Thiofluorination of Carbon–Carbon Multiple Bonds Using Electrochemically Generated $ArS(ArSSAr)^+BF_4^-$

Shunsuke Fujie, Kouichi Matsumoto, Seiji Suga,[†] and Jun-ichi Yoshida*
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University,
Nishikyo-ku, Kyoto 615-8510

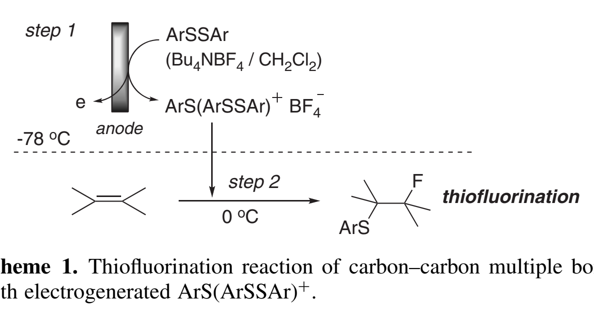
(Received September 29, 2009; CL-090879; E-mail: yoshida@sbchem.kyoto-u.ac.jp)

The reaction of alkenes and alkynes with $ArS(ArSSAr)^+BF_4^-$, which was generated and accumulated by the low-temperature anodic oxidation of ArSSAr in Bu_4NBF_4/CH_2Cl_2, led to the addition of an ArS group and fluoride across the carbon–carbon multiple bond to give thiofluorinated compounds in good yields.

Organofluorine compounds attract significant research interest in materials and pharmaceutical chemistry, because the introduction of fluorine atom into an organic molecule often dramatically changes its physical and chemical properties to give a new function or a new biological activity.[1,2] Thiofluorination of carbon–carbon multiple bonds serves as a useful method for synthesizing organofluorine compounds,[3] because an organosulfanyl group can be utilized for future transformations. For instance, $PhCl/Et_3N–3HF$,[4] $MeS^+SMe_2/Et_3N–3HF$,[5] $ArNHSPh/BF_3–OEt_2$,[6] or *N*-phenylsulfanylphthalimide/pridine–9HF[7] has been reported to effect thiofluorination reactions. However, these methods require unstable and hazardous reagents.

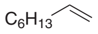
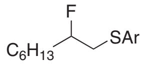
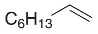
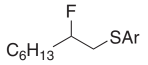
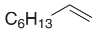
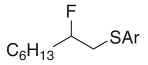
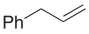
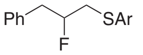
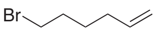
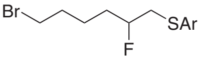
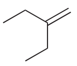
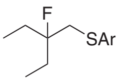
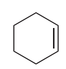
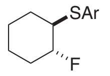
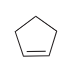
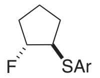
Recently, we revealed that highly reactive arylbis(arylsulfanyl)sulfonium ions $[ArS(ArSSAr)^+]$[8] can readily be generated by the low-temperature electrochemical oxidation[9] of diaryl disulfide[10] in CH_2Cl_2 using Bu_4NBF_4 as supporting electrolyte, and that $ArS(ArSSAr)^+$ serves as an effective reagent to generate alkoxycarbenium ion pools[11] from thioacetals.[12] Herein we report that $ArS(ArSSAr)^+$ serves as an effective reagent for thiofluorination of alkenes and alkynes. The counter anion, BF_4^- acted as a fluoride donor (Scheme 1).

A typical procedure is as follows. In the first step, a solution of $ArS(ArSSAr)^+BF_4^-$ (Ar = *p*-FC_6H_4) was generated and accumulated by the anodic oxidation of ArSSAr (1.80 mmol) in Bu_4NBF_4/CH_2Cl_2 (12 mL) at −78 °C (0.67 F mol^{-1}).[13] In the second step, 1-octene (0.15 mmol) was added to the anodic solution (0.113 M $ArS(ArSSAr)^+$ at −78 °C, 4.0 mL, 0.45 mmol) at 0 °C, and the solution was stirred for 10 min. Then, Et_3N (1 mL) was added to quench the reaction. The reaction gave thiofluorinated compound **1a** (Table 1, Entry 1) in 93% yield. It is noteworthy that the regioselectivity is very high. The other regioisomer was not detected. The reactions of $ArS(ArSSAr)^+BF_4^-$ (Ar = *p*-ClC_6H_4 and *p*-$CH_3C_6H_4$) also gave **1b** and **1c** (Entries 2 and 3). The introduction of a cation-stabilizing electron-donating group such as CH_3 on the aromatic ring resulted in lower yield of the product.



Scheme 1. Thiofluorination reaction of carbon–carbon multiple bond with electrogenerated $ArS(ArSSAr)^+$.

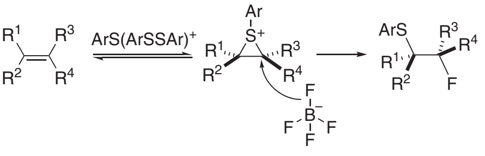
Table 1. Thiofluorination of alkenes with electrochemically generated $ArS(ArSSAr)^+$ [a]

Entry	Alkene	Product		Yield/%
1			**1a**	93
2[b]			**1b**	82
3[c]			**1c**	52
4			**1d**	79
5			**1e**	99
6			**1f**	54
7			**1g**	67
8			**1h**	60

[a] Typical procedure: ArSSAr (Ar = *p*-FC_6H_4; 1.80 mmol) was electrolyzed in 0.3 M Bu_4NBF_4/CH_2Cl_2 (12 mL) at −78 °C by using 0.67 F mol^{-1} of electricity. The solution thus obtained (0.113 M at −78 °C, 4.0 mL, 0.45 mmol) was allowed to react with an alkene (0.15 mmol) at 0 °C for 10 min. Then the reaction was quenched with Et_3N (1.0 mL). [b] ArSSAr (Ar = *p*-ClC_6H_4) was used. [c] ArSSAr (Ar = *p*-$CH_3C_6H_4$) was used.

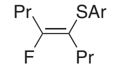
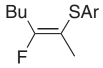
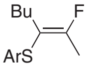
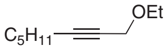
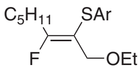
To examine the scope of the present reaction, the reactions of $ArS(ArSSAr)^+BF_4^-$ with various alkenes were examined at 0 °C (Table 1). Terminal alkenes bearing benzyl and 4-bromobutyl groups gave the corresponding thiofluoroinated products in good yields (Entries 4 and 5). A 1,1-dialkyl-substituted alkene also gave the corresponding products (Entry 6). Internal alkenes such as cyclohexene and cyclopentene could also be used as substrates (Entries 7 and 8). ^1H NMR analysis of the product **1g** indicated the anti addition of ArS and F groups.

Although the detailed mechanism has not been clarified as yet, the reaction seems to proceed by the initial reaction of $ArS(ArSSAr)^+$ with an alkene to give an episulfonium ion intermediate,[14] which undergoes a nucleophilic substitution reaction with BF_4^- from the backside on the episulfonium carbon to give the corresponding thiofluorination product (Scheme 2). The stereochemistry of the product is consistent with this mechanism.

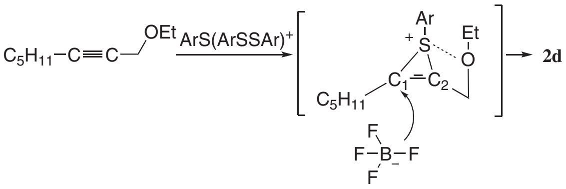


Scheme 2. A proposed reaction mechanism.

Table 2. Thiofluorination of alkynes with electrochemically generated $ArS(ArSSAr)^+$ [a]

Entry	Alkyne	Product		Yield/%
1			**2a**	81
2			**2b**	35
			**2c**	32
3			**2d**	86

[a] Reactions were carried out using 1 equiv of $ArS(ArSSAr)^+$ (Ar = p-FC_6H_4).



Scheme 3. Formation of the episulfonium ion intermediate having an ethoxy group and its structure obtained by DFT calculation (B3LYP/6-31G(d)).

The regiochemisry indicates that fluoride attacks on the more substituted carbon preferentially. Presumably, the displacement proceeds via a partially developed carbocation.

Next, the reactions of $ArS(ArSSAr)^+BF_4^-$ with alkynes were examined, and the results obtained are shown in Table 2. 4-Octyne, a symmetrically disubstituted alkyne, gave the corresponding thiofluorinated product in 81% (Entry 1). The E stereoselectivity indicated that the reaction proceeded by anti addition. The reaction with an unsymmetrically disubstituted alkyne gave a mixture of two regioisomers (Entry 2). However, it is interesting to note that the reaction with an unsymmetrical alkyne having an ethoxy group in an appropriate position led to the formation of a single regioisomer (Entry 3). Presumably, the ethoxy group serves as a directing group by coordinating the sulfur atom of the episulfonium ion intermediate (Scheme 3).[15] In fact, the DFT calculation of the episulfonium ion intermediate indicated the interaction between sulfur and oxygen (3.369 Å). The longer bond length of C_1–S (1.893 Å) than C_2–S (1.838 Å) is consistent with regioselective reaction at C_1.

In conclusion, we have developed a convenient thiofluorination reaction of alkenes or alkynes using electrochemically generated $ArS(ArSSAr)^+BF_4^-$.[16] The reaction provides easy access to organofluorine compounds, and the ArS group can be used for further transformations. Further detailed mechanistic studies and synthetic applications are currently in progress in our laboratory.

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References and Notes

† Present address: Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530

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