Very Important Publication

The Shuttle of Sulfur Dioxide: Iridium/Copper-Cocatalyzed Trifluoromethylfluorosulfonylation of Alkenes

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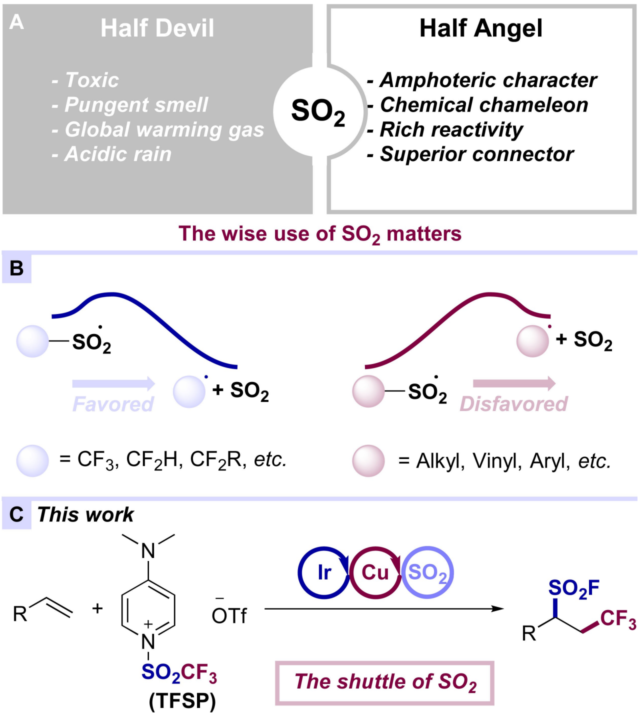
Abstract: Depending on the nature of the attached functional moiety, the sulfonyl radical can either undergo an automatic SO_2 liberation or react directly as the thermodynamically favored sulfonyl radical. Taking advantage of this unique property, we envisioned that through rational reaction design, the *in situ* release and re-insertion of SO_2, i.e., the shuttle of SO_2, can be realized. Herein we report our recent progress in copper metallaphotoredox co-catalyzed trifluoromethyl-fluorosulfonylation of alkenes with **TFSP** as both the CF_3 and SO_2 source. Valuable functional groups are added across the double bonds. Besides, A wide array of synthetically useful moieties featuring distinct electronic patterns and various nitrogenous heterocycles are well tolerated by this strategy.

Keywords: SO_2 shuttle; synergistic catalysis; fluorosulfonylation; pyridinium salt; one-pot two-step



Scheme 1. A) Two sides nature of SO_2. B) Unique reactivity profile of sulfonyl radical. C) This work.

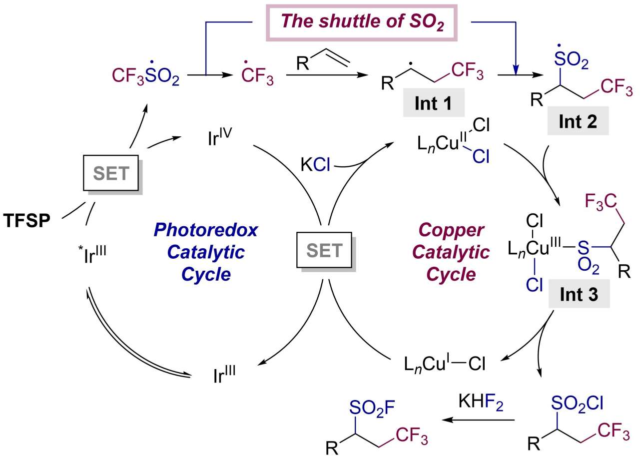
SO_2 (also referred to as sulfonyl moiety), considered as one of the most notorious gas pollutants, however, can serve as a prominent connecter in modern organic synthesis due to its electronic neutral character and muted polarity (Scheme 1A).[1] Along with its continuing contribution in pharmaceuticals,[2] the utility of SO_2 in synthetic community has seen a renaissance during the last decade thanks to the introduction of several robust SO_2 surrogates.[3] From a structural perspective, SO_2 is beloved by organic chemists for its amphoteric character owing to its high-lying σ-based HOMO and low-lying π-symmetry LUMO.[4] Under varied conditions, SO_2 can react with either electrophiles or nucleophiles to efficiently introduce sulfonyl or sulfinyl moieties. Meanwhile, characterized by a sufficiently stable SOMO, the involvement of sulfur dioxide in radical chemistry is among one of the top active areas in the context of SO_2 chemistry.[5] On the one hand, trifluoromethyl-, difluoromethyl- and difluoroalkylsulfonyl radicals typically prefer to liberate SO_2, delivering the thermodynamically more stable multi-fluoro substituted alkyl radicals. On the other hand, alkyl, vinyl, and aryl radicals are generally thermodynamically less stable species and the capture of free SO_2 would take place instead to generate the corresponding sulfonyl radicals (Scheme 1B).[6]

Based on the aforementioned unique profile of sulfonyl radical, we envisioned that using a proper trifluoromethyl sulfonyl radical precursor, both CF_3 and sulfonyl moiety can be introduced across the carbon-carbon double bonds through the *in situ* release and re-insertion of SO_2, i.e., the shuttle of SO_2 (Scheme 1C).[7] In this regard, several pioneering work has been reported by Liu,[8] Liao,[9] Akita,[10] Glorious[11] and Hong[12] group, respectively. However, this intriguing concept was still in its infancy. With this in mind, we considered our newly developed reagent **TFSP** a competent source of both CF_3 and SO_2.[13] Herein, we reported our recent progress in trifluoromethyl-fluorosulfonylation of alkenes through SO_2 shuttle under Ir/Cu co-catalysis.

With this strategy, synthetically useful functional groups can be added across the double bond.[14] Besides, a wide variety of connectors and (hetero)aryl motifs, including highly nitrogenous ones, are compatible under this optimized reaction condition, highlighting the synthetic utility of this method.

While typically featuring thermodynamic, acid-base, and redox stability, the reactivity of SO_2F can be switched on through fluoride-proton or fluoride-silicon interaction. This unique stability-reactivity pattern sparks the nearly moribund SO_2F motif to life and endows it a hallmark as a key moiety in the second generation of click chemistry.[1] The last decade has witnessed a widespread application of SO_2F-containing molecules among pharmaceuticals, agrochemicals, and material science,[15] which in turn spurs the requirement of novel and practical methods for the introduction of sulfonyl fluoride moiety.[16] In this context, we made an effort in constructing SO_2F-containing molecules through SO_2 shuttle.

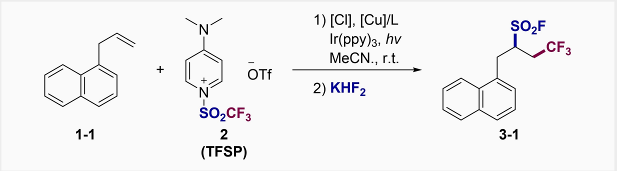
Intrigued by the reported literatures and our comprehension in sulfonyl radical, we envisaged the following reaction process (Scheme 2).[17] First, oxidative quenching of excited Ir^{III} catalyst by **TFSP** releases the trifluoromethylsulfonyl radical along with the oxidized Ir^{IV} catalyst. A thermodynamically favored α-scission of sulfonyl radical then takes place to liberate the CF_3 radical, which subsequently undergoes a radical addition to alkene to afford the alkyl radical **Int 1**. At this stage, since the sulfonyl radical is thermodynamically more stable than the corresponding alkyl radical, an automatic SO_2 re-insertion would dominate to generate the sulfonyl radical **Int 2**.[18] This relatively stable radical can then be intercepted by a chloride-ligated Cu^{II} species, which leads to the formation of Cu^{III} **Int 3**. A reductive elimination followed by fluoride-chloride exchange would give the final product and reduced Cu^{I} species. Finally, the single electron transfer (SET) between Ir^{IV} catalyst and Cu^{I} catalyst would regenerate the redox active species and close both photoredox and copper catalytic cycle.



Scheme 2. Conceived reaction process.

Since preliminary investigation has indicated that nucleophilic fluoride anion can readily attack **TFSP** (**2**) to deliver the redox insensitive side product CF_3SO_2F, we commenced our study through a "one-pot two-step" strategy, which meant that trifluoromethyl-chlorosulfonation intermediate was generated first through Ir/Cu synergistic catalysis, then a fluoride-chloride exchange took place to afford the final product. Based on this reaction design, we initiated our investigation with 1-allylnaphthalene as model substrate, **TFSP** as both CF_3 and SO_2 source, KCl as chloride source, in the presence of $Ir(ppy)_3$ and $Cu(OTf)_2$ as photocatalyst and copper catalyst, respectively (Table 1, Entry 1). Gratifying, 31% yield of the desired product was detected through ^{19}F NMR analysis. *N,N*-bidentate ligands with different scaffold including bipyridine, bisoxazoline and phenanthroline were then tested to slightly modulate the reactivity of the Cu catalyst (Entry 2–4). Although the non-substituted ligands failed to improve the yields, 2-MePhen was found to be a superior ligand for this transformation (Entry 5). It is worth noting that further attaching a methyl group at C9 position of 2-MePhen had a detrimental effect on the reaction (Entry 6), which suggested that a rigid phenanthroline ligand bearing a single C2 substituent served as a suitable platform for improving the efficiency of Cu catalyst. Several other ligands of this category were then evaluated while neither of them outperformed 2-MePhen (Entry 7–8). Further investigation implied that 4-Me or 5-Me substituted analogue also reduced the reaction yield (Entry 9–10. Please see the Supporting Information for a detailed screening of ligands). With 2-MePhen as the optimal ligand, a wide array of Cu catalysts was then scanned (Entry 11–13). Both Cu^{I} and Cu^{II} showed comparable catalytic reactivity, which

Table 1. Optimization of reaction condition.[a]



Entry	[Cu]/L	[Cl]	Yield (%)[b]
1	$Cu(OTf)_2$/–	KCl	31
2	$Cu(OTf)_2$/Bpy	KCl	31
3	$Cu(OTf)_2$/BOX	KCl	29
4	$Cu(OTf)_2$/Phen	KCl	26
5	$Cu(OTf)_2$/2-MePhen	KCl	36
6	$Cu(OTf)_2$/2,9-diMePhen	KCl	25
7	$Cu(OTf)_2$/2-ClPhen	KCl	32
8	$Cu(OTf)_2$/2-BrPhen	KCl	34
9	$Cu(OTf)_2$/4-MePhen	KCl	25
10	$Cu(OTf)_2$/5-MePhen	KCl	29
11[c]	CuOTf/2-MePhen	KCl	41
12[c]	$[Cu(MeCN)_4]BF_4$/2-MePhen	KCl	40
13[c]	CuCl/2-MePhen	KCl	38
14	$Cu(OTf)_2$/2-MePhen	LiCl	13
15	$Cu(OTf)_2$/2-MePhen	CsCl	23
16	$Cu(OTf)_2$/2-MePhen	TBACl	4
17[d]	$Cu(OTf)_2$/2-MePhen	KCl	52
18[d]	–/–	KCl	13
19[d,e]	$Cu(OTf)_2$/2-MePhen	KCl	5
20[d,f]	$Cu(OTf)_2$/2-MePhen	KCl	n. d.

[a] Reaction condition: 1–1 (0.2 mmol), 2 (1.5 equiv.), [Cl] (1.1 equiv.), [Cu] (5 mol%), Ligand (6 mol%), and $Ir(ppy)_3$ (2 mol%) in MeCN (2 mL) were irradiated with 11.5 W blue LEDs at r.t. for 15 h under nitrogen. The system was cooled by a fan. Then the mixture was allowed to stir for another 2 h with KHF_2 (2.0 equiv.)

[b] Yield was determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.

[c] **2** (2.0 equiv.) was used instead.

[d] **2** (2.5 equiv.), [Cl] (1.0 equiv.), Ligand (5 mol%), $Ir(ppy)_3$ (1 mol%) in MeCN (1.5 mL) were irradiated for 18 h instead. Then KHF_2 (3.0 equiv.) was added.

[e] Without $Ir(ppy)_3$.

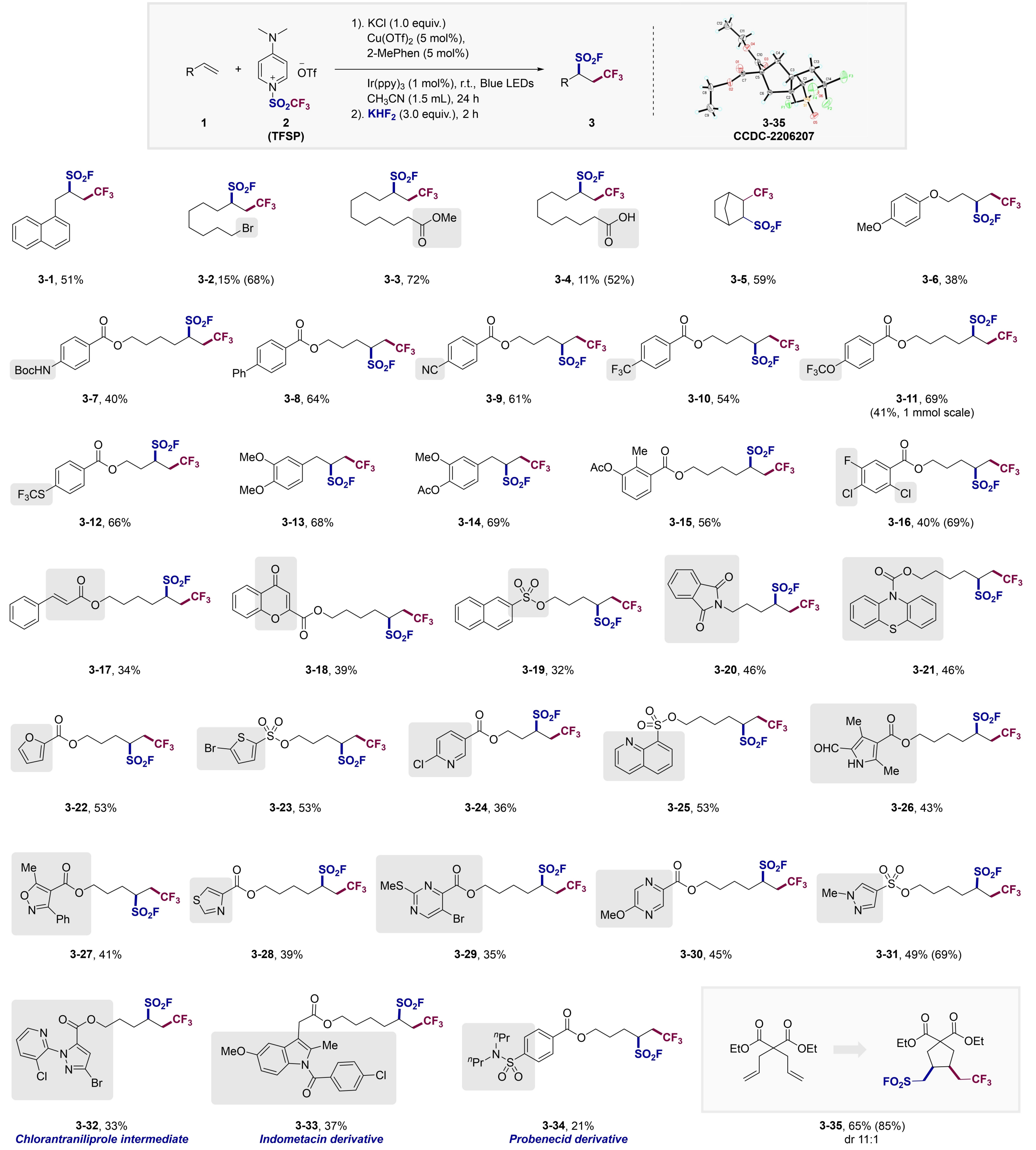
[f] In one pot. r.t. = room temperature. Bpy = 2,2'-Bipyridine. BOX = 2,2′-bis(2-oxazoline). Phen = Phenanthroline. n. d. = not detected.

may be ascribed to the *in situ* activation of the precatalyst. When other common chloride sources were charged into the reaction system, only diminished yields were obtained (Entry 14–16). Finally, various reaction parameters including reagent loading, catalyst loading, solvent, concentration, and reaction time were examined and the yield can be improved to 52%. Control experiments indicated that both Cu/L and photoredox catalysts were indispensable for the reaction to proceed effectively (Entry 18–19). It should be further noted that "one-pot two-step" strategy was still essential under this optimized condition (Entry 20. Please see the Supporting Information for detailed optimization study and control experiments).

With the optimized reaction condition in hand, we then explored the substrate scope of this synergistic catalysis reaction (Table 2). A wide array of functional groups with distinct electronic patterns, including halides (F, Cl, Br), ester, cyanide, aldehyde, methoxy, CF_3, OCF_3, SCF_3, OAc, SMe were all shown to be compatible. Specifically, several protic functional groups and moieties such as carboxylic acid (**3–4**), protected amine (**3–7**), and pyrrole (**3–26**), were also suitable for this transformation. Cinnamate and chromone derivative reacted chemoselectively at the electronically unbiased terminal alkenes, affording the corresponding adducts in synthetically useful yields (**3–17**, **3–18**). In addition to terminal alkenes, their internal counterpart was also amenable substrate for this difunctionalization platform (**3–5**). Under this mild manifold, a set of connectors, like ether, ester, sulfonate, imide, carbamate, and sulfonamide, can remain untouched along the reaction course. To further extend the boundary of this method, a diverse array of heterocycles tethered with a terminal alkene group were evaluated (**3–19** to **3–34**). To our delight, for the tested heterocycles including furan, thiophen, pyridine, quinoline, pyrrole, isoxazole, thiazole, indole, phthalimide, and phenothiazine, this approach performed well to furnish the SO_2 re-insertion products. Besides, highly nitrogenous heterocycles attached with a terminal alkene highlighted by pyrimidine, pyrazine, and pyrazole were all viable substrates. The late-stage derivatization of several highly functionalized pharmaceutically and agrochemically relevant molecules has also been realized (**3–31** to **3–34**). It should be specially noted that when diallylmalonic acid diethyl ester was subjected into the system, a cascade radical addition-cylization-SO_2 reinsertion procedure would predominate, leading to a five-membered ring product, which also indicated the radical nature of this transformation (**3–35**). X-ray crystallographic analysis unambiguously confirmed the structure of **3–35** (Please see the Supporting Information for an extended evaluation of reaction scope and limitations). A larger scale reaction was then conducted (**3–11**). Longer reaction time (48 h) has been found necessary and a non-negligible decrease (69% to 41%) in conversion was detected, indicating that further optimization may be required for larger scale.

Considering that an alkenyl sulfonyl radical is also thermodynamically more stable than the corresponding alkenyl radical. We proposed that a relevant SO_2 shuttle with alkyne is also reasonable under a slightly modified condition. However, relatively low yield was observed for alkynes, which may be due to the stronger propensity of copper catalyst to coordinate with the alkenyl radical featuring a higher *s*-character.[19] Fur-

Table 2. Scope of trifluoromethyl-fluorosulfonylation of alkenes.[a]



3-1, 51%
3-2,15% (68%)
3-3, 72%
3-4, 11% (52%)
3-5, 59%
3-6, 38%
3-7, 40%
3-8, 64%
3-9, 61%
3-10, 54%
3-11, 69%
(41%, 1 mmol scale)
3-12, 66%
3-13, 68%
3-14, 69%
3-15, 56%
3-16, 40% (69%)
3-17, 34%
3-18, 39%
3-19, 32%
3-20, 46%
3-21, 46%
3-22, 53%
3-23, 53%
3-24, 36%
3-25, 53%
3-26, 43%
3-27, 41%
3-28, 39%
3-29, 35%
3-30, 45%
3-31, 49% (69%)
3-32, 33%
Chlorantraniliprole intermediate
3-33, 37%
Indometacin derivative
3-34, 21%
Probenecid derivative
3-35, 65% (85%)
dr 11:1

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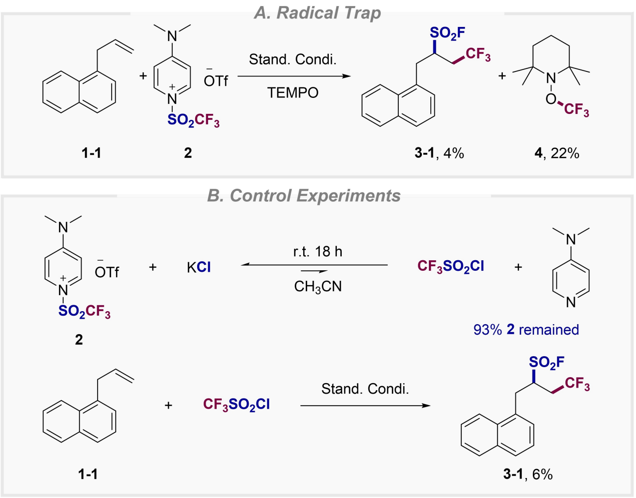
[a] Reaction condition: 1 (0.4 mmol), 2 (2.5–3.0 equiv.), KCl (1.0 equiv.), Cu(OTf)$_2$ (5 mol%), 2-MePhen (5 mol%), and Ir(ppy)$_3$ (1 mol%) in MeCN (3 mL) were irradiated with 11.5 W blue LEDs at r.t. for 24 h under nitrogen. Then the mixture was allowed to stir for another 2 h with KHF$_2$ (3.0 equiv.). Isolated yields are shown. Yields in parentheses were determined by ^{19}F NMR using PhOCF$_3$ as an internal standard.

ther optimization study is being conducted recently in our lab.

Having established the applicable scope and limitation of this method, we then turned our attention to



Scheme 3. Mechanistic investigation.

verify the conceived mechanism. First, a radical trap experiment was conducted using TEMPO as a radical scavenger (Scheme 3A). The formation of the desired product was significantly hindered while 22% yield of TEMPO-CF_3 adduct was detected. Combined with the previously mentioned cascade cyclization sequence, a radical pathway, without involving a $LnCuCF_3$ species,[20] can be inferred. Besides, to ascertain whether CF_3SO_2Cl, which is also redox-sensitive, was generated and involved in this condition,[21] several control experiments were performed (Scheme 3B). When **2** and KCl were stirred for 18 h in CH_3CN, 93% of **2** still remained intact, which preliminary ruled out the participation of CF_3SO_2Cl. If it was used in place of **TFSP** under otherwise identical condition, only 6% of the trifluoromethyl-fluorosulfonylation product can be obtained. These two experiments together demonstrated that **TFSP**, instead of CF_3SO_2Cl, was the photoredox active species during the reaction course.

In summary, taking advantage of the unique property of sulfonyl radical, we have developed an Ir/Cu co-catalyzed approach for the introduction of both CF_3 and SO_2F through SO_2 shuttle. A diverse range of functional groups and pharmaceutically relevant heterocycles, represented by the nitrogenous ones, were suitable under this mild protocol. Additionally, preliminary mechanistic probe confirmed the radical nature of this methodology and excluded the involvement of CF_3SO_2Cl.

Experimental Section

General Procedure for Trifluoromethyl-Fluorosulfonylation of Alkenes

To a 10 mL Schlenk tube equipped with a PTFE-coated stirring bar were added **2** (1.0–1.2 mmol, 2.5–3.0 equiv.), KCl (29.8 mg, 0.4 mmol, 1.0 equiv.), and $Ir(ppy)_3$ (2.6 mg, 0.004 mmol, 1 mol%) in air. The tube was then transferred into a glove box filled with nitrogen followed by the addition of $Cu(OTf)_2$ (7.2 mg, 0.02 mmol, 5 mol%) and 2-MePhen (3.9 mg, 0.02 mmol, 5 mol%). Subsequently, the tube was sealed with a screw cap and taken out of the glovebox. MeCN (3 mL) and **1** (0.4 mmol) were added in turn under nitrogen counterflow. The mixture was then stirred mildly at r.t. under the irradiation of 11.5 W blue LEDs for 24 h with a fan serving as a cooler. Upon completion, KHF_2 (93.7 mg, 1.2 mmol, 3.0 equiv.) was added and the reaction mixture was allowed to stir for another 2 h. The crude mixture was evaporated under reduced pressure and subjected to flash column chromatography to afford the final product **3**.

CCDC-2206207 (**3–35**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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