Direct C–H difluoromethylation of heterocycles via organic photoredox catalysis

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The discovery of modern medicine relies on the sustainable development of synthetic methodologies to meet the needs associated with drug molecular design. Heterocycles containing difluoromethyl groups are an emerging but scarcely investigated class of organofluoro molecules with potential applications in pharmaceutical, agricultural and material science. Herein, we developed an organophotocatalytic direct difluoromethylation of heterocycles using O2 as a green oxidant. The C–H oxidative difluoromethylation obviates the need for pre-functionalization of the substrates, metals and additives. The operationally straightforward method enriches the efficient synthesis of many difluoromethylated heterocycles in moderate to excellent yields. The direct difluoromethylation of pharmaceutical molecules demonstrates the practicability of this methodology to late-stage drug development. Moreover, 2′-deoxy-5-difluoromethyluridine (F2TDR) exhibits promising activity against some cancer cell lines, indicating that the difluoromethylation methodology might provide assistance for drug discovery.

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Organofluoro compounds are widely used in the fields of pharmaceutical, agricultural, and material science. The introduction of fluoride atoms or fluorine-containing groups into the framework of organic molecules often changes the physicochemical properties or biological activities of compounds, and has become an essential topic for chemists. During the past few decades, much attention has been focused on the synthesis of fluorinated and trifluoromethylated molecules. On the other hand, the difluoromethyl group is also a critical fluorinated functional group due to its use as a lipophilic hydrogen bond donor. In addition, CF₂H group can be considered as the isostere of a thiol, a hydroxyl, and an amide, which brings out its potential value in drug development with novel scaffold. However, these above-mentioned fluoromethylated heterocycles include deoxyfluorination of aldehydes and the introduction of fluorine atoms or fluorine-containing groups into the framework of organic molecules often changes the physicochemical properties or biological activities of compounds, and has become an essential topic for chemists. During the past few decades, much attention has been focused on the synthesis of fluorinated and trifluoromethylated molecules. On the other hand, the difluoromethyl group is also a critical fluorinated functional group due to its use as a lipophilic hydrogen bond donor. In addition, CF₂H group can be considered as the isostere of a thiol, a hydroxyl, and an amide, which brings out its potential value in drug development with novel scaffold. Recently, difluoromethylation of heteroaromatic compounds has been reported. Therefore, it is highly desirable to develop new methods to synthesize and functionalize these molecules without the need for expensive and toxic metal catalysts or external oxidants and strictly inert conditions, which narrow the functional group tolerance and limit the substrate scope. During the submission of this manuscript, Duan and Xia reported an efficient photocatalytic strategy for C–H perfluoroalkylation of quinoxalinones under aerobic oxidation conditions, however, the corresponding difluoromethylation has not been reported. Therefore, it is highly desirable to develop new methods to synthesize and functionalize these molecules without the need for expensive and toxic metal catalysts or external oxidants and strictly inert conditions, which narrow the functional group tolerance and limit the substrate scope. During the submission of this manuscript, Duan and Xia reported an efficient photocatalytic strategy for C–H perfluoroalkylation of quinoxalinones under aerobic oxidation conditions, however, the corresponding difluoromethylation has not been reported. Therefore, it is highly desirable to develop new methods to synthesize and functionalize these molecules without the need for expensive and toxic metal catalysts or external oxidants and strictly inert conditions, which narrow the functional group tolerance and limit the substrate scope. During the submission of this manuscript, Duan and Xia reported an efficient photocatalytic strategy for C–H perfluoroalkylation of quinoxalinones under aerobic oxidation conditions, however, the corresponding difluoromethylation has not been reported. Therefore, it is highly desirable to develop new methods to synthesize and functionalize these molecules without the need for expensive and toxic metal catalysts or external oxidants and strictly inert conditions, which narrow the functional group tolerance and limit the substrate scope.
approaches to achieve direct C–H difluoromethylation of heterocycles, which can overcome the above-mentioned defects and avoid the safety problems with stoichiometric oxidant at a larger scale.

In the past decade, visible-light catalysis has attracted extensive attention, by which highly active radical species generated under mild conditions can be involved in various chemical bond formation\textsuperscript{53–59}. Notably, organic dyes are cheaper and more reliable than expensive metal photoredox catalysts in many valuable reactions\textsuperscript{55,56,59}. In this study, we focus our attention on developing a straightforward and practical method for difluoromethylation reactions using the inexpensive, commercially available, and user friendly Hu's reagent sodium difluoromethane sulfonate (CF\textsubscript{2}HSO\textsubscript{2}Na) as the difluoromethyl radical precursor\textsuperscript{60} under mild conditions. This protocol combines organic photocatalysis with green air oxidant for the difluoromethylation of many categories of heterocycles. Notably, the difluoromethylation product 2′-deoxy-5-difluoromethyluridine (F\textsubscript{2}TDR) commendably inhibits the

| Entry | Photocatalysts | Solvent | Time (h) | Yield\textsuperscript{b}/% |
|-------|----------------|---------|----------|--------------------------|
| 1     | Eosin Y        | DMSO    | 15       | 64                       |
| 2     | Rose bengal    | DMSO    | 12       | 72                       |
| 3     | Acridinium salt| DMSO    | 36       | 64                       |
| 4     | DCA            | DMSO    | 15       | Trace                    |
| 5     | MB             | DMSO    | 15       | Trace                    |
| 6     | Ensin B        | DMSO    | 24       | 61                       |
| 7     | Ru(bpy)\textsubscript{3}Cl\textsubscript{2}·6H\textsubscript{2}O| DMSO | 36       | 62                       |
| 8     | fac-Ir(ppy)\textsubscript{3} | DMSO | 36       | 56                       |
| 9     | Rose bengal    | DMF     | 12       | 10                       |
| 10    | Rose bengal    | MeCN    | 12       | 20                       |
| 11    | Rose bengal    | MeOH    | 12       | 51                       |
| 12    | Rose bengal    | CH\textsubscript{3}Cl | 12 | Trace                    |
| 13    | Rose bengal    | Acetone | 12       | 55                       |
| 14    | Rose bengal    | Toluene | 12       | NR                       |
| 15    | Rose bengal    | EtOAc   | 12       | 15                       |
| 16    | Rose bengal    | 1,4-dioxane | 12 | 22                       |
| 17    | Rose bengal    | DMSO    | 12       | NR                       |
| 18    | Rose bengal    | DMSO    | 12       | NR                       |
| 19    | Rose bengal    | DMSO    | 12       | NR                       |

\textsuperscript{a}The reactions were carried out with 1a (0.2 mmol), CF\textsubscript{2}HSO\textsubscript{2}Na 2 (0.4 mmol), photocatalyst (2 mol%) in 1 mL solvent under two 3 W green LEDs irradiation at room temperature.

\textsuperscript{b}Isolated yield.

\textsuperscript{c}The photocatalyst loading was decreased to 1 mol%.

\textsuperscript{d}In the dark.
**Fig. 2 Substrate scope of quinoxalin-2(1H)-ones.** Reaction conditions: 1 (0.2 mmol), CF$_2$HSO$_2$Na 2 (0.4 mmol), rose bengal (2 mol%) in 1 mL DMSO under two 3 W green LEDs irradiation at room temperature. Isolated yields based on 1.

| 1a-1e | 2 | 3a-3o |
|-------|---|-------|
| ![Substrate 1a](image1) | ![Substrate 2](image2) | ![Substrate 3a](image3) |
| ![Substrate 1b](image4) | ![Substrate 2](image5) | ![Substrate 3b](image6) |
| ![Substrate 1c](image7) | ![Substrate 2](image8) | ![Substrate 3c](image9) |
| ![Substrate 1d](image10) | ![Substrate 2](image11) | ![Substrate 3d](image12) |
| ![Substrate 1e](image13) | ![Substrate 2](image14) | ![Substrate 3e](image15) |
| **3a, 72%** | **3b, 68%** | **3c, 60%** |
| ![Substrate 1f](image16) | ![Substrate 2](image17) | ![Substrate 3f](image18) |
| ![Substrate 1g](image19) | ![Substrate 2](image20) | ![Substrate 3g](image21) |
| ![Substrate 1h](image22) | ![Substrate 2](image23) | ![Substrate 3h](image24) |
| ![Substrate 1i](image25) | ![Substrate 2](image26) | ![Substrate 3i](image27) |
| ![Substrate 1j](image28) | ![Substrate 2](image29) | ![Substrate 3j](image30) |
| ![Substrate 1k](image31) | ![Substrate 2](image32) | ![Substrate 3k](image33) |
| **3j, 42%** | **3l, 42%** | **3k, 34%** |
| ![Substrate 1m](image34) | ![Substrate 2](image35) | ![Substrate 3m](image36) |
| ![Substrate 1n](image37) | ![Substrate 2](image38) | ![Substrate 3n](image39) |
| ![Substrate 1o](image40) | ![Substrate 2](image41) | ![Substrate 3o](image42) |
| ![Substrate 1p](image43) | ![Substrate 2](image44) | ![Substrate 3p](image45) |
| ![Substrate 1q](image46) | ![Substrate 2](image47) | ![Substrate 3q](image48) |
| ![Substrate 1r](image49) | ![Substrate 2](image50) | ![Substrate 3r](image51) |
| ![Substrate 1s](image52) | ![Substrate 2](image53) | ![Substrate 3s](image54) |
| ![Substrate 1t](image55) | ![Substrate 2](image56) | ![Substrate 3t](image57) |
| **3i, 56%** | **3j, 52%** | **3k, 73%** |
| ![Substrate 1u](image58) | ![Substrate 2](image59) | ![Substrate 3u](image60) |
| ![Substrate 1v](image61) | ![Substrate 2](image62) | ![Substrate 3v](image63) |
| ![Substrate 1w](image64) | ![Substrate 2](image65) | ![Substrate 3w](image66) |
| ![Substrate 1x](image67) | ![Substrate 2](image68) | ![Substrate 3x](image69) |
| ![Substrate 1y](image70) | ![Substrate 2](image71) | ![Substrate 3y](image72) |
| ![Substrate 1z](image73) | ![Substrate 2](image74) | ![Substrate 3z](image75) |
| **3l, 60%** | **3m, 52%** | **3n, 87%** |

**Fig. 3 Substrate scope of heteroaromatics.** Reaction conditions: 4 (0.1 mmol), CF$_2$HSO$_2$Na 2 (0.4 mmol), rose bengal (5 mol.%) in 1 mL DMSO under two 3 W green LEDs irradiation at room temperature. Isolated yields based on 4. bWith CF$_2$HSO$_2$Na 2 (0.4 mmol), rose bengal (2 mol%) in 1 mL DMSO.
Results
Investigation of the reaction conditions. We started our investigation by the model reaction of 1-methyl quinoxalin-2-one 1a with CF$_2$HSO$_2$Na 2 as a fluorine source and eosin Y as a photocatalyst in DMSO at room temperature under green LEDs irradiation. To our delight, the difluoromethylation product 3a was obtained in 64% yield (Table 1, entry 1). Then, different photocatalysts were examined (Table 1, entries 2–8), in which rose bengal (RB) was the best one, providing 3a in 72% yield in 12 h. After identifying the optimal photocatalyst, we found that DMSO was the best reaction media through solvent screening (Table 1, entries 2 and 9–16). The yield of product reduced obviously when the loading of the photocatalyst was further decreased to 1 mol% (Table 1, entry 17). Control experiments indicated that photocatalyst and green light source were both essential for the reaction efficiency (Table 1, entries 18 and 19).

Scope of quinoxalin-2(1H)-ones on the phenyl ring. With the optimal reaction conditions in hand, the substrate scope of various quinoxalin-2(1H)-ones was then investigated. As exhibited in Fig. 2, the reactions worked well with a range of substituted quinoxalin-2(1H)-ones bearing either electron-donating or withdrawing substituents (methyl, fluoro, chloro, bromo, methoxy, nitro, and naphthyl), giving the desired difluoromethylation products 3a–3j in moderate to good yields. To highlight the utility of this transformation, a variety of N-substituted quinoxalin-2(1H)-ones (1k–1n) were also tested. As a result, all the N-substituted quinoxalin-2(1H)-ones are compatible with the reaction, furnishing the expected products 3k–3n in 34–73% yields. Notably, N-unsubstituted quinoxalin-2(1H)-one also proceeded smoothly, delivering the desired product 3o in 87% yield.

Fig. 4 Substrate scope of bioactive molecules. Reaction conditions: 4 (0.1 mmol), CF$_2$HSO$_2$Na 2 (0.4 mmol), rose bengal (5 mol%) in 1 mL DMSO under two 3 W green LEDs irradiation at room temperature. Isolated yields based on 4. a With CF$_2$HSO$_2$Na 2 (0.4 mmol), rose bengal (2 mol%) in 1 mL DMSO. b Large scale with 2 mmol heteroarenes. c The minor regioisomeric position is labeled with the respective carbon atom number.
**Scope of heteroaromatics.** To further extend the scope of this methodology, some other heteroaromatic substrates were investigated (Fig. 3). A wide range of five- and six-membered difluoromethylated heteroaromatics, such as pyrazines (5a and 5b), quinoxalines (5c and 5d), pyrrole (5e), imidazoles (5f and 5g), thiophene (5i), pyridines (5j), thiazole (5k), indoles (5l and 5m), and RNA-based dimethyluracils (5n and 5o), quinoline (5p), purine derivatives (5q and 5r), and pyrimidine (5s) provided final products with good yields. Several heteroaromatics with potentially sensitive functional groups (OH, NH2, or CHO) (5a, 5k, and 6j) were also compatible with this difluoromethylation strategy. Moreover, this direct C–H difluoromethylation method also suitable for some arenes (5t and 6j).

**Scope of bioactive molecules.** The methodology can also be applied to late-stage functionalization of complex nitrogen-containing bioactive molecules (Fig. 4). For example, the modification of caffeine and its derivatives delivers the desired difluoromethylated products 6a–6c in 38–74% yields. In addition, deoxyuridine, uridine, and 2′-fluoro-2′-deoxyuridine, which have free OH group as well as amide group, could tolerate this difluoromethylation reaction, giving the difluoromethylation products 6d–6f in 57–81% yields. Furthermore, melatonin, allopurinol, and uracil, which bear free secondary N–H groups, furnished the difluoromethylation reaction with moderate to good yields (6g, 6h, and 6i). Moreover, some other bioactive heteroarenes substrates, such as voricinazole, flavorant, metyrapone, and sulfonylureas, can also proceed well with the reaction, giving the difluoromethylated products 6j, 6k, and 6m in acceptable yields.

**Site-selectivity study.** The substrate scope results of Figs. 2–4 show that most of the difluoromethylation occurs on the C2–H bond adjacent to the heteroatom. Some heterocycle substrates bearing more than one radical attacked carbon center were also examined (Fig. 5). As a result, the unsubstituted indole substrate 7 gave the major product at the C2 position in 54% yield with 10:1 regioselectivity. The 5-nitro-substituted indole substrate 9 can obtain a single regioselective difluoromethylation product 10 with 71% yield. When 4-chloro-7H-pyrrolo[2,3-d] pyrimidine was used as substrate, the reaction furnishes the mixture of product 12 (C2/C6 = 5:1) in 46% yield. Notably, other electron-rich heteroarenes (benzofuran 13 and thianaphthene 15), which have not been investigated as substrates in previous reported radical difluoromethylation reactions58–59, also exhibited good reaction efficiency, producing the difluoromethylation products 14 and 16 in 92% and 65% yield, respectively. Unfortunately, other types of heteroarenes, including phenanthrene, 1,3,5-triazine, and thiazine, are not ideal substrates in this difluoromethylation reaction (Supplementary Fig. 2).

**Synthetic applications.** To evaluate the synthetic potential of this methodology, sunlight-driven experiment was performed. When the reaction was conducted under sunlight irradiation, the desired product 3a was obtained in 68% yield (Fig. 6a). Furthermore, a slight reduction of yields with large scale preparation of 6d and 6g also prove the practicability of this difluoromethylation strategy (Fig. 4, yields in parentheses for 6d and 6g). We further explored the potential application of the synthesized difluoromethylated product in medicinal chemistry. The F2TDR 6d has a similar structure to the trifluridine, which has been approved by FDA for the treatment of adult patients with metastatic colorectal cancer (for details, see https://www.drugbank.ca/drugs/DB00432). Therefore, we selected four tumor cell lines to evaluate the inhibitory activities of 6d, and made the comparison of the result with trifluridine. As shown in Fig. 6b, 6d higher tumor cell inhibitory capability than the trifluridine with relatively low IC50 values. Notably, the IC50 values of 6d against HCT116 and HepG-2 cells reach low micromolar level, which are about 57- and 6-fold lower than that of trifluridine, respectively. The improvement of antitumor activity indicates the practicality of this difluoromethylation methodology and the potential in the field of discovery of active drug molecules.

**Mechanistic investigations.** To gain insights into the current studied reaction, control experiments were conducted. When a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 1,1-diphenylethylene (Fig. 7a, b) was existing in the mixture containing 1a and CF3H2SO4Na, the reaction was completely suppressed, while the radical intermediate was detected by ESI-HRMS (Supplementary Fig. 5), indicating the existence of CF3H radical. When the reaction was carried out under inert atmosphere (Fig. 7c), the formation of 3a was completely inhibited, revealing that oxygen is crucial for the reaction. In situ 1H NMR experiment demonstrated that hydrogen peroxide (H2O2) does not form after irradiation of the reaction mixture in DMSO-d6 for 12 h under the optimized reaction condition. In addition, the observed water peak (H2O) growth indicating that the oxygen was eventually converted to H2O rather than H2O2 (Supplementary Figs. 6 and 7). The generated H2O2 could participate in the catalytic cycle and ultimately converted to H2O as the byproduct61. These experimental results illustrated an available radical pathway. Moreover, we also conducted the light/dark experiment. As shown in Fig. 7, the desired product 3a formed only under continuous irradiation, which ruled out the possibility of a radical chain propagation. On the basis of our experimental observations and previous studies59, a possible mechanism was proposed (Fig. 7e). Upon absorption of visible light, the
photocatalyst RB is excited into RB* (E_{red} = 0.99 V vs SCE) and a single electron is transferred from CF_{2}HSO_{2}Na (E = 0.59 V vs SCE) to RB*, which affords CF_{2}H radical and generates an RB\(^{−}\) radical anion. The photoredox cycle is completed by the molecular oxygen oxidation of RB\(^{−}\), giving RB and O_{2}^{−}.

After that, addition of CF_{2}H radical to 1a occurs, leading to intermediate A, which undergoes a 1,2-H shift to generate carbon radical intermediate B. The intermediate B loses a hydrogen atom to O_{2}^{−} to furnish the desired product 3a.

**Discussion**

In summary, we have achieved a visible-light triggered direct C–H difluoromethylation of heterocycles by using commercially available and inexpensive sodium difluoromethane sulfonate as CF_{2}H radical source. The process is under mild conditions using O_{2} as a green oxidant and without using metal additive. Furthermore, we also use this highly efficient methodology for direct difluoromethylation of some nitrogen-containing biological and pharmaceutical active molecules. In addition, the bioactivity evaluation of a representative difluoromethylation product 2'-deoxy-5-difluoromethyluridine (6d) exhibited promising activity against cancer cell lines. We expect this simple protocol to be of broad utility for the development of new drugs. Further synthetic applications and bioactivity tests are ongoing.

**Methods**

**Procedure for difluoromethylation of quinoxalin-2(1H)-ones.** To a 10 mL Schlenk tube equipped with a magnetic stir bar added quinoxalin-2(1H)-ones 1 (0.2 mmol), CF_{2}HSO_{2}Na 2 (0.4 mmol), and RB (0.004 mmol, 2 mol%) in DMSO (1.0 mL). The mixture was stirred and irradiated by two 3 W green LEDs at room temperature for 12 h. The residue was added water (10 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic phase was dried over Na_{2}SO_{4}.

**Procedure for difluoromethylation of other heterocycles.** To a 10 mL Schlenk tube equipped with a magnetic stir bar added heterocycles 4 (0.1 mmol), CF_{2}HSO_{2}Na 2 (0.4 mmol), and RB (0.002–0.005 mmol, 2–5 mol%) in DMSO (1.0 mL). The mixture was stirred and irradiated by two 3 W green LEDs at room temperature for 24 h. The residue was added water (10 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic phase was dried over Na_{2}SO_{4}.
The resulting crude residue was purified via column chromatography on silica gel to afford desired products.

Data availability
The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information files. Extra data are available from the author upon reasonable request. The X-ray crystallographic coordinates for structures of 3a reported in this article have been deposited at the Cambridge Crystallographic Data Center as CCDC 1920406. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Received: 16 September 2019; Accepted: 9 January 2020; Published online: 31 January 2020

Fig. 7 Mechanistic investigations. a Investigation on the effect of TEMPO. b Radical trapping with 1,1-diphenylethylene. c Investigation on the effect of oxygen. d Light/dark experiment. e Proposed reaction mechanism.

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Acknowledgements
The project was supported by NSFC (21971120, 21933008, and 81573354). We thanks Prof. Bin Chen and Dr Xu-Zhe Wang at the Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, for helpful discussions.

Author contributions
X.L. and W.Z. conceived and designed the experiments. W.Z. and X.-X.X. expanded the substrate scope, performed the synthetic application, and characterized all the products. J.Y.C performed the bioactive tests. C.Y. gave some helpful suggestions for the reaction.

Competing interests
The authors declare no competing interests.
