

Divergent Generation of the Difluoroalkyl Radical and Difluorocarbene via Selective Cleavage of C–S Bonds of the Sulfox-CF₂SO₂Ph Reagent

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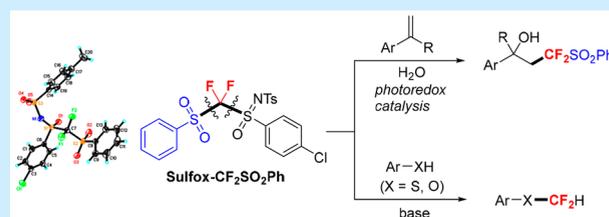
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ABSTRACT: A new difluoroalkylation reagent Sulfox-CF₂SO₂Ph bearing both sulfoximine and sulfone moieties was prepared from commercially available SulfoxFluor and PhSO₂CF₂H. On one hand, the Sulfox-CF₂SO₂Ph reagent could act as a (phenylsulfonyl)-difluoromethyl radical source under photoredox catalysis, in which the arylsulfoximidoyl group is selectively removed. On the other hand, under basic conditions, Sulfox-CF₂SO₂Ph could serve as a difluorocarbene precursor for S- and O-difluoromethylations with S- and O-nucleophiles, respectively, in which the phenylsulfonyl group in Sulfox-CF₂SO₂Ph is selectively removed (followed by α -elimination of the arylsulfoximidoyl group).

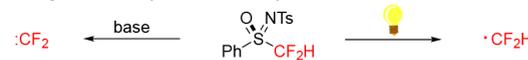


The selective introduction of fluorine atoms or fluorinated moieties into organic molecules can often bring about profound changes in the latter's physical and biological properties. For instance, the difluoromethyl (CF₂H) and difluoroalkyl (CF₂R, where R ≠ H) groups have found wide applications in pesticides,¹ functional materials,² and pharmaceuticals.³ The synthesis of difluoromethylated and difluoroalkylated compounds generally relies on the use of corresponding CF₂H- and CF₂R-transfer reagents,⁴ such as Si-based,⁵ Zn-based,⁶ P-based,⁷ I-based,⁸ and S-based⁹ difluoromethylation and difluoroalkylation reagents, among which the difluoromethyl sulfoximines¹⁰ and sulfones^{9,11} have attracted a great deal of attention owing to their unique reactivity in organic synthesis.

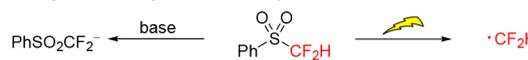
Highly tunable functionalities of difluoroalkyl sulfoximine and sulfone reagents showed divergent reactivities and selectivities under different reaction conditions. Hu and co-workers reported that *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine [PhS(O)NTsCF₂H] could release difluorocarbene in the presence of NaH, trapped by S-, N-, and C-nucleophiles (Scheme 1a, left).^{10a} On the contrary, the photocatalysis rendered PhS(O)NTsCF₂H as a source of difluoromethyl radical species for oxididifluoromethylation of alkenes.¹² A similar activation strategy was used in the case of difluoromethyl phenyl sulfone (PhSO₂CF₂H), in which the deprotonation by LHMDs as a base produced a nucleophilic PhSO₂CF₂⁻ species,¹³ while the electrophilic PhSO₂CF₂ radical species was obtained under electrochemical conditions (Scheme 1b).¹⁴ However, the different reactivities and selectivities of difluoroalkylated reagents bearing both sulfoximine and sulfone functionalities have never been reported (Scheme 1c).

Scheme 1. Tuning the Reactivity of Difluoromethylated Sulfoximines and Sulfones

a) Tuning the reactivity of difluoromethylated sulfoximine under different conditions



b) Tuning the reactivity of difluoromethylated sulfone under different conditions



c) **This work:** tuning the reactivity of **1** under different conditions



To explore the reaction conditions to tune the reactivity and selectivity of sulfone and sulfoximine within the same molecule, we tried to synthesize Sulfox-CF₂SO₂Ph reagent **1a** from SulfoxFluor and PhSO₂CF₂H. Notably, the practical synthetic methods for SulfoxFluor on a large scale have been developed by us.¹⁵ The treatment of SulfoxFluor and PhSO₂CF₂H by LiHMDS and HMPA afforded product **1a** in 77% yield and 97% purity, together with 3% (PhSO₂)₂CF₂ (Scheme 2). The reduction potential of **1a** was found to be -0.939 V (see the Supporting Information for details), which

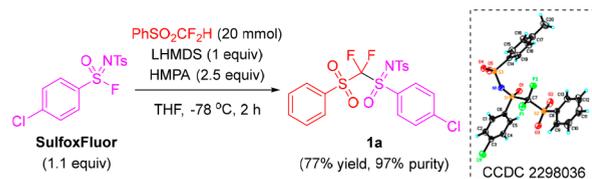
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Scheme 2. Synthetic Route of **1a**

indicates that **1a** is easily reduced under a single electron-transfer process. With target compound **1a** in hand, we next investigated which C–S bond of **1a** would be preferentially cleaved and whether the different reaction conditions could control the selective cleavage of each C–S bond.

Initially, the selective C–S bond cleavage of **1** in the photocatalyzed radical difluoroalkylation of 1,1-diphenylethylene (**2a**) was evaluated (Table 1). Notably, the

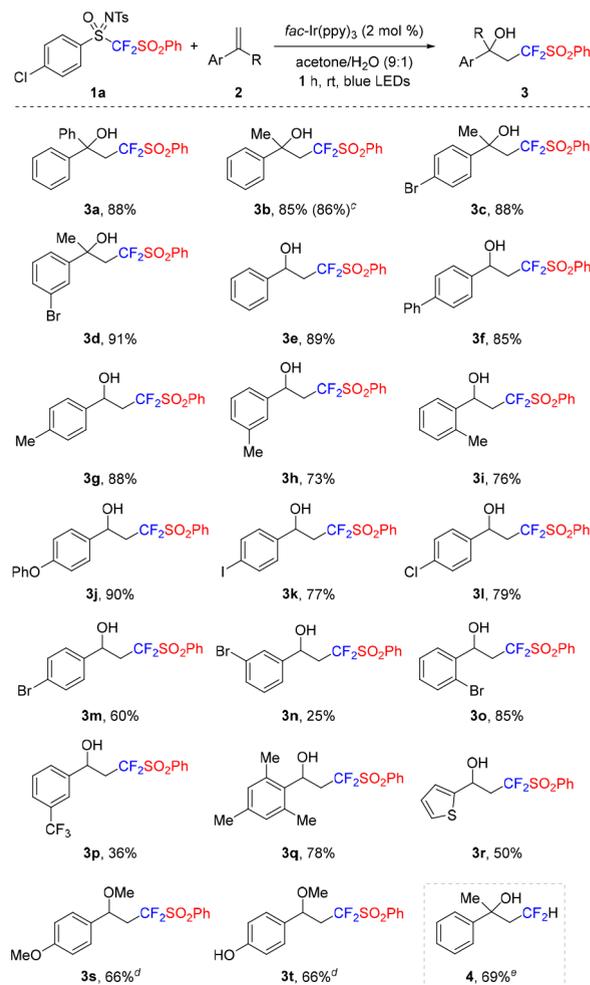
Table 1. Optimization of the Reaction Conditions

entry	variation from the above conditions ^a	yield of 3a (%) ^b
1	none	95
2	1b instead of 1a	99
3	Eosin Y instead of <i>fac</i> -Ir(ppy) ₃	0
4	Ru(bpy) ₃ ·6H ₂ O instead of <i>fac</i> -Ir(ppy) ₃	0
5	white LEDs instead of blue LEDs	95
6	without <i>fac</i> -Ir(ppy) ₃	0
7	in the dark	0
8	in air	70
9	addition of TEMPO or 1,4-benzoquinone	0

^aStandard reaction conditions: **1a** (0.24 mmol, 1.2 equiv), **2a** (0.2 mmol), *fac*-Ir(ppy)₃ (2 mol %), acetone (4.5 mL), H₂O (0.5 mL), blue LEDs, room temperature, 1 h, Ar. ^bYields were determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard.

sulfoximine moiety of **1a** was predominantly cleaved to generate the PhSO₂CF₂ radical species, which was used to react with alkene **2a**. Under the irradiation of blue LEDs and catalysis of *fac*-Ir(ppy)₃ (2.0 mol %), alkene **2a** (1.0 equiv) smoothly reacted with **1a** (1.2 equiv) in acetone and water at room temperature in 1 h, affording oxy(phenylsulfonyl)-difluoromethylation product **3a** in 95% NMR yield (entry 1). When the nonchlorinated version of reagent **1b** was used instead of **1a** under the standard reaction conditions, product **3a** was produced in 99% NMR yield, which rules out the influence of a chlorine substituent on the selective C–S bond cleavage of **1a** (entry 2). Other common photocatalysts such as Eosin Y and Ru(bpy)₃·6H₂O failed to yield product **3a**, probably due to their reduction potentials being lower than that of *fac*-Ir(ppy)₃ (entries 3 and 4, respectively). *fac*-Ir(ppy)₃ in combination with white LEDs also succeeded in catalyzing this transformation (entry 5). Starting material **1a** was completely recovered in the absence of either light or a photocatalyst (entry 6 or 7, respectively). The decreased yield of **3a** was observed when this reaction was performed in air (entry 8). This transformation could be inhibited in the presence of radical scavengers such as TEMPO and 1,4-benzoquinone, which supports the involvement of the PhSO₂CF₂ radical species during this process (entry 9).

To demonstrate the reactivity of **1a** as a (phenylsulfonyl)-difluoromethyl radical source under the optimized reaction conditions (Table 1, entry 1), a wide range of styrenes were examined (Scheme 3). Using α -substituted styrenes, 1,1-

Scheme 3. Substrate Scope of Radical (Phenylsulfonyl)-difluoromethylation with **1a**^{a,b}

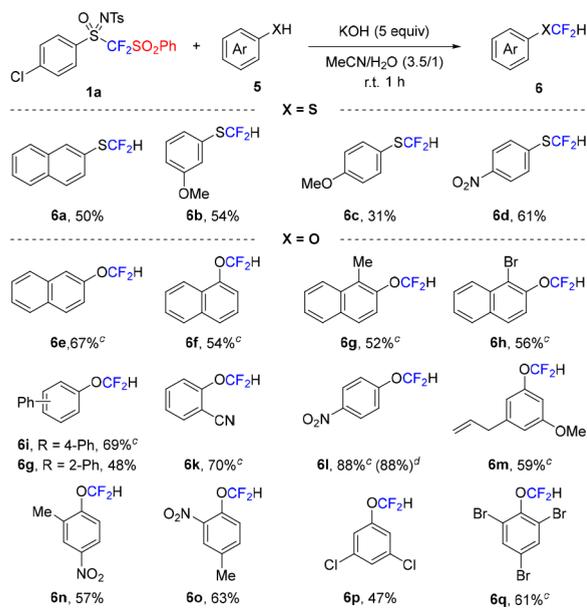
^aReaction conditions: **1a** (0.24 mmol, 1.2 equiv), **2** (0.2 mmol), *fac*-Ir(ppy)₃ (2 mol %), acetone (4.5 mL), H₂O (0.5 mL), blue LEDs, room temperature, 1 h, Ar. ^bIsolated yields. ^cOn a 1 mmol scale, 4 h. ^dUsing MeOH instead of H₂O. ^eReaction conditions: **3b** (0.3 mmol), Mg (6 mmol, 20 equiv), BrCH₂CH₂Br (12 mol %), MeOH (4.5 mL), 3 h, room temperature, in air.

diphenyl ethylene and α -methylstyrenes, this new synthetic method gave products **3a–3d** in good yields (on a 0.2 or 1 mmol scale). Various styrenes with an electron-rich group such as phenyl (**2f**), methyl (**2g–2i**), and phenoxy (**2j**) were all compatible with the current reaction conditions, affording products **3f–3j**, respectively, in 73–90% yields. Styrenes bearing different halogens at different positions (**2k–2o**) were also viable (**3k–3o**, respectively). In addition, when a CF₃ group is substituted at the *meta* position of styrene, the corresponding product **3p** was obtained in low yield (36%). Moreover, multiple functionalities and heteroaryl groups on the styrenes were compatible with this reaction, and the corresponding products **3q** and **3r** were formed in 78% and 50% yields, respectively. For the reactions with 4-methoxysty-

ene (**2s**) and 4-hydrostyrene (**2t**), methanol was used as the oxylation agent, and products **3s** and **3t** were obtained in 66% yield, respectively. Finally, desulfonation of **3b** was successfully conducted in the presence of Mg and methanol to give difluoromethylated product **4** in 69% yield.

Inspired by the aforementioned results, we further discovered that **1a** could act as a difluorocarbene precursor under basic conditions (Scheme 4). Various thiophenols or

Scheme 4. S- and O-Difluoromethylation with **1a**^{a,b}



^aReaction conditions: **1a** (1.0 mmol, 2.0 equiv), **5** (0.5 mmol, 1.0 equiv), KOH (5.0 equiv), CH₃CN (3.5 mL), H₂O (1.0 mL), room temperature, 1 h, air. ^bIsolated yields. ^cReactions were performed at 50 °C. ^dUsing **1b** instead of **1a**. The yields were determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard.

phenols could smoothly react with **1a** (2.0 equiv) in the presence of KOH (5.0 equiv) in MeCN and H₂O at room temperature for 1 h. As shown in Scheme 4, the difluoromethylation of thiophenols gave difluoromethyl phenyl sulfides (**6a–6d**) in 31–61% yields. Furthermore, it was found that this synthetic protocol was efficient for the difluoromethylation of naphthols **5e–5h** (in 52–67% yields). When a phenyl group of phenols was substituted at the *ortho* position, O-difluoromethylated product **6i** was obtained in a yield (48%) lower than that with *para*-substituted phenol (**6g**, 69%). The phenols bearing electron-withdrawing groups were successfully difluoromethylated to give the corresponding products **6l** and **6n–6q** in 47–88% yields. It is noteworthy that when *p*-nitrophenol **5l** was subjected to this transformation, product **6l** was obtained in a high yield (88%). When reagent **1b** was used instead of **1a** under the standard reaction conditions, the same product **6l** was also obtained in 88% yield. Furthermore, an alkenyl group on phenol could be well tolerated in this reaction, and product **6m** was obtained in 59% yield. It is hypothesized that KOH attacked the sulfur atom of the phenylsulfone moiety of **1a** to generate ArS(O)NTsCF₂⁻ and the benzenesulfonate ion. The in situ-formed difluorocarbene [from highly unstable ArS(O)NTsCF₂⁻] was captured by the S- and O-nucleophiles, delivering the difluoromethylated products after protonation.

Indeed, the benzenesulfonate ion was detected by HPLC (see Scheme S1).

In summary, we have developed a novel difluoroalkylation reagent, **1**, which is prepared from commercially available and inexpensive SulfoxFluor and PhSO₂CF₂H. This newly developed reagent **1** could act as an amphoteric synthetic equivalent of the (phenylsulfonyl)difluoromethyl radical and difluorocarbene. On one hand, under photocatalysis, the sulfoximine moiety of **1** is selectively removed, which enables radical (phenylsulfonyl)difluoromethylation of alkenes. On the other hand, under basic conditions, the sulfonyl moiety of **1** is cleaved (followed by α -elimination of the sulfoximidoyl moiety), and the generated difluorocarbene is captured by S- and O-nucleophiles to give corresponding difluoromethylated products. Our results showcase the unique reactivity of the newly synthesized Sulfox-CF₂SO₂Ph reagent and provide intriguing insights into the fluorinated sulfone and sulfoximine chemistry.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c04116>.

Experimental procedures, characterization data and copies of ¹H, ¹⁹F, and ¹³C NMR spectra of new compounds, single-crystal data of **1a**, and cyclic voltammetry study of **1a** (PDF)

Accession Codes

CCDC 2298036 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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