

Metalated N-heterocyclic reagents prepared by the frustrated Lewis pair TMPMgCl-BF₃ and their addition to aromatic aldehydes and activated ketones†

Cite this: *Chem. Commun.*, 2013, **49**, 2124

Received 18th December 2012,
Accepted 28th January 2013

DOI: 10.1039/c3cc39040c

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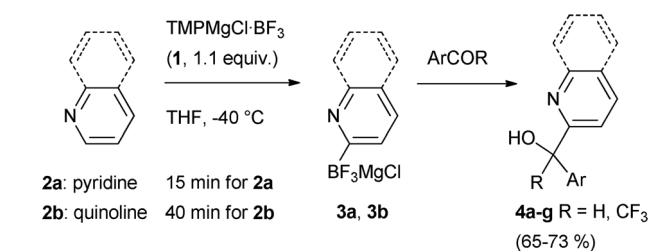
Sophia M. Manolikakes, Milica Jaric, Konstantin Karaghiosoff and Paul Knochel*

Treatment of pyridines, quinoline and methylthiopyrazine with the frustrated Lewis pair TMPMgCl-BF₃ (1) leads to organotrifluoroborates 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 pair² TMPMgCl-BF₃ (**1**, TMP = 2,2,6,6-tetramethylpiperidyl) made by mixing TMPMgCl-LiCl³ with BF₃·OEt₂ 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 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).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**

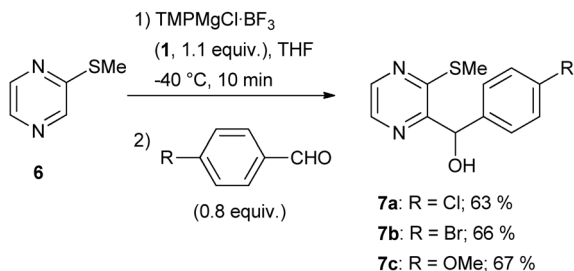
Table 1 Addition of 2-pyridyl trifluoroborates to aromatic aldehydes or activated ketones



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

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 München, Germany. E-mail: Paul.Knochel@cup.uni-muenchen.de

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



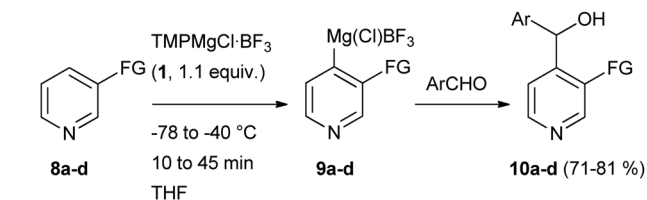
Scheme 1 Metalation of **7** followed by trapping with aromatic aldehydes.

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 $\text{TMPMgCl}\cdot\text{BF}_3$ (**1**) at $-40\text{ }^\circ\text{C}$ or $-78\text{ }^\circ\text{C}$ 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**

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



Entry	N-Heterocycle	Carbonyl compound	Product
1		5c	 10a: Ar = <i>p</i> -C ₆ H ₄ Br; 72 %
2		5c	 10b: Ar = <i>p</i> -C ₆ H ₄ Br; 81 %
3		5b	 10c: Ar = <i>p</i> -C ₆ H ₄ Cl; 71 %
4		5d	 10d: Ar = 3,4-C ₆ H ₃ Cl ₂ ; 81 %

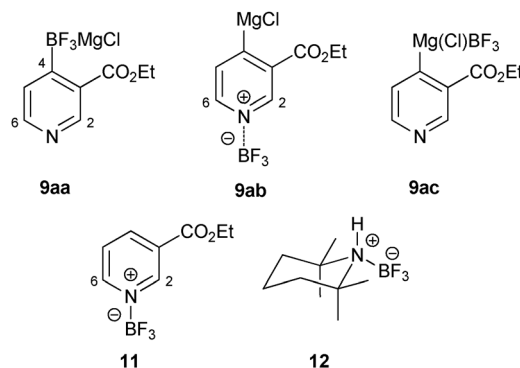


Fig. 1 Structure of N-heterocycles metalated by $\text{TMPMgCl}\cdot\text{BF}_3$ (**1**) and BF_3 complexes.

(1.1 equiv., $-40\text{ }^\circ\text{C}$, 30 min) provides after the addition to 4-bromobenzaldehyde (**5c**, 0.8 equiv. $-40\text{ }^\circ\text{C}$ to $25\text{ }^\circ\text{C}$, 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 $\text{TMPMgCl}\cdot\text{BF}_3$ (**1**, 1.1 equiv.) at $-78\text{ }^\circ\text{C}$ 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 diethyl-nicotinamide (**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-metallated pyridines obtained by treatment of **8a–d** with the Lewis pair **1**, we have performed low temperature ^1H -, ^{13}C - ^{11}B - and ^{19}F -NMR studies. In contrast to the 2-metallated species (**3a** and **3b**) where a $^2J_{^{19}\text{F}-^{13}\text{C}}$ between C2 and the fluorine atoms can be observed,⁴ such couplings could not be found for the 4-metallated species **9a**,⁷ thus excluding the formation of an aryl trifluoroborate of structure **9aa** (Fig. 1). Also no $^3J_{^{19}\text{F}-^{13}\text{C}}$ 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 $\text{BF}_3\cdot\text{OEt}_2$ in THF-d_8 and found the expected $^3J_{^{19}\text{F}-^{13}\text{C}}$ 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.

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- 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 $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv.) at 0 °C, see ESI†.