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Synthetic Methods

Electrochemical Fluorination Using Alkali-Metal Fluorides**

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Electrochemical partial fluorination of organic compounds has been established as a powerful tool for selective fluorination under mild reaction conditions in the last two decades.[1] Electrochemical fluorination has generally been carried out in organic solvents containing HF salts such as $Et_3N{\cdot}n$HF and $Et_4NF{\cdot}n$HF as both a supporting electrolyte and fluorine source. The selective electrochemical fluorination of aromatic compounds and heteroatom compounds has been achieved using these HF salts.[1] However, these salts are costly and in particular, HF salts having a high HF content are toxic and need to be handled carefully.

Inorganic fluoride salts such as alkali-metal fluorides (MFs) are stable, easy to handle, and inexpensive. Therefore they are strong candidates for reagents in nucleophilic fluorination as well as supporting electrolytes in chemical and electrochemical fluorination. The challenge to overcome problems such as poor solubility and low nucleophilicity of MF in organic solvents is important.

Phase-transfer catalysts such as crown ethers and quaternary ammonium or phosphonium salts are known to reduce the Coulombic interactions of MFs and are commonly used.[2] Recently, Kim and co-workers have demonstrated that either tri- or tetraethylene glycol (terminal group: OH) could dissociate MF into the fluoride anion and the metal cation in aprotic polar solvents. As a result, nucleophilic fluorination of organic compounds using potassium fluoride (KF) was achieved in tri- and tetraethylene glycol.[3] However, this method has a few drawbacks in that the reaction requires a large amount of poly(ethylene glycol) solvent and harsh reaction conditions such as high temperatures. In addition, the substrates have to bear good leaving groups such as tosylate and mesylate for the fluorination to proceed.

With this knowledge, we expected electrochemical fluorination using MF as both the fluorine source and supporting electrolyte in the presence of poly(ethylene glycol) as an additive would proceed smoothly (Figure 1). Herein, we report successful anodic fluorination in combination with an electrochemical method using a poly(ethylene glycol)/MF system where MF is either KF or CsF.

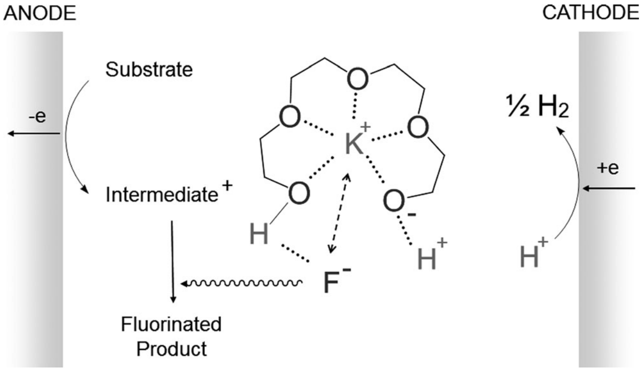

Figure 1. Poly(ethylene glycol) having two terminal hydroxy groups serves as a multifunctional additive for anodic fluorination using KF.

We previously reported that poly(ethylene glycol) additives have a positive effect on anodic fluorination in ionic liquid hydrogen fluorides ($Et_4NF{\cdot}n$HF).[4] To improve the nucleophilicity of fluoride ions on anodic fluorination, poly(ethylene glycol) [$M_n \approx 200$; PEG 200] having the ability to coordinate a cation was introduced as an additive into the reaction system in $Et_4NF{\cdot}n$HF. It was found that PEG 200 served as a good solvating agent for the ammonium cations because of their coordination ability. Its stability for anodic oxidation was also promising. According to a previous study, we selected PEG 200 as a MF-solvating additive. To prove the effect of poly(ethylene glycol) additives on the solubilization of MF, we first examined the solubility of CsF and KF in anhydrous MeCN in the presence of PEG 200 (0.3 M) by using neutralization titration techniques. The results are summarized in Table 1. Although CsF and KF were hardly soluble in MeCN without additives, the addition of PEG 200 improved the solubility of CsF and KF up to 500 and 700 times, respectively. Moreover, the linear sweep voltammograms of KF only (Figure 2, trace a) and KF in the presence of 0.3 M PEG 200 (Figure 2, trace b) were measured in MeCN. For KF only, no current was observed within the range of the applied potential, that is, KF was hardly dissolved in MeCN, thus making it difficult to provide sufficient ionic conductivity in the MeCN solution. In sharp contrast, for KF in the presence of PEG 200 an oxidation current for MeCN [over a range of

Table 1: Solubility of MF in anhydrous MeCN with and without a poly(ethylene glycol) additive.

Entry	MF	Additive	Solubility in MeCN[a]
1	CsF	–	0.1 mM (15.2 $mg\,L^{-1}$)
2	CsF	PEG[b]	50 mM (7.6 $g\,L^{-1}$)
3	KF	–	0.04 mM (2.3 $mg\,L^{-1}$)
4	KF	PEG[b]	28 mM (1.63 $g\,L^{-1}$)

[a] Determined by neutralizing titration techniques. [b] 0.3 M PEG.

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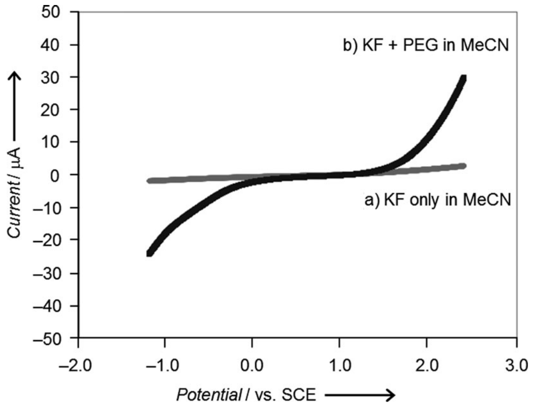
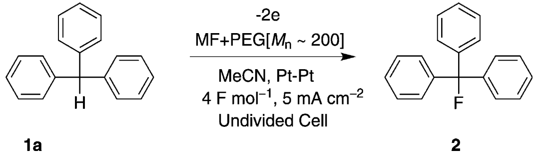


Figure 2. Linear sweep voltammograms of a) KF (0.04 mM) in MeCN and b) KF (28 mM) in the presence of 0.3 M PEG 200 in MeCN. Recorded with a Pt disk working electrode (ϕ = 1.6 mm). The scan rate was 100 mV s^{-1}.

2.0 V versus a saturated calomel electrode (SCE)] and a reduction current for the H$^+$ ion from PEG 200 could be clearly observed. The result indicates that KF is dissolved in the presence of PEG 200 in MeCN and serves as an ionic carrier. With these results, the PEG/MF system appeared to be applicable to electrochemical fluorination of organic compounds.

We then investigated the anodic fluorination of triphenylmethane (**1a**) as a model substrate in the presence of MF and PEG 200 in MeCN. As shown in Table 2, anodic fluorination using CsF in the absence of additives at 40 °C provided fluorinated product **2** in extremely low yield (entry 1), whereas anodic fluorinations using CsF and PEG 200 proceeded efficiently at 20 °C and 40 °C to provide **2** in moderate and excellent yields, respectively (entries 2 and 3). Surprisingly, the use of the more inactive KF instead of CsF afforded the similar results (entries 4 and 5). To the best of our knowledge, other chemical nucleophilic partial fluorinations using KF requires high reaction temperatures of up to at least 100 °C.[3,5] Hence, the electrochemical method is of great significance. In contrast, when we used [18]crown-6 ether and poly(ethylene glycol)dimethyl ether [$M_n \approx 250$] as an additive, for which a hydrogen-bonding effect with MF is not expected, the fluorination proceeded in much lower yield than that using PEG 200 (entries 6 and 7). These facts indicated that the additive, PEG 200, worked not only to dissolve MF in MeCN, but also to accelerate the anodic fluorination under very mild reaction conditions. MeCN was found to be a better medium than nitromethane (MeNO$_2$) and dimethoxyethane (DME; entries 4, 8, and 9).

Table 2: Anodic fluorination of triphenylmethane using MF.[a]



Entry	MF (5 equiv)	Solvent	T [°C]	Yield [%][b]
1[c]	CsF	MeCN	40	2
2	CsF	MeCN	20	52
3	CsF	MeCN	40	95 (85)[d]
4	KF	MeCN	20	47
5	KF	MeCN	40	91 (79)[d]
6[e]	KF	MeCN	40	22
7[f]	KF	MeCN	20	18
8	KF	MeNO$_2$	20	8
9	KF	DME	20	trace

[a] Used 0.3 M PEG. [b] Determined by ^{19}F NMR spectroscopy. [c] Run in the absence of PEG. [d] Yield of isolated product is given within parentheses. [e] Used 0.3 M [18]crown-6 ether as an additive. [f] Used 0.3 M poly(ethylene glycol)dimethyl ether [$M_n \approx 250$] as an additive.

Moreover, after electrolysis, the fluorinated product was easily and solely extracted from the electrolytic solution with *n*-hexane and the residual solution containing MF and PEG could be reused for subsequent runs (Figure 3). As shown in Figure 3, the yield of **2** was kept at more than 80 % upon the reuse of the electrolytic solution containing KF and PEG through the fourth run. The use of excess amounts of KF and PEG relative to the substrate is suitable for repeat runs of the fluorination. In addition, anodic passivation (formation of nonconductive polymeric films on the anode) did not take place at all during the electrolysis. This is in sharp contrast to conventional anodic fluorination using amine HF salts, which very often cause serious anode passivation.[1]

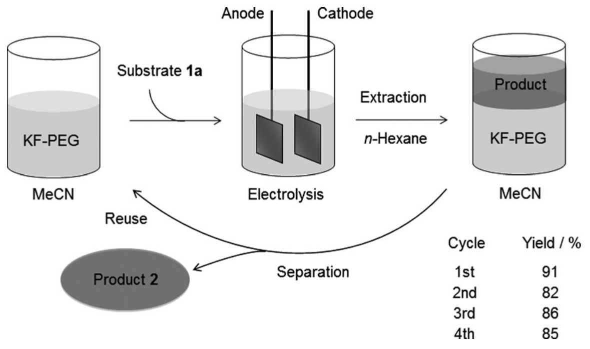
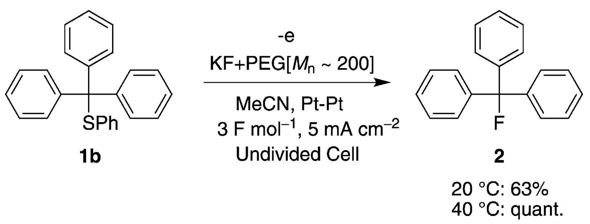


Figure 3. Experimental schematic for anodic fluorination of **1a**. Data for the reusability of electrolytic solution containing KF and PEG.

This clearly suggests that the MF/PEG/MeCN electrolytic system is recyclable for the selective fluorination of **1a**.

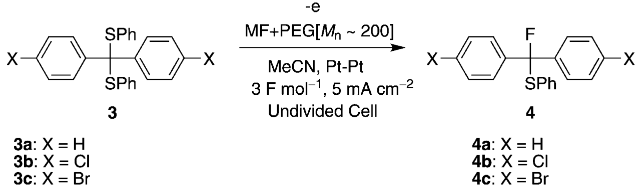
Next, we investigated the anodic fluorodesulfurization of phenyltriphenylmethylsulfide (**1b**) and dithioacetals **3** with either CsF or KF in MeCN in the presence of 0.3 M PEG 200. Phenyltriphenylmethylsulfide (**1b**; Scheme 1) was also con-



Scheme 1. Anodic fluorination of phenyltriphenylmethylsulfide using the KF/PEG system.

verted into the corresponding fluorodesulfurization product **2** in quantitative yield by using KF at 40 °C. In the case of the dithioacetals **3**, we previously found that the anodic fluorination of **3** showed a selectivity dependence on electrolysis method.[6,7] The direct anodic fluorination of **3** provided difluorinated compounds as a major product,[6] while indirect anodic fluorination using a bromine mediator provided monofluorinated compound as a major product.[7] Interestingly, we selectively obtained the corresponding monofluorodesulfurization products **4** without formation of the difluorinated product by the direct electrochemical fluorination of **3** in this system (Table 3). In entry 1, the anodic fluorination of **3a** using CsF in the absence of PEG 200 gave a trace amount of the monofluorinated product because of the low solubility of CsF. However, in the CsF/PEG system, the fluorinated product **4a** was obtained quantitatively at 20 °C (entry 2). When we used KF as the fluorine source and supporting electrolyte, the anodic fluorodesulfurization of **3a** proceeded effectively in 82 % yield at 20 °C, and quantitatively at 40 °C (entries 3 and 4). Compounds **3b** and **3c**, in which a chlorine or bromine substituent was introduced at the *para* position of the benzene ring, also provided monofluorodesulfurization products quantitatively using KF at 40 °C (entries 8 and 9). The MF/PEG-based anodic fluorination seems to be a promising method for smoothly converting C−S bonds into C−F bonds.

Table 3: Anodic fluorination of dithioacetals using MF.[a]

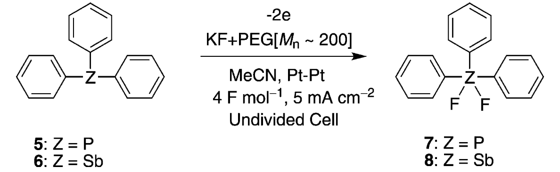


Entry	X	MF (5 equiv)	T [°C]	Yield [%][b,c]
1[d]	H	CsF	20	trace
2	H	CsF	20	quant.
3	H	KF	20	82
4	H	KF	40	quant. (89)[e]
5	Cl	CsF	20	75
6	Cl	CsF	40	quant.
7	Cl	KF	20	48
8	Cl	KF	40	quant. (84)[e]
9	Br	KF	40	quant. (85)[e]

[a] Used 0.3 M PEG. [b] Determined by ^{19}F NMR spectroscopy. [c] Difluorinated compound was not obtained. [d] Run in the absence of PEG. [e] Yield of isolated product is given within parentheses.

In 1968, Kobayashi and his co-workers reported that difluorotriphenylphosphine (**7**) had utility as a fluorinating agent for alcohols.[8] We therefore applied this electrolytic system to the anodic fluorine addition reaction of triphenylphosphine (**5**) and triphenylantimony (**6**) in the presence of KF and PEG 200 in MeCN (Table 4). As expected, corresponding difluorinated products **7** and **8** were obtained in good to moderate yields. Thus, the KF/PEG system in MeCN was also applicable to the fluorine addition reaction of **5** and **6**.

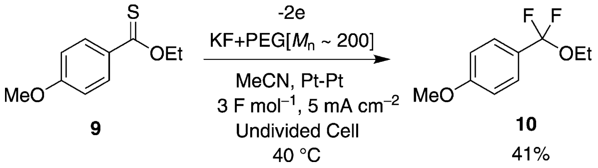
Table 4: Anodic fluorination of triphenylphosphine and triphenylantimony using KF.[a]



Entry	Z	T [°C]	Yield [%][b]
1[c]	P	40	**7**: trace
2	P	20	**7**: 26
3	P	40	**7**: 74 (64)[d]
4	Sb	40	**8**: 52 (39)[d]

[a] Used 0.3 M PEG. [b] Determined by ^{19}F NMR spectroscopy. [c] In the absence of PEG. [d] Yield of isolated product given within parentheses.

The anodic difluorination of thionoester **9** was also investigated using this KF/PEG system (Scheme 2). The reaction proceeded to give the difluorinated product **10** in moderate yield, whereas the product was hardly obtained by the conventional method using on HF salts.[4b]



Scheme 2. Anodic difluorination of thionoester using the KF/PEG system.

In conclusion, we have developed a novel electrolytic system for selective anodic fluorination of various organic compounds using MF/PEG in MeCN. The PEG 200 additive effectively enhanced the solubility of KF and CsF, and the yield of the fluorinated products. This system has many practical advantages and characteristics: a) it proceeds under very mild reaction conditions (20–40 °C); b) it uses cheap and safe MF and PEG; c) the MF plays roles as both the fluorine source and the supporting electrolyte; d) the fluorinated products can be easily separated from the electrolytic solution containing MF and PEG; and e) the electrolytic solution is electrochemically stabile and can be recycled. We expect to develop this new methodology as a basic concept in electroorganic synthesis. For example, we are currently conducting the use of cheap and safe inorganic salts dissolved by PEG in MeCN for a variety of electrolytic reactions. The scope and limitations of the method are now under investigation.

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