

Anodic Fluorination Based on Cation Exchange between Alkali-Metal Fluorides and Solid-Supported Acids**

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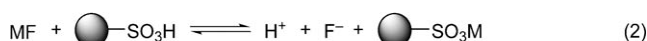
A considerable number of studies have been conducted over the past few decades on the synthesis of organofluorine compounds because of their unique physical, chemical, and biological properties.^[1] Efficient methods for the synthesis of organofluorine compounds are indispensable for the design of new pharmaceutical drugs, agrochemicals, and materials such as liquid crystals. From the viewpoint of atom economy, direct selective fluorination is the best method for these syntheses. Although the simplest nucleophilic fluorinating reagent is hydrogen fluoride (HF), HF and its derivatives are usually expensive, toxic, and corrosive and, therefore, require careful handling.^[2] Alkali-metal fluorides, on the other hand, are both stable, and thus easy to handle, and inexpensive, and potassium fluoride (KF) is one of the cheapest fluorinating reagents known. However, the solubility of alkali-metal salts in many organic solvents is extremely low; therefore, to enhance the solubility and nucleophilicity of alkali-metal salts in these solvents, phase-transfer catalysts such as crown ethers^[3] and quaternary ammonium or phosphonium salts^[4] are commonly used to shift the equilibrium of Equation (1) to



the right. Ionic liquids also work well for nucleophilic substitution reactions using alkali-metal salts.^[5]

Inorganic salts, especially alkali-metal salts, are often used as supporting electrolytes for electrolyses in water since many of them occur naturally and are cheap. However, it is difficult to use them as supporting electrolytes in organic solvents because of their limited solubility. Although inorganic salts are ideal supporting electrolytes from an atom-economical and environmental point of view, synthetic tetraalkylammonium salts that are soluble in many organic solvents are generally used in electro-organic synthesis.^[6] For example, Et₃N·*m*HF and Et₄NF·*n*HF are used as supporting electro-

lytes in anodic fluorination.^[7] Although alkali-metal fluorides such as KF have potential as both fluorinating reagents and supporting electrolytes, their poor solubility in organic solvents restricts their use. It is well known that the proton (H⁺) of solid-supported acids (terminal group: SO₃H) can be exchanged for metal ions;^[8] therefore, such acids should promote the dissociation of alkali-metal fluorides in organic solvents [Eq. (2)]. The resulting in situ generated HF should



then act as a fluorinating reagent and as a supporting electrolyte. Herein, we report a novel electrolytic system for anodic fluorination based on a cation-exchange reaction between alkali-metal fluorides and solid-supported acids.

First of all, we measured the cyclic voltammogram of KF in MeCN (0.8 M based on the used KF). However, as shown in Figure 1, trace a, hardly any ionic conductivity was observed.

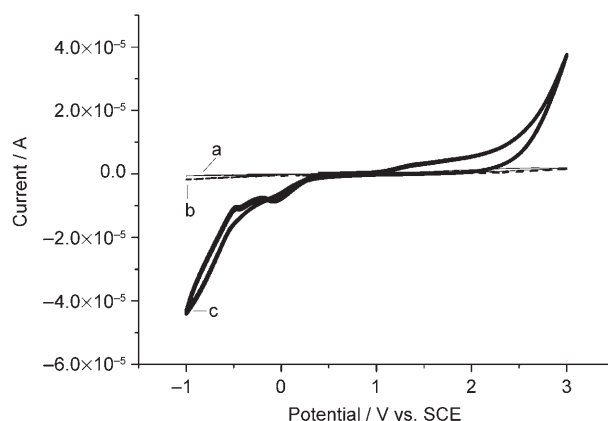


Figure 1. Cyclic voltammograms of a) 0.8 M KF/MeCN, b) 0.6 M Amberlyst15Dry/MeCN, and c) 0.8 M KF/0.6 M Amberlyst15Dry/MeCN, recorded at a Pt disk electrode (diameter: 0.8 mm). Scan rate: 100 mV s⁻¹.

We then measured the cyclic voltammogram of Amberlyst15Dry (terminal group: SO₃H) in MeCN (0.6 M based on the concentration of SO₃H); no oxidation or reduction current was observed (Figure 1, trace b). This result means that the ion pair containing the SO₃⁻ anion and a proton is held together by Coulombic forces,^[9] which makes it difficult to provide sufficient electrical conductivity to the MeCN solvent. In order to confirm the cation-exchange reaction between KF and solid-supported acids, we measured the cyclic voltammogram in the presence of both 0.8 M KF and 0.6 M Amberlyst15Dry in MeCN. As shown in Figure 1, trace c, an oxidation current for MeCN (over a range of 2.5 V

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versus a saturated calomel electrode (SCE)) and a reduction current for the H^+ ion can clearly be observed. This result indicates that a cation-exchange reaction between KF and Amberlyst15Dry has taken place [Eq. (2)] and that the resulting ions act as electronic-charge carriers.

We then decided to investigate the anodic fluorination of ethyl α -phenylthioacetate (**1**)^[10] in the presence of alkali-metal fluorides and Amberlyst15Dry. The typical experimental procedure is shown in Figure 2. As shown in Table 1,

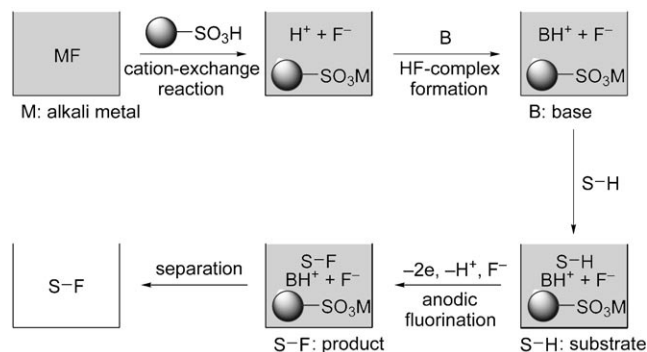


Figure 2. Schematic representation of the experimental procedure.

Table 1: Anodic fluorination of **1** based on the cation-exchange reaction between alkali-metal fluorides and Amberlyst15Dry.

MF / Base / MeCN				
	0.6 M	SO ₃ H		
	3 faraday mol ⁻¹ , 10 mA cm ⁻² , Pt - Pt			
Entry	MF (0.8 M)	Base (0.4 M)	<i>T</i> ^[a]	Yield ^[b,e] [%]
1	KF	—	RT	trace ^[c]
2	KF	Et ₃ N	RT	trace ^[d]
3	KF	2,6-lutidine	RT	27
4	KF	2,6-lutidine	reflux	72 (60)
5	LiF	2,6-lutidine	reflux	5
6	NaF	2,6-lutidine	reflux	25
7	CsF	2,6-lutidine	reflux	65 (60)
8	KHF ₂	2,6-lutidine	reflux	81 (75)

[a] RT = room temperature. [b] Yield determined by ¹⁹F NMR spectroscopy with monofluorobenzene as internal standard. [c] The α -hydroxylated product and diphenyl disulfide were the main products. [d] **1** was mostly recovered. [e] Yield of isolated product in parentheses.

entry 1, anodic fluorination of **1** did not take place and the corresponding α -hydroxylated product and diphenyl disulfide were the main products. We, therefore, decided to try to enhance the nucleophilicity of F^- by adding a base (Et_3N) to form a complex with HF .^[11] However, Et_3N was oxidized at the anode because it has a lower oxidation potential ($E_d^{\text{ox}} = 0.75$ V vs. SCE) than **1** ($E_p^{\text{ox}} = 1.55$ V vs. SCE). Compound **1** was mostly recovered after the experiment (entry 2). We then tried 2,6-lutidine ($E_d^{\text{ox}} = 2.25$ V vs. SCE) as an oxidation-resistant base and were delighted to find that the corresponding α -fluorinated product **2** was obtained in 27% yield (Table 1, entry 3). This suggests that 2,6-lutidine· $x\text{HF}$ is formed in solution. The ¹⁹F NMR chemical shift of the

mixture in the presence of 2,6-lutidine ($\delta = -70.3$ ppm) was found at a lower magnetic field than that in its absence ($\delta = -104.6$ ppm), which supports our suggestion.

In order to confirm the identity of the 2,6-lutidine· $x\text{HF}$ species we compared the ¹⁹F NMR spectra of the solution (containing KF, Amberlyst15Dry, and 2,6-lutidine) and a genuine sample of 2,6-lutidine· $x\text{HF}$ ($x = 1-3$). As shown in Table 2, the ¹⁹F NMR chemical shift of the solution ($\delta =$

Table 2: ¹⁹F NMR chemical shifts of HF complexes.

Entry	Complex	δ [ppm]
1	0.8 M KF + 0.6 M Amberlyst15Dry + 0.4 M 2,6-lutidine	-70.3
2	2,6-lutidine·HF	-71.9
3	2,6-lutidine·2HF	-78.3
4	2,6-lutidine·3HF	-87.2

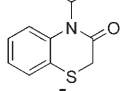
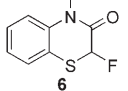
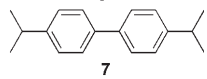
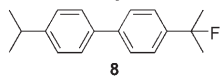
-70.3 ppm) is almost identical to that of 2,6-lutidine·HF ($\delta = -71.9$ ppm). The solution equilibrium of KF in MeCN [Eq. (1)] suggests that the equilibrium of Equation (2) should shift to the right with increasing temperature, which would enhance the nucleophilicity of F^- . Indeed, anodic fluorination of **1** at reflux provided **2** in 72% yield (Table 1, entry 4).

We then focused on the cation-exchange selectivity of Amberlyst15Dry. It is well known that the selectivity sequence of solid-supported acids (terminal group: SO_3H) for monovalent cations is $\text{Li}^+ < \text{H}^+ < \text{Na}^+ < \text{K}^+ < \text{Cs}^+$.^[8] When anodic fluorination of **1** was carried out in the presence of LiF, NaF, KF, and CsF, **2** was obtained in yields of 5, 25, 72, and 65%, respectively (Table 1, entries 4–7). LiF, NaF, and KF have almost the same solubility in MeCN;^[12] therefore, the yield of **2** is correlated with the selectivity sequence of Amberlyst15Dry with these salts rather than with their solubility in MeCN. These figures also indicate that the concentration and nucleophilicity of F^- depend mainly on the selectivity sequence of Amberlyst15Dry in this system. The cation-exchange reaction between KF and Amberlyst15Dry seems to be most effective in enhancing the nucleophilicity of F^- . Finally, KHF_2 was also investigated because the cation-exchange reaction between KHF_2 and Amberlyst15Dry would provide two equivalents of F^- anion per K^+ cation. In its presence, anodic fluorination of **1** proceeded smoothly to provide **2** in 81% yield (Table 1, entry 8).

It is clear from these results that this system for generation of 2,6-lutidine·HF in situ, which is based on the cation-exchange reaction between alkali-metal fluorides and solid-supported acids, is effective for anodic fluorination. Furthermore, it is notable that this system enables us to use an undivided cell because the proton liberated from Amberlyst15Dry is reduced to hydrogen at the cathode.

In light of the above results with KF and Amberlyst15Dry we investigated the anodic fluorination of other organic compounds. The results for sulfide **3**, the heterocyclic compound **5**, and the biaryl **7** are shown in Table 3. They demonstrate that this system is suitable for a wide range of anodic fluorinations.

Table 3: Anodic fluorination of some organic compounds based on the cation-exchange reaction between KF and Amberlyst 15Dry in the presence of 2,6-lutidine.

0.8 M KF, 0.6 M  SO ₃ H 0.4 M 2,6-lutidine, MeCN substrate $\xrightarrow{10 \text{ mA cm}^{-2}, \text{ Pt - Pt, reflux}}$ product				
Entry	Substrate	Current passed [faraday mol ⁻¹]	Product	Yield ^[a,b] [%]
1		4		71 (60)
2		2		68 ^[c] (55)
3		4.5		93

[a] Yield determined by ¹⁹F NMR spectroscopy with monofluorobenzene as internal standard. [b] Yield of isolated product in parentheses. [c] A small amount of the difluorinated product was also formed.

In conclusion, we have developed a novel electrolytic system for anodic fluorination based on the cation-exchange reaction between alkali-metal fluorides and solid-supported acids. This exchange reaction promotes the dissociation of alkali-metal fluorides in MeCN in the presence of 2,6-lutidine to generate 2,6-lutidine-HF, which acts as both a fluorinating reagent and a supporting electrolyte. It is notable that this system enables us to generate 2,6-lutidine-HF in situ without the need to handle HF itself. We expect that this new methodology will make a significant contribution to both organofluorine chemistry and electrochemistry and open up a new field of electro-organic synthesis. The limitations of this new methodology and its further application in electro-organic synthesis are currently under investigation.

Experimental Section

The anodic fluorination of the substrate (1 mmol) was carried out under reflux in an undivided cell equipped with a reflux condenser and platinum electrodes (2 × 2 cm²; distance between electrodes: 3 mm) in 0.8 M KF/0.6 M Amberlyst 15Dry/0.4 M 2,6-lutidine/MeCN (50 mL) under constant-current conditions (10 mA cm⁻²; cell voltage: 3–5 V). Charge was passed through the reaction mixture until complete consumption of the substrate, then the electrolytic solution was passed through a chromatographic silica gel column with CHCl₃ as eluent. The eluent was evaporated under vacuum. The yield of the product was calculated by ¹⁹F NMR spectroscopy with monofluor-

obenzene (1 mmol) as an internal standard. The product was isolated by preparative liquid chromatography with MeCN as eluent.

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