

Chapter 2

Organotrifluoroborate Preparation

2.1 Introduction

2.1.1 Preparation of *R*-BF₃K Salts

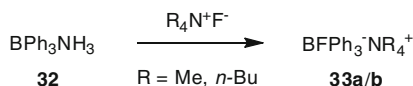
2.1.1.1 Initial Reports

The first report of an organofluoroborate salt was in 1940 by Fowler and Krauss [1], who prepared tetramethyl/butylammonium triphenylfluoroborate (**33a/b**) from an amine-borane complex **32** with tetramethyl/butylammonium fluoride, Scheme 2.1.

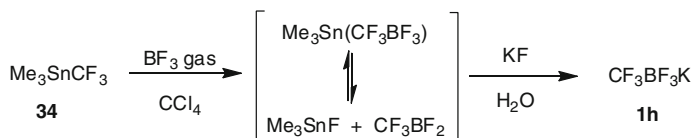
It took a further twenty years before a potassium organotrifluoroborate (**1**) appeared in the literature. In 1960, Chambers [2] prepared potassium (trifluoromethyl)trifluoroborate (**1h**) by treatment of (trifluoromethyl)trimethylstannane (**34**) with BF₃ gas followed by a work-up with aqueous potassium fluoride, Scheme 2.2. The barium and ammonium salts were also prepared *via* this method but showed inferior stability to the potassium salt, which was described as being ‘thermally stable and non-hygroscopic’.

This strategy, of boron displacement of tin to form the C–B bond, was further developed by Stafford [3] in 1963, who synthesised the first potassium vinyl and methyltrifluoroborates. Shortly after, Chambers and Chivers [4] prepared potassium pentafluoro phenyl trifluoroborate, and Chivers [5] in 1970 synthesised potassium 2-(trifluoromethyl) phenyl trifluoroborate.

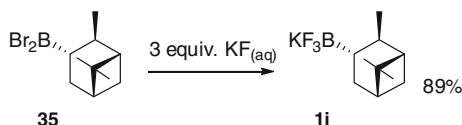
The alternative strategy involves heteroatom/fluoro exchange on boron, which was first realised by Kaufmann [6] in 1988. A dibromoborane camphenyl derivative **35** was treated with potassium fluoride to give isopinocampheyl trifluoroborate salt **1i** in good yield, Scheme 2.3, although this was the only example reported.



Scheme 2.1 First report of an organofluoroborate salt



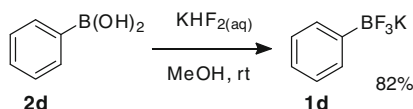
Scheme 2.2 First preparation of a potassium organotrifluoroborate salt by C–B bond formation



Scheme 2.3 Preparation of isopinocampheyl trifluoroborate salt **1i** by B–F bond formation

2.1.1.2 Introduction of KHF₂

Intermediate preparation of the exceptionally reactive and unstable dihaloboranes, in combination with the toxicity associated with gaseous boron trifluoride and tin reagents, did not make any of the preparative routes thus far, ideal for the chemistry of organotrifluoroborate salts to flourish. In 1995 an elegant procedure was published by Vedejs [7], who demonstrated that potassium bifluoride was an efficient fluorinating agent for organoboronic acids. Inspiration was taken from a publication by Umland and Thierig in 1967 [8], who employed KHF₂ to transform Ph₂BOH to the tetravalent KPh₂BF₂ salt. They proceeded to report that PhBF₃K could be produced by further heating of KPh₂BF₂ in glacial acetic acid. Their paper contained no experimental information, spectral data, or yields; so Vedejs developed the method, with the incentive of preparing stable precursors for organodifluoroboranes, [Sect. 1.1.1 *vide supra*](#). A saturated aqueous solution of KHF₂, added to the organoboronic acid (**2**) in methanol, was also found to convert any boroxines, or boronic acid dimers present in commercial samples, to the organotrifluoroborate salt (**1**), [Scheme 2.4](#). Isolation of pure product was then achieved by evaporation of all solvents, followed by multiple extractions with acetone.



Scheme 2.4 KHF₂ as a fluorinating agent for the preparation of **1d** from **2d**

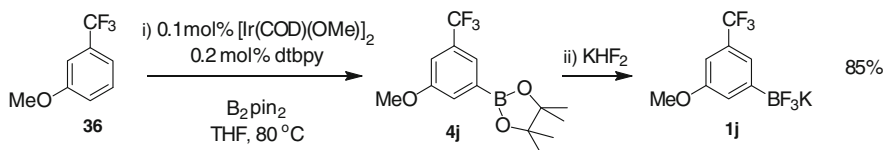
The scope of this reaction is evidently vast due to the availability and wide spread use of organoboronic acids, and, as such, they have become the primary starting materials for the preparation of R-BF₃K salts.

Organoboronic acid pinacol esters (**4**) are important building blocks in organic synthesis, and are important precursors for R-BF₃K salts. Aside from cost and atom-economy, the monomeric nature and stability towards silica-gel of pinacol esters renders them advantageous in many contexts when compared to boronic acids. Their applications are diverse, ranging from direct use in SM cross-coupling reactions [9] to the generation of enantiopure tertiary alcohols [10]. Pinacol esters are conveniently prepared *via* the Miyaura borylation; a palladium catalysed conversion of an organohalide to the corresponding boronic ester [11]. The transformation is highly functional group tolerant and uses cheap, commercially available starting materials, allowing access to a wide substrate variety. Iridium has recently been found to catalyse the C–H activation of 3, 5-bis-substituted arenes, thus bypassing the requirement for inclusion of a halide leaving group [12]. Treatment of the pinacol ester with KHF₂, and purification from residual pinacol, yields pure R-BF₃K salt, Scheme 2.5.

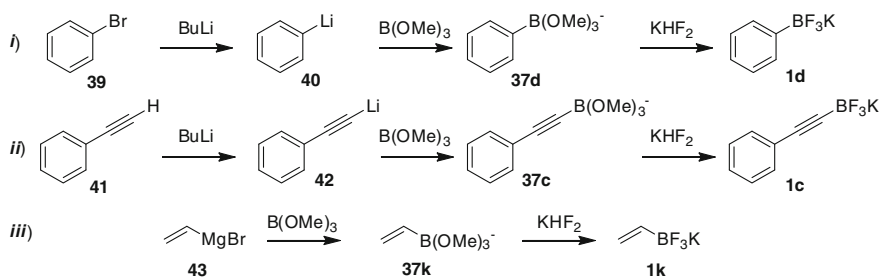
Direct conversion from pinacol esters to the more Lewis acidic boronic acid is problematic, due to difficulties in separation and subsequent recombination of the boronic acid and diol. This problem can be averted by the intermediate preparation and hydrolysis of the organotrifluoroborate salt [13]. Thus, boronic ester conversion to R-BF₃K salts, becomes a key transformation, widely used throughout academic research and industrial application.

Organoboronic acid methyl (**37**)/isopropyl (**38**) esters are another class of important intermediates for the generation of organotrifluoroborate salts (**1**). Primarily they are generated *in situ* from, (i) lithium-halogen exchange *via* treatment of an organohalide with BuLi, or (ii) *via* deprotonation of a suitably acidic proton, e.g. of a terminal alkyne, followed by workup with B(OMe)₃ or B(Oi-Pr)₃. Genet [14] demonstrated these could be taken through in a “one-pot” process to the corresponding potassium organotrifluoroborate by direct treatment with KHF₂, Scheme 2.6. Grignard reagents, (iii), e.g. vinylmagnesium bromide, are also suitable nucleophiles for the borylation/fluorination protocol, allowing moieties such as ethynyl and vinyl to be incorporated into the growing repertoire of known R-BF₃K salts, Scheme 2.6.

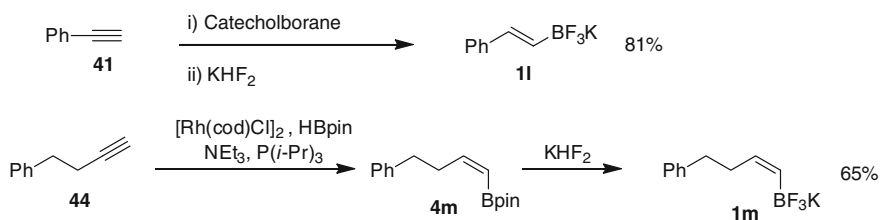
Finally, treatment of boronic esters with KHF₂, which have been prepared from the hydroboration of alkynes, forms an important route to alkenyltrifluoroborate



Scheme 2.5 Iridium-catalysed C–H activation for the borylation of arene **36** and subsequent “one-pot” transformation to organotrifluoroborate salt **1j**



Scheme 2.6 Organotrifluoroborate (**1d**, **1c** and **1k**) preparation from the generation of intermediate boronic esters **37d**, **37c** and **37k**



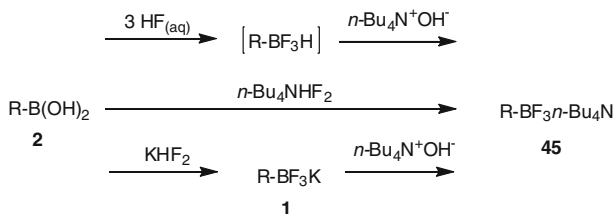
Scheme 2.7 Preparation of organotrifluoroborate **1l** and **1m** via the hydroboration of alkynes **41** and **44**

salts. The *E* stereoisomers can be conveniently prepared *via* syn hydroboration [15], Scheme 2.7. Preparation of the *Z* stereoisomer is achieved *via* isolation of the intermediate pinacol ester, obtained from rhodium catalysed hydroboration of alkynes [16], followed by treatment with KHF_2 [17], Scheme 2.7.

A wide range of potassium organotrifluoroborates have since been synthesised using KHF_2 as the fluorinating agent, including potassium alkyl [18, 19], alkenyl [15], alkynyl [14], allyl [20, 21], perfluoroalkyl [22] /alkenyl [23], acyl [24] and amino [25, 26] trifluoroborates. However, addition of $\text{HF}_{(\text{aq})}$ in conjunction with KHF_2 , is still required for the perfluorinated examples [22], presumably due to the greater stability of the alkoxo-ligated boron intermediates.

2.1.2 Preparation of $R\text{-BF}_3^-$ Salts with Different Counter Cations

The counter cation of organotrifluoroborate salts, not only dictates the physical properties of the compound, but also the solubility characteristics in which it inherits. Therefore, it is possible to tune the solubility of the reagent to a particular process. The potassium salts have generated the most attention, due to their free-flowing crystalline physical properties and ease in preparation, through the



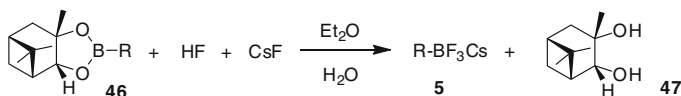
Scheme 2.8 Preparation of the tetrabutylammonium organotrifluoroborate salt **45** from **2**

commercial availability of KHF_2 . Other salts of organotrifluoroborates have been isolated, including other alkali metals and tetraalkylammonium, *e.g.* tetrabutylammonium ($n\text{-Bu}_4\text{N}^+$) [27].

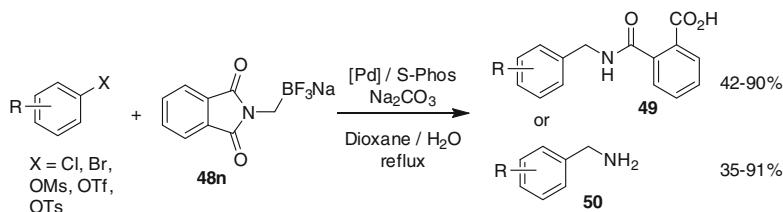
Tetrabutylammonium organotrifluoroborate salts (**45**) offer a greater range of solubility in apolar solvents, but they suffer in their physical handling properties, as they are often oils or low melting solids. The $n\text{-Bu}_4\text{N}^+$ salts are prepared from the organoboronic acid by either treatment with tetrabutylammonium hydroxide and $\text{HF}_{(\text{aq})}$ [27], or more conveniently with preformed tetrabutylammonium bifluoride; [28] an alternative procedure employs a cation exchange protocol on the corresponding potassium salt, Scheme 2.8 [27].

Along with the potassium salt, Batey [27] was able to prepare a range of metal salts with the HF/MOH methodology, Scheme 2.8, including lithium, sodium and cesium. However this was only demonstrated on a single substrate (PhB(OH)_2), with little experimental details or spectroscopic evidence. Matteson [29] reported on the preparation of cesium alkyltrifluoroborate salts (**5**) from pinanediol boronic esters (**46**). This was developed after attempts to form the potassium salt were complicated by difficulties in purification from free pinanediol and KHF_2 in solution; the cesium salt was preferred as it readily precipitated from Et_2O . Primary and secondary alkyltrifluoroborates were prepared in good to excellent yields, by treatment of the boronic ester with a premixed solution of $\text{HF}_{(\text{aq})}$ and CsF , Scheme 2.9.

The cesium salt has an increased cost disadvantage in comparison to the potassium salt, but it does provide a difference in its solubility properties, which allows a broader range of applications for organotrifluoroborate salts in general. As CsHF_2 is not commercially available, Matteson's HF/CsF methodology forms the primary way to prepare the cesium salts. The toxicity and associated handling problems of $\text{HF}_{(\text{aq})}$, has therefore meant the chemical applications of the cesium salts have not grown as rapidly as their potassium analogous.



Scheme 2.9 Matteson's preparation of cesium alkyltrifluoroborate salts (**5**) from **46**; an excess of HF with CsF forms CsHF_2 *in situ*



Scheme 2.10 Tanaka's cross-coupling of sodium phthalimidomethyltrifluoroborate (**48n**) to give amides **49** and benzylic amines **50**

There are fewer reports on the preparation and utility of sodium organotrifluoroborate salts (**48**). Although NaHF₂ is commercially available and cheaper than KHF₂, this may be due to a lower stability that the harder counter cation induces. However, Batey [27] claimed the phenyl moiety induced sufficient stability and a large number of aromatic examples do exist in the patent literature. Additionally, Tanaka [30] recently reported on the SM coupling of sodium phthalimidomethyl trifluoroborate (**48n**) with aryl halides. Unfortunately, no rationale is given to their preference for employing the sodium over the potassium salts, but their couplings achieve good to excellent yields, Scheme 2.10, implying there is little disadvantage in their use.

2.1.3 Problems and Proposals

The KHF₂ method avoids many of the handling problems associated with employing HF_(aq) or BF₃ gas, but it still comes at a practical cost due to the severe etching effect of glassware it exerts. The damage from the *in situ* release of HF on a small scale may be relatively insignificant compared to the costs of reagents or substrates; however, on an industrial scale this damage can be tremendously costly, rendering the process undesirable. Moreover, current procedures employ a large excess of KHF₂, (2–6 equivalents), which provokes further waste concerns. The isolation and purification is laborious, requiring separation of the RBF₃K salt from the mixture of potassium salts (KF/KOH/KHF₂) remaining after the removal of methanol/water *in vacuo*. Often the removal of solvents requires high vacuum for long periods of time, e.g. overnight, and the isolation of R-BF₃K salts sometimes necessitates multiple extractions at different temperatures [14] or Soxhlet extraction [31], which is impractical on a large scale.

Due to the wide ranging and ever increasing applications of organotrifluoroborate salts, an improved methodology is required to deal with the issues stated above: a fluorinating agent that does not involve the *in situ* generation of HF will suppress glassware etching, and an operationally simple workup and isolation to give pure R-BF₃K is desired.

2.2 Preparation of R-BF₃K Salts from Boronic Acids

2.2.1 Optimisation

In Vedejs' pioneering publication [7], potassium fluoride was found to be ineffective at forming Ph-BF₃K salts from boronic acids, as "the fluoride exchange did not take place when KF was used in place of KHF₂". However preliminary studies in our hands showed (¹⁹F and ¹¹B NMR) complete consumption of 4-fluorophenylboronic acid (**2a**) upon treatment with 4 equivalents of potassium fluoride in methanol, Fig. 2.1. The exact identity of the partially methoxylated/hydroxylated/fluorinated 'ate' product **51a** was unknown, but integration of the ¹⁹F NMR peaks suggested two fluorine atoms were ligated to boron; and due to the very much greater concentration of methanol to water, a methoxyl ligand was likely to have displaced hydroxide. Consistent with Vedejs' observations, equilibrium was established, and no potassium 4-fluorophenyltrifluoroborate (**1a**) was detected.

From studies on the hydrolysis of organotrifluoroborates (**1**) (Sect. 4.2, *vide infra*) to boronic acids (**2**), it was demonstrated that the transformation can be catalysed by a specific acid pathway, and thus microscopic reversibility infers the forward reaction should also be catalysed by acid. Additionally, in order to push the equilibrium in favour of the trifluoroborate, KOH sequestration is required, which can in principle be achieved by the addition of stoichiometric quantities of acid. Therefore, by replacing HF in KHF₂, with a weak acid (HA) in the presence of KF, it was envisaged that complete conversion to the trifluoroborate would take place, under HF-free, non-etching conditions, Scheme 2.11.

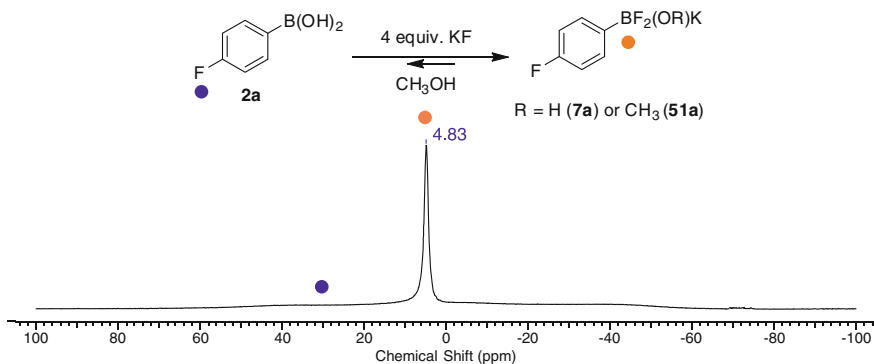
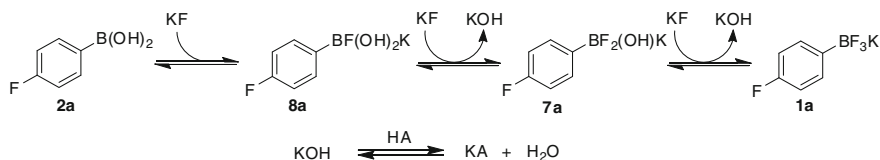


Fig. 2.1 ¹¹B NMR spectrum of the 'ate' species formed after the addition of KF to **2a**. Baseline due to background borosilicate glass signals



Scheme 2.11 Mechanistic proposal for the non-etching preparation of **1a** from **2a**

2.2.1.1 Methanol and Acetic Acid

Acetic acid was initially chosen due to its low cost and high availability, and 4-fluorophenylboronic acid (**2a**) was employed as a test substrate due to the ease of *in situ* reaction monitoring offered by ^{19}F NMR. To explore the system, the loadings of potassium fluoride and acetic acid were varied in a solution of **2a** in methanol. It was found the conversion to **1a** was dependent on both KF and acetic acid concentrations, requiring over 30 equivalents of the latter to reach a satisfactory conversion, Table 2.1.

2.2.1.2 Solvent Study

With the proof of principle established, the solvent was studied in order to find a suitable system, which would give the most operationally facile procedure, combined with the highest yields and purities. Ideally, either the product **1a**, or co-products (KA), would precipitate out of solution, thus requiring only a simple filtration and evaporation to isolate pure R-BF₃K.

Unfortunately, methanol dissolved all reactants and products thereby rendering it less than ideal. A range of alternative solvents were tested, where unsurprisingly, the relatively nonpolar solvents e.g. THF, toluene and DCM gave 0 % conversion,

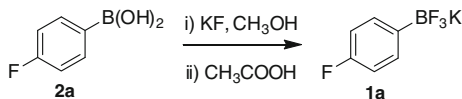


Table 2.1 Initial investigations into the use of acetic acid and KF in the preparation of **1a**

Entry	Acetic acid/equiv.	KF/equiv.	Conversion ($\rightarrow$ 1a)/ % ^a
1	2	3	44
2	3	3	47
3	5	3	57
4	5	4	68
5	14	3	87
6	32	3	98

^a % **1a** ($\delta_{\text{F}} = -118.8$ and -141 ppm) by ^{19}F NMR

presumably due to the poor solubility of the KF. Although KF was initially insoluble in most solvents tested, upon the addition of acetic acid in some solvents e.g. acetone, EtOAc, CH₃CN and Et₂O, it subsequently dissolved and gave good conversions to **1a**, Table 2.2.

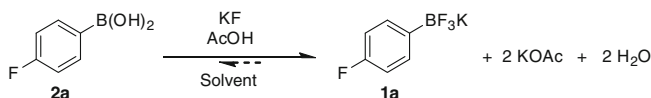


Table 2.2 Variation of the solvent in the preparation of **1a** from **2a**

Entry	Solvent	Acetic acid/equiv.	KF/equiv.	Conversion (→ 1a)/ % ^a
1	CH ₃ OH	50	3	98
2	DCM	50	3	0
3	THF	50	3	0
4	Toluene	50	3	0
5	Et ₂ O	50	3	81 ^b
6	Acetone	50	3	99
7	EtOAc	50	3	75
8	CH ₃ CN	30	4	99

^a % **1a** ($\delta_{\text{F}} = -118.8$ to -119.7 and -140 to -142 ppm) by ¹⁹F NMR

^b **1a** isolated, due to precipitation from solution

For reasons currently not understood, diethyl ether gave satisfactory conversions when other non-polar solvents did not. The R-BF₃K salt precipitated out of solution, which was initially promising due to the ease in isolation it offered. But when performed on a preparative (0.71 mmol) scale, only 64 % of **1a** could be isolated. Product was lost during purification from the co-precipitated KOAc and KF, and acetic acid contamination, which was difficult to remove under reduced pressure. Switching to acetone, in which the conjugate base, KOAc, and KF were not soluble, but **1a** was, also gave a 64 % isolated yield (0.71 mmol scale). However, purification was again required due to the acetic acid contamination.

2.2.1.3 Acid Study

Evidently the acetic acid contamination was problematic due to the large excesses (20–50 equivalents) required. A stoichiometric acid which would allow facile isolation of pure **1a** by precipitation of all co-products would thus be beneficial. The use of formic acid effected good conversions (99 %) in methanol, but still required an excess (30 equivalents) and thus gave rise to similar problems as acetic acid. The use of a strong acid such as HCl_(aq) (2 N) gave only traces of **1a**, possibly due to a competing acid catalysed protodeboronation degradation of **2a**, or intermediates **7a** and **8a**. Eventually, L-(+)-tartaric acid (**3**) was identified as fitting the criteria: not only is it a safe, easily handled and cheap solid, but it could be

used stoichiometrically (2 equivalents) as the conjugate base, potassium bitartrate (cream of tartar, **52**), is extremely insoluble in all common organic solvents.

2.2.1.4 Flocculating Agent

Initial optimisations of **2a–1a** with tartaric acid (**3**) were undertaken (0.15 mmol scale) in methanol, and employing stoichiometric quantities of KF (3 equiv.) and **3** (2 equiv.). Although 75 % conversion was reached, potassium bitartrate (**52**) precipitated out of solution as a very fine suspension, thus causing significant problems during the filtration of the co-products. On a small test scale (0.15 mmol) filtration of **52** was found to be slow, however, when moving to a large scale it was envisaged that efficient filtration would become impossible.

Attempts were made at controlling the precipitation rate of potassium bitartrate (**52**) to increase the particle size through slow addition of tartaric acid (**3**), however, no long lasting effect was observed. Additionally the use of low temperature, slow diffusion with layering, seeding and increasing the concentration, all had no influence on the suspension. A suitable flocculating agent, to agglomerate the fine suspension, was sought. A range of inorganic salts were screened, *via* addition to a solution of **52** in methanol, Table 2.3.

Few salts had any initial effect, with the exception of KOH and brine. The strong basicity of the former hampered the inertness of an ideal flocculating agent, but use of the latter was more encouraging. Unfortunately, when the procedure was performed on a larger scale (0.5 mmol) and brine was used to flocculate the suspension, isolation of pure **1a** still proved difficult, due to contamination with

Table 2.3 Inorganic salts tested for the flocculation of potassium bitartrate in methanol

Entry	Salt	Initial effect ^a	Longer term effect ^b
1	MgSO ₄	Nil	Slight flocculation
2	KCl	Nil	Nil
3	K ₂ CO ₃	Nil	Slow flocculation
4	KOAc	Nil	Slight flocculation
5	NaHCO ₃	Nil	Slight flocculation
6	KI	Nil	Nil
7	KBF ₄	Nil	Slow flocculation
8	KOCN	Nil	Nil
9	KBr	Nil	Nil
10	Na ₂ SO ₄	Nil	Nil
11	NH ₄ Cl	Nil	Nil
12	CaCl ₂	Nil	Nil
13	KOH	Rapid flocculation	Flocculation
14	NaCl	Nil	Nil
15	NaCl _(aq)	Rapid flocculation	Flocculation

^a Initial observation after 1–2 min

^b Upon standing for 1–2 h

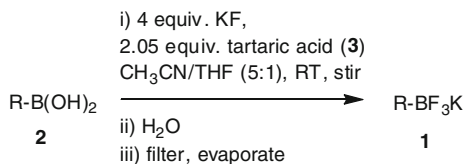
NaCl. Interestingly, the addition of a larger volume of pure water also effected this physical change, however it was slow, and too much water remained after filtration, raising concerns over its removal *in vacuo*, and the instability of some of R-BF₃K salts to an aqueous medium.

2.2.1.5 Water as a Flocculating Agent

Although water was found to successfully flocculate the suspension, a further problem experienced in methanol was the formation of small quantities of a stable partially methoxylated/fluorinated ‘ate’ species **51a** detected (¹¹B, ¹⁹F NMR) *in situ*. This warranted efforts into sourcing an alternative solvent system where the level of methanol in the mixture could be reduced.

Various ratios of methanol/THF were tested in the formation of **1a** from **2a**, followed by the use of water to flocculate the bitartrate. Increasing proportions of methanol led to increasing quantities of **51a**; but increasing proportions of THF led to the insolubility of KF, which caused the reaction to take longer to proceed to completion. However, it was noted under these ‘low methanol conditions’ that the addition of smaller quantities of water could effect flocculation of bitartrate **52** more efficiently. It was speculated that the flocculation mechanism involved water forming a strong hydrogen bonded network to **52**, which forced the suspension to coagulate. A single crystal X-ray structure of **52**, recrystallised from water, confirmed the solid could contain a high proportion of water. Consequently, a large excess of methanol would easily disturb this structure and slow down flocculation.

The solvent system needed to accommodate all R-BF₃K salts, which are generally only soluble in very polar solvents, yet avoid the use of protic alcohol solvents, which disturb flocculation of bitartrate **52**. Naturally acetonitrile was chosen because of the solubility it offers to R-BF₃K salts and partially to KF. However, a proportion of THF (16.7 %) was still required to dissolve the tartaric acid, which exhibited no solubility in acetonitrile. Under these conditions the loadings of KF and tartaric acid were varied, and 4 and 2.05 equivalents respectively gave the most reliable results. The conversion of **2a**–**1a** generally proceeded in 2 h (*in situ* ¹⁹F NMR), with the KF dissolution being the rate-limiting process. Following the addition of water to flocculate **52**, filtration and evaporation of the filtrate, good yields of high purity **1a** were achieved. To test the methodology, a range of electron poor and electron rich arylboronic acids were tested (0.75 mmol scale; 0.2 M), Table 2.4.

**Table 2.4** A range of R-BF₃K salts prepared with KF/tartaric acid in CH₃CN/THF (5:1)

Entry	Substrate		Isolated yield/ % ^a	Time/hr ^b	Added H ₂ O/mL ^c
1	4-F-C ₆ H ₄	2a	99 (99) ^d	2	0.1
2	<i>E</i> -β-styryl	2 l	82	3	0.1
3	4-MeO-C ₆ H ₄	2o	64	3	0
4	1-naphthyl	2p	96	3	0.1
5	3,5-(CF ₃) ₂ -C ₆ H ₃	2q	0	4	0.1
6	4-NO ₂ -C ₆ H ₄	2r	58	3	0.3
7	3-Cl-C ₆ H ₄	2 s	0	3	0
8	4-CN-C ₆ H ₄	2t	64	4	0.1
9	3-MeCO-C ₆ H ₄	2u	88	3	0.1
10	4-CHO-C ₆ H ₄	2v	51	3	0
11	<i>cyclo</i> -hexyl	2w	43	4	0.1

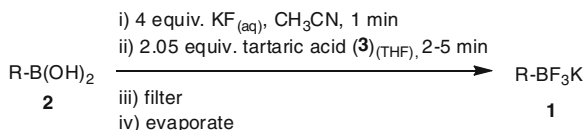
^a Isolated yield of pure (¹H, ¹¹B and ¹⁹F NMR) R-BF₃K (**1**)^b Reaction completion monitored by ¹⁹F and ¹¹B NMR^c 0.1 mL initially added to the suspension and stirred for 5 min. If insufficient flocculation resulted, further aliquots of 0.1 mL were added^d 35 mmol scale

Aside from two exceptions, the yields were average to excellent, especially on scale-up (35 mmol), where **2a** gave 7.07 g (<99 %) of **1a**. However, variations in the water required to flocculate the bitartrate, the yield, and the time required for complete conversion of **2**, still rendered the current process less than ideal in comparison to the KHF₂ method.

Two possible problems remained: firstly, the entropically favoured dehydration of boronic acids to form linear or cyclic boroxines under the dry reaction conditions of CH₃CN/THF (5:1), possibly stabilised the boronic acid towards fluoride exchange. This problem is avoided in the KHF₂ procedure, due to the large excesses of water present that readily rehydrate the boroxines. Secondly, the time taken for each of the reactants (boronic acid/KF/tartaric acid) to dissolve is responsible for the extended and variable reaction times. Therefore, through the addition of water from the start, and ensuring all reactants are initially dissolved, both problems could be averted: KF could be conveniently added as an aqueous solution, and tartaric acid as a solution in THF.

2.2.2 The Optimised Procedure

Pleasingly, on a number of test substrates, when KF (aq) was added to the boronic acid in acetonitrile followed by the addition of tartaric acid (**3**) in THF,



Scheme 2.12 Preparation of R-BF₃K salts with KF_(aq) and tartaric acid_(THF)

Scheme 2.12, this improved methodology proceeded well; giving **1a** from **2a** in a 99 % isolated yield. Flocculation of bitartrate **52** occurred rapidly and generally without the need for additional water. The stoichiometry of both KF and tartaric acid were again screened, and found that 4 and 2.05 equivalents respectively gave the most reliable results. It was found that the increasing concentrations of KF_(aq), lead to increasing rates of flocculation. This is likely due to an increase in the volume of the aqueous biphasic formed from the excess KF_(aq) in acetonitrile. **52** is drawn into this bilayer, which initiates the hydrogen bonded network and subsequent rapid coagulation and flocculation. The excess KF additionally aides fluoride complexation to the Lewis acidic **2a**. The small excess in **3** would reliably accommodate the variations in stoichiometry arising from boroxine anhydrides in commercial samples of boronic acids.

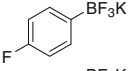
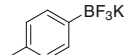
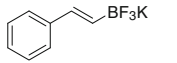
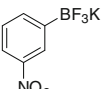
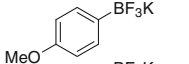
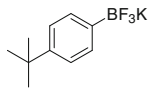
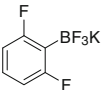
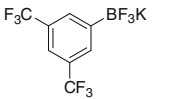
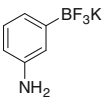
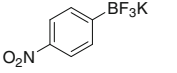
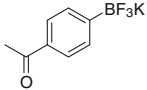
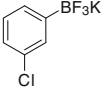
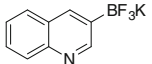
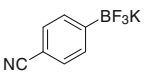
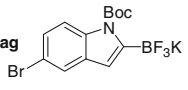
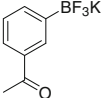
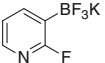
After the addition of KF in water (ca. 10 M) to **2** in acetonitrile, the biphasic mixture was stirred until complete dissolution of **2**. Hydration of all boroxines and precomplexation by fluoride, as confirmed by ¹¹B and ¹⁹F NMR, occurred at this point. The mixture was stirred rapidly as **3** in THF (ca. 1.4 M) was added dropwise. **52** precipitated, and rapidly flocculated before the solution was filtered, washed through with further acetonitrile, and evaporated to give the pure R-BF₃K salt. Under these conditions, a number of boronic acids were cleanly converted to the corresponding R-BF₃K salts, Table 2.5.

Electron poor and electron rich aryl systems, heteroaryl, vinylic and alkyl systems were all reliably accommodated by the methodology. Reaction times were almost instantaneous, requiring less than 20 min, from start to finish to isolate pure (¹H, ¹³C, ¹¹B, ¹⁹F NMR, elemental analysis) R-BF₃K salts, using commercial grade solvents at room temperature.

A number of substrates initially did not undergo complete conversion (unreacted boronic acid detected by ¹H, ¹⁹F and ¹¹B NMR). By employing a slight excess protocol (4.5 equiv. KF, 2.5 equiv. **3**) conversions increased. However, it was found that recrystallisation of the starting material **2** from water, improved yields and purities of the final product **1** when the original protocol (4 equiv. KF, 2.05 equiv. **3**) was reemployed. It is likely that these commercial samples contained large proportions of boroxines, thus causing problems in establishing the correct stoichiometry for the reaction. The recrystallisation avoided these problems by ensuring all were hydrolysed to the boronic acid **2**.

However, for the reaction of electron-poor boronic acids **2q**, **2aa**, **2af** and **2ah** recrystallisation from water was not enough to improve the conversions when reemploying the regular quantities (4 equiv. KF, 2.05 equiv. **3**) and therefore the excess (4.5 equiv. KF, 2.5 equiv. **3**) protocol was still required. Analysis (¹H, ¹⁹F

Table 2.5 The preparation of a range of R-BF₃K salts using the optimised conditions, Scheme 2.12

R-BF ₃ K (1)	R =	Isolated yield ^a /%	R-BF ₃ K (1)	R =	Isolated yield ^a /%
1a		>99 / 96 ^b	1y		57 ^d
1d		90	1z		89
1l		90	1aa		87 ^d
1o		84	1ab		98
1p		96 (>99) ^c	1ac		78
1q		96 ^d	1ad		76
1r		78	1ae		57
1s		93	1af		69 ^{d,e,f}
1t		88	1ag		90
1u		82 (95) ^c	1ah		85 ^{d,e}
1x		70 ^d			

^a Isolated yield of analytically pure R-BF₃K (1)^b Average of 30 runs^c Value in parenthesis: 18-fold scale-up^d 4.5 equiv. KF and 2.5 equiv. tartaric acid^e CH₃OH/CH₃CN (1:1), dilute with CH₃CN^f Putilised, due to the lower product refined with K₂CO₃ in acetone

and ¹¹B NMR) of the isolated material indicated the presence of an intermediate mixed species of the type **7** or **8**, suggesting incomplete conversion. Interestingly, although observed *in situ* in reactions involving boronic acid **2a**, these mixed species are not stable enough to be isolated and characterised, thus suggesting a greater induction of stability from very electron poor moieties.

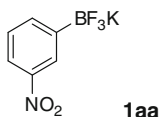
For the reaction of heteroaryl boronic acids **2af** and **2ah**, the solvent system optimised for pinacol esters, Sect. 2.3.1 *vide infra*, was utilised, due to the lower solubility of heteroaryl boronic acids in acetonitrile. The proportion of methanol present successfully facilitates fluoride complexation to **2**, thereby ensuring its complete conversion upon addition of **3**. Due to the basic nitrogen, **2af** was initially isolated as a mixture of the potassium salt and the internal salt (quinoliniumtrifluoroborate), as confirmed by elemental analysis. Treatment with K₂CO₃ (acetone, room temp, 10 min) readily deprotonated any internal salts to the desired product.

Upon increasing the scale 18 fold (18 mmol), **2p** and **2u** were cleanly converted to trifluoroborates **1p** and **1u** in an improved 95 % (3.9 g) and >99 % (4.2 g) yield respectively. This demonstrates the potential utility of this new procedure towards industrial application. Furthermore, as isolation *via* filtration is preferred on large scale, rather than evaporation of the filtrate, an anti-solvent e.g. Et₂O, can be slowly added to crystallise the R-BF₃K salt from the filtrate.

To confirm that precipitation of bitartrate **52** was responsible for the stoichiometric requirement of tartaric acid (**3**), *o*-iodobenzoic acid (**53**) was titrated into a solution of **2a** in acetonitrile and KF_(aq) (4 equiv.). **53** exhibits a similar pK_a (2.9) to **3** (3.0), but the conjugate base (potassium *o*-iodobenzoate **54**) was expected to be more soluble than potassium bitartrate (**52**) in the reaction medium. Indeed, the use of this acid required 4 equivalents to reach complete conversion, thus supporting the conclusion that a precipitation-driven equilibrium is in operation.

2.2.3 Purity Comparison

To check inorganic (e.g. KF or KHF₂) contamination, the purity of **1aa** was compared with samples prepared *via* the KHF₂ route, KF/tartaric acid route and with commercial material. To reach complete conversion, this substrate required a larger excess of KF (4.5 equiv.) and tartaric acid (**3**; 2.5 equiv.) thereby providing the worst case scenario in terms of possible contaminants. The KHF₂ and KF/tartaric acid methods were run in parallel, gave isolated yields of 86 and 87 % respectively, and were assessed by elemental analysis. All samples being compared were close to that calculated; however, pleasingly the KF/tartaric acid method gave the purest product in the best yield, Table 2.6.

**Table 2.6** Comparison of the purity of **1aa** prepared from the two routes

	Found C	Found H	Found N
Commercial	30.19	1.84	5.73
KHF ₂	31.90	1.79	5.93
KHF ₂ ^a	31.31	1.80	5.67
KF/Tartaric acid	31.64	1.78	5.98
	Calc'd C	Calc'd H	Calc'd N
C ₆ H ₄ BF ₃ KNO ₂	31.47	1.76	6.12

^a From Ref. [32]

2.2.4 Glassware Etching

The newly developed KF/tartaric acid procedure avoids the *in vacuo* removal of large volumes of water and the often laborious series of acetone extractions necessary in the KHF₂ method to isolate the pure R-BF₃K salts. Furthermore, the use of KHF₂ is notorious for the etching it effects on regular glassware, producing irreversible damage. To test how the KF/tartaric acid methodology and the KHF₂ method compared in this regard, **1a** was repeatedly prepared (0.75 mmol scale) by each method in two brand new 25 mL round bottomed flasks. The KHF₂ method was repeated 20 times and the KF/tartaric acid method 30 batch times, Figs. 2.2 and 2.3.

There was no trace of clouding in the glass of the round bottomed flask from reactions undertaken using the KF/tartaric acid method, Figs. 2.2 and 2.3. In contrast, the flask used for the KHF₂ method was severely etched. When each method was compared *in situ* (¹⁹F NMR), in PTFE vessels so as to not consume

Fig. 2.2 The *left* hand flask has had 30 batch reactions using the KF/tartaric acid method to synthesise **1a** from **2a**, and the *right* hand flask has had 20 batch runs using the KHF₂ method to synthesise **1a** from **2a**



Fig. 2.3 The *left* hand flask has had 30 batch reactions using the KF/tartaric acid method to synthesise **1a** from **2a**, and the *right* hand flask has had 20 batch runs using the KHF₂ method to synthesise **1a** from **2a**

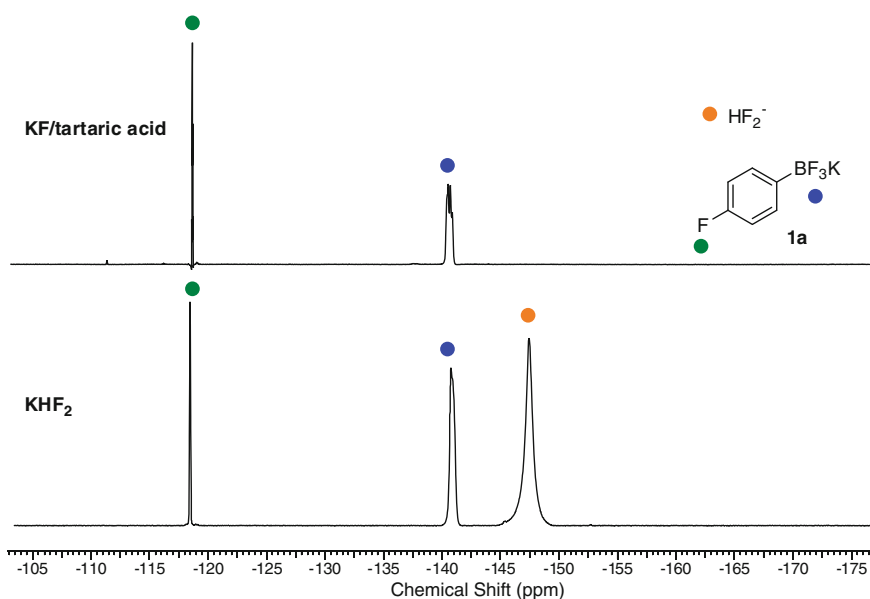
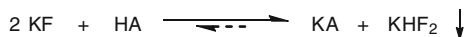


Fig. 2.4 ¹⁹F NMR spectra of the *in situ* preparation of **1a** via the KF/tartaric acid and KHF₂ methods conducted in PTFE. HF₂[−] is clearly observed ($\delta_F = -147$ ppm) in solution in the KHF₂ method but is absent in the KF/tartaric acid method. The chemical shift (δ_F) of KHF₂ is highly dependent on the water content of the solution and ranges, in our hands, from -180 to 139 ppm

any HF by glass, a large peak was observed for the HF₂[−] anion in the KHF₂ method, but not the KF/tartaric acid method, Fig. 2.4.

When KF is subjected to an acidic medium it will form KHF₂ *in situ*, Scheme 2.13. But due to the complexation of fluoride to boronic acid and the slow addition of tartaric acid (**3**) to push the equilibrium to the right, this process is



Scheme 2.13 The *in situ* formation and precipitation of KHF₂ in acetonitrile/THF

avoided. However, any excess KF (1 equiv.) and **3** (5 %) will combine to form KHF₂ (5 %).

Under the optimised solvent system (CH₃CN/THF) any KHF₂ generated was shown to precipitate out of solution, Scheme 2.13, as is indicated by ¹⁹F NMR analysis of the filter cake, and is therefore considered to be unproblematic. Whilst **1a** was prepared from **2a** *via* the KHF₂ route, it was observed that the aqueous stock solution of KHF₂ was considerably more etching than the overall reaction in methanol containing **2a**. In contrast, aqueous stock solutions of KF and **3** in THF are both completely non-etching.

2.3 Preparation of R-BF₃K Salts from Boronic Esters

2.3.1 Pinacol Esters

2.3.1.1 Optimisation

The conditions optimised for boronic acids (4 equiv. KF_(aq), 2.05 equiv. **3**_(THF), CH₃CN) were employed for the conversion of 4-fluorophenylboronic acid pinacol ester **4a–1a**. Although the desired product was synthesised, nearly a stoichiometric amount of pinacol remained after filtration and evaporation. When KHF₂ is employed for the preparation of R-BF₃K salts, there are two general methods to purify the product from pinacol: firstly, Hartwig [12] demonstrated that it could be ‘sublimed’ (6 mTorr, 60 °C) from a mixture containing R-BF₃K (which melt or decompose at temperatures greater than 250 °C). Secondly, Aggarwal [33] demonstrated that pinacol forms an azeotrope with methanol/water, and by the repetitive addition and evaporation of the solvents, it can be removed from a mixture containing the R-BF₃K salt and excess KHF₂. The number of cycles varied from 1 to 9 and depended on the substrate and precise make-up of the azeotrope.

The Aggarwal procedure was initially tested, by the repetitive addition and evaporation of methanol/water (4:1), to the concentrated filtrate, containing only a mixture of pure R-BF₃K and pinacol. However, due to the solvolytic conditions, hydrolysis to boronic acid **2a** occurred, which condensed with pinacol to reform the starting material. Under the KHF₂ conditions, refluorination of hydrolysed boronic acid by the excess KHF₂ present, results in complete conversion to the R-BF₃K salt as pinacol is slowly removed. Hartwig’s ‘sublimation’ procedure was more effective, as the anhydrous, non-solvolytic conditions left only pure R-BF₃K salt. However, contrary to the original report, pinacol was observed to melt, then

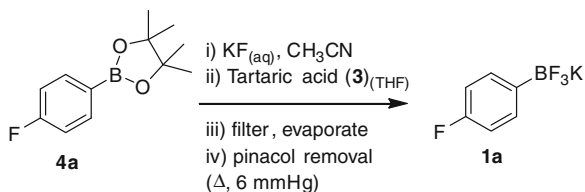
Table 2.7 Variation of the equivalents of added KF and tartaric acid (**3**) in the reaction of **4a** to **1a**

Entry	KF/equiv.	Tartaric acid/equiv.	Conversion ($\rightarrow$ 1a)/ % ^a
1	4	2.05	84
2	5	3	95
3	5.5	3.5	85

^a % **1a** ($\delta_F = -118.8$ and -141 ppm) by ¹⁹F NMR

evaporate and condense as a liquid, rather than a solid; therefore ‘evaporation’ not ‘sublimation’ is a more precise description of the process. Aggarwal reported the Hartwig procedure did not work in the presence of KHF₂, implying that strong hydrogen bonding between KHF₂ and pinacol attenuated its thermolytic removal.

With the purification method established, the loadings of KF and **3** were screened in the conversion of **4a–1a** (0.25 mmol scale) under the conditions optimised for boronic acids, Table 2.7.



An increase in the stoichiometry of KF and **3** did not directly correlate with an increase in the conversion to **1a**. When the methodology, employing 5.5 equiv. KF and 3.5 equiv. **3**, was scaled up (1 mmol scale), incomplete conversion (82 %) again resulted, highlighting the capriciousness of the current protocol.

Analysis (¹⁹F and ¹¹B NMR) of a solution of boronic ester **4a** containing 4 equiv. KF_(aq) in CH₃CN indicated no complexation of fluoride to **4a**. By comparison, fluoride complexation to the more Lewis acidic boronic acid **2a** was observed, Fig. 2.5, under the same conditions. The greater Lewis acidity must aid fluoride transfer from the aqueous biphasic, Fig. 2.6.

Under these non-complexing conditions of **4a**, the addition of tartaric acid (**3**) is likely to generate/precipitate KHF₂ out of solution, thus leading to the decreased conversions. It was also observed that the bitartrate (**52**) precipitate was more physically defined by the aqueous biphasic and thus less mobile in the stirred reaction vessel. This latter problem will further restrict the solubility of KF in the organic phase due to the loss of water to the bitartrate/KHF₂ cluster. Therefore, bringing the KF into solution by moving to a more homogeneous solvent system would alleviate these issues.

Analysis (¹⁹F and ¹¹B NMR) of **4a** treated with 4 equiv. KF_(aq) in pure methanol indeed showed complete consumption of the starting material to give two unknown ‘ate’ species. Returning to the loadings of KF (4 equiv.) and tartaric acid (2.05 equiv.) employed for boronic acids, but switching the solvent system to methanol,

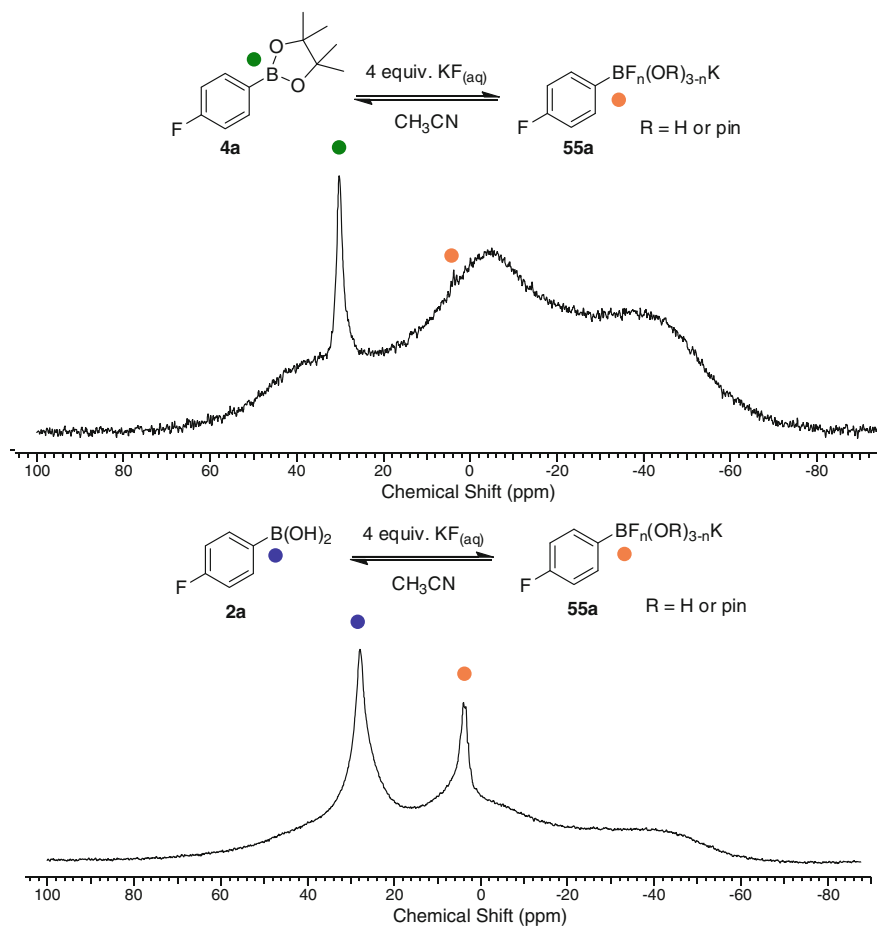
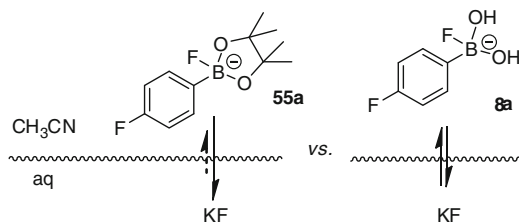


Fig. 2.5 Upper ^{11}B NMR spectrum: KF addition to pinacol ester **4a** in CH_3CN , indicating no significant complexation of fluoride. Lower ^{11}B NMR spectrum: KF addition to boronic acid **2a** in CH_3CN , indicating complexation of fluoride to form mixed fluoro/pinacol ester **55a**. Baseline due to background borosilicate glass signals

Fig. 2.6 The increased Lewis-acidity of boronic acid **2a** aids complexation of F^- from the aqueous biphasic to form mixed fluoro/hydroxy species **8a**



gave 87 % conversion to product **1a** from **4a**. Unfortunately, as previously noted, problems associated with the flocculation of bitartrate **52** in methanol occurred, but was found to improve with substantial dilution with CH₃CN. In addition, generation of stable methoxylated ‘ate’ species (**51a**) hampered complete conversions; therefore a balance between CH₃CN and CH₃OH was clearly sought

Partial complexation of fluoride to **4a** was observed (¹⁹F NMR, ¹¹B NMR) in a 9:1 CH₃CN:CH₃OH system. However, when test reactions were scaled up to (1 mmol,) 4-acetylphenylboronic acid pinacol ester (**4ae**) was again incompletely converted (80 %) to the corresponding trifluoroborate salt **1ae**. This was due to problems of **52** precipitations leading to KHF₂ generation/precipitation. A ratio of 3:1 CH₃CN:CH₃OH was tested only to exhibit a better, but similar outcome.

2.3.1.2 Optimised Procedure for the Preparation of R-BF₃K Salts from Pinacol Esters

A mixture of 1:1 CH₃CN:CH₃OH, allowed for fluoride complexation of **4a** to give two species (¹¹B NMR), Fig. 2.7, and complete conversion to **1a** was observed upon addition of 2.05 equiv. **3**. Subsequent dilution with CH₃CN aided flocculation and effected precipitation of all co-products and excess reagents.

The conditions were tested on alkyl, allylic and electron rich and poor aryl systems, which were all cleanly converted to the corresponding R-BF₃K salts, Table 2.8. Reactions were instantaneous, allowing isolation of the R-BF₃K/pinacol mixture less than 20 min. The majority (>90 %) of the pinacol could be evaporated in 5 min (6 mmHg, gentle heat), but a further 15–20 min heating was found to be necessary to ensure good purity.

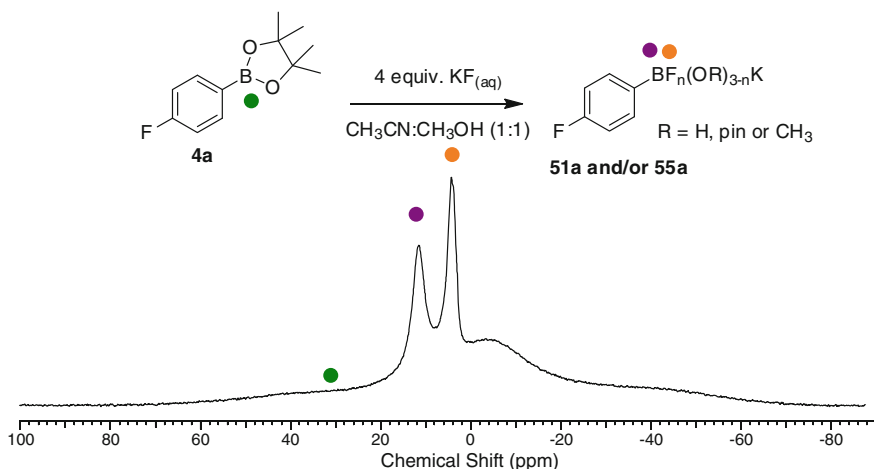


Fig. 2.7 ¹¹B NMR spectrum of KF addition to **4a** in CH₃CN:CH₃OH (1:1), showing its complete consumption to form two mixed species (**51a** and/or **55a**). Baseline due to background borosilicate glass signals

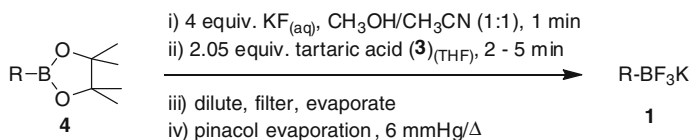
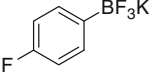
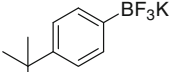
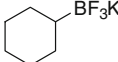
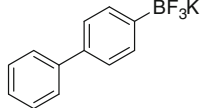
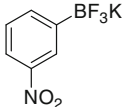
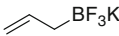


Table 2.8 The preparation of a range of R-BF₃K salts from pinacol esters

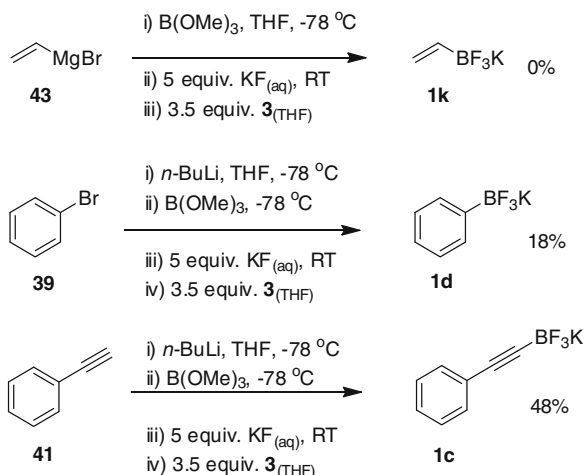
R-BF ₃ K (1)	R =	Isolated yield ^a /%	R-BF ₃ K (1)	R =	Isolated yield ^a /%
1a		94	1ab		95
1w		83	1ai		72
1aa		89	1aj		75

^a Isolated yield of analytically pure R-BF₃K

2.3.2 Methyl/Isopropyl Esters Prepared *In Situ*

Application of the KF/tartaric acid methodology to the *in situ* generated methyl (**37**) or isopropyl (**38**) boronate esters, Scheme 2.6, would provide another useful route to R-BF₃K salts. To ensure ease of isolation, the lithium/magnesium salts would ideally co-precipitate with potassium bitartrate (**52**), thus leaving a simple filtration to yield pure R-BF₃K salt. As protonation of the additional alkoxy ligand on the intermediate boronate ester is required, the stoichiometry in tartaric acid (**3**) necessitated adjustment; the loadings of both KF (5 equiv.) and **3** (3.05–3.5 equiv.) were thus increased.

Unfortunately, all attempts at preparing potassium vinyltrifluoroborate (**1k**) from vinyl magnesium bromide (**43**) failed, Scheme 2.14. Possible explanations include the instability of the intermediate fluorinated ‘ate’ species towards **3**, or alternatively, possible magnesium interference with fluoride (MgF₂ generation). More encouraging was the formation of potassium phenyltrifluoroborate (**1d**) from phenyllithium (**40**), but purification *via* recrystallisation was required, which reduced the yield. Finally, phenylacetylene (**41**) was smoothly converted to potassium phenylethynyl trifluoroborate (**1c**) in a reasonable 48 % yield,



Scheme 2.14 Preparation of R-BF₃K salts from *in situ* generated boronate esters

Scheme 2.14. For comparison, the KHF₂ method generated the product in a 32 % yield, possibly inferring complications in the formation of the intermediate boronate ester **37c**, rather than the organotrifluoroborate salt **1c**.

These unoptimised results clearly demonstrate the potential for the process, but presently, further investigation is required in warranting it a useful procedure.

2.4 Preparation of R-BF₃[−] Salts with Different Counter Cations

2.4.1 Cesium Salts

2.4.1.1 Prepared from Boronic Acids

As noted above, the solubility of organotrifluoroborate salts can be manipulated and tuned to a process by modification of the counter cation. Cesium salts in particular offer the same free-flowing crystalline physical properties as potassium but dissolve more readily into apolar solvents. By switching KF for CsF it was envisaged that the corresponding cesium organotrifluoroborate salt (**5**) could be formed. Pleasingly, on three substrates of varying electron demands, good to excellent isolated yields of pure (elemental analysis) **5** were observed, Table 2.9. Cesium bitartrate (**56**, identity confirmed by ¹H NMR and elemental analysis) was found to be equally insoluble under the reaction conditions, which drives the equilibrium, Scheme 2.11, towards **5**.

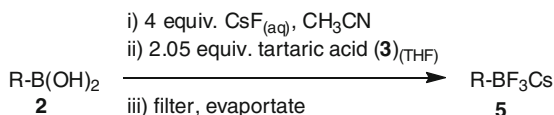


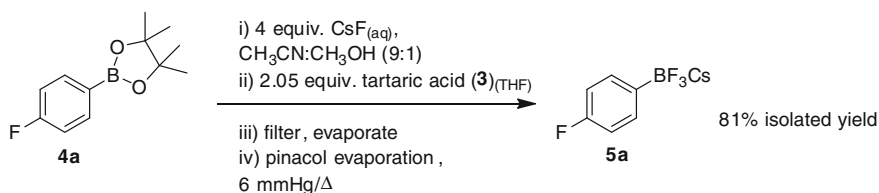
Table 2.9 The preparation of R-BF₃Cs salts from boronic acids

R-BF ₃ Cs (5)	R =	Isolated yield ^a /%
5p		87
5r		84
5z		94

^a Isolated yield of analytically pure R-BF₃Cs

2.4.1.2 Prepared from Pinacol Esters

Preparation of cesium organotrifluoroborate salts (**5**) from boronic acid pinacol esters (**4**) would demonstrate the wider application of the KF/tartaric acid methodology. The same procedure (CH₃CN:CH₃OH, 1:1, followed by dilution with CH₃CN) employed for the generation of **1a** from **4a**, was initially attempted. Pleasingly, complete conversion was achieved, although the increased solubility of CsF in CH₃CN:CH₃OH (1:1) caused it to contaminate the R-BF₃Cs salt (**5a**), after concentration of the filtrate. A reduction in the proportion of methanol (9:1 CH₃CN:CH₃OH) was found to successfully avert CsF contamination, whilst still enabling complexation of fluoride to **4a** to ensure complete conversion, Scheme 2.15. Analogous to the preparation of **1a** from **4a**, when solely CH₃CN was employed, incomplete conversions resulted.



Scheme 2.15 Preparation of **5a** from **4a** using the newly developed KF/tartaric acid methodology

2.4.2 Sodium Salts

2.4.2.1 Prepared from Boronic Acids

In a similar vein to the cesium organotrifluoroborate salts (**5**), sodium organotrifluoroborates (**48**) have a characteristically different solubility to their potassium analogues. By switching KF for NaF in the general procedure, Scheme 2.12, it was envisaged that the sodium salt could be isolated *via* sodium bitartrate (**57**) precipitation/filtration.

Studies were conducted using 1-naphthyl boronic acid (**2p**), NaF_(aq) (4 equiv.) in acetonitrile followed by treatment with tartaric acid (**3**) in THF. Upon the addition of 2 equivalents of tartaric acid (**3**), only naphthalene (**58**) was isolated. It was proposed that disodium tartrate formed, thus necessitating only 1 equivalent of **3**. Unfortunately, although *in situ* analysis (¹⁹F and ¹¹B NMR) indicated formation of sodium 1-naphthyl trifluoroborate (**48p**), with one equivalent of **3**, **48p** could not be isolated in pure form. Elemental analysis of the precipitate was not indicative of either mono or disodium tartrate, suggesting significant contamination by NaF, possibly through poor solubility in the organic phase. Although various sodium organotrifluoroborate salts (**48**) have been prepared [27, 30], there are no specific reports on the stability of **48p**. Alternatively, if the sodium cation is not sufficiently soluble in the organic phase, then a hydronium cation could be neutralising the naphthyl trifluoroborate anion, as observed (¹⁹F and ¹¹B NMR) *in situ*. The hydronium coordinated organotrifluoroborate salts (**59**) are known to be unstable upon isolation [27].

2.5 Summary

A new methodology for the preparation of potassium (**1**) and cesium (**5**) organotrifluoroborates has been developed, employing KF and tartaric acid (**3**) in a completely non-etching and operationally simple manner. Boronic acids (**2**) and pinacol esters (**4**) are accommodated as starting materials in the procedure, which is rapid and can be conducted at room temperature with bench grade solvents. A wide range of organic moieties proceeded well, giving good to excellent isolated yields of pure R-BF₃K/Cs. The procedure was shown to scale-up proficiently, proving its potential for both academic and industrial application.

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Organotrifluoroborate Preparation, Coupling and
Hydrolysis

Lennox, A.J.J.

2013, XV, 223 p. 308 illus., 96 illus. in color., Hardcover

ISBN: 978-3-319-01133-2