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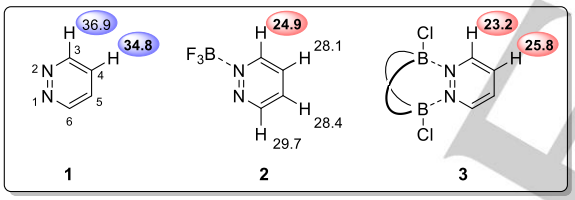
Lewis Acid Directed Regioselective Metalations of Pyridazine

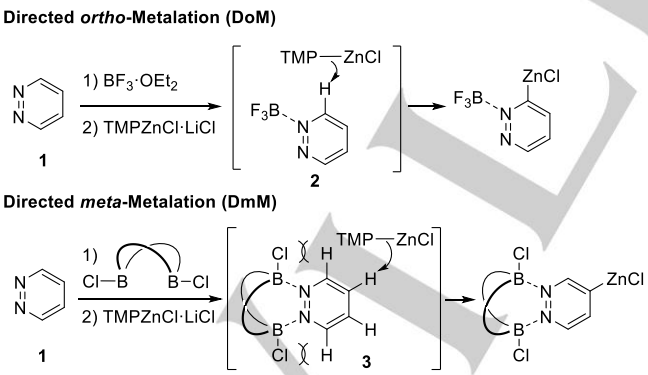
Moritz Balkenhohl, Harish Jangra, Tobias Lenz, Marian Ebeling, Hendrik Zipse, Konstantin Karaghiosoff, and Paul Knochel*

In memory of Friedhelm Balkenhohl

Abstract: Mono- or bidentate boron Lewis acids trigger a regioselective magnesiation or zincation of pyridazine in position C3 (*ortho*-product) or C4 (*meta*-product). The metalation regioselectivity was rationalized with the help of calculated pK_a values of both pyridazine and pyridazine-Lewis acid complexes.

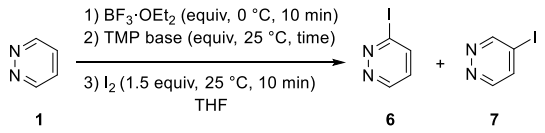
N-Heterocycles are invaluable scaffolds in pharmaceutical and material research.[1] Whereas the functionalization of pyridines is well established, other diazines such as pyrimidines and pyrazines are much less investigated and the regioselective functionalization of the pyridazine scaffold (**1**) is still in its infancy.[2] Pyridazines are especially important *N*-heterocycles since they are present in various pharmaceuticals and agrochemicals.[3] Also, they play the role of bioisosteres of pyridines and are therefore important in drug design.[4] They belong to the so-called heterocycles of the future.[5] Although a metalation of pyridazine (**1**) using TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) in the presence of $ZnCl_2$·TMEDA (TMEDA = tetramethylethylenediamine) has been reported by Mongin, the *ortho*-regioselectivity was only 83%.[2b] Earlier metalations were found to proceed in moderate yields (16-32%).[2a] Kondo has shown, that a C4-functionalization of **1** could be achieved using an excess of a bulky Schwesinger base.[6] Previously, we have reported that magnesium and zinc organometallics are compatible with strong Lewis acids including BF_3·OEt_2.[7] These frustrated Lewis pairs[8] proved to be exceptional reagents for the regioselective metalation of various *N*-heterocycles.[9] So far, directed *ortho*-metalations (DoM) of *N*-heterocycles have been the privileged strategy for performing regioselective metalations.[10] *Meta*-metalations of arenes have been achieved using mixed alkali-metal-mediated metalations in which the second metal sodium plays a pivotal role in the stability of the formed organometallic species.[11] Remote lithiations are also feasible on sterically hindered silylated arenes.[12] That Lewis acids strongly acidify the protons of pyridazine (**1**) was demonstrated by calculations,[13] showing that the ease of deprotonation may increase by mono-complexation (see **2**)[14] and further by a bis-complexation as shown in **3** (Scheme 1). These calculations led us to examine the metalation of **1** using mono- or bidentate Lewis acids. Herein, we wish to report, that the appropriate choice of a Lewis acid further facilitates a metalation and, combined with steric effects, allows the regioselective metalation of the pyridazine scaffold (**1**) either in position C3 (*ortho*-product) or in position C4 (*meta*-product; Scheme 1).





Scheme 1. Calculated pK_a values of pyridazine (**1**), the pyridazine-BF_3 adduct (**2**), and a bidentate Lewis acid-pyridazine adduct (**3**), and the directed *ortho*- and *meta*-metalation of pyridazine (**1**) using TMPZnCl·LiCl.

Table 1. Optimization of the reaction conditions for the directed *ortho*-metalation of pyridazine (**1**).



entry	TMP base	BF_3·OEt_2	time [h]	yield[a]	ratio (**6**:**7**)[b]
1	TMPMgCl·LiCl (**4**)[c] (1.05 equiv)	-	0.25	12%	32:68
2	TMPMgCl·LiCl (**4**)[c] (1.05 equiv)	1.1 equiv	0.25	1%	96:4
3	TMPZnCl·LiCl (**5**) (1.10 equiv)	-	2	45%	60:40
4	TMPZnCl·LiCl (**5**) (1.30 equiv)	1.1 equiv	2	45%	96:4
5	TMPZnCl·LiCl (**5**) (1.30 equiv)	1.1 equiv	6	64%	n.d.
6	TMPZnCl·LiCl (**5**) (1.50 equiv)	1.1 equiv	6	72% (57%)[d]	97:3

[a] NMR yield using trimethoxybenzene as standard. [b] Determined by NMR analysis. [c] The reaction was run at -78 °C. [d] Isolated yield of **6**.

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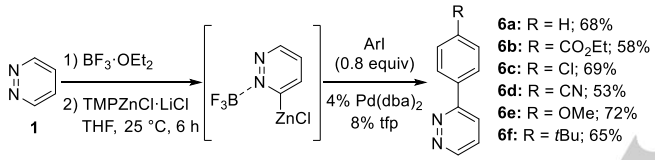
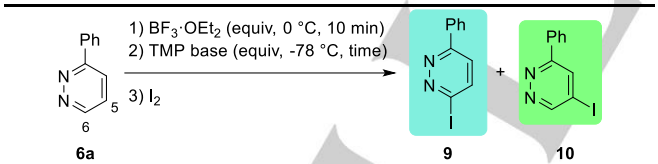
Thus, we have examined the metalation of pyridazine (**1**) with TMPMgCl·LiCl (**4**)[15] in THF in the absence or presence of BF_3·OEt_2. In both cases, yields were low due to instability of the magnesium species, and a regioselective metalation could only be achieved in the presence of the Lewis acid (Table 1, entries 1-2). Higher yields were obtained, using the more covalent metal amide TMPZnCl·LiCl (**5**, entries 3-6).[16] A low regioselectivity of the zincation was observed in the absence of BF_3·OEt_2 (entry 3). However, in the presence of BF_3·OEt_2 (1.1 equiv), a room temperature metalation of **1** proceeds within 2 h reaction time (entry 4). A crude NMR-determination showed a 96:4 ratio between 3-iodopyridazine (**6**) and 4-iodopyridazine (**7**). By using 1.5 equiv of TMPZnCl·LiCl (**5**) and extending the reaction time to 6 h a maximum conversion and excellent regioselectivity (**6**:**7** = 97:3) was obtained, leading, after iodolysis, to pure 3-iodopyridazine (**6**) in 57% isolated yield. Further functionalizations were performed and an arylation using palladium-catalyzed Negishi cross-couplings[17] with various electron-rich and -poor aryl iodides, provided 3-arylated pyridazines **6a-f** in 53-72% yield (Scheme 2).



Scheme 2. BF_3·OEt_2 mediated *ortho*-zincation and arylation of pyridazine (**1**). tfp = tri-(2-furyl)phosphine.[18]

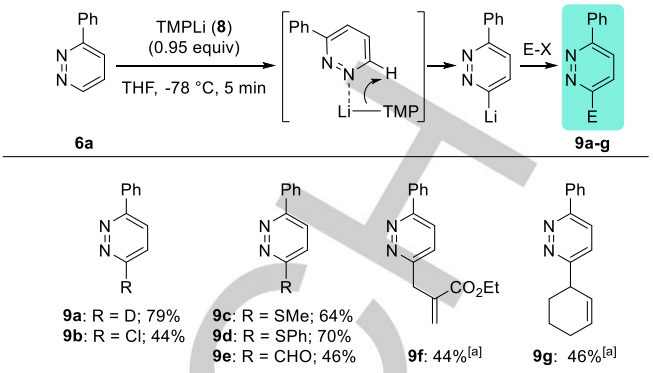
In order to expand the scope of such metalations, 3-phenylpyridazine (**6a**, prepared according to Scheme 2) was submitted to various metalation conditions (Table 2). The very strong and kinetically active base TMPLi (**8**, 0.95 equiv) led to an almost completely regioselective lithiation at position C6 (**9**:**10** ratio = 96:4), providing, after iodolysis and isolation, the pure iodopyridazine **9** in 72% yield (Table 2, entry 1). These conditions were used for further reactions of the lithiated pyridazine **6a** with D_2O, $(Cl_3C)_2$, $MeSSO_2Me$, $PhSSO_2Ph$, and *N*-formylmorpholine, as well as allylic bromides, to give various 3,6-disubstituted pyridazines **9a-g** in 44-79% yield (Scheme 3).

Table 2. Optimization of the reaction conditions for the directed C5- and C6-metalation of 3-phenylpyridazine (**6a**).



entry	TMP base (equiv)	BF_3·OEt_2	time	yield	ratio (**9**:**10**)[a]
1	TMPLi (**8**) (0.95 equiv)	-	5 min	72%[b]	96:4
2	TMPMgCl·LiCl (**4**) (1.1 equiv)	1.1 equiv	20 min	65%[c]	44:56
3	TMPMgCl·LiCl (**4**) (2.0 equiv)	1.1 equiv	20 min	82%[c] (58%)[b]	27:73
4	TMPMgCl·LiCl (**4**) (3.0 equiv)	1.1 equiv	20 min	45%[c]	26:74

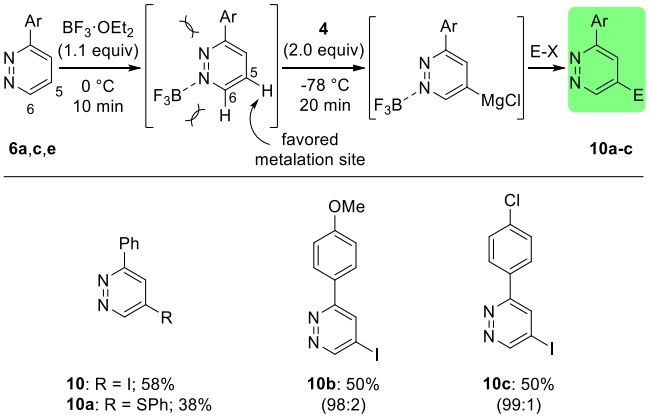
[a] Determined by NMR analysis. [b] Isolated yield of the main regioisomer. [c] NMR yield using trimethoxybenzene as standard.



[a] A 1 M CuCN·2LiCl solution was used for transmetalation.

Scheme 3. Directed *ortho*-metalation of 3-phenylpyridazine (**6a**) using TMPLi (**8**).

Alternatively, using TMPMgCl·LiCl (**4**, 1.1 equiv) in the presence of BF_3·OEt_2 (1.1 equiv) led to an unselective deprotonation. In this case, after iodolysis, a 44:56 ratio between the iodides **9** and **10** was obtained (Table 2, entry 2). Interestingly, increasing the amount of **4** (2.0 equiv) led to an improved regioselectivity of 27:73 (Table 2, entry 3). This result may be explained by assuming that 1.0 equiv of **4** is used up to activate the heterocycle in addition to BF_3·OEt_2, also playing the role of a Lewis acid.[19] The additional equivalent of **4** acts as deprotonating agent. Further increase of the amount of **4** did not improve this regioselectivity (entry 4). This enhanced selectivity proved to be sufficient for preparative applications. Thus, the treatment of various 2-arylpyridazines (**6a**,**c**,**e**) with TMPMgCl·LiCl (**4**) in the presence of BF_3·OEt_2 led, after iodolysis or thiolation, to the regiomerically pure products **10** and **10a** in 38-58% yield (Scheme 4).



Scheme 4. Directed *meta*-metalation of 3-arylpyridazines **6a**,**c**,**e** using BF_3·OEt_2 and TMPMgCl·LiCl (**4**).

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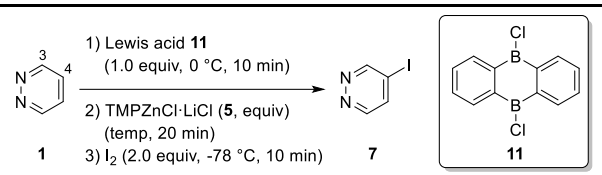
Table 3. Optimization of the reaction conditions for the Lewis acid directed C4-metalation of pyridazine (**1**).

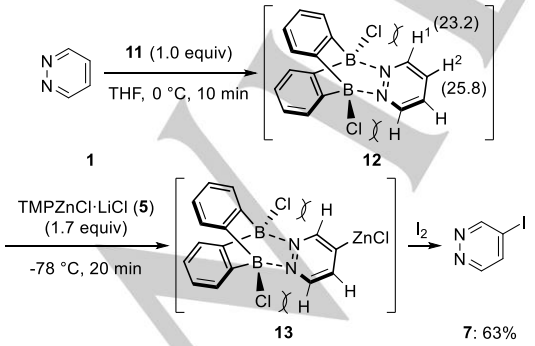


entry	equiv	temperature	yield[a]	ratio (C4:C3)[b]
1	1.3	0 °C	40%[c]	99:1
2	1.3	-78 °C	52%	99:1
3	1.7	-78 °C	86% (63%)[c]	99:1
4	2.0	-78 °C	69%	99:1

[a] NMR yield using trimethoxybenzene as standard. [b] Determined by NMR analysis. [c] Isolated yield.

Interestingly, replacing the 3-phenyl substituent of **6a** with a *para*-anisyl or *para*-chlorophenyl substituent, led, with the same base system, to an almost perfectly regioselective metalation (regioisomeric ratio = 98:2 (**10b**) and 99:1 (**10c**)). After iodolysis, the pyridazines **10b** and **10c** were obtained in 50% yield (Scheme 4). To confirm the regioselectivity, an X-ray measurement of **10c** was performed.[20]

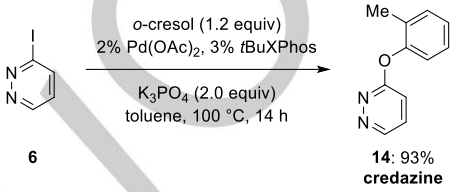
These results led us to examine further possibilities for a Lewis acid directed C4-metalation (*meta*-product). After several experiments, we chose the bidentate diboroanthracene **11** first reported by Kaufmann.[21] Thus, mixing equimolar amounts of **11** and **1** at 0 °C led to a yellow solution, indicating the formation of a 1:1 complex. The structure of this complex **12** was confirmed by NMR-studies.[22] Treatment of **12** with TMPZnCl·LiCl (**5**) at 0 °C led to the formation of the zincated pyridazine **13**, which, after iodolysis, exclusively gave 4-iodopyridazine (**7**) in 40% yield (Table 3, entry 1). Lowering the temperature to -78 °C resulted in an increased yield of 52% (entry 2). An additional variation of stoichiometry showed, that with 1.7 equiv of **5**, the optimal reaction conditions were obtained, leading to **7** in 63% isolated



Scheme 5. Directed *meta*-metalation and functionalization of pyridazine using the bidentate Lewis acid **11** and TMPZnCl·LiCl (**5**).

yield (Table 3, entries 3-4; Scheme 5). According to the calculations,[13] H1 is the most acidic proton (pK_a(H1) = 23.2). However, due to steric effects combined with a high acidity (pK_a(H2) = 25.8), exclusively H2 is deprotonated.

Finally, to prove the synthetic utility of these regioselective metalations, the herbicide credazine (**14**)[23] was prepared. Thus, 3-iodopyridazine (**6**) was dissolved in toluene and mixed with *o*-cresol (1.2 equiv), $Pd(OAc)_2$ (2 mol%), *t*BuXPhos (3 mol%) and potassium phosphate (2.0 equiv).[24] After stirring at 100 °C for 14 h, credazine (**14**) was obtained in 93% yield (Scheme 6).



Scheme 6. Synthesis of the herbicide credazine (**14**) starting from 3-iodopyridazine (**6**).

In summary, we have developed a highly regioselective Lewis acid directed C3- and C4-metalation and functionalization of pyridazine. The choice of the Lewis acid is key for the success and the regioselectivity of the reaction, allowing the first Lewis acid directed *meta*-metalation using a TMP-base. This unprecedented reactivity opens up new perspectives for the metalation of heterocycles using metal amide bases. Further extensions of this work are currently underway in our laboratories.

Acknowledgements

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Keywords: frustrated Lewis pairs • magnesiation • pyridazine • TMP-bases • zincation

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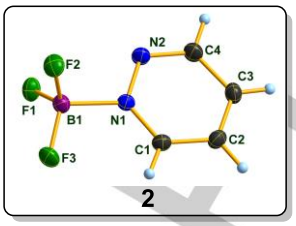
[13] For further details, see the Supporting Information.

[14] A crystal structure of the pyridazine-BF_3 adduct **2** was obtained:



2

For further details, see the Supporting Information.

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[19] We propose, that the first equivalent of TMPMgCl·LiCl, $BF_3{\cdot}OEt_2$ and pyridazine form a complex, in which both reagents act as Lewis acids. The second equivalent of TMPMgCl·LiCl may then deprotonate the C5-position.

[20] CCDC 1906337 (**10c**), CCDC 1906338 (**9c**), CCDC 1906339 (**6a**), and CCDC 1906340 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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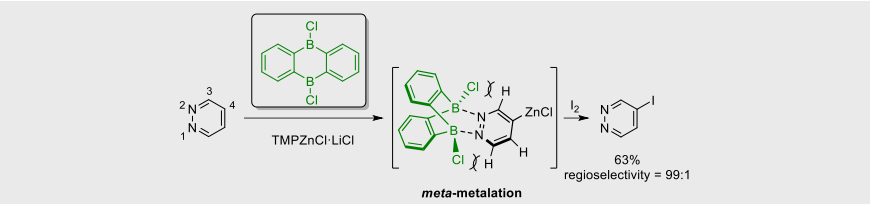

Chelation is key: By chelating the diazine pyridazine with a bidentate diboroanthracene Lewis acid, a rare C4-metalation was achieved. Additionally, a highly regioselective *ortho*-metalation was obtained when the monodentate Lewis acid $BF_3{\cdot}OEt_2$ was employed. A rationalization of the regioselectivity was possible using calculated pK_a values of the pyridazine-Lewis acid complexes.

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