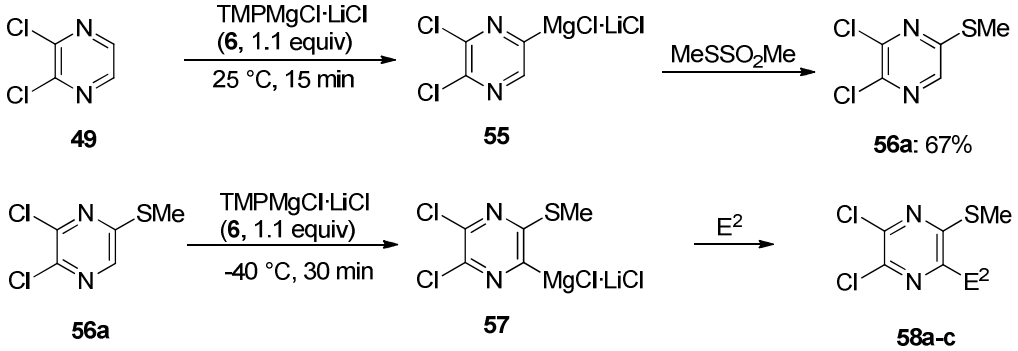
Table 4: Products obtained by metalation of 2,6-dichloropyrazine (**24**) with TMPZnCl·LiCl (**9**) and TMPMgCl·LiCl (**6**) and trapping with electrophiles.

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **24**	I_2	 **52a**	91
2	**24**		 **52b**	91[b]
3	**24**		 **35**	86[b]
4	**24**		 **52c**	82[c]
5	 **35**		 **54a**	78[d]
6	**35**		 **54b**	74[c]
7	**35**	$PhSSO_2Me$	 **54c**	94

8	**35**	TosCN	 **54d**	55

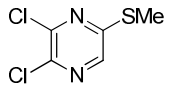
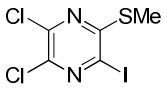
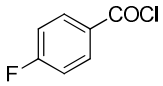
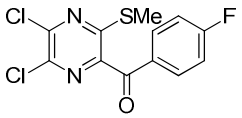
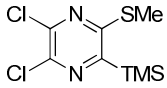
[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] 5 mol% CuCN·2LiCl were added [d] The organozinc reagent was transmetalated with CuCN·2LiCl (1.1 equiv).

Other dichloropyrazines are metalated as well under mild conditions. Thus, the treatment of 2,3-dichloropyrazine (**49**) with TMPMgCl·LiCl (**6**; 1.1 equiv, 25 °C, 15 min) provides the 5-magnesiated pyrazine **55** which reacts with electrophiles such as $MeSSO_2Me$ and the pyrazine **56a** can be isolated in 67% yield (Scheme 29). A further magnesiation at the last position was achieved by the addition of TMPMgCl·LiCl (**6**; 1.1 equiv). Thus, 2,3-dichloro-5-(methylthio)pyrazine **56a** is converted to the 6-magnesiated species **57** within 30 min at -40 °C (Scheme 29). Reaction with iodine furnishes the iodopyrazine **58a** in 80% (Table 5, entry 1). An acylation with 4-fluorobenzoyl chloride after transmetalation with CuCN·2LiCl[33] or trapping the metal species **57** with TMSCN leads to the new substituted pyrazines **58b-c** in 72-88% (entries 2-3).



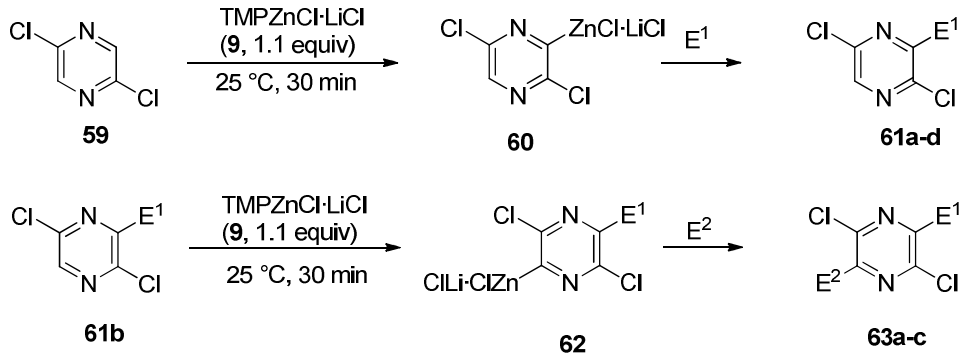
Scheme 29: Metalation of 2,3-dichloropyrazine (**49**) at positions 5 and 6 using TMPMgCl·LiCl (**6**) and trapping with electrophiles.

Table 5: Products obtained by metalation of 2,3-dichloropyrazine **49** with TMPMgCl·LiCl (**6**) and trapping with electrophiles.

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **56a**	I_2	 **58a**	80
2	**56a**		 **58b**	72[b]
3	**56a**	TMSCN	 **58c**	88[c]

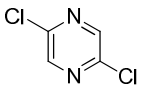
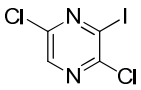
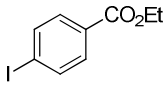
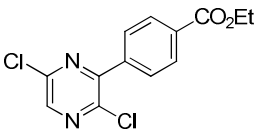
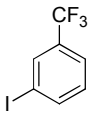
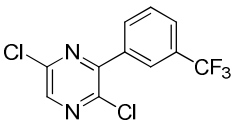
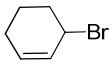
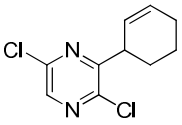
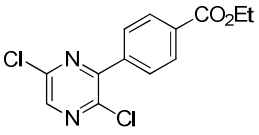
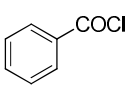
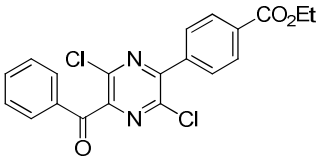
[a] Yield of analytically pure product; [b] The organozinc reagent was transmetalated with CuCN·2LiCl (1.1 equiv).

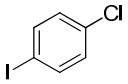
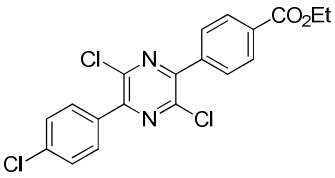
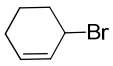
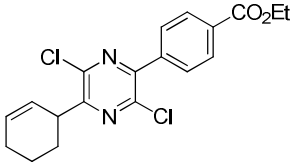
Similarly, 2,5-dichloropyrazine (**59**) undergoes smooth zincation using TMPZnCl·LiCl (**9**; 1.1 equiv, 25 °C, 30 min) affording the zinc reagent **60** (Scheme 30). Iodolysis leads to the 2,5-dichloro-3-iodopyrazine **61a** in 76% (Table 6, entry 1). Negishi cross-coupling[34] with ethyl 4-iodobenzoate and 1-iodo-3-(trifluoromethyl)benzene provides the substituted heterocycles **61b-c** in 86-91% yield (entries 2-3). An allylation with 3-bromocyclohexene after addition of a catalytic amount of CuCN·2LiCl[33] gives the corresponding pyrazine **61d** in 82% yield (entry 4). Subsequent metalation of the ester derivative **61b** using TMPZnCl·LiCl (**9**; 1.1 equiv, 25 °C, 30 min) gives the zinc species **62**, which was benzoylated (after transmetalation with CuCN·2LiCl) giving the ketopyrazine **63a** in 90% yield (entry 5). Negishi cross-coupling[34] or allylation with 3-bromocyclohexene (in the presence of CuCN·2LiCl[33] (5 mol %) furnish the fully substituted pyrazines **63b** and **63c** in 78% and 85% yield (entries 6-7).



Scheme 30: Metalation of 2,5-dichloropyrazine (**59**) at positions 2 and 5 using TMPZnCl·LiCl (**9**) and trapping with electrophiles.

Table 6: Products obtained by metalation of 2,5-dichloropyrazine of type **59** with TMPZnCl·LiCl (**9**) and TMPMgCl·LiCl (**6**) and trapping with electrophiles.

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **59**	I_2	 **61a**	76
2	**59**		 **61b**	91[b]
3	**59**		 **61c**	86[b]
4	**59**		 **61d**	82[c]
5	 **61b**		 **63a**	90[d]

6	**61b**		 **63b**	78[b]
7	**61b**		 **63c**	85[c]

[a] Yield of analytically pure product; [b] Obtained after a Pd-catalyzed cross-coupling reaction; [c] 5 mol% CuCN·2 LiCl were added [d] The organozinc reagent was transmetalated with CuCN·2 LiCl (1.1 equiv).

2.4. Application to the Total Synthesis of Coelenterazine

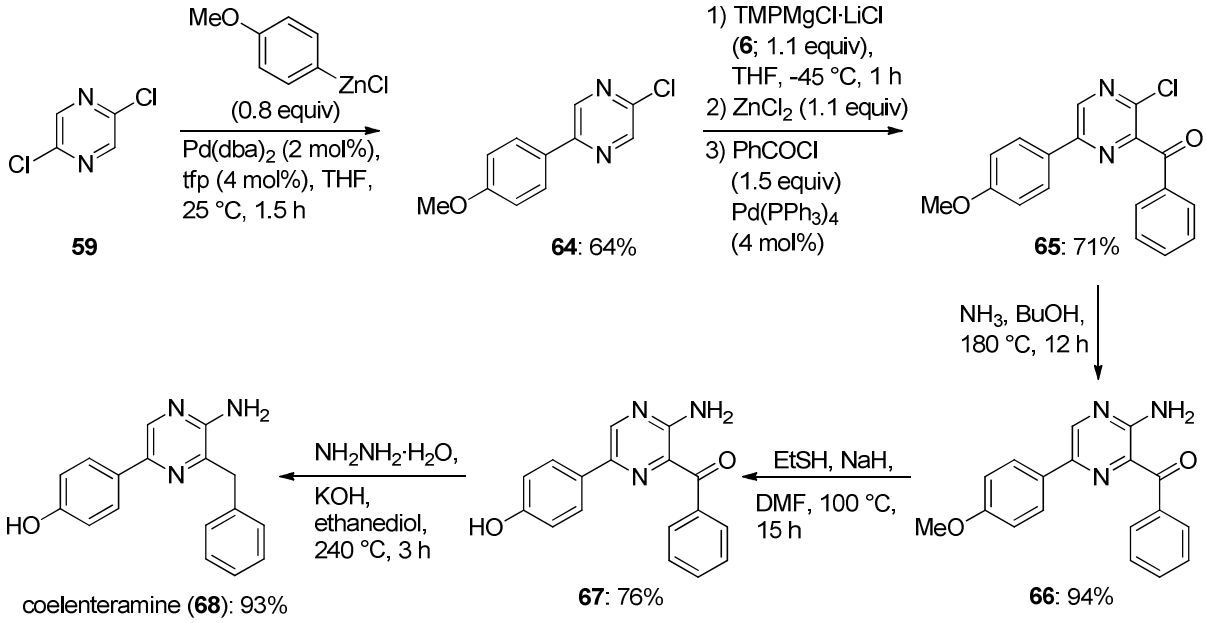
As an application, we have carried out the total synthesis of coelenterazine (**46**)[42a,47] in 9 steps and 9% overall yield. Thus, a Negishi cross-coupling[34] with a zinc reagent (prepared from 4-iodoanisole by an iodo-magnesium exchange reaction using **5** and subsequent transmetallation with $ZnCl_2$) using 2,5-dichloropyrazine (**59**) as electrophile provides the arylpyrazine **64** in 64% yield (Scheme 31). A magnesiation with TMPMgCl·LiCl (**6**; 1.1 equiv, -45 °C, 1 h) gives after transmetalation with $ZnCl_2$ and acylation with benzoyl chloride the ketopyrazine **65** in 71% yield. The chlorine substitution is then achieved using NH_3 in BuOH[48] furnishing the aminopyrazine **66** in 94% yield. Cleavage of the methyl ether with sodium ethanethiolate in DMF[49] yields the corresponding alcohol **67** in 76%. The reduction of the ketone is finally carried out using a Wolff-Kishner[50] reduction affording coelenteramine (**68**) in 93% yield (Scheme 31).

[47] 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) Adamczyk, M.; Rao Akireddy, S.; Johnson, D. D.; Mattingly, P. G.; Pan, Y.; Reddy, R. E. *Tetrahedron* **2003**, *59*, 8129. (g) Gonzalez-Trueba, G.; Paradisi, C.; Zoratti, M. *Anal. Biochem.* **1996**, *240*, 308. (h) Jones, K.; Keenan, M.; Hibbert, F. *Synlett*, **1996**, 509. (i) Keenan, M.; Jones, K.; Hibbert, F. *Chem. Commun.* **1997**, *3*, 323. (j) Kakoi, H *Chem. Pharm. Bull.* **2002**, *50*, 301.

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

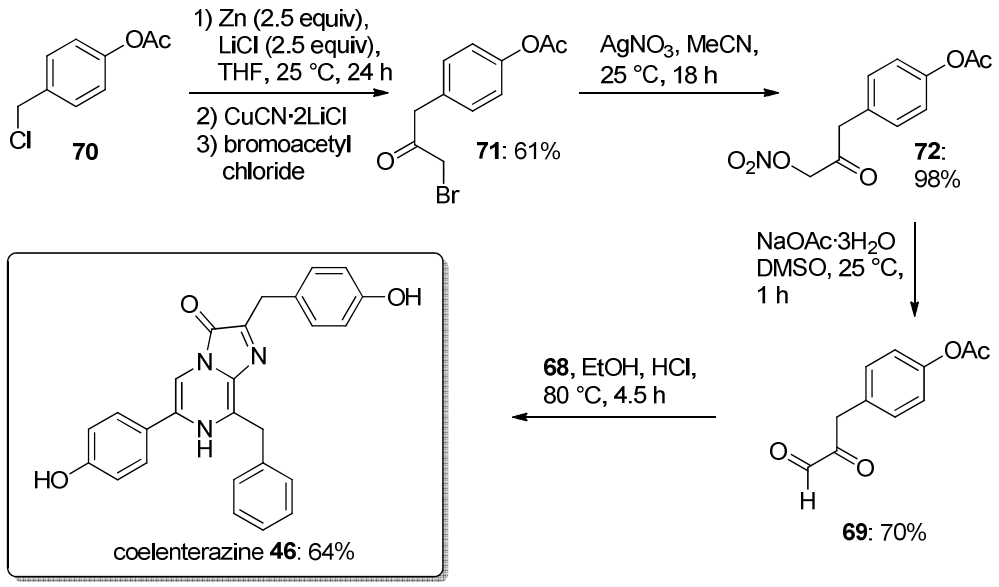
[49] Burton, M.; De Tollenaere, C.; Dussart, F.; Marchand, C.; Rees, J.F.; Marchand-Brynaert, J. *Synthesis* **2001**, 768.

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



Scheme 31: Synthesis of coelenteramine (**68**).

The preparation of the second moiety is presented as followed (Scheme 32).



Scheme 32: Synthesis of coelenterazine (**46**).

The preparation of the diazine ring in coelenterazine (**46**) requires a condensation of coelenteramine (**68**) with the ketoaldehyde **69**. The addition of 4-(chloromethyl)phenyl acetate (**70**) to commercial Zn dust (2.5 equiv) in the presence of LiCl (2.5 equiv) at 25 °C is complete within 24 h.[51] Trapping with bromoacetyl chloride after transmetalation with CuCN·2LiCl[33] furnishes the acylated derivative **71** in 61% yield. Addition of silver nitrate at 25 °C gives after 18 h the nitrate ester **72** in 98% yield.[52] Subsequent reaction of **72** with $NaOAc \cdot 3H_2O$ in DMSO at 25 °C for 1 h affords the corresponding acetoxy α-keto aldehyde **69** in 70% yield.[52] Finally, the condensation of the 1,2-dicarbonyl derivative **69** with coelenteramine (**68**) provides the bioluminescent natural product coelenterazine (**46**) in 64% yield.[47h,52]

[51] Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107.
[52] Chen, F.-Q.; Zheng, J.-L.; Hirano, T.; Niwa, H.; Ohmiya, Y.; Ohashi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *17*, 2129.

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

3.1. Introduction

The metalation of functionalized unsaturated substrates provides useful intermediates in organic synthesis. Besides traditional and well investigated Li-reagents, a number of mixed ate-bases have been developed.[16, 24, 32] Although these efforts seem to be promising, there is still a need for neutral chemoselective bases for the metalation of organic substrates. Recently, it was reported that the reaction of TMPMgCl·LiCl[22] (**6**) with metallic chlorides such as $ZnCl_2$,[25] $MnCl_2 \cdot 2LiCl$,[53] $FeCl_2 \cdot 2LiCl$[54] and $LaCl_3 \cdot 2LiCl$[55] leads to room temperature-stable and kinetically highly active metalation agents. The metalations occur under mild conditions (usually close to 25 °C) and display a high atom economy since all TMP moieties can be used for the directed metalation. The resulting organometallics contain a variety of functional groups and they react with a number of electrophiles (in the presence of appropriate catalysts if needed). Usually, the optimization of these metalation procedures has been carried out on 1-2 mmol scales. Thus, the extension of metalation reagents (Mn, Fe, La) to experiments in larger scales (approx. 3 g scale) were investigated.

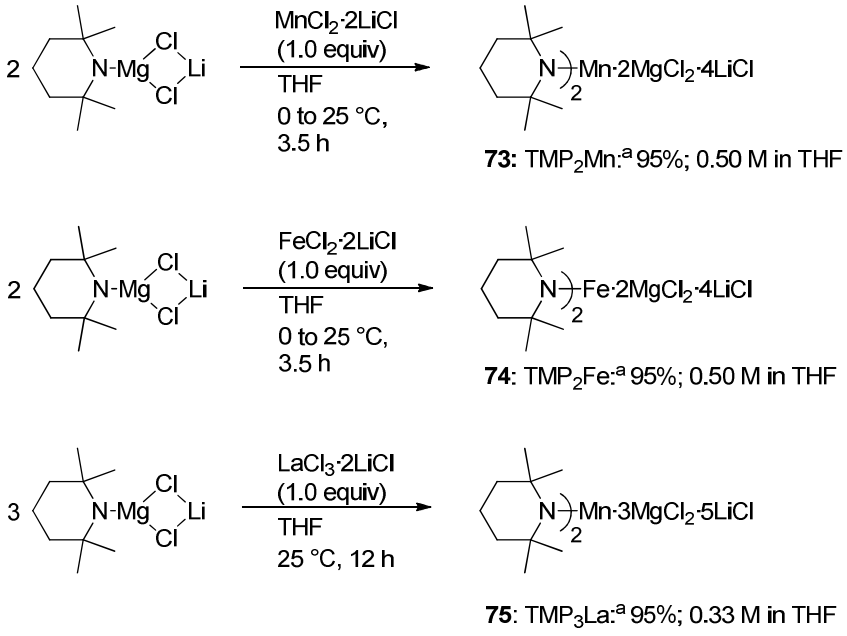
3.2. Results and Discussion

First, the amide bases **73-75** were efficiently prepared by the transmetalation of TMPMgCl·LiCl (**6**; Scheme 33). Thus, the reaction of TMPMgCl·LiCl (**6;** 2.0 equiv) with a solution of $MnCl_2 \cdot 2LiCl$[53] (1 M in THF) provides the reagent $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**73**) in >95% yield by stirring the mixture for 30 min at 0 °C and further for 3 h at 25 °C. Similarly, the Fe(II)-base $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**74**) is obtained by the reaction of TMPMgCl·LiCl (**6;** 2.0 equiv) with a solution of $FeCl_2 \cdot 2LiCl$[54] (1 M in THF). Additionally, $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**75**) is prepared

[53] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256.
[54] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.
[55] S. H. Wunderlich, P. Knochel, *Chem. Eur. J.*. **2010**, *16*, 3304.

by the reaction of TMPMgCl·LiCl (**6**; 3.0 equiv) with the THF soluble complex $LaCl_3$·2LiCl[55] in THF for 12 h. All three bases can be stored under inert-gas atmosphere for at least 2 months without decomposition. In general, changing the metal of the amide bases also changes the behavior of the corresponding organometallic reagent.

Thus, the metalation of methyl 3-fluorobenzoate (**76**) is finished within 1 h at 25 °C using $TMP_2Mn·2MgCl_2·4LiCl$ (**73**; 0.6 equiv). A copper-catalyzed allylation with 3-bromocyclohexene furnishes the 1,2,3-trisubstituted arene **77a** in 90% yield (Table 7, entry 1). Furthermore, the manganation of 4-fluorobenzonitrile (**78**) takes place at 25 °C within 2 h using $TMP_2Mn·2MgCl_2·4LiCl$ (**73**; 0.6 equiv). A subsequent CuCN·2LiCl-mediated acylation with benzoyl chloride leads to the benzophenone **79a** in 68% yield (entry 2).



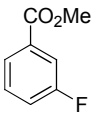
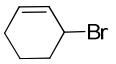
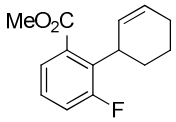
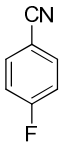
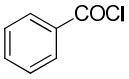
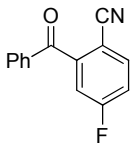
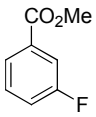
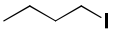
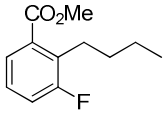
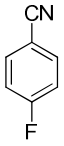
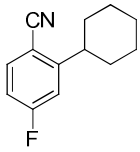
Scheme 33: Preparation of the bases **73-75**. [a] LiCl and $MgCl_2$ have been omitted for the sake of clarity.

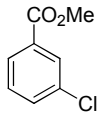
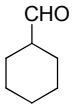
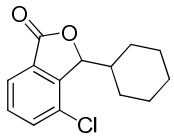
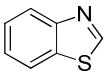
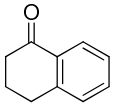
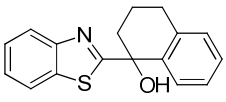
Furthermore, the directed ferration can also be carried out in larger scales. Thus, the ferration of methyl 3-fluorobenzoate (**76**) using $TMP_2Fe·2MgCl_2·4LiCl$ (**74**; 0.75 equiv) is also finished within 3 h at 25 °C. An subsequent alkylation with 1-iodobutane in the presence of 4-fluorostyrene[54] furnishes the alkylated arene **77b** in 83% yield (entry 3). Arenes bearing cyano

groups can also be used for this ferration procedure. Thus, the metalation of 4-fluorobenzonitrile (**78**) is readily finished within 18 h at 25 °C using $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**74**; 0.75 equiv). An alkylation with iodocyclohexane in the presence of 4-fluorostyrene[54] furnishes the functionalized benzonitrile **79b** in 69% yield (entry 4).

Furthermore, the lanthanations were investigated. Thus, methyl 3-chlorobenzoate (**80**) is converted into the fully lanthanated species within 3.5 h at 0 °C using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**75**; 0.35 equiv). The subsequent additions to electrophiles bearing carbonyl groups like cyclohexane carbaldehyde or benzoyl chloride furnish the lactone **81** in 73% yield (entry 5). Furthermore, the metalation of benzothiazole (**82**) is finished after 30 min at 0 °C using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**77**; 0.35 equiv) and the reaction of the metalated species with α-tetralone leads to the tertiary alcohol **83** in 87% yield (entry 6).

Table 7: Metalation of aromatics and heteroaromatics **76**-**82** using bases **73**-**75**.

Entry	Substrate	Base	Electrophile	Product	Yield [%][a]
1	 **76**	TMP_2Mn (**73**)		 **77a**	90[b]
2	 **78**	TMP_2Mn (**73**)		 **79a**	68[c]
3	 **76**	TMP_2Fe (**74**)		 **77b**	83[d]
4	 **78**	TMP_2Fe (**74**)		 **79b**	69[d]

5	 **80**	TMP_3La (**75**)		 **81**	73
6	 **82**	TMP_3La (**75**)		 **83**	87

[a] Yield of analytically pure product; [b] 5 mol% CuCN·2LiCl was used [c]; 20mol% CuCN·2 LiCl was used; [d] 10 mol% fluorostyrene was used.

4. Selective Magnesiation or Zincation of Highly Functionalized Alkenes and Cycloalkenes using TMP Bases

4.1. Introduction

The preparation of substituted aromatics and heterocycles is of great importance due to the potential biological activity of such structures, which are present in many pharmaceuticals or agrochemicals.[56] Their functionalization has often been achieved by directed metalation using various bases.[57] Mg and Zn TMP-bases complexed with lithium chloride such as TMPMgCl·LiCl (**6**)[22], TMP_2Mg·2LiCl (**7**)[23], TMPZnCl·LiCl (**9**)[26] and TMP_2Zn·2$MgCl_2$·2LiCl (**8**)[25] have proven to be especially versatile metalating agents. In contrast to aromatics and heteroaromatics, the directed deprotonation of functionalized *non-aromatic and olefinic* systems is more difficult and sensitive functions such as a nitro- or a trifluoroacetyl-group are usually not tolerated. Furthermore, an ester or a nitrile substituent in alkenes requires lithiation temperatures between -113 and -95 °C.[58]

4.2. Results and Discussion

The kinetically very active TMP-bases **6-9** allow a smooth metalation of various substituted olefins of type **84** under practical reaction conditions leading to highly functionalized unsaturated organometallics of type **85** (Scheme 34). Their quenching with various electrophiles provides polyfunctional alkenes of type **86-88** with high chemoselectivity. Remarkably, this method allows for the first time to prepare α-zincated nitroolefins (**85**: $FG^1 = NO_2$; MetX = ZnCl) and β-zincated trifluoromethyl ketones (**85**: $FG^2 = COCF_3$; $FG^1 = NMe_2$; MetX = ZnCl) (Scheme 34).

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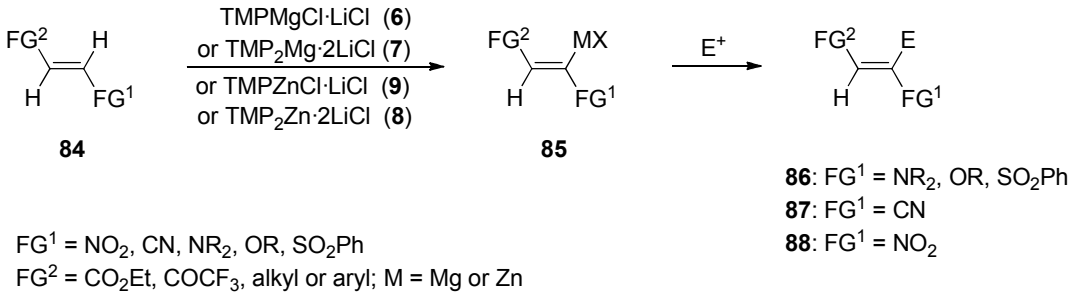
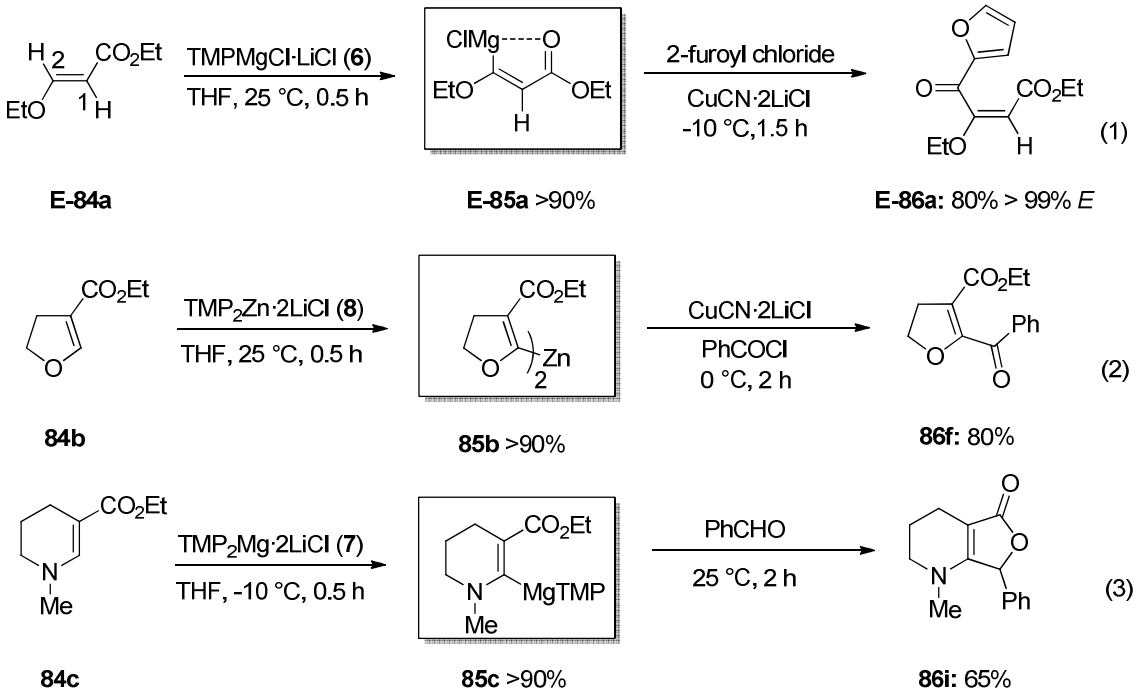
[56] (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles* **1995**, Thieme, Stuttgart. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
[57] (a) Kondo, Y.; Shilai, H.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otami, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514. (c) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (d) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921. (e) Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E.; O'Hara, C. T.; Russo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 731. (f) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102.
[58] Schmidt, T.; Talbiersky, J.; Russegger, P. *Tetrahedron Lett.* **1979**, 4273.



Scheme 34: Chemoselective metalation of functionalized alkenes.

Also, the zincation or magnesiation of various unsaturated esters can now be carried out under practical conditions (between -30 °C and 25 °C). Thus, the reaction of ethyl (2*E*)-3-ethoxyacrylate (***E*-84a**) with TMPMgCl·LiCl (**6**; 1.2 equiv, THF, 25 °C, 0.5 h) leads to a highly regioselective magnesiation at position 2 affording the magnesium reagent ***E*-85a** (>90%, eq. 1, Scheme 35). Its copper-mediated acylation[33] with 2-furoyl chloride (2 equiv) provides stereoselectively the *E*-ketoester (***E*-86a**) in 80% yield. Similarly, the functionalized magnesium reagent ***E*-85a** was acylated with pivaloyl chloride and morpholine-4-carbonyl chloride leading to the *E*-1,4-dicarbonyl compounds ***E*-86b-c** in 58-84% (Table 8, entries 1-2).



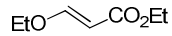
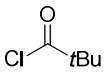
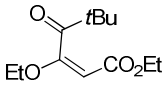
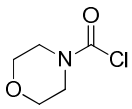
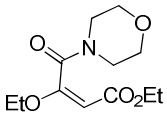
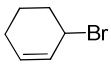
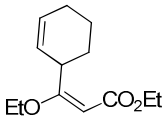
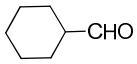
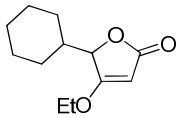
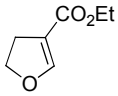
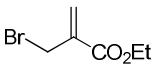
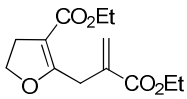
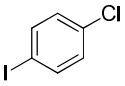
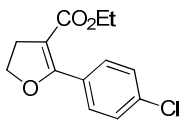
Scheme 35: *β*-Metalation of unsaturated esters using TMP-bases **6**, **7** and **8** and subsequent functionalization with electrophiles.

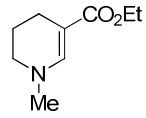
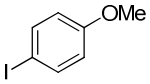
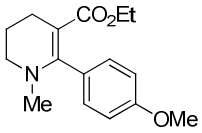
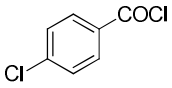
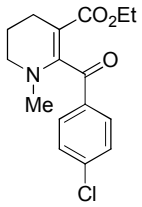
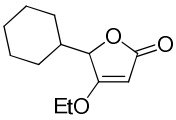
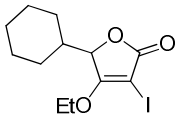
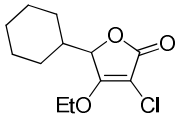
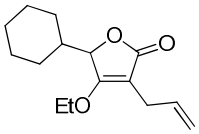
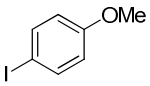
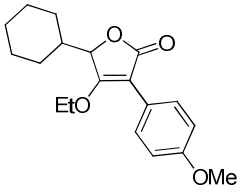
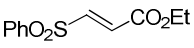
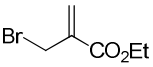
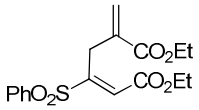
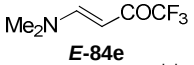
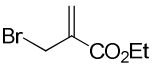
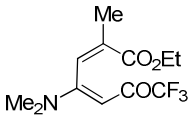
Copper-catalyzed allylation[33] of ***E*-85a** with 3-bromocyclohexene or its addition to *c*-HexCHO provides stereoselectively the ester ***E*-86d** (83%; entry 3) and the lactone **86e** (85%; entry 4). The sensitive dihydrofurane **84b**[59] was cleanly metalated with $TMP_2Zn·2LiCl$ (**8**; 0.6 equiv, 25 °C, 0.5 h) affording the diorganozinc **85b** (>90%). A copper-mediated acylation[33] with PhCOCl provides the ketoester **86f** in 80% yield (eq. 2, Scheme 35). The zinc reagent **85b** was also allylated with ethyl (2-bromomethyl)acrylate[46] or underwent a Negishi cross-coupling reaction[34] with 4-chloroiodobenzene (3% $Pd(dba)_2$, 6% $P(2\text{-furyl})_3$, 25 °C, 3 h) leading to the expected dihydrofurans **86g-h** in 55-83% yield (entries 5-6). The related tetrahydropyridine **84c**[60] requires a stronger TMP-base: $TMP_2Mg·2LiCl$ (**7**). This base magnesiates the N-heterocycle **84c** at -10 °C within 0.5 h leading to the magnesium species **85c** (>90%). Its reaction with PhCHO (2 equiv) gives the bicyclic lactone **86i** in 65% yield (eq. 3, Scheme 35). Similarly, an acylation of the copper derivative of **85c**[33] with 4-chlorobenzoyl chloride or a Pd(0)-catalyzed cross-coupling reaction[34] using 4-iodoanisole lead to the new tetrahydropyridines **86j-k** in 50-80% yield (entries

[59] Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis*, **1986**, 1016.
[60] (a) Lamborg, M. R.; Burton, R.M.; Kaplan, N. O. *J. Am. Chem. Soc.* **1957**, *79*, 6173. (b) Wemkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G.; Oishi, T.; Stevens, R. V.; Terashima, M. *J. Org. Chem.* **1968**, *33*, 747.

7-8). A deprotonation of the lactone **86e** using $TMP_2Mg{\cdot}2LiCl$ (**7**; -30 °C, 20 min) gives the corresponding Mg intermediate which was quenched with iodine to give the iodolactone **86l** in 88% yield (entry 9).

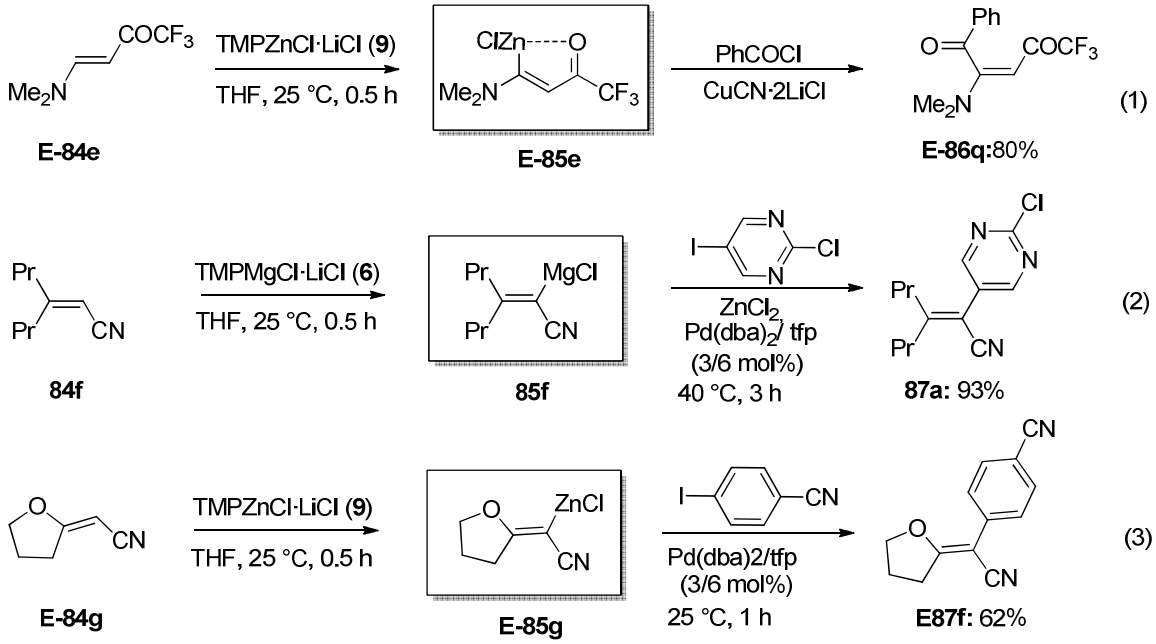
Table 8: *β*-Magnesiation or zincation of unsaturated carbonyl compounds using TMP-bases **7**-**9** and subsequent quenching with electrophiles.

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 ***E*-84a** (25 ℃, 0.5 h) [b,c]		 ***E*-86b**	84[b]
2	***E*-84a**		 ***E*-86c**	58 [b]
3	***E*-84a**		 ***E*-86d**	83[c]
4	***E*-84a**		 **86e**	85
5	 **84b** (25 ℃, 0.5 h) [b,f]		 **86g**	83[c]
6	**84b**		 **86h**	55[d]

7	 **84c** (-10 ℃, 0.5 h) [b,h]		 **86j**	80[d]
8	**84c**		 **86k**	50[b]
9	 **86e** (-30 ℃, 20 min) [b,h]	I_2	 **86l**	88
10	**86e**	$Cl_3F_3C_2$	 **86m**	67
11	**86e**		 **86n**	64[c]
12	**86e**		 **86o**	68[d]
13	 ***E*-84d** (25 ℃, 15 min) [b,i]		 ***E*-86p**	67[c]
14	 ***E*-84e** (25 ℃, 0.5 h) [b,i]		 **86r**	85[c]

[a] Yield of analytically pure product; [b] In the presence of 5 mol% CuCN·2LiCl; [c] The organozinc reagent was transmetalated with CuCN·2 LiCl (1.1 equiv); [d] Obtained after a Pd-catalyzed cross-coupling reaction.

A chlorination of this Mg reagent with $Cl_3F_3C_2$ or a copper-catalyzed allylation with allyl bromide[33] or a Pd-catalyzed Negishi cross-coupling reaction[34] yielded the functionalized lactones **86m-o** in 64-68% (entries 10-12). Ethyl (2*E*)-3-(phenylsulfonyl)acrylate (***E*-84d**)[61] was also smoothly zincated at 25 °C using TMPZnCl·LiCl (**9**; 1.2 equiv, 15 min). The metalation also occurs at the *β*-position affording the corresponding organozinc that undergoes a copper-mediated allylation[33] with ethyl (2-bromomethyl)acrylate[46] furnishing the ester ***E*-86p** in 67% yield (entry 13). Remarkably, TMPZnCl·LiCl (**9**) also allows the *β*-zincation (25 °C, 0.5 h) of (3*E*)-4-(dimethylamino)-1,1,1-trifluorobut-3-en-2-one (***E*-84e**)[62] which bears a sensitive CF_3CO-group. Acylation[33] of the resulting organozinc ***E*-85e** with PhCOCl leads to the expected new functionalized amine ***E*-86q** in 80% yield (eq. 1, Scheme 36). An allylation of intermediate ***E*-85e** leads after double bond isomerisation during chromatographic purification to the dienic trifluoromethyl ketone **86r** (85%, entry 14). Alkenylmagnesium compounds of type **85**, which bear an electron-withdrawing group like a nitrile[63], were previously prepared by a Br/Mg-exchange using *i*PrMgCl·LiCl starting from an *α*-bromonitrile.[64]

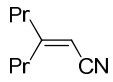
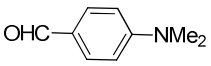
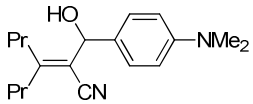
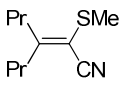


Scheme 36: Metalation of an unsaturated trifluoromethyl ketone and nitriles using TMP-bases **6** and **9** and subsequent functionalization.

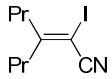
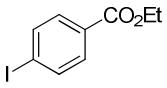
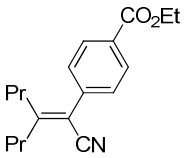
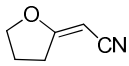
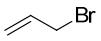
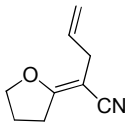
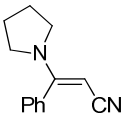
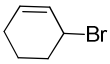
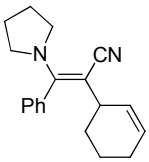
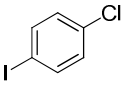
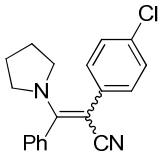
[61] Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Eur. J. Org. Chem.* **1999**, 937.
[62] Guan, Z.-H.; Zuo, W.; Zhao, L.-B.; Ren, Z.-H.; Liang, Y. M. *Synthesis* **2007**, 1465.
[63] Fleming, F. F.; Qunzhao, W.; *Chem. Rev.* **2003**, *103*, 2035.
[64] Thibonnet, J.; Anh Vu, V.; Bérillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787.

Remarkably, using TMPMgCl·LiCl (**9**; 1.2 equiv), the unsaturated nitrile **84f**[65] was directly metalated (25 °C, 0.5 h) leading to the magnesium reagent **85f** (>90%) that undergoes a Pd(0)-catalyzed cross-coupling with 2-chloro-5-iodopyrimidine[34] giving the unsaturated nitrile **87a** in 93% yield (eq. 2, Scheme 36). The magnesium reagent **85f** was also trapped with 4-(dimethylamino)benzaldehyde, $MeSSO_2Me$, iodine or submitted to a Negishi cross-coupling[34] providing the new functionalized unsaturated nitriles **87b-e** in 68-94% yield (entries 1-4, Table 9). For the dihydrofuran acetonitrile ***E*-84g**,[66] TMPZnCl·LiCl (**9**; 1.2 equiv) leads to a stereoselective zincation (25 °C, 0.5 h) affording the alkenylzinc ***E*-85g** that undergoes a Pd-catalyzed cross-coupling with 4-iodobenzonitrile[34] yielding the dinitrile ***E*-87f** in 62% yield (eq. 3, Scheme 36). The zinc reagent ***E*-85g** is remarkably stable with respect to *β*-elimination. It reacts with allyl bromide giving ***E*-87g** in 67% yield (entry 5). Also, the pyrrolidyl acrylonitrile (***E*-84h**)[67] was easily magnesiated with TMPMgCl·LiCl (**6**; 1.2 equiv, 25 °C, 1.5 h) providing the Mg species which was allylated with 3-bromocyclohexene in the presence of 5% $CuCN \cdot 2LiCl$[33] giving the aminonitrile ***Z*-87h** in 63% yield (entry 6). Pd-catalyzed cross-coupling of the Mg-compound with 4-chloro-iodobenzene[34] generates the nitrile **87i** as *E*/*Z* mixture (88%, entry 7).

Table 9: *α*-Metalation of unsaturated nitriles using TMP-bases **6** and **9** and subsequent functionalization with electrophiles.

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **84f** (25 °C, 0.5 h) [b,c]		 **87b**	68
2	**84f**	$MeSSO_2Me$	 **87c**	70

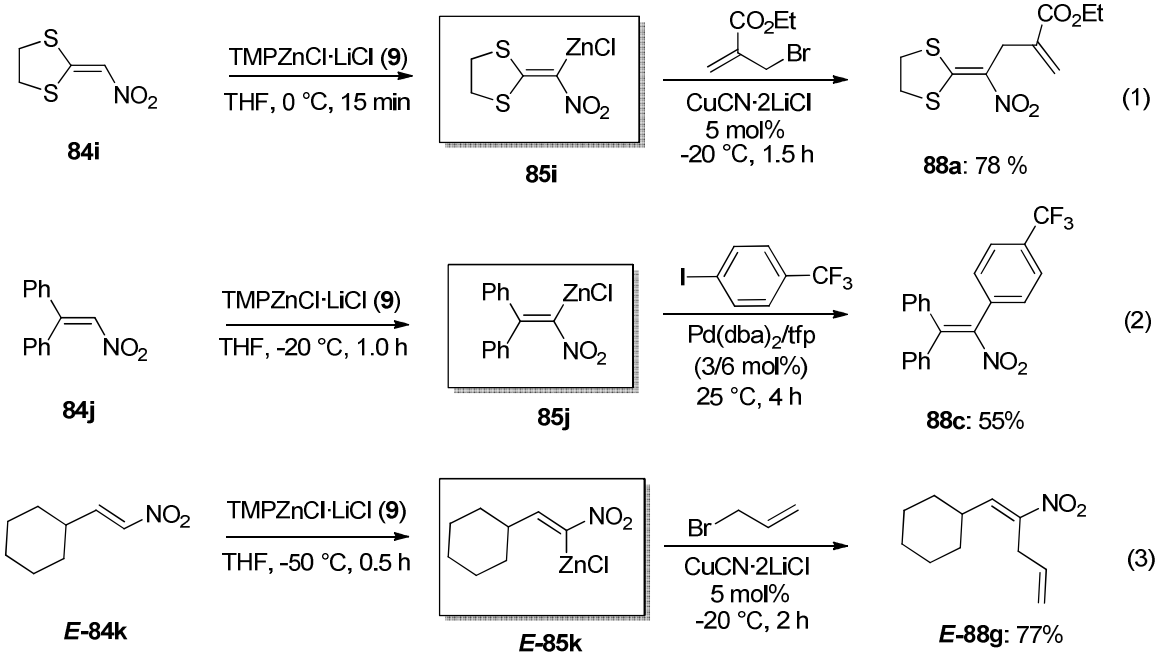
[65] DiBiase, S. A. ; Lipisko, B. A. ; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.
[66] Langer, P.; Holtz, E.; Karimé, I.; Saleh, N. N. R. *J. Org. Chem.* **2001**, *66*, 6057.
[67] Cartaya-Marin, C. P.; Henderson, D. G.; Soeder, R. W. *Synth. Commun.* **1997**, 27, 4275.

3	**84f**	I_2	 **87d**	94
4	**84f**		 **87e**	80[b]
5	 ***E*-84g** (25 °C, 0.5 h) [b,e]		 ***E*-87g**	67[c]
6	 ***E*-84h** (25 °C, 1.5 h) [b,c]		 ***Z*-87h**	63[c]
7	***E*-84h**		 ***87*i** (*E*/*Z* = 50:50)	88[b]

[a] Yield of analytically pure product; [b] The organozinc reagent was transmetalated with CuCN·2 LiCl (1.1 equiv); [c] 5 mol% CuCN·2 LiCl were added; [d] Obtained after a Pd-catalyzed cross-coupling reaction.

α-Metalated nitroolefins are elusive intermediates and their preparation has not been reported.[68] This metalation can be achieved using TMPZnCl·LiCl (**9**) (Scheme 37).

[68] (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. (b) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (c) Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95. (d) Kamimura, A.; Ono, N. *Tetrahedron. Lett.* **1989**, *30*, 731.



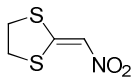
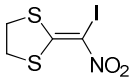
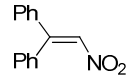
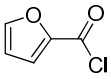
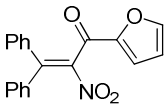
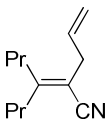
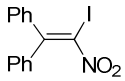
Scheme 37: α-Metalation of unsaturated nitroolefins using TMPZnCl·LiCl (**9**) and subsequent functionalization with electrophiles.

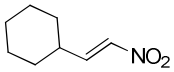
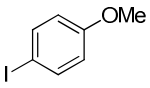
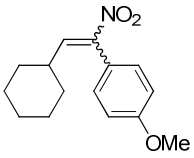
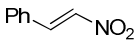
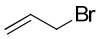
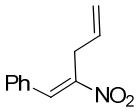
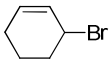
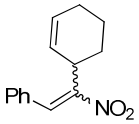
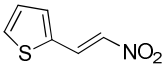
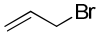
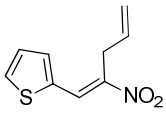
Thus, the dithiolane nitroolefin (**84i**)[69] is smoothly zincated using TMPZnCl·LiCl (**9**; 1.2 equiv) at 0 °C within 15 min providing the α-zincated nitroolefin **85i** (>95%) which was allylated with ethyl (2-bromomethyl)acrylate[46] affording the nitroolefin **88a** in 78% yield (eq. 1, Scheme 37). The zinc species **85i** was also iodinated and the resulting tetrasubstituted alkene **88b** was isolated in 89% yield (entry 1, Table 10). Remarkably, the diphenylnitroolefin (**84j**)[70] can be converted into the alkenylzinc **85j** using TMPZnCl·LiCl (**9**; 1.2 equiv, -20 °C, 1.0 h). This zinc reagent underwent a Pd-catalyzed cross-coupling with 4-iodo(trifluoromethyl)benzene[34] giving the triarylated nitroalkene **88c** in 55% yield (eq. 2, Scheme 37). Additionally, the zincated nitroolefin was quenched with 2-furoyl chloride, allyl bromide or iodine providing the corresponding nitroolefins **88d-f** in 55-70% yield (entries 2-4). Similarly, 2-cyclohexylnitroethylene (***E*-84k**)[71] is zincated with TMPZnCl·LiCl (**9**; 1.2 equiv, -50 °C, 0.5 h) leading to the zinc species ***E*-85k**, which was trapped with allyl bromide[33] to give the α-functionalized nitroolefin ***E*-88g** in 77% yield (eq. 3, Scheme 37). Furthermore, the zincated nitroolefin ***E*-85k** underwent a Pd(0)-

[69] Shibuya, I.; Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Katoh, E. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3048.
[70] Hsieh, T. H. H.; Dong, V. M. *Tetrahedron* **2009**, *65*, 3062.
[71] Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438.

catalyzed cross-coupling[34] with ethyl 4-iodobenzoate leading to the nitro derivative **88h** (57% yield, *E*/*Z* = 80:20, entry 5). Likewise, *β-trans*-nitrostyrene (***E*-84l**) reacts with the zinc base (**9**; 1.2 equiv, -50 °C, 1.0 h) and the resulting alkenylzinc reagent undergoes a copper-mediated allylation[33] with allyl bromide giving ***E*-88i** as one isomer in 70% yield (entry 6). However, trapping the zincated nitrostyrene ***E*-85l** with 3-bromocyclohexene leads to the allylated product **88j** in a 60:40 mixture of isomers (49%, entry 7). Finally, 2-[(*E*)-2-nitrovinyl]thiophene (***E*-84m**)[71] is metalated in *α*-position to the nitro group with TMPZnCl·LiCl (**9**; 1.2 equiv, 0.5 h, –50 °C) and the resulting zinc species is trapped with allyl bromide giving the new substituted olefin ***E*-88k** in 72% yield (entry 8).

Table 10: *α*-Metalation of unsaturated nitroolefins using TMPZnCl·LiCl (**9**) and subsequent functionalization with electrophiles

Entry	Substrate	Electrophile	Product	Yield [%][a]
1	 **84i** (0 °C, 15 min) [b,c]	I_2	 **88b**	89
2	 **84j** (-20°C, 1.0 h) [b,c]		 **88d**	55[b]
3	**84j**		 **88e**	70[c]
4	**84j**	I_2	 **88f**	70

5	 ***E*-84k** (-50°C, 0.5 h) [b,c]		 **88h:** *E*/*Z* = 80:20	57[d]
6	 ***E*-84l** (-50°C, 1.0 h) [b,c]		 ***E*-88i**	70[c]
7	***E*-84l**		 ***E*-88j** (E/Z = 60:40)	49[c]
8	 ***E*-84m** (-50°C, 0.5 h) [b,c]		 ***E*-88k**	72[c]

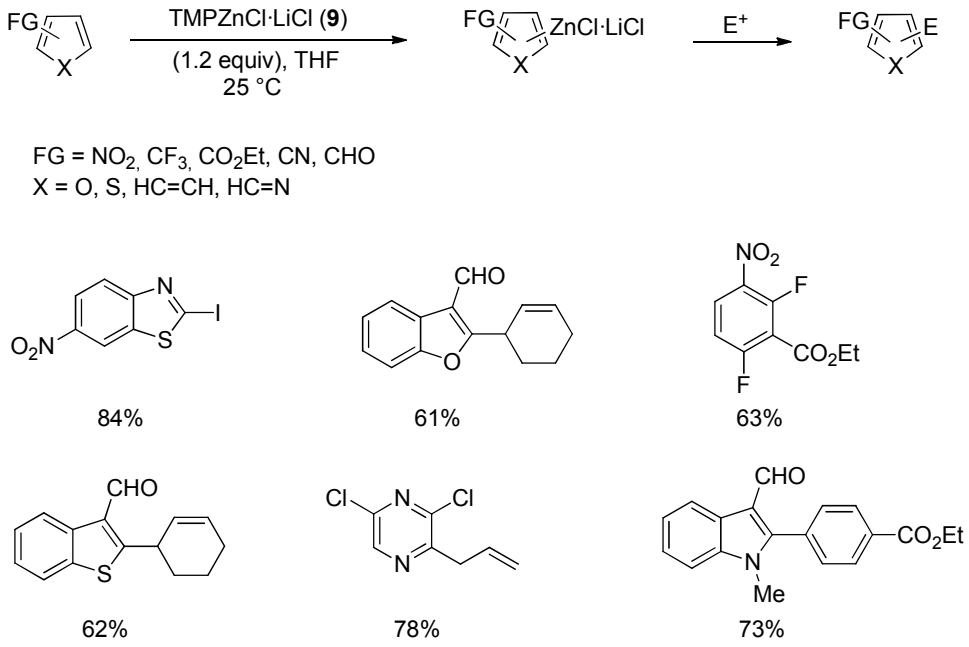
[a] Yield of analytically pure product; [b] The organozinc reagent was transmetalated with CuCN·2LiCl (1.1 equiv); [c] 5 mol% CuCN·2 LiCl were added; [d] Obtained after a Pd-catalyzed cross-coupling reaction.

5 Summary and Outlook

This work was focused on the formation of highly substituted organometallics through directed metalation using hindered TMP-bases. Different aromatics, heteroaromatics and alkenes were successfully functionalized using this method. Furthermore, an application to the total synthesis of the bioluminescent natural product Coelenterazine (isolated from jellyfish) was performed.

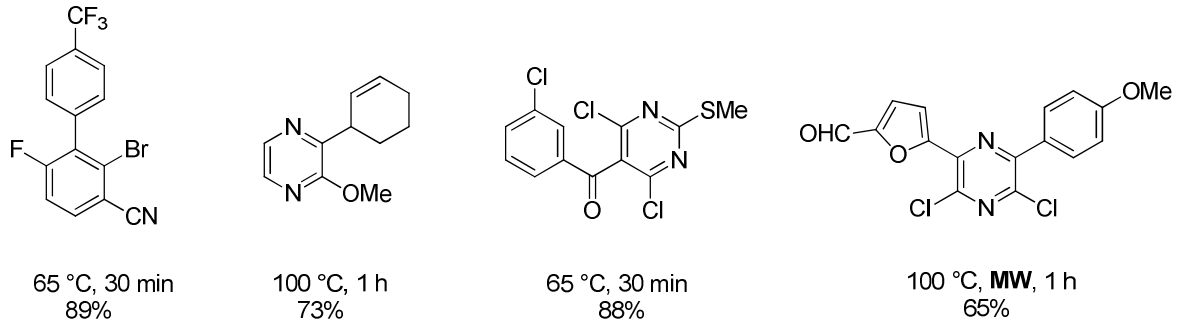
5.1. Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl·LiCl

In summary it was reported that aromatic and heterocyclic substrates, bearing electron-withdrawing groups or several heterocyclic nitrogen atoms, undergo smooth and selective zincations at room temperature using TMPZnCl·LiCl (**9**) (Scheme 38).



Scheme 38: Zincation and functionalization of sensitive aromatics and heteroaromatics using TMPZnCl·LiCl (**9**) at 25 °C.

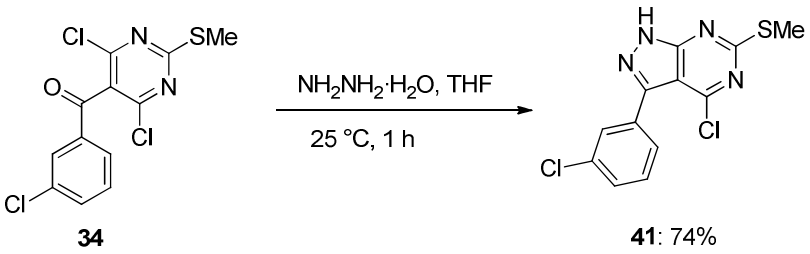
On the other hand, the metalation of moderately activated arenes and heteroarenes occurs only on conventional heating (65-100 °C) or microwave irradiation, allowing a regio- and chemoselective zincation in excellent yields. Remarkably, sensitive functionalities like an ester or a nitrile are tolerated at these high temperatures (Scheme 39).



without heating or microwave: max. 60 % conversion

Scheme 39: Zincation of moderately activated aromatics and heteroaromatics using TMPZnCl·LiCl (**9**) and conventional heating or microwave irradiation.

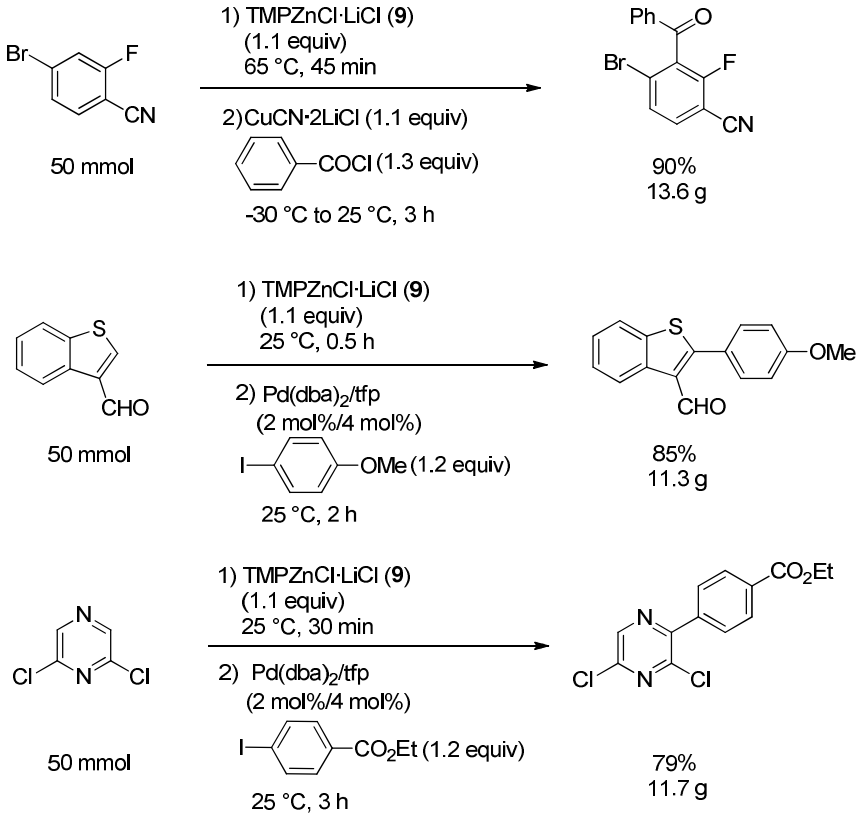
As a further reaction, a ring closure was performed starting from the new functionalized pyrimidine **34** by treatment with hydrazine in THF at 25°C for 1 h. The formed pyrazolopyrimidine **41** was isolated in 74% yield (Scheme 40).



34 **41**: 74%

Scheme 40: Ringclosure of dichloropyrimidine **34** using hydrazine.

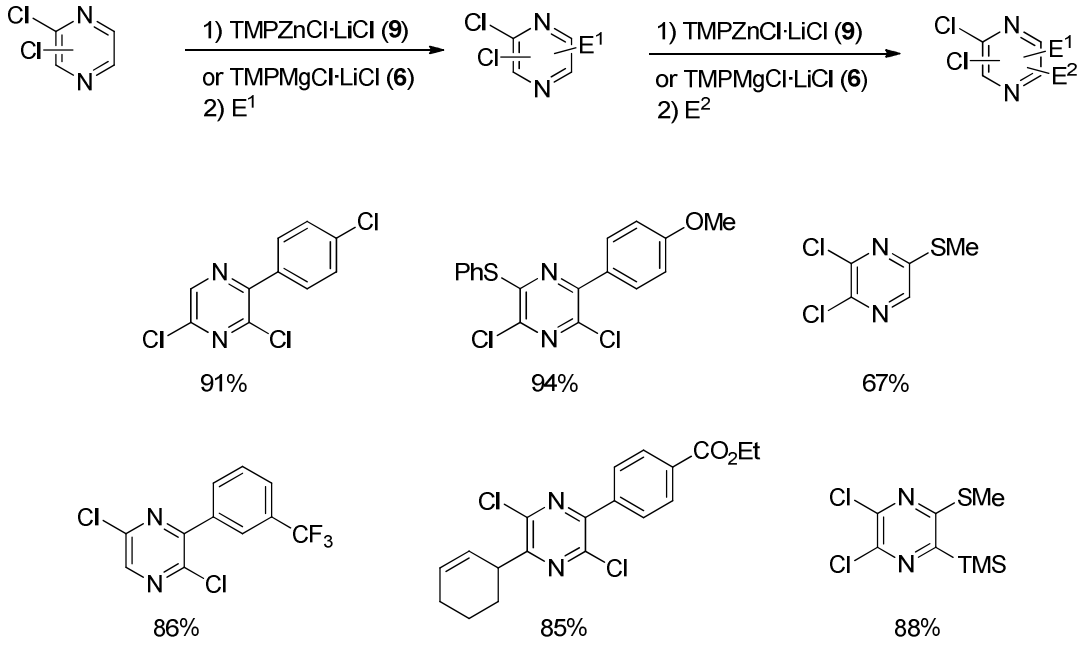
It was also demonstrated that regioselective zincations of highly sensitive arenes and heteroaromatics using the mild base TMPZnCl·LiCl (**9**) can safely be carried out on multigram scales with yields comparable to small scales conversions, tolerating sensitive functions like an aldehyde, a nitro group, an ester or a nitrile (Scheme 41).



Scheme 41: Large scale zincations of aromatics and heteroaromatics using TMPZnCl·LiCl (**9**) and subsequent reactions with electrophiles.

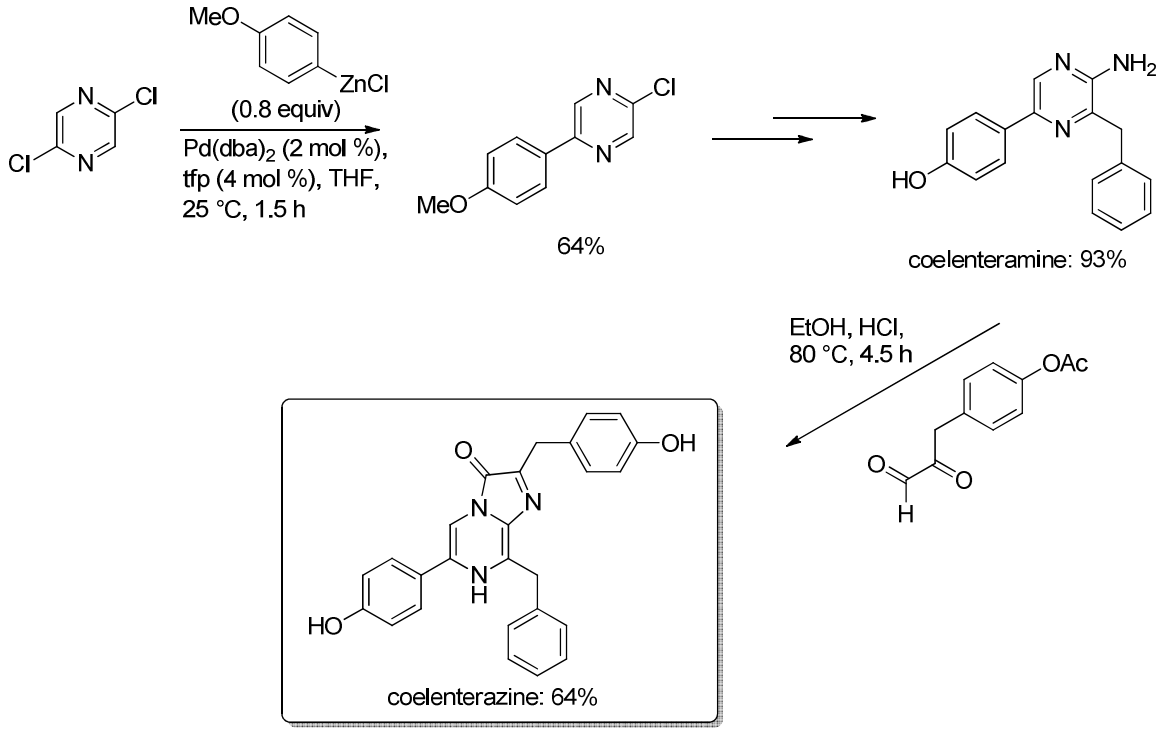
5.2. Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the synthesis of Coelenterazine

The multiple functionalization of the pyrazine scaffold using TMPMgCl·LiCl (**6**) and TMPZnCl·LiCl (**9**) as effective bases was also described (Scheme 42).



Scheme 42: Successive metalations of chloropyrazine derivatives using TMPMgCl·LiCl (**6**) TMPZnCl·LiCl (**9**) and functionalization with electrophiles.

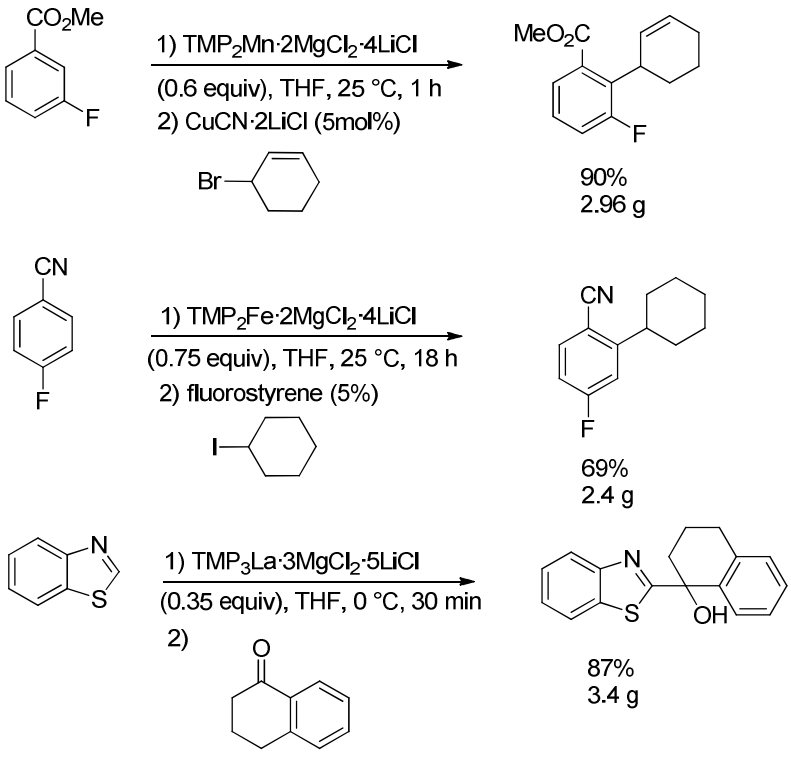
A nine step synthesis of the natural product coelenterazine was also reported (Scheme 43).



Scheme 43: Synthesis of coelenterazine.

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

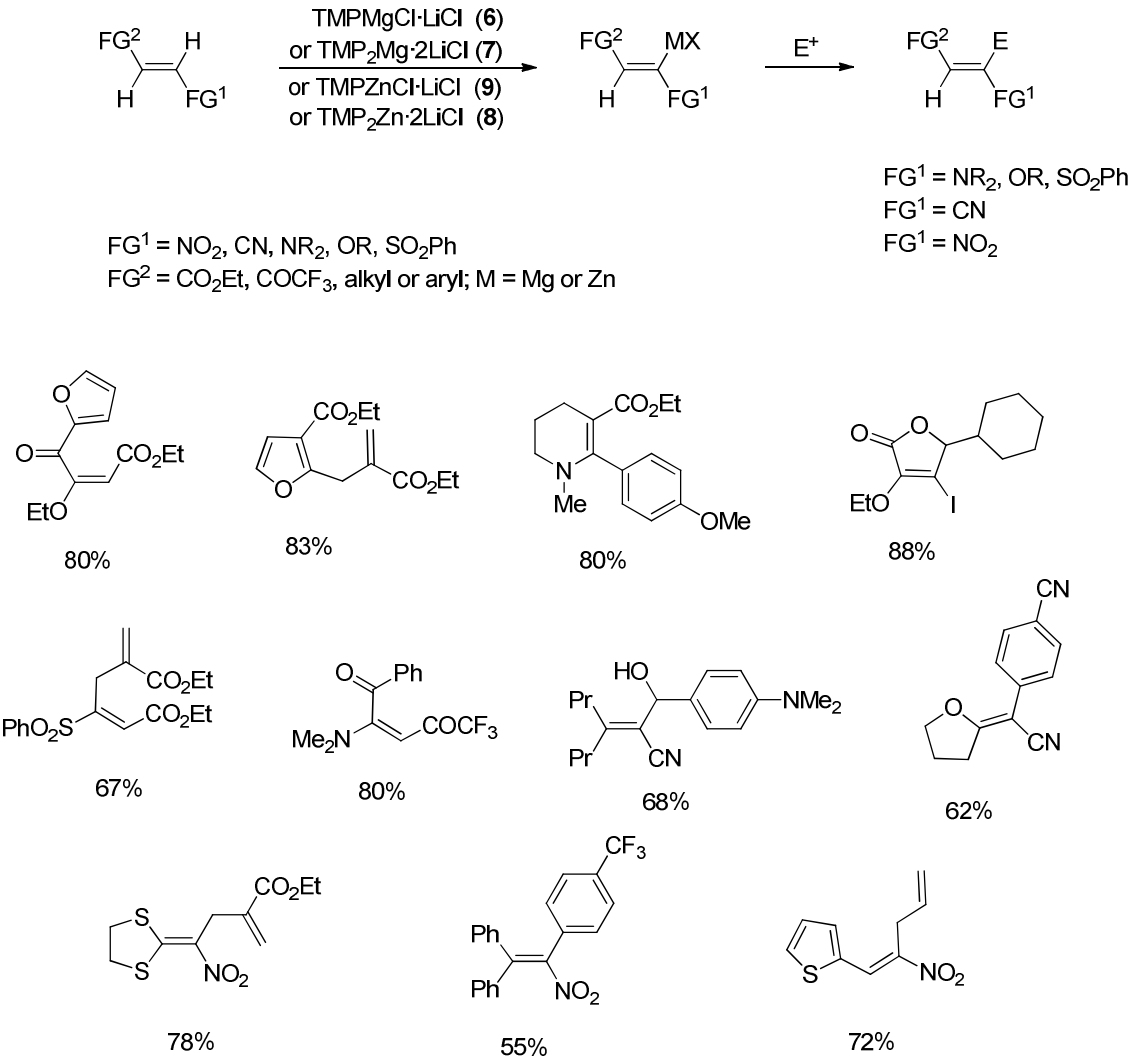
It was also demonstrated that the use of the bases $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**73**), $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**74**), $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**75**) leads smoothly to the corresponding organometallics. The reactions are carried out in larger scales and important functional groups like esters or cyano groups can be easily tolerated during the metalation protocols. Efficient and atom economical reactions with electrophiles provide the desired products in good to excellent yields (Scheme 44).



Scheme 44: Efficient metalation of aromatics and heteroaromatics using TMP-bases of Mn, Fe and La and subsequent functionalization with electrophiles.

5.4. Selective Magnesiation or Zincation of Highly Functionalized Alkenes and Cycloalkenes using TMP Bases

It was also shown that the kinetically highly active bases **6-9** allow a smooth magnesiation or zincation of several new classes of highly functionalized olefins. Especially, new *β*-zincated unsaturated trifluoromethyl ketones and *α*-zincated nitroolefins have been prepared and successfully reacted with electrophiles (Scheme 45).



Scheme 45: Chemoselective metalation of functionalized alkenes.

C. EXPERIMENTAL SECTION

1. General Considerations

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

1.1. Solvents

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

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

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

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

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

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

Pyridine was dried over KOH and distilled

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

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

Triethylamine was dried over KOH and distilled.

Solvents for column chromatography were distilled prior to use.

1.2. Reagents

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

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

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

TMPMgCl·LiCl was prepared according to a literature procedure (ref. 22).

TMPZn·LiCl was prepared according to a literature procedure (ref. 26).

$TMP_2Zn·2MgCl_2·2LiCl$ was prepared according to a literature procedure (ref. 25).

$TMP_2Mg·2LiCl$ was prepared according to a literature procedure (ref. 23).

$TMP_3La·3MgCl_2·5LiCl$ was prepared according to a literature procedure (ref. 55).

$TMP_2Mn·2MgCl_2·4LiCl$ was prepared according to a literature procedure (ref. 53).

$TMP_2Fe·2MgCl_2·4LiCl$ was prepared according to a literature procedure (ref. 54).

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a *Schlenk*-tube under vacuum at 140 °C for 5 h. After cooling, 80 mL of dry THF were added and stirring was continued until the salts were dissolved.

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (100 mmol, 136 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL of dry THF were added and stirring was continued until the salt was dissolved.

$MnCl_2·2LiCl$ solution (1.00 M) was prepared by drying LiCl (6.8 g, 160 mmol) in a *Schlenk*-flask at 150 °C under high vacuum for 3 h. After cooling to room temperature under argon, $MnCl_2$ (10.1 g, 80 mmol, 99% pure) was added under inert atmosphere inside a glove-box. The Schlenk-flask was further heated to 130 °C for 3 h under high vacuum, cooled to room temperature, charged with freshly distilled THF (80 mL) under argon with vigorous stirring. The mixture was stirred for at least 24 h at 25 °C. The reagent $MnCl_2·2LiCl$ (1.0 M in THF) appears as a yellow solution.

$FeCl_2·2LiCl$ solution (1.00 M) was prepared by drying LiCl (4.7 g, 110 mmol)) in a *Schlenk*-flask at 150 °C under high vacuum for 3 h. After cooling to room temperature under argon, $FeCl_2$ (6.34 g, 50 mmol, 98% pure) was added under inert atmosphere inside a glove-box. The Schlenk-flask was further heated to 130 °C for 5 h under high vacuum, cooled to room temperature, charged with freshly distilled THF (50 mL) under argon and wrapped in aluminium foil to protect it from light. The mixture was vigorously stirred until all solid goes in solution (ca. 6 h). The reagent $FeCl_2·2LiCl$ (1.0 M in THF) appears as a brown solution.

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1.3. Content determination of organometallic reagents

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

Organolithium reagents were titrated with menthol against 1,10-phenanthroline in THF.

TMPMgCl·LiCl, **TMPZnCl·LiCl**, **$TMP_2Mg·2LiCl$**, **$TMP_2Zn·2MgCl_2·2LiCl$**, **$TMP_3La·3MgCl_2·5LiCl$**, **$TMP_2Mn·2MgCl_2·4LiCl$** and **$TMP_2Fe·2MgCl_2·4LiCl$** were titrated with benzoic acid against 4-(phenylazo)diphenylamine in THF.

1.4. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.

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

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

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

1.5. Analytical data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H: 7.25, δ_C: 77.0). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad). The stereochemistry of new compounds was determined by 2D-NMR experiments (NOESY, COESY, HSQC, HMBC).

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

For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1})

Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

2. Typical Procedures (TP)

2.1. Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with TMPZnCl·LiCl (9) at 25 °C (TP1):

A dry and argon flushed flask, equipped with a magnetic stirring bar was charged with a solution of the corresponding arene or heteroarene (1.0 mmol) in dry THF (1-2 mL). The zinc base (1.1 mmol) was added and the reaction mixture was stirred at 25 °C for the indicated times. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. The subsequent reactions with electrophiles were carried out with the indicated conditions.

2.2. Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with TMPZnCl·LiCl (9) using conventional heating or microwave irradation (TP2):

A 10-mL pressurized vial, equipped with a magnetic stirring bar was charged with a solution of the corresponding arene or heteroarene (1.0 mmol) in dry THF (1-2 mL). The zinc base (1.1 mmol) was added and the reaction mixture was heated at the corresponding temperatures by using an oil bath or by using a Discover BenchMate Microwave system under the indicated conditions. After setting up the desired reaction conditions, the reaction mixture temperatures were displayed on the microwave screen during irradiation. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. The subsequent reactions with electrophiles were carried out with the indicated conditions.

2.3. Typical procedure for the metalation of polyfunctionalized heterocycles with TMPMgCl·LiCl (6) or TMPZnCl·LiCl (9) (TP3):

A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with a solution of the corresponding arene or heteroarene (1.0 mmol) in dry THF. After setting the desired temperature, the magnesium base (**6**; 1.1 equiv) or the zinc base (**9**; 1.1 equiv) was dropwise added and stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

2.4. Typical procedure for the manganation of functionalized aromatics and heteroaromatics using $TMP_2Mn·2MgCl_2·4LiCl$ (73) (TP4):

In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material was dissolved in THF (1 mL per mmol). This solution was brought to the given temperature, then $TMP_2Mn·2MgCl_2·4LiCl$ (**73**; 0.5 M in THF, 2.4 mL, 2.4 mmol) was added dropwise and stirred at this temperature for the indicated time. Complete metalation was monitored by GC-analysis of reaction aliquots which were quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

2.5. Typical procedure for the ferration of functionalized aromatics using $TMP_2Fe·2MgCl_2·4LiCl$ (74) (TP5):

In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material was dissolved in THF (1 mL per mmol). Then $TMP_2Fe·2MgCl_2·4LiCl$ (**74**; 0.5 M in THF, 3.0 mL, 3.0 mmol) was added dropwise at 25 °C and stirred at this temperature for the indicated time. The metalation progress was monitored by GC-analysis of reaction aliquots which were quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

2.6. Typical procedure for the lanthanation of functionalized aromatics and heteroaromatics using $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (75) (TP6):

In a dry argon-flushed 100 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum the given starting material was dissolved in THF (1 mL per mmol). This solution was brought to the given temperature, then $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**75**) (0.33 M in THF, 2.2 mL, 0.72 mmol) was added dropwise and stirred at this temperature for the indicated time. The metalation progress was monitored by GC-analysis of reaction aliquots which were quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF using tetradecane as internal standard.

2.7. Typical Procedure for the metalation of substituted vinylic substrates with 6-9 (TP7):

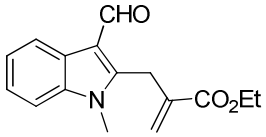
A dry and argon flushed flask, equipped with a magnetic stirring bar and a rubber septum was charged with a solution of the corresponding olefin (1.0-3.0 mmol) in dry THF (1-3 mL). The base (1.2 equiv) was added dropwise at the indicated temperature and the reaction mixture was stirred for the indicated times. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of 3 drops of CuCN·2LiCl (1 M in THF) and 5 drops allyl bromide in 0.5 mL THF. The subsequent reactions with electrophiles were carried out under the indicated conditions.

3. Preparation of Products

3.1. Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl·LiCl

3.1.1. Metalations of Sensitive Substrates using TMPZnCl·LiCl (9) at 25 °C

Ethyl 2-[(3-formyl-1-methyl-1*H*-indol-2-yl)methyl]acrylate (14):



To a solution of 1-methylindole-3-carboxyaldehyde (**10**) (159 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP1**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 5 min of stirring at the same temperature, the mixture was cooled to -60 °C and ethyl 2-(bromomethyl)acrylate (290 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm up slowly to -20 °C within 2 h. The reaction 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 (Et_2O/pentane 3:7) furnished the compound **14** (179 mg, 66 %) as a yellowish solid.

mp: 121.3 – 123.0 °C.

1H-NMR (CDCl3, 300 MHz) δ: 10.12 (s, 1H), 8.30 – 8.26 (m, 1 H), 7.35 – 7.38 (m, 3 H), 6.31 (s, 1 H), 5.24 (s, 1 H), 4.30 – 4.32 (q, *J* = 7.0 Hz, 2 H), 4.12 (s, 2 H), 3.66 – 3.65 (m, 3 H), 1.33 (t, *J* = 7.0 Hz, 3 H).

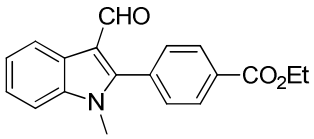
13C-NMR (CDCl3, 75 MHz) δ: 184.1, 166.0, 146.9, 137.2, 136.7, 126.9, 125.6, 123.5, 123.0, 121.1, 115.0, 109.5, 61.4, 29.9, 26.5, 14.2.

MS (70 eV, EI) m/z (%): 271 [M^+] (78), 255 (60), 196 (14).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2980, 1912, 1720, 1707, 1631, 1608, 1579, 1533, 1472, 1442, 1420, 1395, 1374, 1328, 1252, 1202, 1186, 1174, 1137, 1095, 1043, 1018, 968, 948, 911, 868, 854, 815, 782, 765, 757, 750, 730, 668, 658.

HRMS (ESI) Calcd for $C_{16}H_{17}NO_3$, 271.1208; Found, 271.1282.

Ethyl 4-(3-formyl-1-methyl-1*H*-indol-2-yl)benzoate (15):



To a solution of 1-methylindole-3-carboxyaldehyde (**10**) (159 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP1**. $Pd(dba)_2$ (17 mg, 3 mol%), $P(2\text{-furyl})_3$ (14 mg, 6 mol%) and mixed with ethyl 4-iodobenzoate (360 mg, 1.3 mmol) were then added via cannula and the resulting mixture was stirred at 25 °C for 3 h. The reaction 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 (Et_2O/pentane 1:1) furnished the compound **15** (224 mg, 73%) as a colourless solid.

mp: 162.0 – 163.8 °C.

1H-NMR (CDCl3, 300 MHz) δ: 9.72 (s, 1 H), 8.43 – 8.41 (m, 1 H), 8.22 (d, *J* = 8.3 Hz, 2 H), 7.57 (d, *J* = 6.8 Hz, 2 H), 7.41 – 7.32 (m, 3 H), 4.44 (q, d, *J* = 7.3 Hz, 2 H), 3.68 – 3.66 8m, 3 H), 1.43 (t, d, *J* = 7.1 Hz, 3 H).

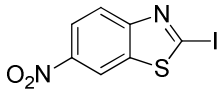
13C-NMR (CDCl3, 75 MHz) δ: 186.0, 165.8, 149.8, 137.5, 133.0, 131.8, 130.9, 129.7, 125.1, 124.4, 123.5, 122.3, 116.0, 109.8.

MS (70 eV, EI) m/z (%): 307 [M^+] (100), 278 (49), 255 (24), 233 (14), 157 (8).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2978, 2926, 2803, 2768, 2730, 1711, 1649, 1608, 1577, 1568, 1537, 1493, 1466, 1442, 1416, 1372, 1326, 1312, 1278, 1182, 1156, 1127, 1106, 1071, 1029, 1018, 991, 951, 883, 861, 848, 812, 759, 741, 710, 693, 628, 613.

HRMS (ESI) Calcd for $C_{19}H_{17}NO_3$, 307.1208; Found, 307.1281.

2-Iodo-6-nitro-1,3-benzothiazole (16):



To a solution of 6-nitro-1,3-benzothiazole (**12**) (159 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture

was stirred for 10 min according to **TP1**. Iodine (381 mg, 1.5 mmol) in 2 mL THF was then added and the mixture was stirred for additional hour. The reaction mixture was then quenched with a sat. aq. $Na_2S_2O_3$ (30 mL) and NH_4Cl solution (10 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 (Et_2O/pentane 1:4) furnished the compound **16** (257 mg, 84 %) as a yellowish solid.

mp: 179.0 – 181.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.80 (dd, *J* = 2.0 Hz, *J* = 0.4 Hz, 1 H), 8.31 (dd, *J* = 6.6 Hz, *J* = 2.3 Hz, 1 H), 8.13 (dd, *J* = 8.4 Hz, *J* = 0.6 Hz, 1 H).

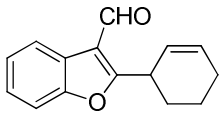
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.5, 145.2, 139.5, 122.8, 121.9, 116.9, 112.1.

MS (70 eV, EI) m/z (%): 306 [M^+] (100), 276 (31), 133 (31), 69 (5).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3104, 3054, 1598, 1567, 1505, 1425, 1398, 1332, 1260, 1232, 1120, 1045, 957, 881, 844, 844, 823, 750, 744, 720, 637.

HRMS (EI) Calcd for $C_7H_3IN_2O_2S$, 305.8960; Found, 305.8920.

2-Cyclohex-2-en-1-yl-1-benzofuran-3-carbaldehyde (18):



To a solution of 1-benzofuran-3-carbaldehyde (**17**) (146 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP1**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 5 min of stirring at the same temperature, the mixture was cooled to -60 °C and 3-bromocyclohexene (242 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm up slowly to -20 °C within 2 h. The reaction 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 (Et_2O/pentane 5:95) furnished the compound **18** (138 mg, 61 %) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.34 (s, 1H), 8.18 – 8.12 (m, 1 H), 7.49 – 7.43 (m, 1 H), 7.35 – 7.29 (m, 2 H), 6.06 – 6.00 (m, 1 H), 5.78 – 5.73 (m, 1 H), 4.18 – 4.10 (m, 1 H), 2.29 – 2.09 (m, 3 H), 2.04 – 1.88 (m, 2 H), 1.81 – 1.67 (m, 1 H).

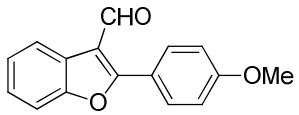
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 185.3, 172.3, 153.8, 130.6, 125.2, 124.5, 12..0, 117.3, 111.0, 35.3, 29.1, 24.5, 21.1.

MS (70 eV, EI) m/z (%): 226 [M^+] (100), 209 (16), 197 (20), 183 (20), 169 (32), 141 (13), 115 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3326, 3060, 3024, 2935, 2859, 2835, 2755, 1786, 1667, 1573, 1478, 1451, 1432, 1402, 1377, 1342, 1278, 1251, 1222, 1180, 1150, 1095, 1060, 1044, 1027, 1010, 952, 925, 892, 872, 857, 814, 799, 741, 724, 652, 632.

HRMS (EI) Calcd for $C_{15}H_{14}O_2$, 226.0994; Found, 226.0982.

2-(4-methoxyphenyl)-1-benzofuran-3-carbaldehyde (19):



To a solution of 1-benzofuran-3-carbaldehyde (**17**) (146 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP1**. $Pd(dba)_2$ (17 mg, 3 mol%), P(2-furyl)$_3$ (14 mg, 6 mol%) and mixed with 4-iodoanisole (304 mg, 1.3 mmol) were then added via cannula and the resulting mixture was stirred at 25 °C overnight. The reaction 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 (Et_2O/pentane 15:85) furnished the compound **19** (164 mg, 65%) as a yellowish solid.

mp: 116.3 – 118.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.31 (s, 1 H), 8.26 – 8.22 (m, 1 H), 7.83 – 7.79 (m, 2 H), 7.55 – 7.49 (m, 1 H), 7.40 – 7.33 (m, 2 H), 7.08 – 7.03 (m, 2 H), 3.89 (s, 3 H).

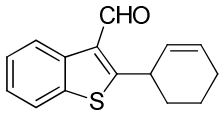
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 186.5, 165.5, 161.2, 152.7, 130.7, 125.6, 124.7, 122.4, 121.0, 116.5, 114.6, 110.9, 55.5.

MS (70 eV, EI) m/z (%): 252 [M^+] (100), 237 (13), 221 (19), 209 (21), 181 (20), 152 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2915, 2822, 2037, 1948, 1651, 1606, 1578, 1501, 1477, 1446, 1399, 1374, 1342, 1309, 1259, 1247, 1176, 1135, 1107, 1075, 1029, 934, 912, 834, 787, 742.

HRMS (EI) Calcd for $C_{15}H_{12}O_3$, 252.0786; Found, 252.0775.

2-Cyclohex-2-en-1-yl-1-benzothiophene-3-carbaldehyde (21)



To a solution of 1-benzothiophene-3-carbaldehyde (**20**) (162 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP1**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 5 min of stirring at the same temperature, the mixture was cooled to -60 °C and 3-bromocyclohexene (242 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm up slowly to -20 °C within 2 h. The reaction 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 (Et_2O/pentane 1:9) furnished the compound **21** (150 mg, 62 %) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.41 (s, 1 H), 8.61 – 8.58 (m, 1 H), 7.78 – 7.75 (m, 1 H), 7.47 – 7.33 (m, 2 H), 6.04 – 5.97 (m, 1 H), 5.84 – 5.79 (m, 1 H), 4.53 – 4.47 (m, 1 H), 2.28 – 2.11 (m, 3 H), 1.92 – 1.65 (m, 3 H).

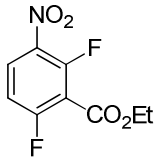
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 184.1, 168.9, 137.6, 137.1, 130.5, 128.9, 127.9, 125.8, 125.0, 124.0, 121.7, 35.5, 33.1, 24.7, 20.9.

MS (70 eV, EI) m/z (%): 242 [M^+] (100), 225 (26), 213 (36), 187 (17), 185 (27), 171 (11), 147 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 3022, 2928, 2855, 2833, 2741, 1663, 1591, 1557, 1509, 1460, 1432, 1398, 1356, 1293, 1260, 1175, 1154, 1145, 1052, 1021, 967, 862, 838, 753, 729.

HRMS (EI) Calcd for $C_{15}H_{14}OS$, 242.0765; Found, 242.0764.

Ethyl 2,6-difluoro-3-nitrobenzoate (23):



To a solution of 2,4-fluoronitrobenzene (**22**) (776 mg, 5.0 mmol) dissolved in THF (5 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 3.9 mL, 5.5 mmol) at 25 °C and the resulting mixture was stirred for 1 h at 25 °C according to **TP1**. $Pd(PPh_3)_3$ (5 mol %, 290 g) dissolved in THF (7 mL) and mixed with ethylchloroformate (1.36 g, 10 mmol) were then added via cannula to the reaction mixture. The resulting mixture was allowed to stirr at 25 °C overnight. The reaction 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 (Et_2O/pentane 15:85) furnished the compound **23** (728 mg, 63 %) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.21 – 8.16 (m, 1H), 7.13 – 7.07 (m, 1H), 4.48 – 4.40 (m, 2H), 1.41 – 1.35 (m, 3H).

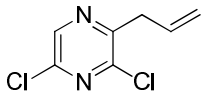
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.6 (dd, *J* = 266.3 Hz, *J* = 5.9 Hz), 159.4, 154.4, (dd, *J* = 274.0 Hz, *J* = 7.7 Hz), 134.2 (m), 129.15 (d, *J* = 12.6 Hz), 114.0 (t, *J* = 20.4 Hz), 112.4 (dd, *J* = 23.7 Hz, *J* = 4.7 Hz), 63.0, 14.0.

MS (70 eV, EI) m/z (%): 231 [M^+] (3), 203 (35), 186 (100), 171 (38), 140 (65), 112 (44), 62 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3104, 2988, 1734, 1624, 1599, 1537, 1474, 1449, 1369, 1351, 1291, 1261, 1221, 1174, 1151, 1128, 1036, 1011, 860, 833, 791, 747, 654, 617.

HRMS (EI) Calcd for $C_9H_7F_2NO_4$, 231.0343; Found, 231.0345.

2-Allyl-3,5-dichloropyrazine (25)



To a solution of 2,6-dichloropyrazine (**24**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min according to **TP1**. After cooling to -30 °C, CuCN·2LiCl (1 M solution in THF, 5 drops) was added and the reaction mixture was then cooled to –60 °C. Allyl bromide (181 mg, 1.5 mmol) was added dropwise at -60 °C and the reaction mixture was allowed to warm up slowly to 0 °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 solvents were evaporated *in vacuo*. Purification

by flash chromatography (CH_2Cl_2/pentane 1:6) furnished the compound **25** (148 mg, 78%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44 (s, 1 H), 6.07 – 5.93 (m, 1 H), 5.22 – 5.14 (m, 2 H), 3.70 (dt, *J* = 6.6 Hz, 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.

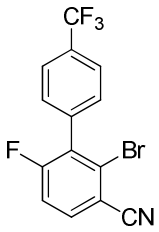
MS (70 eV, EI) m/z (%): 188 (36) [^{35}Cl-M^+], 187 (100), 153 (13), 86 (2).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3453, 3081, 3055, 2985, 2938, 2680, 1722, 1646, 1533, 1516, 1455, 1419, 1377, 1323, 1289, 1250, 1142, 1101, 1058, 1023, 965, 931, 893, 877, 801, 746.

HRMS (EI) Calcd for $C_7H_6Cl_2N_2$; 187.9908; Found, 187.9888.

3.1.2. Metalations of less Activated Substrates using TMPZnCl·LiCl (9) and conventional heating

2-bromo-6-fluoro-(4'-trifluoromethyl)biphenyl-3-carbonitrile (27):



To a solution of 2-bromo-4-fluorobenzonitrile (**26**) (200 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 65 °C and for 30 min according to **TP2**. $Pd(dba)_2$ (14 mg, 2 mol%), P(2-furyl)$_3$ (10 mg, 4 mol%) and 4-iodo-(trifluoromethyl)benzene (353 mg, 1.3 mmol) were then added and the resulting mixture was stirred at 25 °C for 2 h. The reaction 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 1:3) furnished the compound **27** (305 mg, 89%) as a colourless solid.

m.p.: 145.3 – 147.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.77 – 7.71 (m, 3 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.28 (t, *J* = 8.5 Hz, 1 H).

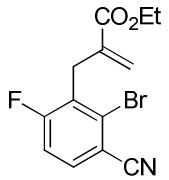
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.8 (d, *J* = 259.8 Hz), 136.4 (d, *J* = 1.3 Hz), 135.3, (d, *J* = 10.1 Hz), 131.8 (d, *J* = 19.6 Hz), 130.1 (d, *J* = 32.7 Hz), 130.2, 131.8 (d, *J* = 1.0 Hz), 129.2, 128.0, 131.8 (d, *J* = 3.6 Hz), 125.5, 131.8 (d, *J* = 3.6 Hz), 122, 116.7, 131.8 (d, *J* = 1.29 Hz), 116.1, 131.8 (d, *J* = 24.5 Hz), 133.3, 131.8 (d, *J* = 3.9 Hz).

MS (70 eV, EI) m/z (%): 343 [^{79}Br-M^+] (100), 264 (10), 244 (30), 195 (35), 168 (7).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 2924, 2230, 1921, 1619, 1592, 1569, 1520, 1463, 1408, 1392, 1322, 1278, 1257, 1191, 1160, 1109, 1071, 1053, 1020, 955, 905, 847, 834, 813, 766, 739, 696, 677.

HRMS (EI) Calcd for $C_{14}H_6BrF_4N$, 342.9620; Found, 342.9610.

2-(2-bromo-3-cyano-6-fluoro-benzyl)-acrylic acid ethyl ester (28):



To a solution of 2-bromo-4-fluorobenzonitrile (**26**) (200 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 65 °C for 30 min according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 15 min of stirring at the same temperature, ethyl 2-(bromomethyl)acrylate (250 mg, 1.3 mmol) was added and the resulting mixture was allowed to warm up slowly to 20 °C within 2 h. The reaction 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 **28** (273 mg, 88 %) as a colourless solid.

m.p.: 39.8 – 40.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.63 – 7.58 (m, 1 H), 7.16 (t, *J* = 8.6 Hz, 1 H), 6.22 (t, *J* = 1.7 Hz, 1 H), 5.07 (t, *J* = 1.7 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 3.84 (q, *J* = 1.9 Hz, 2 H), 1.3 (q, *J* = 7.1 Hz, 3 H).

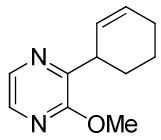
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.0, 163.3 (d, *J* = 259.8 Hz), 135.7, 134.1 (d, *J* = 10.6 Hz), 129.6 (d, *J* = 5.4 Hz), 129.2 (d, *J* = 18.8 Hz), 125.6, 116.9 (d, *J* = 1.3 Hz), 115.6 (d, *J* = 24.8 Hz), 113.0 (d, *J* = 3.9 Hz), 61.1, 31.2 (d, *J* = 3.1 Hz), 14.1.

MS (70 eV, EI) m/z (%): 311 [^{79}Br-M^{+}] (4), 268 (19), 232 (100), 205 (26), 204 (62), 176 (63), 159 (96), 158 (67), 133 (22), 132 (17).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2985, 2938, 2235, 1926, 1704, 1635, 1579, 1469, 1432, 1403, 1369, 1348, 1280, 1256, 1207, 1170, 1136, 1094, 1025, 956, 864, 832, 755, 700, 685.

HRMS (EI) Calcd for $C_{13}H_{11}BrFNO_2$, 310.9957; Found, 310.9997.

2-cyclohex-2-enyl-3-methoxy-pyrazine (30):



To a solution of 2-methoxypyrazine (**29**) (110 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 100 °C for 1 h according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 15 min of stirring at the same temperature, 3-bromocyclohexene (209 mg, 1.3 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction 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) furnished the compound **30** (139 mg, 73 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.05 – 8.04 (m, 1 H), 7.9 – 7.89 (m, 1 H), 5.96 – 5.9 (m, 1 H), 5.75 – 5.71 (m, 1 H), 3.95 – 3.94 (m, 3 H), 3.92 – 3.89 (m, 1 H), 2.14 – 1.99 (m, 3 H), 1.84 – 1.57 (m, 3 H).

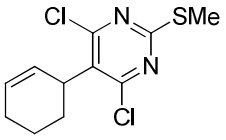
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 158.1, 150.6, 138.0, 135.7, 128.8, 128.0, 53.4, 37.3, 27.9, 24.8, 21.4.

MS (70 eV, EI) m/z (%): 190 [^{35}Cl-M^{+}] (72), 189 (26), 175 (25), 162 (26), 161 (100), 149 (11), 124 (61).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 3025, 2983, 2934, 1836, 1893, 1787, 1685, 1651, 1574, 1540, 1457, 1444, 1394, 1378, 1345, 1328, 1314, 1266, 1248, 1223, 1184, 1167, 1138, 1127, 1076, 1062, 1043, 1009, 988, 932, 891, 863, 840, 804, 780, 768, 721, 703, 679.

HRMS (EI) Calcd for $C_{11}H_{14}N_2O$, 190.1106; Found, 190.1106.

4,6-dichloro-5-cyclohex-2-enyl-2-methylsulfanyl-pyrimidine (32):



To a solution of 4,6-dichloro-2-methylsulfanyl-pyrimidine (**31**) (196 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 65 °C for 30 min according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 15 min of stirring at the same temperature, 3-bromocyclohexene (209 mg, 1.3 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction 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 1:4) furnished the compound **32** (241 mg, 90 %) as a colourless solid.

m.p.: 99.9 – 101.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.87 – 5.80 (m, 1 H), 5.53 – 5.47 (m, 1 H), 4.13 – 4.03 (m, 1 H), 2.53 (s, 3 H), 2.14 – 2.06 (m, 2 H), 1.99 – 1.83 (m, 3 H), 1.76 – 1.63 (m, 1 H).

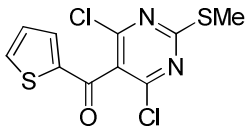
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.1, 161.3, 129.0, 128.2, 127.0, 37.9, 26.0, 24.2, 22.6, 14.3.

MS (70 eV, EI) m/z (%): 274 [^{35}Cl-M^+] (100), 248 (17), 246 (26), 220 (13), 211 (11), 208 (11), 150 (10).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 1534, 1480, 1337, 1309, 1258, 1181, 1119, 1043, 979, 882, 856, 825, 803, 769, 757, 717.

HRMS (EI) Calcd for $C_{11}H_{12}Cl_2N_2S$, 274.0098; Found, 274.0086.

(4,6-dichloro-2-methylsulfanyl-pyrimidin-5-yl)-thiophen-2-yl-methanone (33):



To a solution of 4,6-dichloro-2-methylsulfanyl-pyrimidine (**31**) (196 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 65 °c for 30 min according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30

min of stirring at the same temperature, 2-thiophenecarbonylchloride (293 mg, 2.0 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and NH_3 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 **33** (268 mg, 88 %) as a colourless solid.

m.p.: 126.1 – 127.4 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 4.8 Hz, 1 H), 7.49 (d, *J* = 3.8 Hz, 1 H), 7.17 (t, *J* = 4.3 Hz, 1 H), 2.60 (s, 3 H).

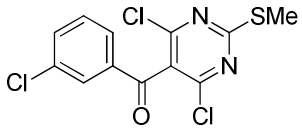
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 181.0, 174.5, 157.9, 142.1, 137.0, 135.5, 128.8, 125.7, 14.5.

MS (70 eV, EI) m/z (%): 304 [^{35}Cl-M^+] (78), 110 (100).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3115, 3088, 2462, 2154, 2161, 1657, 1639, 1540, 1478, 1409, 1356, 1345, 1321, 1283, 1245, 1181, 1098, 1086, 1077, 1055, 976, 907, 884, 859, 826, 819, 768, 744, 740, 729, 686.

HRMS (EI) Calcd for $C_{10}H_6Cl_2N_2OS_2$, 303.9299; Found, 303.9288.

(3-chlorophenyl)[4,6-dichloro-2-(methylthio)pyrimidin-5-yl]methanone (34)



To a solution of 4,6-dichloro-2-methylsulfanyl-pyrimidine (**31**) (590 mg, 3.0 mmol) dissolved in THF (3 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 2.35 mL, 3.3 mmol) at 25 °C and the resulting mixture was heated at 65 °c for 30 min according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-chlorobenzoylchloride (787 mg, 4.5 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and NH_3 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 **34** (880 mg, 88 %) as a colourless solid.

mp: 158.4 – 160.5 °C.

1H-NMR (CDCl3, 600 MHz) δ: 7.82 (s, 1 H), 7.68 (d, *J* = 8.6 Hz, 1 H), 7.64 – 7.62 (m, 1 H), 7.47 – 7.44 (m, 1), 2.62 (s, 3 H).

13C-NMR (CDCl3, 150 MHz) δ: 188.4, 175.0, 158.1, 136.7, 135.9, 135.0, 130.7, 129.4, 127.9, 125.3, 14.8.

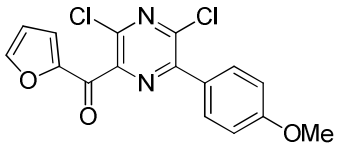
MS (70 eV, EI) m/z (%): 332 [^{35}Cl-M^{+}] (35), 221 (16), 139 (100), 111 (58), 75 (44), 50 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2920, 2851, 1728, 1672, 1582, 1569, 1548, 1467, 1399, 1346, 1321, 1286, 1244, 1230, 1218, 1177, 1091, 1077, 1012, 968, 919, 847, 814, 747, 721, 664.

HRMS (EI) Calcd for $C_{12}H_7Cl_3N_2OS$, 331.9345; Found, 331.9334.

3.1.3. Metalations of less Activated Substrates using TMPZnCl·LiCl (9) and microwave irradiation

[3,5-Dichloro-6-(4-methoxyphenyl)pyrazin-2-yl](2-furyl)methanone (36)



To a solution of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**35**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 100 °C (200 W) for 1 h according to **TP2**. The reaction mixture was then cooled to -20 °C and CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-furoyl-chloride (170 mg, 1.3 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °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 1:1) furnished the compound **36** (244 mg, 70 %) 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).

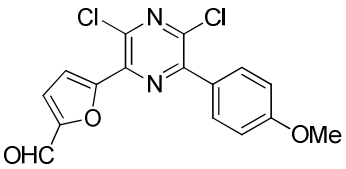
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 176.8, 161.3, 150.9, 149.6, 148.7, 145.7, 145.6, 142.0, 131.2, 126.3, 123.0, 113.9, 112.9, 55.4.

MS (70 eV, EI) m/z (%): 348 [^{35}Cl-M^{+}] (36), 320 (20), 95 (100).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{16}H_{10}Cl_2N_2O_3$, 348.0068; Found, 348.0067.

4-[3,5-Dichloro-6-(4-methoxyphenyl)pyrazin-2-yl]-2-furaldehyde (37)



To a solution of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**35**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 100 °C (200 W) for 1 h according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (13 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 5-iodo-2-furancarbaldehyde (290 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_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 **37** (226 mg, 65%) as a colourless solid.

m.p.: 110.9 – 112.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 9.80 (s, 1 H), 7.88 (d, *J* = 9.1 Hz, 2 H), 7.52 (d, *J* = 3.8 Hz, 1 H), 7.36 (d, *J* = 3.8 Hz, 1 H), 7.0 (d, *J* = 8.6 Hz, 2 H), 3.86 (s, 3 H).

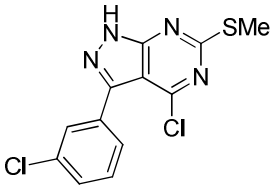
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 178.3, 161.2, 153.4, 150.3, 140.0 , 139.0, 131.2, 126.6, 116.5, 113.8, 55.4.

MS (70 eV, EI) m/z (%): 348 [^{35}Cl-M^{+}] (100), 180 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3127, 2838, 2156, 2040, 1690, 1611, 1570, 1530, 1514, 1464, 1408, 1379, 1338, 1312, 1300, 1257, 1245, 1225, 1180, 1143, 1116, 1048, 1027, 1015, 969, 947, 869, 841, 818, 794, 770, 735, 665, 638.

HRMS (EI) Calcd for $C_{16}H_{10}Cl_2N_2O_3$, 348.0068; Found, 348.0067.

4-Chloro-3-(3-chlorophenyl)-6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidine (41)



To a solution of (3-chlorophenyl)[4,6-dichloro-2-(methylthio)pyrimidin-5-yl]methanone (**34**; 334 mg, 1.0 mmol) dissolved in THF (2 mL) was added hydrazine (70.5 mg, 2.2 mmol) at 25 °C. After 1 h of stirring at the same temperature the resulting mixture was quenched with a sat. aq. Na_2CO_3 solution (20 mL), extracted with dichloromethane (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/diethylether1:9) furnished the compound **41** (230 g, 74 %) as a colourless solid.

m.p.: 216.8 – 218.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.78 – 7.77 (m, 1 H), 7.72 – 7.69 (m, 1 H), 7.58 – 7.52 (m, 2 H), 2.59 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.7, 156.4, 153.0, 143.5, 133.4, 132.8, 130.0, 129.4, 128.9, 128.5, 107.0, 13.9.

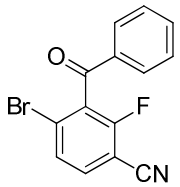
MS (70 eV, EI) m/z (%): 310 (100) [^{35}Cl-M^+], 264 (13), 229 (40), 193 (20), 111(9).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3182, 3143, 3019, 2970, 2934, 2890, 1608, 1599, 1533, 1502, 1458, 1359, 1321, 1311, 1257, 1231, 1160, 1085, 1075, 995, 868, 875, 814, 777, 758, 740, 685.

HRMS (EI) Calcd for $C_{12}H_8Cl_2N_4S$, 309.9847; Found, 309.9772.

3.1.4. Scaleable Preparation of Sensitive Functionalized Aromatics and Heteroaromatics *via* Directed Metalation Using TMPZnCl·LiCl (9)

3-Benzoyl-4-bromo-2-fluorobenzonitrile (43)



To a solution of 4-bromo-2-fluorobenzonitrile (**42**; 9.95 g, 50 mmol) dissolved in THF (50 mL) was added TMPZnCl·LiCl (**9**; 1.35 M in THF, 40.7 mL, 55 mmol) at 25 °C and the resulting mixture was heated for 45 min at 65 °C. The reaction mixture was then cooled to -30 °C and CuCN·2LiCl (1 M solution in THF, 55 mL, 55 mmol) was added. After 30 min of stirring at the same temperature, benzoyl chloride (9.1 g, 65 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 3 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (300 mL), extracted with diethyl ether (3 × 250 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:4) furnished the compound **43** (13.6 g, 90 %) as a colourless solid.

m.p.: 97.5 – 98.9 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81 – 7.79 (m, 2 H), 7.70 – 7.62 (m, 1 H), 7.60 – 7.59 (m, 2 H), 7.54 – 7.48 (m, 2 H).

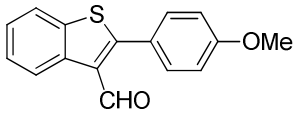
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 189.2, 159.5 (d, J = 263.7 Hz), 135.0, 134.9, 134.3, 130.7 (d, J = 21.0 Hz), 129.7, 129.6, 129.2, 126.4 (d, J = 5.2 Hz), 112.7, 101.3 (d, J = 6.1 Hz).

MS (70 eV, EI) m/z (%): 303 [M^+] (28), 105 (100), 77 (33), 51 (11).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3090, 3073, 2240, 1928, 1740, 1681, 1594, 1578, 1564, 1456, 1449, 1422, 1313, 1284, 1272, 1248, 1171, 1125, 1077, 1001, 987, 966, 938, 886, 832, 789, 715, 688, 673.

HRMS (EI) Calcd for $C_{14}H_7BrFNO$, 302.9695; Found, 302.9689.

2-(4-Methoxyphenyl)-1-benzothiophene-3-carbaldehyde (44)



To a solution of benzothiophene-3-carbaldehyde (**20**; 8.1 g, 50 mmol) dissolved in THF (50 mL) was added TMPZnCl·LiCl (**9**; 1.35 M in THF, 40.7 mL, 55 mmol) at 25 °C and the resulting mixture was stirred for 30 min. $Pd(dba)_2$ (565 mg, 2 mol%) and P(2-furyl)$_3$ (465 mg, 4 mol%) dissolved in THF (20 mL) and mixed with 4-iodoanisole (14.0 g, 60 mmol) were then transferred via cannula and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (300 mL), extracted with diethyl ether (3 × 250 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification

by flash chromatography (diethyl ether/pentane 15:85) furnished the compound **44** (11.3 g, 85%) as a yellowish solid.

m.p.: 81.3 – 84.9 °C.

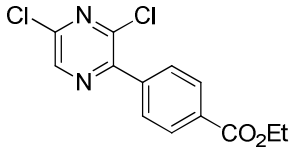
^{1}H-NMR (600 MHz, $CDCl_3$) δ: 10.0 (s, 1 H), 8.77 (d, *J* = 8.2 Hz, 1 H), 7.73 (d, *J* = 7.9 Hz, 1 H), 7.51 – 7.45 (m, 3 H), 7.42 – 7.36 (m, 1 H), 7.01 – 6.97 (m, 2 H), 3.84 (s, 3 H).

^{13}C-NMR (150 MHz, $CDCl_3$) δ: 186.5, 161.0, 160.8, 137.5, 137.1, 126.0, 125.5, 124.8, 123.7, 121.4, 114.3, 55.3.

MS (70 eV, EI) m/z (%): 268 [M^+] (100), 253 (12), 237 (19), 225 (12), 197 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3295, 3028, 2918, 2848, 2767, 1651, 1620, 1602, 1526, 1493, 1458, 1431, 1397, 1351, 1298, 1254, 1222, 1181, 1176, 1097, 1038, 1019, 826, 817, 751, 729, 697. **HRMS (EI) Calcd for $C_{16}H_{12}O_2S$**, 268.0558; Found, 268.0552.

Preparation of ethyl 4-(3,5-dichloropyrazin-2-yl)benzoate (45)



To a solution of 2,6-dichloropyrazine (**24**; 7.45 g, 50 mmol) dissolved in THF (50 mL) was added TMPZnCl·LiCl (**9**; 1.35 M in THF, 40.7 mL, 55 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min. $Pd(dba)_2$ (565 mg, 2 mol%) and $P(2\text{-furyl})_3$ (465 mg, 4 mol%) dissolved in THF (50 mL) and mixed with ethyl 4-iodobenzoate (16.5 g, 60 mmol) 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 (300 mL), extracted with diethyl ether (3 × 250 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:9) furnished the compound **45** (11.7 g, 79%) as a colourless solid.

mp: 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, 61.2, 14.3.

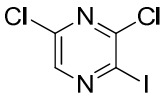
MS (70 eV, EI) m/z (%): 296 [^{35}Cl-M^+] (32), 270 (24), 268 (38), 251 (100), 223 (26).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3086, 3005, 2985, 2359, 1966, 1708, 1611, 1569, 1537, 1507, 1482, 1466, 1446, 1423, 1366, 1310, 1283, 1190, 1175, 1140, 1131, 1114, 1098, 1028, 1021, 1009, 915, 858, 843, 786, 758, 719, 698, 675, 634, 621, 616, 610, 602.

HRMS (EI) Calcd for $C_{13}H_{10}Cl_2N_2O_2$, 296.0119; Found, 296.0119.

3.2. Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the synthesis of Coelenterazine

3,5-Dichloro-2-iodopyrazine (52a)



To a solution of 2,6-dichloropyrazine (**24**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min according to **TP3**. Iodine (381 mg, 1.5 mmol) dissolved in THF (2 mL) was added and the reaction mixture was stirred for 1 h at 25 °C. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), and $Na_2S_2O_3$ and 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 **52a** (250 mg, 91 %) as a colourless solid.

mp: 101.3 – 103.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.3 (s, 1 H).

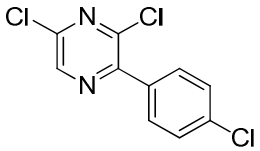
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 153.1, 146.9, 142.4, 115.7.

MS (70 eV, EI) m/z (%): 274 [^{35}Cl-M^+] (100), 147 (75), 86 (32), 57 (21), 44 (94).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2969, 2633, 2281, 1784, 1738, 1510, 1491, 1379, 1353, 1323, 1274, 1230, 1217, 1175, 1162, 1143, 1018, 893, 843, 655, 634, 618, 611, 604.

HRMS (EI) Calcd for $C_4HCl_2IN_2$, 273.8561; Found, 273.8555.

3,5-Dichloro-2-(4-chlorophenyl)pyrazine (52b)



To a solution of 2,6-dichloropyrazine (**24**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min according to **TP3**. $Pd(dba)_2$ (16 mg, 2 mol%) and P(2-furyl)$_3$ (10 mg, 4 mol%) dissolved in THF (2 mL), and mixed with 4-chloro-iodobenzene (310 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 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 **52b** (233 mg, 91 %) 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).

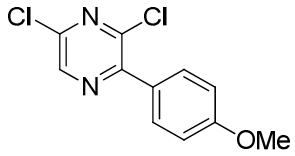
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.0, 145.6, 145.3, 142.0, 136.3, 133.4, 130.8, 128.6.

MS (70 eV, EI) m/z (%): 258 [^{35}Cl-M^+] (100), 223 (55), 137 (22).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{10}H_5Cl_3N_2$, 257.9518; Found, 257.9353.

3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (35)



2,6-Dichloropyrazine (**24**) (1,49 g, 10.0 mmol) dissolved in THF (10 mL) was reacted with a solution of TMPZnCl·LiCl (**9**) (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 **TP3**. $Pd(dba)_2$ (113 mg, 2 mol%) and P(2-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 **35** (2.18 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).

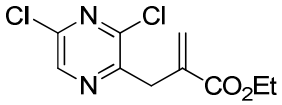
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.9, 150.8, 145.0, 144.4, 141.7, 131.0, 127.2, 113.7, 55.4.

MS (70 eV, EI) m/z (%): 254 [^{35}Cl-M^+] (100), 239 (12), 219 (35), 133 (11), 44 (16).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{11}H_8Cl_2N_2O$, 254.0014; Found, 254.0012.

Ethyl 2-[(3,5-dichloropyrazin-2-yl)methyl]acrylate (52c)



To a solution of 2,6-dichloropyrazine (**24**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min according to **TP3**. 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. Ethyl 2-(bromomethyl)acrylate (576 mg, 3.0 mmol) was added dropwise at -60 °C and the reaction mixture was allowed to warm slowly to 25 °C for 1 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 1:2) furnished the compound **52c** (213 mg, 82%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.38 (s, 1 H), 6.38 (s, 1 H), 5.56 (s, 1 H), 4.14 (qd, *J* = 0.5 Hz, , *J* = 7.3 Hz, 2 H), 3.92 (s, 2 H), 1.22 (td, , *J* = 0.5, , *J* = 7.1 Hz, 3 H).

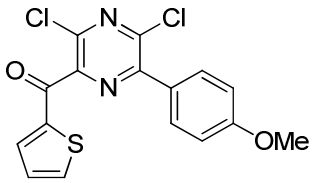
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.0, 151.5, 146.8, 145.0, 141.5, 136.0, 127.6, 60.9, 36.7, 14.0.

MS (70 eV, EI) m/z (%): 260 [^{35}Cl-M^+] (10), 225 (50), 215 (52), 186 (100), 152 (33), 124 (11).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2934, 2873, 1712, 1636, 1537, 1514, 1477, 1464, 1444, 1415, 1370, 1346, 1316, 1299, 1288, 1272, 1257, 1208, 1145, 1132, 1066, 1025, 949, 927, 874, 816, 800, 782, 668, 641, 609.

HRMS (EI) Calcd for $C_{10}H_{10}Cl_2N_2O$, 260.0119; Found, 260.0196.

[3,5-Dichloro-6-(4-methoxyphenyl)pyrazin-2-yl](2-thienyl)methanone (54a)



A mixture of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**35**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C for 1 h according to **TP3**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-thiophenecarbonylchloride (293 mg, 2.0 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and NH_3 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 **54a** (284 mg, 78 %) as a colourless oil.

1H-NMR (CDCl3, 300 MHz) δ: 7.91 – 7.86 (m, 2 H), 7.81 – 7.78 (m, 2 H), 7.18 – 7.15 (m, 1 H), 7.03 – 6.98 (m, 2 H), 3.87 (s, 3 H).

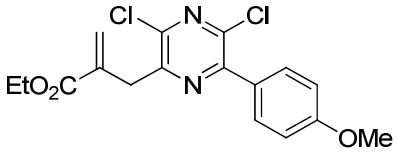
13C-NMR (CDCl3, 75 MHz) δ: 181.4, 161.3, 149.4, 145.6, 142.1, 140.9, 136.8, 131.3, 128.4, 126.2, 113.9, 55.4.

MS (70 eV, EI) m/z (%): 364 [^{35}Cl-M^+] (15), 111 (100).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3111, 3002, 2944, 2840, 2045, 1737, 1642, 1603, 1513, 1491, 1453, 1414, 1364, 1348, 1301, 1258, 1233, 1183, 1154, 1123, 1114, 1085, 1073, 1048, 1024, 1010, 946, 928, 869, 847, 834, 816, 796, 781, 753, 740, 724, 705, 662, 642, 633, 622, 611, 604.

HRMS (EI) Calcd for $C_{16}H_{10}Cl_2N_2O_2S$, 363.9840; Found, 363.9832.

Ethyl 2-{[3,5-dichloro-6-(4-methoxyphenyl)pyrazin-2-yl]methyl}acrylate (54b)



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**35**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C for 1 h according to **TP3**. 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. Ethyl 2-(bromomethyl)acrylate (293 mg, 2.0 mmol) was added dropwise at -60 °C and the reaction mixture was allowed to warm up slowly to -20 °C for 3 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 1:4) furnished the compound **54b** (272 mg, 74%) as a colourless solid.

m.p.: 81.3 – 83.0 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 9.00 Hz, 2 H), 6.07 (d, *J* = 8.99 Hz, 2 H), 6.33 (d, *J* = 0.73 Hz, 1 H), 5.56 (d, *J* = 0.96 Hz, 1 H), 4.18 (q, *J* = 7.29 Hz, 2 H), 3.99 (s, 2 H), 3.85 (s, 3 H), 1.22 (t, *J* = 7.29 Hz, 3 H).

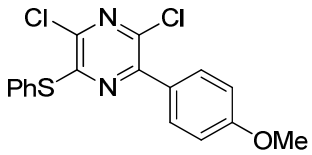
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.5, 160.1, 150.6, 150.0, 143.4, 142.2, 136.4, 131.1, 127.3, 113.7, 61.0, 55.4, 36.7, 14.2.

MS (70 eV, EI) m/z (%): 366 [^{35}Cl-M^+] (49), 339 (14), 337 (21), 320 (38), 296 (24), 295 (38), 294 (84), 293 (54), 292 (100), 157 (17), 133 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2992, 2969, 2843, 2042, 1890, 1729, 1607, 1580, 1530, 1512, 1500, 1486, 1467, 1456, 1447, 1439, 1421, 1375, 1342, 1311, 1302, 1253, 1209, 1182, 1163, 1123, 1115, 1070, 1022, 1007, 952, 929, 863, 828, 794, 765, 729, 661, 634, 620, 610.

HRMS (EI) Calcd for $C_{17}H_{16}Cl_2N_2O_3$, 366.0538; Found, 366.0535.

2,6-Dichloro-3-(4-methoxyphenyl)-5-(phenylthio)pyrazine (54c)



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**35**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C

for 1 h according to **TP3**. $PhSSO_2Ph$ (500 mg, 2 mmol) dissolved in 2 mL THF was added dropwise at -40 °C and the reaction mixture was allowed to warm up slowly to 0 °C for 3 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 1:3) furnished the compound **54c** (339 mg, 94 %) as a colourless solid.

m.p.: 133.9 – 135.7 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.06-7.55 (m, 4H), 7.47-7.41 (m,3H), 6.85-6.80 (m, 2H), 3.81 (s, 3H).

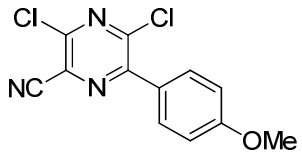
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 160.9, 153.2, 149.0, 139.6, 135.8, 131.0, 129.2, 128.0, 126.9, 113, 4, 55.3.

MS (70 eV, EI) m/z (%): 362 [^{35}Cl-M^+] (100), 361 (45), 329 (13), 327 (37), 291 (16), 163 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3012, 2960, 2926, 2830, 2050, 1738, 1604, 1576, 1515, 1503, 1488, 1472, 1451, 1442, 1457, 1432, 1419, 1361, 1311, 1274, 1257, 1178, 1151, 1113, 1088, 1068, 1047, 1029, 1009, 997, 968, 922, 887, 839, 808, 797, 754, 725, 706, 690, 669, 660, 651, 630, 615, 604.

HRMS (EI) Calcd for $C_{17}H_{12}Cl_2N_2OS$, 362.0047; Found, 362.0040.

3,5-Dichloro-6-(4-methoxyphenyl)pyrazine-2-carbonitrile (54d)



3,5-Dichloro-2-(4-methoxyphenyl)pyrazine (**35**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C for 1 h according to **TP3**. TosCN (220 mg, 1.2 mmol) dissolved in THF (2 mL) was then added and the resulting mixture was allowed to warm to 25 °C for 1 h. The reaction 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 1:3) furnished the compound **54d** (154 mg, 55 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.86 – 7.81 (m, 2 H), 7.04 – 6.99 (m, 2 H), 3.88 (s, 3 H).

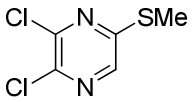
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.8, 152.0, 148.1, 146.3, 131.3, 127.1, 125.3, 114.1, 113.3, 55.5.

MS (70 eV, EI) m/z (%): 279 [^{35}Cl-M^+] (100), 244 (16), 133 (22), 44 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 2935, 2837, 2240, 1738, 1605, 1577, 1524, 1506, 1457, 1437, 1420, 1374, 1338, 1306, 1295, 1255, 1217, 1174, 1126, 1083, 1020, 1006, 960, 926, 837, 796, 775, 730, 692, 679, 666, 636, 622, 615.

HRMS (EI) Calcd for $C_{12}H_7Cl_2N_3O$, 278.9966; Found, 278.9955.

2,3-Dichloro-5-(methylthio)pyrazine (56a)



2,3-dichloropyrazine (**49**) (148 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at 25 °C for 15 min according to **TP3**. 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 **56a** (131 mg, 67 %) as a yellow solid.

m.p.: 62.1-64.1.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 2.56 (s, 3H).

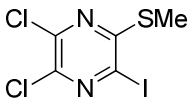
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 155.9, 146.7, 141.8, 139.8, 13.3.

MS (70 eV, EI) m/z (%): 193 [^{35}Cl-M^+] (100), 163 (54), 161 (80), 97 (13), 83 (11), 71 (14), 69 (16), 57 (26), 44 (53), 43 (19), 41 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_5H_4Cl_2N_2S$, 193.9472; Found, 193.9458.

2,3-Dichloro-5-iodo-6-(methylthio)pyrazine (58a)



2,3-Dichloro-5-methylsulfanyl-pyrazine (**56a**) (195 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C and

the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. Iodine (508 mg, 2 mmol) was added in THF (2 mL) and the mixture was allowed to warm up to -10 °C for 1 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL) and a sat. aq. $Na_2S_2O_3$ (30 mL) was added, 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 1:9) furnished the compound **58a** (256 mg, 80%) as a yellow solid.

m.p.: 95.6 – 97.2 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 2.52 (s, 3 H).

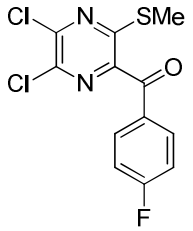
^{13}C-NMR (150 MHz, $CDCl_3$) δ:.161.3, 146.1, 140.0, 111.1, 16.2.

MS (70 eV, EI) m/z (%): 320 [^{35}Cl-M^+] (45), 194 (36), 129 (33), 111 (15), 105 (12), 57 (26), 55 (20), 44 (100), 43 (23).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2157, 2003, 1922, 1470, 1415, 1359, 1324, 1294, 1265, 1188, 1132, 1056, 960, 881, 660.

HRMS (EI) Calcd for $C_5H_3Cl_2IN_2S$, 319.8439; Found, 319.8436.

[5,6-Dichloro-3-(methylthio)pyrazin-2-yl](4-fluorophenyl)methanone (58b)



2,3-Dichloro-5-methylsulfanyl-pyrazine (**56a**) (195 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. 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 transferred and the resulting mixture was stirred at -40 °C for 30 min. 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 **58b** (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).

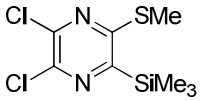
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 188.7, 166.0 (d, *J* = 256.2 Hz), 159.0, 147.9, 142.0, 138.9, 133.5 (d, *J* = 9.5 Hz), 131.9 (d, *J* = 2.8 Hz), 115.6 (d, *J* = 21.9 Hz), 14.5.

MS (70 eV, EI) m/z (%): 316 [^{35}Cl-M^+] (18), 301 (16), 283 (13), 123 (100), 95 (48), 75 (16), 46 (57).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{12}H_7Cl_2FN_2OS$, 315.9640; Found, 315.9647.

2,3-Dichloro-5-(methylthio)-6-(trimethylsilyl)pyrazine (58c)



2,3-Dichloro-5-methylsulfanyl-pyrazine (**56a**) (195 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (1.0 M in THF, 1.1 mL, 1.1 mmol) at -40 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. TMSCN (129 mg, 1.3 mmol) was added and the mixture was allowed to warm up to -10 °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 1:9) furnished the compound **58c** (234 mg, 88%) as a colourless solid.

m.p.: 75.0 – 76.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 2.54 (s, 3 H), 0.39 (s, 9 H).

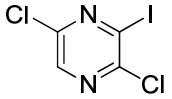
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 160.4, 159.3, 145.6, 142.2, 13.9, 1.8.

MS (70 eV, EI) m/z (%): 266 [^{35}Cl-M^+] (23), 251 (100), 254 (20), 253 (71), 105 (35), 73 (46), 72 (11), 44 (59).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2928, 2606, 2274, 1913, 1734, 1477, 1427, 1419, 1372, 1322, 1307, 1255, 1243, 1163, 1131, 1073, 973, 963, 902, 840, 772, 755, 742, 699, 661.

HRMS (EI) Calcd for $C_8H_{12}Cl_2N_2SSi$, 265.9867; Found, 265.9870.

2,5-Dichloro-3-iodopyrazine (61a)



2,5-Dichloropyrazine (**59**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**9**) (1.52 M in THF, 0.72 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. I_2 (508 mg, 2.0 mmol) dissolved in 3 mL THF was added dropwise at 25 °C and the reaction mixture was stirred for 1 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL) and a sat. aq. $Na_2S_2O_3$ (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 1:4) furnished the compound **61a** (208 mg, 76%) as a colourless solid.

m.p.: 95.6 – 97.2 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.30 (s, 1H).

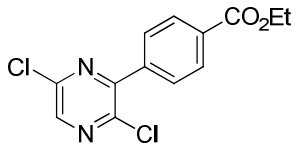
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 152.9, 146.6, 142.2, 115.5.

MS (70 eV, EI) m/z (%): 274 [^{35}Cl-M$^+$] (100), 148 (49), 146 (76), 127 (20), 86 (26), 44 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3791, 3665, 3071, 2970, 2632, 2348, 2283, 2049, 1939, 1784, 1737, 1649, 1555, 1510, 1492, 1380, 1353, 1323, 1274, 1205, 1176, 1162, 1143, 1018, 893, 844, 738, 655, 640, 633, 627, 620, 614, 607.

HRMS (EI) Calcd for C_4HCl_2I, 273.8562; Found, 273.8562.

Ethyl 4-(3,6-dichloropyrazin-2-yl)benzoate (61b)



2,5-Dichloropyrazine (**59**) (444 mg, 3.0 mmol) dissolved in THF (3 mL) was reacted with a solution of TMPZnCl·LiCl (**9**) (1.4 M in THF, 2.36 mL, 3.3 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. $Pd(dba)_2$ (51 mg, 3 mol%) and P(2-furyl)$_3$ (42 mg, 6 mol%) dissolved in THF (5 mL), and mixed with ethyl 4-iodobenzoate (1.07 g, 3.9 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °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 1:1) furnished the compound **61b** (710 mg, 80%) as a colourless solid.

m.p.: 82.4 – 84.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.6 (s, 1 H), 8.16 (d, *J* = 8.58 Hz, 2 H), 7.86 (d, *J* = 8.58 Hz, 2 H), 4.41 (q, *J* = 7.15 Hz, 2 H), 1.41 (t, *J* = 7.15 Hz, 3 H).

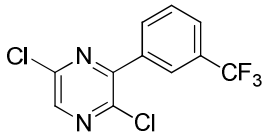
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.9, 150.2, 146.0, 145.5, 142.1, 139.1, 131.6, 129.4, 61.3, 14.3.

MS (70 eV, EI) m/z (%): 296 [^{35}Cl-M^+] (30), 270 (22), 268 (37), 253 (63), 252 (14), 251 (100), 225 (14), 223 (22).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3812, 3660, 3086, 3049, 2985, 2348, 2284, 1965, 1827, 1709, 1650, 1626, 1610, 1591, 1573, 1536, 1508, 1482, 1466, 1446, 1421, 1408, 1366, 1344, 1317, 1310, 1281, 1263, 1188, 1175, 1140, 1130, 1098, 1026, 1021, 1008, 983, 916, 875, 858, 843, 786, 758, 718, 698, 657, 642, 633, 624, 618, 610.

HRMS (EI) Calcd for $C_{12}H_{10}Cl_2N_2O_2$, 296.0119; Found, 296.0115.

3,5-Dichloro-2-[3-(trifluoromethyl)phenyl]pyrazine (61c)



To a solution of 2,6-dichloropyrazine (**59**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.84 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min according to **TP3**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(2-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 3-iodo(trifluoromethyl)benzene (354 mg, 1.3 mmol) 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 solvents were evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:5) furnished the compound **61c** (242 mg, 83%) as a 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).

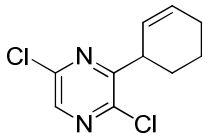
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 149.6, 146.1, 145.5, 142.2, 135.7, 132.6 (q, *J* = 2.7 Hz), 131.0 (q, *J* = 32.6 Hz), 128.9, 126.6 (q, *J* = 3.9 Hz), 126.5 (q, *J* = 3.9 Hz), 123.7 (q, *J* = 272.7 Hz).

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) Calcd for $C_{11}H_5Cl_2F_3N_2$, 291.9782; Found, 291.9782.

2,5-Dichloro-3-cyclohex-2-en-1-ylpyrazine (61d)



To a solution of 2,6-dichloropyrazine (**59**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was stirred at this temperature for 30 min according to **TP3**. After cooling 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 -20 °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 1:3) furnished the compound **61d** (178 mg, 78 %) as a colourless oil.

1H-NMR (CDCl3, 600 MHz) δ: 8.44 (s, 1H), 5.99 – 5.95 (m, 1H), 5.65 (d, *J* = 10.0 Hz, 1H), 4.00 – 3.98 (m, 1H), 2.16 – 206 (m, 3H), 1.86 – 1.83 (m, 1H), 1.71 – 160 (m, 2H).

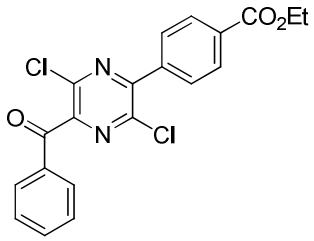
13C-NMR (CDCl3, 150 MHz) δ: 156.6, 146.2, 144.4, 141.7, 129.3, 126.2, 39.1, 27.9, 24.3, 21.0.

MS (70 eV, EI) m/z (%): 228 [35Cl-M$^+$] (100), 215 (15), 201 (76), 199 (100), 187 (20), 174 (27), 164 (26), 79 (12), 67 (46).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3661, 3319, 3026, 2934, 2860, 2835, 1807, 1656, 1533, 1512, 1446, 1414, 1349, 1330, 1268, 1252, 1145, 1071, 1041, 987, 890, 861, 822, 786, 768, 721, 666, 633, 618, 611, 601.

HRMS (EI) Calcd for $C_{10}H_{10}Cl_2N_2$, 228.0221; Found, 228.0209.

Ethyl 4-(5-benzoyl-3,6-dichloropyrazin-2-yl)benzoate (63a)



4-(3,6-Dichloro-pyrazin-2-yl)-benzoic acid ethyl ester (**61b**) (296 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**9**) (1.52 M in THF, 0.72 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. After cooling to –20 °C, CuCN·2LiCl (1 M solution in THF, 1 mL, 1.1 mmol) was added and benzoyl chloride (183 mg, 1.3 mmol) was added dropwise at -20 °C. The resulting mixture was stirred 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 **63a** (360 mg, 90%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.78 Hz, 2 H), 7.90 – 7.86 (m, 4 H), 7.66 – 7.62 (m, 1 H), 7.52 – 7.47 (m, 2 H), 4.38 (q, *J* = 7.21 Hz, 2 H), 1.38 (t, *J* = 7.01 Hz, 3 H).

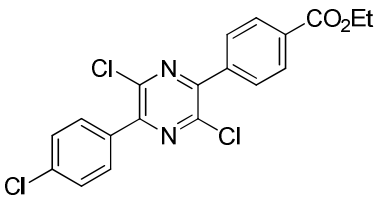
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 189.9, 165.7, 149.2, 147.9, 145.8, 143.0, 138.2, 134.7, 134.4, 131.8, 130.2, 129.6, 129.4, 128.8, 61.3, 14.2.

MS (70 eV, EI) m/z (%): 400 [^{35}Cl-M^+] (8),105(100), 77 (19).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2981, 1713, 1678, 1612, 1583, 1597, 1515, 1450, 1409, 1365, 1312, 1271, 1218, 1180, 1154, 1126, 1102, 1085, 1020, 1000, 955, 862, 807, 788, 768, 723, 684, 657.

HRMS (EI) Calcd for $C_{20}H_{14}Cl_2N_2O_3$, 400.0381; Found, 400.0388.

Ethyl 4-[3,6-dichloro-5-(4-chlorophenyl)pyrazin-2-yl]benzoate (63b)



4-(3,6-Dichloro-pyrazin-2-yl)-benzoic acid ethyl ester (**61b**) (296 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**9**) (1.52 M in THF, 0.72 mL, 1.1

mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. $Pd(dba)_2$ (13 mg, 2 mol%) and $P(2\text{-furyl})_3$ (10 mg, 4 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 1.5 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/pentane 1:2.5) furnished the compound **63b** (316 mg, 78%) as a colourless solid.

m.p.: 99.9 – 101.5 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 8.10 Hz, 2 H), 7.93 (d, *J* = 8.10 Hz, 2 H), 7.84 (d, *J* = 8.10 Hz, 2 H), 7.48 (d, *J* = 8.58 Hz, 2 H), 4.42 (q, *J* = 7.16 Hz, 2 H), 1.41 (t, *J* = 7.16 Hz, 3 H).

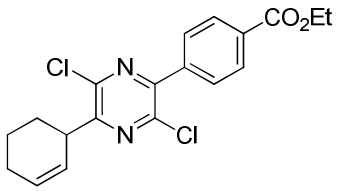
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 165.9, 149.4, 143.3, 139.0, 136.4, 133.2, 131.7, 130.9, 129.5, 128.7, 61.3, 14.2.

MS (70 eV, EI) m/z (%): 406 [^{35}Cl-M^+] (100), 380 (32), 378 (31), 365 (28), 363 (83), 361 (90), 335 (20), 333 (20), 263 (11), 160 (46), 126 (10).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 1720, 1595, 1484, 1403, 1352, 1312, 1273, 1178, 1136, 1123, 1101, 1092, 1007, 895, 857, 784, 766, 739, 716, 699.

HRMS (EI) Calcd for $C_{19}H_{13}Cl_3N_2O_2$, 406.0043; Found, 406.0037.

Ethyl 4-(3,6-dichloro-5-cyclohex-2-en-1-ylpyrazin-2-yl)benzoate (63c)



4-(3,6-Dichloro-pyrazin-2-yl)-benzoic acid ethyl ester (**61b**) (296 mg, 1.0 mmol) dissolved in THF (1 mL) was reacted with a solution of TMPZnCl·LiCl (**9**) (1.52 M in THF, 0.72 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP3**. After cooling to -20 °C, CuCN·2LiCl (1 M solution in THF, 0.1 mL) and 3-bromocyclohexene (161 mg, 1.3 mmol) were added dropwise at -20 °C. The resulting mixture was allowed to warm up to 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 1:3) furnished the compound **63c** (319 mg, 85%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.74 Hz, 2 H), 7.89 (d, *J* = 8.75 Hz, 2 H), 5.94 – 5.87 (m, 1 H), 5.74 – 5.69 (m, 1 H), 4.40 (q, *J* = 7.05 Hz, 2 H), 4.06 – 4.00 (m, 1 H), 2.13 – 2.07 (m, 3 H), 1.95 – 1.68 (m, 3 H), 1.40 (t, *J* = 7.05, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.0, 156.3, 149.1, 144.7, 142.2, 139.4, 131.4, 129.3, 126.2, 61.2, 39.5, 27.6, 24.6, 21.3, 14.3.

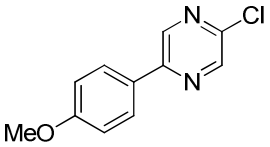
MS (70 eV, EI) m/z (%): 376 [^{35}Cl-M$^+$] (93), 375 (23), 349 (28), 347 (40), 341 (60), 319 (26), 312 (65), 310 (100), 227 (27), 67 (52).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3424, 3026, 2981, 2934, 2861, 2836, 2649, 1936, 1715, 1650, 1611, 1573, 1520, 1499, 1475, 1446, 1409, 1392, 1365, 1355, 1340, 1310, 1270, 1179, 1171, 1148, 1128, 1101, 1084, 1020, 989, 926, 895, 885, 861, 828, 783, 762, 717, 705, 670, 642.

HRMS (EI) Calcd for $C_{19}H_{18}Cl_2N_2O_2$, 376.0745; Found, 376.0737.

3.3. Synthesis of Coelenterazine (46)

2-Chloro-5-(4-methoxyphenyl)pyrazine (64)



This compound was prepared from 2,5-dichloropyrazine (**59**). 4-Iodoanisole (10.8 g, 46 mmol) was charged with freshly titrated *i*-PrMgCl·LiCl (**5**; 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 $P(2\text{-furyl})_3$ (395 mg, 4 mol%) were then introduced, the resulting mixture was then transferred dropwise at 25 °C via cannula to a solution of **59** (8.9 g, 60 mmol) dissolved in THF (60 mL) and stirred for 1.5 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 **66** (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).

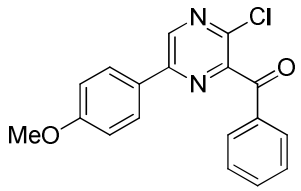
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 161.6, 141.3, 138.6, 128.6, 127.2, 114.5, 55.4.

MS (70 eV, EI) m/z (%): 220 [^{35}Cl-M^+] (100), 205 (16), 177 (12), 167 (21), 149 (57).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{11}H_9ClN_2O$, 220.0403; Found, 220.0396.

[3-Chloro-6-(4-methoxyphenyl)pyrazin-2-yl](phenyl)methanone (65)



2-Chloro-5-(4-methoxyphenyl)pyrazine (**64**) (5.8 g, 26.7 mmol) dissolved in THF (25 mL) was reacted with a solution of TMPMgCl·LiCl (**6**) (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 **TP3**. A solution of $ZnCl_2$ (1 M in THF, 30 mL, 30 mmol) was added at -45 °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 **65** (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).

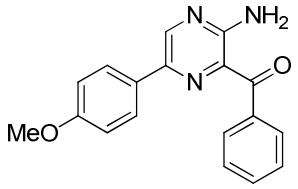
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 191.3, 162.1, 152.9, 146.6, 145.9, 137.4, 135.1, 134.1, 130.2, 128.9, 128.6, 126.4, 114.6, 55.4.

MS (EI, 70 eV) m/z (%): 324 (54) [^{35}Cl-M^+], 296 (21), 105 (100).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{18}H_{13}ClN_2O_2$, 324.0666; Found, 324.0658.

[3-Amino-6-(4-methoxyphenyl)pyrazin-2-yl](phenyl)methanone (66)



(3-Chloro-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (**65**) (324 mg, 1.0 mmol) dissolved in BuOH (2 mL) and 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 solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **66** (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).

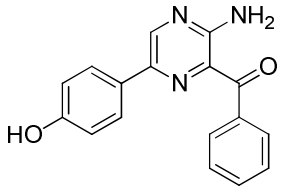
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 195.1, 161.9, 155.5, 153.7, 138.4, 131.8, 130.4, 129.7, 129.1, 128.0, 127.9, 127.8, 114.4, 55.4.

MS (EI, 70 eV) m/z (%): 305 [M^+] (100), 276 (23), 105 (27), 77 (23).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{18}H_{15}N_3O_2$, 305.1164; Found, 305.1166.

[3-Amino-6-(4-hydroxyphenyl)pyrazin-2-yl](phenyl)methanone (67)



A mixture of (3-amino-6-(4-methoxyphenyl)pyrazin-2-yl)(phenyl)methanone (**66**) (305 mg, 1.0 mmol) and sodium ethanethiolate (494 mg, 5 mmol) in DMF (5 mL) was 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), 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 **67** (220 mg, 76%) as a yellowish solid.

m.p.: 204.5 – 206.2 °C.

^{1}H-NMR (DMSO-d_6, 400 MHz) 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).

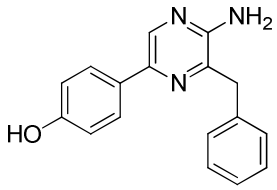
^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 194.4, 160.3, 155.6, 153.5, 138.7, 131.3, 130.1, 129.3, 128.7, 127.6, 126.6, 126.0, 115.8.

MS (EI, 70 eV) m/z (%): 291 [M^+] (100), 290 (95), 263 (12), 262 (24), 105 (25).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{17}H_{13}N_3O_2$, 291.1008; Found, 291.1001.

4-(5-Amino-6-benzylpyrazin-2-yl)phenol (68)



A stirred solution of (3-amino-6-(4-hydroxyphenyl)pyrazin-2-yl)(phenyl)methanone (**67**) (291 mg, 1.0 mmol), ethylene glycol (2 mL) and hydrazine hydrate (0.5 mL) was 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 sand bad 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. Purification by flash chromatography (CH_2Cl_2/Et_2O, 1,5:1) furnished the compound **68** (257 mg, 93%) as a colourless solid.

m.p.: 201.6 – 203.1 °C.

^{1}H-NMR (DMSO-d_6, 400 MHz) 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).

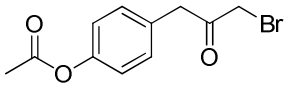
^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 158.3, 152.7, 147.3, 138.5 (2), 128.9, 128.2, 127.6 (2), 127.4, 126.0, 115.4, 38.3.

MS (EI, 70 eV) m/z (%): 277 [M^+] (100), 276 (83), 130 (8).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / 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) Calcd for $C_{17}H_{15}N_3O$, 277.1215; Found, 277.1201.

4-(3-Bromo-2-oxopropyl)phenyl acetate (71)

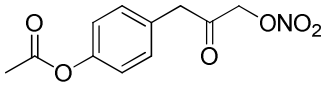


A Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (42 g, 48.9 mmol, 2.5 equiv). The flask was heated with a heat gun (400 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Zinc dust (3.18 g, 48.9 mmol, 2.5 equiv) 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 (**70**; 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 **71** 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.

4-[3-(Nitrooxy)-2-oxopropyl]phenyl acetate (72)

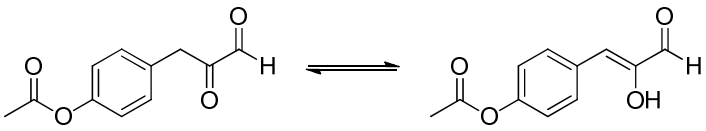


This compound was prepared according to the known procedure. A solution of $AgNO_3$ (390 mg, 2.3 mmol, 2.3 equiv) in MeCN (1 mL) was added to a solution of **71** (274 mg, 1 mmol) in MeCN (1 mL). The resulting mixture was then stirred for 18 h at 25 °C, filtrated, quenched with a sat. aq. NH_4Cl solution (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 **72** as a colourless solid (246 mg, 98%).

^{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.

4-(2,3-Dioxopropyl)phenyl acetate (69)

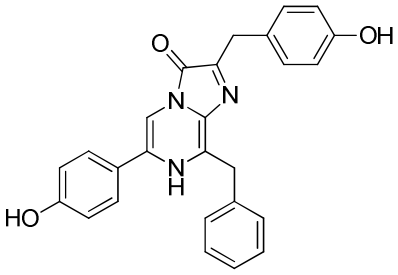


$NaOAc \cdot 3H_2O$ (700 mg, 5 mmol) was slowly added to a solution of **72** (1.28 g, 5 mmol) in DMSO (50 mL). The reaction mixture was stirred at 25 °C for 1 h and then poured into ice-water. The resulting mixture was saturated with sodium chloride and then extracted with diethyl ether (3 × 50 mL). The organic phase was washed with water (50 mL), aqueous sodium hydrogen carbonate (50 mL) and then again with water. Removal of the solvent by distillation under reduced pressure followed by drying *in vacuo* afforded the pure expected derivative **69** as a colourless solid (721 mg, 70%).

^{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 (46):



A mixture of **69** (145 mg, 0.7 mmol), Coelenteramine **68** (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 (**46**) (134 mg, 64%) as a yellowish solid.

m.p.: 175.2 – 178.5 °C.

^{1}H-NMR (600 MHz, DMSO-d_6) δ: 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 [M^+] (24), 393 (23), 317 (24), 277 (55), 261 (100), 107 (32), 91 (25).

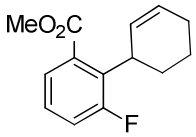
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3164, 3043, 3028, 1612, 1512, 1440, 1373, 1229, 1152, 826, 697.

HRMS (EI) Calcd for $C_{26}H_{21}N_3O_3$, 423.1583; Found, 423.1570.

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

3.4.1. Metalations with $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (73)

Methyl 2-cyclohex-2-en-1-yl-3-fluorobenzoate (77a):



3-fluoro-benzoic acid methyl ester (**76**; 2.46 g, 16.0 mmol) dissolved in THF (10 mL) was reacted with a solution of $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**75**) (0.52 M in THF, 16.2 mL, 8.4 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP4**. The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 1.6 mL) and 3-bromocyclohexene (2.7 g, 16.8 mmol) were then 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 (60 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 (Et_2O/pentane 1:9) furnished the compound **77a** (2.96 g, 90%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.42-7.39 (m, 1 H), 7.28-7.10 (m, 2 H), 5.85-5.77 (m, 1 H), 5.66-5.60 (m, 1 H), 4.12-4.01 (m, 1 H), 3.88 (s, 3 H), 2.22-2.00 (m, 3 H), 1.96-1.83 (m, 2 H), 1.80-1.63 (m, 1H).

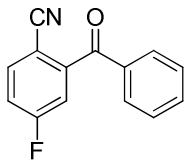
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 168.5 (d, *J* = 3.9 Hz), 161.9 (d, *J* = 248.7 Hz) , 133.4 (dd, *J* = 5.2 Hz, *J* = 44.3 Hz), 129.3 (d, *J* = 1.3 Hz), 127.2 (d, *J* = 9.3 Hz), 126.8 (d, *J* = 2.3 Hz), 124.9 (d, *J* = 3.4 Hz), 118.5 (d, *J* = 23.5 Hz), 52.1, 36.2 (d, *J* = 1.3 Hz), 29.1 (d, *J* = 1.6 Hz), 24.6, 22.9.

MS (EI, 70 eV) m/z (%): 234 [M^+] (16), 202 (100), 184 (34), 159 (16), 146 (23), 133 (21), 73 (16), 69 (17), 40 (18).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3021, 2933, 2860, 2837, 1722, 1651, 1609, 1576, 1452, 1432, 1283, 1254, 1240, 1192, 1169, 1140, 1130, 1072, 1049, 999, 932, 903, 871, 812, 802, 794, 770, 734, 719, 693, 684, 622.

HRMS (EI) Calcd for $C_{14}H_{15}FO_2$, 234.1056; Found, 234.1058.

2-Benzoyl-4-fluorobenzonitrile (79a):



4-fluoro-benzonitrile (**78**; 1.9 g, 16 mmol) dissolved in THF (15 mL) was reacted with a solution of $TMP_2Mn \cdot 2MgCl_2 \cdot 4LiCl$ (**75**) (0.44 M in THF, 22 mL, 9.6 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 2 h according to **TP4**. The reaction mixture was then cooled to –30 °C, CuCN·2LiCl (1 M solution in THF, 3.2 mL) and benzoyl chloride (2.9 g, 20.8 mmol) were then added dropwise and the reaction mixture was allowed to warm up slowly

to 20 °C for 3 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (60 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 (Et_2O/pentane 2:8) furnished the compound **79a** (2.4 g, 68%) as a colourless solid.

mp.: 77.8 – 88.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.87 – 7.77 (m, 4 H), 7.67 – 7.62 (m, 1 H), 7.52 – 7.17 (m, 2 H), 7.30 (t, *J* = 8.8 Hz, 1 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 190.8, 162.0 (d, *J* = 262.1 Hz), 136.6 (d, *J* = 9.8 Hz), 136.3, 135.5 (d, *J* = 4.6 Hz), 134.2, 129.8 (d, *J* = 0.8 Hz), 128.8, 117.9 (d, *J* = 23.5 Hz), 117.2, 109.2 (d, *J* = 3.9 Hz).

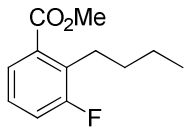
MS (EI, 70 eV) m/z (%): 225 [M^+] (29), 148 (14), 105 (100), 77 (30), 74 (16), 59 (22), 45 (15).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3348, 3103, 1066, 1049, 2921, 2229, 1963, 1908, 1733, 1652, 1637, 1597, 1578, 1533, 1484, 1449, 1404, 1363, 1316, 1302, 1280, 1230, 1198, 1178, 1134, 1106, 1072, 1024, 1000, 974, 922, 881, 853, 830, 807, 740, 728, 714, 696, 672, 645, 623.

HRMS (EI) Calcd for $C_{14}H_8FNO$, 225.0590; Found, 225.0589.

3.4.2. Metalations with $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (74)

Methyl 2-butyl-3-fluorobenzoate (77b):



3-fluoro-benzoic acid methyl ester (**76**; 2.46 g, 16.0 mmol) dissolved in THF (10 mL) was reacted with a solution of $TMP_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$ (**76**) (0.43 M in THF, 28.0 mL, 12.0 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h according to **TP5**. 1-iodo-butane (3.5 g, 19.2 mmol) and fluorostyrene (370 mg) were then added dropwise and the reaction mixture was allowed to stirr at 25°C overnight. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (60 mL), 2N HCl (20 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 (Et_2O/pentane 1:9) furnished the compound **77b** (2.7 g, 83%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.63-7.6 (m, 1 H), 7.22-7.11 (m, 2 H), 3.88 (s, 3 H), 2.97-2.92 (m, 2 H), 1.60-1.50 (m, 2 H), 1.46-1.33 (m, 2 H), 0.93 8 (t, *J* = 7.2 Hz, 3 H).

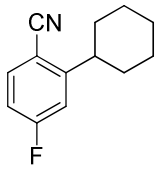
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 167.3 (d, *J* = 3.6 Hz), 161.4 (d, *J* = 244.1 Hz), 132.0, 126.3 (d, *J* = 8.8 Hz), 126.0 (d, *J* = 3.6 Hz), 118.5 (d, *J* = 24.0 Hz), 52.1, 32.7, 25.7 (d, *J* = 4.1 Hz), 22.8, 13.8.

MS (EI, 70 eV) m/z (%): 210 [M^+] (15), 181 (20), 179 (57), 168 (35), 149 (100), 136 (64), 109 (63), 83 (12), 41 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2931, 2873, 1724, 1610, 1579, 1456, 1433, 1379, 1360, 1199, 1166, 1141, 1091, 999, 931, 879, 832, 812, 773, 754.

HRMS (EI) Calcd for $C_{12}H_{15}FO_2$, 210.1056; Found, 210.1043.

2-Cyclohexyl-4-fluorobenzonitrile (79b):



4-fluoro-benzonitrile (**78**; 2.1 g, 17.0 mmol) dissolved in THF (10 mL) was reacted with a solution of $TMP_2Fe \cdot 2MgCl_2 \cdot 4LiCl$ (**76**) (0.45 M in THF, 28.5 mL, 12.8 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 18 h according to **TP5**. 1-iodo-cyclohexane (4.28 g, 20.4 mmol) and fluorostyrene (370 mg) were then added dropwise and the reaction mixture was allowed to stirr at 25°C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (60 mL), 2N HCl (20 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 (Et_2O/pentane 1:9) furnished the compound **79b** (2.4 g, 69%) as a colourless solid.

mp.: 56.4 – 58.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.53 (dd, *J* = 6.7 Hz, *J* = 4.5 Hz, 1 H), 7.49 – 7.44 (m, 1 H), 7.11 – 7.04 (m, 1 H), 2.92 – 2.80 (m, 1 H), 1.93 – 1.71 (m, 5 H), 1.49 – 1.17 (m, 5 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 163.0 (d, *J* = 256.0 Hz), 136.4 (d, *J* = 16.2 Hz), 132.3 (d, *J* = 6.7 Hz), 131.6 (d, *J* = 9.8 Hz), 118.5, 116.5 (d, *J* = 25 Hz), 108.4 (d, *J* = 3.9 Hz), 36.9, 32.7, 26.5, 25.9.

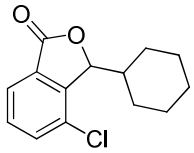
MS (EI, 70 eV) m/z (%): 203 [M^+] (32), 160 (13), 148 (19), 147 (100), 135 (12), 134 (33), 41 (15).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929, 2852, 2226, 1605, 1585, 1489, 1448, 1409, 1372, 1289, 1238, 1183, 1135, 1097, 1011, 945, 926, 914, 890, 811, 778, 735, 687, 607.

HRMS (EI) Calcd for $C_{13}H_{14}FN$, 203.1110; Found, 203.1099.

3.4.3. Metalations with $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (75)

4-Chloro-3-cyclohexyl-2-benzofuran-1(3*H*)-one (81):



Methyl-3-chloro-benzoate (**80**; 2.56 g, 15 mmol) dissolved in THF (12 mL) was reacted with a solution of $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**77**) (0.35 M in THF, 15 mL, 5.52 mmol) at 0 °C and the reaction mixture was then stirred at this temperature for 3.5 h according to **TP6**. Cyclohexane carboxaldehyde (2.24 g, 20.0 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C for 2 h. The resulting mixture was then quenched with a sat. aq. NaCl solution, a small amount of NH_4Cl solution (60 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 [Al_3O_3: (Et_2O/pentane 1:9)] furnished the compound **81** (2.7 g, 73%) as a colourless solid.

mp.: 114.3 – 119.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.74 (d, *J* = 7.7 Hz, 1 H), 7.57 (dt, *J* = 7.7 Hz, *J* = 1.2 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1 H), 5.4 (s, 1H), 2.47 – 2.33 (m, 1 H), 1.95 – 1.75 (m, 2 H), 1.69 – 1.53 (m, 3 H), 1.37 – 0.98 (m, 3 H), 0.95 – 0.74 (m, 2 H).

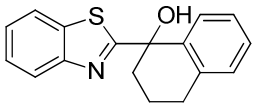
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 169.4, 145.6, 134.3, 130.5, 128.9, 128.6, 123.8, 84.9, 38.9, 30.4, 26.4, 25.8, 25.6, 23.9.

MS (EI, 70 eV) m/z (%): 250 [M^+] (1), 170 (27), 168 (100), 83 (4), 41 (2).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3503, 3073, 2927, 2856, 1757, 1601, 1585, 1459, 1450, 1373, 1344, 1317, 1307, 1280, 1253, 1205, 1135, 1066, 1050, 976, 958, 925, 897, 862, 844, 819, 790, 769, 741, 689, 658, 619, 603.

HRMS (EI) Calcd for $C_{14}H_{15}ClO_2$, 250.0761; Found, 250.0768.

1-(1,3-Benzothiazol-2-yl)-1,2,3,4-tetrahydronaphthalen-1-ol (83)



Benzothiazole (**82**; 1.9 g, 14 mmol) dissolved in THF (14 mL) was reacted with a solution of $TMP_3La \cdot 3MgCl_2 \cdot 5LiCl$ (**77**) (0.35 M in THF, 14 mL, 4.9 mmol) at 0 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP6**. *α*-Tetralone (2.46 g, 16.8 mmol) was then added dropwise and the reaction mixture was allowed to warm up slowly to 20 °C for 2 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (60 mL), 2N HCl (20 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 (Et_2O/pentane 1:5) furnished the compound **83** (3.4 g, 87%) as a yellowish solid.

mp.: 107.8 – 111.1 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.01 – 7.87 (m, 2 H), 7.51 – 7.37 (m, 2 H), 7.28 – 7.13 (m, 4 H), 3.98 – 3.93 (m, 1 H), 3.06 – 2.90 (m, 2 H), 2.57 – 2.48 (m, 1 H), 2.39 – 2.31 (m, 1 H), 2.21 – 1.98 (m, 2 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 180.1, 139.0, 137.3, 135.5, 129.2, 128.6, 128.3, 126.5, 125.9, 124.8, 123.9, 121.6, 75.3, 39.4, 29.4, 19.3.

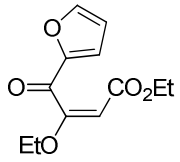
MS (EI, 70 eV) m/z (%): 281 [M^+] (15), 263 (81), 262 (100), 136 (24), 135 (14), 91 (15).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3319, 3063, 2932, 2873, 2832, 1895, 1595, 1499, 1491, 1455, 1439, 1393, 1333, 1316, 1276, 1238, 1221, 1180, 1168, 1117, 1094, 1042, 1015, 913, 875, 860, 777, 730, 724, 702, 648.

HRMS (EI) Calcd for $C_{17}H_{15}NOS$, 281.0874; Found, 281.0876.

3.4. Selective Magnesiation or Zincation of Highly Functionalized Alkenes and Cycloalkenes using TMP Bases

Ethyl (2*E*)-3-ethoxy-4-(2-furyl)-4-oxobut-2-enoate (*E*-86a)



To a solution of ethyl (2*E*)-3-ethoxyacrylate (***E*-84a**) (144 mg, 1.0 mmol) dissolved in THF (1.0 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 1.1 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 equiv) was added. After 30 min of stirring at the same temperature, 2-furoylchloride (196 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm slowly to -10 °C for 1.5 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:2) using 3% Et_3N furnished the compound ***E*-86a** (190 mg, 80%) as a yellowish solid.

mp: 76.8 – 78.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.60 (s, 1 H), 7.17 (d, *J* = 3.6 Hz, 1 H), 6.53 (q, *J* = 19 Hz, 1 H), 5.27 (s, 1 H), 4.03 – 3.95 (m, 4 H), 1.37 (t, *J* = 7.5 Hz, 3 H), 1.07 (t, *J* = 6.7 Hz, 3 H).

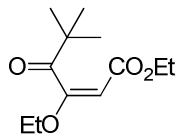
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 178.1, 165.9, 165.5, 151.1, 147.4, 119.5, 112.5, 94.3, 65.9, 60.2, 13.9.

MS (70 eV, EI) m/z (%): 238 [M^+] (34), 210 (22), 193 (15), 165 (10), 95 (100).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3148, 3126, 3095, 2987, 1701, 1663, 1620, 1567, 1461, 1407, 1390, 1374, 1354, 1307, 1257, 1142, 1107, 1234, 1142, 1107, 1056, 1031, 1023, 973, 908, 891, 880, 856, 816, 790, 757, 610.

HRMS (EI) Calcd for $C_{12}H_{14}O_5$, 238.0841; Found, 238.0835.

Ethyl (2*E*)-3-ethoxy-5,5-dimethyl-4-oxohex-2-enoate (*E*-86b)



To a solution of ethyl (2*E*)-3-ethoxyacrylate (***E*-84a**) (721 mg, 5.0 mmol) dissolved in THF (5.0 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 5.45 mL, 6.0 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and CuCN·2LiCl (1 M solution in THF, 5.5 mL, 5.5 mmol) was added. After 30 min of stirring at the same temperature, ethyl 2,2-dimethylpropanoyl chloride (1.2 g, 10.0 mmol) was added and the resulting mixture was allowed to warm slowly to -10 °C for 1.5 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3

× 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl lether/pentane 1:9) using 3% Et_3N furnished the compound ***E*-86b** (960 mg, 84%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.05 (s, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 3.91 (q, *J* = 6.9 Hz, 2 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.22 (s, 9 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

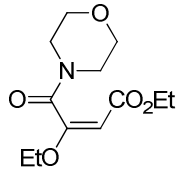
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 207.2, 168.9, 166.6, 91.9, 65.6, 60.1, 43.1, 26.6, 14.0.

MS (70 eV, EI) m/z (%): 228 [M^+] (1), 183 (16), 172 (38), 171 (84), 143 (100), 115 (47), 87 (20), 57 (17).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979, 2939, 2907, 2873, 1704, 1608, 1480, 1462, 1446, 1392, 1372, 1346, 1294, 1210, 1136, 1109, 1294, 1210, 1136, 1109, 1063, 1029, 1014, 990, 894, 863, 812, 784, 758, 707.

HRMS (EI) Calcd for $C_{12}H_{20}O_4$, 228.1362; Found, 228.1421.

Ethyl (2E)-3-ethoxy-4-morpholin-4-yl-4-oxobut-2-enoate (*E*-86c)



To a solution of ethyl (2*E*)-3-ethoxyacrylate (***E*-84a**) (288 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 2.18 mL, 2.4 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) was added. After 30 min of stirring at the same temperature, morpholine-4-carbonyl chloride (449 mg, 3.0 mmol) was added and the resulting mixture was allowed to warm slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/isohexane 6:4) using 3% Et_3N furnished the compound ***E*-86c** (298 mg, 58%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.09 (s, 1 H), 4.07 (q, *J* = 7.8 Hz, 2 H), 3.87 (q, *J* = 7.0 Hz, 2 H), 3.70 – 3.58 (m, 6 H), 3.28 (t, *J* = 4.4 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.18 (t, *J* = 7.5 Hz, 3 H).

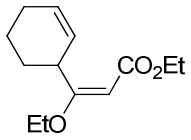
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.6, 163.9, 163.4, 93.0, 66.1, 65.5, 60.0, 46.3, 41.4, 14.1, 13.8.

MS (70 eV, EI) m/z (%): 257 [M^+] (9), 212 (31), 184 (23), 142 (67), 115 (41), 86 (100), 70 (28), 69 (54), 56 (15), 42 (16).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 2923, 2858, 1707, 1655, 1614, 1465, 1441, 1392, 1371, 1342, 1271, 1213, 1137, 1109, 1071, 1046, 1033, 1020, 945, 893, 859, 841, 813, 786, 752, 626.

HRMS (EI) Calcd for $C_{12}H_{19}NO_5$, 257.1263; Found, 257.1256.

Ethyl (2*E*)-3-cyclohex-2-en-1-yl-3-ethoxyacrylate (*E*-86d)



To a solution of ethyl (2*E*)-3-ethoxyacrylate (***E*-84a**) (144 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 1.1 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -60 °C and CuCN·2LiCl (1 M solution in THF, 0.05 mL, 5 mol%) and 3-bromocyclohexene (209 mg, 1.3 mmol) was added. The resulting mixture was allowed to warm slowly to 25 °C overnight and was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:99) using Al_2O_3 furnished the compound ***E*-86d** (188 mg, 83%) as a colourless oil.

^{1}H-NMR (Acetone, 400 MHz) δ: 5.74 – 5.69 (m, 1 H), 5.47 – 5.44 (m, 1 H), 4.97 (s, 1 H), 4.57 – 4.51 (m, 1 H), (q, *J* = 7.1 Hz, 2 H), 3.85 (q, *J* = 7.1 Hz, 2 H), 2.05 – 1.95 (m, 2 H), 1.85 – 1.75 (m, 2 H), 1.69 – 1.52 (m, 2 H), 1.28 (t, *J* = 6.8 Hz, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

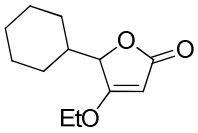
^{13}C-NMR (Acetone, 100 MHz) δ: 206.0, 178.0, 167.7, 127.3, 91.0, 64.6, 59.5, 38.0, 27.6, 25.1, 22.5, 14.7, 14.3.

MS (70 eV, EI) m/z (%): 224 [M^+] (34), 178 (100), 150 (21), 134 (24), 121 (13), 108 (10), 105 (25), 87 (13), 79 (19), 77 (11).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3024, 2934, 2863, 2838, 1705, 1608, 1477, 1445, 1392, 1376, 1295, 1278, 1259, 1246, 1131, 1112, 1094, 1055, 984, 928, 906, 864, 839, 812, 723, 669, 609.

HRMS (EI) Calcd for $C_{13}H_{20}O_3$, 224.1412; Found, 224.1411.

5-Cyclohexyl-4-ethoxyfuran-2(5*H*)-one (86e)



To a solution of ethyl (2*E*)-3-ethoxyacrylate (***E*-84a**) (288 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 2.0 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -60 °C and cyclohexane carbaldehyde (247 mg, 2.2 mmol) was added and the resulting mixture was allowed to warm to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl lether/pentane 1:9) using Al_2O_3 furnished the compound **86e** (357 mg, 85%) as a yellowish solid.

mp: 55.8 – 57.6 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.99 – 4.98 (m, 1 H), 4.57 (s, 1 H), 4.09 – 3.99 (m, 2 H), 1.82 – 1.53 (m, 5 H), 1.38 (td, *J* = 7.1 Hz, , *J* = 2.0 Hz, 3 H), 1.33 – 1.06 (m, 6 H).

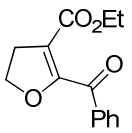
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 180.4, 173.1, 89.1, 82.8, 68.4, 39.2, 28.9, 26.1, 25.9, 25.7, 25.0, 14.0.

MS (70 eV, EI) m/z (%): 210 [M^+] (5), 128 (100), 100 (55), 83 (16), 55 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3094, 2985, 2922, 2852, 1738, 1623, 1470, 1454, 1445, 1375, 1349, 1223, 1310, 1240, 1162, 1114, 1099, 1084, 1075, 1032, 986, 945, 917, 890, 875, 847, 811, 790, 757, 742, 678, 657.

HRMS (EI) Calcd for $C_{12}H_{18}O_3$, 210.1256; Found, 210.1260.

Ethyl 2-benzoyl-4,5-dihydrofuran-3-carboxylate (86f)



To a solution of ethyl 4,5-dihydrofuran-3-carboxylate (**84b**) (142 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Zn·2MgCl_2·2LiCl$ (**8**) (0.44 M in THF, 1.36 mL, 0.6 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and CuCN·2LiCl (1 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30

min of stirring at the same temperature, benzoyl chloride (182 mg, 1.3 mmol) was added and the resulting mixture was allowed to warm slowly to 0 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/pentane 1:3) using 3% Et_3N furnished the compound **86f** (197 mg, 80%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.95 – 7.91 (m, 2 H), 7.63 – 7.57 (m, 1 H), 7.50 – 7.42 (m, 2 H), 4.7 (td, *J* = 1.3 Hz, *J* = 9.7 Hz, 2 H), 3.93 (qd, *J* = 7.1 Hz, *J* = 1.1 Hz, 2 H), 3.10 (td, *J* = 9.9 Hz, *J* = 1.1 Hz, 2 H), 0.87 (td, *J* = 7.1 Hz, *J* = 0.9 Hz, 3 H).

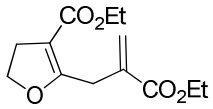
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 188.9, 163.9, 161.3, 135.0, 134.2, 129.3, 128.7, 107.7, 73.0, 60.2, 29.6, 13.6.

MS (70 eV, EI) m/z (%): 246 [M^+] (34), 201 (21), 141 (15), 105 (100), 77 (46).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2927, 1703, 1681, 1639, 1597, 1581, 1450, 1394, 1374, 1337, 1316, 1291, 1246, 1189, 1172, 1114, 1046, 1024, 1000, 981, 941, 883, 860, 820, 794, 759, 709, 687.

HRMS (EI) Calcd for $C_{14}H_{14}O_4$, 246.0892; Found, 246.0881.

Ethyl 2-[2-(ethoxycarbonyl)prop-2-en-1-yl]-4,5-dihydrofuran-3-carboxylate (86g)



To a solution of ethyl 4,5-dihydrofuran-3-carboxylate (**84b**) (142 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**8**) (0.44 M in THF, 1.36 mL, 0.6 mmol) at 25 ^oC and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -60 °C and CuCN·2LiCl (1 M solution in THF, 0.05 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, ethyl 2-(bromomethyl)acrylate (425 mg, 2.2 mmol) was added and the resulting mixture was allowed to warm slowly to -30 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography using (diethyl lether/pentane 20:80) 3% NEt_3 furnished the compound **86g** (211 mg, 83%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.21 (s, 1 H), 5.50 (t, *J* = 1.6 Hz, 1 H), 4.36 (td, *J* = 9.6 Hz, *J* = 1.4 Hz, 2 H), 4.21 – 4.11 (m, 4 H), 3.67 (d, *J* = 1.0 Hz, 2 H), 2.87 (td, *J* = 9.8 Hz, *J* = 1.0 Hz, 2 H), 1.27 – 1.21 (m, 6 H).

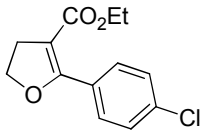
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 167.9, 166.3, 165.6, 135.7, 126.1, 103.2, 70.5, 60.8, 59.5, 30.1, 29.6, 14.3, 14.1.

MS (70 eV, EI) m/z (%): 254 [M^+] (46), 208 (100), 180 (98), 135 (49), 107 (20), 79 (20), 67 (13), 41 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2979, 2903, 2936, 2873, 1714, 1692, 1633, 1477, 1464, 1445, 1418, 1396, 1368, 1334, 1272, 1240, 1182, 1171, 1111, 1048, 1028, 988, 954, 893, 862, 834, 816, 758, 638.

HRMS (EI) Calcd for $C_{13}H_{18}O_5$, 254.1154; Found, 254.1131.

Ethyl 2-(4-chlorophenyl)-4,5-dihydrofuran-3-carboxylate (86h)



To a solution of ethyl 4,5-dihydrofuran-3-carboxylate (**84b**) (142 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**8**) (0.44 M in THF, 1.36 mL, 0.6 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(2-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 4-chloro-iodo benzoate (308 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was allowed to warm to 25 °C fot 1 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 5:95) using 3% Et_3N furnished the compound **86h** (139 mg, 55%) as a yellowish solid.

mp: 51.0 – 54.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.74 (dq, *J* = 8.6 Hz, *J* = 1.9 Hz, 2 H), 7.32 (dq, *J* = 8.6 Hz, *J* = 2.6 Hz, 2 H), 5.54 – 4.46 (m, 2 H), 4.13 (qd, *J* = 2.4 Hz, 2 H), 3.08 (td, *J* = 2.9 Hz, 2 H), 1.21 (td, *J* = 2.4 Hz, 3 H).

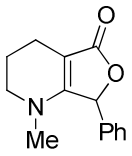
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.1, 164.2, 136.1, 130.7, 127.8, 103.2, 69.9, 59.8, 31.7, 14.2.

MS (70 eV, EI) m/z (%): 252 [^{35}Cl-M^{+}] (41), 182 (11), 180 (41), 178 (24), 140 (28), 138 (100), 115 (15), 111 (23).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3110, 3085, 2977, 2928, 2095, 2871, 1693, 1620, 1593, 1563, 1488, 1460, 1441, 1404, 1367, 1333, 1307, 1296, 1280, 1241, 1190, 1183, 1172, 1152, 1110, 1092, 1076, 1038, 1028, 1014, 1004, 965, 926, 835, 753, 728, 657, 627.

HRMS (EI) Calcd for $C_{13}H_{13}ClO_3$, 252.0553; Found, 252.0545.

1-Methyl-7-phenyl-2,3,4,7-tetrahydrofuro[3,4-*b*]pyridin-5(1*H*)-one (86i)



To a solution of ethyl 1-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**84c**) (168 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Mg\cdot 2LiCl$ (**7**) (0.7 M in THF, 1.7 mL, 1.2 mmol) at -10 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -60 °C and benzaldehyde (212 mg, 2.0 mmol) was added dropwise. The resulting mixture was then allowed to warm to 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/isohexane 1:1) furnished the compound **86i** (149 mg, 65%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.39 – 7.27 (m, 5 H), 5.66 (s, 1 H), 3.22 – 3.09 (m, 2 H), 2.58 (s, 3 H), 2.43 – 2.23 (m, 2 H), 2.02 – 1.83 (m, 2 H).

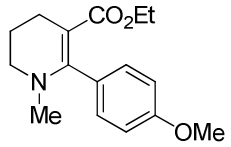
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 173.0, 165.0, 135.1, 129.3, 128.9, 127.7, 92.2, 78.4, 49.9, 37.9, 21.2, 17.2.

MS (70 eV, EI) m/z (%): 229 [M^{+}] (100), 184 (26), 124 (16), 115 (10), 95 (16), 77 (13), 67 (27), 42 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2927, 2852, 2809, 1726, 1624, 1586, 1505, 1496, 1455, 1446, 1419, 1370, 1340, 1297, 1265, 1226, 1201, 1173, 1149, 1070, 1045, 988, 936, 920, 778, 749, 707, 675, 641.

HRMS (EI) Calcd for $C_{14}H_{15}NO_2$, 229.1103; Found, 229.1095.

Ethyl 2-(4-methoxyphenyl)-1-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (86j)



To a solution of ethyl 1-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**84c**) (168 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Mg \cdot 2LiCl$ (**7**) (0.7 M in THF, 1.7 mL, 1.2 mmol) at -10 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and $ZnCl_2$ (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was added and the resulting mixture was stirred for 30 min at the same temperature. The mixture was allowed to warm to 25 °C and then $Pd(dba)_2$ (11 mg, 2 mol%) and $P(2\text{-furyl})_3$ (9 mg, 4 mol%) dissolved in THF (2 mL) and mixed with 4-iodoanisole (304 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The reaction mixture was stirred at 25 °C overnight and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 3:7) furnished the compound **86j** (220 mg, 80%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.07 – 7.02 (m, 2 H), 6.88 – 6.83 (m, 2 H), 3.85 – 3.72 (m, 5 H), 3.20 – 3.1672 (m, 2 H), 2.50 (s, 3 H), 2.48 – 2.44 (m, 2 H), 1.88 – 1.80 (m, 2 H), 0.85 (t, *J* = 7.2 Hz, 3 H).

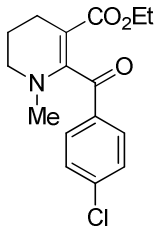
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 168.9, 159.1, 156.7, 131.0, 129.3, 113.3, 97.1, 58.4, 55.0, 50.8, 40.2, 23.8, 21.3, 13.9.

MS (70 eV, EI) m/z (%): 275 [M^+] (65), 146 (44), 230 (35), 202 (100), 148 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 2898, 2935, 2840, 1685, 1653, 1609, 1561, 1510, 1479, 1462, 1442, 1388, 1368, 1322, 1297, 1244, 1220, 1187, 1171, 1116, 1068, 1033, 920, 826, 785, 763, 731, 700, 611.

HRMS (EI) Calcd for $C_{16}H_{21}NO_3$, 275.1521; Found, 275.1516.

Ethyl 2-(4-chlorobenzoyl)-1-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (86k)



To a solution of ethyl 1-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**84c**) (340 mg, 2.0 mmol) dissolved in THF (2 mL) was added $TMP_2Mg \cdot 2LiCl$ (**7**) (0.7 M in THF, 3.42 mL, 2.4 mmol) at -10 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and $CuCN \cdot 2LiCl$ (1 M solution in THF, 2.2 mL, 2.2 mmol) was added. After 30 min of stirring at the same temperature, 4-chlorobenzoyl chloride (700 mg, 4.0 mmol) was added and the resulting mixture was allowed to warm slowly to 25 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 4:6) furnished the compound **86k** (307 mg, 50%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.96 – 7.91 (m, 2 H), 7.47 – 7.42 (m, 2 H), 3.96 – 3.88 (m, 2 H), 3.25 – 3.22 (m, 2 H), 2.69 (s, 3 H), 2.49 – 2.43 (m, 2 H), 2.01 – 1.93 (m, 2 H), 1.02 (t, *J* = 7.1 Hz, 3 H).

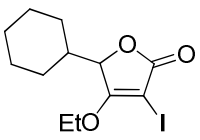
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 193.0, 167.3, 153.1, 139.6, 134.6, 129.8, 129.1, 95.0, 59.4, 50.3, 39.3, 21.1, 14.1.

MS (70 eV, EI) m/z (%): 307 [^{35}Cl-M^+] (100), 262 (46), 234 (68), 198 (20), 139 (77), 111 (46).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3325, 3088, 2958, 2934, 2846, 1733, 1669, 1559, 1481, 1461, 1451, 1418, 1397, 1386, 1367, 1339, 1299, 1267, 1251, 1217, 1197, 1164, 1142, 1104, 1065, 1035, 1009, 940, 915, 835, 819, 798, 764, 743, 733, 723, 669.

HRMS (EI) Calcd for $C_{16}H_{18}ClNO_3$, 307.0975; Found, 307.0975.

5-Cyclohexyl-4-ethoxy-3-iodofuran-2(5*H*)-one (86l)



To a solution of ethyl 5-cyclohexyl-4-ethoxyfuran-2(5*H*)-one (**86e**) (210 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Mg \cdot 2LiCl$ (**7**) (0.7 M in THF, 1.7 mL, 1.2 mmol) at -30 °C and the resulting mixture was stirred for 20 min according to **TP7**. Iodine (517 mg, 2.0 mmol) dissolved in THF (2 mL) was then added and the resulting mixture was stirred for additional 20 min. The reaction mixture was then quenched with a sat. aq. $Na_2S_2O_3$ solution (5 mL) and a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by

flash chromatography (diethyl ether/pentane 3:7) furnished the compound **86l** (296 mg, 88%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.74 (q, *J* = 7.1 Hz, 2 H), 4.6 (d, *J* = 2.8 Hz, 1 H), 1.98 – 1.69 (m, 6 H), 1.4 (t, *J* = 6.9 Hz, 3 H), 1.85 – 1.0 (m, 5 H).

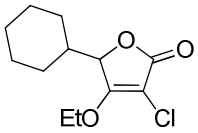
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 178.0, 171.0, 82.3, 68.0, 46.9, 39.5, 28.9, 26.2, 25.8, 25.7, 24.6, 15.4.

MS (70 eV, EI) m/z (%): 336 [M^+] (34), 254 (100), 226 842), 83 (13), 55 (17).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2926, 2853, 1749, 1609, 1470, 1449, 1372, 1318, 1292, 1272, 1257, 1182, 1103, 1086, 1041, 995, 976, 941, 914, 985, 870, 746, 691, 657.

HRMS (EI) Calcd for $C_{12}H_{17}IO_3$, 336.0222; Found, 336.0218.

3-Chloro-5-cyclohexyl-4-ethoxyfuran-2(5*H*)-one (86m)



To a solution of ethyl 5-cyclohexyl-4-ethoxyfuran-2(5*H*)-one (**86e**) (210 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Mg\cdot 2LiCl$ (**7**) (0.7 M in THF, 1.7 mL, 1.2 mmol) at -30 °C and the resulting mixture was stirred for 20 min according to **TP7**. The mixture was then cooled to -50 °C and $Cl_3F_3C_2$ (281 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 3:7) furnished the compound **86m** (164 mg, 67%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 4.66 (q, *J* = 6.9 Hz, 2 H), 4.51 (d, *J* = 3.0 Hz, 1 H), 1.85 – 1.56 (m, 5 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.81 – 1.04 (m, 6 H).

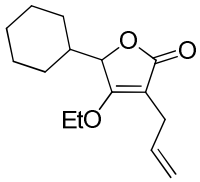
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 169.1, 92.6, 81.8, 68.1, 39.2, 28.8, 26.1, 25.7, 25.6, 24.6, 15.3.

MS (70 eV, EI) m/z (%): 244 [^{35}Cl-M^+] (15), 164 (35), 162 (100), 134 (46), 83 (35), 71 (32), 55 (41).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2983, 2930, 2856, 1722, 1643, 1473, 1451, 1375, 1318, 1297, 1288, 1254, 1201, 1182, 1082, 1012, 951, 921, 866, 833, 791, 774, 749, 679.

HRMS (EI) Calcd for $C_{12}H_{17}ClO_3$, 244.0866; Found, 244.0852.

3-Allyl-5-cyclohexyl-4-ethoxyfuran-2(5*H*)-one (86n)



To a solution of ethyl 5-cyclohexyl-4-ethoxyfuran-2(5*H*)-one (**86e**) (210 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Mg \cdot 2LiCl$ (**7**) (0.7 M in THF, 1.7 mL, 1.2 mmol) at -30 °C and the resulting mixture was stirred for 20 min according to **TP7**. $CuCN \cdot 2LiCl$ (1 M solution in THF, 0.05 mL, 5 mol%) and allyl bromide (240 mg, 2 mmol) were then added and the resulting mixture was allowed to warm to 25 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 3:7) furnished the compound **86n** (160 mg, 64%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.93 – 5.8 (m, 1 H), 5.06 – 4.96 (m, 2 H), 4.49 (d, *J* = 2.6 Hz, 1 H), (d, 4.39 – 4.26 (m, 2 H), 3.09 (d, *J* = 6.4 Hz, 2 H), 1.84 – 1.56 (m, 5 H), 1.42 – 1.02 (m, 6 H), 1.35 (td, *J* = 6.9 Hz, 3 H).

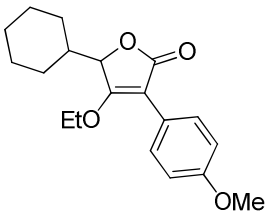
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.8, 173.0, 135.7, 115.4, 99.6, 81.6, 67.0, 39.2, 29.3, 27.3, 26.3, 26.0, 25.8, 24.8, 15.3.

MS (70 eV, EI) m/z (%): 250 [M^+] (38), 221 (25), 204 (11), 168 (100), 140 (37), 122 (22), 111 (42), 83 (17), 55 (36), 41 (17).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 2983, 2927, 2854, 1747, 1654, 1479, 1449, 1432, 1412, 1376, 1342, 1324, 1301, 1253, 1184, 1137, 1111, 1084, 1074, 1033, 992, 958, 912, 891, 784, 772, 762, 722, 695, 658.

HRMS (EI) Calcd for $C_{15}H_{22}O_3$, 250.1569; Found, 250.1562.

5-Cyclohexyl-4-ethoxy-3-(4-methoxyphenyl)furan-2(5*H*)-one (86o)



To a solution of ethyl 5-cyclohexyl-4-ethoxyfuran-2(5*H*)-one (**86e**) (210 mg, 1.0 mmol) dissolved in THF (1 mL) was added $TMP_2Mg \cdot 2LiCl$ (**7**) (0.7 M in THF, 1.7 mL, 1.2 mmol) at -30 °C and the resulting mixture was stirred for 20 min according to **TP7**. $ZnCl_2$ (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was then added and the resulting mixture was stirred for 30 min at the same temperature. The mixture was allowed to warm to 25 °C and then $Pd(dba)_2$ (17 mg, 3 mol%) and P(2-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 4-iodoanisole (304 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The reaction mixture was stirred at 25 °C overnight and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:8) furnished the compound **86o** (215 mg, 68%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.39 – 7.34 (m, 2 H), 6.89 – 6.84 (m, 2 H), 4.63 (d, *J* = 3.0 Hz, 1 H), 4.05 – 3.95 (m, 2 H), 3.78 (s, 3 H), 1.94 – 1.63 (m, 5 H), 1.50 – 1.13 (m, 6 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

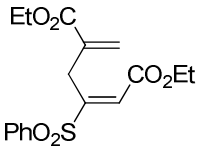
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 173.5, 172.3, 159.1, 130.9, 122.2, 113.5, 104.3, 81.1, 68.4, 55.1, 39.5, 29.4, 26.3, 25.9, 25.8, 24.7, 15.0.

MS (70 eV, EI) m/z (%): 316 [M^+] (100), 234 (41), 205 (33), 149 (26), 119 (20), 108 (10), 55 (14).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2927, 2853, 1742, 1652, 1607, 1511, 1450, 1377, 1343, 1322, 1308, 1289, 1246, 1169, 1103, 1076, 1046, 1032, 1005, 994, 973, 940, 877, 833, 803, 758, 728, 696.

HRMS (EI) Calcd for $C_{19}H_{24}O_4$, 316.1675; Found, 316.1669.

Diethyl (2*E*)-5-methylene-3-(phenylsulfonyl)hex-2-enedioate (*E*-86p)



To a solution of ethyl (2*E*)-3-(phenylsulfonyl)acrylate (***E*-84d**) (240 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.92 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 15 min according to **TP7**. The mixture was then cooled to -60 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 10 mol%) was added. After 5 min of stirring at the same temperature, ethyl 2-(bromomethyl)acrylate (289 mg, 1.5 mmol) was added and the

resulting mixture was allowed to warm slowly to -20 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography using (diethyl ether/pentane 1:2) furnished the compound ***E*-86p** (235 mg, 67%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.86 – 7.82 (m, 2 H), 7.65 – 7.60 (m, 1 H), 7.55 – 7.49 (m, 2 H), 7.13 (d, *J* = 0.7 Hz, 1 H), 6.07 (s, 1 H), 5.34 (t, *J* = 1.7 Hz, 1 H), 4.23 – 4.09 (m, 4 H), 3.75 (s, 2 H), 1.34 – 1.16 (m, 6 H).

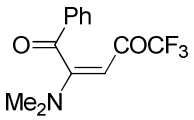
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.8, 163.8, 153.9, 137.7, 135.1, 134.1, 129.4, 128.9, 128.6, 125.7, 61.5, 61.0, 28.7, 14.0.

MS (70 eV, EI) m/z (%): 352 [M^+] (1), 307 (18), 243 (12), 211 (58), 165 (100), 140 (16), 137 (67), 124 (36), 109 (39), 77 (36), 52 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3447, 3064, 2984, 2940, 1773, 1727, 1635, 1585, 1467, 1447, 1393, 1369, 1308, 1270, 1235, 1191, 1180, 1147, 1084, 1017, 998, 857, 753, 732, 687.

HRMS (EI) Calcd for $C_{17}H_{20}O_6S$, 352.0981; Found, 352.0984.

(2*E*)-2-(Dimethylamino)-5,5,5-trifluoro-1-phenylpent-2-ene-1,4-dione (*E*-86q)



To a solution of (3*E*)-4-(dimethylamino)-1,1,1-trifluorobut-3-en-2-one (***E*-84e**) (334 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.85 mL, 2.4 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -30 °C and CuCN·2LiCl (1 M solution in THF, 2.2 mL, 2.2 mmol) was added. After 30 min of stirring at the same temperature, benzoyl chloride (560 mg, 4.0 mmol) was added and the resulting mixture was allowed to warm slowly to 0 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/pentane 1:1) furnished the compound ***E*-86q** (433 mg, 80%) as a yellow solid.

mp: 123.0 – 124.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.92 – 7.88 (m, 2 H), 7.62 – 7.56 (m, 1 H), 7.50 – 7.44 (m, 2 H), 5.44 (s, 1 H), 3.11 (s, 3 H), 2.94 (s, 3 H).

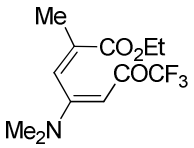
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 192.4, 175.4 (q, *J* = 33.0 Hz), 165.1, 134.3, 129.2 (d, *J* = 71.2 Hz), 117.3, (q, *J* = 290.7 Hz), 87.6, 40.7 (d, *J* = 56.7 Hz).

MS (70 eV, EI) m/z (%): 271 [M^+] (94), 202 (38), 166 (94), 116 (45), 105 (100), 82 (27), 77 (67), 51 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3959, 2932, 1674, 1641, 1595, 1542, 1494, 1452, 1411, 1377, 1322, 1310, 1282, 1244, 1224, 1179, 1133, 1102, 1062, 1026, 1001, 980, 939, 915, 849, 825, 774, 748, 734, 703, 694.

HRMS (EI) Calcd for $C_{13}H_{12}F_3NO_2$, 271.0820; Found, 271.0814.

Ethyl (2*E*,4*E*)-4-(dimethylamino)-7,7,7-trifluoro-2-methyl-6-oxohepta-2,4-dienoate (86r)



To a solution of (3*E*)-4-(dimethylamino)-1,1,1-trifluorobut-3-en-2-one (***E*-84e**) (334 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.85 mL, 2.4 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -60 °C and CuCN·2LiCl (1 M solution in THF, 0.10 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, ethyl 2-(bromomethyl)acrylate (579 mg, 3.0 mmol) was added and the resulting mixture was allowed to warm slowly to 0 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/pentane 1:1) furnished the iosomerized compound **86r** (474 mg, 85%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.28 (br, 1 H), 5.22 (s, 1 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 3.02 (s, 6 H), 1.71 (d, *J* = 1.2 Hz, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H).

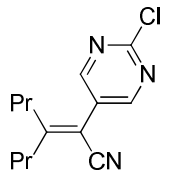
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 175.1 (q, *J* = 31.4 Hz), 166.9, 163.7, 133.8, 132.7, 117.9 (q, *J* = 292.0 Hz), 87.3, 61.5, 41.7 (d, *J* = 57.8 Hz), 13.8 (d, *J* = 19.9 Hz).

MS (70 eV, EI) m/z (%): 279 [M^+] (5), 234 (14), 206 (100), 138 (12), 44 (9).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2451, 3081, 2980, 2905, 2201, 1772, 1738, 1650, 1455, 1430, 1376, 1317, 1286, 1235, 1219, 1181, 1111, 1043, 990, 950, 925, 847, 773, 721, 630.

HRMS (EI) Calcd for $C_{12}H_{16}F_3NO_3$, 279.1082; Found, 279.1075.

2-(2-Chloropyrimidin-5-yl)-3-propylhex-2-enenitrile (87a)



To a solution of 3-propylhex-2-enenitrile (**84f**) (274 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 2.2 mL, 2.4 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -20 °C and $ZnCl_2$ (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was then added and the resulting mixture was stirred for 30 min at the same temperature. $Pd(dba)_2$ (34 mg, 3 mol%) and $P(2\text{-furyl})_3$ (28 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 2-chloro-5-iodopyrimidine (576 mg, 2.4 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was then heated at 40 °C for 3 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 2:8) furnished the compound **87a** (463 mg, 93%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.53 (s, 2 H), 2.6 – 2.55 (m, 2 H), 2.16 – 2.10 (m, 2 H), 1.68 – 1.56 (m, 2 H), 1.52 – 1.39 (m, 2 H), 1.02 (t, *J* = 7.3 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H).

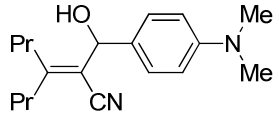
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 168.2, 160.9, 127.2, 117.0, 103.5, 37.6, 34.0, 21.6, 13.9.

MS (70 eV, EI) m/z (%): 249 [^{35}Cl-M^+] (27), 194 (21), 168 (26), 166 (100), 158 (13), 84 (29), 55 (12), 40 (27).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2933, 2873, 2213, 1610, 1573, 1530, 1465, 1457, 1398, 1344, 1255, 1160, 1094, 1076, 1009, 945, 930, 843, 773, 746, 635.

HRMS (EI) Calcd for $C_{13}H_{16}ClN_3$, 249.1033; Found, 249.1025.

2-[[4-(Dimethylamino)phenyl](hydroxy)methyl]-3-propylhex-2-enenitrile (87b)



To a solution of 3-propylhex-2-enenitrile (**84f**) (274 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 2.2 mL, 2.4 mmol) at 25 °C and the resulting mixture

was stirred for 30 min according to**TP7**. The resulting mixture was then cooled to -60 °C and 4-(dimethylamino)benzaldehyde (358 mg, 2.4 mmol) dissolved in THF (3 mL) was added. The mixture was allowed to warm to -10 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/pentane 2:8) furnished the compound **87b** (389 mg, 68%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.33 – 7.28 (m, 2 H), 6.74 – 6.69 (m, 2 H), 5.51 (s, 1 H), 2.94 (s, 6 H), 2.41 (t, *J* = 8.1 Hz, 2 H), 2.25 (t, , *J* = 7.9 Hz, 2 H), 1.61 – 1.35 (m, 5 H), 0.96 (q, , *J* = 8.3 Hz, 6 H).

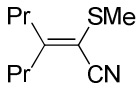
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 100.4, 150.3, 128.8, 126.8, 117.4, 115.0, 112.4, 69.3, 40.4, 38.0, 33.6, 21.4, 14.1, 13.8.

MS (70 eV, EI) m/z (%): 286 [M^+] (32), 268 (66), 243 (43), 239 (65), 150 (100), 134 (34), 121 (28), 120 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3443, 2960, 2932, 2872, 2830, 2212, 1613, 1521, 1455, 1349, 1227, 1184, 1164, 1129, 1034, 945, 818, 765, 737.

HRMS (EI) Calcd for $C_{18}H_{26}N_2O$, 286.2045; Found, 286.1899.

2-(Methylthio)-3-propylhex-2-enenitrile (87c)



To a solution of 3-propylhex-2-enenitrile (**84f**) (274 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 2.2 mL, 2.4 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. The mixture was then cooled to -20 °C and *S*-methyl methanethiosulfonate (303 mg, 2.4 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:9) furnished the compound **87c** (256 mg, 70%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.44 – 2.31 (m, 7 H), 1.57 – 1.37 (m, 4 H), 0.95 – 0.90 (m, 6 H).

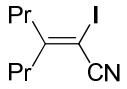
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 164.1, 115.3, 105.0, 38.3, 34.9, 21.4, 21.0, 16.8, 13.9, 13.6.

MS (70 eV, EI) m/z (%): 183 [M^+] (100), 154 (42), 140 (20), 126 (62), 113 (11), 99 (54), 84 (17), 79 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2930, 2872, 2212, 1731, 1586, 1530, 1464, 1456, 1435, 1380, 1341, 1320, 1277, 1256, 1205, 1125, 1092, 1070, 1037, 970, 936, 893, 775, 745, 707.

HRMS (EI) Calcd for $C_{10}H_{17}NS$, 183.1082; Found, 183.1071.

2-Iodo-3-propylhex-2-enenitrile (87d)



To a solution of 3-propylhex-2-enenitrile (**84f**) (137, 1. mmol) dissolved in THF (1 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 1.1 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. Then iodine (336 mg, 1.3 mmol) dissolved in THF (3 mL) was added the the resulting mixture was stirred for 1 h and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:9) furnished the compound **87d** (247 mg, 94%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.54 – 2.49 (m, 2 H), 2.32 – 2.26 (m, 2 H), 1.59 – 1.41 (m, 4 H), 0.95 (q, *J* = 7.31 Hz, 6 H).

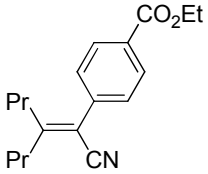
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 170.6, 117.5, 54.1, 41.3, 38.2, 21.5, 20.5, 13.6.

MS (70 eV, EI) m/z (%): 263 [M^+] (100), 222 (62), 94 (65), 67 (42), 56 (42), 61 (56).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2932, 2872, 2208, 1586, 1464, 1456, 1381, 1339, 1282, 1250, 1198, 1129, 1092, 1076, 1016, 915, 892, 829, 764, 744, 666.

HRMS (EI) Calcd for $C_9H_{14}IN$, 263.0171; Found, 263.0167.

Ethyl 4-(1-cyano-2-propylpent-1-en-1-yl)benzoate (87e)



To a solution of 3-propylhex-2-enenitrile (**84f**) (137 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 1.1 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to**TP7**. The mixture was then cooled to -20 °C and $ZnCl_2$ (1.0 M solution in THF, 1.2 mL, 1.1 mmol) was then added and the resulting mixture was stirred for 30 min at the same temperature. $Pd(dba)_2$ (17 mg, 3 mol%) and P(2-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with ethyl 4-iodobenzoate (360 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 2:8) furnished the compound **87e** (228 mg, 80%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.05 – 8.03 (m, 2 H), 7.24 – 7.32 (m, 2 H), 4.37 (q, *J* = 7.2 Hz, *J* = 1.0 Hz, 2 H), 2.56 – 2.53 (m, 2 H), 2.15 – 2.13 (m, 2 H), 1.65 – 1.59 (m, 2 H), 1.15 – 1.89 (m, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.02 (t, *J* = 7.6 Hz, 3 H), 0.80 (t, *J* = 7.2 Hz, 3 H).

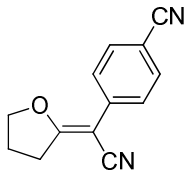
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.7, 163.9, 138.5, 130.1, 129.6, 128.7, 18.1, 110.4, 60.9, 37.1, 33.6, 21.4, 21.0, 14.0, 13.7.

MS (70 eV, EI) m/z (%): 285 [M^+] (66), 202 (80), 228 (32), 173 (100), 156 (46), 142 (30), 129 (33), 115 (38).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2934, 2973, 2210, 1716, 1608, 1568, 1465, 1405, 1367, 1308, 1270, 1178, 1100, 1012, 932, 861, 773, 707, 627, 576.

HRMS (EI) Calcd for $C_{18}H_{23}NO_2$, 285.1729; Found, 285.1724.

4-[(*E*)-Cyano(dihydrofuran-2(3*H*)-ylidene)methyl]benzonitrile (*E*-87f)



To a solution of (2*E*)-dihydrofuran-2(3*H*)-ylideneacetonitrile (***E*-84g**) (330 mg, 3.0 mmol) dissolved in THF (3 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 2.77 mL, 3.6 mmol) at 25 °C and the resulting mixture was stirred for 30 min according to **TP7**. $Pd(dba)_2$ (33 mg, 2 mol%) and P(2-furyl)$_3$ (27 mg, 4 mol%) dissolved in THF (2 mL) and mixed with 4-iodo-benzonitrile (824 mg, 3.6 mmol) were then transferred via cannula to the reaction mixture. The

reaction mixture was stirred at 25 °C for 1 h and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/isohexane 4:6) furnished the compound ***E*-87f** (384 mg, 62%) as a yellowish solid.

mp: 165.7 – 167.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.81 – 7.77 (m, 2H), 7.61 – 7.57 (m, 2 H), 4.62 (t, *J* = 7.1 Hz, 2 H), 3.13 (t, *J* = 7.8 Hz, 2 H), 2.24 (5, *J* = 7.1 Hz, 2 H).

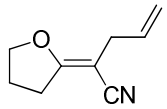
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.5, 136.6, 132.1, 126.8, 118.8, 109.7, 84.9, 33.5, 23.1.

MS (70 eV, EI) m/z (%): 210 [M^+] (58), 168 (100), 140 (68), 113 (9), 41 (4).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3122, 3079, 3044, 3007, 2971, 2909, 2854, 2217, 2204, 1923, 1791, 1725, 1669, 1617, 1601, 1550, 1509, 1502, 1477, 1462, 1429, 1413, 1381, 1311, 1283, 1267, 1228, 1197, 1175, 1141, 1123, 1102, 1010, 946, 927, 879, 853, 834, 781, 745, 723, 647.

HRMS (EI) Calcd for $C_{13}H_{10}N_2O$, 210.0793; Found, 210.0786.

(2*E*)-2-(Dihydrofuran-2(3*H*)-ylidene)pent-4-enenitrile (*E*-87g)



To a solution of (2*E*)-dihydrofuran-2(3*H*)-ylideneacetonitrile (***E*-84g**) (330 mg, 3.0 mmol) dissolved in THF (3 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 2.77 mL, 3.6 mmol) at 25 °C and the resulting mixture was stirred for 30 according to **TP7**. The mixture was then cooled to -60 °C and CuCN·2LiCl (1 M solution in THF, 0.15 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, allyl bromide (720 mg, 6.0 mmol) was added and the resulting mixture was allowed to warm slowly to -20 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 2:8) furnished the compound ***E*-87g** (299 mg, 67%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.78 – 6.65 (m, 1 H), 5.08 – 4.96 (m, 2 H), 4.26 (td, *J* = 7.1 Hz, *J* = 0.5 Hz, 2 H), 2.84 – 2.77 (m, 4 H), 2.11 – 2.02 (5, *J* = 7.5 Hz, 2 H).

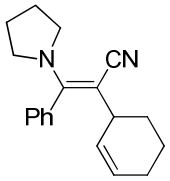
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 171.6, 133.8, 120.4, 116.0, 80.1, 73.7, 30.4, 23.8.

MS (70 eV, EI) m/z (%): 149 [M^+] (79), 121 (80), 107 (100), 79 (61), 52 (37), 42 (28).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2451, 3081, 2980, 2905, 2201, 1772, 1738, 1650, 1455, 1430, 1376, 1317, 1286, 1235, 1219, 1181, 1111, 1043, 990, 950, 925, 847, 773, 721, 630.

HRMS (EI) Calcd for $C_9H_{11}NO$, 149.0841; Found, 149.0842.

(2*E*)-2-Cyclohex-2-en-1-yl-3-phenyl-3-pyrrolidin-1-ylacrylonitrile (*Z*-87h)



To a solution of (2*E*)-3-phenyl-3-pyrrolidin-1-ylacrylonitrile (***E*-84h**) (198 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 1.1 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 1.5 h according to **TP7**. CuCN·2LiCl (1 M solution in THF, 0.05 mL, 5 mol%) and 3-bromocyclohexene (322 mg, 2.0 mmol) were then added and the resulting mixture was allowed to warm to 25 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:9) using Al_2O_3 furnished the compound ***Z*-87h** (175 mg, 63%) as a colourless solid.

mp: 137.6 – 139.4 °C.

^{1}H-NMR (Acetone-d_6, 400 MHz) δ: 7.48 – 7.39 (m, 3 H), 7.24 – 7.21 (m, 2 H), 5.66 – 5.61 (m, 1 H), 5.45 – 5.41 (m, 1 H), 3.36 – 3.32 (m, 4 H), 2.41 – 2.34 (m, 1 H), 1.96 – 1.76 (m, 2 H), 1.85 – 1.82 (m, 4 H), 1.74 – 1.67 (m, 1 H), 1.64 – 1.53 (m, 2 H), 1.28 – 1.15 (m, 1 H).

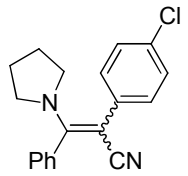
^{13}C-NMR (Acetone-d_6, 150 MHz) δ: 158.7, 138.0, 131.7, 129.6, 128.7, 122.5, 82.6, 51.5, 38.3, 26.0, 25.0, 22.7.

MS (70 eV, EI) m/z (%): 279 [M^+] (14), 249 (100), 221 (21), 198 (40), 160 (11), 130 (17), 104 (13).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3022, 2948, 2923, 2876, 2363, 2337, 2173, 1558, 1491, 1441, 1417, 1345, 1285, 1253, 1207, 1186, 1160, 1069, 1028, 977, 926, 900, 875, 859, 802, 763, 720, 707, 680.

HRMS (EI) Calcd for $C_{19}H_{22}N_2$, 278.1783; Found, 278.1777.

(2/Z*E*)-2-(4-Chlorophenyl)-3-phenyl-3-pyrrolidin-1-ylacrylonitrile (87i)



To a solution of (2*E*)-3-phenyl-3-pyrrolidin-1-ylacrylonitrile (***E*-84h**) (198 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPMgCl·LiCl (**6**) (1.1 M in THF, 1.1 mL, 1.2 mmol) at 25 °C and the resulting mixture was stirred for 1.5 h according to **TP7**. The mixture was then cooled to -20 °C and $ZnCl_2$ (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was then added and the resulting mixture was stirred for 30 min at the same temperature. $Pd(dba)_2$ (17 mg, 3 mol%) and P(2-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed 1-chloro-4-iodobenzene (310 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (EtOAc/pentane 2:8) using Al_2O_3 furnished the compound **87i** (271 mg, 88%) in an mixture of isomers (E/Z = 50/50) as a yellow solid.

mp: 110.8 – 112.3 °C.

^{1}H-NMR (Acetone-d$_6$, 400 MHz) δ: 7.49 (s, 1 H), 7.38 – 7.23 (m, 2.17 H), 7.02 – 6.98 (m, 0.6 H), 6.95 – 6.92 (m, 0.63 H), 3.53 – 3.50 (m, 1 H), 2.97 – 2.93 (m, 1 H), 1.96 – 1.92 (m, 1.2 H), 1.79 – 1.75 (m, 1.1 H).

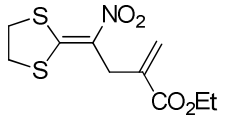
^{13}C-NMR (Acetone-d$_6$, 150 MHz) δ: 160.8, 159.5, 138.0, 137.3, 136.4, 136.2, 131.8, 131.5, 130.8, 130.4, 130.3, 129.8, 129.4, 129.2, 128.5, 128.3, 123.3, 122.7, 81.4, 78.8, 52.7, 52.0, 26.0, 25.8.

MS (70 eV, EI) m/z (%): 308 [M^+] (100), 239 (13), 203 (14), 157 (18), 104 (15).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2962, 2926, 2886, 2363, 2337, 2176, 1905, 1739, 1579, 1564, 1530, 1486, 1475, 1455, 1443, 1418, 1399, 1345, 1299, 1275, 1259, 1208, 1172, 1147, 1086, 1071, 1046, 1011, 967, 946, 930, 918, 881, 854, 833, 821, 765, 730, 708, 694.

HRMS (EI) Calcd for $C_{19}H_{17}ClN_2$, 308.1080; Found, 308. 1082.

Ethyl 2-[2-(1,3-dithiolan-2-ylidene)-2-nitroethyl]acrylate (88a)



To a solution of 2-(nitromethylene)-1,3-dithiolane (**84i**) (163 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.92 mL, 1.2 mmol) at 0 °C and the resulting mixture was stirred for 15 min according to **TP7**. The mixture was then cooled to -60 °C and CuCN·2LiCl (1 M solution in THF, 0.10 mL, 10 mol%) was added. After 5 min of stirring at the same temperature, ethyl 2-(bromomethyl)acrylate (289 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm slowly to –20 °C for 1.5 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography using Al_2O_3 (diethyl ether/pentane 2:1) furnished the compound **88a** (215 mg, 78%) as a yellowish solid.

mp: 105.1 – 106.7°C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.20 (s, 1 H), 5.43 (s, 1 H), 4.21 (qd, *J* = 7.1 Hz, *J* = 2.9 Hz, 2 H), 3.82 – 3.80 (m, 2 H), 3.50 (d, *J* = 1.5 Hz, 4 H), 1.29 (tt, *J* = 2.7 Hz, *J* = 1.5 Hz, 3 H)

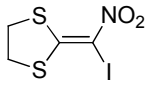
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 166.2, 134.3, 125.0, 61.0, 39.8, 37.8, 34.4, 14.1.

MS (70 eV, EI) m/z (%): 275 [M^+] (0.21), 229 (100), 201 (22), 199 (28), 155 (12).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3407, 2982, 2965, 2942, 2900, 1712, 1631, 1532, 1446, 1423, 1409, 1247, 1238, 1151, 1114, 1056, 996, 983, 931, 985, 884, 857, 821, 809, 765, 720, 678.

HRMS (EI) Calcd for $C_{10}H_{13}NO_4S_2$, 275.0286; Found, 275.0276.

2-[Iodo(nitro)methylene]-1,3-dithiolane (88b)



To a solution of 2-(nitromethylene)-1,3-dithiolane (**84i**) (163 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.92 mL, 1.2 mmol) at 0 °C and the resulting mixture was stirred for 15 min according to **TP7**. Then iodine (303 mg, 1.2 mmol) dissolved in THF (2 mL) was added dropwise and the resulting mixture was stirred for 1 h. The reaction mixture was then quenched with a sat. aq. $Na_2S_2O_3$ solution (5 mL), and an aq. NH_4Cl solution (3 mL) and extracted with ethylacetate (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography using Al_2O_3 (EtOAc/pentane 1:2) furnished the compound **88b** (250 mg, 89%) as a yellowish solid.

mp: 174.9 – 176.7 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.98 – 3.84 (m, 2 H), 3.58 – 3.54 (m, 2 H).

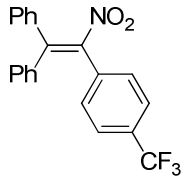
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 42.1, 37.3.

MS (70 eV, EI) m/z (%): 289 [M^+] (100), 215 (70), 162 (23), 92 (12), 88 (38).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2923, 2852, 1463, 1433, 1415, 1264, 1238, 1153, 1108, 1045, 992, 957, 933, 846, 805, 737, 729, 673.

HRMS (EI) Calcd for $C_4H_4INO_2S_2$, 288.8728; Found, 288.8728.

1-(1-Nitro-2,2-diphenylvinyl)-4-(trifluoromethyl)benzene (88c)



To a solution of 1,1'-(2-nitroethene-1,1-diyl)dibenzene (**84j**) (225 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.92 mL, 1.2 mmol) at -20 °C and the resulting mixture was stirred for 1 h according to **TP7**. $Pd(dba)_2$ (17 mg, 3 mol%) and $P(2\text{-furyl})_3$ (14 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 4-iodo(trifluoromethyl)benzene (354 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was allowed to warm to 25 °C for 4 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 5:95) furnished the compound **88c** (203 mg, 55%) as a yellowish solid.

mp: 125.5 – 127.2 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.57 – 7.53 (m, 2 H), 7.44 – 7.22 (m, 10 H), 7.10 – 7.06 (m, 2 H).

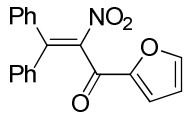
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 148.0, 141.3, 137.6 (d, *J* = 51.9 Hz), 136.0, 131.2 (q, *J* = 33.1 Hz), 130.3 (d, *J* = 54.4 Hz), 129.4 (d, *J* = 15.7 Hz), 128.8, 128.5 (d, *J* = 4.5 Hz), 125.7 (q, *J* = 3.7 Hz), 123.6 (d, *J* = 272.6 Hz).

MS (70 eV, EI) m/z (%): 369 [M^+] (28), 323 (100), 283 (13), 253 (25), 126 (5).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2862, 1760, 1658, 1628, 1612, 1521, 1444, 1408, 1353, 1319, 1165, 1157, 1125, 1110, 1066, 1019, 999, 871, 791, 769, 759, 699, 671.

HRMS (EI) Calcd for $C_{21}H_{14}F_3NO_2$, 369.0977; Found, 369.0976.

1-(2-Furyl)-2-nitro-3,3-diphenylprop-2-en-1-one (88d)



To a solution of 1,1'-(2-nitroethene-1,1-diyl)dibenzene (**84j**) (338 mg, 1.5 mmol) dissolved in THF (1.5 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.5 mL, 1.95 mmol) at -20 °C and the resulting mixture was stirred for 1 h according to **TP7**. Then CuCN·2LiCl (1 M solution in THF, 1.65 mL, 1.65 mmol) was added at -30 °C. After 30 min of stirring at the same temperature, 2-furoylchloride (391 mg, 3.0 mmol) was added and the resulting mixture was allowed to warm slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 3:7) furnished the compound **88d** (235 mg, 55%) as a yellowish solid.

mp: 125.7 – 127.5 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.52 – 7.40 (m, 4 H), 7.37 – 7.23 (m, 5 H), 7.20 – 7.16 (3 H), 6.43 (q, *J* = 2.0 Hz, 1 H).

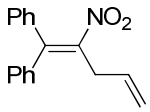
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 174.7, 151.1, 149.4, 147.8, 144.4, 136.7, 130.7, 130.3, 128.8, 128.6, 120.6, 112.9.

MS (70 eV, EI) m/z (%): 208 (100), 205 (13), 178 (43), 165 (13), 95 (41).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3112, 3139, 3060, 1658, 1599, 1565, 1516, 1489, 1456, 1444, 1385, 1333, 1283, 1154, 1117, 1081, 1024, 984, 902, 884, 810, 795, 762, 752, 697.

HRMS (EI) Calcd for $C_{19}H_{13}NO_4$, 319.0845; Found, 319.0956.

1,1'-(2-Nitropenta-1,4-diene-1,1-diyl)dibenzene (88e)



To a solution of 1,1'-(2-nitroethene-1,1-diyl)dibenzene (**84j**) (338 mg, 1.5 mmol) dissolved in THF (1.5 mL) was added TMPZnCl·LiCl 3) (1.3 M in THF, 1.5 mL, 1.95 mmol) at -20 °C and the resulting mixture was stirred for 1 h according to **TP7**. Then CuCN·2LiCl (1 M solution in THF, 0.075 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, allyl

bromide (360 mg, 3.0 mmol) was added and the resulting mixture was allowed to warm slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 5:95) furnished the compound **88e** (261 mg, 70%) as a yellowish solid.

mp: 91.8 – 93.4 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.43 – 7.39 (m, 3 H), 7.37 – 7.32 (m, 3 H), 7.30 – 7.18 (m, 4 H), 5.96 – 5.83 (1 H), 5.31 – 5.22 (m, 2 H), 3.47 (dt, *J* = 5.9 Hz, 1.7 Hz, 2 H).

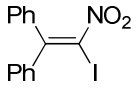
MS (70 eV, EI) m/z (%): 265 [M^+] (18), 248 (38), 224 (42), 218 (73), 203 (39), 191 (22), 178 (27), 141 (42), 91 (100).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 148.6, 140.8, 138.0, 131.8, 128.0, 128.5, 128.1, 118.5, 35.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 3029, 2991, 2855, 1971, 1905, 1877, 1741, 1639, 1574, 1515, 1490, 1443, 1419, 1347, 1297, 1278, 1226, 1185, 1075, 1030, 995, 959, 936, 871, 790, 768, 728, 702.

HRMS (EI) Calcd for $C_{17}H_{15}NO_2$, 265.1103; Found, 265.1099.

1,1'-(2-Iodo-2-nitroethene-1,1-diyl)dibenzenem (88f)



To a solution of 1,1'-(2-nitroethene-1,1-diyl)dibenzene (**84j**) (338 mg, 1.5 mmol) dissolved in THF (1.5 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.5 mL, 1.95 mmol) at -20 °C and the resulting mixture was stirred for 1 h according to **TP7**. Then iodine (774 mg, 3 mmol) dissolved in THF (3 mL) was added dropwise and the resulting mixture was stirred for 30 min. The reaction mixture was then quenched with a sat. aq. $Na_2S_2O_3$ solution (5 mL), and an aq. NH_4Cl solution (3 mL) and extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 5:95) furnished the compound **88f** (367 mg, 70%) as a yellowish solid.

mp: 114.1 – 116.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.43 – 7.38 (m, 3 H), 7.35 – 7.28 (m, 5 H), 7.22 – 7.16 (m, 2 H).

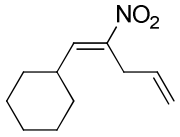
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 150.8, 140.1, 137.0, 129.4, 129.0, 128.7, 128.6, 128.0.

MS (70 eV, EI) m/z (%): 350 [M^+] (15), 194 (34), 178 (100), 168 (14), 166 (17), 165 (16).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2842, 1954, 1886, 1572, 1519, 1488, 1445, 1387, 1330, 1277, 1171, 1161, 1106, 1074, 1032, 989, 915, 897, 826, 769, 759, 738, 695.

HRMS (EI) Calcd for $C_{14}H_{10}INO_2$, 350.9756; Found, 350.9751.

[(1*E*)-2-Nitropenta-1,4-dien-1-yl]cyclohexane (*E*-88g)



To a solution of [(*E*)-2-nitrovinyl]cyclohexane (***E*-84k**) (310 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.84 mL, 2.4 mmol) at -50 °C and the resulting mixture was stirred for 30 min according to **TP7**. Then CuCN·2LiCl (1 M solution in THF, 0.10 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, allyl bromide (480 mg, 4.0 mmol) was added and the resulting mixture was allowed to warm slowly to -20 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 1:9) furnished the compound ***E*-88g** (391 mg, 77%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.97 (dd, *J* = 8.5 Hz, *J* = 1.9 Hz, 1 H), 5.85 – 5.72 (m, 1 H), 5.09 – 5.02 (m, 2 H), 3.33 – 3.30 (m, 2 H), 2.32 – 2.20 (m, 1 H), 1.75 – 1.63 (m, 5 H), 1.35 – 1.13 (m, 5 H).

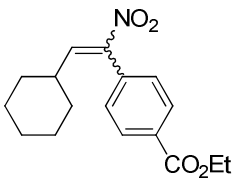
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 147.9, 141.8, 132.8, 116.6, 37.4, 31.7, 30.3, 25.1.

MS (70 eV, EI) m/z (%): 195 [M^+] (0.8), 179 (52), 105 (29), 91 (61), 79 (64), 67 (83), 55 (70), 44 (100).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3083, 2972, 2853, 1665, 1640, 1516, 1448, 1424, 1332, 1223, 1107, 1024, 990, 971, 913, 855, 796, 745, 688.

HRMS (EI) Calcd for $C_{11}H_{17}NO_2$, 195.1259; Found, 195.1278.

Ethyl 4-[(*E*/*Z*)-2-cyclohexyl-1-nitrovinyl]benzoate (88h)



To a solution of [(*E*)-2-nitrovinyl]cyclohexane (***E*-84k**) (310 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.84 mL, 2.4 mmol) at -50 °C and the resulting mixture was stirred for 30 min according to **TP7**. $Pd(dba)_2$ (34 mg, 3 mol%) and P(2-furyl)$_3$ (28 mg, 6 mol%) dissolved in THF (2 mL) and mixed with ethyl 4-iodobenzoate (718 mg, 2.6 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was allowed to warm to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/pentane 1:9) furnished the compound **88h** (338 mg, 57%) as a yellowish solid in a mixture of isomers (E/Z=80:20).

mp: 97.9 – 99.9 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.14 (d, *J* = 8.5 Hz, 2 H, E), 8.06 (d, *J* = 8.5 Hz, 0.58 H, Z), 7.40 (d, *J* = 8.5 Hz, 0.58 H, Z), 7.30 (d, *J* = 8.5 Hz, 2 H, E), 7.29 (d, *J* = 10.9 Hz, 1 H, E), 6.0 (d, *J* = 10.2 Hz, 0.41 H, Z), 4.42 (q, *J* = 7.0 Hz, 2.6 H), 2.56 – 2.43 (m, 0.67 H, Z), 2.09 – 1.96 (m, 1.4 H), 1.91 – 1.65 (m, 6.8 H), 1.42 – 1.40 (m, 3.9 H), 1.35 – 1.11 (m, 6.4 H).

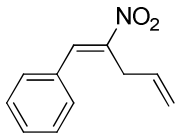
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 165.8 , 165.6, 149.0, 143.6, 135.3, 134.3, 134.2, 131.5, 130.3, 129.9, 129.6, 125.9, 61.2, 37.9, 37.7, 32.1, 31.7, 25.5, 25.3, 25.1, 24.8, 14.3.

MS (70 eV, EI) m/z (%): 303 [M^+] (72), 286 (100), 258 (51), 175 (57), 141 (39), 115 (20), 55 (46).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2992, 2930, 2851, 1708, 1519, 1448, 1405, 177, 1363, 1328, 1272, 1258, 1173, 1122, 1104, 1021, 972, 942, 810, 783, 743, 720, 697.

HRMS (EI) Calcd for $C_{17}H_{21}NO_4$, 303.1471; Found, 303.1465.

[(1*E*)-2-Nitropenta-1,4-dien-1-yl]benzene (*E*-88i)



To a solution of β-trans-nitrostyrene (***E*-84l**) (450 mg, 3.0 mmol) dissolved in THF (3 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 2.77 mL, 3.6 mmol) at -50 °C and the resulting mixture was stirred for 1 h according to **TP7**. Then CuCN·2LiCl (1 M solution in THF, 0.15 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, allyl bromide (720 mg, 6.0 mmol) was added and the resulting mixture was allowed to warm slowly to -20 °C within 2 h. The

reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 1:9) furnished the compound ***E*-88i** (397 mg, 70%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.15 (s, 1H), 7.44 (s, 5 H), 6.03 – 5.91 (m, 1 H), 5.23 – 5.15 (m, 2 H), 3.59 (dt, *J* = 5.3 Hz, *J* = 1.7 Hz, 2 H).

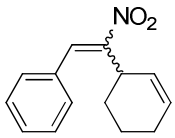
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 148.9, 134.8, 132.2, 131.9, 130.1, 129.6, 128.8, 117.1, 31.0.

MS (70 eV, EI) m/z (%): 189 [M^+] (14), 141 (100), 128 (93), 91 (46), 77 (18), 65 (20), 40 (20).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3028, 2982, 2920, 2833, 1651, 1601, 1576, 1515, 1495, 1448, 1421, 1369, 1321, 1236, 1204, 1204, 1184, 1078, 1039, 1028, 991, 919, 866, 833, 760, 738, 691, 645.

HRMS (EI) Calcd for $C_{11}H_{11}NO_2$, 189.0790; Found, 189.0785.

[(*E*/*Z*)-2-Cyclohex-2-en-1-yl-2-nitrovinyl]benzene (88j)



To a solution of β-trans-nitrostyrene (***E*-84l**) (149 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 0.92 mL, 1.2 mmol) at -50 °C and the resulting mixture was stirred for 1 h according to **TP7**. Then CuCN·2LiCl (1 M solution in THF, 0.05 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, 3-bromocyclohexene (242 mg, 1.5 mmol) was added and the resulting mixture was allowed to warm slowly to -20 °C within 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (pentane) furnished the compound **88j** (112 mg, 49%) as a yellowish oil in a mixture of isomers (E/Z=60:40).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.98 (s, 1 H), 7.50 – 7.24 (m, 5.86 H), 6.36 (s, 0.65 H), 6.07 – 6.01 (m, 0.49 H), 5.86 – 5.79 (m, 0.93 H), 5.75 – 5.68 (m, 0.5 H), 5.58 – 5.52 (m, 0.9 H), 3.93 – 3.83 (m, 1.18 H), 3.57 – 3.49 (m, 0.71 H), 2.26 – 1.87 (m, 5.47 H), 1.81 – 1.56 (m, 2.52 H).

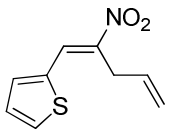
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 155.1, 154.3, 133.6, 132.2, 132.0, 131.7, 129.6, 129.4, 128.9, 128.7, 128.4, 127.8, 126.7, 124.9, 123.7, 38.9, 36.0, 27.1, 26.8, 24.9, 24.3, 22.3, 19.2.

MS (70 eV, EI) m/z (%): 229 [M^+] (5), 182 (94), 167 (82), 154 (42), 141 (66), 115 (48), 91 (100), 81 (74), 77 (57), 57 (65), 44 (95), 41 (51).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 3026, 2932, 2863, 2836, 1642, 1516, 1447, 1332, 1283, 1211, 1158, 1138, 1075, 1051, 1029, 968, 928, 904, 844, 803, 764, 733, 721, 691, 659.

HRMS (EI) Calcd for $C_{14}H_{15}NO_2$, 229.1103; Found, 229.1092.

2-[(1*E*)-2-Nitropenta-1,4-dien-1-yl]thiophene (*E*-88k)



To a solution of 2-[(*E*)-2-nitrovinyl]thiophene (***E*-84m**) (319 mg, 2.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**9**) (1.3 M in THF, 1.85 mL, 2.4 mmol) at -50 °C and the resulting mixture was stirred for 30 min according to **TP7**. Then CuCN·2LiCl (1 M solution in THF, 0.1 mL, 5 mol%) was added. After 5 min of stirring at the same temperature, allyl bromide (480 mg, 4.0 mmol) was added and the resulting mixture was allowed to warm slowly to 25 °C for 2 h. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (5 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. Purification by flash chromatography (diethyl ether/isohexane 5:95) furnished the compound ***E*-88k** (280 mg, 72%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.33 (d, *J* = 0.56 Hz, 1 H), 7.62 (dd, *J* = 5.1 Hz, *J* = 0.75 Hz, 1 H), 7.42 (dd, *J* = 3.7 Hz, *J* = 0.75 Hz, 1 H), 7.17 – 7.14 (m, 1 H), 5.95 – 5.82 (m, 1 H), 5.24 – 5.11 (m, 2 H), 3.75 – 3.72 (m, 2 H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 145.7, 135.0, 134.2, 132.0, 130.9, 128.1, 128.0, 117.3, 31.4.

MS (70 eV, EI) m/z (%): 195 [M^+] (33), 147 (100), 115 (87), 103 (19), 84 (67), 65 (32), 45 (50).

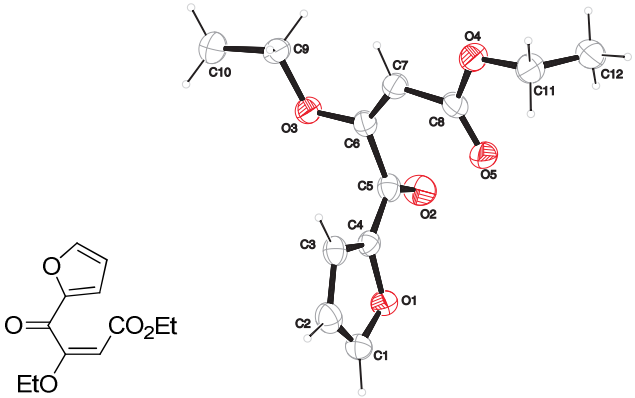
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3107, 3084, 1637, 1512, 1498, 1418, 1375, 1330, 1303, 1237, 1206, 1121, 1079, 1053, 1028, 989, 918, 859, 838, 762, 741, 708, 605, 634.

HRMS (EI) Calcd for $C_9H_9NO_2S$, 195.0354; Found, 195.0348.

D. APPENDIX

1. Data of the X-ray Analysis

Ethyl (2*E*)-3-ethoxy-4-(2-furyl)-4-oxobut-2-enoate (*E*-86a)

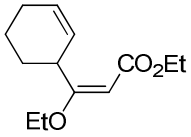


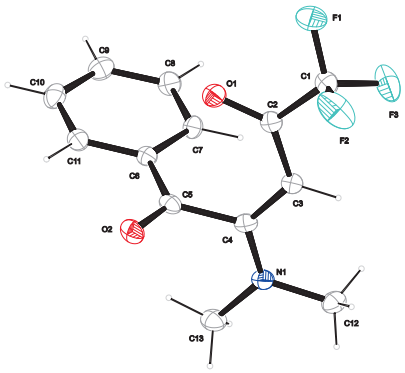
Crystal Data

net formula	$C_{12}H_{14}O_5$
M_r/g mol^{-1}	238.237
crystal size/mm	0.29 × 0.25 × 0.06
T/K	200(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	7.5403(4)
b/Å	8.8297(4)
c/Å	17.7796(8)
α/°	90
β/°	90
γ/°	90
V/Å^3	1183.74(10)
Z	4
calc. density/g cm^{-3}	1.33680(11)
μ/mm^{-1}	0.104

absorption correction	'multi-scan'
transmission factor range	0.95969–1.00000
refls. measured	9386
R_{int}	0.0294
mean σ(*I*)/*I*	0.0244
θ range	4.14–26.33
observed refls.	1151
x, *y* (weighting scheme)	0.0391, 0
hydrogen refinement	constr
Flack parameter	2.4(10)
refls in refinement	1401
parameters	156
restraints	0
$R(F_{obs})$	0.0266
$R_w(F^2)$	0.0630
S	0.977
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.124
min electron density/e Å^{-3}	−0.124

Ethyl (2*E*)-3-cyclohex-2-en-1-yl-3-ethoxyacrylate (*E*-86d)



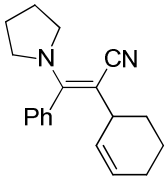


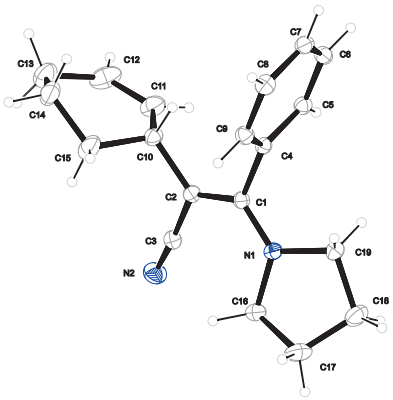
Crystal Data

net formula	$C_{13}H_{12}F_3NO_2$
M_r/g mol^{-1}	271.235
crystal size/mm	0.50 × 0.18 × 0.16
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$Pna2_1$
a/Å	7.4016(5)
b/Å	17.0805(13)
c/Å	9.9297(6)
α/°	90
β/°	90
γ/°	90
V/Å^3	1255.34(15)
Z	4
calc. density/g cm^{-3}	1.43516(17)
μ/mm^{-1}	0.126
absorption correction	'multi-scan'
transmission factor range	0.36768–1.00000
refls. measured	4946
R_{int}	0.0448
mean σ(I)/I	0.0494
θ range	4.52–26.35
observed refls.	954
x, y (weighting scheme)	0.0746, 0
hydrogen refinement	constr
Flack parameter	2.7(14)
refls in refinement	1352
parameters	174
restraints	1
$R(F_{obs})$	0.0429

$R_w(F^2)$	0.1088
S	0.893
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.189
min electron density/e Å^{-3}	−0.157

(2*E*)-2-Cyclohex-2-en-1-yl-3-phenyl-3-pyrrolidin-1-ylacrylonitrile (*Z*-87h)





Crystal Data

net formula	$C_{19}H_{22}N_2$
M_r/g mol^{-1}	278.391
crystal size/mm	0.29 × 0.05 × 0.04
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1/n$
a/Å	9.8493(5)
b/Å	16.0903(10)
c/Å	10.3195(6)
α/°	90
β/°	107.238(3)
γ/°	90
V/Å^3	1561.95(15)

Z	4
calc. density/g cm^{-3}	1.18387(11)
μ/mm^{-1}	0.070
absorption correction	none
refls. measured	10364
R_{int}	0.0659
mean $\sigma(I)/I$	0.0514
θ range	4.14–25.36
observed refls.	1931
x, y (weighting scheme)	0.0481, 0.7810
hydrogen refinement	constr
refls in refinement	2858
parameters	190
restraints	0
$R(F_{obs})$	0.0542
$R_w(F^2)$	0.1357
S	1.036
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.194
min electron density/e Å^{-3}	−0.210

2. Curriculum Vitae

Tomke Bresser

Personal Informations

Date of Birth	06.11.1982
Place of Birth	Tegernsee
Citizenship	German

Publications

1. Bresser, T.; Knochel, P. "**Selective Magnesiation or Zincation of Highly Functionalized Alkenes and Cycloalkenes using 2,2,6,6-Tetramethylpiperidyl Bases."** *Angew. Chem. Int. Ed.* **2011**, *50*, 1914.

2. Bresser, T.; Monzon, G.; Mosrin, M.; Knochel, P. "**Scaleable Preparation of Sensitive Functionalized Aromatics and Heteroaromatics via Directed Metalation Using TMPZnCl•LiCl."** *Org. Process Res. Dev.* **2010**, *14* (*6*), 1299-1303.

3. Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. "**Regio- and Chemoselective Zincation of Sensitive and Moderately Activated Aromatics and Heteroaromatics Using TMPZnCl•LiCl."** *J. Org. Chem.* **2010**, *75(14)*, 4686-4695.

4. Wunderlich, S. H.; Bresser, T.; Dunst, C.; Monzon, G.; Knochel, P. "**Efficient Preparation of Polyfunctional Organometallics via Directed *ortho*-Metalation."** *Synthesis* **2010**, *15*, 2670-2678.

5. Piller, F. M.; Bresser, T.; Fischer, M. K. R.; Knochel, P. "**Preparation of Functionalized Cyclic Enol Phosphates by Halogen-Magnesium Exchange and Directed Deprotonation Reactions."** *J. Org. Chem.* **2010**, *75(13)*, 4365-4375.

6. Mosrin, M.; Bresser, T.; Knochel, P. "**Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine."** *Org. Lett.* **2009**, *11(15)*, 3406-3409.

7. Mosrin, M.; Monzon, G.; Bresser, T.; Knochel, P. "**High temperature zincation of functionalized aromatics and heteroaromatics using TMPZnCl•LiCl and microwave irradiation."** *Chem. Commun.* **2009**, *37*, 5615-5617.

Poster Presentations

"Bresser, T.; Mosrin, M.; Knochel, P.; "**Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine"** at CarLa Winter School, March 2008, Heidelberg, Germany.

Talks

"**Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine"**; Presentation at BASF, May 27th 2009 in Ludwigshafen, Germany.