Photo-Electrochemical Geminal α-Fluorosulfenylation of Diazo Compounds through Carbene Radical Anion Intermediate

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Abstract

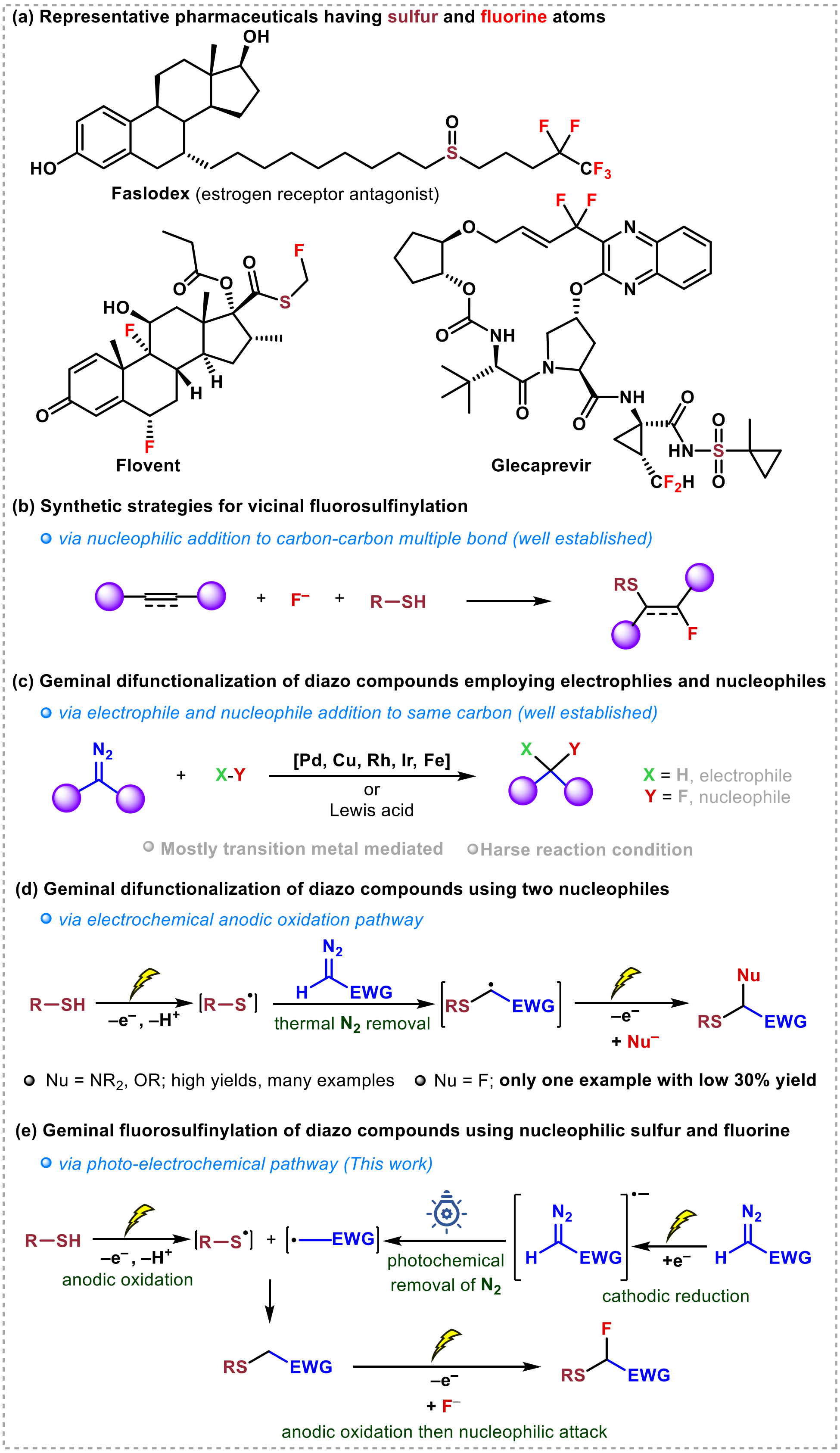
α-Fluorosulfenyl compounds are privileged building blocks found in pharmaceuticals and agrochemicals. While the geminal difunctionalization of diazo compounds with two different nucleophiles under mild and sustainable conditions could be envisioned as a versatile method for constructing α-fluorosulfinyl molecules, it remains a significant unmet challenge. Herein, we present geminal α,α'-difunctionalization of diazo compounds by merging photo- and electro-catalysis. A wide range of α-fluorosulfinyl products were synthesized using commercial ionic liquid as a fluorine source with moderate to good yields and excellent selectivities. Several experiments were performed to detail the reaction mechanism and elucidate the cooperativity of photo- and electro-catalysis in facilitating the reaction under milder conditions.

Introduction

Molecules containing both fluorine and sulfur atoms have found widespread application in material science,[1-3] agrochemicals,[4] and drug design.[5, 6] For example, there are many pharmaceutical drug molecules such as Faslodex,[7] Flovent,[8] and Glecaprevir[9] whose activity is largely controlled by sulfur and fluorine, both atoms present in the drug (Scheme 1a). Moreover, the incorporation of fluorine atoms into biologically active molecules is well documented, and at the present date, approximately 25% of pharmaceutical drugs contain at least one fluorine atom.[10, 11] ^{18}F-containing organic molecules are also used as radiotracers for positron emission tomography in clinical pharmaceutical research and diagnostic medicine.[12]

Accordingly, because of these multifaceted applications, installing these two heteroatom-containing nucleophilic functional groups in a molecule under mild reaction conditions has always been in high demand. Among the available tools for accessing fluorosulfenyl compounds, the sequential addition of sulfur and fluorine atoms to unsaturated carbon-carbon bonds consists of one major protocol (Scheme 1b).[13-20] However, most of these excellent developed methods for fluorosulfenylation were in a vicinal manner. On the other hand, methods for the geminal fluorosulfenylation of two nucleophilic fluorine and sulfur atoms containing functional groups remain challenging.

Due to the amphiphilic nature of the diazo compound, two different functional groups can be easily introduced to the carbon of the diazo compound to access the advanced structure from a simple starting material.[21-23] In the last two decades, geminal difunctionalization of the diazo compound was much explored by using transition metal catalysts and different Lewis acid catalysis (Scheme 1c).[21, 24-29] In most cases, the difunctionalization of diazo compounds takes place with one electrophilic and another nucleophilic functional group. The methods for geminal difunctionalization of the diazo compound with two different nucleophilic heteroatoms have not been well studied. In this regard, in a seminal report, Yang et al. disclosed the difunctionalization of the diazo compound with two different nucleophiles under electrochemical conditions, where thermal dissociation of dinitrogen generated the key carbene intermediate (Scheme 1d).[30] However, while this method enabled the incorporation of diverse nucleophiles, the simultaneous incorporation of fluorine and sulfur gave a low yield for the single example studied.



Scheme 1 (a) Representative pharmaceuticals having sulfur and fluorine atoms; (b) Synthetic strategies for vicinal fluorosulfinylation; (c) Geminal difunctionalization of diazo compounds employing electrophiles and nucleophiles; (d) Geminal difunctionalization of diazo compounds using two nucleophiles. (e) Geminal fluorosulfinylation of diazo compounds using nucleophilic sulfur and fluorine (This work).

In the past decades, electrochemistry and photochemistry have attracted a renewed and uprising interest in organic synthesis.[31-36] Various challenging transformations through an entirely different mechanistic pathway can be accomplished by merging electrochemistry and photochemistry, where electrons and photons could be used as reagents for driving challenging organic reactions under green and sustainable conditions.[37, 38]

In this context, we envisioned two possible pathways for geminal difunctionalization of the diazo compound under electro-photochemical conditions (Scheme 1e). (a) Pathway A: A carbene, generated from the diazo compound upon the dinitrogen at room temperature under light irradiation,[23] could undergo insertion with thiophenol. Two single electron oxidations of the in situ generated thioether intermediate under electrochemical conditions followed by nucleophilic addition fluorides can give the difunctionalized product. (b) Pathway B: Under combined electro-photochemical conditions, the diazo compound may undergo cathodic reduction followed by dinitrogen removal and protonation to form a stabilized alkyl radical through a carbene radical anion. The alkyl radical could then couple with the thiolate radical to form a thioether upon single electron oxidation at the anode surface. Two subsequent single-electron oxidations of the resulting thioether at the anode will form the sulfonium ion, which will be intercepted by fluoride to give respective geminal difunctionalized products.

In an effort to advance the field of electro-photochemistry for the geminal difunctionalization of diazo compounds under green and sustainable conditions, we report a novel method for the regioselective monofluorination of diazo compounds to synthesize fluorosulfenyl compounds. This innovative electro-photochemical approach has been successfully applied to gram-scale synthesis, enabling the late-stage fluorination of biologically relevant diazo compounds. The proposed mechanism for electro-photochemical geminal fluorosulfenylation is supported by control experiments and cyclic voltammetric studies, providing a robust foundation for this sustainable and efficient transformation.

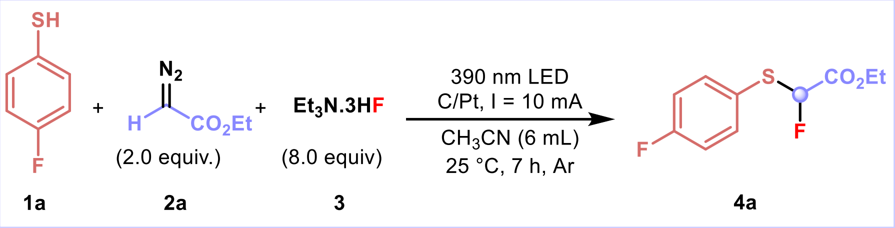
Results and discussion

We initiated our studies using 4-fluorothiophenol (**1a**) and ethyldiazoacetate (**2a**) as model substrates and the commercially available ionic liquid salt triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$, **3**) as fluorine source (Tables 1, S5.1-5.6). The target product ethyl 2-fluoro-2-((4-fluorophenyl)thio)acetate **4a** was obtained with 25% yield when the reaction was performed in an undivided cell equipped with a graphite plate as anode and platinum plate as cathode, under 10 mA constant current electrolysis in bottle-grade acetonitrile solvent in the presence of $^{n}Bu_4NBF_4$ as a supporting electrolyte at 25 °C under argon atmosphere (Table 1, entry 1).

According to our hypothesis, when we performed our same electrochemical reaction under irradiation of 12 W white LEDs, the product yield was increased to 73% (Table 1, entry 2). After that, to specify the wavelength of the light and improve product yield, we verified several commercial blue LEDs with narrow wavelength distribution (Table 1, entries 3-5, Table S5.1). The optimum yield of **4a** was obtained in the presence of 390 nm blue light irradiation along with other electrochemical conditions (Table 1, entry 3). Several commonly used electrodes (such as graphite plate, graphite felt, RVC, Pt, Ni plate, and Ni-foam) were tested as cathode and anode (Table 1, entries 6-7, Table S5.2). When we used graphite plate as cathode instead of Pt or Pt as anode instead of graphite plate, we observed a deleterious effect on the yield of **4a** in both cases.

Decreasing the constant current to 5 mA or increasing the constant current to 15 mA afforded the product with a low yield (Table 1, entry 8, Table S5.3). Among the commonly used supporting electrolytes, including $LiClO_4$, Et_4NBF_4, $^{n}Bu_4NBr$, $^{n}Bu_4NI$, $^{n}Bu_4NBF_4$, and $^{n}Bu_4NPF_6$, only $^{n}Bu_4NBF_4$ gave a promising yield (Table 1, entry 9, Table 5.4). We found that without electricity, no targeted product was formed; instead, we isolated ~ 5% of unwanted thioether product, and most of the starting material remained as such (entry 10). The reaction was also found to be sensitive to the solvents used (Table 1, entry 11, Table S5.3). Except for wet acetonitrile, other commonly used solvents gave a poor yield of **4a**.

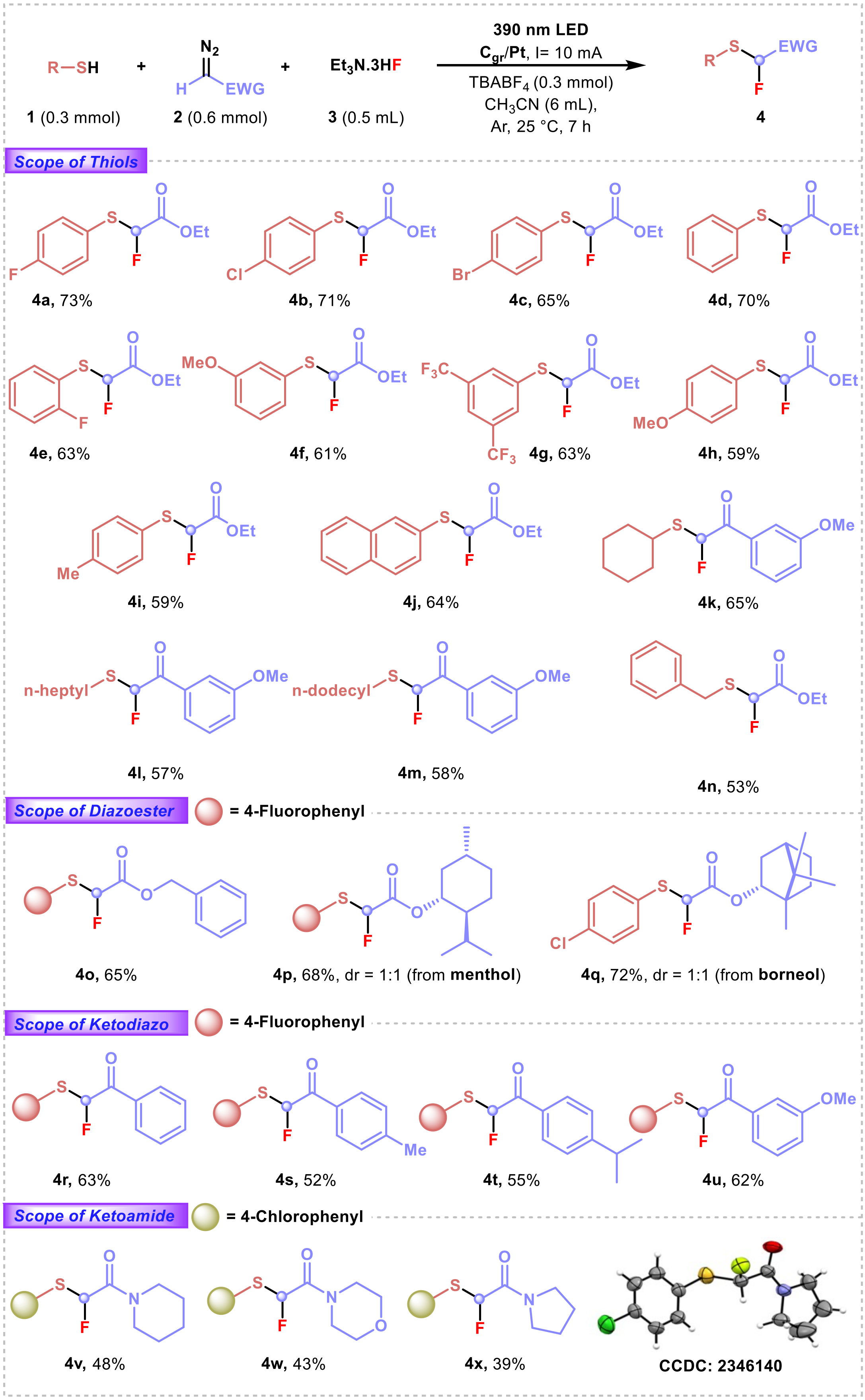
Table 1 Optimization of electro-photochemical fluorosulfinylation.[a]



Entry	Deviation from the above conditions	Yield (%)
1	Without light	25
	Light source	
2	white LED, 12W instead of 390 nm, 34 W	73
3	none	78 (73)
4	405 nm, 2 × 5 W instead of 390 nm, 34 W	68
5	427 nm, 34 W instead of 390 nm, 34 W	41
	Electrochemical parameters	
6	C_{gr}-plate or Ni-plate or Ni-foam instead of Pt-plate as cathode	18/55/51
7	Pt-plate or RVC or graphite felt instead of C_{gr}-plate as anode	15/58/65
8	5 mA or 8mA or 15 mA instead of 10 mA constant current	12/35/54
9	Et_4BF_4 or $LiClO_4$ or $^nBu_4NBr$ or $^nBu_4NPF_6$ instead of $^nBu_4NBF_4$ as supporting electrolyte	55/57/32/58
10	No electricity	0
	solvent	
11	or DCE or DME or DMF instead of wet CH_3CN as the solvent	34/32/35/5

[a]**Reaction conditions**: Undivided cell, Graphite plate (C_{gr}-plate, 5.0 × 0.8 × 0.2 cm) anode, platinum-plate (5.0 × 0.8 × 0.01 cm) cathode, **1a** (0.3 mmol), **2a** (0.6 mmol), **3** (0.5 mL), wet MeCN (6 mL), $^nBu_4NBF_4$ (0.3 mmol), 10 mA, 390 nm LED (34 W), 7 h at 15 °C. All yields were determined by GC-FID using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in the parenthesis. [b]Thiol insertion product formed ~ 5%.

With the optimal reaction conditions, we first investigated the scope of the reaction (Scheme 2). Initially, the scope of the thiol was tested. Various aromatic thiols with different electron-donating and withdrawing functional groups underwent smooth geminal fluorosulfinylation reactions to yield the corresponding products with moderate to good yield. Aromatic thiols containing different halogen atoms (fluoro, chloro, and bromo) at the *p*-position were well tolerated to deliver product **4a-c** with good 65-73% yields. Thiophenol was also an amenable substrate, affording the desired product **4d** with a promising 70% yield. Aromatic thiophenols containing *o*-F and the *m*-methoxy group delivered the products **4e** and **4f** with 63 and 61% yields, respectively. Moreover, strongly electron-withdrawing 3,5-trifluoromethyl and electron-donating *m*-methoxy and *m*-methyl functional groups containing aromatic thiols were also compatible, delivering the desired products **4g-i** with moderate to good yields. 2-Naphthyl thiol was also a suitable substrate for the reaction, providing **4j** in 64% yield. We also investigate the compatibility of different aliphatic thiols, including cyclohexyl, *n*-heptyl, *n*-dodecyl, and benzyl thiol, to the standard reaction conditions, delivering the desired products **4k-n** with 53-65% yields.



Scheme 2 Scope of electrophotochemical fluorosulfinylation of diazo compounds. Reaction conditions: Table 1, entry 3.

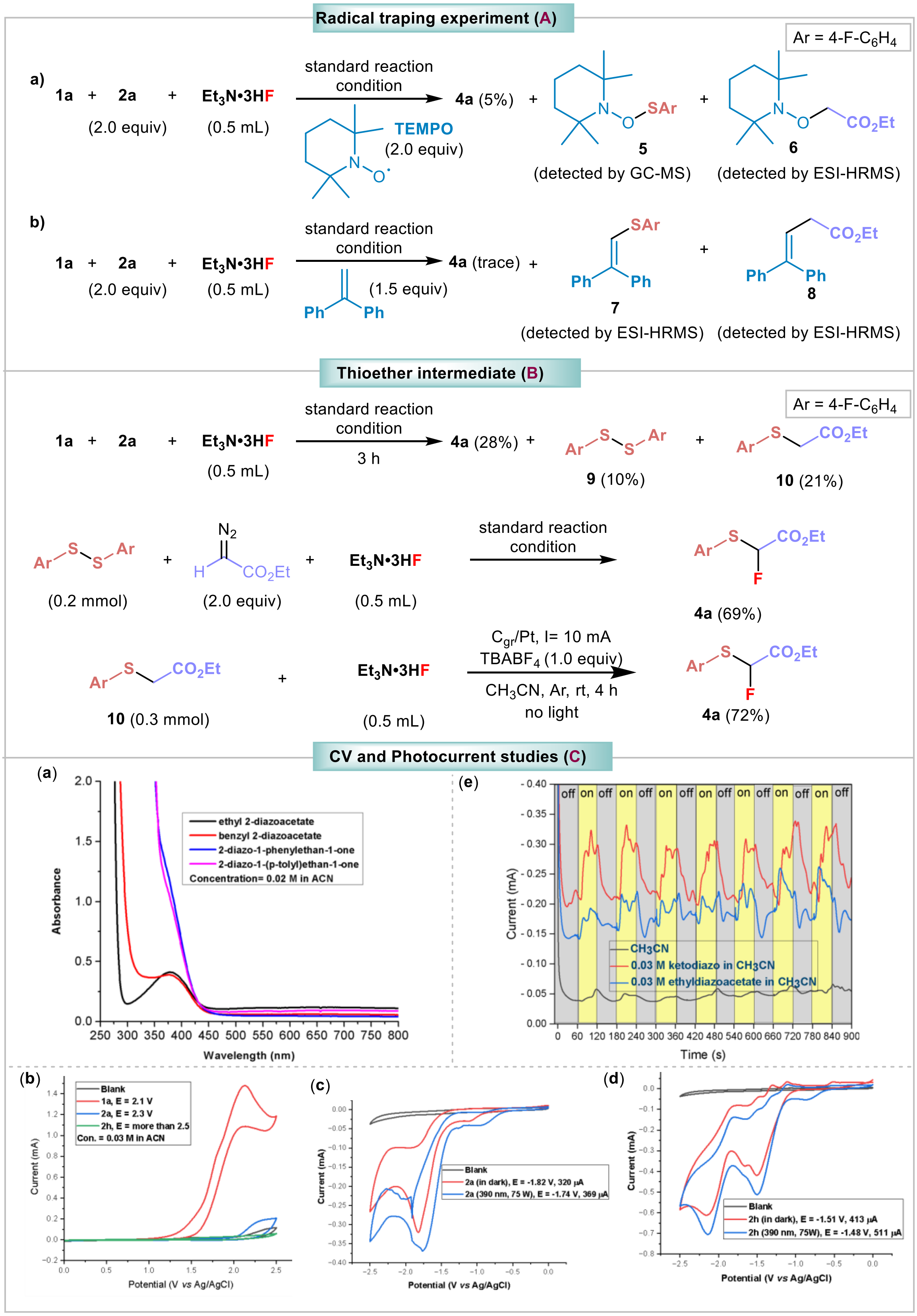
Next, the scope of different diazoester derivatives was evaluated. Diazoester derived from benzyl alcohol, menthol, and borneol underwent the reaction smoothly, providing corresponding products **4o-q** with good 65-72% yields. Further, we investigated the reactivity of different diazoketone derivatives under these conditions. The α-fluoro-α'-thio ketones **4r-u** were isolated in 52-63% yields. Gratifyingly, different diazoamides were also compatible with this photo-electrochemical fluorosulfinylation protocol, affording corresponding products **4v-x** with moderate 39-48% yields. The structure of **4x** was confirmed by single-crystal X-ray diffractometry.[39]

Various control experiments were conducted to gain insights into the reaction mechanism (Scheme 3). The desired product yield was suppressed when 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was used as a radical trapper under the standard reaction conditions (Scheme 3Aa). We detected the TEMPO adducts **5** and **6** by GC-MS and ESI-HRMS analysis. Further, when we added 1,1-diphenylethyele as a radical scavenger, we encountered products **7** (detected by ESI-HRMS) and **8** (detected by ESI-HRMS) (Scheme 3Ab). Both these experiments supported the existence of a thiyl radical and an acceptor-stabilized alkyl radical during the course of the reaction.

We envisioned that thiyl radical could dimerize to a disulfide **9**. In parallel, the radical thiyl radical could undergo cross-coupling with the stabilized alkyl radical and form the thioether **10**. When we quenched the reaction after 3h, along with product **4a**, the disulfide **9** and the thioether **10** were isolated (Scheme 3Ba). Using the disulfide **9** as the sulfur source produced the product **4a** with a 69% yield under the same conditions (Scheme 3Bb). Furthermore, when we treated thioether **10** with $Et_3N\cdot 3HF$ under standard electrochemical conditions (in the absence of light), we obtained the product **4a** with 72% yield. (Scheme 3Bc) The high yield of **4a** from thioether **10** under electrochemical conditions suggested that thioether might be an intermediate in our reaction and that conversion of **10** to the product **4a** does not need light assistance.

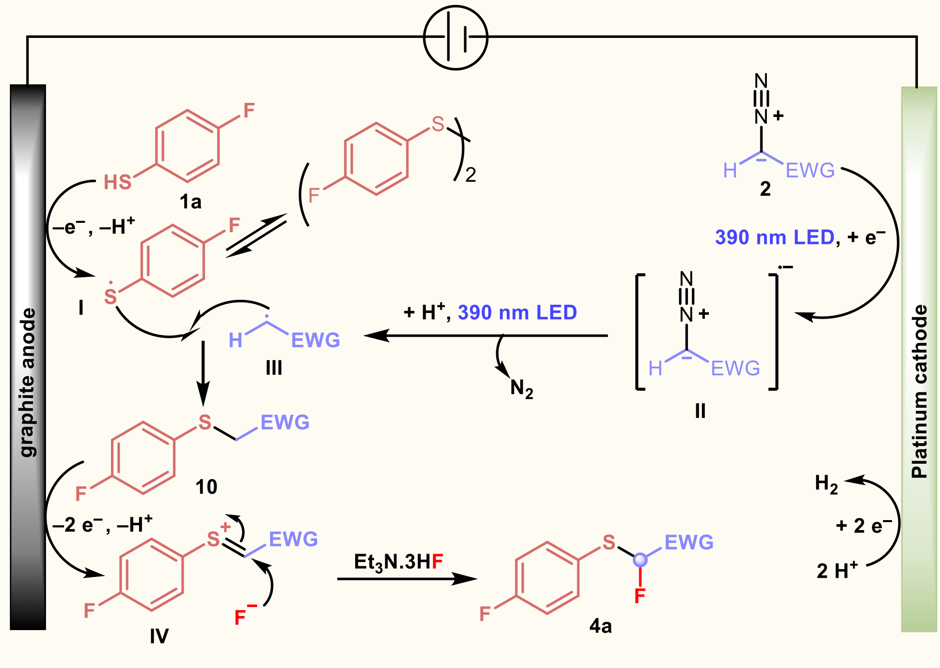
Furthermore, during optimization studies (Table 1, entries 1-3), we observed product yield enhancement under light irradiation. Further, to investigate the role of light, we recorded the UV-Vis spectra of diazo-compounds **2a**, **2b**, **2h**, and **2i** (Scheme 3Ca). We found that all these diazo-compounds have significant absorption in the 300 nm to 450 nm region. Then, we studied the cyclic voltammetry (CV) of ethyldiazoacetate (**2a**) and 2-diazo-1-phenylethan-1-one (**2h**) in the presence and absence of light to understand the effect of light on their electrochemical behavior (Scheme 3C and see the ESI for details). For the **1a**, we observed an oxidation peak at 2.1 V (*vs* Ag/AgCl) (Scheme 3Cb). On the other hand, for **2a** and **2h**, we observed the oxidation peaks above 2.5 V (*vs* Ag/AgCl). These clearly indicated preferential anodic oxidation of **1a** over the diazo-compounds. Moreover, we measured the reduction potential of **1a** and the diazo-compounds **2a** and **2h** and observed that **1a** does not reduce up to 2.5 V. The reduction peak at –1.82 V (*vs* Ag/AgCl) for **2a** and –1.51 V and –2.1 V (*vs* Ag/AgCl) for **2h** were located (Schemes 3Cc, 3Cd). These indicated a preferential reduction of diazo-compounds over thiophenol. We then repeated the electrochemical measurements in the presence of 390 nm light irradiation. We observed an increase in reduction current and a shift in the reduction peak potential toward less negative values (at –1.74 V for **2a** and –1.48 V for **2h** (*vs* Ag/AgCl under 390 nm irradiation). These indicated that the reduction of the diazo-compound is facilitated under light irradiation.

Additionally, we conducted photocurrent response measurements by toggling 390 nm LED light on and off at 2.0 V (vs Ag/AgCl) (Scheme 3Ce). We observed a significant increase in reduction current when the light was on, confirming the critical role of light irradiation in the reaction mechanism. It suggested that light irradiation facilitates the generation of alkyl radicals through cathodic reduction of the diazo-compound, followed by dinitrogen elimination and protonation. This insight underscores the synergistic interplay between light and electrochemical processes, enabling the geminal difunctionalization of diazo compounds using fluoride and thiol nucleophiles at milder conditions at room temperature.



Scheme 3 (A) Radical trapping experiments. (B) Thioether intermediate detection and conversion to final product under electrochemical conditions. (C) Cyclic voltammetry (CV) studies and photocurrent measurement.

Based on the control experiments, cyclic voltammetry studies, photocurrent measurements, and prior literature, we propose the mechanism outlined in Scheme 4. Under a constant current, the thiophenol **1a** undergoes anodic oxidation. The generated a thiyl radical **I** can either dimerize to disulfide **9** or participate in coupling with other persistent radical species. The disulfide **9** remains in equilibrium with the thiyl radical **I** under electro-photochemical conditions. Simultaneously, diazo compounds are converted to alkyl radical **III** under light irradiation and electrochemical bias via a radical anion intermediate **II**. The coupling of the thiyl radical **II** and alkyl radical **III** formed the thioether intermediate **10**. Subsequent anodic oxidation of **10** generates a sulfonium ion intermediate **IV**, which undergoes nucleophilic attack by fluoride ions to yield the desired product **4a**.



Scheme 4 Proposed mechanism of the electro-photochemical fluorosulfinylation reaction.

Conclusions

In conclusion, we have established a mild and sustainable photo-electrochemical protocol for the geminal difunctionalization of diazo compounds using two distinct nucleophiles: fluoride and thiols. This work highlights the critical role of light irradiation in facilitating the electrochemical reduction of diazo compounds to generate reactive radical species. Cyclic voltammetry studies conducted both with and without light irradiation and photocurrent experiments confirmed the formation of a carbene radical anion intermediate. This method demonstrates broad substrate compatibility, accommodating a wide range of diazoesters, diazoketones, and diazoamides, and delivers the desired products in good yields. We anticipate that this innovative approach, leveraging the synergistic effects of photo- and electrochemistry to generate alkyl radicals from diazo compounds, will inspire the development of new photo-electrochemical reactions with diverse diazo derivatives in the future.

Author Contributions

RM and BM conceived and directed the project. RM performed all the experiments. Both authors contribute to the discussion of the results, the manuscript, and the supplemental material preparation.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability

All the data supporting this manuscript have been included as part of the Supplementary Information.

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39. Deposition number 2346140 for 4x contains the supplementary crystallographic data for this paper.