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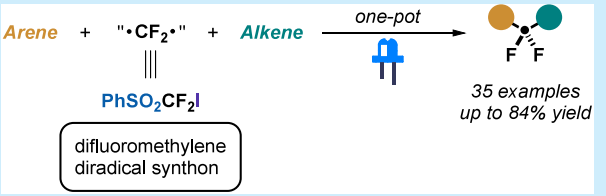
# $PhSO_2CF_2I$-Enabled Sequential Radical Formation for One-Pot $CF_2$-Linked Molecular Construction

Yunlong Zhao, Feng Zhao, Chuanfa Ni, and Jinbo Hu*

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**ABSTRACT:** A one-pot strategy for the construction of $CF_2$-linked molecules using iododifluoromethyl phenyl sulfone ($PhSO_2CF_2I$) as a difluoromethylene diradical synthon is described. With the advantage of the distinct reactivity of the C−I and C−S bonds in $PhSO_2CF_2I$, two chemically differentiated $CF_2$-centered radicals are generated sequentially under visible light irradiation. The stepwise generation and trapping of two distinct $CF_2$-centered radicals enables arenes and alkenes to be sequentially installed in one pot, offering a streamlined route to a wide array of $CF_2$-linked molecules. The method proceeds under mild conditions with a broad substrate scope and excellent functional group compatibility and is applicable to the late-stage modification of bioactive molecules.

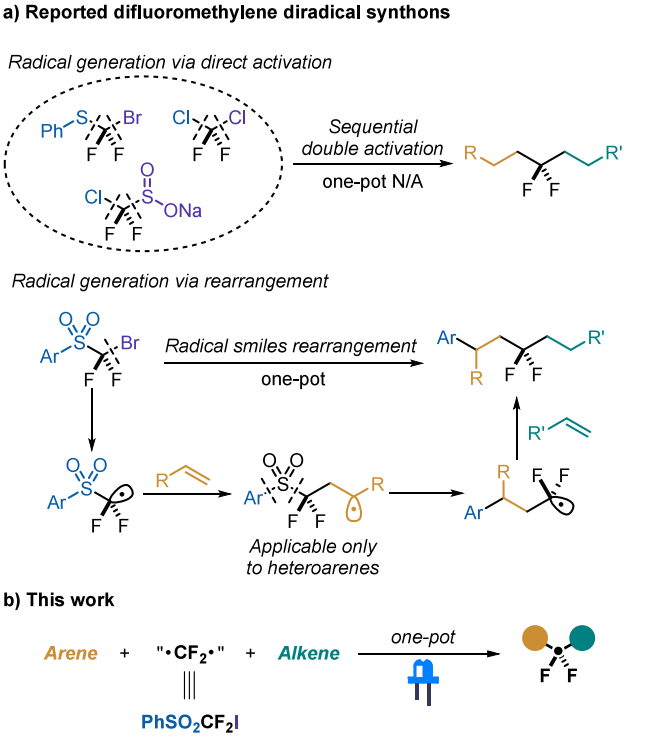



Fluorinated organic compounds play a central role in pharmaceuticals,[1,2] agrochemicals,[3] and materials sciences[4,5] due to their ability to modulate key physicochemical properties, such as metabolic stability, lipophilicity, and bioavailability. Among these motifs, the difluoromethylene ($CF_2$) units serve as versatile carbon linkers that can mimic ether oxygen or carbonyl groups while imparting unique steric and electronic features.[6] The presence of $CF_2$ motifs in clinically relevant molecules, such as voxilaprevir, tafluprost, and lenacapavir, highlights the importance of developing efficient and general methods for their selective installation.[7−10]

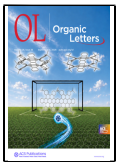
The construction of $CF_2$-containing frameworks has been achieved through several types of reactive intermediates (or synthons), including difluorocarbene,[11−13] difluoromethylene dianions,[14−17] difluoromethylene radical anions,[18−28] and difluoromethylene diradicals.[29−35] Each of these approaches enables distinct bond-forming scenarios depending on the reaction partners involved. Despite the significant progress achieved in difluoromethylene diradical synthon strategies, most existing methods still rely on single-reactivity modes or pre-functionalized substrates, thereby limiting their step economy and structural diversity (Scheme 1a).

Fluoroalkyl sulfones represent a versatile class of $CF_2$-containing building blocks. For example, difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) and related derivatives can participate in diverse transformations,[36,37] including dianion-type reactivity and radical-mediated processes.[16] Chlorodifluoromethyl sulfone derivatives, such as $ClCF_2SO_2Na$, have also been widely used as $CF_2$ diradical synthons.[33] However, to date, (phenylsulfonyl)difluoromethylated reagents of the type $PhSO_2CF_2X$ have received little attention as platforms for controlled sequential radical generation.

**Scheme 1. Background and Reaction Design**




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Herein, we report a $PhSO_2CF_2I$-enabled strategy for one-pot construction of $CF_2$-linked molecules by sequential generation of two distinct $CF_2$-centered radicals and their selective trapping with arenes and alkenes (Scheme 1b). This strategy exploits the distinct reactivity of the C−I and C−S bonds in $PhSO_2CF_2I$, enabling the sequential generation of two distinct $CF_2$-centered radicals under unified reaction conditions. Initial C−I bond cleavage generates a (phenylsulfonyl)difluoromethyl radical that is selectively trapped by electron-rich arenes. Subsequent C−S bond activation furnishes an aryldifluoromethyl radical, which undergoes alkene addition, thereby enabling sequential incorporation of arene and alkene partners in one pot.

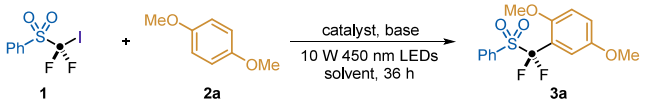
A key challenge in realizing this strategy was therefore to identify a simple and efficient reaction system that enables a fully one-pot, two-step radical sequence in which both transformations proceed continuously without isolation or purification of intermediates, allowing seamless progression from arene functionalization to alkene incorporation.

To this end, we focused on identifying conditions that enable efficient C−I bond activation compatible with the subsequent radical transformation. Our initial studies employed the readily available photocatalyst *fac*-Ir(ppy)$_3$ with 1,3,5-trimethoxybenzene to screen a range of reaction conditions. The results revealed that this strategy exhibited a limited arene substrate scope and was highly sensitive to the electronic nature of the arenes (see the Supporting Information for details). Consequently, alternative activation strategies need to be developed to achieve broad arene compatibility while remaining compatible with the subsequent reaction steps.

It has been previously reported that triarylphosphine-based systems represent a mild approach for the activation of fluoroalkyl iodides.[38−45] Inspired by Zhang's elegant demonstration that triarylphosphines can activate C−I bonds through electron donor−acceptor (EDA) interactions to generate fluoroalkyl radicals for arene addition,[43] we envisioned that this activation mode could be adapted to initiate the first-step radical transformation in our sequential process. Using 1,4-dimethoxybenzene (**2a**) as the model substrate, we systematically evaluated a series of triarylphosphines (entries 1−6), solvents (entries 7 and 8), and bases (entries 9−14). Among the catalysts examined, tris(4-trifluoromethylphenyl)phosphine [P(4-$CF_3C_6H_4$)$_3$] delivered the highest yield of the desired product. Optimal performance was achieved using DMSO as the solvent and $K_2CO_3$ as the base. Notably, DMSO was also compatible with the subsequent transformation, allowing the entire one-pot sequence to proceed without solvent exchange. Although acetonitrile is a good solvent for the first-step transformation, the subsequent C−S activation step proceeded less efficiently in this solvent, making DMSO the preferred choice for the overall sequential process. Finally, decreasing the catalyst loading resulted in a gradual decrease in the yield (entries 15 and 16), indicating that a sufficient catalyst concentration is required to sustain efficient radical generation and maintain the sequential transformation (Table 1).

Following optimization of the first-step conditions, we next developed the one-pot sequential protocol. Building on our previously established C−S bond activation of fluoroalkyl sulfones,[28] *N*-phenylacrylamide, Hantzsch ester (HE), and CsOAc were added *in situ* after completion of the first step and the reaction mixture was further irradiated with blue LEDs for 12 h. Gratifyingly, the desired product **5a** was obtained in 80%

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | catalyst | solvent | base | yield of **3a** (%)[b] |
|---|---|---|---|---|
| 1 | $PPh_3$ | DMSO | $K_2CO_3$ | 71 |
| 2 | $PCy_3$ | DMSO | $K_2CO_3$ | 77 |
| 3 | $P(OC_6H_4)_3$ | DMSO | $K_2CO_3$ | 65 |
| 4 | $P(4\text{-}MeC_6H_4)_3$ | DMSO | $K_2CO_3$ | 69 |
| 5 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | $K_2CO_3$ | 87 |
| 6 | $CH_2(PPh_2)_2$ | DMSO | $K_2CO_3$ | 78 |
| 7 | $P(4\text{-}CF_3C_6H_4)_3$ | DMF | $K_2CO_3$ | 58 |
| 8 | $P(4\text{-}CF_3C_6H_4)_3$ | MeCN | $K_2CO_3$ | 76 |
| 9 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | DIEPA | 7 |
| 10 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | DBU | N.D. |
| 11 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | CsOAc | 24 |
| 12 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | KOAc | 37 |
| 13 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | NaOAc | 44 |
| 14 | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | LiOAc | 35 |
| 15[c] | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | $K_2CO_3$ | 69 |
| 16[d] | $P(4\text{-}CF_3C_6H_4)_3$ | DMSO | $K_2CO_3$ | 62 |

[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv), base (0.4 mmol, 2.0 equiv), catalyst (25 mol %), and solvent (1.0 mL), irradiated with 10 W 450 nm LEDs at 20 °C for 36 h. [b]Determined by $^{19}F$ NMR spectroscopy with $PhOCF_3$ as an internal standard. [c]Catalyst (20 mol %). [d]Catalyst (10 mol %). N.D. = not detected.

isolated yield. Based on these results, the standard one-pot conditions were established as follows: **1** (0.4 mmol, 2.0 equiv), **2a** (0.6 mmol, 3.0 equiv), $K_2CO_3$ (0.8 mmol, 4.0 equiv), P(4-$CF_3C_6H_4$)$_3$ (50 mol %), and DMSO (2.0 mL), irradiated with 10 W 450 nm LEDs at 20 °C for 36 h. Subsequently, *N*-phenylacrylamide (1.0 equiv), Hantzsch ester (2.0 equiv), and CsOAc (2.0 equiv) were added, and irradiation was continued under identical conditions for an additional 12 h.

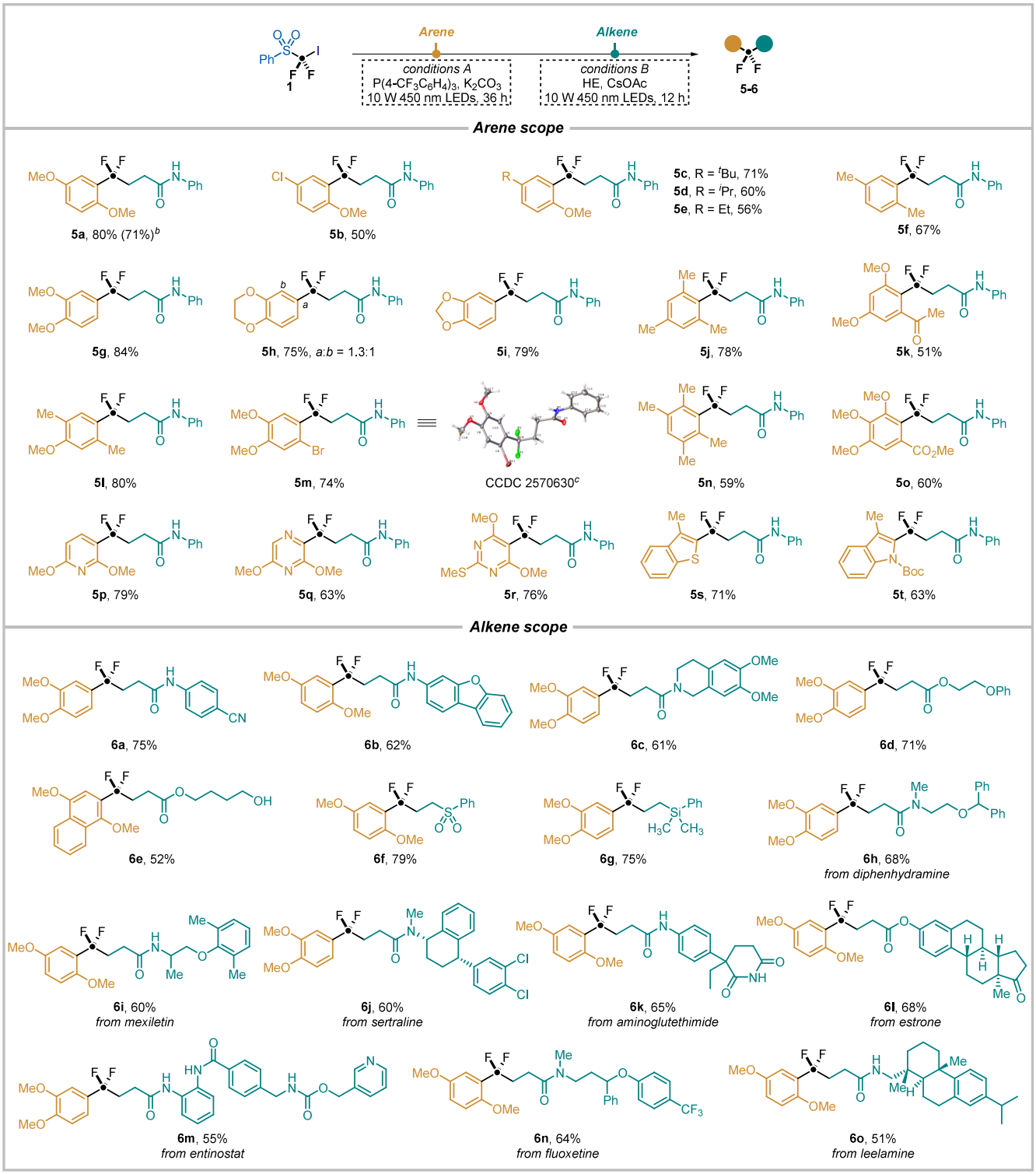
With the optimized one-pot protocol in hand, we next examined the substrate scope of this sequential radical process (Scheme 2). For arene substrates, disubstituted (**5a−5i**), trisubstituted (**5j−5m**), and tetrasubstituted (**5n** and **5o**) benzenes all furnished the desired products in moderate to good yields. A range of heterocycles, including pyridine (**5p**), pyrazine (**5q**), pyrimidine (**5r**), benzothiophene (**5s**), and indole (**5t**), were also well-tolerated. Notably, when multiple reactive sites were present, exclusive or predominant monofunctionalization was observed (**5b−5e**, **5g**, **5i**, **5k−5m**, and **5p**), likely due to steric hindrance imparted by the benzenesulfonyldifluoromethyl radical as well as electronic differentiation among arene positions. The structure of **5m** was unambiguously confirmed by single-crystal X-ray diffraction analysis (see Scheme 2). For alkene substrates, acrylamides (**6a−6c**), acrylates (**6d** and **6e**), and alkenes bearing sulfone (**6f**) or silyl (**6g**) substituents reacted smoothly under the standard conditions. Simple acrylamides and acrylates were also compatible with reaction conditions. Acrylamide and ethyl acrylate afforded the corresponding products in 39 and 60% yields, respectively, as determined by $^{19}F$ NMR analysis (see the Supporting Information for details). Finally, this strategy was successfully applied to the late-stage aryldifluoromethylation of bioactive molecules. Derivatives of diphenhydramine (**6h**), mexiletine (**6i**), sertraline (**6j**), aminoglutethimide (**6k**),

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**Scheme 2. One-Pot Synthesis of $CF_2$-Containing Compounds**[a]




[a]Reaction conditions: **1** (0.4 mmol, 2.0 equiv), arene (0.6 mmol, 3.0 equiv), $P(4\text{-}CF_3C_6H_4)_3$ (0.1 mmol, 50 mol %), $K_2CO_3$ (0.8 mmol, 4.0 equiv), and DMSO (2.0 mL), irradiated with 10 W 450 nm LEDs at 20 °C for 36 h, and then the addition of alkene (0.2 mmol, 1.0 equiv), HE (0.4 mmol, 2.0 equiv), and CsOAc (0.4 mmol, 2.0 equiv), irradiated with 10 W 450 nm LEDs at 20 °C for 12 h. All yields are isolated yields and were calculated based on the amount of alkene. [b]The reaction was performed on a 1 mmol scale. [c]Thermal ellipsoids are drawn at the 50% probability level.

estrone (**6l**), entinostat (**6m**), fluoxetine (**6n**), and leelamine (**6o**) all underwent efficient functionalization in moderate yields, highlighting the applicability of this protocol for the late-stage modification of complex molecules.

To gain insights into the reaction mechanism, a series of mechanistic experiments was conducted (Figure 1). Radical inhibition experiments with TEMPO showed that both the arene difluoroalkylation and the subsequent alkene difluor-



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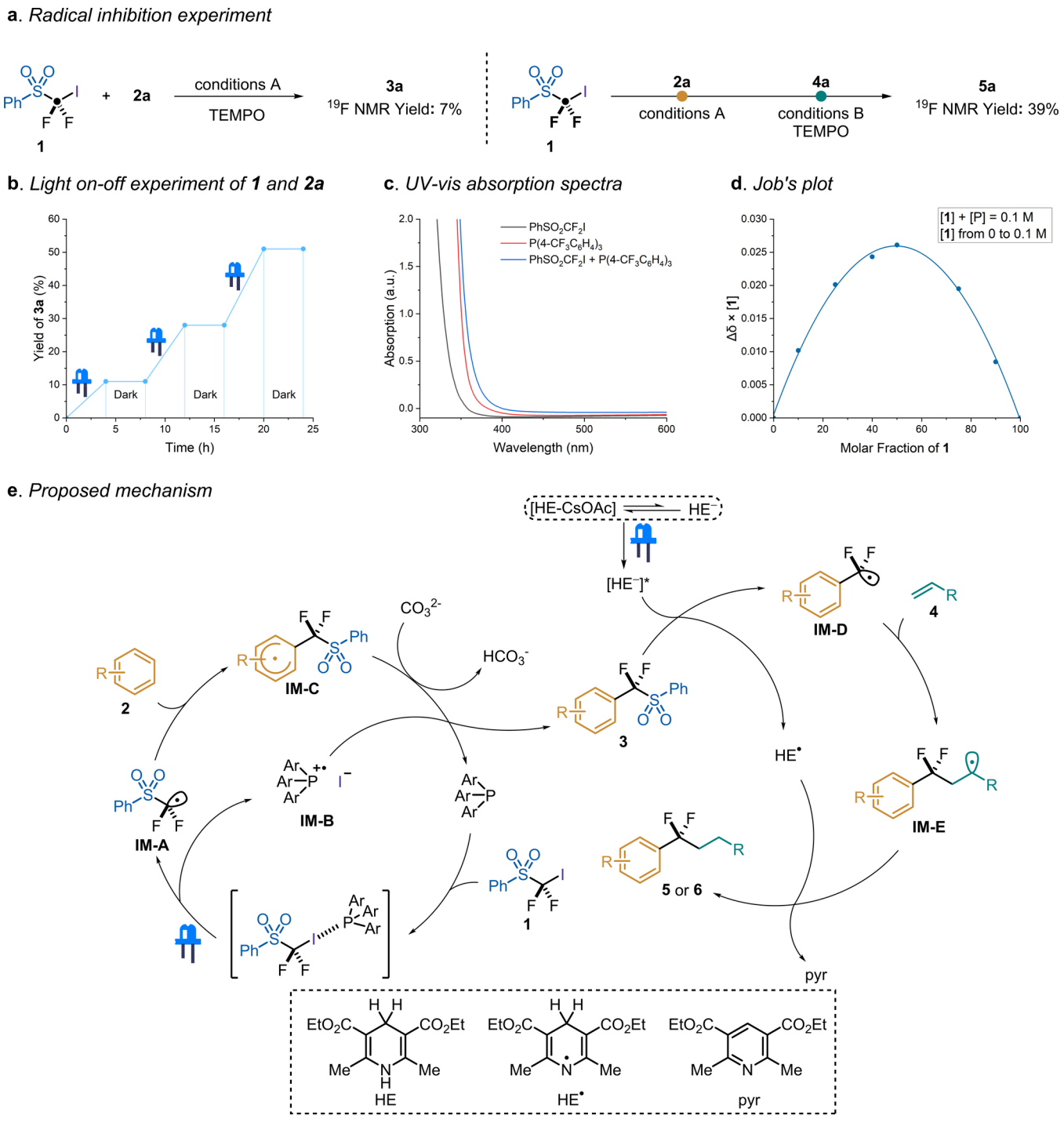



**Figure 1.** Mechanistic investigations and proposed mechanism. (a) Radical inhibition experiments. (b) Light on/off experiment of **1** and **2a**. (c) UV−vis absorption spectrum. Each component was 0.1 M. (d) Job's plot. The total concentration of **1** and $P(4\text{-}CF_3C_6H_4)_3$ was maintained constant at 0.1 M. (e) Proposed mechanism.

oalkylation were significantly suppressed (Figure 1a), while light on/off experiments demonstrated that product formation occurred only under continuous irradiation (Figure 1b). Collectively, these results are consistent with a radical pathway. The UV−vis absorption spectrum of a mixture of $PhSO_2CF_2I$ (**1**) and $P(4\text{-}CF_3C_6H_4)_3$ exhibited a noticeable red shift relative to those of the individual components, consistent with the formation of an electron donor−acceptor (EDA) complex (Figure 1c). In addition, the 1:1 molar ratio between **1** and $P(4\text{-}CF_3C_6H_4)_3$ in the EDA complex was established using Job's method[46] with $^{19}F$ NMR spectroscopy, in which the maximal corrected chemical shift difference appeared at 50% molar fraction of **1** (Figure 1d).

Based on these experimental findings and previous studies,[28,47−52] a plausible reaction mechanism is proposed (Figure 1e). Photoexcitation of the EDA complex formed between $PhSO_2CF_2I$ (**1**) and $PAr_3$ triggers single-electron transfer (SET), generating the (phenylsulfonyl)difluoromethyl radical ($PhSO_2CF_2^{\bullet}$, **IM-A**) together with phosphine radical cation species **IM-B**. Radical addition of **IM-A** to arene **2**



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affords intermediate **IM-C**, which undergoes SET with **IM-B** followed by base-promoted deprotonation to furnish intermediate **3**. In the second stage of the one-pot sequence, compound **3** undergoes photoinduced, SET-mediated C−S bond activation under the HE/CsOAc system, potentially involving the corresponding Hantzsch N anion, to generate the aryl difluoromethyl radical ($ArCF_2^•$, **IM-D**), which is subsequently trapped by alkene **4** to give alkyl radical **IM-E**. Hydrogen atom transfer from the Hantzsch ester radical ($HE^•$) then affords the desired product **5** or **6**.

In summary, we have developed a $PhSO_2CF_2I$-enabled one-pot strategy for the construction of $CF_2$-linked molecules through sequential radical formation. By exploitation of the differential reactivity of the C−I and C−S bonds in $PhSO_2CF_2I$, two distinct carbon fragments can be introduced sequentially under unified reaction conditions. The broad substrate scope and compatibility with late-stage functionalization demonstrate the versatility of $PhSO_2CF_2I$ as a practical difluoromethylene diradical synthon for modular $CF_2$-linked molecular construction.

## ■ 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.6c02986.

Experimental procedures, copies of NMR spectra, and X-ray crystallographic data (PDF)

### Accession Codes

Deposition Number 2570630 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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