

# Electrochemistry Enabled Selective Vicinal Fluorosulfonylation and Fluorosulfoxidation of Alkenes

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## Abstract

Both sulfur and fluorine play important roles in organic synthesis, the life science, and materials science. The direct incorporation of these elements into organic scaffolds with precise control of the oxidation states of sulfur moieties is of great significance. Herein, we report the highly selective electrochemical vicinal fluorosulfonylation and fluorosulfoxidation reactions of alkenes, which were enabled by the unique ability of electrochemistry to dial in the potentials on demand. Preliminary mechanistic investigations revealed that the fluorosulfonylation reaction proceeded through a radical-polar crossover mechanism involving a key episulfonium ion intermediate. Subsequent electrochemical oxidation of fluorosulfides to fluorosulfoxides were readily achieved under a higher applied potential with the adventitious H<sub>2</sub>O in the reaction mixture.

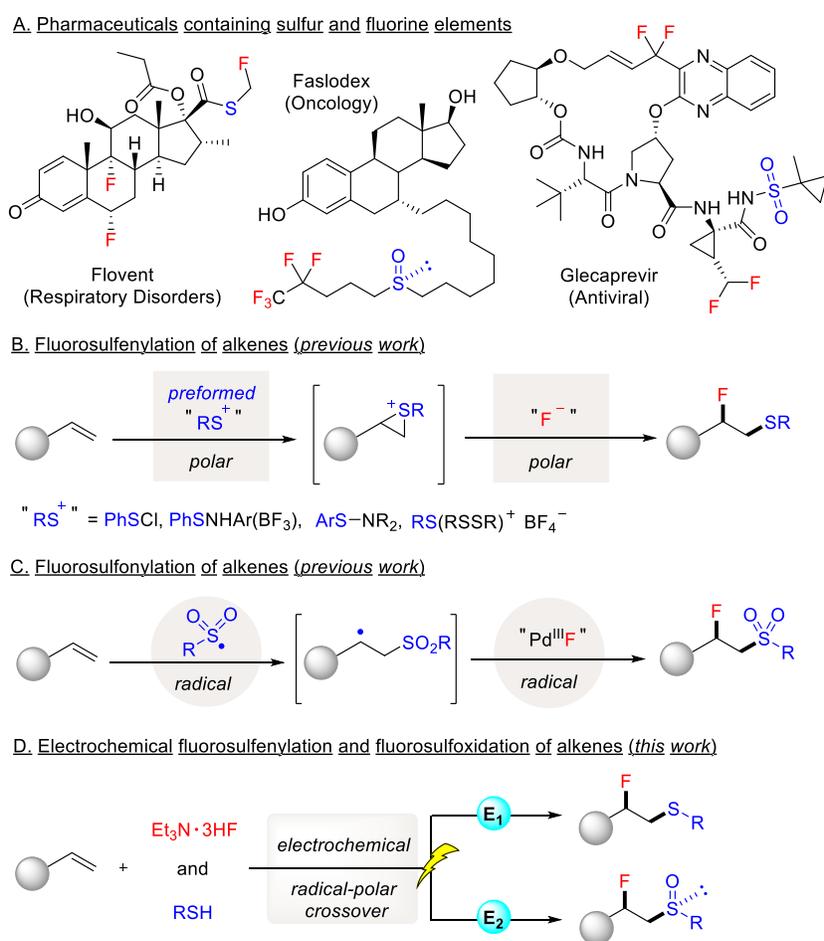
## Keywords

alkene • chemoselectivity • electrochemistry • fluorine • sulfur

## Introduction

Alkenes are among the most prevalent and valuable feedstocks in organic synthesis. Direct and selective difunctionalization of alkenes, which simultaneously adds two synthetically valuable functionalities across a double bond, is a straightforward and economical approach to construct functionalized targets with high

molecular complexities.<sup>1-3</sup> Specifically, the direct incorporation of sulfur<sup>4,5</sup> and fluorine<sup>6</sup> into alkenes has attracted intensive research interest of synthetic chemists due to the important roles of both elements in organic synthesis, life science, and materials science. For instance, organic molecules containing both sulfur and fluorine are present in many well-received pharmaceuticals, such as Flovent, Faslodex, and Glecaprevir (Scheme 1A). Additionally, the spatial vicinity of these two elements further renders these types of compounds as ideal research targets of the fundamentally intriguing sulfur–fluorine gauche effect.<sup>7</sup> It was found that the oxidation states of sulfur in these compounds are strongly correlated with their functions. Therefore, it is highly desirable to develop synthesis protocols to simultaneously introduce sulfur and fluorine elements into targeted molecules with precise control of the oxidation states of the sulfur moieties.<sup>8-10</sup>



**Scheme 1** | Direct Incorporation of Sulfur and Fluorine Elements into Alkenes

Typically, the vicinal fluorosulfonylation of alkenes is achieved by the reaction of alkenes with a chemically<sup>11-17</sup> or electrochemically<sup>18</sup> generated electrophilic thiolating agent (“RS<sup>+</sup>”) to form an episulfonium ion<sup>19</sup> followed by nucleophilic fluorination (Scheme 1B). Such a polar approach, however, is limited by the requisite preparation of highly reactive and toxic thiolating agents. Notably, Liu and co-workers<sup>20</sup> developed an elegant radical strategy for the intermolecular fluorosulfonylation of styrenes *via* a high-valence palladium species.<sup>21-22</sup> However, a superstoichiometric strong oxidizing agent (NFSI) was required (Scheme 1C). In contrast, the analogously direct fluorosulfoxidation of alkenes has not been reported yet due to the difficulty in accessing the electrophilic or radical sulfoxide species.<sup>23</sup>

Green and sustainable electrosynthesis<sup>24-29</sup> could provide innovative solutions to address the challenges associated with conventional organic synthesis. To this end, one of the most prominent features of electrochemistry in organic synthesis is its unique capability to control reactivity *via* "dialed-in" specific potential when necessary. By contrast, chemical agents only bear their innately fixed redox potentials and thus extensively screening of various chemical oxidants or reductants are generally required in a typical redox reaction. Therefore, electrosynthesis is capable to regulate reactions within a much wider redox window.<sup>30,31</sup> In addition, the precise control of a minimally sufficient potential also allows better functional compatibility.<sup>32</sup> In particular, electrochemical methods have been demonstrated to be capable of incorporating either sulfur<sup>33,34</sup> or fluorine<sup>35-38</sup> functionalities into diverse organic frameworks. Inspired by the elegant sulfonyl fluoride (RSO<sub>2</sub>—F) synthesis *via* the electrochemical oxidative coupling of thiols (RSH) and potassium fluoride (KF) reported by Noël and co-workers,<sup>39,40</sup> we speculated that electrochemistry should be an ideal solution to simultaneously<sup>41</sup> introduce both fluorine and sulfur in a controllable oxidation state into alkenes. Herein, we report an electrochemical radical-polar crossover approach for the highly selective fluorosulfonylation and fluorosulfoxidation of alkenes in which the selectivity was well controlled by the judicious choice of the applied potential (Scheme 1D).

## Experimental Methods

General procedure for the electrochemical vicinal fluorosulfonylation of alkenes (constant cell-potential electrolysis): In an oven-dried undivided three-necked glassware (25 mL) equipped with a stirring bar, thiophenol substrate (0.3 mmol) were added. The glassware was equipped with carbon cloth (15 mm × 15 mm × 0.1 mm) as the anode and platinum plate (15 mm × 15 mm × 0.3 mm) as the cathode. Under the protection of N<sub>2</sub>, olefin substrate (1.5 equiv.), Et<sub>3</sub>N·3HF (0.5 mL), and CH<sub>3</sub>CN (10 mL) were injected respectively into the glassware via syringes. The reaction mixture was stirred and electrolyzed at a constant cell potential of 1.8 V at 40 °C for 6 h. The reaction mixture was subsequently poured into a saturated sodium bicarbonate solution (ca. 15 mL). The aqueous layer was separated and extracted with dichloromethane (3×5 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. Following concentration in vacuo, the crude residue was subjected to flash column chromatography on silica gel to yield the desired product.

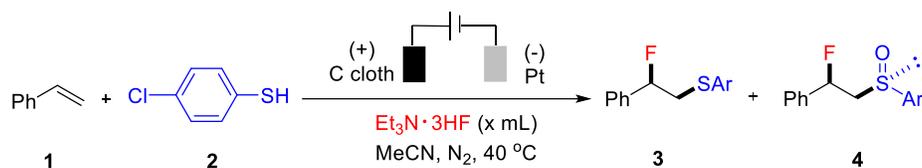
General procedure for the electrochemical vicinal fluorosulfoxidation of alkenes: In an oven-dried undivided three-necked glassware (25 mL) equipped with a stir bar, thiophenol substrate (0.3 mmol) were added. The glassware was equipped with carbon cloth (15 mm × 15 mm × 0.1 mm) as the anode and platinum plate (15 mm × 15 mm × 0.3 mm) as the cathode. Under the protection of N<sub>2</sub>, olefin substrate (1.7 equiv.), Et<sub>3</sub>N·3HF (1 mL), CH<sub>3</sub>COOH (3 equiv.), CCl<sub>4</sub> (1.0 equiv.) and CH<sub>3</sub>CN (10 mL) were injected respectively into the glassware via syringes. The reaction mixture was stirred and the electrolysis was initiated at a constant cell potential of 2.8 V at 40 °C. The electrical input was removed after 4 h. The reaction mixture was subsequently poured into a saturated sodium bicarbonate solution (ca. 15 mL). The aqueous layer was separated and extracted with dichloromethane (3×5 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. Following concentration in vacuo, the crude residue was subjected to flash column chromatography on silica gel to yield the desired product. More details and characterization of products are available in Supporting Information.

## Results and Discussion

### *Reaction optimizations*

We commenced our investigations on the direct vicinal fluorosulfenylation by choosing styrene (**1**), 4-chlorothiophenol (**2**), and triethylamine trihydrofluoride ( $\text{Et}_3\text{N}\cdot 3\text{HF}$ ) as the model substrates. With a carbon cloth anode and a Pt cathode in an undivided cell, constant-cell-potential electrolysis ( $E_{\text{cell}} = 1.8 \text{ V}$ ) in MeCN at  $40^\circ \text{C}$  delivered the desired fluorosulfide (**3**) in an optimal 77% isolated yield (Table 1, entries 1–3). No overoxidation of the sulfide product was observed under these conditions. Notably,  $\text{Et}_3\text{N}\cdot 3\text{HF}$  in this reaction served not only as the fluorinating agent but also as the electrolyte owing to its ionic nature.<sup>42</sup> The isolated yield of fluorosulfide was depressed along with decrease of the loading of  $\text{Et}_3\text{N}\cdot 3\text{HF}$ . Other fluorinating agents such as Olah's reagent ( $\text{Py}\cdot 9\text{HF}$ ), however, did not promote this transformation, and the formation of aryl disulfide was observed instead. A proof-of-concept experiment with the synthesis of fluorosulfoxide (**4**) by increasing the applied cell potential (2.5 V) was conducted (entry 4). Interestingly, the employment of  $\text{CCl}_4$  (1 equiv.) as the additive was found to be pivotal for the formation of fluorosulfoxide.<sup>43,44</sup> The higher applied cell potential (2.8 V) and the higher loading of styrene (1.7 equiv.) and  $\text{Et}_3\text{N}\cdot 3\text{HF}$  (1 mL) were found to be beneficial (entries 5 and 6). Ultimately, the optimal yield of fluorosulfoxide (**4**, 66%) was achieved under constant-current electrolysis (CCE) conditions (CCE at 20 mA for 4 h, entry 7). Note that the oxidation of fluorosulfide (**3**) to fluorosulfoxide (**4**) with a terminal chemical oxidant such as *m*-CPBA led to a low yield (47%) accompanied by the overoxidized fluorosulfone (*Supporting Information*).

**Table 1.** Optimization of Reaction Conditions<sup>a</sup>



| entry            | x (mL) | condition                 | time (h) | yield ( <b>3</b> , %) | yield ( <b>4</b> , %) |
|------------------|--------|---------------------------|----------|-----------------------|-----------------------|
| 1                | 0.5    | $E_{cell} = 1.5\text{ V}$ | 6        | 67                    | —                     |
| 2                | 0.5    | $E_{cell} = 1.8\text{ V}$ | 6        | 78 (77) <sup>b</sup>  | —                     |
| 3                | 0.5    | $E_{cell} = 2.0\text{ V}$ | 6        | 75                    | —                     |
| 4 <sup>c</sup>   | 0.5    | $E_{cell} = 2.5\text{ V}$ | 6        | 15                    | 12                    |
| 5 <sup>c,d</sup> | 0.5    | $E_{cell} = 2.8\text{ V}$ | 4        | 15                    | 40                    |
| 6 <sup>c,d</sup> | 1      | $E_{cell} = 2.8\text{ V}$ | 4        | —                     | 57 (63) <sup>b</sup>  |
| 7 <sup>c,d</sup> | 1      | <b>CCE = 20 mA</b>        | 4        | —                     | 66 <sup>b</sup>       |

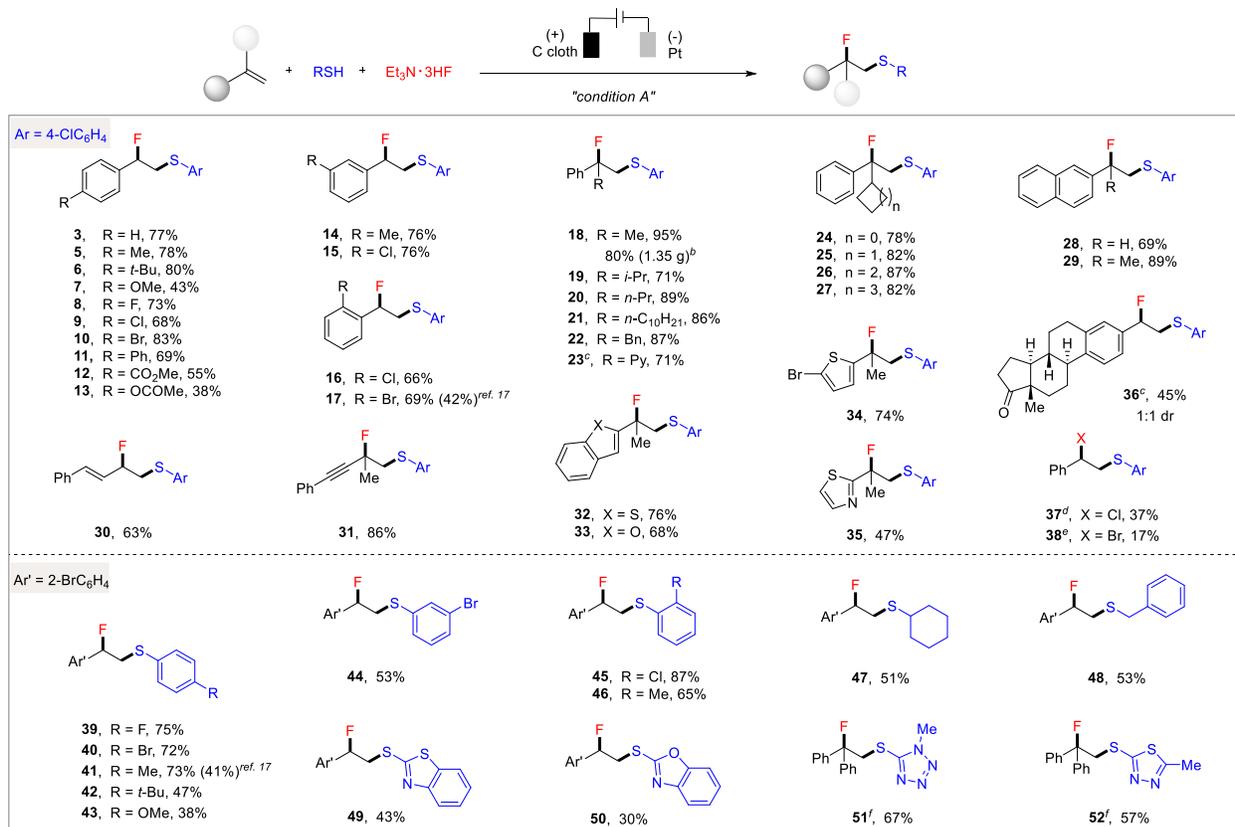
<sup>a</sup> Reaction conditions: undivided cell, carbon cloth anode, Pt cathode, **1** (0.45 mmol), **2** (0.3 mmol), Et<sub>3</sub>N·3HF (0.5 or 1 mL), MeCN (10 mL) at 40 °C; yield was determined by <sup>19</sup>F NMR with (trifluoromethoxy)benzene as the internal standard; <sup>b</sup> isolated yield; <sup>c</sup> 1 equiv. of CCl<sub>4</sub> as the additive; <sup>d</sup> 0.51 mmol of **1** used.

### Substrate scope

With the optimal reaction conditions determined, we first evaluated the scope of the electrochemical fluorosulfenylation of alkenes (Table 2). This reaction accommodated a wide array of *para*-, *meta*-, and *ortho*-substituted styrenes (**5–17**). Additionally, alkyl (**18–21**), benzyl (**22**), pyridyl (**23**), and cycloalkyl (**24–27**)  $\alpha$ -substituted styrenes were all found to be well tolerated. Moreover, the gram-scale preparation of fluorosulfide **18** (1.35 g, 80%) further underscored the practicality of this protocol. Alkenes substituted by a naphthalene (**28** and **29**), alkene (**30**), alkyne (**31**), heterocycle (**32–35**) or estrone derivative (**36**) also underwent the desired transformations. This protocol was also readily transferred to the preparation of the analogous chlorosulfide (**37**) and bromosulfide (**38**). Furthermore, a variety of thiophenols bearing electron-donating or electron-withdrawing groups all reacted to afford the desired fluorosulfides in moderate to good yields (**39–46**, 38%–87%). Encouragingly, cyclohexyl- (**47**), benzyl- (**48**), and heterocycle-containing (**49–52**) thiols were all competent thiolating agents. Note that the applied cell potential was readjusted to 2.8 V when the electro-

deficient 5-mercapto-1-methyltetrazole (**51**) and 2-mercapto-5-methyl-1,3,4-thiadiazole (**52**) were employed as the thiolating agents.

**Table 2.** Substrate Scope of the Electrochemical Fluorosulfenylation of Alkenes.

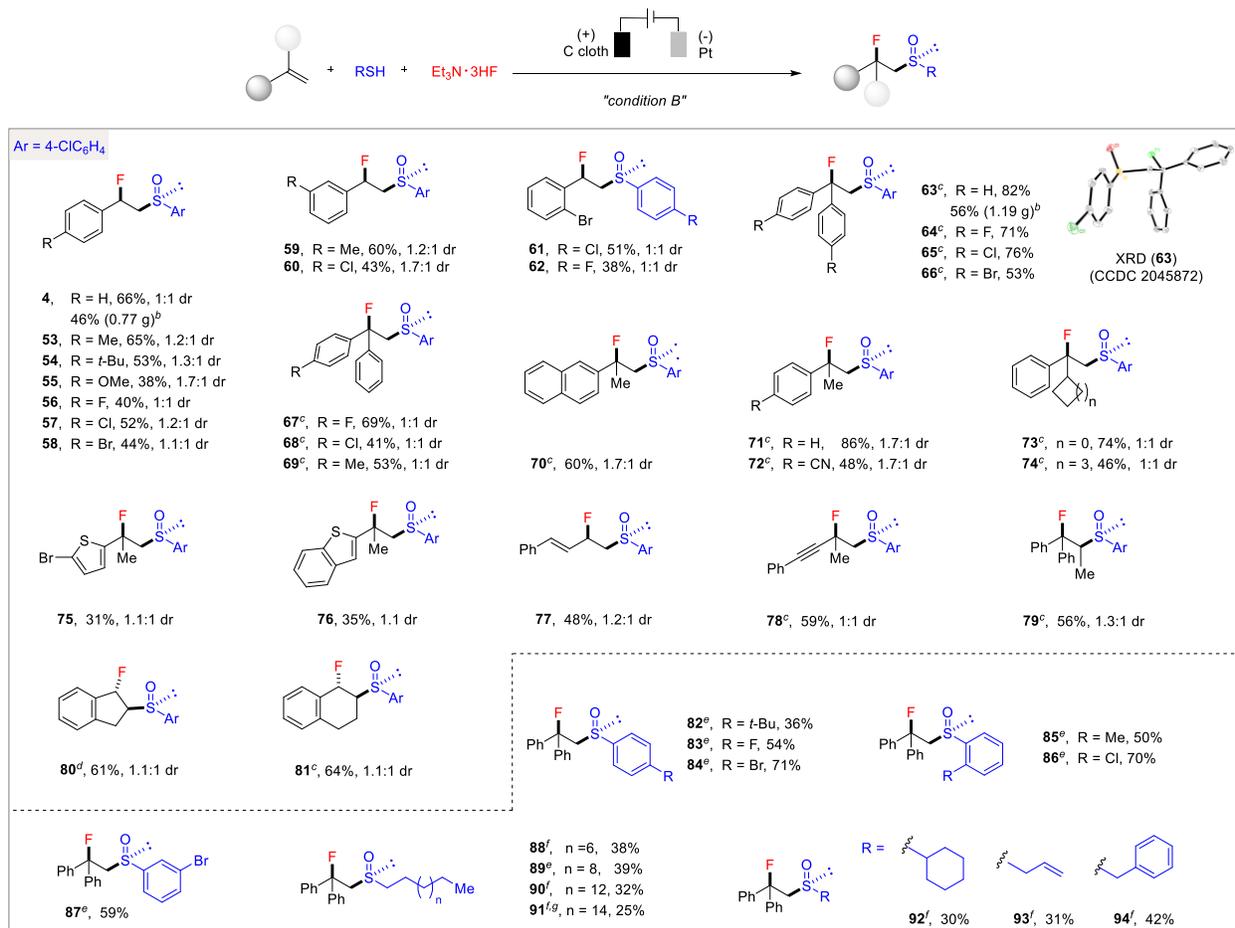


<sup>a</sup> "Condition A": undivided cell, carbon cloth anode, Pt cathode, alkene (0.45 mmol), thiophenol (0.3 mmol), Et<sub>3</sub>N·3HF (0.5 mL), MeCN (10 mL) at 40 °C,  $E_{cell}$  = 1.8 V for 6 h, unless otherwise noted; yields of purified products; <sup>b</sup> gram-scale reaction, 60 h; <sup>c</sup> 20 mA, 75 min; <sup>d</sup> Et<sub>3</sub>N·HCl (5 equiv.) used instead; <sup>e</sup> Bu<sub>4</sub>NBr (3 equiv.) used instead; <sup>f</sup> 2.8 V, 4 h.

Compared with the existing methods, this electrochemical fluorosulfenylation of alkenes exhibited several advantages. First, thiols were directly used to mitigate the tedious preparation of the highly reactive and toxic electrophilic thiolating agents as shown in Scheme 1B.<sup>11-18</sup> Therefore, previously challenging alkyl and heterocycle substituted fluorosulfides could be readily obtained (Table 2). With respect to alkenes, literature protocols were typically restricted to electron-rich alkyl substituted ones. To the best of our knowledge, only few *ortho*-substituted styrenes were reported by Xu and co-workers in the fluorosulfenylation reaction using

N-thiosuccinimides in moderate yields (**17** and **41**).<sup>17</sup> In contrast, our method not only provided much higher yields of the same products but also tolerated a very broad scope of alkenes including styrenes, alkenyl, alkynyl, and heterocycle substituted alkenes (Table 2). Therefore, this electrochemical fluorosulfenylation should serve as a very general approach to fluorosulfides and is complementary to the existing methods.

**Table 3.** Substrate scope of the Electrochemical Fluorosulfoxidation of Alkenes.



<sup>a</sup> "Condition B": undivided cell, carbon cloth anode, Pt cathode, alkene (0.51 mmol), thiophenol (0.3 mmol), Et<sub>3</sub>N·3HF (1 mL), CCl<sub>4</sub> (1 equiv.), MeCN (10 mL) at 40 °C, CCE at 20 mA for 4 h, unless otherwise noted; yields of purified products; <sup>b</sup> gram-scale reaction, CCE at 160 mA for 6 h; <sup>c</sup> 3.0 equiv. of CH<sub>3</sub>COOH were added; <sup>d</sup> 3.5 h; <sup>e</sup> 2.8 V; <sup>f</sup> CCE at 15 mA for 5 h; <sup>g</sup> 55 °C.

We further applied this electrochemical difunctionalization to the facile preparation of synthetically challenging vicinal fluorosulfoxides directly from alkenes (Table 3). The target fluorosulfoxides were obtained

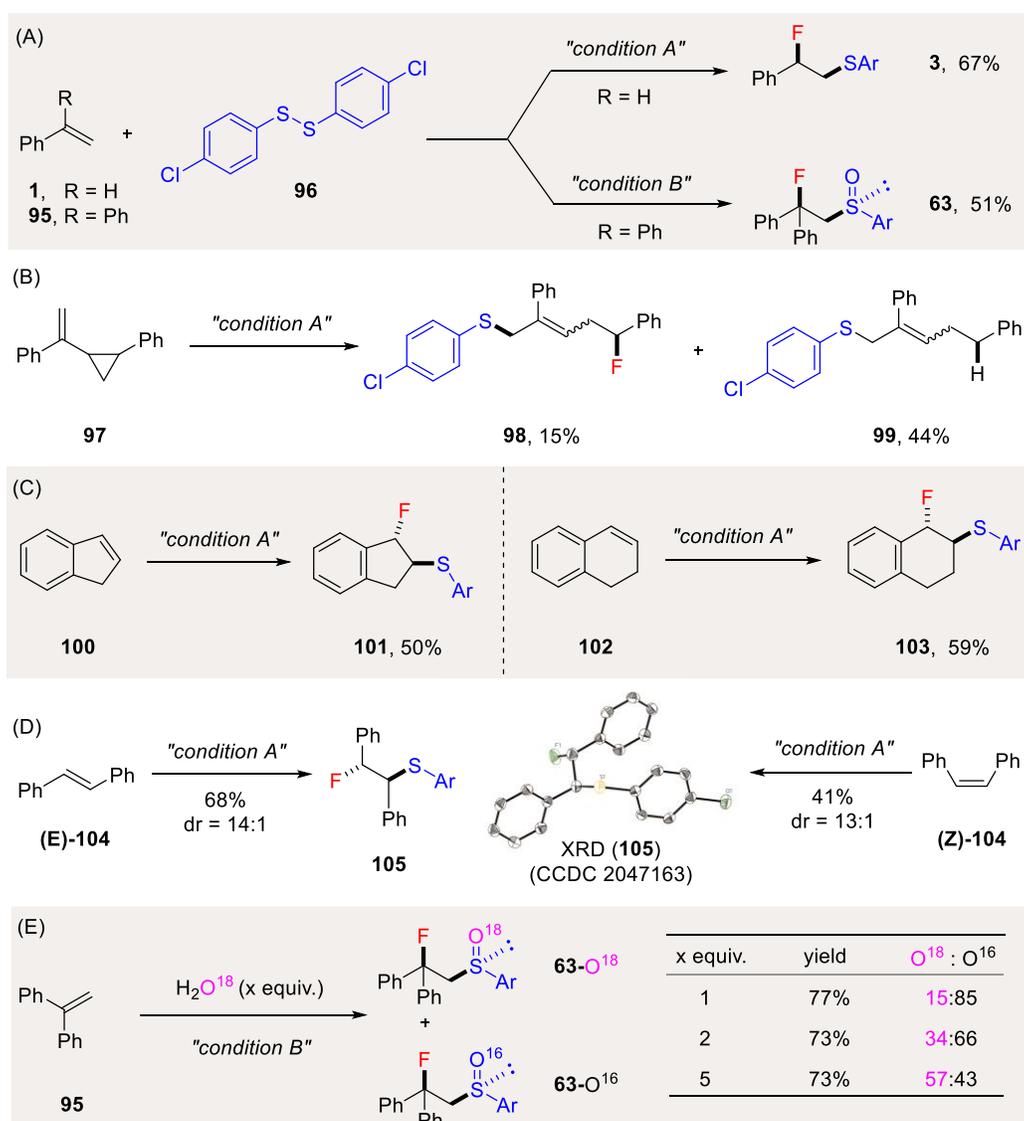
as a pair of diastereoisomers since two stereogenic centers were generated. This reaction again was found to tolerate a diverse array of substrates, including substituted styrenes (**53–62**) and 1,1-diaryl alkenes (**63–69**). Our method was also well suited for the gram-scale preparation of the vicinal fluorosulfoxides **4** (0.77 g, 46% yield) and **63** (1.19 g, 56% yield). The structure of fluorosulfoxide **63** was unambiguously confirmed by X-ray diffraction analysis, which featured a profound sulfur-fluorine gauche effect ( $\phi_{\text{FCCS(O)}} = 50.6^\circ$ ). Furthermore, 1,1-disubstituted aryl ethylenes containing a methyl (**70** and **71**), cyano (**72**), cycloalkyl (**73** and **74**), heterocycle (**75** and **76**) group reacted to yield the desired fluorosulfoxides readily. Conjugated diene (**77**), enyne (**78**) and trisubstituted alkene (**79**) were also well tolerated. The vicinal fluorosulfoxidation of cyclic alkenes such as indene (**80**) and 1,2-dihydronaphthalene (**81**) afforded exclusively *trans*-difunctionalization products. With respect to the thiolating agents, a multitude of thiophenols (**82–87**) and alkyl (**88–91**), cyclohexyl (**92**), allyl (**93**), and benzyl (**94**) mercaptans were all able to provide various vicinal fluorosulfoxides in moderate to good yields (25%–71%). The relatively low yields of fluorosulfoxidation with aliphatic mercaptans was consistent with the observation of appreciate amounts of alkyl disulfides even after electrolysis.

### ***Mechanistic studies***

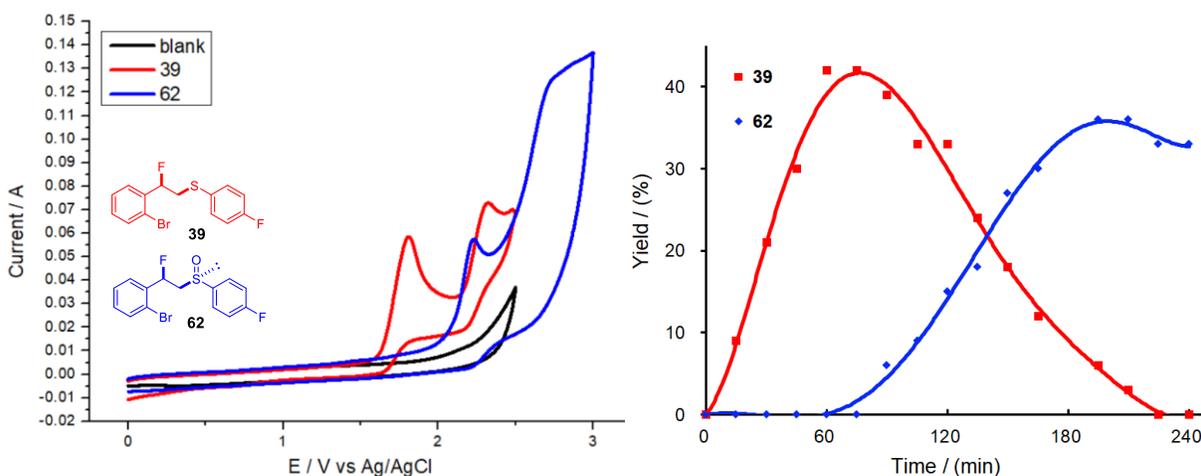
To gain some insights into the reaction mechanism, several mechanistic experiments were then conducted. Replacement of the 4-chlorothiophenol by its disulfide derivative (**96**) under standard conditions led to the desired fluorosulfide (**3**, 67%) and fluorosulfoxide (**63**, 51%) products (Scheme 2A). Consistent with this result, disulfide species were constantly observed during electrolysis, suggesting that the *in-situ*-generated disulfide might be a viable intermediate. The involvement of radical intermediates was substantiated by a radical rearrangement experiment (Scheme 2B).<sup>45</sup> Additionally, the stereospecific *trans*-fluorosulfonylation of indene (**100**) and 1,2-dihydronaphthalene (**102**) indicated that the reaction mechanism proceeded through an episulfonium ion intermediate (Scheme 2C). Interestingly, both the (*Z*)- and (*E*)-stilbenes (**104**) were transformed to fluorosulfide (**105**) with the same stereochemistry (Scheme 2D). Monitoring the reaction revealed that a facile *Z*→*E* isomerization of (*Z*)-stilbene<sup>46</sup> occurred before the anticipated fluorosulfonylation,

which was likely a thiyl-radical-mediated process.<sup>47</sup> The oxygen atoms in the sulfoxide product likely originated from the adventitious H<sub>2</sub>O in the reaction mixture<sup>48</sup> rather than O<sub>2</sub>, as a similar yield of fluorosulfoxide (**63**) was obtained under rigorously oxygen-free conditions. This was further substantiated by the O<sup>18</sup> isotope labelling experiments, which showed that the degree of O<sup>18</sup> incorporation in the fluorosulfoxide (**63**) was roughly proportional to the amount of H<sub>2</sub>O<sup>18</sup> added (Scheme 2E).<sup>49</sup>

## Scheme 2. Mechanistic Experiments



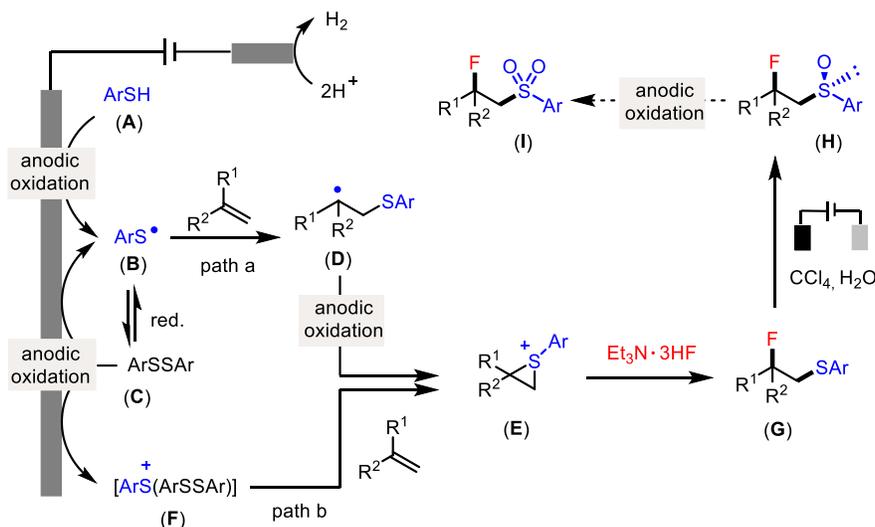
The highly selective fluorosulfonylation and fluorosulfoxidation reactions well demonstrated the unique ability of the electrosynthesis to control the reactivity *via* “dialed-in” potentials. Cyclic voltammetry studies further supported that a judicious choice of an applied potential ( $E_{cell} = 1.8$  V,  $E_{anode} = 0.99$ – $1.19$  V vs. Ag/AgCl during the electrolysis) was the key to achieving selective fluorosulfonylation without overoxidation (Figure 1, left). Additionally, sampling experiments of fluorosulfoxidation (**62**) showed that the first hour of electrolysis only led to the accumulation of fluorosulfide (**39**, Figure 1, right). Further oxidation to fluorosulfoxide (**62**) was observed thereafter along with the increase in the anodic potential (CCE at 20 mA,  $E_{anode} = 1.10$ – $1.95$  V vs. Ag/AgCl during the electrolysis).



**Figure 1** | Left: Cyclic Voltammograms of Fluorosulfide (**39**) and Fluorosulfoxide (**62**). Right: Sampling Experiments of Fluorosulfoxidation (**62**, CCE = 20 mA, condition B). Refer Supporting Information for details.

A proposed mechanism is shown in Scheme 3. Thiophenol (**A**) first underwent anodic oxidation to form a thiyl radical (**B**), which readily dimerized to disulfide (**C**).<sup>50,51</sup> This disulfide (**C**) was further oxidized anodically<sup>52</sup> to a thiyl radical (**B**) for subsequent addition to the alkene<sup>53</sup> An alternative route to this thiyl radical *via* cathode reduction of disulfide (**C**) was possible<sup>54</sup> but not requisite in line with the success of this reaction even in a divided cell (refer *Supporting Information* for details). An episulfonium ion (**E**) could then be anticipated *via* an additional oxidation event (path a). However, an alternative pathway for forming this

episulfonium ion from the reaction between the alkene and arylbis(arythio)sulfonium ion (**F**) was also possible (path b).<sup>55</sup> At this stage, nucleophilic attack of the fluoride to the episulfonium ion formed a corresponding fluorosulfide (**G**).<sup>56</sup> The oxidation state of sulfur can be further fine-tuned by applying a higher cell potential to generate fluorosulfoxide (**H**). Though the exact roles of  $\text{CCl}_4$  in this electrochemical oxidation of fluorosulfide to fluorosulfoxide still need to be investigated in detail, the reductive generated chlorospecies ( $\text{Cl}^-$  or  $\text{Cl}\cdot$ ) from  $\text{CCl}_4$  was proposed to facilitate this oxidation process.<sup>57-59</sup> Further attempts to access the fluorosulfone (**I**) with increases of the applied potential ( $E_{\text{cell}} = 2.8\text{--}3.8\text{ V}$ ), however, only led to the decomposition of the starting material.<sup>60</sup>



**Scheme 3** | *Proposed Mechanism of the Electrochemical Fluorosulfenylation and Fluorosulfoxidation*

## Conclusion

In conclusion, we developed a highly selective, applied-potential-controlled process for the vicinal fluorosulfenylation and fluorosulfoxidation of alkenes. The protocol allowed the facile preparation of a diverse array of fluorosulfides and fluorosulfoxides that are otherwise challenging to obtain. Mechanistic investigations revealed that the judicious choice of an applied potential is the key to achieving high selectivity. Such a unique feature of electrosynthesis to control the reactivity *via* “dialed-in” potentials could serve as a

conceptual inspiration for other new reaction designs. We speculated that this protocol will find broad applications for the synthesis of sulfur- and fluorine-containing molecules in the life science and materials science.

## Supporting Information

Supplemental Information is available and includes description of reaction setups, synthesis procedures, compounds characterization methods and data, spectra, cyclic voltammograms, and crystallographic information (CIF) files.

## Conflict of Interest

The authors declare no competing interests

## Funding Information

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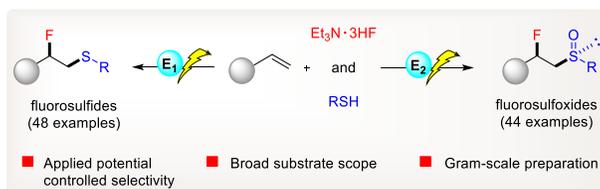
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59. However, preliminary results revealed the replacement of  $\text{CCl}_4$  by  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Bu}_4\text{NCl}$ ,  $\text{NCS}$ , or  $\text{Et}_3\text{N}\cdot\text{HCl}$  did not lead to the desired products. Mechanistic investigation on the roles of  $\text{CCl}_4$  is currently undergoing in our lab aiming to use a greener chemical with similar effects on this oxidation step.
60. Chemical oxidation of fluorosulfoxides to fluorosulfones were readily achieved, see *Supporting Information* for details.

## Table of Contents Graphic (required)



A highly selective electrochemical process for the vicinal fluorosulfenylation and fluorosulfoxidation reactions of alkenes has been developed. The precise control of the oxidation state of sulfur moieties were enabled by the unique ability of electrosynthesis to dial in potentials on demand.