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

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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.

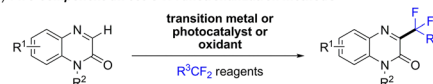
Difluoroalkylated compounds have remarkably important applications in agrochemicals, pharmaceuticals and materials science¹ due to their unique chemical and biological properties.² Meanwhile, quinoxalin-2(1H)-ones are a crucial class of heterocyclic units, endowed with significant pharmaceutical activities, 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.

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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).

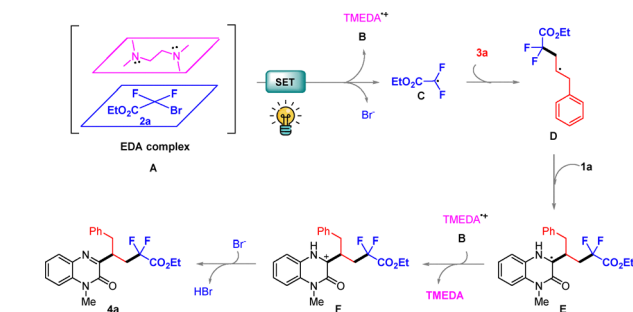
On the basis of previous literature reports and the above experimental results,^{14,15} a possible mechanism was illustrated as shown in Scheme 5. Firstly, this reaction commences with the formation of an electron donor–acceptor (EDA) complex between compound **2a** and TMEDA. Upon irradiation with visible 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.

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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>.

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