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Preparation of Organotrifluoroborate Salts: Precipitation-Driven Equilibrium under Non-Etching Conditions**

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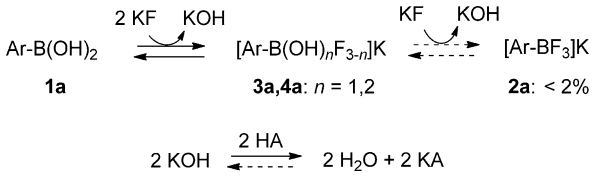
Dedicated to Professor Stefan Toma on the occasion of his 75th birthday

Although potassium organotrifluoroborates (RBF_3K) were first explored in the 1960s,[1] it was not until the mid 1990s that the utility of these air-, moisture-, and thermally stable, free-flowing crystalline solids began to be more fully appreciated.[2,3] They have now become extremely popular reagents in synthesis, with three major areas of application: 1) as precursors to difluoroboranes[2a,d–g] for allylation,[2d,4] boronic Mannich reactions,[5] and ether couplings;[6] 2) as readily handled boron intermediates, thus facilitating distal functional-group manipulation,[7] pinacol boronate cleavage,[8] and halo,[9] oxidative,[10] or nitrosative[11] deboronations; and 3) in metal-catalyzed coupling reactions, such as copper-catalyzed etherification[12] and rhodium-catalyzed additions to aldehydes,[13] imines,[14] and enones,[15] as well as palladium-catalyzed Suzuki–Miyaura reactions.[16] The latter has become an area of intense activity,[3,16] with organotrifluoroborates proving to be versatile and reliable reagents for a wide range of direct or indirect[17] couplings.

Despite this diverse repertoire, there are only two general routes to RBF_3K reagents: C–B bond formation by reaction of R-$SnMe_3$ with BF_3/KF[1] and B–F bond formation[18] by reaction of R-$B(OR')_2$ with HF/KOH,[19] or with KHF_2.[2a,20] The latter procedure was introduced by Vedejs et al. and involves addition of excess aqueous KHF_2 to the parent boronic acid ($R' = H$) or ester ($R' =$ alkyl) in methanol.[2a] This procedure was extended by Genet and co-workers to boronates generated in situ from RMgX or RLi,[2b,c] and has become the standard method for potassium organotrifluoroborate preparation. Its generality and reliability has engendered their remarkably diverse application not only in synthesis, but also ranging, for example, from carriers for ^{18}F PET imaging[21] through to precursors for ionic liquids.[22] However, although KHF_2 is safer to handle than HF or BF_3, it is nonetheless corrosive, thus causing extensive etching of glassware.[23] Moreover, the procedure usually requires separation of the RBF_3K product from the mixture of salts remaining after evaporation and sometimes necessitates Soxhlet extraction. Herein we report a new and operationally simple method for RBF_3M preparation (M = for example, K, Cs) that can be routinely conducted in regular glassware by employing readily handled reagents. It has been applied to a wide range of boronic acids and pinacol boronates, allows facile isolation of the trifluoroborate, and is readily scaled.

In their pioneering study on the generation of RBF_3K reagents, Vedejs et al. found that whilst KHF_2 in MeOH smoothly converted boronic acids (**1**) into potassium organotrifluoroborates (**2**), the much more readily handled KF did not.[2a] We began with an in situ ^{19}F NMR analysis of this latter process, thus reacting the fluorine-bearing aryl boronic acid *p*-$FC_6H_4B(OH)_2$ (**1a**) with 4 equivalents of KF. This study confirmed that whilst equilibrium with intermediates **3a**/**4a**[24] (see Scheme 1 for structures) is rapidly established, the generation of the *p*-$FC_6H_4BF_3K$ species **2a** could not be detected (< 2%).

To consume the KOH that is formally liberated by HO^- displacement with F^-, and to catalyze the equilibration,[17b,25] we tested the effect of addition of mild organic acids (HA; Scheme 1). Simple carboxylic acids were found to drive the



Scheme 1. Equilibrium between the boronic acid **1a** (Ar = *p*-FC_6H_4) and KF with the mixed species **3a**/**4a** in either MeOH or MeCN as monitored by ^{19}F NMR spectroscopy. The second equation shows the potential for acid (HA) to drive the generation of the trifluoroborate **2a**.

equilibrium in the desired direction, however a large excess was required to effect a greater than 99% conversion into **2a**. Replacing MeOH with diethyl ether led to co-precipitation of **2a** with other potassium salts (KF/RCO_2K etc.), thus making isolation of pure **2a** nonfacile. Switching to MeCN kept trifluoroborate **2a** in solution, but an excess of carboxylic acid (e.g. acetic or *ortho*-iodobenzoic acid) was still required (Scheme 2).

We thus sought an acid that could be used stoichiometrically, rather than in excess, and that also allowed facile isolation of the pure trifluoroborate **2a**. L-(+)-Tartaric acid (**5**) was found to fit these criteria well: it is a cheap and readily handled solid, and the monopotassium salt (potassium

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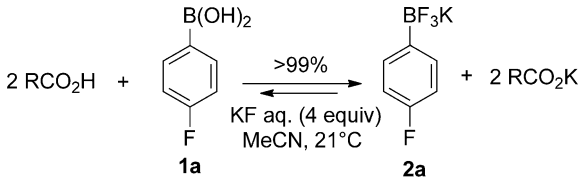


RCO_2H = AcOH, 30 equiv
= *o*-$IC_6H_4CO_2H$, 4 equiv
= L-(+)-tartaric acid (**5**), 2 equiv
(stoichiometric: RCO_2K fully precipitates)

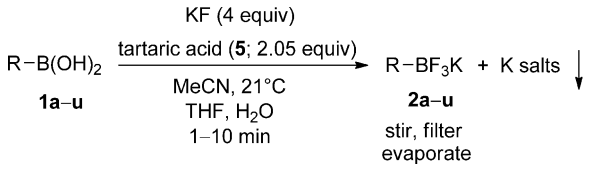
Scheme 2. Number of equivalents of acetic (pK_a 4.8), *ortho*-iodobenzoic (pK_a 2.9), and L-(+)-tartaric acid (**5**, pK_a 3.0) acids required for a greater than 99% conversion of **1a** into **2a**.

bitartrate, "cream of tartar") is of very low solubility in most organic solvents. By using just a stoichiometric amount of **5**, added as a THF solution, the precipitation of bitartrate (RCO_2K; Scheme 2) rapidly drives complete conversion of **1a** into **2a**.

Potassium bitartrate tends to precipitate as a metastable suspension, thus making filtration problematic and leading us to screen a wide range of inorganic salts and additives to find a suitable flocculating agent. Ultimately, a small quantity of water (conveniently added as aqueous KF, ca. 10 M) was found to readily effect flocculation, thus allowing rapid filtration. A slight excess of L-(+)-tartaric acid (2.05 equiv) reliably accommodated variations in stoichiometry arising from anhydrides (boroxines) and boric acid in commercial samples of boronic acids.[26] As residual KF and water, as well as any traces of in situ generated KHF_2 co-flocculate with the potassium bitartrate, the product isolation simply involves filtration and then evaporation[27] to directly obtain the RBF_3K reagent **2** in high yield and analytically pure form ($^{19}F/^{11}B/^{1}H$ NMR spectroscopy, elemental analysis).[26,28] With these reaction conditions in hand, a range of aromatic, vinylic, allylic, and alkyl boronic acids were smoothly converted into the corresponding trifluoroborates (**2a–u**; 1 mmol scale; Table 1) using commercial grade solvents under air.

Upon scale-up, the KF/L-(+)-tartaric acid process was equally efficient and easy to conduct, thus generating, for example, 4.2 g (99%) of **1j** and 3.9 g (95%) of **1l** (Table 1, entries 10 and 12). Of note is the rapid and simple procedure for product isolation, thus contrasting the extensive extraction processes which can be required with the classic KHF_2 method.[29] In addition, the HF_2^- anion can result in extensive etching of glassware,[23] with most reports advocating use of PTFE or polyethylene vessels. In stark contrast, there was no evidence for either etching or the solution-phase HF_2^- anion (^{19}F NMR spectroscopy) with the KF/L-(+)-tartaric acid procedure. To further test this, **2a** (0.75 mmol) was prepared by each method using two new 25 mL glass round bottomed flasks, and the procedures were repeated several times using the same flask for each method. With the KHF_2 method, cumulative etching soon led to the entire flask becoming opaque.[23] In contrast, with the KF/L-(+)-tartaric acid procedure, even after 30 sequential preparations (average yield 96%), no trace of etching could be detected (see the Supporting Information).

Table 1: Potassium trifluoroborate **2a–u** preparation by bitartrate precipitation.

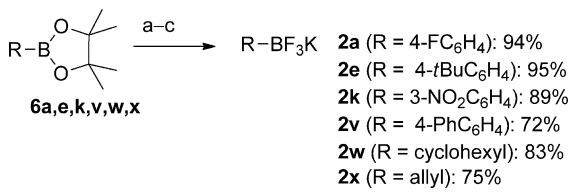


Entry	R	Yield [%][a]
1	4-FC_6H_4 (**1a**)	96[b] (**2a**)
2	C_6H_5 (**1b**)	90 (**2b**)
3	4-MeC_6H_4 (**1c**)	89 (**2c**)
4	4-$MeOC_6H_4$ (**1d**)	84 (**2d**)
5	4-*t*-BuC_6H_4 (**1e**)	98 (**2e**)
6	*E*-β-styryl (**1f**)	90 (**2f**)
7	4-$MeCOC_6H_4$ (**1g**)	57 (**2g**)
8	4-CNC_6H_4 (**1h**)	88 (**2h**)
9	4-$NO_2C_6H_4$ (**1i**)	78 (**2i**)
10	1-naphthyl (**1j**)	96 (99)[c] (**2j**)
11	3-$NO_2C_6H_4$ (**1k**)	87[d] (**2k**)
12	3-$MeCOC_6H_4$ (**1l**)	82 (95)[c] (**2l**)
13	3-ClC_6H_4 (**1m**)	93 (**2m**)
14	3,5-$(CF_3)_2C_6H_3$ (**1n**)	96[d] (**2n**)
15	2,6-$F_2C_6H_3$ (**1o**)	78 (**2o**)
16	3-$NH_2C_6H_4$ (**1p**)	76 (**2p**)
17	cyclopropyl (**1q**)	70[d] (**2q**)
18	cyclobutyl (**1r**)	57[d] (**2r**)
19	2-F-3-pyridyl (**1s**)	85[d,e] (**2s**)
20	*N*-Boc-5-Br-2-indolyl (**1t**)	90 (**2t**)
21	3-quinolinyl (**1u**)	69[d,e,f] (**2u**)

[a] Yield of isolated and analytically pure RBF_3K;[28] see the Supporting Information for full details. [b] Average of 30 runs. [c] Value within parentheses is for an 18-fold scale-up; [d] Used 4.5 equiv KF and 2.5 equiv **5**. [e] Used MeCN/MeOH (1:1) as the solvent. [f] The crude product obtained after evaporation, predominantly the K salt, was refined with K_2CO_3/acetone to give **2u** (69%).

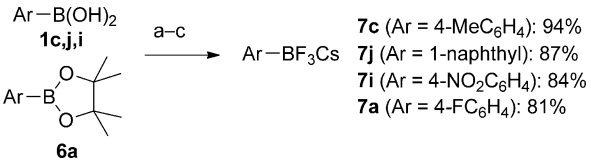
We next explored whether pinacol boronates (**6**) undergo analogous transformations. These species are of considerable utility in synthesis, but are often converted with KHF_2 into the corresponding trifluoroborate to aid hydrolysis or isolation.[8] A slight modification of solvent was required with the KF/L-(+)-tartaric acid methodology as, unlike boronic acids (Scheme 1), the pinacol boronate does not substantially precomplex[30] the KF (^{19}F NMR spectroscopy) in MeCN, thereby resulting in incomplete conversion of **6** into **2** before the onset of bitartrate flocculation. Reaction in MeCN/MeOH (1:1) negated this problem, thus giving RBF_3K products in good yield and high purity (Scheme 3).[28,31] We also briefly tested whether boronates prepared in situ[2b,c] from organolithium[32] species can be converted into trifluoroborates using KF/**5**. Sequential addition of 1.0 equivalent of BuLi, 1.01 equivalents of $B(OMe)_3$, 5.0 equivalents of KF, and then 3.05 equivalents of **5** to phenyl acetylene gave the alkynyl trifluoroborate in comparable yield to that obtained with the KHF_2 procedure (see the Supporting Information).

Finally, we note that the solubility and stability of the organotrifluoroborate salts can be tuned by variation of the



Scheme 3. Reaction conditions: a) KF (10 M aq.; 4 equiv) MeCN/MeOH (1:1), 21 °C, 1 min; b) L-(+)-tartaric acid (**5**, 2.05 equiv, THF) 2–5 min; c) filter, evaporate, remove pinacol (6 mmHg, gentle heating, 15 min).[8b,31]

counterion.[2a,8a,19,33] The RBF_3Cs salts **7**, for example, can be conveniently prepared by using the reaction conditions shown in Table 1, but replacing KF with CsF (Scheme 4); previous procedures require use of HF.[19,33]



Scheme 4. Reaction conditions: a) CsF (10 M aq.; 4 equiv), MeCN, 21 °C, 1 min; b) **5** (2.05 equiv, THF) 1-5 min; c) dilute with MeCN, filter, evaporate. For **6a**, MeCN/MeOH (9:1) employed.

In summary, we have developed a new procedure for the preparation of potassium organotrifluoroborate salts in good yield and high purity by pre-equilibration of the boronic acid or boronate with KF and then addition of a mild acid. By using L-(+)-tartaric acid (**5**) the process is efficiently driven to completion by precipitation of potassium bitartrate, thus making product isolation very simple.[34–36] It is effective for a wide range of boronic acids and pinacol boronates, including aliphatic, vinylic, and allylic systems, as well as electron-poor and electron-rich aryl rings. The method can also be effectively applied for the preparation of RBF_3Cs reagents. Compared to current methodologies involving HF or MHF_2, the reaction conditions are very mild, thus allowing the use of regular glassware, as there is no etching, and a simple and safe scale-up.[27] In addition, the low solubility of K^+ and Cs^+ bitartrate salts suggests considerable potential for application of L-(+)-tartaric acid (**5**) as an alkali-metal sponge in other processes, for example by reaction of MF with **5** to release HF/MHF_2 in situ for silyl deprotection.

Experimental Section

Preparation of potassium 3-acetylphenyltrifluoroborate (**21**; Table 1, entry 12): a solution of KF (4 equiv, 72 mmol, 4.18 g) in H_2O[34] (7.2 mL) was added to a suspension of the boronic acid **11** (2.95 g, 18 mmol) in MeCN (72 mL), and the mixture was stirred until complete dissolution (1 min). L-(+)-Tartaric acid (**5**, 2.05 equiv, 37 mmol, 5.54 g in 27 mL THF) was added dropwise to the rapidly stirring biphasic solution over a period of approximately 5 min, during which a white precipitate formed and rapidly flocculated. The mixture was filtered, washed through with more MeCN, and the filtrate was concentrated in vacuo to give **21** (3.86 g, 95%). ^{11}B NMR (96 MHz, [D$_6$]DMSO): $\delta = 2.2$ (br);[7a] ^{19}F NMR (283 MHz, [D$_6$]DMSO): $\delta = -139.3$ (br). See the Supporting Information for full details.

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[23] In the procedure reported by Vedejs et al., aqueous KHF_2 and the residue obtained after concentration of the reaction mixture (prior to extraction of RBF_3K), are both substantially more corrosive towards the glassware than the reaction mixture itself. Whilst KF/L-(+)-tartaric acid can generate KHF_2, this is transient/low in concentration and removed by co-precipitation with the bitartrate.
[24] Intermediates **3a**/**4a** have also been observed in basic aq. THF: a) M. Butters, J. N. Harvey, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones, P. M. Murray, *Angew. Chem.* **2010**, *122*, 5282 – 5286; *Angew. Chem. Int. Ed.* **2010**, *49*, 5156 – 5160; and on reaction of **1a** with $n$$Bu_4NF$ in DMF: b) C. Amatore, A. Jutand, G. Le Duc, *Angew. Chem.* **2012**, *124*, 1408 – 1411; *Angew. Chem. Int. Ed.* **2012**, *51*, 1379 – 1382.
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[26] $B(OH)_3$ present in, or derived from **1** is converted into KBF_4. Thus KBF_4 is generally detected as a minor contaminant (typically 0–0.7%) in the product **2** and is also present in commercial samples and reference samples prepared using KHF_2. Prior recrystallization of **1** from water, affords **2** in higher yield and purity.
[27] For scale-up, filtration after flocculation then addition of an anti-solvent, for example, Et_2O, allows isolation of **2** after a second filtration.
[28] Elemental analysis of the RBF_3K reagent obtained directly from evaporation was indicative of comparable or higher purity to commercial samples, and to reference materials prepared using the KHF_2 procedure (see the Supporting Information). If required, further purification can be effected by crystallisation from MeCN/Et_2O.
[29] See for example: G. A. Molander, S. L. J. Trice, S. D. Dreher, *J. Am. Chem. Soc.* **2010**, *132*, 17701 – 17703.
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[31] Pinacol can be separated by evaporation[8b] or by a MeOH/H_2O azeotrope.[8c] The latter works well with the procedure by Vedejs et al. (albeit with much bumping during evaporation) as KHF_2 in the residue supresses net regeneration of the pinacolate by solvolysis. With the KF/L-(+)-tartaric acid procedure, removal of the pinacol is best achieved under nonsolvolytic[17b] conditions (6 mmHg/Δ), thus leaving pure RBF_3K as the residue. Pinacol evaporates more readily from pure RBF_3K, than when excess KF/KHF_2 is present.[8c]
[32] The presence of magnesium salts, from analogous reactions of RMgX species with borates (conditions from Ref. [2b]), led to a 0% yield of isolated RBF_3K using the KF/**5** methodology. Instead, the crude product should be isolated as the pinacol boronate before conversion into RBF_3K by using the reaction conditions outlined in Scheme 3.
[33] D. S. Matteson, D. Maliakal, P. S. Pharazyn, B. J. Kim, *Synlett* **2006**, 3501 – 3503.
[34] A reviewer who tested the procedure (3 examples; unspecified, all successful) noted that a reduction in the amount of water facilitated more efficient solvent evaporation and drying, especially on scale-up. We note that a balance must be struck between efficiency of filtrate evaporation versus the efficacy of bitartrate flocculation; this latter issue is dependent on the identity of the trifluoroborate being prepared.
[35] For $RB(OH)_2$/RBF_3K systems of low solubility, for example, some heterocyclic systems, we recommend the use of MeOH/MeCN (1:1) rather than pure MeCN. After addition of tartaric acid the reaction mixture should then be diluted with an equal volume of MeCN. See the Supporting Information for full details. e.g. for preparation of **2s**.
[36] For basic substrates, there is the possibility of generation of the internal salt (J. Raushel, D. L. Sandrock, K. V. Josyula, D. Packyz, G. A. Molander, *J. Org. Chem.* **2011**, *76*, 2762 – 2769). The aniline **2p** and pyridine **2s** gave pure potassium salts (elemental analysis), however, the crude quinoline **2u** was slightly deficient in potassium (elemental analysis). Stirring an acetone solution of the crude **2u** over K_2CO_3 gave the pure potassium salt (69%) after filtration/evaporation.

