

# Modular synthesis of $\text{CF}_2$ -containing compounds with $\text{PhSO}_2\text{CF}_2\text{H}$ reagent through difluoromethylene radical anion synthon strategy

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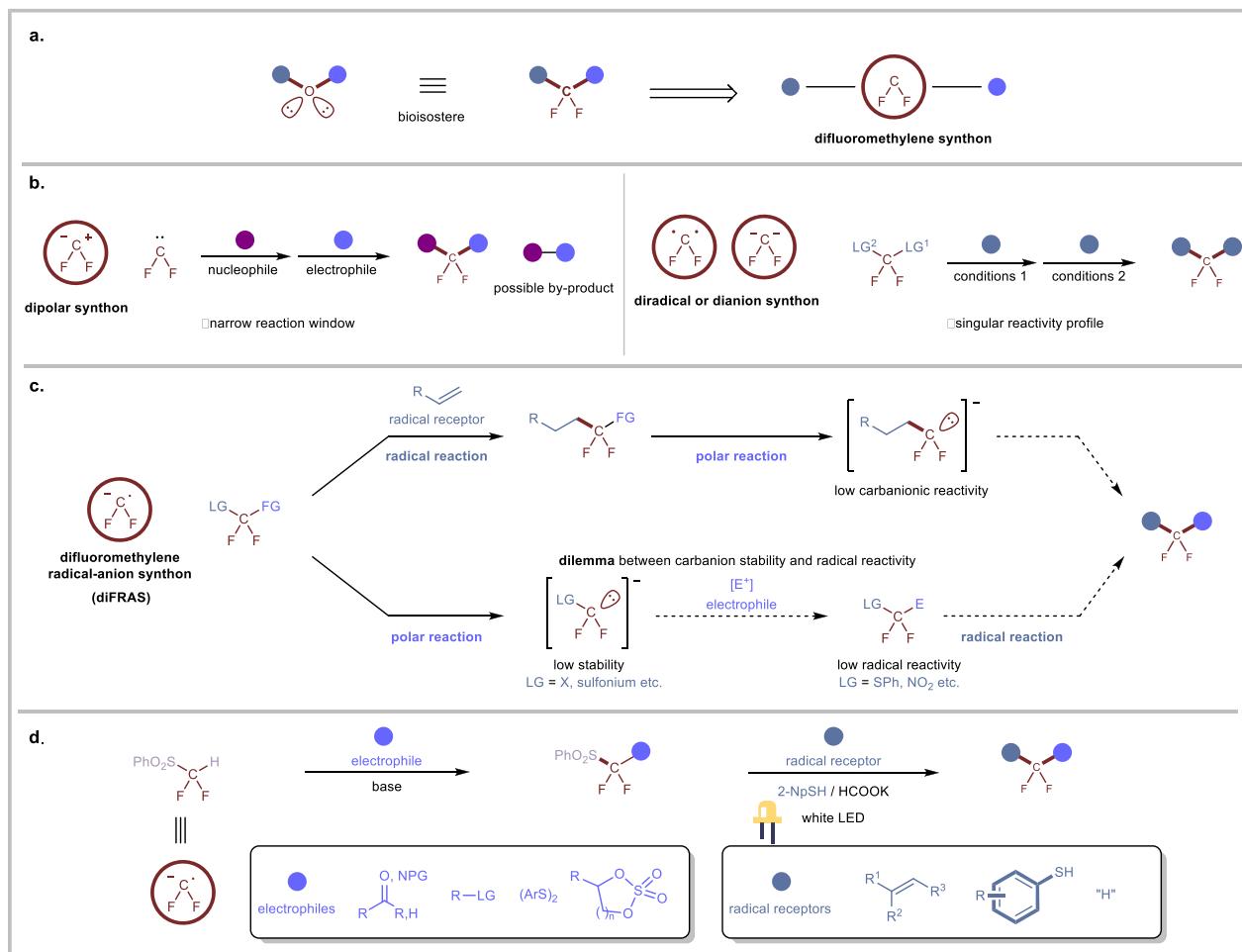
Difluoromethylene moiety has gained widespread applications in pharmaceuticals, agrochemicals, and materials owing to its augmented lipophilicity and being bioisosteric to ethereal oxygen. Possessing two orthogonal reactivity modes for bridging an electrophile and a radical acceptor to give *gem*-difluorides ( $\text{R}^1\text{-CF}_2\text{-R}^2$ ), the efficient difluoromethylene radical anion synthon (diFRAS) has been long sought after. In this work, we successfully utilize the readily available difluoromethyl phenyl sulfone ( $\text{PhSO}_2\text{CF}_2\text{H}$ ) to couple with electrophiles and radical acceptors, thereby enabling  $\text{PhSO}_2\text{CF}_2\text{H}$  to serve as a novel diFRAS in organic synthesis. The generation of radicals ( $\cdot\text{CF}_2\text{R}$ ) via visible light-promoted homolytic cleavage of C–S bonds in (phenylsulfonyl)difluoromethylated derivatives ( $\text{PhSO}_2\text{CF}_2\text{R}$ ) is the linchpin in the diFRAS strategy to construct *gem*-difluorides ( $\text{R}^1\text{-CF}_2\text{-R}^2$ ) with structural complexity.

The incorporation of fluorine into pharmaceutical candidates often leads to improvements in metabolic stability, lipophilicity, and augmented biological activity<sup>1,2</sup>. Among fluorinated motifs, difluoromethylene has been known to serve as a bioisostere of ethereal oxygen and is increasingly applied in medicinal chemistry<sup>3–6</sup>. The conventional route to *gem*-difluorides ( $\text{R}^1\text{-CF}_2\text{-R}^2$ ) is the direct fluorination (C–F bond formation), which necessitates pre-functionalized molecular frameworks and often meets limitations due to functional group incompatibility<sup>7–9</sup>. Synthetic chemists aspire to connect two distinct components with the difluoromethylene moiety, fabricating difluorides in a modular fashion (Fig. 1a). Difluorocarbene is an equivalent of bipolar difluoromethylene unit, and its tandem reactions are among the most extensively employed in difluoromethylene synthon strategies. Reactions involving difluorocarbene typically proceed via interception by a nucleophile ( $\text{Nu}^-$ ), yielding a difluoroalkyl carbanion ( $\text{Nu-}\text{CF}_2^-$ ). Subsequently, the carbanion attacks an electrophile ( $\text{E}^+$ ), leading to the construction of a *gem*-difluoride ( $\text{Nu-}\text{CF}_2\text{-E}^+$ )<sup>10–12</sup>.

However, this difluorocarbene protocol is limited by the potential reaction between the nucleophile ( $\text{Nu}^-$ ) and electrophile ( $\text{E}^+$ ). On the other hand, synthetic protocols with difluoromethylene diradical<sup>13–15</sup> and dianion<sup>16–19</sup> synthons also have drawbacks such as the singular reactivity profile (Fig. 1b).

Bearing two orthogonal reactivity modes, difluoromethylene radical anion synthon (diFRAS,  $\cdot\text{CF}_2^-$ ) has significant advantages in the modular synthesis of *gem*-difluorides<sup>20</sup>. However, in spite of the benefits of the diFRAS, the intrinsic dilemma between its two activation modes poses a considerable obstacle (Fig. 1c). For the initial introduction of an electrophile to the potential diFRAS, the generation of carbanion is often challenging; even if the difluoroalkyl carbanion is successfully generated, its nucleophilicity is low in the absence of an auxiliary group owing to the negative fluorine effect<sup>21</sup>. Initiating the polar reaction encounters a dilemma between carbanion stability and radical reactivity: on one hand, for highly reactive radical precursors, such as halides and sulfonium salts, their corresponding unstable

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**Fig. 1 | Synthesis of gem-difluorides.** **a** Synthetic route to gem-difluorides and its bioisostere. **b** Previously developed difluoromethylene synthon. **c** Challenges for difluoromethylene radical anion synthon (diFRAS). **d** This work:  $\text{PhSO}_2\text{CF}_2\text{H}$  as

diFRAS for modular synthesis of gem-difluorides with chemical complexity. FG functional group, LG leaving group, PG protecting group.

carbanions have a propensity to decompose into difluorocarbene<sup>22–24</sup>, impeding the introduction of electrophiles. On the other hand, regarding the leaving groups (such as arylthio, arylphosphoryl, and nitro groups) which are compatible with carbanion generation, the corresponding radical reactions are usually difficult to be initiated<sup>15,20,25–28</sup> (Fig. 1c). Previous work pertaining to the diFRAS-involved radical reaction has been only limited to intramolecular cyclizations<sup>20,29–34</sup>. The diFRAS-enabled double intermolecular processes involving the annexation of two additional molecules to forge difluorides ( $\text{R}^1-\text{CF}_2-\text{R}^2$ ) still remains a challenging task.

In 2016, we reported the first example of sulfone-enabled radical fluoroalkylation via S–C bond cleavage of difluoromethyl benzothiazolyl sulfone (BTSO<sub>2</sub>CF<sub>2</sub>H, **1b**)<sup>35</sup>. Although the radical fluoroalkylation with **1b** has found different applications<sup>35–45</sup>, the instability of the corresponding carbanion of **1b** (BTSO<sub>2</sub>CF<sub>2</sub><sup>–</sup>)<sup>22</sup> precludes **1b** from serving as an efficient diFRAS. On the other hand, we have found that difluoromethyl phenyl sulfone (PhSO<sub>2</sub>CF<sub>2</sub>H, **1a**), a readily available and easy-to-handle compound<sup>46</sup>, can serve as a robust nucleophilic difluoroalkylation reagent<sup>47–49</sup> for various electrophiles such as alkyl halides<sup>50,51</sup>, disulfides<sup>18</sup>, aldehydes, ketones<sup>52,53</sup>, and imine<sup>54,55</sup>. The obtained products (PhSO<sub>2</sub>CF<sub>2</sub>R) constitute a library of broad range of fluoroalkyl sulfones, and therefore, we envisioned that **1a** could be developed as a privileged diFRAS if we can tackle the challenge of the homolytic cleavage of the S–C bond of PhSO<sub>2</sub>CF<sub>2</sub>R to generate difluoroalkyl radical species ( $\cdot\text{CF}_2\text{R}$ ). Herein, we reported a visible light-promoted desulfonylation of the phenyl sulfones to

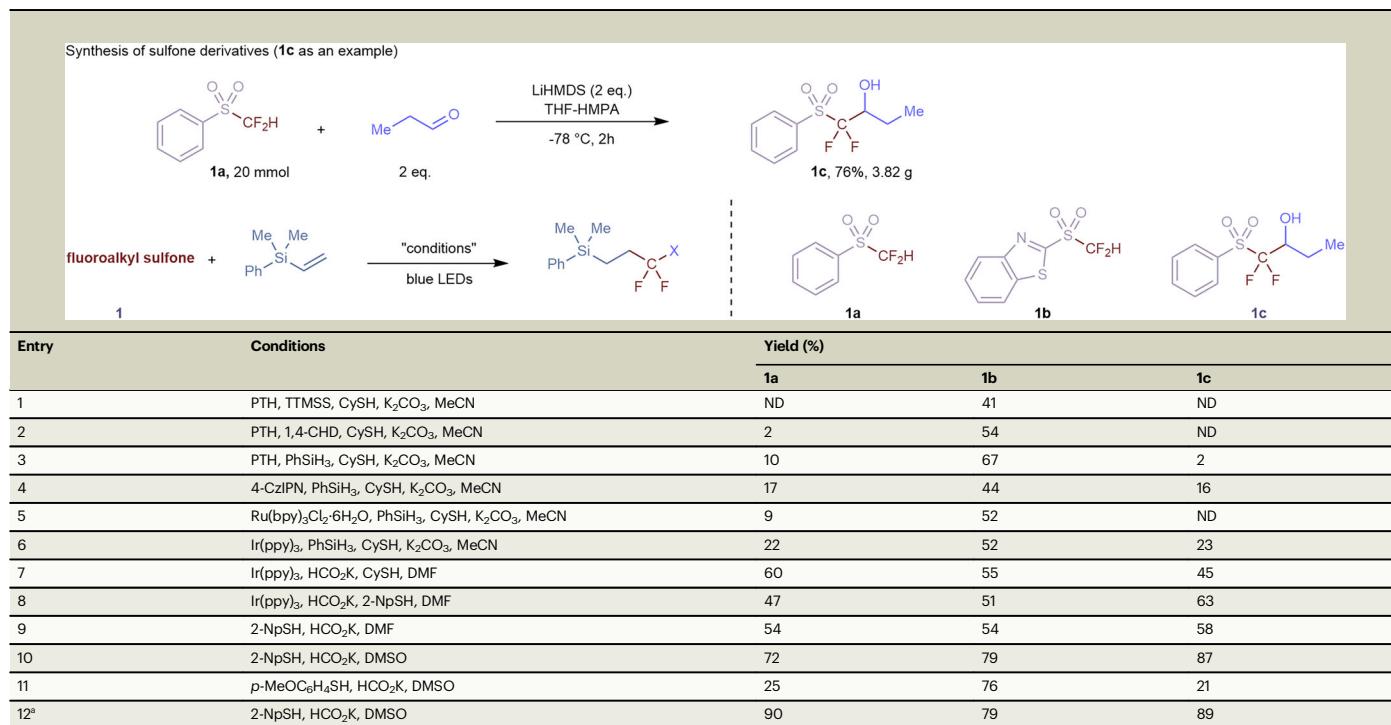
generate difluoroalkyl radicals. Merging nucleophilic (phenylsulfonyl) difluoromethylation of electrophiles with a sequential radical coupling with radical acceptors, we designed a strategy for modular synthesis of gem-difluorides using PhSO<sub>2</sub>CF<sub>2</sub>H as a diFRAS that introduces two distinct components and unlocks great chemical complexity (Fig. 1d).

## Results

### Reaction optimization

In light of the radical-anion-promoted desulfonylation and the potential risk of uncontrolled overreduction of fluoroalkyl radical by harsh reductants (e.g., Na–Hg, Mg–HOAc)<sup>56–58</sup>, robust yet mild conditions are crucial for the radical cleavage of the PhSO<sub>2</sub>–CF<sub>2</sub>R bond<sup>59</sup>. Photocatalysis is a powerful tool in radical chemistry<sup>60–62</sup>, and most processes in which sulfones break to generate radicals revolve around photocatalysis<sup>24,35–43,45,63,64</sup>. Using vinylphenyldimethylsilane (**2a**) as a radical acceptor, we explored the hydrofluoroalkylation with functionalized phenyl sulfones (**1c**) obtained from the nucleophilic addition of propionaldehyde with PhSO<sub>2</sub>CF<sub>2</sub>H<sup>52</sup> (Table 1). BTSO<sub>2</sub>CF<sub>2</sub>H (**1b**), a widely-used fluoroalkyl radical precursor, and PhSO<sub>2</sub>CF<sub>2</sub>H (**1a**) were also tested under the series of conditions. BTSO<sub>2</sub>CF<sub>2</sub>H showed a moderate to good reactivity in various conditions (Table 1, entries 1–6). Meanwhile, phenyl sulfones **1a** and **1c** were hardly activated, and either no target product or only a small amount of the target product was obtained. Inspired by radical defluorination of trifluoromethylarenes<sup>65,66</sup>, potassium formate was applied as a reductant to react with phenyl sulfones, affording the products in moderate

Table 1 | Optimization of reaction conditions



The table shows the optimization of reaction conditions for the synthesis of sulfone derivatives. The first part illustrates the synthesis of **1c** from **1a** and methyl acrylate using LiHMDS and THF-HMPA at -78 °C for 2h. The second part shows the general reaction scheme where a fluoroalkyl sulfone (**1**) reacts with an alkene in the presence of "conditions" (blue LEDs) to form a radical intermediate. The final part shows the structures of **1a**, **1b**, and **1c**.

Entry	Conditions	Yield (%)		
		<b>1a</b>	<b>1b</b>	<b>1c</b>
1	PTH, TTMS, CySH, K <sub>2</sub> CO <sub>3</sub> , MeCN	ND	41	ND
2	PTH, 1,4-CHD, CySH, K <sub>2</sub> CO <sub>3</sub> , MeCN	2	54	ND
3	PTH, PhSiH <sub>3</sub> , CySH, K <sub>2</sub> CO <sub>3</sub> , MeCN	10	67	2
4	4-CzIPN, PhSiH <sub>3</sub> , CySH, K <sub>2</sub> CO <sub>3</sub> , MeCN	17	44	16
5	Ru(bpy) <sub>3</sub> Cl <sub>2</sub> ·6H <sub>2</sub> O, PhSiH <sub>3</sub> , CySH, K <sub>2</sub> CO <sub>3</sub> , MeCN	9	52	ND
6	Ir(ppy) <sub>3</sub> , PhSiH <sub>3</sub> , CySH, K <sub>2</sub> CO <sub>3</sub> , MeCN	22	52	23
7	Ir(ppy) <sub>3</sub> , HCO <sub>2</sub> K, CySH, DMF	60	55	45
8	Ir(ppy) <sub>3</sub> , HCO <sub>2</sub> K, 2-NpSH, DMF	47	51	63
9	2-NpSH, HCO <sub>2</sub> K, DMF	54	54	58
10	2-NpSH, HCO <sub>2</sub> K, DMSO	72	79	87
11	p-MeOC <sub>6</sub> H <sub>4</sub> SH, HCO <sub>2</sub> K, DMSO	25	76	21
12 <sup>a</sup>	2-NpSH, HCO <sub>2</sub> K, DMSO	90	79	89

Reaction conditions: sulfone **1** (0.4 mmol, 2.0 equiv), alkene **2a** (0.2 mmol, 1.0 equiv), photocation, thiol (20 mol%), reductant (3.0 equiv), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), solvent (1.6 mL), blue LED, room temperature, 18 h. PC: PTH (10 mol%), 4-CzIPN (0.2 mol%), Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O (0.2 mol%), Ir(ppy)<sub>3</sub> (0.2 mol%). All yields were based on <sup>19</sup>F NMR analysis with PhCF<sub>3</sub> as an internal standard.

PTH 10-phenyl-10H-phenothiazine, TTMS tris(trimethylsilyl)silane, CySH cyclohexanethiol, 4-CzIPN 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, 1,4-CHD 1,4-cyclohexadiene, Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O tris(2,2'-biphenyl)triruthenium(II) Chloride Hexahydrate, Ir(ppy)<sub>3</sub> tris(2-phenylpyridine)iridium, 2-NpSH 2-naphthalenethiol, p-MeOC<sub>6</sub>H<sub>4</sub>SH 4-methoxybenzenethiol, ND not detected.

<sup>a</sup>White LED instead of blue LED as light source.

yields<sup>67-69</sup> (Table 1, entry 7). Subsequently, it was discovered that when 2-naphthalenethiol (2-NpSH) was used as a hydrogen atom transfer (HAT) catalyst, a moderate yield could still be observed without additional expensive photocatalysts<sup>70</sup> (Table 1, entries 8,9). Using DMSO as solvent resulted in better yields (Table 1, entry 10). During our investigation, the catalytic activity of arenethiol as both photocatalyst and HAT catalyst was reported by Shang<sup>71,72</sup> and Molander<sup>73,74</sup>. The catalytic performance of other arenethiols was evaluated, and all showed lower activity compared to 2-NpSH (Table 1, entry 11; see Supplementary Information, Table S1 for performance of additional arenethiols). Finally, when blue light was replaced with the most widely used white light, it gave the products in the highest yield (Table 1, entry 12). Hence, 2-NpSH/HCO<sub>2</sub>K in DMSO under white light irradiation was identified as the optimal condition.

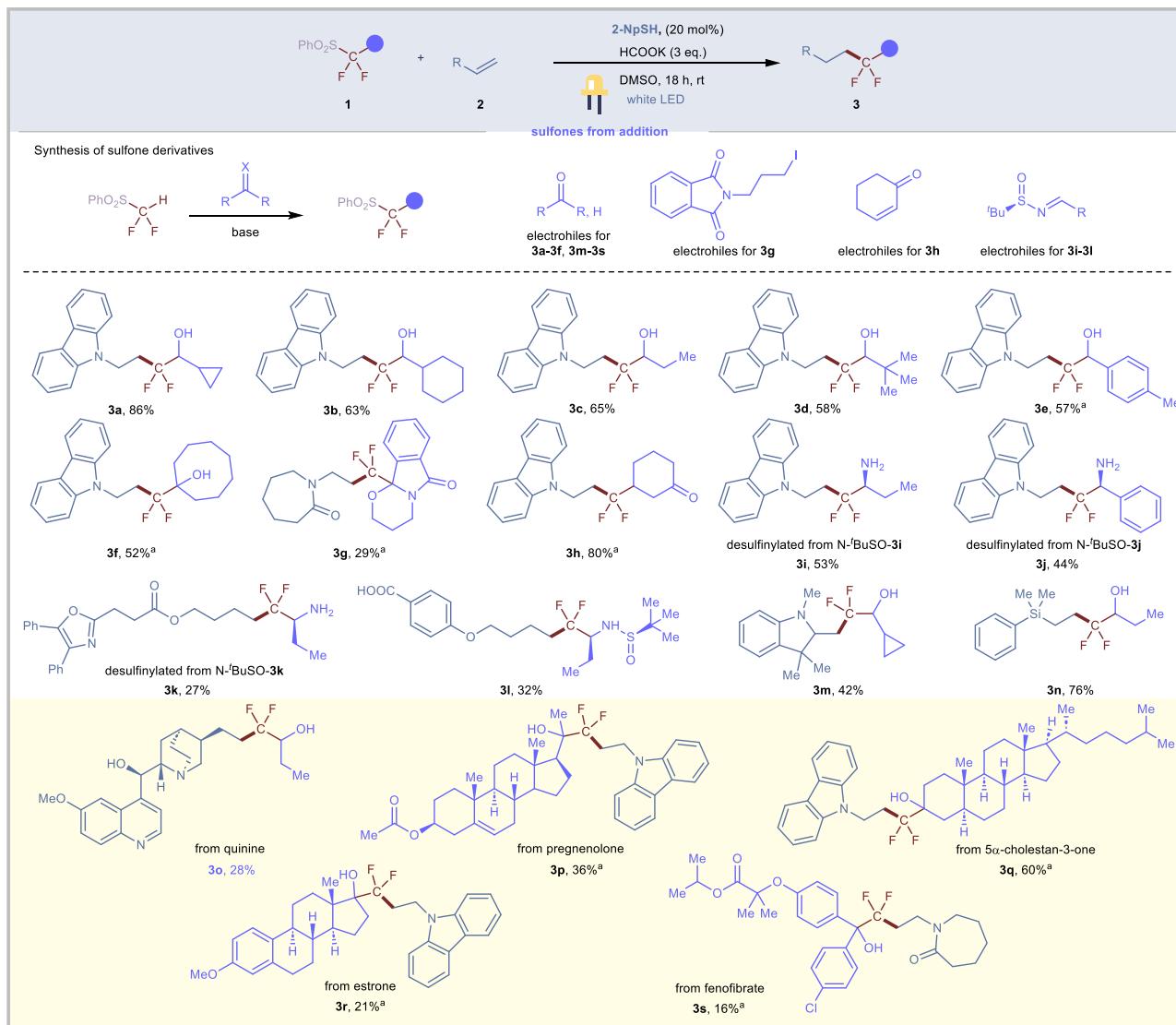
### Substrate scope

The robustness of the optimized reaction conditions was illustrated across the substrate scope (Fig. 2). Initially, evaluation was conducted on the sulfone derivatives that were obtained through the nucleophilic addition of PhSO<sub>2</sub>CF<sub>2</sub>H (**1a**)<sup>47-49</sup>. The sulfones derived from a wide range of cyclic (**3a**, **3b**), linear (**3c**), sterically hindered (**3d**), and aryl aldehydes (**3e**), as well as ketone (**3f**), showed compatibility in our methodology. This reaction was also applicable to sulfones obtained through cascade cyclization (**3g**) (see Supplementary Information, Fig. S4 and Table S3) and Michael addition (**3h**). Imine-derived sulfones enabled the synthesis of  $\beta$ -amino- $\alpha$ , $\alpha$ -difluorides (**3i**-**3l**). Amino and silyl groups were tolerated in the method (**3m**, **3n**). Notably, naturally occurring bioactive motifs could be coupled to either radical or anion ends of diFRAS. The incorporation of radical linkers like quinine (**3o**), and electrophilic linkers, for instance, pregnenolone (**3p**), 5a-cholestane-3-one (**3q**), estrone (**3r**) and fenofibrate (**3s**) into diFRAS was demonstrated. Because of steric hindrance, several of their

corresponding radicals preferentially abstract hydrogen atoms in HAT catalysts rather than react with alkenes.

A comprehensive evaluation has been conducted on sulfone derivatives (derived from substitutions involving PhSO<sub>2</sub>CF<sub>2</sub>H)<sup>18,50,51,75</sup>, showcasing their potential applications in organic synthesis (Fig. 3). The coupling proceeded effectively for sulfones adorned with a distal hydroxyl group derived from cyclic sulfates (**4a**-**4c**). Linear difluoroalkyl sulfones, obtained from the substitution reactions between PhSO<sub>2</sub>CF<sub>2</sub>H and alkyl halides, were also compatible with this protocol (**4d**-**4i**). Arylthio-modified sulfones derived from disulfides were likewise converted into SCF<sub>2</sub>-containing species (**4j**-**4l**), underscoring the broad functional group tolerance of this approach. The scope of radical acceptors featuring alkene moieties was also explored with various functional groups such as sulfonyl (**4m**), amino (**4n**), hydroxy (**4o**,**4p**), and carboxylic acid (**4q**). The methodology can be extended to drug derivatives, including alibendol (**4r**), ibuprofen (**4s**), tarenfluril (**4t**), and paclitaxel (**4u**). The inherent chemical versatility of hydroxyl groups facilitates further derivatization of  $\gamma$ -hydroxyl- $\alpha$ , $\alpha$ -difluoroalkyl phenyl sulfones, underscoring their potential for structural modification. A peptide-embellished difluoroalkyl moiety was integrated into a paclitaxel derivative, linking two bioactive motifs via diFRAS (**4v**). To further substantiate the synthetic utility, we synthesized a bioisostere of pitolisant (**4w**), an FDA-approved drug for the treatment of narcolepsy<sup>76</sup>, wherein the oxygen was replaced by a difluoromethylene group.

Apart from employing alkenes as radical acceptors, we delved deeper into investigating the feasibility of our method with different types of radical acceptors (Fig. 4). Our research efforts were centered around the construction of CF<sub>2</sub>-S structure, which not only holds critical importance in pharmaceutical chemistry but also garners substantial interest among synthetic chemists<sup>77-84</sup>. With DBU as a base in lieu of a reductive formate, we expanded the scope of radical



**Fig. 2 | Scope of *gem*-difluorides from sulfones generated via additions using alkenes as radical acceptors.** Reaction conditions: **2** (0.5 mmol, 1.0 equiv), **1** (2.0 equiv), 2-NpSH (20 mol%), HCOOK (3.0 equiv), DMSO (4 mL), white LED, room temperature, 18 h. All yields are isolated yields. <sup>a</sup>**1** (0.5 mmol, 1.0 equiv), **2** (2.0 equiv).

acceptors to include arenethiols (**5a**–**5e**). Sulfones **1a**–**4a** underwent reactions with various thiophenols to produce a series of thioethers (**5f**–**5o**) with the additional photocatalyst Ir(ppy)<sub>3</sub> under blue LED. In addition to electrically neutral arenethiols, both electron-rich and electron-deficient ones proved to be effective coupling partners in this reaction. *Ortho*- and *meta*-substituted and multi-substituted arenethiols exhibited compatibility under the reaction conditions (**5k**, **5m**–**5o**). Remarkably, Ar-CF<sub>3</sub> was stable under the conditions (**5l**–**5n**), experiencing minimal defluorination. Furthermore, the conversion of 2-PySH (**5p**), a prevalent structural motif in numerous bioactive molecules<sup>35</sup>, was successfully conducted.

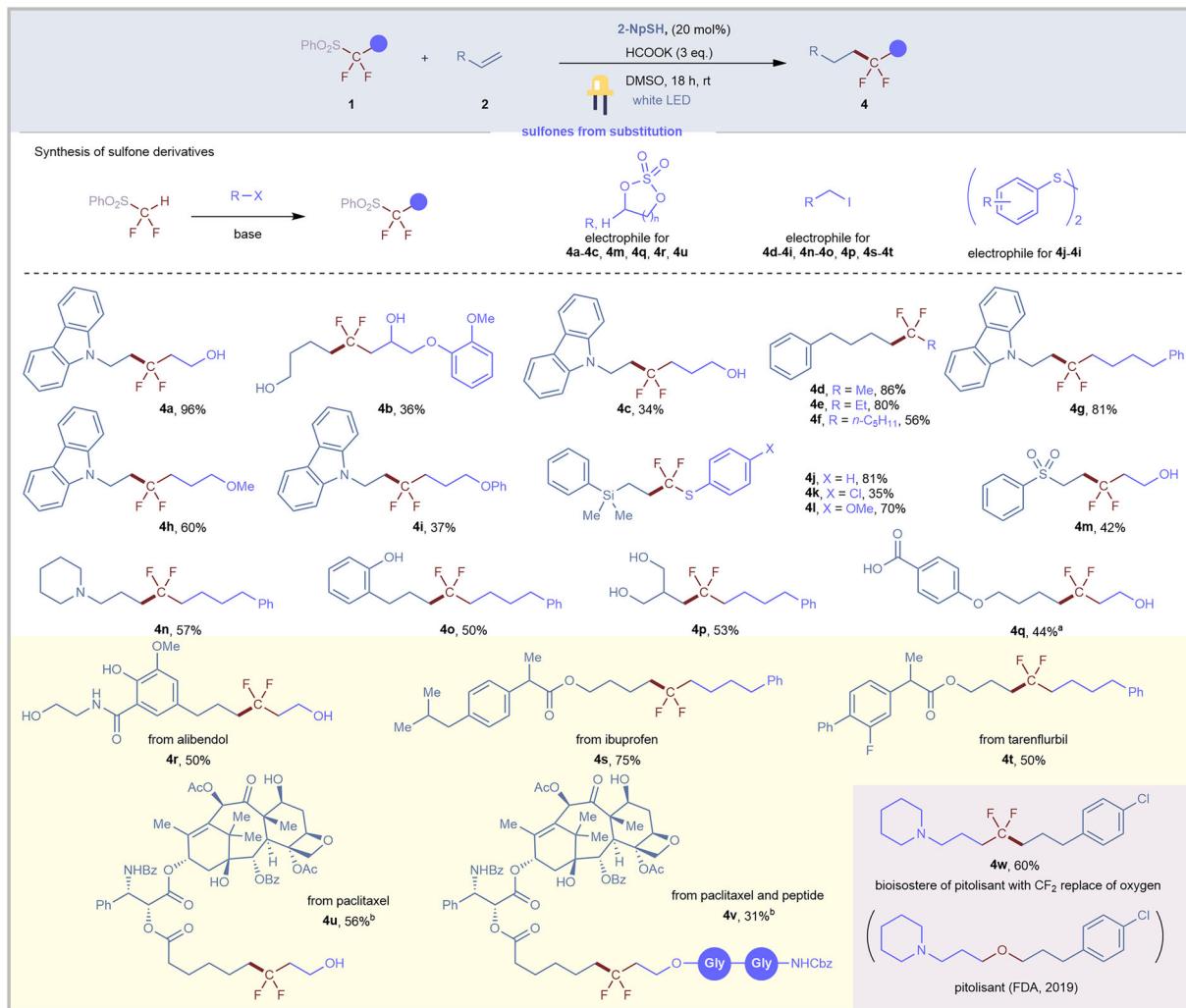
In scenarios without radical acceptors, the generation of difluoromethyl-containing products can be achieved via hydro-desulfonylation process from sulfone derivatives. Conventionally, this transformation was accomplished under acidic conditions employing highly reactive metals such as sodium amalgam and magnesium<sup>56–58</sup>. Herein, our tactic offers a moderate and efficient method for converting a (phenylsulfonyl)difluoromethyl group to a difluoromethyl group (Figs. 5 and 6a–i).

Besides a range of structurally diverse fluoroalkyl sulfones, the parent sulfone PhSO<sub>2</sub>CF<sub>2</sub>H (**1a**) also proved to be suitable for the reaction conditions (Fig. 6). The hydrodifluoromethylation of alkenes

demonstrated commendable functional group tolerance (**7a**–**7m**), as observed with the sulfone derivatives (Figs. 2 and 3). Difluoromethylation of arenethiol (**7n**) could be achieved following the procedure outlined in Fig. 4. Late-stage modification of a range of pharmaceutical compounds, namely tarenfluril (**7o**), oxaprozin (**7p**), ibuprofen (**7q**), mefenamic acid (**7r**) and alibendol (**7s**), and naturally occurring molecules, such as allylestrenol (**7t**), boldenone undecylate (**7u**) and caryophyllene oxide (**7v**), was also found to be fruitful (Fig. 6).

### Synthetic applications

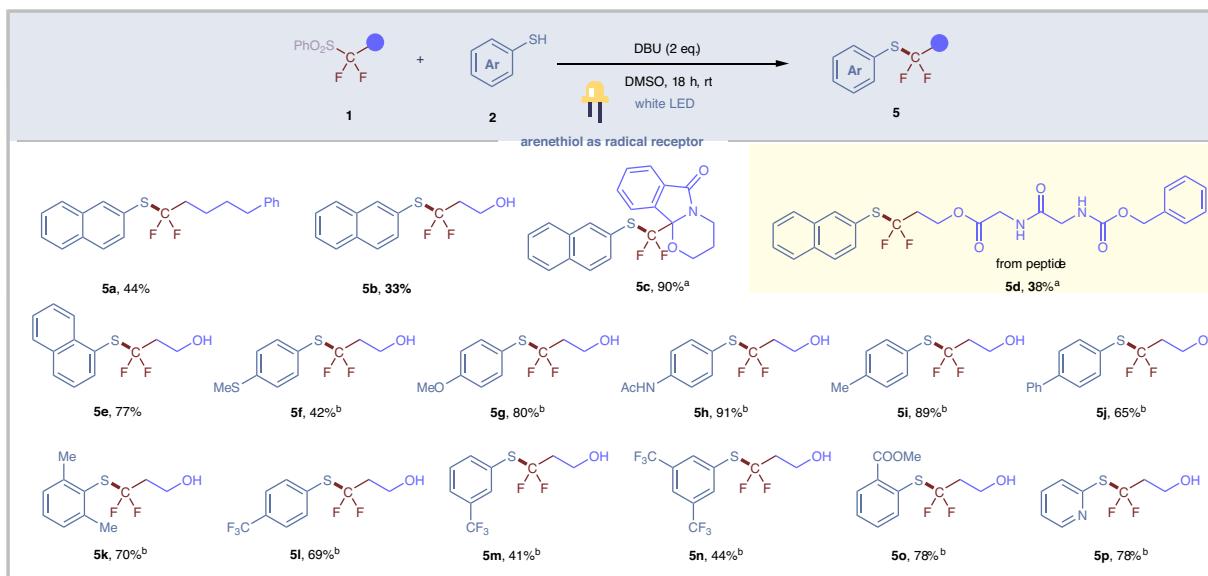
When sabinene, bearing a radical clock, was subjected to the reactions, the cyclopropane ring-opening product (**8a**) was isolated with a 5:1 selectivity for the 6-membered over the 5-membered ring (Fig. 7a). The methodology also lightened a route to the synthesis of saturated rings via radical cyclization of unconjugated dienes. Octahydronentalene (**8b**) was constructed following the tactic from cycloocta-1,5-diene (Fig. 7b). Of particular note, sunlight, the most ubiquitous and cost-free light source, proved highly effective in promoting the transformation (Fig. 7c). The practicality of this method was further confirmed through a gram-scale synthesis of *gem*-difluorides in a good yield (Fig. 7d).

**Fig. 3 | Scope of gem-difluorides from sulfones generated via substitutions**

**using alkenes as radical acceptors.** Reaction conditions: **2** (0.5 mmol, 1.0 equiv), **1** (2.0 equiv), 2-NpSH (20 mol%), HCO<sub>2</sub>K (3.0 equiv), DMSO (4 mL), white LED, room

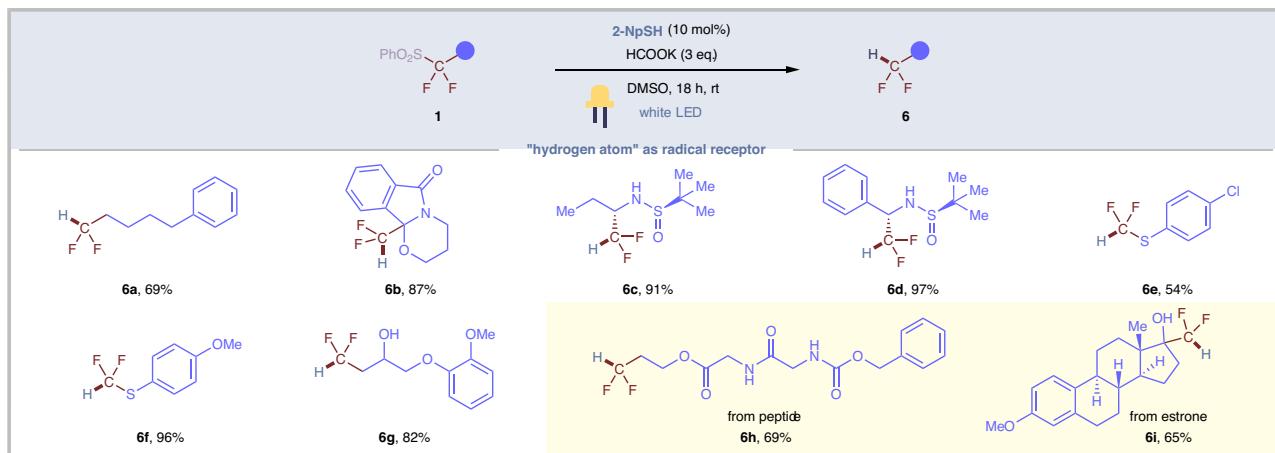
temperature, 18 h. All yields are isolated yields. <sup>a</sup>K<sub>2</sub>CO<sub>3</sub> (1.0 equiv) as an additive.

<sup>b</sup>The reaction was conducted on 0.2 mmol scale.

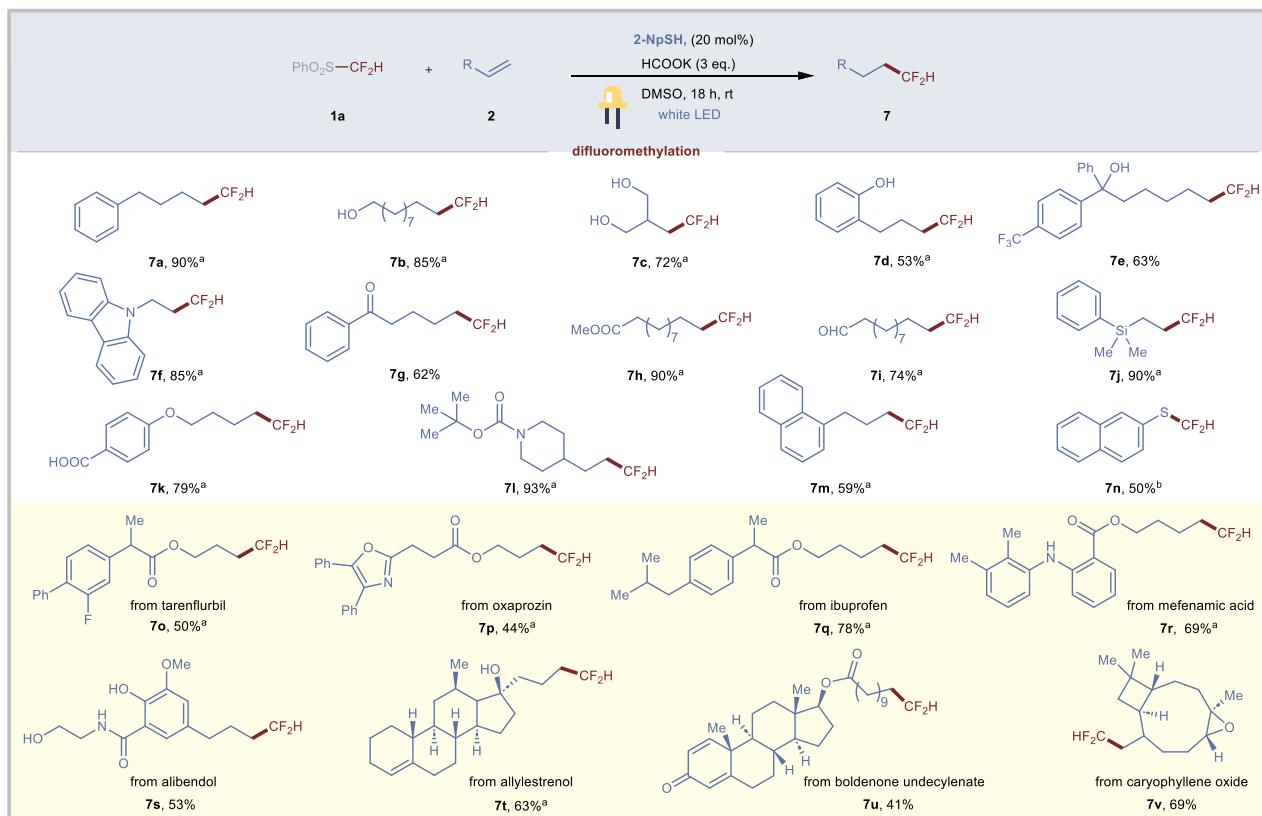
**Fig. 4 | Scope of gem-difluorides from sulfones with thiols as radical acceptors.**

Reaction conditions: **2** (0.5 mmol, 1.0 equiv), **1** (2.0 equiv), DBU (2.0 equiv), DMSO (4 mL), white LED, room temperature, 18 h. All yields are isolated yields. <sup>a</sup>1

(0.5 mmol, 1.0 equiv), **2** (2.0 equiv), <sup>b</sup>fac-Ir(ppy)3 (0.2 mol%) as an additive, blue LED instead of white LED. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



**Fig. 5 | Scope of *gem*-difluorides from sulfones with hydrogen atom as radical acceptor.** Reaction conditions: 1 (0.5 mmol), 2-naphthalenethiol (10 mol%), HCOOK (3.0 equiv), DMSO (4 mL), white LED, room temperature, 18 h. All yields are isolated yields.

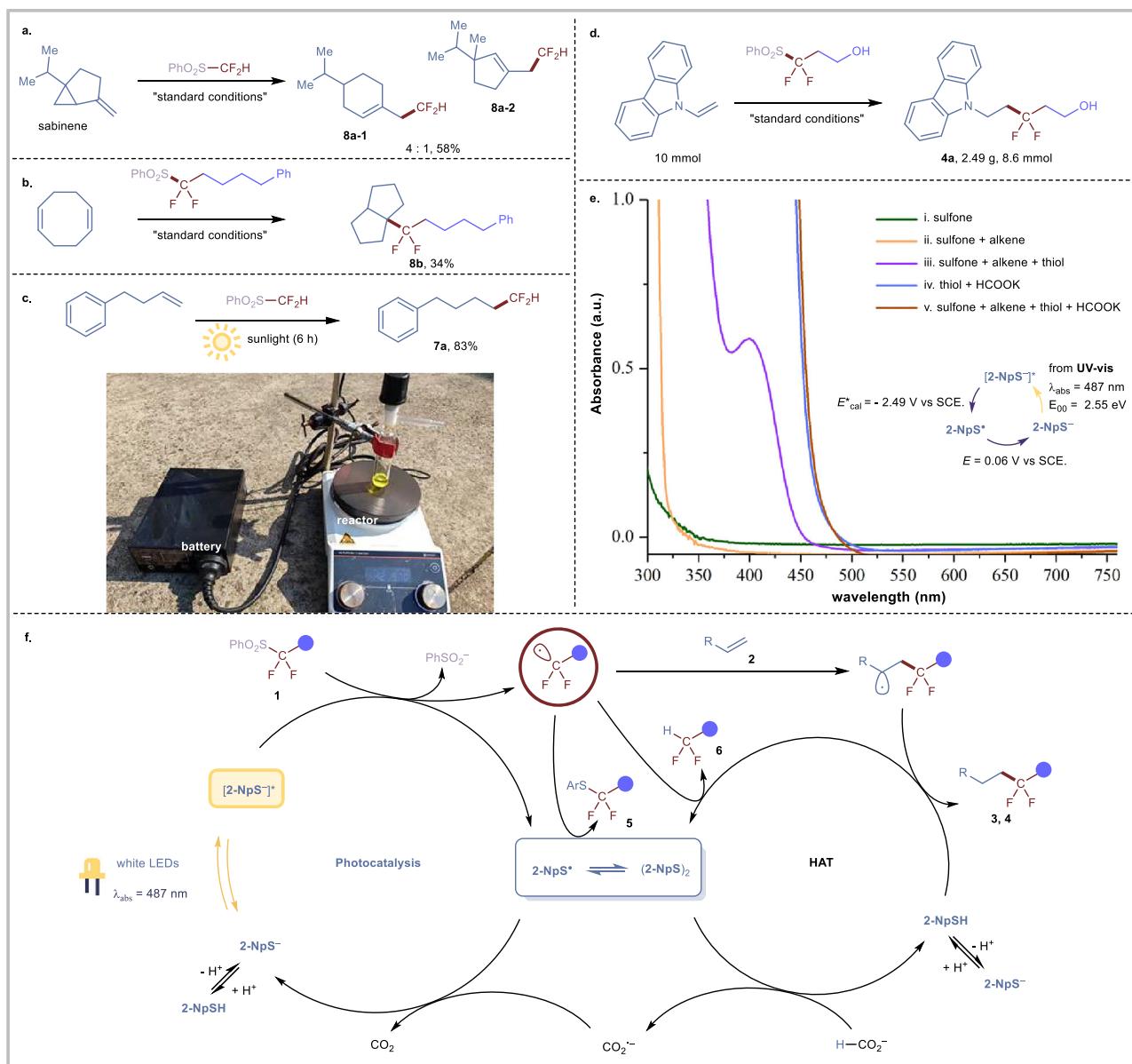


**Fig. 6 | Scope of hydrodifluoromethylation of alkenes.** Reaction conditions: 2 (0.5 mmol, 1.0 equiv), 1 (2.0 equiv), 2-NpSH (20 mol%), HCOOK (3.0 equiv), DMSO (4 mL), white LED, room temperature, 18 h. All yields are isolated yields. <sup>a</sup>Additional H<sub>2</sub>O (0.5 mL) was added. <sup>b</sup>Following conditions for construction of CF<sub>2</sub>-S bond in Fig. 4.

### Mechanistic investigation

The UV-vis absorption spectra unambiguously show that 2-naphthalenethiol exhibits absorption onset wavelength at 487 nm, which falls within the visible light range. Additionally, it indicates that the photoexcitation of 2-NpS<sup>−</sup> is more facile compared to reported arenethiolates<sup>71–74</sup>, as the latter necessitate irradiation at shorter wavelengths for excitation. Additionally, although *p*-MeOC<sub>6</sub>H<sub>4</sub>SH showed low activity under 450 nm blue LED irradiation (Table 1, entry 11), the thiol effectively catalyzed the reaction under 420 nm violet LED irradiation in 79% yield (see supplementary information, Table S5, entry 3). The negligible hypsochromic shift

observed between iv and v (as shown in Fig. 7e) supports that the thiolate directly participates in photoexcitation without undergoing electron donor-acceptor (EDA) complexation. Based on the spectra and electrochemical data ( $E_{p/2}(2\text{-NpS}^{\cdot}/2\text{-NpS}^{\cdot}) = 0.09$  V, see supplementary information, Fig. S13), strong reducibility of the excited thiolate was confirmed ( $E_{\text{cal}}(2\text{-NpS}^{\cdot}/[2\text{-NpS}^{\cdot}]^{\cdot}) = -2.49$  V)<sup>86</sup>. The low quantum yield ( $\Phi = 0.20$ ) does not strongly support a chain process (see Supplementary Information 2.4.4). In reference to previous reports<sup>65,66,71</sup>, we propose a thiol-catalyzed reductive radical mechanism (Fig. 7f). Upon photoexcitation, thiolate (2-NpS<sup>−</sup>) transitions to its excited state [2-NpS<sup>·</sup>]<sup>·</sup>. This strong reducing agent [2-



**Fig. 7 | Applications and mechanistic studies.** **a** Radical clock reaction. **b** Radical cyclization of unconjugated dienes. **c** Sunshine-induced difluoroalkylation. **d** Gram-scale reaction. **e** UV-vis absorption spectra of species in the transformation and oxidative quenching cycle of 2-naphthalenethiolate. **f** Proposed mechanism.

$\text{NpS}^*_{\text{1}}$  readily undergoes a single electron transfer (SET) to a sulfone, resulting in the generation of a fluoroalkyl radical and a thiol radical ( $2\text{-NpS}^*$ ). The thiol radical can then undergo a tandem reaction with formate, yielding a carbon dioxide radical anion ( $\text{CO}_2^-$ ) and regenerating the thiolate. Alternatively, the thiol radical ( $2\text{-NpS}^*$ ) can also undergo SET process with the carbon dioxide radical anion ( $\text{CO}_2^-$ ), leading to the regeneration of the thiolate ( $2\text{-NpS}^-$ ). Meanwhile, the alkene synchronously reacts with the fluoroalkyl radical, forming an adduct intermediate. As a hydrogen atom transfer (HAT) catalyst, the thiol ( $2\text{-NpSH}$ ) facilitates the transfer of a hydrogen atom to the adduct intermediate, culminating in the formation of *gem*-difluorides (**3,4**). Besides alkenes, the fluoroalkyl radical may be converted to  $\text{ArSCF}_2\text{R}$  (**5**) with a thiol radical (see supplementary information 2.4.3 for more details). Additionally, the fluoroalkyl radical can be directly hydrogenated to generate  $\text{RCF}_2\text{H}$  (**6**).

## Discussion

In conclusion, we discover  $\text{PhO}_2\text{S}-\text{CF}_2\text{H}$  (**1a**), a readily available reagent, as a remarkably versatile difluoromethylene radical anion synthon

(diFRAS,  $\cdot\text{CF}_2^-$ ), which serves as an efficient  $\cdot\text{CF}_2^-$  bridge between an electrophile and a radical acceptor. Naturally occurring molecules and pharmaceutically relevant molecules can be late-stage functionalized by either radical or anion end of the diFRAS ( $\cdot\text{CF}_2^-$ ). This synthetic protocol not only offers a powerful and practical tool for the assembly of a wide range of structurally diverse *gem*-difluorides ( $\text{R}^1\text{-CF}_2\text{-R}^2$ ), it also provides new insights into the privileged chemical reactivities of fluoroalkyl sulfones.

## Methods

### General procedure for incorporation of an alkene with sulfone **1**

To a dry Schlenk tube were added 2-Naphthalenethiol (0.1 mmol, 20 mol%), and potassium formate (1.5 mmol, 3.0 equiv), alkene (0.5 mmol, 1.0 equiv), sulfone **1** (1.0 mmol, 2.0 equiv) and dry DMSO (4.0 mL) under argon atmosphere. The mixture was stirred under irradiation with 10 W white LED for 18 h at room temperature. After the reaction was complete, water and brine were added and the mixture was extracted with diethyl ether three times. The combined extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The

residue was purified by column chromatography on silica gel to afford the product.

### General procedure for incorporation of an arenethiol with sulfone 1

To a dry Schlenk tube were added arenethiol (0.5 mmol, 1.0 equiv), sulfone **1** (1.0 mmol, 2.0 equiv), *fac*-Ir(ppy)<sub>3</sub> (0.001 mmol, 0.2 mol%), DBU (1.0 mmol, 2.0 equiv) and dry DMSO (4.0 mL) under argon atmosphere. The mixture was stirred under irradiation with 10 W white LED for 18 h at room temperature. After the reaction was complete, water and brine were added and the mixture was extracted with diethyl ether three times. The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by column chromatography on silica gel to afford the product.

### General procedure for hydrodesulfonylation of sulfone 1

To a dry Schlenk tube were added 2-Naphthalenethiol (0.05 mmol, 10 mol%) and potassium formate (1.5 mmol, 3.0 equiv), sulfone **1** (0.5 mmol, 1.0 equiv), and dry DMSO (4.0 mL) under argon atmosphere. The mixture was stirred under irradiation with 10 W white LED for 18 h at room temperature. After the reaction was complete, water and brine were added and the mixture was extracted with diethyl ether three times. The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by column chromatography on silica gel to afford the product.

### Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Crystallographic data for the structures of sulfone **1i** (precursor of **3g**) reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2452837. Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>. Experimental details and the spectroscopic data of the corresponding compounds are provided in the Supplementary Information. All data supporting the study are available from the corresponding author on request.

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## Author contributions

J.H. conceived the concept. S.S., R.J., X.Z. and J.R. performed the experiments. S.S., R.J., X.Z. Z.W. and C.N. contributed to the analysis and interpretation of the data. S.S., X.Z., and J.H. wrote the paper.

## Competing interests

The authors declare no competing interests.

## Additional information

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