ChemComm

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View Article Online
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Cite this: *Chem. Commun.*, 2013, **49**, 2124

Received 18th December 2012, Accepted 28th January 2013

DOI: 10.1039/c3cc39040c

**www.rsc.org/chemcomm**

# Metalated N-heterocyclic reagents prepared by the frustrated Lewis pair TMPMgCl·BF$_3$ and their addition to aromatic aldehydes and activated ketones†

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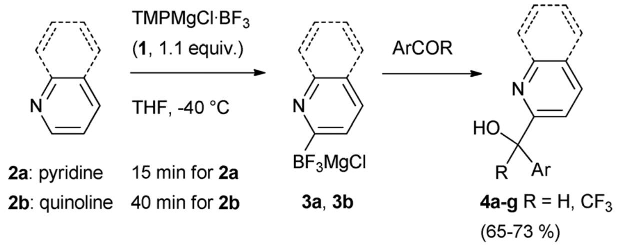
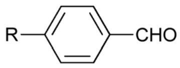
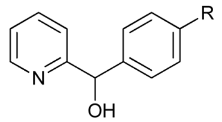
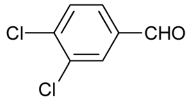
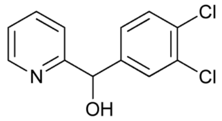
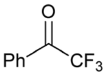
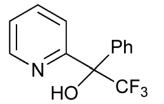
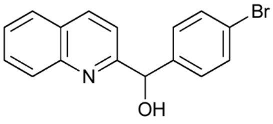
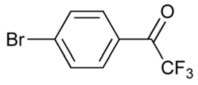
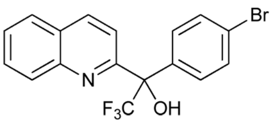
**Treatment of pyridines, quinoline and methylthiopyrazine with the frustrated Lewis pair TMPMgCl·BF$_3$ (1) leads to organotrifluoro borates which react readily with a variety of aromatic aldehydes in the absence of a transition metal catalyst.**

The metalation of pyridines is an important reaction since it allows a convenient functionalization of N-heterocycles.[1] Recently, we have shown that the frustrated Lewis pair[2] TMPMgCl·BF$_3$ (**1**, TMP = 2,2,6,6-tetramethylpiperidyl) made by mixing TMPMgCl·LiCl[3] with BF$_3$·OEt$_2$ below −40 °C is able to metalate a range of pyridines and related N-heterocycles with excellent regioselectivity.[4] The organometallic reagent produced by the treatment of pyridine (**2a**) with the Lewis pair **1** is the pyridyl trifluoroborate **3a**, as shown by a $^2J_{19F-13C}$ coupling of 14.7 Hz between C2 of **2a** and the fluorine atoms (Table 1).[4]

In general, the reactivity of pyridyl trifluoroborates towards aldehydes is quite low and a successful addition usually requires a rhodium, nickel or palladium catalyst.[5] However, we have found that magnesium 2-pyridyl trifluoroborates such as **3a** react readily with various aldehydes and activated ketones providing the pyridyl alcohols of type **4** (Table 1). Thus, the reaction of pyridine (**2a**) with the Lewis pair **1** (1.1 equiv.), prepared by mixing TMPMgCl·LiCl (1.1 equiv.) with BF$_3$·OEt$_2$ (1.1 equiv.) at −40 °C for 10 min, gives after further 15 min at −40 °C the trifluoroborate **3a** which reacts with 4-cyanobenzaldehyde (**5a**, 0.8 equiv., −40 °C to 25 °C, 2 h) leading to the desired pyridyl alcohol **4a** in 73% yield (Table 1, entry 1). Similarly, the substituted benzaldehydes **5b–d** react in the same way (−40 °C to 25 °C, 2–4 h) providing the alcohols **4b–d** in 66–68% yield (Table 1, entries 2–4). Interestingly, PhCOCF$_3$ (**5e**) reacts as well with **3a** affording the tertiary alcohol **4e** in 72% yield (Table 1, entry 5).[6] The metalation of quinoline (**2b**) with the Lewis pair **1** (1.1 equiv.) also proceeds readily under similar conditions (−40 °C, 40 min). The resulting trifluoroborate **3b**

**Table 1** Addition of 2-pyridyl trifluoroborates to aromatic aldehydes or activated ketones



| Entry | Substrate | Carbonyl compound | Product |
|---|---|---|---|
| 1 | **2a** | <br>**5a**: R = CN | <br>**4a**: R = CN; 73 % |
| 2 | **2a** | **5b:** R = Cl | **4b:** R = Cl; 68% |
| 3 | **2a** | **5c:** R = Br | **4c:** R = Br; 67% |
| 4 | **2a** | <br>**5d** | <br>**4d**; 66 % |
| 5 | **2a** | <br>**5e** | <br>**4e**; 72 % |
| 6 | **2b** | **5c** | <br>**4f**; 65 % |
| 7 | **2b** | <br>**5f** | <br>**4g**; 65 % |

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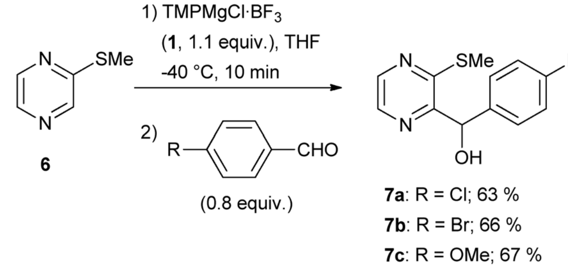
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc39040c



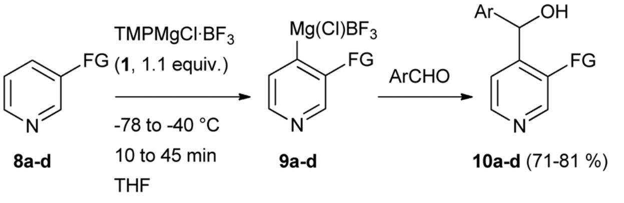
**Scheme 1** Metalation of **7** followed by trapping with aromatic aldehydes.

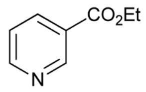
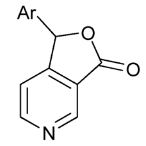
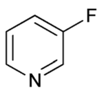
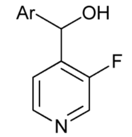
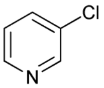
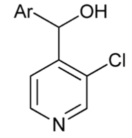
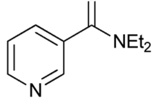
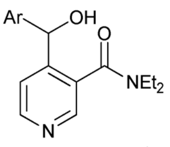
adds smoothly to 4-bromobenzaldehyde (**5c**) and the trifluoromethyl ketone (**5f**) providing the quinolyl alcohols **4f–g** in 65% yield (Table 1, entries 6 and 7).

The pyrazine **6** can also be metalated under these conditions and the addition to various benzaldehydes gives the desired carbinols **7a–c** in 63–67% yield (Scheme 1).

Then, we examined various 3-substituted pyridines (**8a–d**) and found that their treatment with TMPMgCl·BF$_3$ (**1**) at −40 °C or −78 °C affords metalated species of type **9** which react smoothly with several aromatic aldehydes (Table 2). Thus, the treatment of ethyl nicotinate (**8a**) with the Lewis pair **1** (1.1 equiv., −40 °C, 30 min) provides after the addition to 4-bromobenzaldehyde (**5c**, 0.8 equiv. −40 °C to 25 °C, 4 h) and cyclization the lactone **10a** in 72% yield (Table 2, entry 1). Similarly, the 3-chloro and 3-fluoro substituted pyridines **8b** and **8c** are readily metalated by TMPMgCl·BF$_3$ (**1**, 1.1 equiv.) at −78 °C within 10 min and give after quenching with the aldehydes **5c** and **5b**, respectively, the alcohols **10b** and **10c** in 71–81% yield (Table 2, entries 2 and 3). Finally diethylnicotinamide (**8d**) is metalated under the same conditions providing after addition to 3,4-dichlorobenzaldehyde (**5d**) the desired carbinol **10d** in 81% yield (Table 2, entry 4).

**Table 2** Metalation of 3-substituted pyridines followed by trapping with aromatic aldehydes



| Entry | N-Heterocycle | Carbonyl compound | Product |
|---|---|---|---|
| 1 | <br>**8a** | **5c** | <br>**10a**: Ar = *p*-C$_6$H$_4$Br; 72 % |
| 2 | <br>**8b** | **5c** | <br>**10b**: Ar = *p*-C$_6$H$_4$Br; 81 % |
| 3 | <br>**8c** | **5b** | <br>**10c**: Ar = *p*-C$_6$H$_4$Cl; 71 % |
| 4 | <br>**8d** | **5d** | <br>**10d**: Ar = 3,4-C$_6$H$_3$Cl; 81 % |

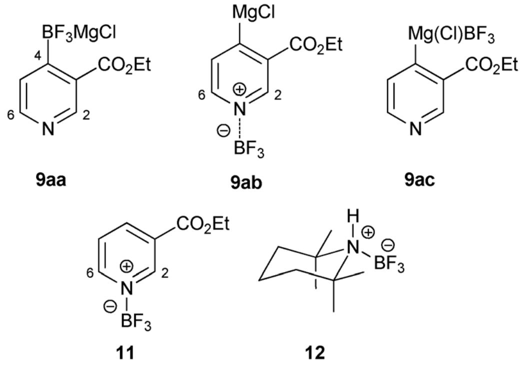


**Fig. 1** Structure of N-heterocycles metalated by TMPMgCl·BF$_3$ (**1**) and BF$_3$ complexes.

In order to provide structural information on the 4-metalated pyridines obtained by treatment of **8a–d** with the Lewis pair **1**, we have performed low temperature $^{1}$H-, $^{13}$C- $^{11}$B-and $^{19}$F-NMR studies. In contrast to the 2-metalated species (**3a** and **3b**) where a $^{2}J_{19F-13C}$ between C2 and the fluorine atoms can be observed,[4] such couplings could not be found for the 4-metalated species **9a**,[7] thus excluding the formation of an arylic trifluoroborate of structure **9aa** (Fig. 1). Also no $^{3}J_{19F-13C}$ coupling between C2 or C6 and fluorine could be observed, suggesting that no, or only a very weak, complexation of BF$_3$ by the pyridyl nitrogen occurs (see complex **9ab**, Fig. 1).

In a control experiment we treated **8a** with BF$_3$·OEt$_2$ in THF-d$_8$ and found the expected $^{3}J_{19F-13C}$ coupling between C2, C6 and the fluorine atoms (see complex **11**, Fig. 1). Also a coordination of TMPH to the BF$_3$-group resulting in a structure like **12** could not be observed. Control experiments showed that coordination of the BF$_3$-group to the solvent THF or the ester group of **8a** does not take place.[8] Thus, we propose that the structure of intermediates of type **9** is a pyridylmagnesium derivative like **9ac** (Fig. 1).

In conclusion, we have reported that the frustrated Lewis pair **1** can be used to prepare either 2-pyridyl trifluoroborates or 4-pyridylmagnesium derivatives which can be trapped with various aromatic aldehydes. Further extension of this research is currently underway.

## Notes and references

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5 (*a*) M. Pucheault, S. Darses and J.-P. Genet, *Chem. Commun.*, 2005, 4714; (*b*) F. Sakurai, K. Kondo and T. Aoyama, *Chem. Pharm. Bull.*, 2009, **57**, 511; (*c*) M. Kuriyama, R. Shimazawa, T. Enomoto and R. Shirai, *J. Org. Chem.*, 2008, **73**, 6939.

6 The use of aliphatic aldehydes leads only to extensive decomposition and no product could be isolated.

7 Low temperature NMR-studies on the organometallic intermediates **9b–d** could not be performed due to their low stability.

8 **12** was generated independently by treating TMPH with $BF_3{\cdot}OEt_2$ (1.1 equiv.) at 0 °C, see ESI†.