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

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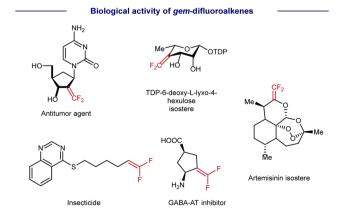
Radical defluorinative functionalization of α-trifluoromethyl styrenes represents an effective way toward gem-difluoroalkenes. There are general interests in developing novel synthetic protocols for defluorinative functionalization with various types of radicals. However, reports on the preparation of 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 gemdifluoroalkenes. 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, SN2-type reactions, in which fluoride is lost by nucleophilic attack on CF₃, 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 CF3 is achieved by a Ni/Cr-promoted β-F elimination³ (Scheme 2A) or a photo-/electro-induced radical/ polar cross-cover4 (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 valueadded chemicals. 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 CF3-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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A. Ni-catalyzed radical defluorinative coupling

radical precursor RP = X,OR, CO₂NPhth etc.

B. Photo-induced radical defluorinative coupling



OF SOLUTION AT
$$A = 18.1 \text{ kcal/mol}$$

OF SOLUTION AT $A = 15.8 \text{ kcal/mol}$

OF SO

C. This work

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

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-βsulfonyl 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(PF₆)₂ as the photocatalyst and NiCl₂ 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(PF₆)₂ and Ni(bpy)₃Cl₂, 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(PF₆)₂, Ni(bpy)₃Cl₂ and irradiation were essential for this organic transformation. Without the nickel catalyst, only a trace amount of product

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) ₃ Cl ₂ was used	96 (90)
6	Without ligand	39
7	Without $Ru(bpy)_3(PF_6)_2$	n.d.
8	Without Ni(bpy) ₃ Cl ₂	Trace
9	Without irradiation	n.d.
10	Eosin Y as photocatalyst	n.d.
11	[Ir(dFCF ₃ ppy) ₂ ((4,4'-dCF ₃ bpy))](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(PF₆)₂ (1.5 mol%), NiCl₂ (10 mol%), ligand (30 mol%) in MeCN (2.0 mL) under N2 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.

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(PF₆)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 CF₃substituted alkenes were also suitable radical acceptors for this organic transformation, including naphthalene (31), 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 welltolerated under the reaction conditions and provided yields of 59-94%. To further explore the potential applications of this synthetic

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Scheme 3 Scope of substrates. Reaction conditions: 1 (0.15 mmol, 1.0 equiv.), **2** (0.2 mmol, 1.33 equiv.), Ru(bpy)₃(PF₆)₂ 1.5 mol%, Ni(bpy)₃Cl₂ 10 mol%, MeCN (2.0 mL), room temperature, N2, 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(PF₆)₂ (0.09 mmol, 1.5 mol%), Ni(bpy)₃Cl₂ (0.6 mmol, 10 mol%), 80 mL CH₃CN, r.t., 465 nm, 12 h.

Scheme 5 Proposed mechanism

We have demonstrated that a radical defluorinative sulfonvla-tion, consisting of the addition of a sulfonvl radical to alkenes and a nickel-promoted β-F elimination, leads to a challenging coupling of sodium sulfinates and CF₃-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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