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Use of Task-Specific Ionic Liquid for Selective Electrocatalytic Fluorination

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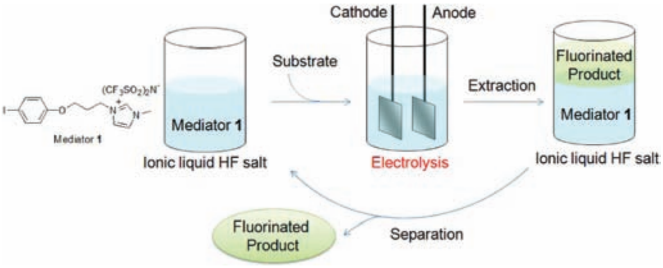
ABSTRACT



Highly selective indirect anodic fluorination of organic compounds was successfully carried out for the first time by using a task-specific ionic liquid of iodoarene as a mediator in ionic liquid hydrogen fluoride salts.

In the context of green sustainable chemistry, ionic liquids (ILs) have become popular as volatile organic solvent-free media for organic synthesis and electrochemical and separation processes, due to their inherent features such as negligible vapor pressure, low flammability, high thermal stability, high ionic conductivity, and reusability.[1] Recent developments in the design of organic salts have made it possible to create task-specific ionic liquids (TSILs), in which a functional group is covalently attached to the cation or the anion or both.[2] This has enabled the supply of various functionalities to conventional IL media for application in many fields of chemistry, especially in organic synthesis and catalysis chemistry.

We have developed a method for the electrochemical fluorination of organic compounds in organic solvents containing ionic liquid hydrogen fluoride (HF) salts as a supporting electrolyte and fluorine source.[3] However, severe passivation of the anode (formation of a polymeric film on the anode, which suppresses anodic current) occurred often.[3] To suppress anodic passivation, we have recently developed solvent-free electrochemical fluorination in neat ionic liquid HF salts.[4] However, even in such HF-based IL electrolytic systems, anode passivation still takes place, depending on the substrates involved.[5] One solution to the passivation problem is to employ indirect electrolysis using mediators. For example, a hypervalent iodoarene difluoride ($ArIF_2$)

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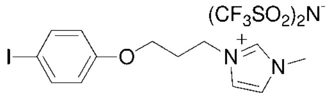
mediator was prepared by anodic oxidation of iodoarene derivatives in HF salt/acetonitrile and applied to the electrochemical fluorodesulfurization of dithioacetal compounds[6a] and fluorination of α-dicarbonyl compounds.[6b] Although the former fluorination was the first successful example of the catalytic use of hypervalent iodoarene for organic synthesis, the fluorinated products had to be separated from the mediator, and the mediator could not be reused. This is a severe drawback from an atom-economical perspective. Therefore, hybridization of mediator systems and TSILs is well worth investigation. In this paper, we report on the first electrochemical mediatory application of a TSIL having an iodoarene moiety. The effect of the TSIL mediator on electrochemical fluorination in a HF-based IL and the reusability of the system were also investigated.

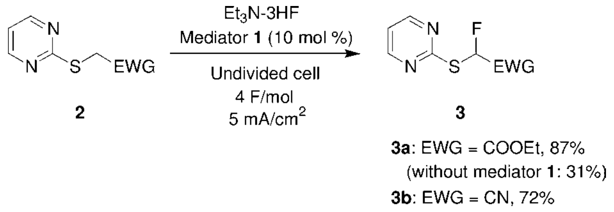
The iodoarene mediator TSIL with an imidazolium cation (**1**) was prepared through ammonium cation formation and subsequent anion exchange. TSIL mediator **1** was readily soluble in several ionic liquids and was not extracted from the ILs by nonpolar organic solvents such as diethyl ether. Cyclic voltammetry measurements of **1** (0.1 mM) in 0.1 M Et$_4$NF-4HF/acetonitrile displayed an oxidation peak at 1.91 V vs saturated calomel electrode (SCE), which is similar to that of the iodoarene devoid of an IL moiety.[6a]



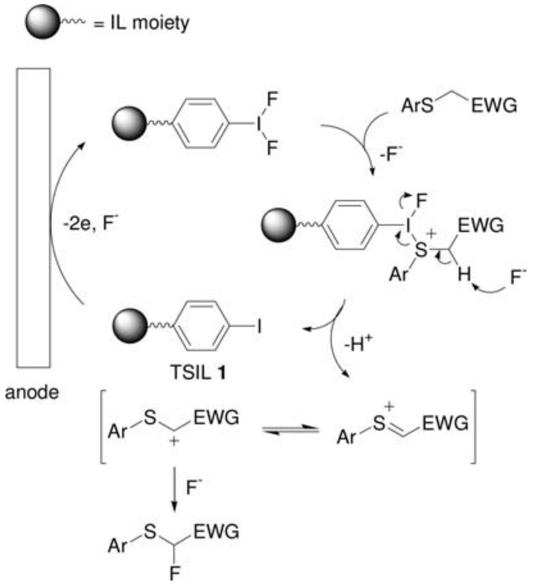
TSIL mediator **1**

In a general indirect anodic reaction, a divided cell is used for the mediator system to prevent cathodic reduction of the oxidized species once generated at the anode. TSIL mediator **1** bears a bulky component; therefore, it can remain in the vicinity of the anode surface in the viscous HF-based IL and encounter the substrate before reduction at the cathode, even in a simple undivided cell. First, the indirect anodic α-fluorination of 2-pyrimidylsulfide **2a** in the absence and presence of a catalytic amount (10 mol %) of TSIL mediator **1** was carried out in HF-based IL (Et$_3$N-3HF) in an undivided cell (Scheme 1). After passage of 4 F/mol charge, the yield of the α-fluorinated product (**3a**) was low (31%) in the absence of **1**, due to the high viscosity of Et$_3$N-3HF and the low basicity of the fluoride ion in Et$_3$N-3HF. In sharp contrast, the use of TSIL mediator **1** significantly enhanced the yield of **3a** (87%). Sulfide **2b** with a CN group as an electron-withdrawing group (EWG) was also converted to the monofluorinated product in good yield by using the TSIL mediator. Deprotonation of the α-position of sulfur (rate-determining step[7]) involves the elimination of trivalent iodoarene with indirect electrolysis, as shown in the plausible reaction mechanism (Scheme 2). It is known that the elimination rate of trivalent iodoarene is extremely high (10^{12} times higher than that of iodine[8]). On the other hand, in the case of direct electrolysis, the leaving group is fluoride (see Supporting Information, Scheme S1). Hence, indirect reaction with the hypervalent iodoarene mediator proceeded efficiently to yield the desired monofluorinated product.

Scheme 1. Indirect Anodic Fluorination of **2** in HF Salt



Scheme 2. Plausible Mechanism of Indirect Anodic Fluorination Using a TSIL Mediator



To elucidate the mediation system, potentiostatic electrolysis (1.80 V vs SCE) was carried out for **2a** ($E_p^{ox} = 2.23$ V vs SCE). In the presence of TSIL mediator **1** ($E_p^{ox} = 1.91$ V vs SCE), **3a** was obtained in 18% yield after passage of 1 F/mol charge, whereas no fluorinated product was obtained in the absence of **1**, which indicates that the fluorination of **2a** with TSIL mediator **1** proceeded via an indirect process.

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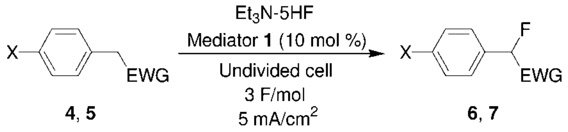
The reusability of the IL system was investigated after simple extraction of the product with diethyl ether. The recovered IL still contained the TSIL mediator and was reused for subsequent runs, maintaining a good yield of **3a** through the fourth run (87−84%).

Table 1. Indirect Anodic Fluorination of **4** and **5**



entry	compound	EWG	X	yield (%)[a]
1	**4a**	COOMe	H	55 (**6a**)
2	**4b**	COOMe	Cl	70 (**6b**)
3	**4c**	COOMe	Br	69 (**6c**)
4	**5a**	CN	H	42 (**7a**)
5	**5b**	CN	Cl	79 (**7b**)
6	**5c**	CN	Br	75 (**7c**)

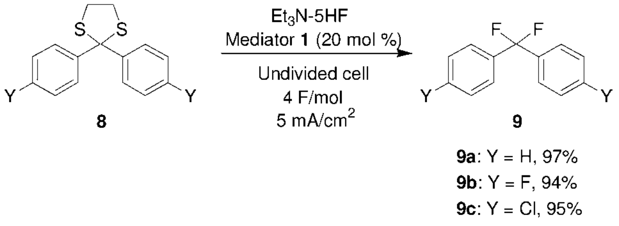
[a] Determined by ^{19}F NMR.

The indirect electrolysis in IL was also applicable to the fluorination of α-(phenyl)acetate (**4**) and α-(phenyl)acetonitrile (**5**). Direct electrochemical oxidation of these compounds is difficult, due to their high oxidation potentials (e.g., E_p^{ox} of **5b**: 2.68 V vs SCE). Furthermore, in conventional HF salt/acetonitrile solution, the benzylic cation generated by oxidation preferentially reacts with acetonitrile and causes acetoamidation instead of fluorination.[9] Table 1 shows the results of the indirect anodic fluorination of **4** and **5** in anodically stable Et_3N-5HF with TSIL mediator **1**. The corresponding monofluorinated products (**6** and **7**, respectively) were obtained in good to moderate yields. The introduction of chlorine and bromine at the para-position of the benzene ring effectively increased the electrophilicity of the benzylic cation intermediate, which resulted in an increase of the product yields. In sharp contrast, Noel et al. quite recently reported the electrochemical fluorination of alkyl phenylacetates in ionic liquid Et_3N-4HF.[10] Although the corresponding α-fluorinated products were obtained as major products, many byproducts, such as hydrolysis products, α,α-difluoro products, and aromatic fluorinated products, were formed. Therefore, indirect electrolysis using the mediator is far superior to direct electrolysis.

Finally, indirect anodic fluorodesulfurization of cyclic dithioacetal (**8**) was investigated in the TSIL mediator system (Scheme 3). Even in the case of fluorodesulfurization, the mediator system worked sufficiently to afford the difluoromethylene product (**9**) in excellent yield.

In conclusion, a novel indirect electrochemical fluorination system was developed by employing a task-specific ionic liquid (TSIL) with an iodoarene moiety as the mediator in a HF-based IL. The mobility of the novel mediator bearing an IL moiety was reduced in viscous IL, which enabled the indirect electrochemical fluorination efficiently in a simple undivided cell. This is a significant advantage compared with conventional mediatory systems. Mediator **1** improved the reaction efficiency for a variety of electrochemical fluorinations and remained intact in the ILs after the extraction process to be reused for subsequent runs. Thus, volatile organic solvent-free indirect electrochemical fluorination of various organic compounds was achieved using a reusable iodoarene mediator bearing an IL moiety. Application of the TSIL mediator **1** to another oxidative reaction in an IL is now under investigation in our laboratory.

Scheme 3. Indirect Anodic Fluorodesulfurization of **8**



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Supporting Information Available: Experimental section and scheme showing the mechanism of direct electrolysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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