


 Cite this: *Chem. Commun.*, 2025, 61, 17890

 Received 18th August 2025,
 Accepted 2nd October 2025

DOI: 10.1039/d5cc04758g

rsc.li/chemcomm

Photoinduced EDA complex triggered difluoroalkylation of quinoxalin-2(1H)-ones with unactivated alkenes and fluoroalkyl bromides

 Huanhuan Cui,^a Xiulin Qiao,^a Tiesheng Shi,^a Wei Wei,^b Huilan Yue,^b Zuli Wang,^d Zhuoming Ma^{*a} and Zi Yang^{ib,c}

A metal-free photo-induced three-component difluoroalkylation reaction between quinoxalin-2(1H)-ones, unactivated alkenes and fluoroalkyl bromides via an EDA strategy has been reported. This reaction was initiated by the photochemistry of electron donor acceptor (EDA) complexes formed by TMEDA and fluoroalkyl bromide. A variety of 3-difluoroalkylated quinoxalin-2(1H)-ones with diverse functional groups could be accessed under mild conditions.

Difluoroalkylated compounds have remarkably important applications in agrochemicals, pharmaceuticals and materials science¹ due to their unique chemical and biological properties.² Meanwhile, quinoxalin-2(1H)-ones are a crucial class of heterocyclic units, endowed with significant pharmaceutical activities, such as aldose reductase inhibitory activity, antitumor activity, antimicrobial activity, antibacterial activity, and antihistaminic activity.³ In particular, 3-difluoroalkylated quinoxalin-2(1H)-ones are a fascinating class of compounds commonly featuring privileged pharmacophores.⁴ To date, several significant achievements for accessing 3-difluoroalkylated quinoxalin-2(1H)-ones have been reported by employing a transition metal catalyzed or photocatalyzed direct two component C3-H functionalization strategy (Scheme 1a, (1)).⁵

Over recent decades, the direct difunctionalization of alkenes has been one of the most attractive strategies to install two functional groups simultaneously into the C=C bond via a one pot procedure.⁶ Recently, some three-component

difunctionalization strategies have been utilized in synthesizing 3-difluoroalkylated quinoxaline-2(1H)-ones. For example, in 2022, the Wang group reported a photo-induced three-component difluoromethylative heteroarylation of unactivated alkenes, quinoxaline-2(1H)-ones and ethyl 2-bromo-2,2-difluoroacetate by using *fac*-Ir(ppy)₃ as a photocatalyst (Scheme 1a, (I)).⁷ In 2023, the Zhang group reported a *fac*-Ir(ppy)₃ catalyzed three-component protocol for the synthesis of difluorobenzylated quinoxalin-2(1H)-ones (Scheme 1a, (II)).⁸ In 2023, the Singh group unveiled a similar Ru(bpy)₃Cl₂ catalyzed three-component reaction of quinoxalin-2(1H)-ones by employing TBHP as the oxidant (Scheme 1a, (III)).⁹ These methods require the addition of

(a) Previous methods for the synthesis of 3-difluoroalkylated quinoxalin-2(1H)-ones

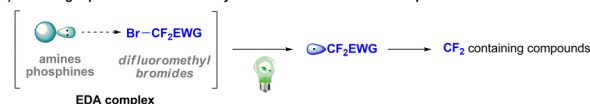
(1) Two-component direct C-H functionalization methods



(2) Three-component C-H functionalization methods



(b) Visible-light-promoted difluoromethyl radical formation via EDA complex



(c) This method for the synthesis of 3-difluoroalkylated quinoxalin-2(1H)-ones



Scheme 1 Strategies for the synthesis of 3-difluoroalkylated quinoxalin-2(1H)-ones and EDA strategies to activate difluoroalkyl bromides.

^a College of Chemistry, Chemical Engineering and Material Science, Zaozhuang University, Zaozhuang, 277160, Shandong, China. E-mail: mazhuoming@uzz.edu.cn

^b Qinghai Provincial Key Laboratory of Tibetan Medicine Research and CAS Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology, Qinghai 810008, China

^c Hunan Provincial University Key Laboratory of the Fundamental and Clinical Research on Functional Nucleic Acid, First Clinical College, Changsha Medical University, Changsha 410219, China. E-mail: yangziyicy@163.com

^d National Engineering Research Center of Low-Carbon Processing and Utilization of Forest Biomass, Nanjing Forestry University, Nanjing 210037, China

photocatalyst or oxidant, which limit their wide application in pharmaceutical synthesis. Therefore, the development of metal-free and operationally convenient strategies for the synthesis of 3-difluoroalkyl-containing quinoxalin-2(1*H*)-ones *via* photo-induced three-component reactions has attracted great interest from chemists.

Photo-induced EDA complexes have been recognized as a powerful and versatile strategy for radical reactions in the absence of extra photocatalysts.¹⁰ In particular, harnessing the EDA complexes constructed from difluoromethyl bromides and amines/phosphines under visible light irradiation could generate the difluoroalkyl radical (Scheme 1b).¹¹ This strategy provides an efficient and simple new method for the synthesis of difluoride compounds. With our interests in photochemical reactions and the development of simple and mild methods for synthesizing diverse alkylated heteroaryl compounds,¹² herein, we wish to report a photo-induced three-component difluoroalkylation of unactivated alkenes with quinoxalin-2(1*H*)-ones and fluoroalkyl bromides *via* an EDA complex strategy (Scheme 1c).

Our investigation was started from using 1-methylquinoxalin-2(1*H*)-one (**1a**), ethyl bromodifluoroacetate (**2a**), and allylbenzene (**3a**) as the model substrates to explore this reaction (Table 1). The desired product **4a** could be obtained in 41% yield by using 2.0 equivalents of TMEDA under the irradiation of blue LEDs (460–475 nm) (entry 1). Then, we tested different electron donors such as HE, DIPEA, PMDETA, DBU and Et₃N, which resulted in lower yields of **4a** (entries 2–6). Increasing TMEDA loading to 3.0 equivalents or 4.0 equivalents gave a lower yield (entries 7 and 8). We then tested different solvents, and the results showed that DMSO was the best solvent (Table S1, SI). Next, we tried to replace the light source using

purple light (390–400 nm), and the desired product **4a** was increased to 83% (entry 9). Shortening the reaction time to 24 hours, the yield did not decrease (entry 10). When the molar ratio of **1a**, **2a** and **3a** was changed to 1:2:2, the yield of the desired product **4a** was improved to 86% (entry 11 and 12). Moreover, no desired product was observed without TMEDA or visible-light irradiation, which illustrated that both of them are necessary for the transformation (entry 13 and 14). When the model reaction was carried out under air, only a trace amount of product was detected (entry 15).

Having identified the optimal conditions, we investigated the substrate scope of various quinoxalin-2(1*H*)-ones (Scheme 2). Quinoxalinones bearing either electron-donating groups or electron-withdrawing groups could proceed smoothly to give the products **4b–4i** in moderate to good yields. Furthermore, a series of the 6,7-disubstituted quinoxalin-2(1*H*)-ones were tested for this reaction and the desired products were obtained in moderate yields (**4j–4k**). It is worth noting that *N*-free protected quinoxalinone was also compatible with this reaction system, generating the desired product **4l** in 47% yield. Besides, some *N*-substituted substrates of quinoxalin-2(1*H*)-ones including

Table 1 Optimization of the reaction conditions^{a,b}



Entry	Additive	Light source (nm)	Yield ^b (%)
1	TMEDA (2.0 equiv.)	460–475	41%
2	HE (2.0 equiv.)	460–475	N.R.
3	DIPEA (2.0 equiv.)	460–475	Trace
4	PMDETA (2.0 equiv.)	460–475	Trace
5	DBU (2.0 equiv.)	460–475	N.R.
6	Et ₃ N (2.0 equiv.)	460–475	<10%
7	TMEDA (3.0 equiv.)	460–475	25%
8	TMEDA (4.0 equiv.)	460–475	23%
9	TMEDA (2.0 equiv.)	390–400	83%
10 ^c	TMEDA (2.0 equiv.)	390–400	83%
11 ^d	TMEDA (2.0 equiv.)	390–400	82%
12 ^e	TMEDA (2.0 equiv.)	390–400	86%
13 ^f	—	390–400	N.R.
14 ^g	TMEDA (2.0 equiv.)	—	N.R.
15 ^h	TMEDA (2.0 equiv.)	390–400	Trace

^a **1a** (0.1 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), additive (2.0–4.0 equiv.), DMSO (1 mL), N₂, room temperature, and 48 h. ^b Isolated yields based on **1a**. ^c 24 h. ^d **1a**:**2a**:**3a** = 1:2:3. ^e **1a**:**2a**:**3a** = 1:2:2. ^f No TMEDA. ^g No light. ^h Under air.



Scheme 2 Substrate scope of quinoxalin-2(1*H*)-ones. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.4 mmol), TMEDA (0.4 mmol), DMSO (2.0 mL), room temperature, N₂, and 24 h. Isolated yield.

N-ethyl, *N*-esteryl, *N*-propargyl, *N*-benzyl, *N*-phenethyl and *N*-cyanomethyl groups also exhibited good applicability (**4m–4r**). Nevertheless, when other heterocycles such as quinoxaline, 1-(1-methyl-1*H*-indol-3-yl)ethan-1-one, 1-(1*H*-pyrrol-3-yl)ethan-1-one, 3,5-dimethyl-1*H*-pyrazole, 1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione, and 2*H*-chromen-2-one were utilized in this reaction system, none of the desired products were observed (see the SI).

After examining the substrate scope of quinoxalin-2(1*H*)-ones, a series of difluoroalkyl bromides **2** and unactivated alkenes **3** were then explored (Scheme 3). A variety of allylbenzenes with electron-donating groups and electron-withdrawing groups on the phenyl ring all worked well, giving the desired products (**5b–5f**). Notably, the allylbenzene containing free hydroxyl group was well tolerated, leading to the desired product **5e** in 38% yield. When 3-phthalamido-substituted propylene was used as the substrate, the corresponding product **5g** could be obtained in 73% yield. Other cycloalkenes such as cyclohexene and cyclopentene were also suitable for this reaction, affording the corresponding products **5h** and **5i** in 40% and 78% yields. When aromatic alkenes such as 4-methoxystyrene, 4-fluorostyrene and 4-chlorostyrene were used in this reaction system, the corresponding products **5j–5l** could be obtained in 64–78% yields. The impact of the steric hindrance was also investigated in this reaction. When more sterically demanding (2-methylallyl)benzene was used as a substrate, the desired product **5m** was obtained in 66% yield. Nevertheless, when 3-methylcyclohex-1-ene was employed in this reaction procedure, none of desired product **5n** was observed. Unfortunately, none of the desired product was detected when propargyl benzene was

used as the substrate under the standard conditions. Finally, various bromodifluoroacetamides were subjected to reaction with **1a** and **3a** under the standard conditions, affording the desired products **5o** and **5p** in moderate yields. When 1-bromo-1,1-difluoroethane was used in this reaction, the desired product **5q** was not obtained. We speculate that the presence of a EWG at the alpha -position of the BrCF₂ functionality is necessary for promoting this reaction.¹³

To gain insight into the possible reaction mechanism, several control experiments were conducted. Firstly, when TEMPO and BHT were added into the reaction system, the formation of **4a** was inhibited (Scheme 4). Meanwhile, the radical adduct **6a** was detected by HRMS analysis (Fig. S1, SI). The above results indicated that this procedure might proceed *via* a radical pathway. Next, light on/off experiments were performed; the results demonstrated that the constant light irradiation was necessary for this transformation (Fig. S2, SI). To further explore whether this reaction was mediated by the EDA complex, UV-vis analysis of **2a** and TMEDA was carried out. When **2a** and TMEDA were mixed in DMSO, the formation of a mixed solution was confirmed by the appearance of a yellow colour and an obvious red shift in the absorption spectrum (Fig. S3, SI). Meanwhile, the ¹⁹F NMR titration experiments performed with **2a** and TMEDA demonstrated that the ¹⁹F NMR signal distinctly moved downfield when the ratios of TMEDA increased (Fig. S4, SI). These results suggested the formation of an EDA complex between **2a** and TMEDA.^{11d} In order to prove the synthetic applicability of this reaction, a scale-up experiment was carried out between 1-methylquinoxalin-2(1*H*)-one **1a**, ethyl bromodifluoroacetate **2a** and allylbenzene **3a**, and the corresponding product **4a** was obtained in 76% yield (SI).

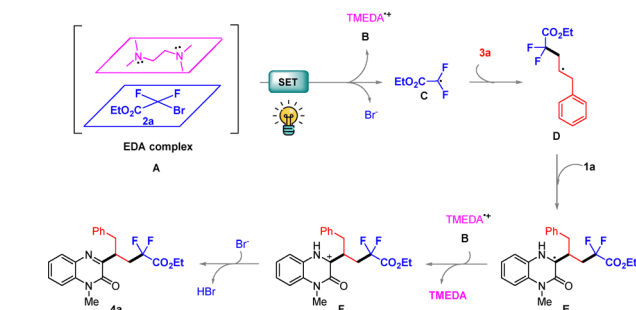
On the basis of previous literature reports and the above experimental results,^{14,15} a possible mechanism was illustrated as shown in Scheme 5. Firstly, this reaction commences with the formation of an electron donor–acceptor (EDA) complex between compound **2a** and TMEDA. Upon irradiation with visible light, the EDA complex undergoes a SET process, generating radical cationic **B**, difluoroalkyl radical **C** and releasing a bromide anion. Next, difluoroalkyl radical **C** undergoes radical addition with alkene **3a** to generate the intermediate **D**. Then, the alkyl radical **D** couples with quinoxalin-2(1*H*)-one **1a** to produce carbon radical intermediate **E**. **E** proceeds through the SET oxidative process by a radical cationic **B** to



Scheme 3 Substrate scope of alkenes and difluoroalkyl bromides. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), **3** (0.4 mmol), TMEDA (0.4 mmol), DMSO (2.0 mL), room temperature, N₂, and 24 h. Isolated yield.



Scheme 4 Control experiments.



Scheme 5 Possible reaction pathway.

give carbon cation intermediate **F**. Finally, the deprotonation of intermediate **F** affords the desired product **4a**.

In summary, we have developed a visible-light-induced EDA complex that promotes a three-component difluoroalkylation reaction of quinoxalin-2(1*H*)-ones, unactive alkenes and difluoroalkyl bromides. Various 3-difluoroalkylated quinoxalin-2(1*H*)-ones could be efficiently obtained with good functional group tolerance under the mild conditions. Mechanistic control experiments indicated that the reaction was triggered by photoactivation through the generation of an EDA complex between TMEDA and $\text{BrCF}_2\text{CO}_2\text{Et}$. It provided a green and efficient strategy to construct difluoroalkylated quinoxalinone derivatives from simple small molecules.

We are grateful to the Natural Science Foundation of Shandong Province (ZR2024QB249) for the financial support.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: general synthetic experimental details, characterization data, and NMR spectra. See DOI: <https://doi.org/10.1039/d5cc04758g>.

Notes and references

- (a) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (b) C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441–5454; (c) K. Yamamoto, J. Li, J. A. O. Garber, J. D. Rolfes, G. B. Boursalian, J. C. Borghs, C. Genicot, J. Jacq, M. van Gastel, F. Neese and T. Ritter, *Nature*, 2018, **554**, 511–514.
- (a) N. J. Carter and G. M. Keating, *Drugs*, 2007, **67**, 2277–2288; (b) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Soroehinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (c) Z. Feng, Y. L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264–2278; (d) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho and F. D. Toste, *Chem. Rev.*, 2018, **118**, 3887–3964.
- (a) H. M. Refaat, A. A. Moneer and O. M. Khalil, *Arch. Pharmacol. Res.*, 2004, **27**, 1093–1098; (b) B. Wu, Y. Yang, X. Qin, S. Zhang, C. Jing, C. Zhu and B. Ma, *ChemMedChem.*, 2013, **8**, 1913–1917; (c) L. L. Shi, W. Hu, J. F. Wu, H. Y. Zhou, H. Zhou and X. Li, *Mini-Rev. Med. Chem.*, 2018, **18**, 392–413; (d) Q. M. Ke, G. B. Yan, J. Yu and X. Wu, *Org. Biomol. Chem.*, 2019, **17**, 5863–5881.
- (a) W. W. Wang, T. H. Zhu and J. Wu, *Org. Chem. Front.*, 2023, **10**, 5375–5382; (b) R. Shaw, N. Sihag, H. Bhartiya and M. R. Yadav, *Org. Chem. Front.*, 2024, **11**, 954–1014.
- (a) G. F. Hong, J. W. Yuan, J. H. Fu, G. Y. Pan, Z. W. Wang, L. R. Yang, Y. M. Xiao, P. Mao and X. M. Zhang, *Org. Chem. Front.*, 2019, **6**, 1173–1182; (b) C. Jin, X. Zhuang, B. Sun, D. Li and R. Zhu, *Asian J. Org. Chem.*, 2019, **8**, 1490–1494; (c) L. Wang, H. Liu, F. Li, J. Zhao, H. Y. Zhang and Y. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 2354–2359; (d) Z. Wei, S. Qi, Y. Xu, H. Liu, J. Wu, H. Li, C. Xia and G. Duan, *Adv. Synth. Catal.*, 2019, **361**, 5490–5498.
- (a) H. Jiang and A. Studer, *Chem. Soc. Rev.*, 2020, **49**, 1790–1811; (b) Y. Q. Li, D. Wu, H. G. Cheng and G. Y. Yin, *Angew. Chem., Int. Ed.*, 2020, **59**, 7990–8003; (c) Q. Feng, J. Hao, Y. Hu, R. Fu, W. Wei and D. Yi, *Chin. Chem. Lett.*, 2025, **36**, 110582; (d) X.-M. Chen, L. Song, J. Pan, F. Zeng, Y. Xie, W. Wei and D. Yi, *Chin. Chem. Lett.*, 2024, **35**, 110112; (e) Y. Wang, J. Wang, C. Chen, L. Song, Z.-L. Wang, W. Wei and D. Yi, *Chem. Commun.*, 2025, **61**, 10812–10815.
- Y. R. Yuan, L. Li, X. Bu, X. Wang, R. Sun, M. D. Zhou and H. Wang, *Asian J. Org. Chem.*, 2022, **11**, e202200139.
- L. Shen, J. W. Yuan, B. Zhang, S. Y. Song, L. R. Yang, Y. M. Xiao, S. R. Zhang and L. B. Qu, *Z. Naturforsch.*, 2023, **78**, 245–250.
- T. Singh, S. R. Nasireddy, G. C. Upreti, S. Arora and A. P. Singh, *Org. Lett.*, 2023, **25**, 5558–5562.
- (a) C. G. S. Lima, T. d. M. Lima, M. Duarte, I. D. Jurberg and M. W. Paixão, *ACS Catal.*, 2016, **6**, 1389–1407; (b) L. M. Kammer, S. O. Badir, R.-M. Hu and G. A. Molander, *Chem. Sci.*, 2021, **12**, 5450–5457; (c) G.-Z. Wang, M.-C. Fu, B. Zhao and R. Shang, *Sci. China. Chem.*, 2021, **64**, 439–444; (d) Y.-M. Tian, E. Hofmann, W. Silva, X. Pu, D. Touraud, R. M. Gschwind, W. Kunz and B. König, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218775; (e) M. Huang, G. Wang, H. Li, Z. Zou, X. Jia, G. Karotsis, Y. Pan, W. Zhang, J. Ma and Y. Wang, *Green Chem.*, 2024, **27**, 413–419.
- (a) D. M. Whalley, H. A. Duong and M. F. Greaney, *Chem. – Eur. J.*, 2019, **25**, 1927–1930; (b) G. Zhao, S. Lim, D. G. Musaeu and M.-Y. Ngai, *J. Am. Chem. Soc.*, 2023, **145**, 8275–8284; (c) S. P. Zhang, J. X. Lan, M. L. Yang, J. Y. Cao, Y. C. Zhang and W. C. Yang, *Org. Lett.*, 2024, **26**, 9990–9995; (d) S. J. Song, C. Luo, G. Wang, J. J. Guo, Z. Chen and J. J. Li, *Chem. Commun.*, 2024, **60**, 11323–11326; (e) K. Mondal and M. Baidya, *Adv. Synth. Catal.*, 2024, **366**, 148–153.
- (a) Y. Lv, H. Ding, J. You, W. Wei and D. Yi, *Chin. Chem. Lett.*, 2024, **35**, 109107; (b) Z. Wang, N. Meng, Y. Lv, W. Wei, H. Yue and G. Zhong, *Chin. Chem. Lett.*, 2023, **34**, 107599; (c) Z. Yang, C. Liu, J. Lei, Y. Zhou, X. Gao and Y. Li, *Chem. Commun.*, 2022, **58**, 13483–13486; (d) C. Liu, Q. Dai, Y. Li, C. Huang, L. Guo and Z. Yang, *J. Org. Chem.*, 2023, **88**, 7281–7289; (e) Z. Yang, Y. Zhou, H. Li, J. Lei, P. Bing, B. He and Y. Li, *Asian J. Org. Chem.*, 2022, **11**, e202100656; (f) Z. Yang, J. Luo, W. Zhang, J. Lei, C. Liu and Y. Li, *Org. Biomol. Chem.*, 2025, **23**, 323–327.
- G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461–5476.
- (a) A. Carrer, J. D. Brion, S. Messaoudi and M. Alami, *Org. Lett.*, 2013, **15**, 5606–5609; (b) K.-J. Li, Y.-Y. Jiang, K. Xu, C.-C. Zeng and B.-G. Sun, *Green Chem.*, 2019, **21**, 4412–4421; (c) Z.-Z. Xie, Y. Zheng, K. Tang, J.-P. Guan, C.-P. Yuan, J.-A. Xiao, H.-Y. Xiang, K. Chen, X.-Q. Chen and H. Yang, *Org. Lett.*, 2021, **23**, 9474–9479.
- (a) W. F. Wang, T. Liu, Y. L. Cheng and Q. H. Song, *Org. Biomol. Chem.*, 2024, **22**, 805–810; (b) J.-C. Hou, J. Jiang, Y.-C. Wen, Y.-Y. Zeng, Y.-H. Lu, J.-S. Wang, L.-J. Ou and W.-M. He, *J. Org. Chem.*, 2024, **89**, 6117–6125; (c) Y.-D. Xu, Y.-M. Xing, H.-T. Ji, L.-J. Ou, W.-B. He, J. Peng, J.-S. Wang, J. Jiang and W.-M. He, *J. Org. Chem.*, 2024, **89**, 17701–17707; (d) J. H. Ji, K. J. Li, X. Z. Zhou, C. Xu, D. Zhang and W. Shao, *Chem. Commun.*, 2025, **61**, 6767–6770.