ChemComm



COMMUNICATION

View Article Online



Cite this: Chem. Commun., 2023, **59**, 3707

Received 2nd November 2022, Accepted 27th February 2023

DOI: 10.1039/d2cc05934q

rsc.li/chemcomm

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

Yiran Xu, Shengchun Wang, Zhao Liu, Mian Guo* and Aiwen Lei **

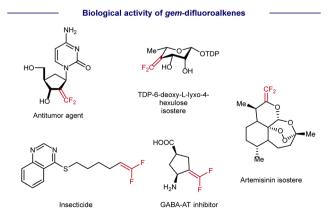
Radical defluorinative functionalization of α-trifluoromethyl styrof radicals to synthesize diversified gem-difluoroalkenes is in crucial demand, yet challenging.

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.

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

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.

College of Chemistry and Molecular Sciences, The Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, P. R. China.

E-mail: aiwenlei@whu.edu.cn, whguomian@whu.edu.cn

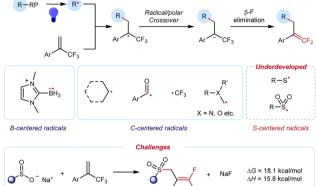
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/ 10.1039/d2cc05934g

Communication ChemComm

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	$\mathrm{Yield}^b \left[\%\right]$
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.

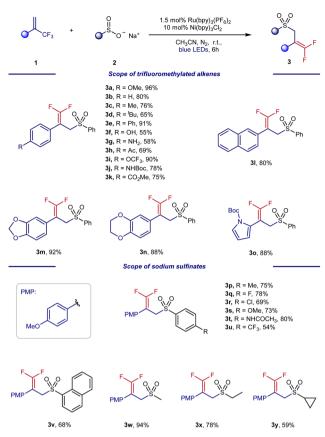
^a Conditions: **1a** (0.15 mmol, 1.0 equiv.), **2a** (0.20 mmol, 1.33 equiv.), Ru(bpy)₃(PF₆)₂ (1.5 mol%), NiCl₂ (10 mol%), ligand (30 mol%) in MeCN (2.0 mL) under N₂ atmosphere and irradiation with blue LED (465 nm) for 6 h. b Yields were determined by GC-FID with decane as the internal standard; isolated 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

ChemComm Communication

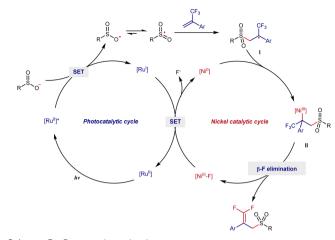


Scheme 3 Scope of substrates. Reaction conditions: 1 (0.15 mmol, 1.0 equiv.), **2** (0.2 mmol, 1.33 equiv.), Ru(bpy)₃(PF₆)₂ 1.5 mol%, Ni(bpy)₃Cl₂ 10 mol%, MeCN (2.0 mL), room temperature, N2, 6 h. Yields of isolated products are shown

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.

This work was supported by the National Key R&D Program of China (No. 2021YFA1500104), the National Natural Science Foundation of China (No. 22031008 and No. 22171216), the Science Foundation of Wuhan (No. 2020010601012192), and the Postdoctoral Foundation of Hubei Province (No. 211000025). We thank Prof. Xiaotian Qi for his efforts in DFT calculations. The numerical calculations in this paper were performed on the supercomputing system at the Supercomputing Center of Wuhan University.

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.