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Photo/Ni dual-catalyzed radical defluorinative sulfonylation to synthesize *gem*-difluoro allylsulfones†

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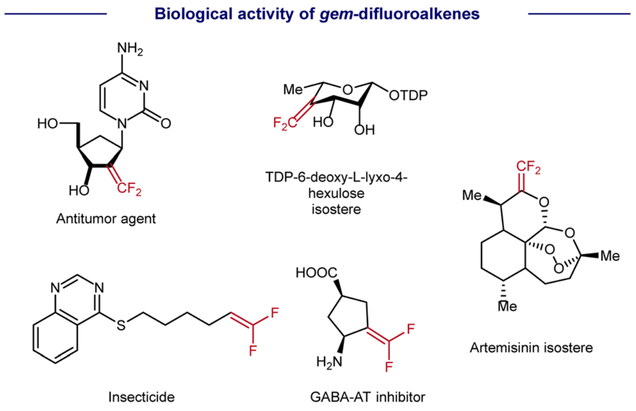
Radical defluorinative functionalization of α-trifluoromethyl styrenes represents an effective way toward *gem*-difluoroalkenes. There are general interests in developing novel synthetic protocols for defluorinative functionalization with various types of radicals. However, reports on the preparation of *gem*-difluoro allylsulfones *via* an *S*-centered radical pathway are limited. Herein, we developed a photo/nickel dual-catalyzed defluorinative sulfonylation that rapidly and reliably synthesizes *gem*-difluoro allylsulfones. The merit of this protocol is exhibited by its mild conditions and wide scope, thus providing a novel strategy for the sulfonyl radical participating in radical defluorinative coupling.

As a type of carbonyl isostere, *gem*-difluoroalkenes are usually of unique metabolic stability, bioactivity, and target specificity, thus providing more opportunities for drug discovery (Scheme 1).[1] Therefore, the synthesis of *gem*-difluoroalkenes has recently been an emerging goal in organic and medicinal chemistry. Until now, several strategies have been developed for the preparation of *gem*-difluoroalkenes. Classic methods, such as Wittig-type and Reformatsky decarboxylation reactions, usually involve highly reactive species and/or harsh conditions, and result in a limited compatibility of functional groups. As a convergent approach, S_N2-type reactions, in which fluoride is lost by nucleophilic attack on CF_3, require strong nucleophiles and may limit their substrate scope.[2] Distinctive in mechanisms, the revival of radical chemistry has provided new opportunities to prepare *gem*-difluoroalkenes, in which the defluorination of CF_3 is achieved by a Ni/Cr-promoted β-F elimination[3] (Scheme 2A) or a photo-/electro-induced radical/polar cross-cover[4] (Scheme 2B). However, most studies of radical defluorinative coupling are focused on *C*-centered radicals or *B*-centered radicals (Scheme 2B). The exploration of other types of radicals to synthesize diversified *gem*-difluoroalkenes is in crucial demand, yet challenging.

Due to the unique properties of the C–S bond, the construction of *S*-containing compounds has drawn much attention from synthetic chemists over recent decades.[5] Among these organic sulfur compounds, allylsulfones serve as versatile synthetic blocks and can be effectively transformed to other value-added chemicals.[6] Thus, we became interested in the synthesis of *gem*-difluoro allylsulfones which have the potential to integrate the nature of both *gem*-difluoro alkenes and allylsulfones. However, the synthesis of *gem*-difluoro allylsulfones *via* an *S*-centered radical pathway remains elusive. Challenges still exist in such desired transformations. Defluorinative sulfonylation to synthesize *gem*-difluoro allylsulfones is endergonic by 17.9 kcal mol^{-1}, which is thermodynamically unfeasible. In addition, an aerobic difunctionalization to produce functionalized CF_3-substituted tertiary alcohol is exergonic by -1.2 kcal mol^{-1}, which is thermodynamically spontaneous (see the detailed DFT calculation in Fig. S1, ESI†).

To address such a thermodynamic challenge, we focused our attention to the photocatalytic organic reaction that utilizes visible light as energy input, providing a green and sustainable



Scheme 1 Representative *gem*-difluoroalkenes with biological activity.

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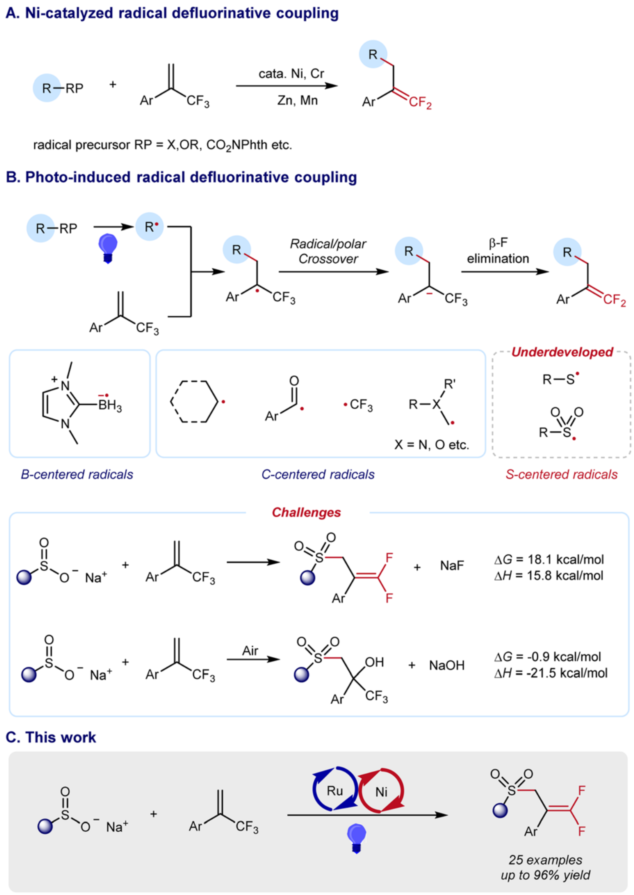
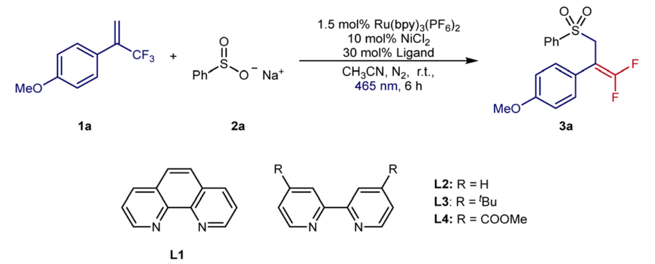


Scheme 2 Recent advances in radical defluorinative functionalization to synthesize gem-difluoroalkenes. (A) Ni catalyzed radical defluorinative coupling. (B) Photo-induced radical defluorinative coupling. (C) Outline of this work.

Table 1 Optimization of reaction conditions^a



Entry	Variation from the standard conditions^a	Yield^b [%]
1	**L1** was used	21
2	**L2** was used	93
3	**L3** was used	65
4	**L4** was used	36
5	10 mol% $Ni(bpy)_3Cl_2$ was used	96 (90)
6	Without ligand	39
7	Without $Ru(bpy)_3(PF_6)_2$	n.d.
8	Without $Ni(bpy)_3Cl_2$	Trace
9	Without irradiation	n.d.
10	Eosin Y as photocatalyst	n.d.
11	$[Ir(dFCF_3ppy)_2((4,4'\text{-}dCF_3bpy))](PF_6)$ as photocatalyst	12
12	DCE as solvent	21
13	THF as solvent	n.d.
14	Air instead of N_2	n.d.

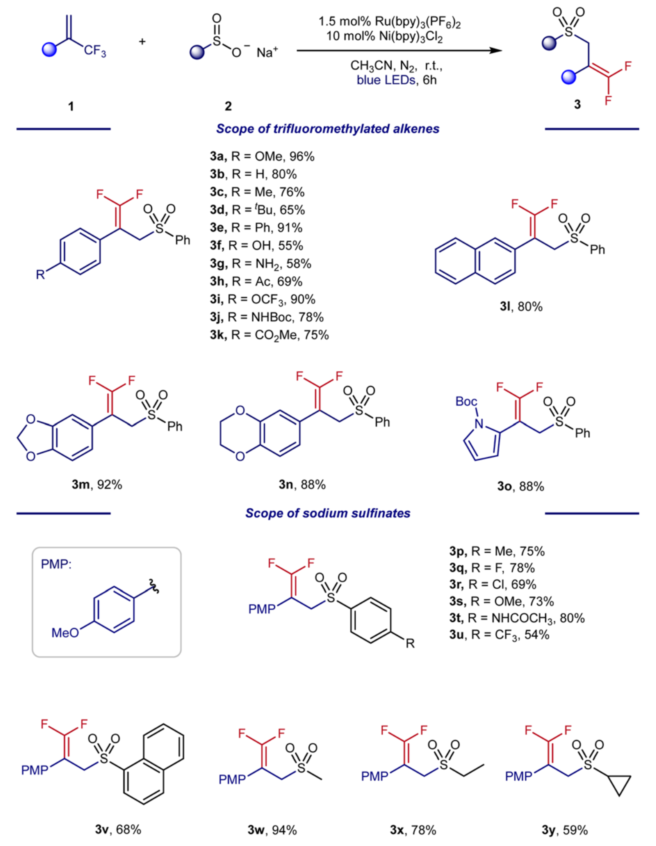
^{a} Conditions: **1a** (0.15 mmol, 1.0 equiv.), **2a** (0.20 mmol, 1.33 equiv.), $Ru(bpy)_3(PF_6)_2$ (1.5 mol%), $NiCl_2$ (10 mol%), ligand (30 mol%) in MeCN (2.0 mL) under N_2 atmosphere and irradiation with blue LED (465 nm) for 6 h. ^{b} Yields were determined by GC-FID with decane as the internal standard; isolated yield is shown in parentheses.

synthetic protocol. Merging photocatalysis and nickel catalysis, we considered that a radical defluorinative coupling could be achieved based on the addition of a sulfonyl radical to α-(trifluoromethyl)-styrenes, where the subsequent β-F elimination could be effectively promoted by a nickel catalyst (Scheme 2C). This dual-catalyzed process would offer a solution to avoid a fast side reaction that leads to α-trifluoromethyl-β-sulfonyl tertiary alcohols with trace air. Herein, we report the successful execution of this design plan.

At the outset of our investigation, we chose 1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene **1a** as the radical acceptor and inexpensive sodium benzenesulfinate **2a** as the sulfonyl radical precursor (Table 1). The initial examination was focused on the ligands with $Ru(bpy)_3(PF_6)_2$ as the photocatalyst and $NiCl_2$ as the metal catalyst (entries 1–4). To our delight, the desired transformation was successfully realized in 93% isolated yield with 30 mol% **L2** as ligand. By merging $Ru(bpy)_3(PF_6)_2$ and $Ni(bpy)_3Cl_2$, the best results were found in MeCN under blue LED irradiation at room temperature to obtain **3a** in 96% GC yield and 90% isolated yield. Control experiments (entries 6–9) proved that $Ru(bpy)_3(PF_6)_2$, $Ni(bpy)_3Cl_2$ and irradiation were essential for this organic transformation. Without the nickel catalyst, only a trace amount of product could obtain and the yield was lowered to 39% without the bipyridine ligand. When using eosin Y or an iridium complex as photocatalysts instead of $Ru(bpy)_3(PF_6)_2$, lower yields of **3a** were found (entries 10 and 11). This transformation exhibited a much lower yield with DCE as the solvent and failed with THF as the solvent (entries 12 and 13). Similar to other radical defluorinative couplings, the synthesis of *gem*-difluoro allylsulfones failed in air (entry 14).

With the optimal conditions in hand, we turned our attention to exploring the generality of our photo/Ni dual-catalyzed radical defluorinative coupling of α-trifluoromethyl styrene. As shown in Scheme 3, the scope was largely insensitive to electronic changes at the *para* and *meta* positions of trifluoromethylated alkenes (**3a–3k**). However, this defluorinative coupling failed with *otho*-substituted trifluoromethylated alkenes (see the ESI†). Interestingly, other cyclic motifs of CF_3-substituted alkenes were also suitable radical acceptors for this organic transformation, including naphthalene (**3l**), benzodioxole (**3m**), benzodioxan (**3n**), and *N*-Boc pyrrole (**3o**).

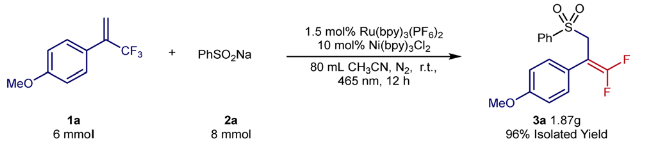
Next, the scope of the sodium sulfinates was examined. A series of *para*-substituted sodium benzenesulfinates, including halides (**3q** and **3r**), amides (**3t**), and trifluoromethyl (**3u**), were all well tolerated, forming the desired products in 54–80% yield. In addition, 2-naphthylsulfinic acid sodium (**3v**) was also a suitable sulfonyl radical precursor for this transformation, providing 64% yield. Pleasingly, sodium alkylsulfinates (**3w–3y**) were also well-tolerated under the reaction conditions and provided yields of 59–94%. To further explore the potential applications of this synthetic



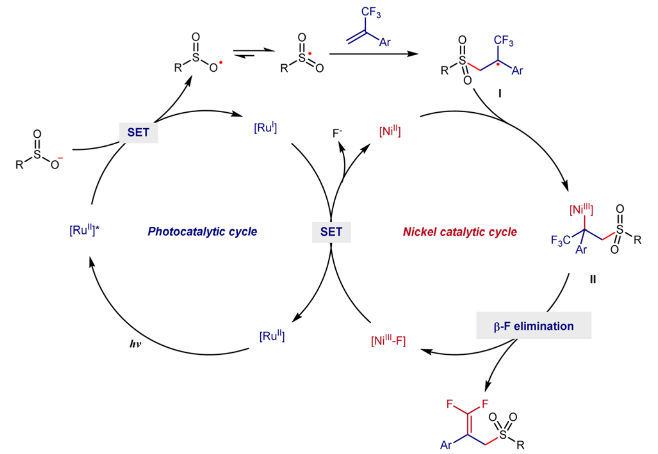
Scheme 3 Scope of substrates. Reaction conditions: **1** (0.15 mmol, 1.0 equiv.), **2** (0.2 mmol, 1.33 equiv.), $Ru(bpy)_3(PF_6)_2$ 1.5 mol%, $Ni(bpy)_3Cl_2$ 10 mol%, MeCN (2.0 mL), room temperature, N_2, 6 h. Yields of isolated products are shown.

method, we carried out a gram-scale experiment (Scheme 4). The gram-scale reaction between **1a** and **2a** afforded the corresponding gem-difluoroalkenes **3a** in 96% isolated yield.

Based on previous reports,[4h,7] a plausible mechanism of this radical defluorinative sulfonylation is shown in Scheme 4. Firstly, sodium benzenesulfonate is preferentially oxidized by photo-excited $Ru^{II}(bpy)_3$ to generate the corresponding sulfonyl radical and Ru^{I} complex. Then, radical addition occurs between the sulfonyl radical and **2a** to form a benzyl carbon radical **I**, which can further react with Ni^{II} to form alkyl-Ni^{III} species **II**. Next, the final product **3a** is obtained *via* a β-F elimination from **II**, and at the same time Ni^{III}-F is generated. Finally, $Ru^{II}(bpy)_3$ and Ni^{II} are regenerated *via* a single electron transfer between the Ru^{I} complex and Ni^{III}-F and the catalytic cycle is completed (Scheme 5).



Scheme 4 Gram-scale experiment. **1a** (6 mmol, 1.0 equiv.), **2a** (8 mmol, 1.33 equiv.), $Ru(bpy)_3(PF_6)_2$ (0.09 mmol, 1.5 mol%), $Ni(bpy)_3Cl_2$ (0.6 mmol, 10 mol%), 80 mL CH_3CN, r.t., 465 nm, 12 h.



Scheme 5 Proposed mechanism.

We have demonstrated that a radical defluorinative sulfonyla-tion, consisting of the addition of a sulfonyl radical to alkenes and a nickel-promoted β-F elimination, leads to a challenging coupling of sodium sulfinates and CF_3-substituted alkenes to synthesize a series of *gem*-difluoro allylsulfones. This protocol features mild conditions, a facile synthesis, and a wide scope of substrates. We believe that this method not only provides a rare example of a sulfonyl radical participating in the synthesis of *gem*-difluoro allylsulfones, but also represents a new strategy of photo/nickel dual-catalyzed defluorinative functionalization.

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Conflicts of interest

There are no conflicts to declare.

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