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Nucleophilic Fluorination Reactions Starting from Aqueous Fluoride Ion Solutions

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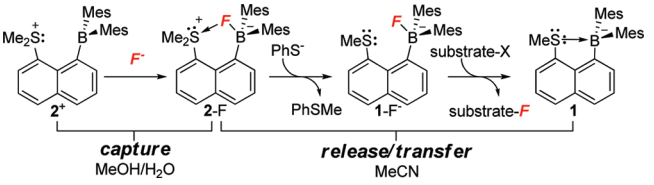
ABSTRACT



The sulfonium borane 2^+ reacts with fluoride anions in MeOH/H_2O mixtures to afford the zwitterionic fluoroborate 2-F as an easily isolable nonhygroscopic solid. In dry acetonitrile, 2-F reacts with PhS^- to afford the anionic fluoroborate $1\text{-}F^-$. The latter is very labile and acts as a nucleophilic fluorination reagent toward a variety of substrates including alkylhalides and electron-deficient aromatic compounds. This approach may become broadly applicable to nucleophilic fluorination procedures that involve wet fluoride sources.

The incorporation of fluorine in organic molecules and materials is gaining momentum because of the beneficial properties imparted by this small and highly electronegative halogen. Such properties may include increased stability in the case of organic materials as well as increased metabolic stability, lipophilicity, and bioavailability in the case of drugs.[1] Fluorination chemistry is also becoming important in the domain of [^{18}F]-positron emission tomography (PET), a technique that necessitates the radiolabeling of organic molecules with [^{18}F]-fluorine atoms.[2]

For the reasons enumerated in the preceding paragraph, the field of fluorination chemistry is experiencing a surge of interest. While electrophilic fluorination strategies remain preponderant,[3] there is a growing need for the development of nucleophilic pathways. These research needs have fueled a series of recent efforts that have already afforded an array of nucleophilic fluorinating agents with very interesting properties.[4] As recently reported by DiMagno, anhydrous TBAF (denoted as TBAF*) can be generated *in situ* by reaction of fluorobenzene derivatives with tetra-*n*-butylammonium cyanide (TBACN) in THF.[4g−i] This method affords fluoride ions (F^-) that, as confirmed by ^{19}F NMR spectroscopy, have a "naked" character. In line with this observation, the *in situ* generated TBAF is a very potent nucleophilic fluorinating agent that reacts with a variety of substrates including aromatic ones. However, because of the use of fluorobenzene derivatives as a source of F^-, this approach may not be directly applicable to wet fluoride sources. For these reasons, the discovery of reagents that could complex F^- ions under aqueous conditions and deliver the said ions to organic molecules should open new routes in fluorination chemistry. With this objective in

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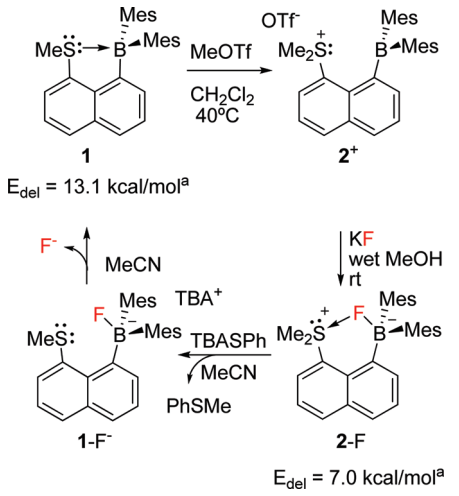
Scheme 1. Reactions Sequence Showing the Use of 2^+ for the Capture of Fluoride Ions and Their Triggered Release[a]



[a] E_{del} corresponds to the energy provided by the lp(S)→p(B) and lp(F)→σ*(S−C) interactions to the stability of **1** or **2**-F, respectively.

mind, we have now developed a strategy which allows for (i) the capture of F^- under wet conditions and (ii) the triggered release of F^- and its transfer to organic substrates in dry organic solutions. This work was partly inspired by the contribution of DiMagno on "aromatic fluoride relay", an approach used to generate TBAF* starting from KF.[4g]

We have previously reported the synthesis and structure of the sulfonium borane salt **2**-OTf.[5] Unlike other cationic boranes, this derivative showed no affinity for F^- in water.[6] Interestingly, when this reaction is carried out in MeOH, **2**-OTf is readily converted into the corresponding fluoride adduct **2**-F. The ^{11}B NMR resonance of **2**-F at 9.0 ppm and the ^{19}F NMR signal at −161.1 ppm are consistent with the presence of a typical triarylfluoroborate anion.[6] Formation of **2**-F does not require the use of dry methanol. Instead, **2**-F also precipitates from concentrated MeOH/H_2O solutions containing large fractions of water. For example, sonicating a mixture of **2**-OTf (21 mg) and KF (45 mg) in 0.5 mL of a MeOH/H_2O (3:2, v/v) solution results in the precipitation of **2**-F (12 mg, 75% yield). These observations show that cationic boranes such as 2^+ can be used to sequester F^- ions under wet conditions, making them compatible with inherently wet F^- salts (Scheme 1). The formation of such fluoroborate sulfonium species is not unprecedented and has been recently observed by our group in two prior instances.[7]

The zwitterion **2**-F can be easily recovered by filtration as an air-stable and nonhygroscopic solid. The crystal structure of **2**-F has been determined. It crystallizes in the monoclinic $P2_{(1)}/c$ space group with two independent molecules in the asymmetric unit (Figure 1). Both independent molecules feature very similar structures. The boron-bound fluorine atom is separated from the sulfur atom by an average distance of 2.53 Å, which is well within the sum of van der Waals radii of the two elements (ca. 3.3 Å).[8] The average F−S−C_{Me} angle of 171.7° indicates that the fluorine atom occupies an axial coordination site directly opposite to one of the sulfur-bound methyl groups. These geometrical parameters, which are reminiscent of those observed in other fluoroborate sulfonium species,[7] suggest the presence of an interaction between the fluorine and sulfur atom. To confirm this view, the structure of **2**-F was computationally optimized (DFT, functional: B3LYP; mixed basis set: B, F: 6-31+g(d′); S: 6-31+g(d); C, H: 6-31 g) and subjected to a Natural Bond Orbital (NBO) analysis. This analysis indicates that the short F−S separation present in **2**-F corresponds to an lp(F)→σ*(S−C) donor−acceptor interaction which contributes 7.0 kcal/mol to the stability of the molecule (Figure 1). Altogether, these results suggest that the ability of 2^+ to complex F^- in wet methanol arises from favorable Coulombic effects which are complemented by the formation of a B−F→S chelate motif. Realizing that the absence of such interactions would greatly increase the lability of the boron-bound fluoride anion,

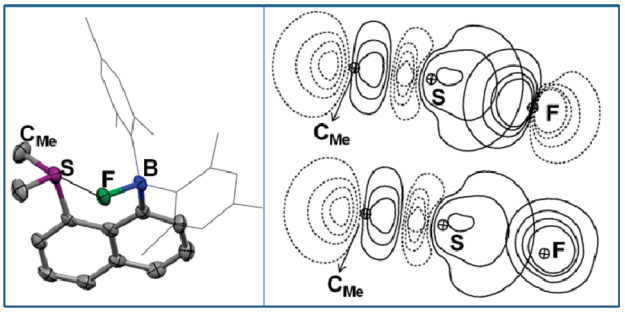


Figure 1. Left: Crystal structure of **2**-F (only one independent molecule is shown, ellipsoids are drawn at 50% probability levels, hydrogen atoms omitted for clarity). Right: NBO contour plot showing the lp(F)→σ*(S−C) donor−acceptor interaction.

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we sought to determine if demethylation of the sulfonium moiety could be used to trigger the release of the fluoride anion.

With this in mind, we tested the reactivity of **2**-F toward soft nucleophiles such as tetrabutylammonium iodide (TBAI). When TBAI was employed in dry CD_3CN or THF, the demethylation of the sulfonium ion at ambient temperature occurred slowly and a new anionic fluoride adduct, namely **1**-F^-, was formed. This demethylation produces MeI which quickly reacts with **1**-F^- to form MeF, as indicated by the appearance of a quartet at −272 ppm in the ^{19}F NMR spectrum of the reaction mixture obtained upon mixing TBAI with **2**-F in THF. Formation of MeF, which supports the notion that **1**-F^- is an active fluorinating agent, indicates that iodide salts cannot be used in this approach. For this reason, we turned our attention to the phenylthiolate anion (pK_a = 10.3). Mixing an equimolar amount of tetrabutylammonium phenylthiolate (TBASPh) and **2**-F in dry CD_3CN at ambient temperature resulted, after 30 min, in elimination of PhSMe and formation of the anionic fluoride adduct **1**-F^-. Formation of the latter was accompanied by the appearance of ca. 5% of neutral borane **1** suggesting partial F^- release possibly caused by traces of water. The anionic fluoride adduct **1**-F^- has been characterized by multinuclear NMR spectroscopy. The ^{11}B NMR resonance at 8.0 ppm is very close to that of **2**-F, consistent with the presence of a typical triarylfluoroborate anion. The ^{19}F NMR signal at −168.9 ppm is shifted upfield compared to the compound **2**-F but remains within the range of triarylfluoroborate anions.[6] Solutions of this anion are stable for up to 3 days in CH_3CN or THF at ambient temperature. The addition of ca. 2 equiv of water to solutions of **1**-F^- in CH_3CN results in the formation of the neutral borane **1** and hydrated fluoride ions as indicated by the appearance of a ^{19}F NMR signal at −121.9 ppm (Figure 2). By contrast,

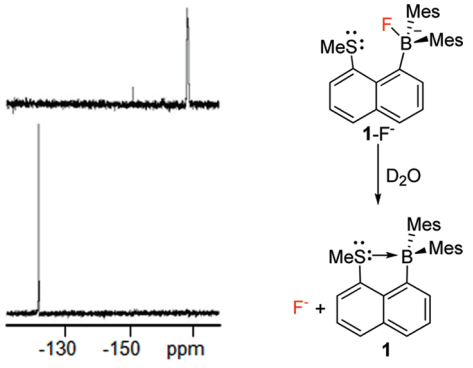
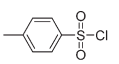
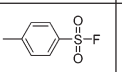
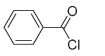
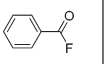
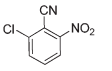
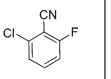
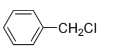
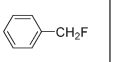


Figure 2. ^{19}F NMR spectra of **1**-F^- in d_3-MeCN before and after addition of water.

solutions of **2**-F in CH_3CN are perfectly stable when the same amount of water is added. This contrasting behavior can be assigned to (i) the absence of stabilizing Coulombic effects in **1**-F^- and (ii) the increased basicity of the sulfur atom in **1**-F^- which competes with F^- for the Lewis acidic boron center. Thermodynamically, fluoride release from **1**-F^- is further promoted by formation of a relatively strong lp(S)→p(B) donor−acceptor interaction in **1** (E_{del} = 13.1 kcal/mol).[7a] The precipitation of the neutral borane from CH_3CN due to its poor solubility also drives the release of F^- ions. These results suggest that **1**-F^- may be sufficiently labile to act as a potent nucleophilic F^- source.

Indeed, the addition of substrates such as *p*-tolylsulfonyl chloride or benzoyl chloride to freshly prepared solutions of **1**-F^- (Table 1, entries 1 and 2) results in the rapid and

Table 1. Fluorination Reaction Results

	substrate	conditions	product	yield (%)[a]
1		**1**-F^- (1.4 equiv) 25 °C CD_3CN, 5 min		>95
2		**1**-F^- (1.4 equiv) 25 °C CD_3CN, 5 min		>95
3		**1**-F^- (1.2 equiv) 25 °C CD_3CN, 2 h		>95
4		**1**-F^- (2 equiv) 70 °C CD_3CN, 1 h		80
5	1-$C_8H_{17}Br$	**1**-F^- (2 equiv) 70 °C CD_3CN, 1 h	1-$C_8H_{17}F$	45

[a] All yields are calculated from integration of the ^1H NMR spectra.

high yield fluorination of the substrates at room temperature. Using the same protocol, fluorination of activated aromatic substrates such as 1-chloro-2-cyano-3-nitrobenzene can also be implemented, albeit with longer reaction times (entry 3). For substrates such as benzylchloride and 1-bromooctane (entries 4 and 5), fluorination occurs upon elevation of the temperature to 70 °C. Formation of 1-fluorooctane is accompanied by elimination which produces 1-octene in 53% yield. The 1-fluoroctane/1-octene ratio observed with **1**-F^- in MeCN at 70 °C is comparable to that observed with TBAF* (~40%/60%) in THF at room temperature[4i] and distinctly lower than that observed for TBAT (~85%/15%) in MeCN upon reflux for 24 h.[4l] These comparisons suggest that the TBA salt of **1**-F^- dissociates upon elevation of the temperature to produce **1** and TBAF*. While preparation of the latter necessitates the use of dry conditions, our approach can be implemented in two simple steps starting from aqueous fluoride solutions. We are currently testing the use of $\mathbf{2}^+$ in [^{18}F]-radiofluorination reactions.

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Supporting Information Available. Experimental procedures, computational data and plots, X-ray data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.