Frustrated Lewis Pairs

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# Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or tmp-Zinc and tmp-Magnesium Bases with $BF_3$·$OEt_2$**

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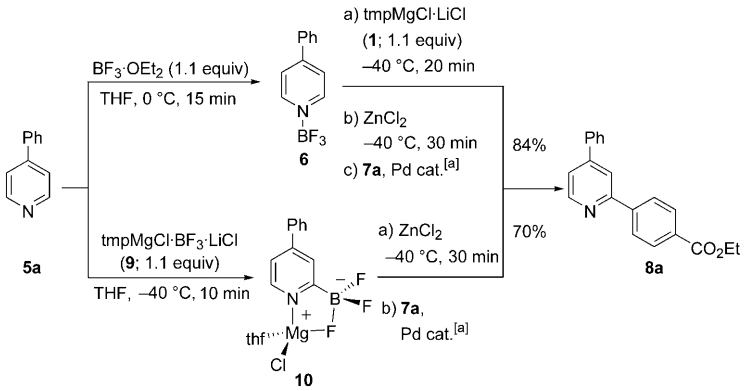
*Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday*

The functionalization of pyridines and quinolines is a major synthetic goal since many of these heterocycles have important biological properties[1] or are of interest as new materials.[2] The regioselective functionalization of these heterocyclic scaffolds has been achieved by direct metalation[3] or metal-catalyzed C–H activation.[4] The stoichiometric lithiation of unactivated pyridines is often complicated because of Tchitchibabin-type dimerizations.[5] An elegant solution has been proposed by Kessar et al., who showed that the complexation of pyridine with $BF_3$ allows the low-temperature α-lithiation of pyridine[6] and other amino derivatives.[7] Michl and co-workers described the $BF_3$-assisted metalation of 3-alkylpyridines with $BF_3$·$OEt_2$ and lithium tmp zincates.[8] Recently, we reported the preparation of highly chemoselective LiCl-complexed 2,2,6,6-tetramethylpiperidyl (tmp) metal amide bases, such as tmpMgCl·LiCl (**1**),[9] tmpZnCl·LiCl (**2**),[10] $tmp_2Zn$·2 $MgCl_2$·2 LiCl (**3**),[11] and $tmp_3Al$·3 LiCl (**4**),[12] which allow the selective metalation of sensitive aromatic compounds and heterocycles. However, attempts to magnesiate, zincate, or aluminate unactivated pyridines with such bases proved to be unsatisfactory. For example, the use of **1** (1.1 equiv, 25 °C) led to only a partial magnesiation being observed (less than 40 %). This led us to consider metalations with the tmp bases **1**–**4** in the presence of $BF_3$·$OEt_2$. Herein, we report a convenient regioselective C–H activation of various polyfunctional pyridines and related heterocycles by a stepwise activation with $BF_3$·$OEt_2$ followed by metalation with the appropriate tmp base. We also describe an unexpected alternative metalation method involving new frustrated Lewis pairs[13,14] such as tmpMgCl·$BF_3$·LiCl (**9**) derived from the strong Lewis base tmp and the strong Lewis acid $BF_3$·$OEt_2$.

The complexation of 4-phenylpyridine (**5a**) with $BF_3$·$OEt_2$ (1.1 equiv, 0 °C, 15 min) furnishes **6**. The subsequent addition of tmpMgCl·LiCl (**1**; 1.1 equiv, −40 °C, 20 min) generates a metalated pyridine derivative, which after transmetalation with $ZnCl_2$ and a subsequent Negishi cross-coupling[15] with ethyl 4-iodobenzoate (**7a**) affords the 2-arylated pyridine **8a** in 84 % yield (Scheme 1).




***Scheme 1.*** $BF_3$-triggered accelerated metalations. [a] Pd cat.: [$Pd(dba)_2$] (5 mol %); P(2-furyl)$_3$ (10 mol %), −40 °C→25 °C, 12 h. dba = *trans,trans*-dibenzylideneacetone.

To clarify the nature of the generated organometallic intermediate we performed an alternative experiment, in which 4-phenylpyridine (**5a**) was treated with a premixed solution of $BF_3$·$OEt_2$ (1.1 equiv) and tmpMgCl·LiCl (**1**; 1.1 equiv, −40 °C, 10 min), tentatively written as tmpMgCl·$BF_3$·LiCl (**9**). Surprisingly, an efficient metalation with the reagent **9** occurs within 10 minutes at −40 °C. Transmetalation with $ZnCl_2$[16] and a Negishi cross-coupling reaction[15] with the aryl iodide **7a** provides product **8a** in comparable yield (70 %). This result implies that the new frustrated Lewis pair **9** is unexpectedly reactive for the metalation of pyridines.[13,14]

We have examined the mechanism and scope of this reaction in more detail. $^{11}B$ NMR, $^{19}F$ NMR, and $^{13}C$ NMR spectroscopic measurements clearly indicate that the intermediate organometallic species **10** contains a carbon–boron

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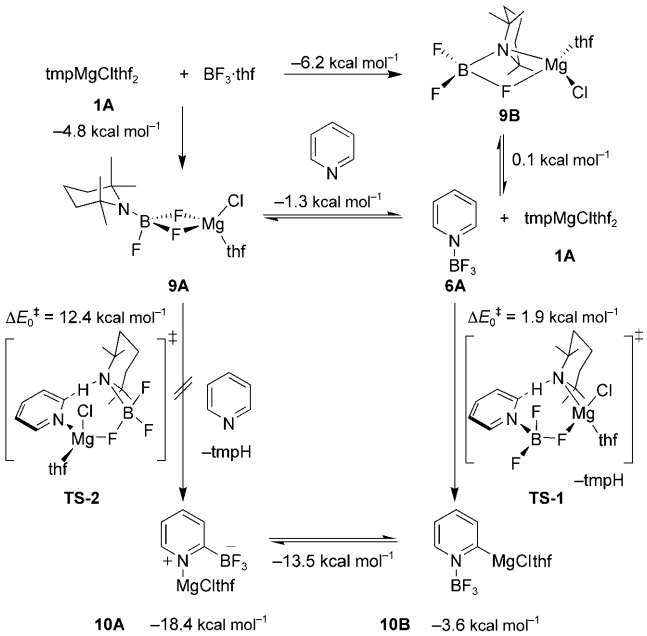
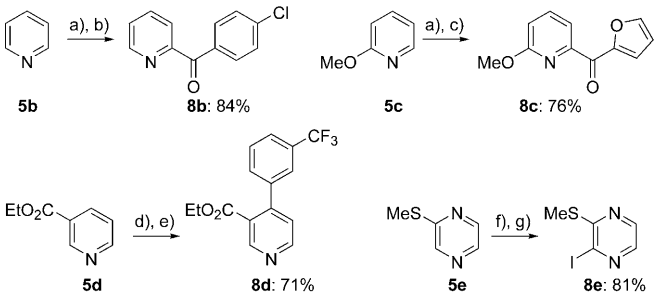
bond, as depicted in Scheme 1.[17,18] This structure has also been supported by DFT calculations.[19] Thermodynamic analysis by DFT calculations shows that the structure **10A** (with a C–B bond) is 13.5 kcal mol$^{-1}$ thermodynamically more stable than the isomeric structure **10B** (with a C–Mg bond; Scheme 2). This finding indicates that otherwise




***Scheme 2.*** Structure and reactivity of the frustrated Lewis pair **9**.

difficult to prepare pyridyltrifluoroborates can be readily obtained in a one-pot procedure by highly regioselective C–H activations.[16,20,21] The exact structure of the reagent **9** could not be clearly defined, despite numerous NMR studies. However, DFT calculations led to the tentative structures **9A** and **9B**, with both energetically favored.[17] NMR studies confirm that **9** exists as several species in solution. The reaction pathways of **9A** and **9B** in the presence of pyridine (Py) have been modeled by DFT calculations, which reveal that **9A** and **9B** may dissociate in the presence of pyridine to furnish a Py·$BF_3$ complex (**6A**) as well as tmpMgCl(thf)$_2$ (**1A**). The reaction of **6A** with **1A** proceeds thereafter via **TS-1**, which has a particularly low activation barrier (1.9 kcal mol$^{-1}$), to eventually afford complex **10A**.[22] The alternative pathway involving the direct metalation of pyridine with **9A** or **9B** (no prior dissociation) via **TS-2** has comparably a much higher activation energy (12.4 kcal mol$^{-1}$). This calculation highlights the frustrated Lewis pair character of **9** and the facile reversibility of its formation in the presence of an appropriate substrate (such as pyridine), and led us to examine the synthetic utility and reaction scope of this new class of reagents.

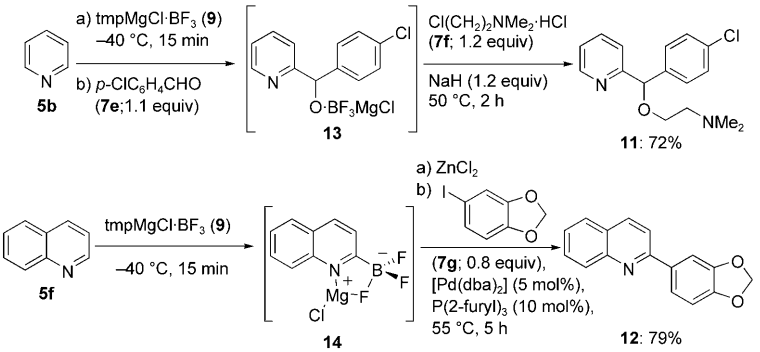
Pyridine (**5b**) similarly reacts with tmpMgCl·$BF_3$·LiCl (**9**; 1.1 equiv, –40 °C, 15 min) and furnishes, after transmetalation with CuCN·2 LiCl[23] and a subsequent acylation with 4-chlorobenzoyl chloride (**7b**; 0.8 equiv, –40 °C to 25 °C, 12 h), the pyridyl ketone **8b** in 84 % yield (Scheme 3). The lithiation of 2-methoxypyridine (**5c**) with lithium superbases produces a mixture of products unless a large excess of




***Scheme 3.*** Regioselective metalation of N heterocycles with the frustrated Lewis pair **9**. a) **9** (1.1 equiv), THF, –40 °C, 15 min; b) CuCN·2 LiCl (1.1 equiv), –40 °C, 30 min; **7b** (0.8 equiv), –40 °C→25 °C, 12 h; c) CuCN·2 LiCl (1.1 equiv), –40 °C, 30 min; **7c** (0.8 equiv), –40 °C to 25 °C, 12 h; d) **9** (1.1 equiv), THF, –40 °C, 30 min; e) $ZnCl_2$ (1.1 equiv), –40 °C, 30 min; **7d** (0.8 equiv), [Pd(dba)$_2$] (5 mol %), P(2-furyl)$_3$ (10 mol %), –40 °C→25 °C, 12 h; f) **9** (1.1 equiv), THF, –40 °C, 10 min; g) $I_2$, (1.5 equiv), –40 °C→25 °C, 10 min.

base is added.[24] However, a regioselective metalation can be achieved by using the frustrated Lewis pair tmpMgCl·$BF_3$·LiCl (**9**) to produce, after acylation with 2-furoyl chloride (**7c**), the 2,6-disubstituted pyridine (**8c**) in 76 % yield. The metalation of electron-poor pyridines such as **5d** cannot be performed with any conventional lithium base because of extensive decomposition.[25] The new reagent **9** allows this synthetic problem to be overcome. Thus, treatment of ethyl nicotinate (**5d**) with **9** (1.5 equiv, –40 °C, 30 min) furnishes an organometallic intermediate, which undergoes a smooth Negishi cross-coupling reaction[15] with 1-iodo-3-(trifluoromethyl)benzene (**7d**) to give the functionalized pyridine **8d** in 71 % yield. Other related sensitive heterocycles, such as 2-(methylthio)pyrazine (**5e**), are metalated with **9** (1.1 equiv, –40 °C, 10 min) to give 2-iodo-3-(methylthio)pyrazine (**8e**) in 81 % yield after iodolysis (Scheme 3).

To demonstrate the synthetic potential of **9** we have prepared two biologically active molecules: an antihistaminic drug, carbinoxamine (**11**),[26] and the haplophyllum alkaloid, dubamine (**12**),[27] in two one-pot procedures (Scheme 4).




***Scheme 4.*** One-pot preparation of carbinoxamine (**11**) and dubamine (**12**).

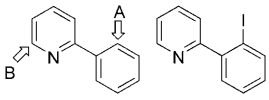
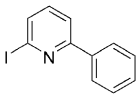
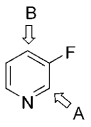
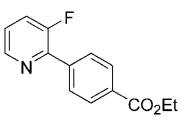
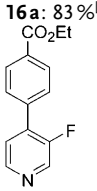
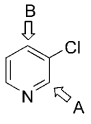
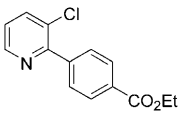
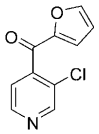
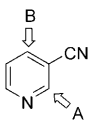
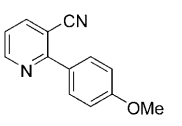
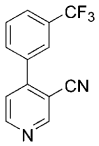
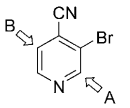
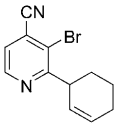
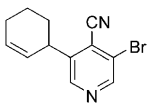
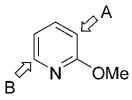
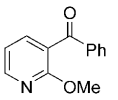
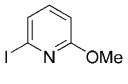
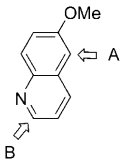
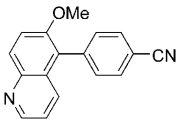
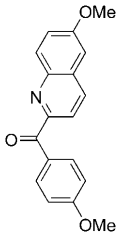
  

Treatment of **5b** with **9** (1.1 equiv, −40 °C, 15 min) followed by the addition of 4-chlorobenzaldehyde (**7e**) led to the alcoholate **13**, which was treated in situ with $Cl(CH_2)_2NMe_2{\cdot}HCl$ (**7f**; 1.2 equiv) and NaH (1.2 equiv, 50 °C, 2 h); this sequence provided carbinoxamine (**11**) in 72 % yield. Similarly, the reaction of quinoline (**5f**) with **9** (1.1 equiv, −40 °C, 15 min) furnishes the intermediate **14**. Transmetalation with $ZnCl_2$ and a subsequent Negishi cross-coupling reaction[15] with the aryl iodide **7g** affords dubamine (**12**) in 79 % yield (Scheme 4).

During the study of the reaction scope of **9**, we realized that a two-step metalation with prior precomplexation with $BF_3{\cdot}OEt_2$ and subsequent addition of TMPMgCl·LiCl (**1**), $TMP_2Zn{\cdot}2\,MgCl_2{\cdot}LiCl$ (**3**), or $[(t\text{Bu})NCH(i\text{Pr})(t\text{Bu})]_3Al{\cdot}3\,LiCl$ (**4a**) in a second step is more flexible and often results in higher yields.[28] This two-step metalation allows, in a number of cases, a complete switch of regioselectivity by using either tmp-derived bases **1**–**4** without $BF_3{\cdot}OEt_2$ (metalation procedure A) or metalation of $BF_3$-precomplexed N heterocycles (metalation procedure B; Table 1).

Thus, 2-phenylpyridine (**5g**) is selectively magnesiated with **1** (2 equiv, 55 °C, 30 h) at the *ortho* position of the phenyl substituent; a subsequent iodolysis then gives the aryl iodide **15a** (85 % yield). In contrast, precomplexation with $BF_3{\cdot}OEt_2$ (1.1 equiv, 0 °C, 15 min) followed by the addition of **1** (1.5 equiv, 0 °C, 30 h) leads to a selective metalation in position 6. Iodolysis of the intermediate affords 2-iodopyridine derivative **16a** (83 % yield). A number of substituted pyridines (**5h–l**; entries 2–6) display this remarkable switch in selectivity. Thus, 3-fluoropyridine (**5h**) is magnesiated with **1** (1.1 equiv, −78 °C, 30 min) at position 2. After transmetalation with $ZnCl_2$ and a Negishi cross-coupling reaction[15] with ethyl 4-iodobenzoate (**7a**), the 2,3-disubstituted pyridine **15b** is obtained in 72 % yield (entry 2). Precomplexation with $BF_3{\cdot}OEt_2$ and metalation with **1** (1.1 equiv, −78 °C, 30 min) provides the 4-metalated pyridine, which after cross-coupling with the aryl iodide **7h** furnished the 3,4-disubstituted pyridine **16b** (74 % yield; entry 2). This complementary functionalization is also observed for 3-chloropyridine (**5i**) and 3-cyanopyridine (**5j**), and leads after similar reaction sequences to the 2,3-disubstituted pyridines **15c** and **15d** (72 and 75 %, respectively) and to the 3,4-disubstituted pyridines **16c** and **16d** (78 and 79 %, respectively; Table 1, entries 3 and 4). The metalation of the electron-poor pyridine **5j** is especially remarkable since such sensitive heterocycles are prone to polymerization during metalations. Thus, **5j** can be selectively metalated in position 2 by using **3** and furnishes, after a Negishi cross-coupling reaction,[15] the 2,3-disubstituted pyridine **15d** in 72 % yield. Precomplexation with $BF_3{\cdot}OEt_2$ and zincation with **3** (−30 °C, 30 min) provides the 3,4-disubstituted product **16d** (79 % yield; entry 4) after cross-coupling. Electron-deficient disubstituted pyridines such as 3-bromo-4-cyanopyridine (**5k**) are metalated with **1** (1.1 equiv, −78 °C, 1 h), and a copper-mediated allylation[29] with 3-bromocyclohexene (**7i**) affords the 1,2,3-trisubstituted pyridine **15e** (65 % yield; entry 5). In contrast, selective zincation occurs in position 4 after precomplexation with $BF_3{\cdot}OEt_2$ (1.1 equiv, 0 °C, 15 min) and subsequent reaction with **3**. Subsequent allylation then affords the 3,4,5-trisubstituted pyridine **16e** (63 % yield; entry 5). Electron-rich pyridines such as 2-methoxypyridine (**5l**) can also be deprotonated regioselectively by using in this case the aluminum base **4a**. In the absence of $BF_3{\cdot}OEt_2$ this reaction leads, after acylation, to the 2,3-substituted pyridine **15f** (68 % yield; entry 6). Precomplexation with $BF_3{\cdot}OEt_2$ followed by metal-

***Table 1:*** Switchable, regioselective metalations of N heterocycles with tmp bases in the presence or absence of $BF_3{\cdot}OEt_2$.

| Entry | Substrate | TMP base metalation (procedure A)[a] | $BF_3$-triggered metalation (procedure B)[a] |
|---|---|---|---|
| |  |  |  |
| 1 | **5g** | **15a**: 85 %[b] | **16a**: 83 %[c] |
| |  |  |  |
| 2 | **5h** | **15b**: 72 %[d,e] | **16b**: 74 %[d,e] |
| |  |  |  |
| 3 | **5i** | **15c**: 75 %[f,e] | **16c**: 78 %[f,g] |
| |  |  |  |
| 4 | **5j** | **15d**: 72 %[h,e] | **16d**: 79 %[i,e] |
| |  |  |  |
| 5 | **5k** | **15e**: 65 %[j] | **16e**: 63 %[k,g] |
| |  |  |  |
| 6 | **5l** | **15f**: 68 %[l,g] | **16f**: 75 %[m] |
| |  |  |  |
| 7 | **5m** | **15g**: 68 %[n,e] | **16g**: 94 %[o,g] |

[a] Yield of analytically pure isolated product. [b] **1** (55 °C, 30 h). [c] **1** (0 °C, 30 h). [d] **1** (−78 °C, 30 min). [e] Obtained by a palladium-catalyzed cross-coupling with $[Pd(dba)_2]$ (5 mol %) and P(2-furyl)$_3$ (10 mol %) at 25 °C for 12 h. [f] **1** (−78 °C, 45 min). [g] Obtained after transmetalation with CuCN·2 LiCl (1.1 equiv). [h] **3** (25 °C, 12 h). [i] **3** (−30 °C, 30 min). [j] **1** (−78 °C, 1 h). [k] **3** (−78 °C, 1 h). [l] **4a** (25 °C, 2 h). [m] **1** (0 °C, 60 h). [n] **4a** (−78 °C, 1 h). [o] **1** (0 °C, 1 h).

ation with **1** and iodolysis provides 2-iodo-6-methoxypyridine (**16f**; 75% yield; entry 6). This regioselectivity has been extended to functionalized quinoline derivatives. Thus, 6-methoxyquinoline (**5m**) is aluminated with **4a** at position 5.[30] After transmetalation with $ZnCl_2$ and a subsequent Negishi cross-coupling,[15] the 5,6-disubstituted quinoline **15g** is obtained in 68% yield. Precomplexation with $BF_3{\cdot}OEt_2$ and metalation with **1** leads, after a copper-mediated acylation, to the 2,6-disubstituted quinoline **16g** (94% yield; entry 7). The regioselectivity of the metalation in the presence of $BF_3$ may be best explained in the case of 3-substituted pyridines by assuming that the complexation of $BF_3$ at the pyridine nitrogen atom leads to a substantial steric hindrance at position 2, thereby favoring metalation at position 4.

In summary, we have reported a new class of frustrated Lewis pairs based on $BF_3{\cdot}OEt_2$ and LiCl-complexed tmpMg or tmpZn amides which allows an efficient, regioselective metalation of various N heterocycles. This approach constitutes an expeditive preparation of versatile magnesium chloride heteroaryl trifluoroborates, expanding on the work of Molander et al.[16,18,21] The metalation of various N heterocycles with or without $BF_3{\cdot}OEt_2$ by using hindered Mg, Zn, or Al bases (**1**, **2**, or **4a**) allows a complementary regioselective functionalization to generate a range of new polyfunctional N heterocycles. An extension of this method to other unsaturated substrates is currently underway.

## Experimental Section

**16c** (Table 1, entry 3): $BF_3{\cdot}OEt_2$ (780 mg, 5.5 mmol) was added dropwise to 3-chloropyridine (568 mg, 5.0 mmol) in dry THF (25 mL) at 0 °C in a flame-dried Schlenk-flask, flushed with argon. The resulting mixture was stirred for 15 min at 0 °C. Then tmpMgCl·LiCl (**1**; 5.5 mmol, 4.6 mL, 1.2 M in THF) was added dropwise at −78 °C and the mixture stirred for 45 min. CuCN·2 LiCl (5.5 mmol, 5.5 mL, 1 M in THF) was then added at −78 °C. After 30 min, 2-furoyl chloride (**7c**; 522 mg, 4 mmol) was added and the reaction mixture was warmed slowly to 25 °C and then stirred for 12 h. The reaction mixture was quenched with saturated $NH_4Cl$ solution (20 mL) and $NH_3$ (conc.; 3 mL) before extracting with diethyl ether (3 × 30 mL). Purification by flash column (pentane/diethyl ether, 1:1) furnished pyridine derivative **16c** as a brown oil (648 mg, 78%).

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