Metalated N-heterocyclic reagents prepared by the frustrated Lewis pair TMPMgCl·BF₃ 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·BF₃ (1) leads to organotrifluorborates 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. Recently, we have shown that the frustrated Lewis pair 2 TMPMgCl·BF₃ (1, TMP = 2,2,6,6-tetramethylpiperidyl) made by mixing TMPMgCl·LiCl with BF₃·OEt₂ below −40 °C is able to metalate a range of pyridines and related N-heterocycles with excellent regioselectivity. The organometallic reagent produced by the treatment of pyridine (2a) with the Lewis pair 1 is the pyridyl trifluoroborate 3a, as shown by a $^{19F}$–$^{13C}$ coupling of 14.7 Hz between C2 of 2a and the fluorine atoms (Table 1).

In general, the reactivity of pyridyl trifluoroborates towards aldehydes is quite low and a successful addition usually requires a rhodium, nickel or palladium catalyst. 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 BF₃·OEt₂ (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, PhCOCF₃ (5e) reacts as well with 3a affording the tertiary alcohol 4e in 72% yield (Table 1, entry 5). 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...
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 TMPCMgCl BF3 (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 BF3 (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).

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 1H-, 13C-, 11B- and 19F-NMR studies. In contrast to the 2-metalated species (3a and 3b) where a 2J19F–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 3J19F–13C coupling between C2 or C6 and fluorine could be observed, suggesting that no, or only a very weak, complexation of BF3 by the pyridyl nitrogen occurs (see complex 9ab, Fig. 1).

In a control experiment we treated 8a with BF3 OEt2 in THF-d8 and found the expected 3J19F–13C coupling between C2, C6 and the fluorine atoms (see complex 11, Fig. 1). Also a coordination of TMPH to the BF3-group resulting in a structure like 12 could not be observed. Control experiments showed that coordination of the BF3-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
2 (a) T. Voss, T. Mahdi, E. Otten, R. Frohlich, G. Kehr, D. W. Stephan and G. Erker, Organometallics, 2012, 31, 2367; (b) G. Erös, K. Nagy,


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 BF3·OEt2 (1.1 equiv.) at 0 °C, see ESI†.