A practical fluorosulfonylating platform via photocatalytic imidazolium-based SO$_2$F radical reagent

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Sulfonyl fluorides are key components in the fields of chemical biology, materials science and drug discovery. In this line, the highly active SO$_2$F radical has been employed for the construction of sulfonyl fluorides, but the utilization of gaseous ClSO$_2$F as radical precursor is limited due to the tedious and hazardous preparation. Meanwhile, the synthesis of sulfonyl fluorides from inert SO$_2$F$_2$ gas through a fluorosulfonyl radical (·SO$_2$F) process has met with inevitable difficulties due to the high homolytic bond dissociation energy of the S(VI)-F bond. Here we report a radical fluorosulfonylation strategy for the stereoselective synthesis of alkenyl sulfonyl fluorides and functional alkyl sulfonyl fluorides with an air-stable crystalline benzimidazolium fluorosulfonate cationic salt reagent. This bench-stable redox-active reagent offers a useful and operational protocol for the radical fluorosulfonylation of unsaturated hydrocarbons with good yield and high stereoselectivity, which can be further transformed into valuable functional SO$_2$F moieties.
The sulfur(VI) fluoride exchange (SuFEx) chemistry that relies on the unique reactivity–stability balance of high-valent organosulfur has emerged as a promising topic for the next-generation click reaction. Sulfonyl fluorides as the most widely used connective hubs of SuFEx click reaction have attracted enormous attention and find widespread applications in the fields of chemical biology, drug discovery, and materials science. Methods have been developed for rapid construction of sulfonyl fluoride moieties, including the chloride-fluoride exchange of sulfonyl chlorides, $SO_2$ insertion/fluorination, electrophilic fluorination of thiols and anodic oxidative fluorination. Compared with the above-mentioned S-F bond formation, direct fluorosulfonylation would provide a concise and redox economic approach for C-SO₂F bond formation. The sulfonyl fluoride building-blocks, including alkynylsulfonyl fluoride (SASE), ethanesulfonyl fluoride (ESF), 1-bromoethene-1-sulfonyl fluoride (BESF) were used to access functionalized sulfonyl fluorides. The highly active SO₂F radical has been recognized as unstable and inaccessible precursor until the observation of this species (from the decomposition of fluorosulfonyl azide) in the recent progress of photoinduced radical fluorosulfonylation using gaseous ClSO₂F₃. However, the application of N₂SO₂F and ClSO₂F were limited by tedious and hazardous preparation. Sulfuryl fluoride (SO₂F₂) as abundant inflammable industrial feedstock could serve as economic sulfonyl fluoride source. Sulfuryl fluoride derived fluorosulfonylation reagents are mainly electrophilic “FSO₂⁺·” synths and have been employed for direct functionalization of different nucloephiles including organometallic reagents, phenols, amines, etc. However, the construction of diversified sulfonyl fluoride compounds was limited by single electrophilic reaction pattern and hindered multifunctionalization of SO₂F₂ and derivatives. In contrast, adopting a radical synthesis strategy can overcome the limitations of electrophilic fluorosulfonylation and expand the scope of application of sulfonyl fluoride. However, the generation of fluorosulfonyl radical (SO₂F·) from inert SO₂F₂ gas has met with inevitable difficulties due to the relatively small magnetic/quadrupole moments and the high homolytic bond dissociation energy of the S(VI)-F bond (BDE = 90.5 ± 4.3 kcal/mol). Thus, the development of single electron transfer (SET) process of SO₂F₂ for radical fluorosulfonylation represents great challenge and in high demand.

A practical procedure for the bench-stable redox-active SO₂F· agent from inexpensive fluorine source would provide appropriate solution to the long-standing issue of radical fluoro-sulfonylation. The imidazolidin-1-sulfonyl cationic salt that developed in our lab has been successfully applied for the activation of triflic acid and arylosulfonates to access SO₂CF₂ and ArS-radicals. We speculated that the cationic benzinidazole salt could harness the highly electrophilic SO₂F· to forge a bench-stable redox-active (Het)N-SO₂F· reagent. The positive charge of the resulting benzinidazolium fluorosulfonate can be delocalized on both nitrogens. By the homolytic cleavage of the weak N–S bond (BDE ≈ 70 kcal/mol), this cationic complex undergoes SET process to generate fluorosulfonyl radical. In this work, we synthesize a series of highly reactive radical fluorosulfonylation reagents IMSF (2a–2e), practical and air-stable crystalline salts for a sequential radical stereoselective fluorosulfonylation, hydrofluorosulfonylation and migratory SO₆F-difunctionalization of unsaturated hydrocarbon to construct a variety of functionalized sulfonyl fluoride compounds.

Results

Reaction optimization. Our study began with N-methyl-N-(1-phenylvinyl)acetamide (1a) as the model substrate (Table 1). After extensive screening of conditions, we found that when using 2 equivalents of benzoimidazolium sulfonate reagent (IMSF, 2a, $E_{1/2}^{red} = –1.07 \text{ V vs SCE}$), 2 mol% of 4CzIPN, 2.5 equivalents of KH₂PO₄ in DME (1 mL) under the irradiation of 60 W blue LEDs, the alkyl sulfonyl fluoride product 3a could be obtained in 62% yield with >20:1 $E/S$ ratio. Different benzoimidazolium sulfonyl fluoride 2b–2e were then examined (Table 1). When imidazolium sulfonate reagent 2b were used, the yield of 3a was obtained in 71% yield and isolated yield is 65% (entry 2). Other arylimidazazole heterocycle with electron withdrawing groups derived IMSF salts 2c and 2d furnished alkyl sulfonyl fluoride 3a in 58% and 64% yield, respectively (entries 3 and 4). The cationic reagent 2e resulted in a lower conversion under irradiation, which may due to the relatively high negative reduction potential (entry 5). When IR(pppy)₃ instead of 4CzIPN as photocatalyst, the yield of product 3a was slightly reduced (entry 6). When using other reaction solvents (Supplementary Table S1), the yield of desired product 3a has significantly decreased and obtained in a low yield (entry 7). The yield of alkyl sulfonyl fluoride was reduced in the absence of KH₂PO₄ because of the hindered α-hydrogen elimination process (entry 8). In addition, control experiments suggested that photocatalyst, and light irradiation are all crucial to the reaction (entries 9–10).

Substrate scope with respect to the radical alkyl sulfonyl fluoride reaction. With the optimized reaction conditions in hand, we next examined the generality of this transformation with different alkenes. Using 2 mol% of 4CzIPN, IMSF salt 2b (2.0 equiv), and KH₂PO₄ (2.5 equiv) at ambient temperature, a range of alkenes underwent radical fluorosulfonylation with high efficiency. As shown in Fig. 2, 1,1-disubstituted alkenes with methyl, aryl, ester, amide groups afforded the desired products (3a–3i) in moderate to good yields with high regio- and stereo-selectivity ($E/Z > 20:1$). Styrene with different substituents including halides, alkyl, ester afforded the desired products (3n–3r, 3v) in moderate to excellent yields and high regio- and stereo-selectivity ($E/Z > 20:1$). In addition, 1,2-dihydropyridine (3s), 2-vinylpyridine (3t), 2-vinlypyridine (3u) could all be smoothly fluorosulfonylated with FSO₂ radical. Moreover, natural products derivatized olefin involving cholesterol and estrone could also be tolerated under the mild photolytic conditions and obtained the corresponding alkyn sulfonyl fluoride in moderate yields. The selective preparation of E-alkenyl sulfonyl fluoride has been readily accessible. Then we try to control the reaction conditions to achieve the synthesis of thermodynamically less favorable Z-alkenyl sulfonyl fluoride. By variation of the reaction conditions (see Supplementary Table S5), we have extended this radical fluorosulfonylation protocol to achieve Z-alkenyl sulfonyl fluoride. Styrene with different substituents including halides, alkyl group afforded the desired products (4b–4e, 4f–4g) in moderate to good yields. Bioactive DL-menthol and bezetorone derived alkenes could afford the desired alkyn sulfonyl fluoride in moderate yields (4h–4i).

Substrate scope with respect to the radical hydro-fluorosulfonylation reaction. The late stage functionalization of sulfonyl fluoride has been unearthed by Sharpless lab in 2014 with the development of SuFEx chemistry. Along this line, this radical fluorosulfonylation protocol was applied to the late-stage modification of complex molecules. Using 2 mol% of the iridium catalyst, 1,4-cyclohexadiene as hydrogen donor (1.5 equiv), and IMSF salt 2 (2.0 equiv) at ambient temperature, unactivated terminal alkenes underwent a radical fluorosulfonylation process to product corresponding alkylsulfonyl fluoride with good regioselectivity (Fig. 3). Terminal alkenes bearing amide and ester functionalities obtained the desired alkylsulfonyl fluorides in...
moderate to good yields (6a-6c, 6e, 6f, 6h-6k). Oxyalkyl-substituted alkenes also furnished the corresponding SO$_2$F adducts (6g). In addition, IMSF reagent 2a were employed in intramolecular cyclization process with diallyl sulphonamides to afford the corresponding sulfonyl fluoride product (6d).

Substrate scope with respect to migration fluorosulfonylation reaction. With slight variation of the optimized conditions, we expanded the scope of this radical fluorosulfonylation protocol to difunctionalization of unsaturated olefins. Using a heteroaryl-substituted unsaturated tertiary alcohol, the distal migration induced by fluorosulfonyl radical proceeded smoothly in a chemoselective fashion. Fluorosulfonyl radical were susceptible to the reaction conditions for achieving the corresponding ketones in good to excellent yields (Fig. 4). The aryl groups with different electronic and steric characters were tolerated (8a-8b). Thiophene and furan functionalities could be compatible under the mild condition (8c-8d). Linear or cyclic alkyl substituted unsaturated tertiary alcohols could also get the difunctionalized sulfonyl fluoride products (8f-8h). Noteworthy, the distal migration cyanation of unsaturated tertiary alcohol mediated by SO$_2$F radical also proceeded smoothly to afford desired product in good yield. The aryl group with electron donating and electron withdrawing groups and furan can afford the desired products (8j-8l) in good yields.

Synthetic applications and mechanistic studies. The utility of the products with sulfonyl fluoride group was demonstrated (Fig. 5a–e). In the presence of NaHCO$_3$ and DBU, alkynylsulfonyl fluoride 3m can easily react with pyrazolone 9 to afford the sulfone product 10 in 50% yield. In addition, sulfonyl fluoride 3m can also efficiently react with 1,3-cyclohexanedione 11 to generate the sultone 12 (Fig. 5a). It is well known that sulfonyl fluoride species can readily undergo various SuFEx reactions to connect other molecules. Several SuFEx reactions of selective modifying the hydroxyl site of drugs were implemented. We tentatively tried the ligation of styrenesulfonyl fluoride 3m with estrone 13, which can afford the desired product 14 in 60% yield (Fig. 5b). Then the ligation of lumacator intermediate derivative (6i) and vitamin E (15) reacted smoothly to furnish the desired product 16 in good yield (Fig. 5c).

To gain insight into this reaction, several mechanistic experiments have been carried out. The radical trapping experiment using 2 equiv. of TEMPO resulted in the inhibition of the radical addition. Instead, TEMPO adduct 17 was detected

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**Table 1 Optimization of the reaction conditions.**

| Entry | Variation from the conditions | Yield of 3a/% | E/Z of 3a |
|-------|-----------------------------|---------------|----------|
| 1     | None                        | 62            | >20:1    |
| 2     | 2b instead of 2a            | 71 (65)       | >20:1    |
| 3     | 2c instead of 2a            | 58            | >20:1    |
| 4     | 2d instead of 2a            | 64            | >20:1    |
| 5     | 2e instead of 2a            | 16            | >20:1    |
| 6     | Ir(ppy)$_3$ instead         | 59            | >20:1    |
| 7     | of 4CzIPN                   | 0-41%         | >20:1    |
| 8     | w/o KH$_2$PO$_4$            | 45            | >20:1    |
| 9     | w/o 4CzIPN                 | 0             | —        |
| 10    | In the darkness             | 0             | —        |

* Yield determined by gas chromatography (GC) using dodecane as an internal standard. The Z/E ratio was determined by $^1$H NMR and GC. *Isolated yield.

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**Fig. 1 Origin of the reaction design. a** The activation of SO$_2$F$_2$ for electrophilic and radical fluorosulfonylation. **b** The design and synthesis of benzimidazolium triflate derived IMSF reagent. **c** This chemistry: Cationic IMSF reagent for radical fluorosulfonylation of alkenes.
in HRMS (Fig. 5d). The radical clock experiment was carried out using cyclopropyl styrene I. Under the standard conditions with MgCl2 additive, the ring-opened product 19 can be obtained in 11% isolated yield (Fig. 5e). Thus, fluorosulfonyl radical (SO₂F) intermediates are possibly involved in reaction. In addition, the treatment of E-alkenylsulfonyl fluoride 3n with iridium catalyst in the absence of IMSF reagent furnished the Z-alkenylsulfonyl fluoride 4c in 43% yield and recovered 3n in 48% yield (Fig. 5f). This control experiment showed that the generation of Z-alkenylsulfonyl fluoride probably underwent an olefin isomerization process.36

**Discussion**

In summary, we have described an air-stable redox-active imidazolium fluorosulfonate reagent IMSF. A key design feature of this radical fluorosulfonylating reagent is the cationic nature, which favors the stepwise formation of fluorosulfonyl radical (SO₂F) via a SET reduction process under photocatalytic conditions. This SO₂F radical reservoir could react with various alkenes to produce alkenyl sulfonfonyl fluoride, alkylsulfonyl fluoride, and migratory fluorosulfonylating products. Further studies of this highly reactive and air-stable solid reagent are underway in our laboratory.
Fig. 3 Substrate scope of the radical hydrofluorosulfonylation. All reactions were carried out with olefins 5 (0.10 mmol), IMSF salt 2 (0.20 mmol, 2.0 equiv), fac-Ir(d-F-(p-t-Bu)ppy)_3 (2 mol%) and cyclohexa-1,4-diene (1.5 equiv) in 2-methyltetrahydrofuran:Acetone = 9:1 (1 mL) under Ar and 60 W blue LEDs. a.IMSF reagent 2a was used. b.IMSF reagent 2b was used.

Fig. 4 Substrate scope of radical migration fluorosulfonylation. All reactions were carried out with alkenes 7 (0.10 mmol), IMSF salt 2a (0.20 mmol, 2.0 equiv.), fac-Ir(d-F-(p-t-Bu)ppy)_3 (2 mol%) in DME:EA = 4:1 (1.0 mL) under Ar and 60 W blue LEDs about 12 h.
**Methods**

**General procedure for the synthesis of sulfonyl fluoride imidazolium salt reagent 2.** Sodium hydride (60% dispersion in mineral oil) (36 mmol, 1.2 equiv.) was added to corresponding imidazole (30 mmol, 1 equiv.) in dry DMF (100 mL). The mixture was stirred for 1 h. A balloon volume of sulfuryl fluoride gas was then added to the reaction system. The reaction progress was monitored by TLC. After the reaction was completed, the solvent was evaporated in vacuo.

**General procedure for the synthesis of product 3.** Condition A: Under argon, to a solution of 4CzIPN (2 mol%), KH$_2$PO$_4$ (2.5 equiv) and IMSF reagent 2b (0.2 mmol, 2 equiv.) in dried EA:DME = 1 mL, Ar, 60 W blue LEDs about 10 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated in vacuo. The crude products were directly purified by flash chromatography on silica gel to give the desired product.

**General procedure for the synthesis of product 4.** Condition B: Under argon, to a solution of PC 1 (2 mol%), KH$_2$PO$_4$ (2.5 equiv) and IMSF reagent 2b (0.2 mmol, 2 equiv.) in dried EA:DME = 4:1 (1 mL) was added corresponding alkenes 1 (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs about 12 h, then 1.5 mL of acetonitrile containing Ir([Ir(dF-CF$_3$ppy)$_3$]ppy)PF$_6$ (2 mol%) was injected into the reaction tube about 12 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated in vacuo. The crude products were directly purified by flash chromatography on silica gel to give the desired product.

**General procedure for the synthesis of product 5.** Condition C: Under argon, to a solution of fac-Ir(ppy)$_3$ (2 mol%), 1,4-cyclohexadiene (1.5 equiv.) and IMSF reagent 2b (0.2 mmol, 2 equiv.) in dried 2-methyltetrahydrofuran:Acetone = 9:1 (1 mL) was added corresponding alkenes 5 (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs about 12 h, then the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated in vacuo. The crude products were directly purified by flash chromatography on silica gel to give the desired product.
General procedure for the synthesis of product 8. Condition D: Under argon, to a solution of 4-FLrF-[F-(p-Bu)ppy] (2 mol%), and IMSF reagent 2a (0.2 mmol, 2 equiv.) in dried EADME = 7:3 (1 mL) was added corresponding alkynes 7 (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs about 12 h, then until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated in vacuo. The crude products were directly purified by flash chromatography on silica gel to give the desired product.

Data availability

The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its Supplementary Information files, or from the corresponding author upon request. X-ray structural data of compound 2a are available free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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**Author contributions**

Y.W. and W.Z. designed and guided this project. H.L. is responsible for the plan and implementation of the experimental work. X.L., Z.Z., M.H., J. L. and X.W. analyzed the data. Y.W. and W.Z. co-wrote the manuscript. S.N. and Y.P. discussed the results and commented on the manuscript.

**Competing interests**

The authors declare no competing interests.

**Additional information**

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