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Nucleophilic trifluoromethylation with organoboron reagents

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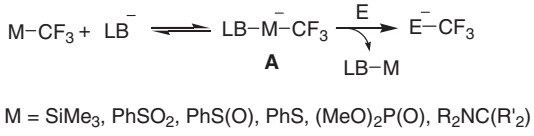
ABSTRACT

Potassium trialkoxy(trifluoromethyl)borates are shown to behave as convenient reagents for nucleophilic trifluoromethylation of non-enolizable aldehydes and *N*-tosylimines to give CF_3-substituted alcohols and *N*-tosylamines in good yields.

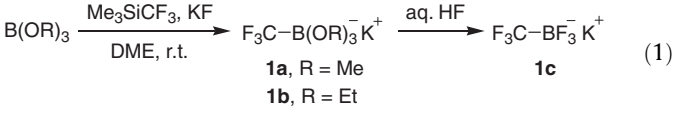
Due to the ability of the trifluoromethyl group to modify physicochemical and biological properties of organic compounds,[1] methods for its direct introduction into organic molecules have attracted considerable attention in recent years.[2] In this regard, nucleophilic trifluoromethylation has become a general and widely used approach for the preparation of CF_3-containing compounds. However, since trifluoromethyl lithium and magnesium derivatives are unstable, even at low temperatures, other reagents are employed which serve as equivalents of a CF_3-carbanion, and several methods for introduction of the CF_3-carbanion have been advanced.[2–10] The most widely exploited route involves the use of a CF_3-containing reagent in combination with a suitable basic activator to generate the anionic species **A** (Scheme 1). The latter intermediate typically exists in low equilibrium concentration and serves as a source of CF_3-carbanions in reactions with electrophiles.[4] According to this scenario, compounds bearing a CF_3-group on silicon,[5] sulfur,[6] or phosphorus,[7] as well as derivatives of trifluoroacetic acid,[4,8] fluoral,[4,9] and trifluoroacetophenone,[10] have been employed as trifluoromethylating agents.

Herein we report a new system for nucleophilic trifluoromethylation using organoboron reagents. The key feature of boron-based species of type **A**, namely CF_3-borate anions, is that they are shelf-stable and easily accessible compounds. Previously, transfer of the CF_3-group from boron has not been considered as a synthetically useful reaction, and it was proposed as an intramolecular elementary step in the chemistry of poly-CF_3-substituted boranes.[11]

The borate complexes **1a,b** were prepared from trialkoxyborates and the Me_3SiCF_3/KF combination in 1,2-dimethoxyethane according to literature procedures,[12] while trifluoroborate salt **1c** was obtained by treatment of **1a** with aqueous HF[12] (Eq. 1).



Scheme 1.



(1)

Benzaldehyde was treated with 1.2 equiv of salts **1a–c** using DMF as the solvent followed by acidic work-up (Table 1, entries 1–3). While trifluoroborate **1c** was unreactive, alkoxyborates **1a,b** reacted slowly, even at room temperature. Though ethoxyborate **1b** was found to react slightly faster, it was noticeably more hygroscopic and more difficult to handle compared to methoxyborate **1a**. Hence, further studies were performed using salt **1a**. Variation of the temperature and solvent demonstrated that complete conversion could be achieved after one hour at 50 °C in DMF, affording trifluoromethylated product **3a** in an isolated yield of 97% (entry 6).

Various carbonyl compounds were subjected to trifluoromethylation using borate **1a** (Table 2). Aromatic aldehydes, as well as cinnamaldehyde, furnished products **3** in excellent yields (entries 1–5). The ester group of substrate **2d** remained unaffected, and the desired alcohol **3d** was formed as the sole product (entry 3). Benzophenone also gave the desired alcohol **3i**, though in this case the reaction had to be carried out at 70 °C (entry 8). However,

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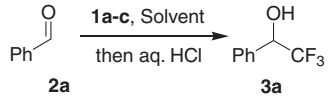
Table 1
Trifluoromethylation of benzaldehyde[a]

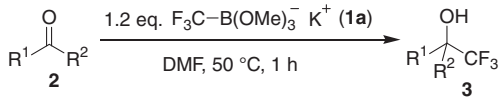


2a 3a

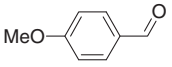
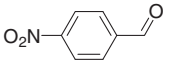
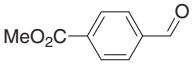
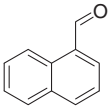
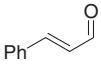
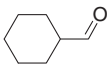
Entry	Borate	T (°C)	Time (h)	Solvent	Conversion[b] (%)
1	**1a**	rt	18	DMF	67
2	**1b**	rt	18	DMF	88
3	**1c**	70	1	DMF	n.r.[c]
4	**1a**	40	1	DMF	56
5	**1b**	40	1	DMF	100
6	**1a**	50	1	DMF	100 (97[d])
7	**1a**	rt	18	MeCN	61
8	**1a**	50	1	MeCN	97
9	**1a**	50	1	THF	39
10	**1a**	50	1	DME	67
11	**1a**	rt	18	MeOH	n.r.[c]

[a] Conditions: PhCHO (1.0 mmol), borate (1.2 mmol), solvent (1.2 mL).
[b] Based on NMR spectroscopy of the crude product.
[c] No reaction.
[d] Isolated yield.

Table 2
Trifluoromethylation of various carbonyl compounds



2 3

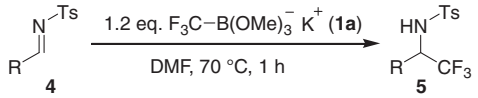
Entry	Substrate	Product	Yield[a] (%)
1		**3b**	85
2		**3c**	87
3		**3d**	78
4		**3e**	96
5		**3f**	97
6		**3g**	33
7		**3h**	43[b]
8[c]		**3i**	90

[a] Isolated yield.
[b] 3-Hydroxy-1,3-diphenylbutan-1-one was obtained as a by-product (ca. 15% yield).
[c] Reaction performed at 70 °C.

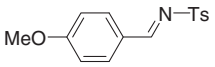
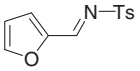
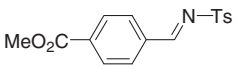
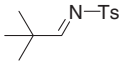
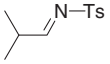
cyclohexane carboxaldehyde afforded product **3g** in only 33% yield, while a further increase in reaction temperature did not lead to an improved yield. Acetophenone also gave a moderate yield of product **3h** accompanied by the self-condensation aldol product (entry 7). These results suggest that enolizable substrates are prone to deprotonation under these reaction conditions.[13]

N-Tosylimines **4** constitute another type of typical electrophile, and their trifluoromethylation is summarized in Table 3. *N*-Tosylimines reacted somewhat more slowly than aldehydes and the reactions were performed at 70 °C. Substrates which did not have α-acidic protons furnished trifluoromethylated amines **5** in good yields. At the same time, reaction of the imine derived from isobutyraldehyde gave only traces of product **5f**; instead, the product of tautomerization of the starting imine, namely, *N*-tosyl-(2-methylprop-1-en-1-yl)amine, was formed as a result of deprotonation of the imine and reprotonation on work-up. *N*-Benzylideneaniline, which bears a phenyl group at the nitrogen was also treated with borate **1a**, but was recovered unchanged.

Table 3
Trifluoromethylation of *N*-tosylimines

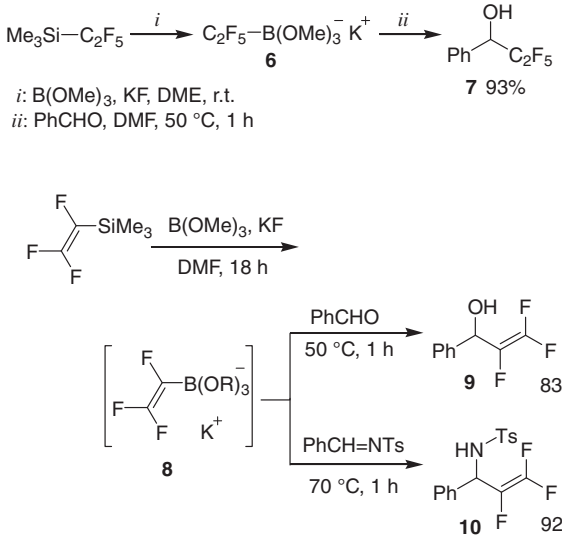


4 5

Entry	Substrate	Product	Yield[a] (%)
1		**5a**	97
2		**5b**	85
3		**5c**	87
4		**5d**	78
5		**5e**	98
6		**5f**	Trace[b]

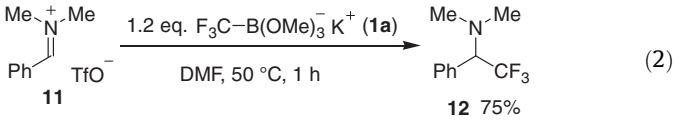
[a] Isolated yield.
[b] *N*-Tosyl-(2-methylprop-1-en-1-yl)amine was obtained.

It was also interesting to evaluate the reactivity of borate salts bearing other fluorinated groups. Thus, borate **6** containing a C_2F_5-group was obtained from the corresponding silane[12a] and smoothly afforded alcohol **7** (Scheme 2). The preparation of a borate salt with a trifluorovinyl group, according to the typical procedure in 1,2-dimethoxyethane, was sluggish. However, formation of borate **8** was achieved using DMF as the solvent, and the solution obtained was used for reactions with benzaldehyde and imine **4a**.[14] Products **9** and **10** were isolated in yields of 83% and 92%, respectively.[15]



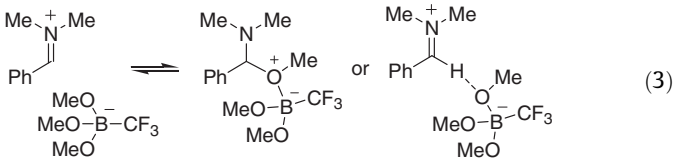
Scheme 2.

We were also interested in reactions of cationic electrophiles, which would be expected to interact rapidly with an anionic borate nucleophile.[16] For this purpose, the iminium salt **11** was treated with borate **1a** (Eq. 2).



(2)

Though the anticipated product **12** was formed, virtually no acceleration compared to the reaction with benzaldehyde was noted. Indeed, when reactions of benzaldehyde and **11** with **1a** were performed under identical conditions (40 °C, 1 h), approximately 50% conversions were observed in both cases. This is surprising, given that the iminium ion is expected to be more electrophilic than the neutral aldehyde. To explain this phenomenon we combined salts **11** and **1a** in DMF-d_7 in an NMR tube. Significant line-broadening of most of the signals was observed, as is clearly seen in the ^{1}H and ^{11}B NMR spectra (Fig. 1). This suggests an equilibrium interaction of iminium and borate ions to generate either semi-aminal-type species or a hydrogen-bonded complex,[17] thereby decreasing the reactivity of the iminium electrophile (Eq. 3).



(3)

Concerning the reaction mechanism, we believe that transfer of the CF_3-group to the C=O or C=N bond occurs without the intermediacy of a free CF_3-carbanion, though the latter pathway and radical mechanism cannot be excluded. It should be pointed out that direct transfer (without assistance of transition metals) of an alkyl(sp^3)-group from neutral boranes to carbonyl compounds or imines is rare, and reported examples involve either radical conditions or Lewis acidic organoboranes.[18] The reaction of sp^3-centered trifluoroborates with reactive *N*-acyliminium ions has only recently been described.[19] In contrast, an alkynyl(sp) group can be readily transferred from both boranes and borates to carbonyl compounds.[20] In this regard, owing to the significant electron-withdrawing effect of fluorines, the trifluoromethyl group may bear some similarities to an alkynyl fragment.

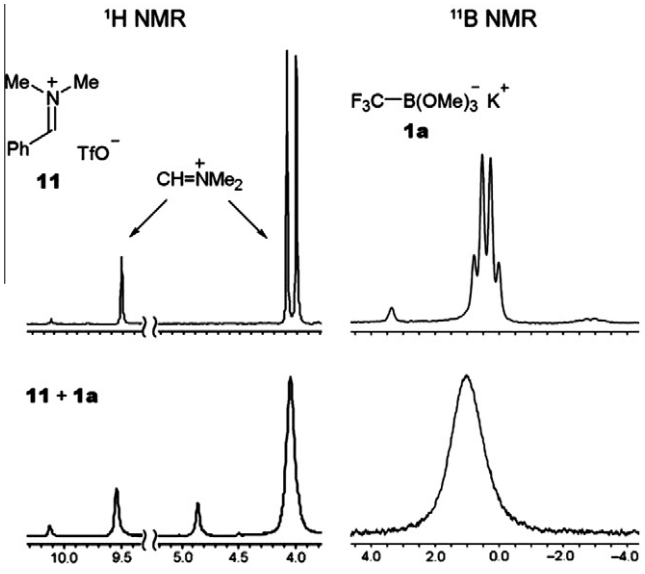


Figure 1. ^{1}H (left) and ^{11}B (right) NMR spectra of **11** and **1a** (top) and their mixture (bottom) in DMF-d_7 at room temperature.

In summary, we have demonstrated that borate salts can be used as efficient reagents for nucleophilic trifluoromethylation. Reactions of non-enolizable carbonyl compounds and *N*-tosylimines with CF_3-borates proceeded under mild conditions furnishing products in good yields. The search for processes involving transfer of the CF_3-group from boron to other electrophiles will constitute the subject of our future work.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.025.

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13. Similarly, it was reported that $[CF_2{=}CFB(OMe)_3]Li$ interacts slowly with acetone at room temperature to give trifluoroethylene, see: Adonin, N. Y.; Bardin, V. V.; Frohn, H. J. *Main Group Met. Chem.* **2009**, *32*, 153–159.
14. A solution of **8** in DMF was kept under vacuum briefly (ca. 12 mmHg) to remove unreacted silane, since on reaction with benzaldehyde the latter provides the TMS–ether of **9**.
15. For reactions of aldehydes with $CF_2{=}CFSiEt_3$, see: Kirij, N. V.; Dontsova, D. A.; Pavlenko, N. V.; Yagupolskii, Y. L.; Scherer, H.; Tyrra, W.; Naumann, D. *Eur. J. Org. Chem.* **2008**, 2267–2272.
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