Frustrated Lewis Pairs

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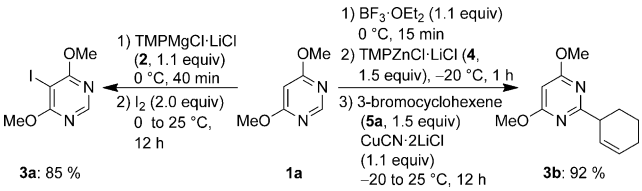
Regioselective Metalations of Pyrimidines and Pyrazines by Using Frustrated Lewis Pairs of BF_3·OEt_2 and Hindered Magnesium– and Zinc–Amide Bases**

*Klaus Groll, Sophia M. Manolikakes, Xavier Mollat du Jourdin, Milica Jaric, Aleksei Bredihhin, Konstantin Karaghiosoff, Thomas Carell, and Paul Knochel**

The functionalization of diazines is of great importance, because these N-heterocycles are present in numerous natural products, pharmaceuticals, and agrochemicals.[1] They also find applications in materials science and polymer chemistry.[2] The directed metalation and further functionalization of these electron-deficient N-heterocycles can be realized with ate bases[3] and in some cases with lithium bases.[4] However, low temperature and carefully designed reaction conditions are required owing to the low stability of the resulting lithiated N-heterocycles. Recently, the C–H activation of various N-heteroaromatics has also been reported.[5] Moreover, a range of LiCl-solubilized TMP–metal bases (TMP = 2,2,6,6-tetramethylpiperidyl) are known.[6] They display a high kinetic basicity and give access to several metalated diazines[7] and purines.[8] It was also found that these metallic amide bases are compatible with a strong Lewis acid, such as BF_3·OEt_2.[9] Thus, the reactivity of the sterically hindered TMP base is not annihilated by BF_3·OEt_2, but on the contrary, a synergetic effect is observed (dual activation). This effect allows a regioselective metalation of various substituted pyridines and derivatives,[10] which is not possible without the use of this Lewis pair combination. This compatibility of a strong Lewis acid with a Lewis base as a result of steric hindrance corresponds directly to the concept of frustrated Lewis pairs.[11] Herein, we report a new BF_3-assisted regioselective metalation of biologically relevant pyrimidine derivatives and purines. As an application, we developed a new strategy for the BF_3-mediated regioselective full functionalization of pyrazines.

Thus, we have found that the use of BF_3·OEt_2 allows the orthogonal metalation of the pyrimidine scaffold. Treating 4,6-dimethoxypyrimidine (**1a**) with TMPMgCl·LiCl (**2**, 1.1 equiv, THF, 0 °C, 40 min) provides a regioselective magnesiation at position 5 (Scheme 1). After iodolysis, the expected iodide **3a** is isolated in 85 % yield. In contrast, the reaction of the pyrimidine **1a** with BF_3·OEt_2 (1.1 equiv, 0 °C, 15 min) then TMPZnCl·LiCl (**4**, 1.5 equiv, THF, −20 °C, 1 h) leads to a quantitative metalation at position 2. After a copper-mediated allylation with 3-bromocyclohexene (**5a**), the desired 2-functionalized pyrimidine **3b** was isolated in 92 % yield (Scheme 1). This behavior might be explained by an increased acidity at position 2 owing to the complexation of BF_3 with the pyrimidine ring rather than with the sterically hindered Lewis base TMPZnCl·LiCl, allowing a complete switch of regioselectivity.[12]



Scheme 1. Switchable, regioselective metalation of the pyrimidine **1a**.

The zincated intermediate derived from **1a** undergoes a smooth Negishi cross-coupling[13] with 4-iodoanisole (**5b**) using 2 % [$Pd(dba)_2$] (dba = dibenzylideneacetone) and 4 % tfp (tfp = tri-(2-furyl)phosphine),[14] affording the 2-arylated pyrimidine **3c** in 89 % yield (Table 1, entry 1). This regioselective metalation is quite general, the pyrimidines **1b–d** are also selectively zincated in position 2 regardless of their substitution pattern. After allylation, iodolysis, or cross-coupling, the expected 2-functionalized pyrimidines **3d–i** are obtained in 66–71 % yield (entries 2–7).

More complex pyrimidine derivatives, such as the thienopyrimidines[15] **6a** and **6b**, display a similar regioselectivity switch (Scheme 2). Thus, the treatment of **6a** (R = NMe_2) with TMPZnCl·LiCl (**4**) leads to a smooth deprotonation of the most acidic proton of **6a** (i.e. position 6) giving, after cross-coupling, the 6-arylated product **7a** in 83 % yield. Alternatively, addition of BF_3·OEt_2 to **6a**,**b** followed by TMPZnCl·LiCl (**4**) leads to a regioselective zincation at position 2 (over 10:1) of the pyrimidine ring. Palladium-catalyzed cross-coupling or copper-mediated allylation furnishes the 2-functionalized thienopyrimidines **8a** and **8b** in 70–77 % yield (Scheme 2).

As a metalation of purines at position 2 is only reported by a lithiation-mediated stannyl transfer,[16] we have investigated the magnesiation of functionalized purine derivatives in this position. Whereas, purine **9** is reluctant to undergo

[*] K. Groll, S. M. Manolikakes, Dr. X. M. du Jourdin, Dr. M. Jaric, Dr. A. Bredihhin, Prof. Dr. K. Karaghiosoff, Prof. Dr. T. Carell, Prof. Dr. P. Knochel
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5-13, Haus F, 81377 München (Germany)
E-mail: paul.knochel@cup.uni-muenchen.de

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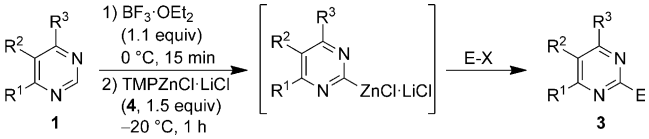
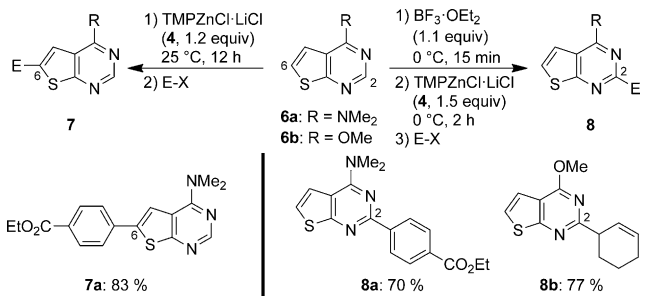
Table 1: Regioselective zincation of pyrimidine derivatives **1** in position 2.



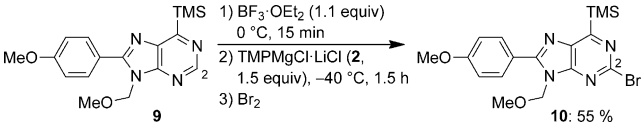
Entry	Substrate	Electrophile E-X	Product, Yield[a]
1	**1a**	**5b**	**3c**: 89%[b]
2	**1b**	**5b**	**3d**: 70%[b]
3	**1b**	**5c**	**3e**: 69%[b]
4	**1b**	**5a**	**3f**: 71%[c]
5	**1c**	**5d**	**3g**: 66%[b]
6	**1d**	I_2	**3h**: 66%
7	**1d**	**5c**	**3i**: 67%[b]

[a] Yield of isolated analytically pure product. [b] Obtained by Pd-catalyzed cross-coupling. [c] Obtained by Cu-mediated allylation.



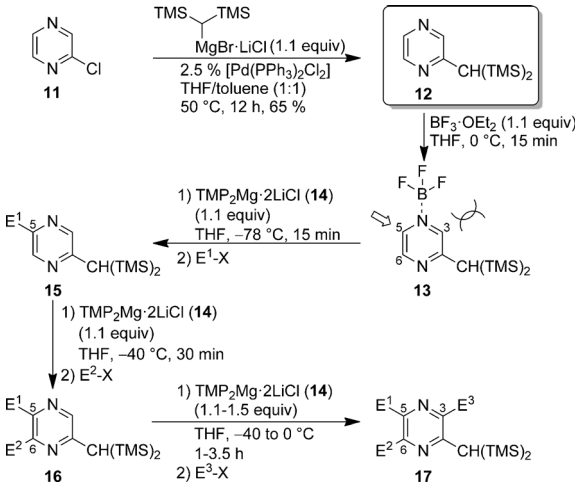
Scheme 2. Switchable, regioselective metalation of the thienopyrimidines **6a** and **6b**.

metalation using various TMP bases in the absence of a Lewis acid, we found that a prior addition of $BF_3{\cdot}OEt_2$ (1.1 equiv) allows a magnesiation at position 2 with TMPMgCl·LiCl (**2**, 1.5 equiv), leading after bromination to the 2-bromopurine derivative **10** in 55% yield (Scheme 3).



Scheme 3. BF_3-assisted metalation of purine **9** in position 2.

We have also applied the frustrated Lewis pair [$TMP_2Mg{\cdot}2\,LiCl$ and $BF_3{\cdot}OEt_2$] to a sequential regioselective full functionalization of the pyrazine scaffold. We attached a bulky $(TMS)_2CH$ substituent to the pyrazine ring, an approach pioneered in selective lithiations on aromatics by Snieckus.[17] Recently, the bis(trimethylsilyl)methyl group[18] has also been used for Wittig rearrangements and Prins cyclizations.[19] Attached to the pyrazine core, this silylated substituent together with $BF_3{\cdot}OEt_2$ as a metalation activator allows a full differentiation of the three remaining C–H bonds, mainly using steric effects.[20] Thus, the Kumada–Corriu cross-coupling[21] of commercially available 2-chloropyrazine (**11**) with $(TMS)_2CHMgBr{\cdot}LiCl$[22] provides 2-(bis(trimethylsilyl)methyl)pyrazine (**12**) in 65% yield (Scheme 4).



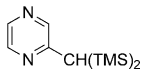
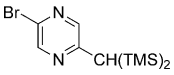
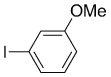
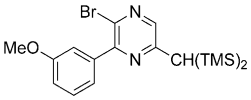
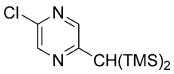
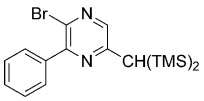
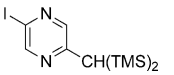
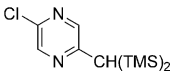
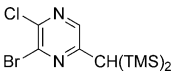
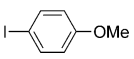
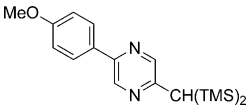
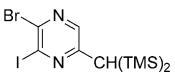
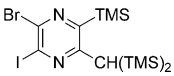
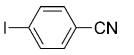
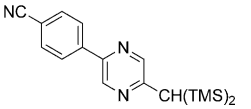
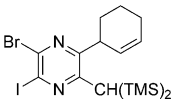
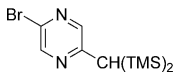
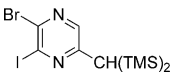
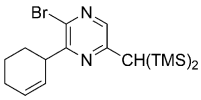
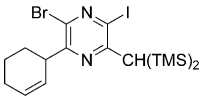
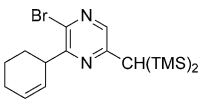
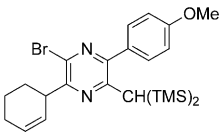
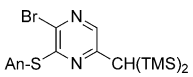
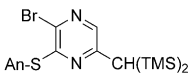
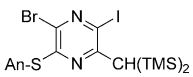
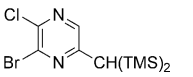
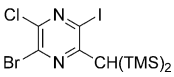
Scheme 4. New strategy for a regioselective full functionalization of pyrazines.

The bulky $(TMS)_2CH$ substituent causes, after addition of $BF_3{\cdot}OEt_2$ (1.1 equiv), a selective complexation at the least hindered heterocyclic N-atom to give the Lewis adduct **13** (Scheme 4).[23] Using $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1 equiv) at −78 °C allows a selective magnesiation at position 5 as this is the most accessible activated proton. Position 3 is not an option for the metalation because of steric hindrance by the bulky $(TMS)_2CH$ group.[24] Likewise, no metalation occurs at position 6, as this position is less activated by the Lewis acid

(inductive effect). The resulting metalated pyrazine reacts with various electrophiles E^1-X, such as $(BrCl_2C)_2$, $PhSO_2Cl$,[25] I_2, or Ar-I, producing the 5-functionalized pyrazines **15a–e** in 61–89% yield (Table 2, entries 1–5).[26]

A second metalation of the pyrazines of type **15** with $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1 equiv, −40 °C, 30 min) results in a regioselective magnesiation at the least sterically hindered position, 6 (Scheme 4). The quenching with various electrophiles (E^2-X = I_2, $(BrCl_2C)_2$, thiosulfonate, allyl bromide, or aryl iodide) provides the trisubstituted pyrazines **16a–f** in 70–93% yield (Table 2, entries 6–11). The remaining position of the pyrazine core bearing a proton is then magnesiated with $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1–1.5 equiv, −40–0 °C, 1–3.5 h) leading,

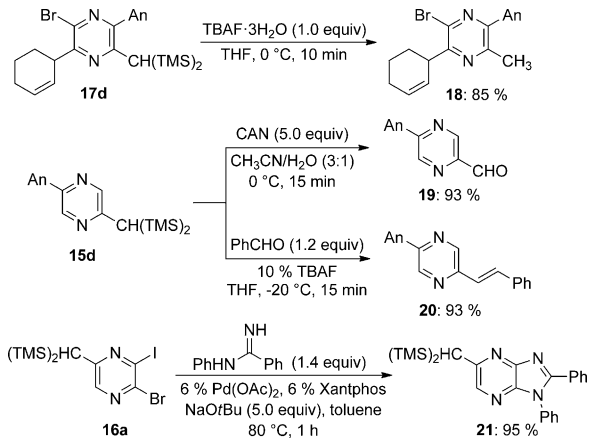
Table 2: Regioselective full functionalization of 2-(bis(trimethylsilyl)methyl)pyrazine (**12**) [An = *p*-MeO-C_6H_4].

Entry	Substrate	Electrophile	Product, Yield[a]	Entry	Substrate	Electrophile	Product, Yield[a]
		$(BrCl_2C)_2$					
1	**12**[b]		**15a**: 89%	9	**15a**[d]	**5g**	**16d**: 74%[c]
		$PhSO_2Cl$					
2	**12**[b]		**15b**: 61%	10	**15a**[d]	**5h**	**16e**: 70%[c]
		I_2				$(BrCl_2C)_2$	
3	**12**[b]		**15c**: 65%	11	**15b**[d]		**16f**: 93%
						TMS-CN	
4	**12**[b]	**5b**	**15d**: 81%[c]	12	**16a**[f]		**17a**: 72%
							
5	**12**[b]	**5e**	**15e**: 74%[c]	13	**16a**[f]	**5a**	**17b**: 59%[e]
		I_2				I_2	
6	**15a**[d]		**16a**: 86%	14	**16b**[g]		**17c**: 78%
							
7	**15a**[d]	**5a**	**16b**: 88%[e]	15	**16b**[g]	**5b**	**17d**: 59%[c]
		$PhSO_2S$-An				I_2	
8	**15a**[d]	**5f**	**16c**: 70%	16	**16c**[h]		**17e**: 72%
						I_2	
				17	**16f**[i]		**17f**: 83%

[a] Yield of isolated analytically pure product. [b] 1) $BF_3{\cdot}OEt_2$ (1.1 equiv), 0 °C, 15 min; 2) $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1 equiv), −78 °C, 15 min. [c] Obtained by Pd-catalyzed cross-coupling after Zn transmetalation. [d] $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1 equiv), −40 °C, 30 min. [e] Obtained by Cu-mediated allylation after Zn transmetalation. [f] $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1 equiv), −40 °C, 3.5 h. [g] $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.3 equiv), 0 °C, 1 h. [h] $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.5 equiv), −20 °C, 3.5 h. [i] $TMP_2Mg{\cdot}2\,LiCl$ (**14**, 1.1 equiv), −40 °C, 2 h.

after quenching with standard electrophiles, to the pyrazines **17a–f** in 59–83% (entries 12–17).

The $(TMS)_2CH$ group can be further manipulated and converted to useful functionalities, as previously shown by Palomo et al. Thus, the treatment of the pyrazine **17d** with 1.0 equiv of tetra-*n*-butylammonium fluoride ($TBAF{\cdot}3H_2O$)[27] furnishes the methylpyrazine derivative **18** in 85% yield (Scheme 5). Oxidation of the bis(trimethylsilyl)methyl group of pyrazine **15d** with ceric ammonium nitrate (CAN)[28] produces the aldehyde **19** in 93% yield.



Scheme 5. Transformations of the regioselectively obtained pyrazine derivatives [An = *p*-MeO-C_6H_4].

Peterson olefination of **15d** with benzaldehyde in the presence of 10% TBAF[29] furnishes the stilbene derivative **20** in 93%. Finally, the $(TMS)_2CH$ group is compatible with NaO*t*Bu as base in a palladium-catalyzed annulation recently developed by You et al.[30] Using this diamination[31] with Xantphos[32] as a ligand affords, in a regioselective manner, the imidazo[4,5-*b*]pyrazine derivative **21**[26] in 95% yield which might be a candidate for a solid-state organic emitter[33] or for fluorescent labeling of cells.[30]

In summary, we have shown that the combination of $BF_3{\cdot}OEt_2$ with TMP–Mg or TMP–Zn bases allows a regioselective functionalization of various diazines, such as pyrimidines, purines, and pyrazines.[34] More importantly, the use of $BF_3{\cdot}OEt_2$ together with TMP–Mg or TMP–Zn bases allows metalation of positions which are not available in the absence of the Lewis acid. In combination with a bulky group such as bis(trimethylsilyl)methyl, this strategy allows a regioselective full functionalization of the pyrazine core. Afterwards, this substituent can be transformed into various useful functionalities. Further study of the use of Lewis acids for triggering the metalation of N-heterocycles is underway.

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