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Difunctionalization of *gem*-difluoroalkenes for amination and heteroarylation *via* metal-free photocatalysis[†]

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gem-Difluoroalkenes are widely used building blocks in fluorine chemistry. Herein, a metal-free photocatalytic amination and heteroarylation method of *gem*-difluoroalkenes with heteroaryl carboxylic acid oxime esters as substrates is reported. This environmentally benign reaction proceeds *via* radical-radical cross-coupling in energy-transfer-mediated photocatalysis and can be used in the rapid construction of heteroaryl difluoroethylamine scaffolds and late-stage modification of complex pharmaceutical structures.

Fluorine-containing compounds have attracted wide attention in the fields of materials science and pharmaceutical chemistry due to their unique physical and chemical properties.^{1–3} Among them, difluoromethyl units are favored in drug development due to the significant improvement in their metabolic properties such as oral bioavailability and long plasma halflives.⁴ In particular, the (hetero)aryl difluoroethylamine structures show great potential value for multiple drug targets. For example, researchers from Merck & Co. developed thrombin inhibitor (DP4088) I with a difluoroethylamine scaffold, which has a good oral bioavailability based on metabolism-directed optimization.⁴ Moreover, antifungal agent II,⁵ nitric oxide synthase inhibitor III^6 and Na_v 1.7 blocker IV^7 all contain this bioactive moiety (Fig. 1).

gem-Difluoroalkenes are very easily obtainable building blocks for synthesizing several fluorine-containing compounds and have sparked interest in recent years.^{8–10} Recent research on functionalization of *gem*-difluoroalkenes has mainly focused

^a Department of Chemistry, Shanghai University, Shanghai 200444, China. E-mail: xubin@shu.edu.cn on the construction of C–X (X = OR, SR, *etc.*) or C(sp3)–C(sp3) bonds, involving the introduction of some functional groups such as alkyl,^{11–13} alkoxyl,^{14,15} alkylthiol,^{16,17} sulfonyl¹⁸ and other groups (Scheme 1a).^{9,10,19,20} However, there are only a few reports on the introduction of aromatic groups to *gem*-difluoroalkenes, and previous reports focused on transitional-metal catalyzed coupling reactions (Scheme 1a).^{21,22} A gentle and environmentally friendly method for the difunctionalization of *gem*-difluoroalkenes would thus be a great complement to the construction of heteroaryl difluoroethylamine structures.

Since 2019, oxime derivatives have been widely used in various reactions, such as decarboxylative functionalization of aryl and alkyl carboxylic acids,²³ decarboxylative imination,^{24,25} decarboxylative fluorosulfonylation of aryl and alkyl carboxylic acids^{26,27} and dual functionalization of various structures.^{28–34} These reactions involve the generation of *N*- and *O*-centered radicals through energy-transfer (EnT) in the presence of suitable photocatalysts with high triplet excited state energy and appropriate light sources. Based on the previous work from our group on functionalization of *gem*-difluoroalkenes and heteroaryl carboxylic oxime esters,^{12,27} we attempted to utilize readily available oxime derivatives to provide imino and heteroaryl radicals for amination and heteroarylation of *gem*-difluoroalkenes simultaneously (Scheme 1b).



Fig. 1 Bioactive molecules containing (hetero)aryl difluoroethylamine structures.

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a) Previous work:



To confirm our hypothesis, we explored the optimal conditions for the reaction with the substrate models of *gem*-difluoroalkene **1a** and oxime ester **2a** (for more details, see the ESI†). Initially, we screened common photocatalysts under a 405 nm wavelength LED and determined thioxanthone (TXT) as the optimal catalyst for the reaction with a yield of 46% (Table 1, entries 1–4). Subsequent solvent screening revealed that DMSO as a solvent was more favorable for the reaction, increasing the yield from 46% to 62% (Table 1, entries 4–7). We further explored the influence of different wavelength LEDs on the reaction and found a slight improvement in yield under 365 nm irradiation (Table 1, entries 7–9). Considering the occurrence of imino radical selfcoupling during the reaction process, increasing the ratio of oxime ester ultimately resulted in a yield of 71% (Table 1, entry 10). The control experiment performed at the end demonstrated the necessity of a light source, a photocatalyst, and an inert atmosphere for the reaction (Table 1, entries 11–13).

After determining the optimal reaction conditions, we explored the generality of this difunctionalization reaction using gem-difluoroalkenes with different substituents on the benzene ring. As shown in Scheme 2, within the tested scope, both substrates with electron-withdrawing and electron-donating substituents reacted smoothly to afford the target compounds in moderate to good yields (3a-3j, 56-76%), and changing the substitution position also gave good yield for meta-substitution (3k, 75%) and acceptable yield for orthosubstitution (3l, 52%). A slightly decreased yield of 3l suggested that the reaction may be influenced by the steric effect of the substituents. It is worth noting that even with some reactive substituents (-Br, -CN, and -COOMe), the yield was not significantly affected, indicating the mildness of this transformation (3h-3l, 52-75% yield). Subsequently, we further expanded the substrate scope to fused anyl and heteroaryl gem-difluoroalkenes, which also reacted well with moderate to good yields (3m-3p, 30-80%).

For the oxime ester part, we also explored the compatibility of the reaction using different substituted pyridine carboxylate oxime esters. As shown in Scheme 3, these reactions proceeded smoothly with yields of 42–63% as expected (4a–4f). To our delight, expanding the substrate to other electrondeficient six-member heterocycles such as pyrimidine (4g, 54% yield), pyrazine (4h, 46% yield) and quinoline (4i, 56% yield) also gave the desired products. Meanwhile, we also used some electron-rich heterocycles (thiophene and furan) and

Table 1	Optimization study			
			Photocatalyst 30 W LED Solvent Inder Ar, rt, 12h	
Entry ^a	Photocatalyst ^b	Solvent	Wavelength	Yield ^c (%)
1	PC-1	EtOAc	405	26
2	PC-2	EtOAc	405	20
3	PC-3	EtOAc	405	30
4	TXT	EtOAc	405	46
5	TXT	MeCN	405	40
6	TXT	DCE	405	23
7	TXT	DMSO	405	62
8	TXT	DMSO	440	Trace
9	TXT	DMSO	365	65
10^d	TXT	DMSO	365	71
11	—	DMSO	365	Trace
12^{e}	TXT	DMSO	365	Trace
13^{f}	TXT	DMSO	_	n.d.

^{*a*} Reaction conditions: **1a** (0.15 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.0 equiv.), photocatalyst (5 mol%), 30 W LED, argon atmosphere, at room temperature in solvent (0.75 mL, 0.2 M) for 12 h. ^{*b*} PC-1: [Ir(dF(CF₃)ppy)₂(dtbbpy)](PF₆); PC-2: *fac*-Ir(dFppy)₃; PC-3: 4CzlPN; TXT: thioxanthone. ^{*c*} Isolated yield. ^{*d*} **2a** (0.45 mmol, 3 equiv.). ^{*e*} Under the air atmosphere. ^{*f*} In the dark.



Scheme 2 Substrate scope of *gem*-difluoroalkenes.^{*a,b a*} Reaction conditions: **1** (0.15 mmol, 1.0 equiv.), **2a** (0.45 mmol, 3 equiv.), thioxanthone (5 mol%), 365 nm LED (30 W), argon atmosphere, at room temperature in DMSO (0.75 mL, 0.2 M) for 12 h. ^{*b*} Isolated yield.



Scheme 3 Substrate scope of the (hetero)aryl radical precursor.^{*a,b*} ^{*a*} Reaction conditions: **1** (0.15 mmol, 1.0 equiv.), **2** (0.45 mmol, 3 equiv.), thioxanthone (5 mol%), 365 nm LED (30 W), argon atmosphere, at room temperature in DMSO (0.75 mL, 0.2 M) for 12 h. ^{*b*} Isolated yield.

electron-withdrawing substituted benzene rings (-COOMe and -CN), but unfortunately, the target products were not obtained due to the difficulty of decarboxylation.

To evaluate the scalability of this protocol, the reaction was successfully scaled up to ten-fold (Schemes 4a, 1.5 mmol, 60% yield). Considering the potential application of the heteroaryl difluoroethylamine structures in the field of medicinal chemistry, we further applied the reaction to the structural modification of natural products or drugs to evaluate the practicality of this difunctionalization reaction. As shown in Scheme 4b, structural modifications were carried out on both asaraldehyde (natural product, COX-2 inhibitor) and picolinafen (herbicide) intermediates with yields of 61% and 54% (yields given for the last step), respectively. It is well known that imine structures can be rapidly hydrolyzed under acidic conditions, and product **3a** was deprotected to give the corresponding amine with a yield of 95% (see the ESI,† S2.6).



Scheme 4 Scale-up reaction and late-stage modification. Isolated yield.

We next turned our attention to the reaction mechanism with a series of experiments. The radical crossover study proved the existence of the aryl radical and *N*-centered imine radical, respectively, as the crossover products were detected by mass spectrometry (Scheme 5a). Moreover, the generation of these two types of radicals was further confirmed *via* radical scavenger trapping experiments with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or azobis-(isobutyronitrile) (AIBN) (Scheme 5b).

Based on the experimental facts mentioned above and previous reports,^{23,27,31} we proposed a possible reaction mechanism as shown in Scheme 5. First, under the irradiation of suitable wavelength light, thioxanthone (TXT) is excited to a triplet excited state. Subsequently, a triplet–triplet energy-transfer process between TXT and oxime ester leads to the sensitization of the oxime ester and homolysis of the N–O bond, forming an imine radical (**B**) and a carboxyl radical (**A**). The carboxyl radical further undergoes decarboxylation to form an aryl radical (**C**), which is then captured by a *gem*-difluoro-alkene to form a carbon-centered radical. Finally, a radical-radical cross-coupling between the carbon-centered radical and the imine radical produces the target product.

In summary, we have developed a metal-free photocatalytic method for the amination and heteroarylation of *gem*-difluoroalkenes. This method features good functional group



Scheme 5 Mechanistic studies. (a) Crossover study. (b) Trapping experiments. (c) Proposed mechanism.

compatibility and mild and metal-free reaction conditions, making it environmentally friendly. Above all, this benign atom-economical method can be used for the rapid construction of heteroaryl difluoroethylamine structures, and at the same time, we expect that this method can be a good complement to the arylation of *gem*-difluoroalkenes.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- 2 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- 3 N. A. Meanwell, J. Med. Chem., 2018, 61, 5822-5880.
- 4 C. S. Burgey, K. A. Robinson, T. A. Lyle, P. E. Sanderson, S. D. Lewis, B. J. Lucas, J. A. Krueger, R. Singh, C. Miller-Stein, R. B. White, B. Wong, E. A. Lyle, P. D. Williams, C. A. Coburn, B. D. Dorsey, J. C. Barrow, M. T. Stranieri, M. A. Holahan, G. R. Sitko, J. J. Cook, D. R. McMasters, C. M. McDonough, W. M. Sanders, A. A. Wallace, F. C. Clayton, D. Bohn, Y. M. Leonard, T. J. Detwiler, Jr., J. J. Lynch Jr., Y. Yan, Z. Chen, L. Kuo, S. J. Gardell, J. A. Shafer and J. P. Vacca, J. Med. Chem., 2003, 46, 461–473.
- 5 G. Deng and J. Peng, CN Pat., CN117069693A, 2023.
- 6 F. Xue, H. Li, S. L. Delker, J. Fang, P. Martasek, L. J. Roman, T. L. Poulos and R. B. Silverman, *J. Am. Chem. Soc.*, 2010, **132**, 14229–14238.
- 7 I. Kers, I. Macsari, G. Csjernyik, M. Nylof, K. Skogholm, L. Sandberg, A. Minidis, T. Bueters, J. Malmborg, A. B. Eriksson, P. E. Lund, E. Venyike, L. Luo, J. E. Nystrom and Y. Besidski, *Bioorg. Med. Chem. Lett.*, 2012, 22, 6108–6115.
- 8 M.-Z. Lu, J. Goh, M. Maraswami, Z. Jia, J.-S. Tian and T.-P. Loh, *Chem. Rev.*, 2022, **122**, 17479–17646.
- 9 J. P. Sorrentino and R. A. Altman, Synthesis, 2021, 3935-3950.
- 10 X. Zhang and S. Cao, Tetrahedron Lett., 2017, 58, 375-392.
- X. Chen, Z. Zhang, W. Y. Shi, Y. N. Ding, Y. Y. Luan, Y. C. Huang, Q. Wang, X. Y. Liu and Y. M. Liang, Org. Lett., 2023, 25, 4456-4461.
 F. Liu, Z. Zhuang, O. Cim, W. Zhang, et al. Wang, J. Comput. Comput.
- 12 F. Liu, Z. Zhuang, Q. Qian, X. Zhang and C. Yang, J. Org. Chem., 2022, 87, 2730–2739.

- 13 X. Y. Wang, M. Yang, Y. Zhou, J. Zhou and Y. J. Hao, Org. Biomol. Chem., 2023, 21, 1033–1037.
- 14 R. M. Herrick, M. K. Abd El-Gaber, G. Coy and R. A. Altman, *Chem. Commun.*, 2023, **59**, 5623–5626.
- 15 X. Han, X. Liu, C. Len, L. Liu, D. Wang, Y. Zhang, X. H. Duan and M. Hu, J. Org. Chem., 2023, 88, 12744–12754.
- 16 J. P. Sorrentino, R. M. Herrick, M. K. Abd El-Gaber, A. Z. Abdelazem, A. Kumar and R. A. Altman, J. Org. Chem., 2022, 87, 16676–16690.
- 17 C. Liu, C. Zhu, Y. Cai and H. Jiang, Angew. Chem., Int. Ed., 2021, 60, 12038–12045.
- 18 W. Zhu, H. Xi, W. Jiao, L. Huang, L. Wang and J. Wu, *Org. Lett.*, 2022, 24, 720–725.
- 19 X. Yu, A. Maity and A. Studer, Angew. Chem., Int. Ed., 2023, 62, e202310288.
- 20 Y. Cai, H. Jiang and C. Zhu, Adv. Synth. Catal., 2023, 365, 342-354.
- 21 B. Zhang and X. Zhang, Chem. Commun., 2016, 52, 1238-1241.
- 22 K. Yuan, T. Feoktistova, P. H. Cheong and R. A. Altman, *Chem. Sci.*, 2021, **12**, 1363–1367.
- 23 T. Patra, S. Mukherjee, J. Ma, F. Strieth-Kalthoff and F. Glorius, Angew. Chem., Int. Ed., 2019, 58, 10514-10520.
- 24 V. K. Soni, S. Lee, J. Kang, Y. K. Moon, H. S. Hwang, Y. You and E. J. Cho, ACS Catal., 2019, 9, 10454–10463.
- 25 J. Kang, H. S. Hwang, V. K. Soni and E. J. Cho, *Org. Lett.*, 2020, 22, 6112–6116.
- 26 Z. D. Chen, X. Zhou, J. T. Yi, H. J. Diao, Q. L. Chen, G. Lu and J. Weng, *Org. Lett.*, 2022, 24, 2474–2478.
- 27 Z. Zhuang, Y. Sun, Y. Zhong, Q. He, X. Zhang and C. Yang, *Org. Lett.*, 2024, **26**, 713–718.
- 28 Y. Zheng, Z. J. Wang, Z. P. Ye, K. Tang, Z. Z. Xie, J. A. Xiao, H. Y. Xiang, K. Chen, X. Q. Chen and H. Yang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212292.
- 29 S. Kim, H. Oh, W. Dong, J. Majhi, M. Sharique, B. Matsuo, S. Keess and G. A. Molander, ACS Catal., 2023, 13, 9542–9549.
- 30 C. P. Yuan, Y. Zheng, Z. Z. Xie, K. Y. Deng, H. B. Chen, H. Y. Xiang, K. Chen and H. Yang, Org. Lett., 2023, 25, 1782–1786.
- 31 X. K. Qi, M. J. Zheng, C. Yang, Y. Zhao, L. Guo and W. Xia, J. Am. Chem. Soc., 2023, 145, 16630–16641.
- 32 J. E. Erchinger, R. Hoogesteger, R. Laskar, S. Dutta, C. Humpel, D. Rana, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2023, **145**, 2364–2374.
- 33 S. S. Li, Y. S. Jiang, X. L. Luo, C. X. Pan and P. J. Xia, Org. Lett., 2023, 25, 1595–1599.
- 34 J. Majhi, R. K. Dhungana, A. Renteria-Gomez, M. Sharique, L. Li, W. Dong, O. Gutierrez and G. A. Molander, *J. Am. Chem. Soc.*, 2022, 144, 15871–15878.