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Angewandte Chemie International Edition

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GDCh German Chemical Society

How to cite: *Angew. Chem. Int. Ed.* **2026**, e8941062
doi.org/10.1002/anie.8941062

RESEARCH ARTICLE

Sulfone Activation Triggered by Iodide Anion for Photoinduced Fluoroalkylations

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Received: 9 April 2026 | **Revised:** 30 June 2026 | **Accepted:** 20 July 2026

Keywords: EDA complex | fluorine chemistry | organic synthesis | photocatalysis | radical fluoroalkylation

ABSTRACT

Radical fluoroalkylation via electron donor–acceptor (EDA) complex photochemistry stands out as a particularly attractive approach, owing to its mild conditions and the absence of an external metal photocatalyst or organic dye. Fluoroalkyl sulfones, valued for their stability, accessibility, and structural tunability, have emerged as versatile precursors for radical fluoroalkylation. Herein, we present a photocatalyst-free and straightforward method for direct fluoroalkylation through an EDA complex, utilizing inexpensive iodide anion as an electron donor and fluoroalkyl sulfones as acceptors. Upon visible light irradiation, the EDA complex undergoes single-electron transfer (SET) to generate fluoroalkyl radicals, which subsequently react with a diverse array of silyl enol ethers with high efficiency. The method features mild reaction conditions, broad functional group compatibility, and an extensive substrate scope that encompasses bioactive molecules and sterically demanding architectures. Mechanistic investigations indicate the involvement of an iodide-mediated EDA complex and support the proposed radical-generation pathway. This work establishes a practical and sustainable platform for fluoroalkylation, underscoring the utility of iodide in EDA-based photochemistry and broadening the scope of radical synthetic methods.

1 | Introduction

The incorporation of fluorinated motifs, particularly fluoroalkyl groups (R_f) [1, 2], has become a fundamental strategy in the development of pharmaceuticals [3], agrochemicals [4], and advanced materials [5–7], driven by the unique properties imparted by fluorine. Radical fluoroalkylation has emerged as a key transformation, leveraging the distinct reactivity of fluoroalkyl radicals relative to their ionic counterparts—cationic species are stabilized through fluorine resonance, whereas anionic species are destabilized by p–π repulsion [8–10]. Photocatalytic fluoroalkylation, particularly via electron donor–acceptor (EDA) complex photochemistry, has gained prominence as a powerful approach due to its mild conditions, operational simplicity, capacity to activate inert substrates, and its independence from exogenous photocatalysts [11, 12]. This strategy enables the generation of reactive fluoroalkyl radicals under visible light through ground-state association between an electron acceptor (A) and a donor (D). In designing an effective EDA-mediated fluoroalkylation system, the selection of both donor and acceptor components is critical. A wide range of fluoroalkyl radical precursors, including fluoroalkyl iodides (R_fI) [1, 13–16], Umemoto's reagent [17], and Togni's reagents [18, 19], have been successfully utilized as electron acceptors in EDA-based transformations [20]. However, many of these reagents suffer from high cost, toxicity, or instability. Consequently, the identification of stable, readily accessible, and cost-effective fluoroalkyl sources remains highly desirable.

Following our initial report in 2016 on sulfone-based radical fluoroalkylation via S—C bond cleavage of difluoromethyl

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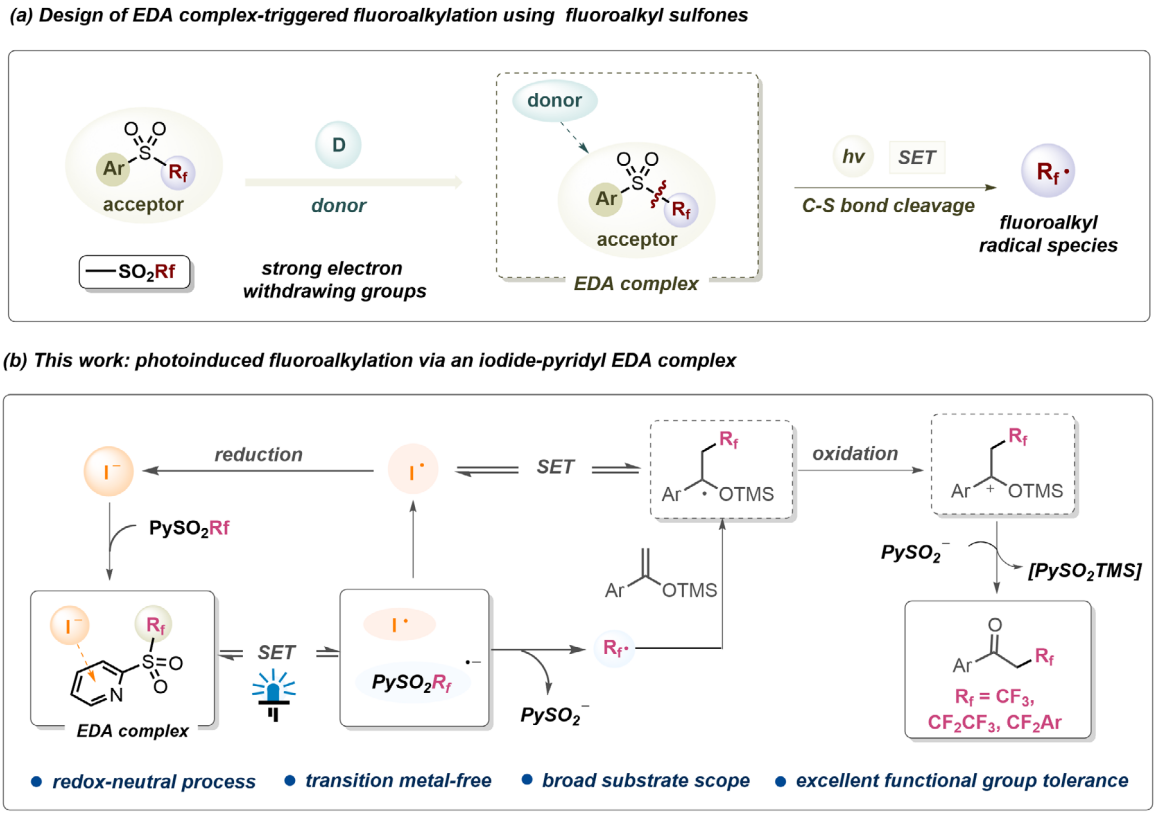


FIGURE 1 | Background and conceptual framework of this work. (a) Design of EDA complex-triggered fluoroalkylation by using fluoroalkyl sulfones. (b) Photoinduced fluoroalkylation via an iodide–pyridyl EDA complex.

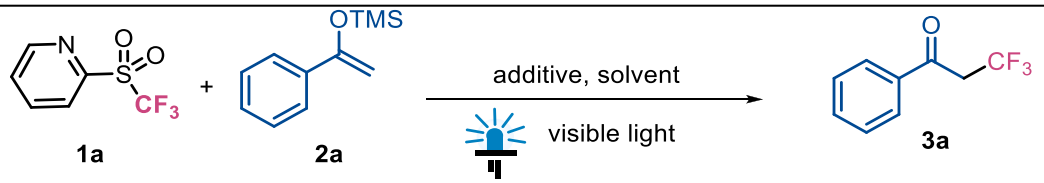
benzothiazolyl sulfone ($BTSO_2CF_2H$) [21], aryl fluoroalkyl sulfones (R_f–SO_2–Ar) have gained recognition as privileged precursors for fluoroalkyl radicals, owing to their stability, ready availability, and ease of handling [22–27]. Benzothiazolyl sulfones have further proven to be excellent acceptors in the formation of EDA complexes for fluoroalkyl radical generation [28, 29]. Continuing our interest in utilizing fluoroalkyl sulfones as fluoroalkyl-transfer reagents, our group reported in 2022 an *S*-trifluoromethylation of thiophenols via a photoactive EDA complex, employing arylthiolate anions as the electron donor and trifluoromethyl phenyl sulfone as the acceptor [30]. This ongoing effort prompted us to consider that a readily accessible EDA donor could enhance the fluoroalkyl transfer efficiency and expand the substrate scope. Tertiary amines [31–34] and organosulfur compounds [35–38] have long been employed as effective electron donors for EDA complex formation. More recently, iodide anions have emerged as inexpensive and distinctive electron donors in EDA complex-mediated transformations [39–46]. The strongly electron-withdrawing nature of the fluoroalkyl sulfone group renders these sulfones highly promising as electron acceptors, positioning them for application in EDA-mediated fluoroalkylation (Figure 1a). Despite prior reports on the photocatalytic trifluoromethylation of silyl enol derivatives, a common feature among these methods is their obligatory use of external metal photocatalysts [47–51]. The elimination of this dependency represents a significant synthetic challenge and serves as the driving force for our present work. By elegantly leveraging pyridyl fluoroalkyl sulfone reagents as electron acceptors and iodide as the electron donor, we herein report a visible light-triggered generation of fluoroalkyl radicals and their subsequent capture by silyl enol ethers, furnishing a diverse array of fluoroalkylated compounds (Figure 1b).

2 | Results and Discussion

Our studies commenced with trifluoromethyl phenyl sulfone as the trifluoromethyl source and electron acceptor, sodium iodide (NaI) as an electron-donor additive, and 1-phenyl-1-trimethylsiloxyethylene **2a** as the fluoroalkyl radical capture agent, in *N*,*N*-dimethylacetamide (DMAc), under blue LED irradiation (450 nm) for 24 h. Although the initial trial resulted in a low yield of 9% (Table S1, entry 2), the formation of even a trace amount of product served as proof of concept, demonstrating that iodide anions can form an EDA complex with the sulfone to initiate the generation of trifluoromethyl radicals. We hypothesized that the low efficiency was likely due to the limited stability of the EDA complex between iodide and the phenyl sulfone, resulting in either insufficient complex concentration or inadequate reactivity to sustain a catalytic cycle. To overcome this limitation, we replaced phenyl sulfone with more electron-deficient analogues to enhance the stability of the EDA complex and charge-transfer process. The bis(trifluoromethyl)-substituted phenyl sulfone gave the product in 76% yield (Table S1, entry 3), while the more electron-deficient trifluoromethyl 2-pyridyl sulfone **1a** proved optimal, affording the product in nearly quantitative yield (Table 1, entry 1). Control experiments demonstrated that removal of NaI, or its replacement with NaCl or NaBr, completely suppressed product formation (Table 1, entries 2–4). We then examined a series of iodide salts, including

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TABLE 1 | Optimization of the reaction conditions[a].



Entry	Additive	Solvent	Light source (nm)	Yield[a] (%)
1	NaI	DMAc	450	96
2	None	DMAc	450	ND
3	NaCl	DMAc	450	ND
4	NaBr	DMAc	450	ND
5	CsI	DMAc	450	97
6	HI	DMAc	450	55
7	CsI	DMF	450	49
8	CsI	NMP	450	70
9	CsI	CH_3CN	450	4
10	CsI	DMSO	450	9
11	CsI	DMAc	365	45
12	CsI	DMAc	510	<1
13	CsI	DMAc	In dark	ND
14[b]	CsI	DMAc	450	92
15[c]	CsI	DMAc	450	82

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), additive (0.15 mmol), solvent (1 mL), N_2 atmosphere, 24 h. Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.
[b]CsI (50 mol%), 48 h.
[c]CsI (20 mol%), 72 h. ND = Not Detected.

LiI, KI, RbI, CsI, TBAI, and Ph_4PI, to assess the influence of the cation on reactivity. All delivered the target product in moderate-to-excellent yields (Table S1), with CsI proving optimal (Table 1, entry 5). Even using HI as the iodide source provided the product in 55% yield, along with 27% of CF_3I as a by-product (Table 1, entry 6). This observation confirms that the iodide ion is essential as the electron donor for the EDA complex. The lower yield likely results from acid-promoted decomposition and hydrolysis of **2a**, which competes with the desired pathway. Considering the potential influence of solvents on EDA complex formation [52, 53], we conducted a solvent screening. The desired product was obtained in 49% and 70% yields when using DMF and NMP, respectively, while the yields dropped markedly to 4% and 9% with CH_3CN and DMSO (Table 1, entries 7–10). This marked solvent dependence is presumably associated with the specific solvation of the iodide anion in CH_3CN and DMSO, which diminishes its electron-donating capability and hinders the formation of the EDA complex [54–56]. Light source optimization identified a blue-light window of 390–450 nm as optimal; deviations from this range resulted in decreased conversion (Table S2). Moreover, control experiments confirmed that light irradiation is essential for the reaction to proceed (Table 1, entries 11–13; Table S2). Notably, even with decreased iodide loading (to 50 or 20 mol%), the desired product could still be obtained in 92% and 82% yields, respectively, upon extending the reaction time (Table 1, entries 14 and 15). This result indicates that the iodide ion can serve as a catalytic donor in the EDA complex.

With the optimized conditions in hand, we first explored the scope of silyl enol ethers using trifluoromethyl 2-pyridyl sulfone (**1a**) as the trifluoromethylating reagent (Figure 2). The reaction exhibited broad functional-group tolerance. Electron-donating substituents, including methoxy (**3b–3d**), methyl (**3e**), *tert*-butyl (**3f**), methylthio (**3g**), and dimethylamino (**3h**), were well tolerated, providing the corresponding α-trifluoromethylated products in good to excellent yields (72%–92%). The reaction of *ortho*- and *meta*-methoxy-substituted substrates proceeded smoothly, affording **3c** and **3d** in 89% and 79% yields, respectively, indicating that the process is largely unaffected by regioelectronic factors.

Electron-withdrawing substituents were also compatible under standard conditions. Halogens (F, Cl, and Br; **3j–3l**), an ester (**3m**), and strongly electron-deficient groups such as trifluoromethyl (**3n**), methanesulfonyl (**3o**), and cyano (**3p**) furnished the desired products in good to excellent yields (61%–97%). Notably, the retention of halogen functionalities provides versatile synthetic handles for downstream derivatization. A range of aromatic systems relevant to materials chemistry, such as naphthalene (**3q**) and phenanthrene (**3r**), as well as pharmacologically important heteroarenes, including pyridine (**3s** and

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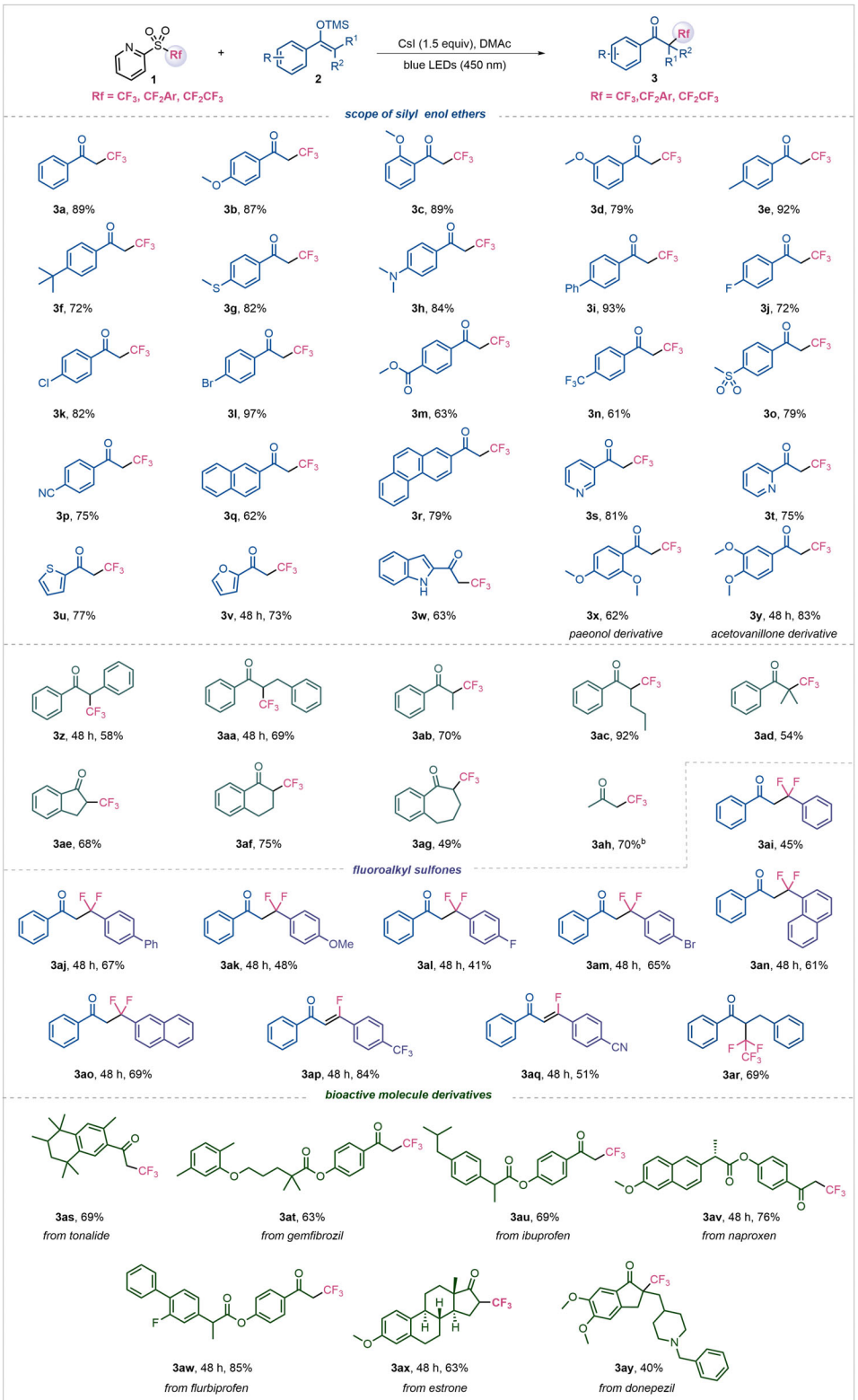


FIGURE 2 | Reactions of silyl enol ethers with fluoroalkyl sulfones. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), CsI (0.3 mmol), DMAc (2 mL), blue LEDs, N_2 atmosphere, 24–48 h, isolated yields. [b] Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

3t), thiophene (**3u**), furan (**3v**), and indole (**3w**), underwent smooth conversion to deliver the corresponding products in good to high yields (62–81%). Disubstituted, bioactive-relevant substrates (**3x**, 62% yield; **3y**, 83% yield) were also efficiently transformed. Next, a series of branched-chain silyl enol ethers was evaluated. Substrates derived from 2-phenylacetone and 2-phenylpropanone afforded the corresponding products (**3z** and **3aa**) in 58% and 69% yield, respectively. Less sterically demanding alkyl chains, including methyl (**3ab**) and propyl (**3ac**), exhibited high reactivity, delivering products in 70%–92% yield.

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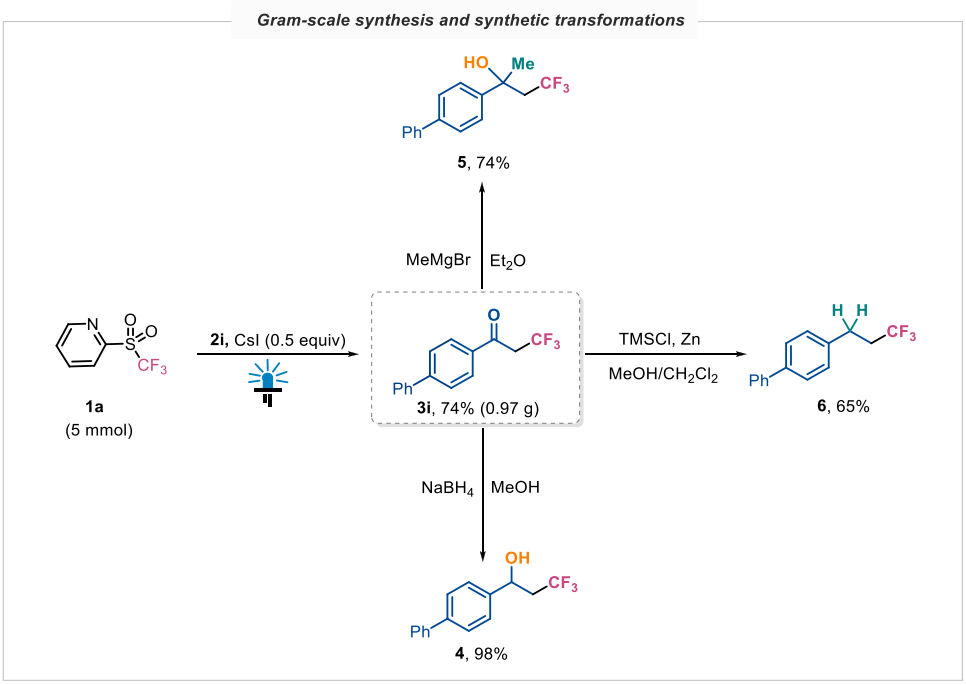


FIGURE 3 | Scale-up synthesis and synthetic applications of α-trifluoromethylated ketones.

Gem-dimethyl-substituted (**3ad**) and cyclic variants featuring cyclopentyl (**3ae**), cyclohexyl (**3af**), or cycloheptyl (**3ag**) moieties all provided the desired products, albeit in only moderate to good yields (49%–75%). Furthermore, the applicability of this protocol was not limited to aryl-substituted silyl enol ethers; the reaction of isopropenyloxytrimethylsilane, an alkyl-substituted enol silyl ether, also proved feasible, affording product **3ah** in 75% yield as determined by ^{19}F NMR spectroscopy. We then examined the scope of fluoroalkyl sulfones. Both difluorobenzyl 2-pyridyl sulfones and pentafluoroethyl 2-pyridyl sulfone served as effective radical precursors, furnishing products (**3ai**–**3ar**) in moderate to good yields (41%–84%). Notably, difluorobenzyl-containing products were prone to partial defluorination during workup, particularly **3ap** and **3aq**, which were isolated as the corresponding monofluoroalkenes.

To evaluate the potential for late-stage functionalization, the protocol was applied to a range of bioactive molecules. A tonalide derivative was trifluoromethylated to give **3as** in 69% yield. Substrates derived from gemfibrozil, naproxen, ibuprofen, and flurbiprofen were also compatible, affording the corresponding products (**3at**–**3aw**) in 63%–85% yield. Importantly, the method successfully functionalized sterically challenging, branched drug scaffolds, such as an estrone derivative (**3ax**, 69% yield) and a donepezil derivative (**3ay**, 40% yield). These results demonstrate the broad applicability of this strategy for modifying diverse pharmacophores and its potential utility in drug discovery and development.

We showcased the synthetic utility of the above processes (Figure 3). A gram-scale synthesis of **3i** was performed, delivering the product in 74% yield. With compound **3i** in hand, we then explored its further transformations. Hydride reduction of **3i** with $NaBH_4$ efficiently afforded the alcohol derivative **4** (98% yield). Treatment with a methyl Grignard reagent yielded compound **5** (74% yield). Additionally, Clemmensen reduction of **3i** under zinc-mediated conditions furnished the hydrogenated product **6** (65% yield).

To gain deeper insights into the reaction mechanism, we conducted a series of mechanistic studies (Figure 4). Radical trapping experiments showed complete suppression of product formation upon the addition of 4 equivalents of TEMPO, and the TEMPO–CF_3 adduct was detected in 10% yield by ^{19}F NMR spectroscopy, indicating the involvement of a radical pathway. When a mixture of **1a** and CsI was irradiated with blue light in the presence of TEMPO but in the absence of **2a**, the formation of the TEMPO–CF_3 adduct was observed in 24% yield. This result supports the EDA complex formed between iodide (I^-) and **1a**, which can generate trifluoromethyl radicals under visible light irradiation (Figure 4a). In a radical clock experiment, in the presence of CsI, the reaction of **7** with **1a** afforded the trifluoromethylated product **8** in 33% yield. This further demonstrates that the formation of an EDA complex between the iodide ion and **1a** is key to the release of the trifluoromethyl radical (Figure 4a). Additional evidence for a radical mechanism was obtained via electron paramagnetic resonance (EPR) experiments. The EPR spectrum of the resulting mixture exhibits a characteristic signal corresponding to the CF_3–PBN spin adduct **9** (Figure 4b), with hyperfine splitting constants of A_N = 14.15 G, A_H = 2.1 G, A_F = 1.49 G, g = 2.006. These values are in good agreement with literature reports for PBN-trapped trifluoromethyl radicals [57–60], thereby unambiguously demonstrating the generation of the trifluoromethyl radical under the reaction conditions. To probe whether molecular iodine is generated and participates in the electron transfer process, we added 10 mol% of I_2 to the reaction. The yield dropped to 4% (Figure 4c). This poisoning effect rules out a productive role for I_2 or I_3^- in the redox cycle. Spectroscopic studies were performed to probe EDA complex formation. UV–vis absorption spectroscopy revealed a distinct red shift upon mixing

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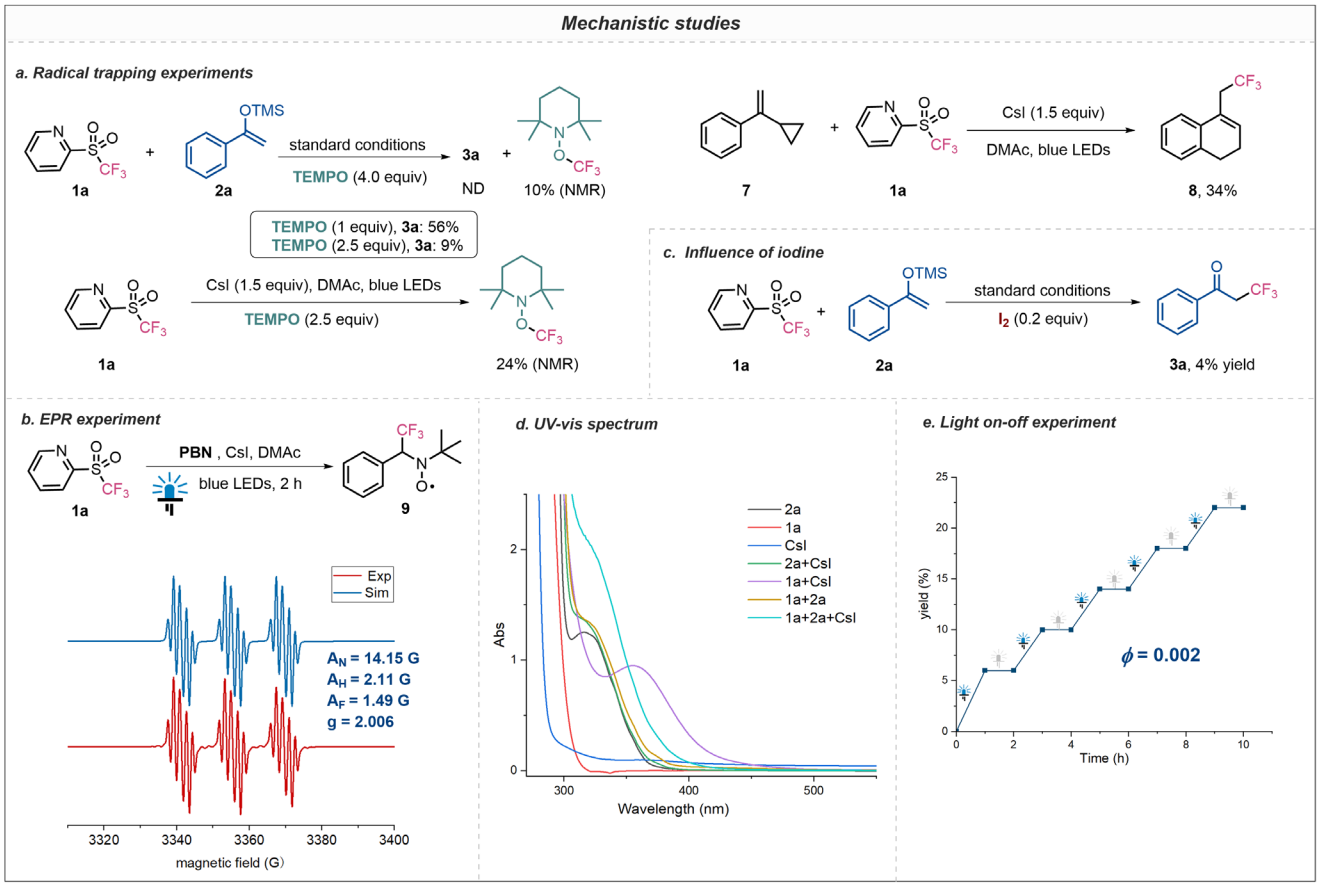


FIGURE 4 | Mechanistic studies. (a) Radical trapping experiments. (b) EPR experiment. (c) Influence of iodine. (d) UV–vis spectrum. (e) Light-on–off experiment.

1a with iodide salt, consistent with the formation of an EDA complex (Figure 4d). Light-on–off experiments confirmed that continuous irradiation is required for the reaction and argued against a long-chain process [61]. Furthermore, the measured quantum yield ($\Phi = 0.002$, << 1) conclusively excludes a radical chain mechanism.

To further elucidate the mechanistic details, DFT calculations were performed (Figure 5, top). Consistent with prior work, a trifluoromethyl pyridyl sulfone–iodide EDA complex is predicted. The complex can adopt two almost isoenergetic conformations in which the iodide binds to opposite faces of the pyridine ring, giving **IM-1** (+4.2 kcal/mol) or **IM-1′** (+4.9 kcal/mol). Excitation of either adduct populates the corresponding triplet state (^{3}**IM-1** or ^{3}**IM-1′**). TD-DFT calculations suggest that, upon excitation of the EDA complex from the ground state to the excited state, an electron is transferred from the HOMO of the iodide anion to the LUMO of the sulfone (for more details, see Supporting Information). Subsequently, the excited states of the EDA complex dissociate into the iodide radical and sulfone radical anion via a thermodynamically favored process. Then, C—S bond cleavage liberates the •CF_3 radical with an energy barrier of +4.3 kcal/mol. Once formed, the •CF_3 radical is trapped competitively by iodide or silyl enol ether. The silyl enol ether pathway is strongly exergonic (−40.6 kcal/mol), whereas the formation of **IM-bp** is mildly endergonic (+2.7 kcal/mol), accounting for the minor amount of trifluoroiodomethane observed.

Based on these investigations, a plausible reaction mechanism is proposed (Figure 5, bottom). Initially, iodide anion (I^-) and substrate **1a** associate to form an EDA complex. Upon visible light excitation, single-electron transfer (SET) occurs. Resulting homolytic cleavage of the S—C bond generates a trifluoromethyl radical (•CF_3) and an iodine radical (I•). The •CF_3 radical then adds across the carbon–carbon double bond of the silyl enol ether, forming alkyl radical intermediate **A**. Subsequent oxidation of **A** by I• generates the key α-carbocation intermediate **B**, simultaneously regenerating iodide anion (I^-). Finally, desilylation of **B** affords the α-trifluoromethylketones, completing the transformation.

3 | Conclusion

In summary, we have developed a photocatalyst-free strategy for direct fluoroalkylation via a photoactive EDA complex, employing inexpensive iodide as the electron donor and fluoroalkyl sulfone as the acceptor. Visible light excitation of the complex triggers single-electron transfer, generating fluoroalkyl radicals that efficiently couple with diverse silyl enol ethers. The method exhibits a broad substrate scope, excellent functional group tolerance, and mild reaction conditions. Mechanistic studies support an iodide-mediated EDA complex pathway. This work establishes a practical, photocatalyst-free fluoroalkylation platform and highlights the role of iodide in EDA photochemistry,

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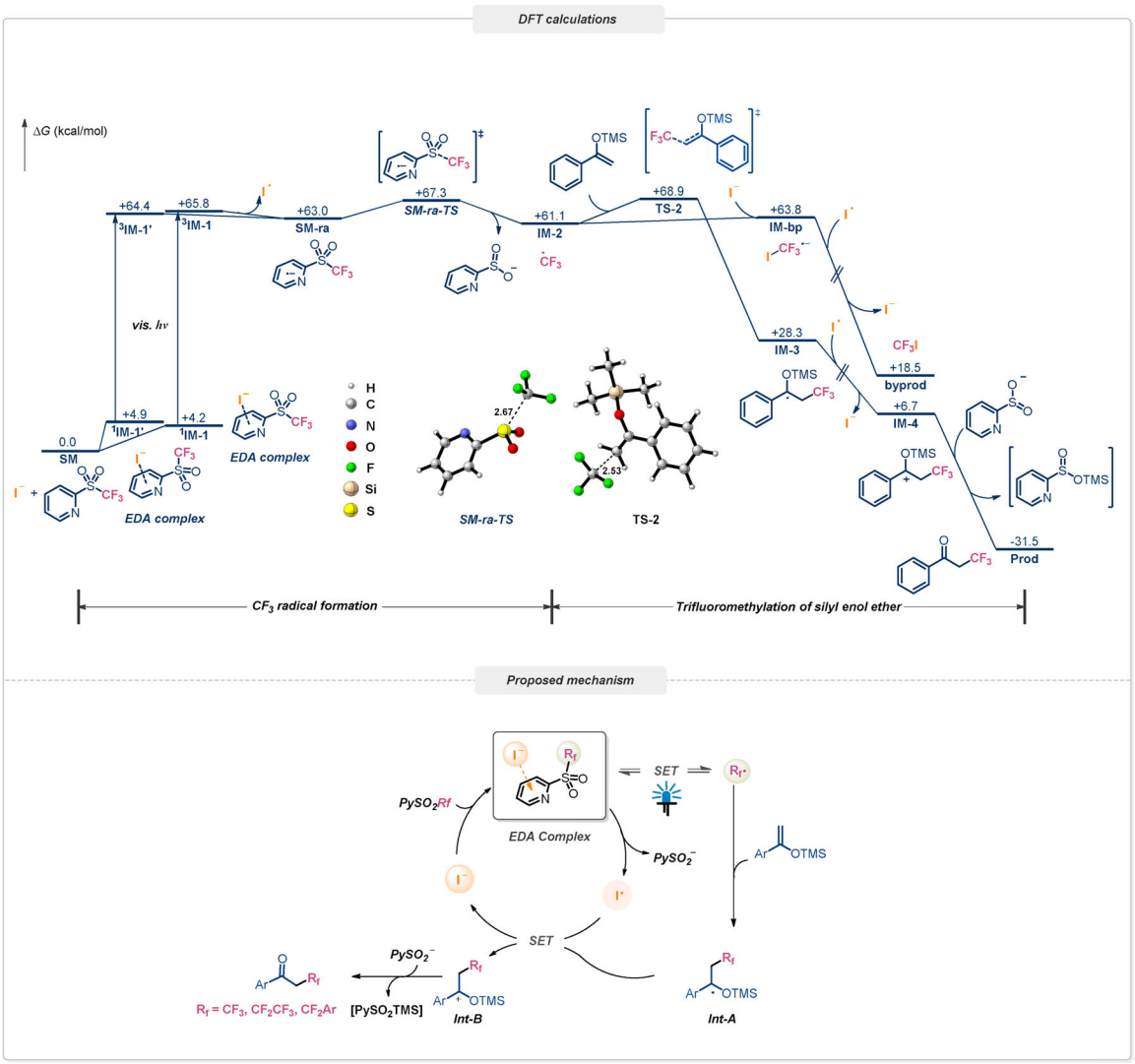


FIGURE 5 | Calculated reaction profile of the trifluoromethylation of silyl enol ethers with pyridyl fluoroalkyl sulfone–iodide EDA complexes and proposed mechanism.

demonstrating robustness in gram-scale synthesis and late-stage functionalization of pharmaceuticals, thereby offering a new paradigm for sustainable radical synthesis.

Author Contributions

Yu He: investigation, writing – original draft, methodology, formal analysis. **Kaidi Zhu:** original draft, and DFT calculations. **Mingyou Hu:** writing – original draft, formal analysis, data curation. **Chuanfa Ni:** writing – original draft, data curation. **Jinbo Hu:** conceptualization, supervision, resources, project administration, writing – review and editing, funding acquisition, visualization.

Acknowledgments

We are grateful for the financial support provided by the National Natural Science Foundation of China (22261132514 and 22271299) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB0590000). We thank Dr. Yanxia Zhang from Shanghai Institute of Organic Chemistry, CAS for conducting the EPR experiment and simulation. We acknowledge Professor Xiaosong Xue for his insight into DFT calculations. We thank the computational resources provided by the High-Performance Computing (HPC) Platform of Shanghai Tech University.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

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