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

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enes 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.

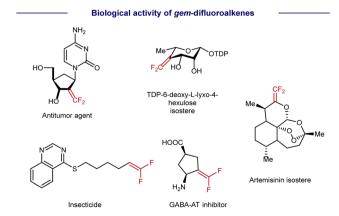
Radical defluorinative functionalization of α-trifluoromethyl styr-

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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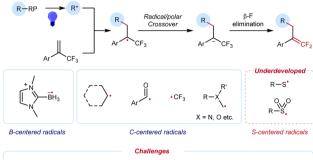
C. This work

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A. Ni-catalyzed radical defluorinative coupling

radical precursor RP = X,OR, CO₂NPhth etc.

B. Photo-induced radical defluorinative coupling



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

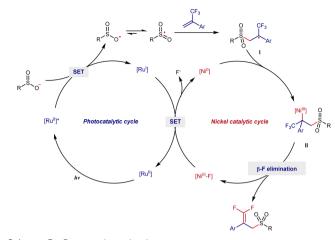
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Scheme 3 Scope of substrates. Reaction conditions: 1 (0.15 mmol, 1.0 equiv.), **2** (0.2 mmol, 1.33 equiv.), Ru(bpy)₃(PF₆)₂ 1.5 mol%, Ni(bpy)₃Cl₂ 10 mol%, MeCN (2.0 mL), room temperature, N2, 6 h. Yields of isolated products are shown

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.

Notes and references

- 1 (a) M. Bobek, I. Kavai and E. De Clercq, J. Med. Chem., 1987, 30, 1494; (b) C. Leriche, X. He, C. W. Chang and H. W. Liu, J. Am. Chem. Soc., 2003, 125, 6348; (c) K. Fujii, Y. Nakamoto, K. Hatan and Y. Kanetsuki, JP2006016331 A, 2006; (d) Y. Pan, J. Qiu and R. B. Silverman, J. Med. Chem., 2003, 46, 5292; (e) G. Magueur, B. Crousse, M. Ourévitch, D. Bonnet-Delpon and J.-P. Bégué, J. Fluorine Chem., 2006, 127, 637.
- (a) G. Chelucci, Chem. Rev., 2012, 112, 1344; (b) X. Zhang and S. Cao, Tetrahedron Lett., 2017, 58, 375; (c) M. Hu, Z. He, B. Gao, L. Li, C. Ni and J. Hu, J. Am. Chem. Soc., 2013, 135, 17302; (d) M. Wang, X. Pu, Y. Zhao, P. Wang, Z. Li, C. Zhu and Z. Shi, J. Am. Chem. Soc., 2018, 140, 9061; (e) P. H. S. Paioti, J. Del Pozo, M. S. Mikus, J. Lee, M. J. Koh, F. Romiti, S. Torker and A. H. Hoveyda, J. Am. Chem. Soc., 2019, 141, 19917.
- 3 (a) Y. Lan, F. Yang and C. Wang, ACS Catal., 2018, 8, 9245; (b) Z. Lin, Y. Lan and C. Wang, ACS Catal., 2018, 9, 775; (c) X. Lu, X. X. Wang, T. J. Gong, J. J. Pi, S. J. He and Y. Fu, Chem. Sci., 2019, 10, 809;

Communication ChemComm

- (d) C. Zhu, Z. Y. Liu, L. Tang, H. Zhang, Y. F. Zhang, P. J. Walsh and C. Feng, *Nat. Commun.*, 2020, **11**, 4860; (e) C. Zhang, Z. Lin, Y. Zhu and C. Wang, *J. Am. Chem. Soc.*, 2021, **143**, 11602; (f) Y. Ping, Q. Pan, Y. Guo, Y. Liu, X. Li, M. Wang and W. Kong, *J. Am. Chem. Soc.*, 2022, **144**, 11626.
- 4 (a) T. Fujita, K. Fuchibe and J. Ichikawa, Angew. Chem., Int. Ed., 2019, 58, 390; (b) F.-L. Qing, X.-Y. Liu, J.-A. Ma, Q. Shen, Q. Song and P. Tang, CCS Chem., 2022, 4, 2518; (c) F. Tian, G. Yan and J. Yu, Chem. Commun., 2019, 55, 13486; (d) W. Xu, H. Jiang, J. Leng, H. W. Ong and J. Wu, Angew. Chem., Int. Ed., 2020, 59, 4009; (e) T. Xiao, L. Li and L. Zhou, J. Org. Chem., 2016, 81, 7908; (f) S. B. Lang, R. J. Wiles, C. B. Kelly and G. A. Molander, Angew. Chem., Int. Ed., 2017, 56, 15073; (g) J. P. Phelan, S. B. Lang, J. Sim, S. Berritt, A. J. Peat, K. Billings, L. Fan and G. A. Molander, J. Am. Chem. Soc., 2019, 141, 3723; (h) L.-H. Wu, J.-K. Cheng, L. Shen, Z.-L. Shen and T.-P. Loh, Adv. Synth. Catal., 2018, 360, 3894; (i) W. J. Yue, C. S. Day and R. Martin, J. Am. Chem. Soc., 2021, 143, 6395; (j) W. Chen, S. Ni, Y. Wang and Y. Pan, Org. Lett., 2022, 24, 3647; (k) X. Yan, S. Wang, Z. Liu, Y. Luo, P. Wang, W. Shi, X. Qi, Z. Huang and A. Lei, Sci. China: Chem., 2022, 65, 762; (l) C. Zhu, M. M. Sun, K. Chen, H. Liu and C. Feng, Angew. Chem., Int. Ed., 2021, 60, 20237; (m) Z. Cai, R. Gu, W. Si, Y. Xiang, J. Sun, Y. Jiao and X. Zhang, Green Chem., 2022, 24, 6830; (n) F. Li, C. Pei and R. M. Koenigs, Angew. Chem., Int. Ed.,
- 2022, **61**, e202111892; (*o*) B. Wang, C. T. Wang, X. S. Li, X. Y. Liu and Y. M. Liang, *Org. Lett.*, 2022, **24**, 6566; (*p*) X. Wang, C. Wang and C. Bolm, *Org. Lett.*, 2022, **24**, 7461.
- 5 (a) P. Chauhan, S. Mahajan and D. Enders, Chem. Rev., 2014,
 114, 8807; (b) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. Hor and X. Liu, Chem. Soc. Rev., 2015, 44, 291; (c) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, Chem. Rev., 2017, 117, 9016; (d) P. Renzi, E. Azzi, A. Lanfranco, R. Moro and A. Deagostino, Synthesis, 2021, 3440.
- 6 (a) A. El-Awa, M. N. Noshi, X. M. du Jourdin and P. L. Fuchs, *Chem. Rev.*, 2009, **109**, 2315; (b) X. Chen, S. Hussain, S. Parveen, S. Zhang, Y. Yang and C. Zhu, *Curr. Med. Chem.*, 2012, **19**, 3578.
- (a) Q. Liu and L.-Z. Wu, Natl. Sci. Rev., 2017, 4, 359; (b) A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath and D. W. C. MacMillan, Chem. Rev., 2022, 122, 1485; (c) Z. Li, C. Li, Y. Ding and H. Huo, Coord. Chem. Rev., 2022, 460, 214479; (d) T. Ichitsuka, T. Fujita and J. Ichikawa, ACS Catal., 2015, 5, 5947; (e) F. Chen, X. Xu, Y. He, G. Huang and S. Zhu, Angew. Chem., Int. Ed., 2020, 59, 5398; (f) C. Yao, S. Wang, J. Norton and M. Hammond, J. Am. Chem. Soc., 2020, 142, 4793; (g) J. S. Lin, X. Y. Dong, T. T. Li, N. C. Jiang, B. Tan and X. Y. Liu, J. Am. Chem. Soc., 2016, 138, 9357.