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Oxidation of Hydroxyl-Substituted Organotrifluoroborates

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The transition metal-catalyzed cross-coupling reaction of organometallic reagents with organic electrophiles has transformed the manner in which synthetic chemists design syntheses of complex molecules.[1] As a result, several classes of organometallic reagents have become indispensable tools for selective carbon−carbon bond formation. Organoboron reagents are often superior to other classes of nucleophilic coupling reagents in their stability and/or functional group compatibility.[2] Additionally, they are more environmentally sound and exhibit minimal toxicity issues.

Recently, potassium organotrifluoroborates have been demonstrated to be useful coupling partners in the Suzuki−Miyaura reaction,[3] the rhodium-catalyzed 1,4-addition,[4] as well as other important synthetic reactions.[5] Their primary advantages are that they are air and moisture stable and can be prepared in large quantities that can be stored indefinitely. In some cases, they show enhanced reactivity compared to other organoboron compounds.[6]

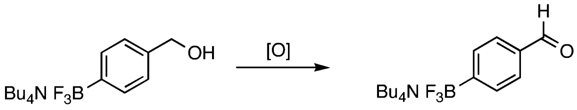
Because organoboron reagents, including trifluoroborates, are often used in complex molecule synthesis,[7] it would be advantageous to introduce functionality and manipulate them as ordinary synthetic intermediates in a multistep synthetic sequence. This would be in contrast to their normal use in synthesis, wherein the organoboron moiety is employed in a coupling reaction immediately after its introduction. In pursuit of this goal, we have shown that potassium organotrifluoroborates are stable to oxidative conditions,[8] including epoxidation[9] and dihydroxylation.[10]

Alcohol oxidation is of fundamental importance in organic synthesis.[11] Herein we report a general reaction of organotrifluoroborates in which a primary or secondary alcohol is converted to an aldehyde or ketone, while retaining the valuable carbon−boron bond. Many common oxidation protocols are tolerated, and both the potassium and the tetra-*n*-butylammonium (TBA) counterion can be used.

The incorporation of a carbonyl moiety into an organoboron compound would be a useful synthetic transformation, because many hydroboration reagents, such as catecholborane[12] and 9-BBN,[13] are incompatible with ketones and aldehydes. Other reagents, such as pinacolborane,[14] are more tolerant, but often require transition metal catalysis to undergo hydroboration at ambient temperatures.

Many oxidation procedures are conducted in chlorinated solvents in which polar organotrifluoroborates are insoluble. Consequently, the TBA organotrifluoroborates were used at the outset of this study because they are readily soluble in dichloromethane.[15] To initiate the study, the crystalline benzyl alcohol derivative **1a**, prepared in one step from the commercially available boronic acid, was subjected to a variety of oxidative conditions (Table 1).

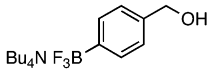
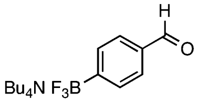
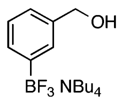
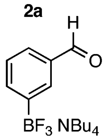
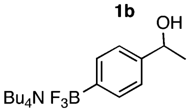
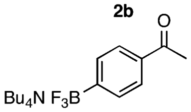
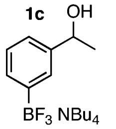
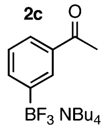
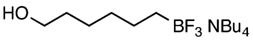
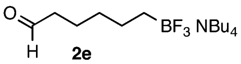
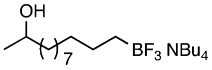
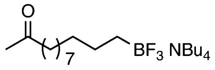
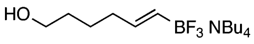
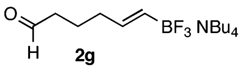
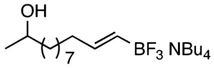
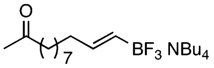
Table 1. Oxidation of TBA Trifluoroborate **1a**



1a **2a**

entry	conditions	% isolated yield
1	1% TPAP/NMO	91
2	Swern	90
3	Dess−Martin	86

Table 2. Oxidation of TBA Organotrifluoroborates[a]

entry	substrate	product	% isolated yield
1	 **1a**	 **2a**	91
2	 **1b**	 **2b**	97
3	 **1c**	 **2c**	94
4	 **1d**	 **2d**	92
5	 **1e**	 **2e**	84
6	 **1f**	 **2f**	93
7	 **1g**	 **2g**	78[b]
8	 **1h**	 **2h**	96[b]

[a] Conditions: 1−2% TPAP, 1.1 equiv NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 18−20 h. [b] 93% conversion.

TPAP/NMO,[16] Swern oxidation conditions,[17] and Dess−Martin periodinane[18] were all successful, providing the 4-formylphenyltrifluoroborate **2a** in good to excellent yields. In most cases, a simple aqueous workup and concentration was all that was required to isolate the pure oxidized product in high purity, with retention of the trifluoroborate moiety, as determined by ^1H, ^{11}B, ^{13}C, and ^{19}F NMR. Other common oxidation conditions, such as TEMPO/bleach,[19] TEMPO/PhI(OAc)$_2$,[20] and IBX,[21] also gave the desired product, albeit with byproducts that were not easily separable.

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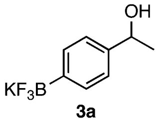
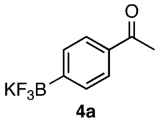
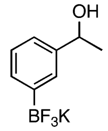
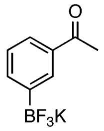
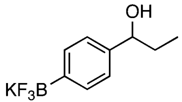
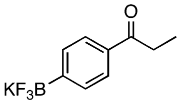
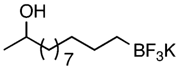
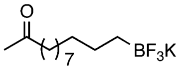
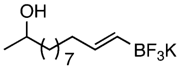
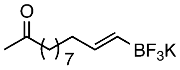
Table 3. Oxidation of Potassium Organotrifluoroborates[a]

entry	substrate	product	% isolated yield
1	 **3a**	 **4a**	92
2	 **3b**	 **4b**	88
3	 **3c**	 **4c**	74
4	 **3d**	 **4d**	b
5	 **3e**	 **4e**	b

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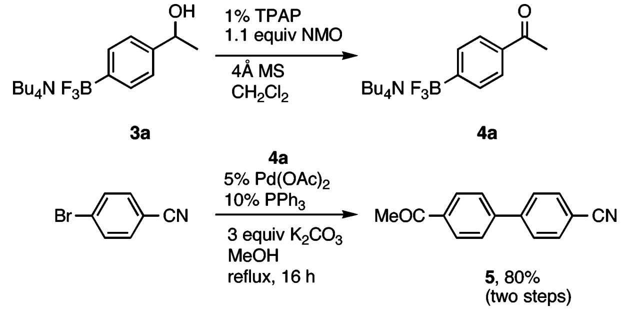
[a] Conditions: 3 equiv IBX, acetone, reflux, 2 h. [b] Product isolated in low yield.

Because of its simplicity in execution, the TPAP/NMO system was to chosen to oxidize a variety of TBA organotrifluoroborates containing primary and secondary alcohols. The use of activated, powdered 4 Å molecular sieves was necessary to promote oxidation. Alkyl, alkenyl, and aryl trifluoroborates were tolerated in this process, and no cleavage of the carbon−boron bond was observed (Table 2).

The use of IBX is often limited to DMSO, or DMSO/THF solvent mixtures. Recently, Finney and co-workers demonstrated that IBX can be used in several solvents at elevated temperatures.[22] We found that the potassium organotrifluoroborates could be oxidized using 3 equiv of IBX in refluxing acetone. In this case, the crystallinity of the potassium organotrifluoroborate salts proved to be beneficial to the workup. Simple filtration of the IBX byproducts gave a filtrate from which the oxidized products were crystallized. Potassium aryltrifluoroborates containing secondary alcohols were effectively oxidized by this method (Table 3). Primary alcohols are not suitable for this oxidation because the resulting aldehydes require methanol for dissolution, which also dissolves the IBX byproducts and impedes crystallization of the organotrifluoroborate.

The use of conditions developed previously in our group to couple these oxidized products was then explored.[23] TBA trifluoroborate **4a**, formed from the secondary alcohol **3a**, was coupled to 4-bromobenzonitrile to provide **5** in 80% yield over two steps after column chromatography (Scheme 1).

Scheme 1



In conclusion, we have synthesized potassium and TBA organotrifluoroborates containing hydroxyl groups and shown that they can be oxidized under several common oxidation conditions. This method allows access to ketone- and aldehyde-containing organoboron compounds, a class that can be difficult to access by other means. Most importantly, it allows practitioners to expand the role of organoborons in their synthetic planning, thus changing in a fundamental manner strategic retrosynthetic analyses involving boron-based cross-coupling.

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Supporting Information Available: Experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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