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A practical photocatalytic strategy for radical (deuterio)difluoromethylation using imidazolium reagents

Chao Sun, Yinpu Shen, Heyin Li, Zhen Wang, Yifan Li, Mengjun Huang, Zhenlei Zou, Jing Liu, Ao Liu, Yi Pan, Weigang Zhang* and Yi Wang^{ib}*

The difluoromethyl group (CF_2H) has garnered significant interest in medicinal chemistry owing to its unique biochemical and physicochemical properties. Its deuterated counterpart (CF_2D), building on the established utility of CF_2H , exhibits multifaceted potential for advancing biomedical research and therapeutic development. While the incorporation of the difluoromethyl group (CF_2H) into drug molecules has matured, efficient installation of its deuterated counterpart (CF_2D) remains a formidable challenge in medicinal chemistry. This study reports a novel (deuterio)difluoromethyl imidazolate reagent $\text{IMDN-SO}_2\text{CF}_2\text{X}$ ($\text{X} = \text{D}, \text{H}$), which is used to successfully construct various highly selective (deuterio)difluoromethyl compounds in the form of (deuterio)difluoromethyl radicals while maintaining high deuteration rates, achieving >99% isotopic purity in deuterium incorporation. The reagent enables precise CF_2D and CF_2H installation in natural products and synthetic bioactive compounds, showing broad substrate compatibility. This establishes a robust deuteration platform for drug discovery.

Introduction

Deuterium labeling technology, capitalizing on kinetic isotope effects (KIEs), enables precise molecular tracing while preserving the structural integrity of chemical configurations, biological functionalities, and thermodynamic stability.^{1–5} This methodology provides an atomic-level toolkit for real-time monitoring of biomedical material interfaces and systematic deciphering of metabolic networks in multiscale biological systems.^{6–8} Deuterium incorporation strategies have emerged as a key tool in medicinal chemistry for modulating the pharmacokinetic profiles (absorption, distribution, metabolism, and excretion; ADME) of drug candidates, particularly by altering C–H bond cleavage kinetics through kinetic isotope effects.^{9,10} In recent years, multiple deuterated drugs (deutetrabenazine/Austedo® for Huntington's disease treatment) have advanced into clinical trials, signifying accelerated industrial translation of deuterium-incorporated drug development¹¹ (Fig. 1A).

Recently, the difluoromethyl group (CF_2H) has attracted significant attention owing to its unique biochemical and physicochemical properties^{12–16} (Fig. 1A). The introduction of CF_2H groups can modulate key pharmacokinetic parameters, including membrane permeability, target binding affinity, and metabolic stability.^{17–19} Building upon the well-established

applications of the difluoromethyl group (CF_2H),^{20–31} its deuterated counterpart the CF_2D group exhibits multifunctionality and developmental potential, holding significant research value and promising applications in biomedical fields. Synthetic strategies for deuteriodifluoromethyl (CF_2D) compounds can be broadly categorized into three classes (Fig. 1B): the defunctionalization of α -functionalized difluoromethyl compounds, followed by deuteration, yields deuteriodifluoromethyl (CF_2D) compounds with moderate-to-high deuterium incorporation;^{32–41} synthesis of deuteriodifluoromethyl (CF_2D) compounds *via* deuteriodifluoromethylation reagents;^{42–44} deuteriodifluoromethyl compounds can also be prepared by functional group conversion from deuterated precursors.^{45–47} It is noteworthy that the direct construction of target compounds using deuteriodifluoromethyl radicals remains challenging, primarily due to the lack of universal synthesis methods.^{48–51}

Conventional methods for generating the deuteriodifluoromethyl radical ($\cdot\text{CF}_2\text{D}$) *via* activation of deuteriodifluoromethylation reagents are primarily categorized into two types: the deuterated difluoromethyl 2-pyridyl sulfone reagent developed by Hu's work, *etc*, which focuses on validating the radical generation mechanism^{48–50} and deuterated sodium difluoromethylsulfonate ($\text{CF}_2\text{DSO}_2\text{Na}$) reported by Li's research group. Although this reagent can generate $\cdot\text{CF}_2\text{D}$ radicals through metal catalysis and selectively modify the C2 position of indole compounds,⁵¹ its substrate applicability remains limited (Fig. 1C).

State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, Collaborative Innovation Center of Advanced Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China. E-mail: yiwang@nju.edu.cn



Fig. 1 (A) Application of deuterium and fluorine atoms in medicinal chemistry. (B) Strategies for the synthesis of deuteriodifluoromethyl compounds. (C) The traditional activation and novel activation modes. (D) The design and synthesis of benzimidazolium triflate derived IMDN-SO₂CF₂X reagent. (E) IMDN-SO₂CF₂X reagent for radical (deutero)difluoromethylation of unsaturated hydrocarbons.

Fluorosulfonyl difluoroacetic acid methyl ester (FSO₂CF₂-CO₂Me, MFSDA or Chen's reagent) is a versatile precursor widely used in trifluoromethylation, difluorocarbene generation, and difluoroalkylation reactions to access diverse fluorinated products.^{52–54} Our group has dedicated extensive efforts to the exploration of imidazole-salt-derived fluorinating reagents.^{55–61} By leveraging the heteroaromatic activation (HetAr activation) strategy, we have developed diverse reagent systems enabling trifluoromethylation, polyfluoroalkylation, and fluorosulfonylation. Nevertheless, the design of deuterium-labeled difluoromethylation reagents and their application in selective difluoromethylation remain a significant challenge.

Therefore, we attempted to combine Chen's reagent with imidazole to construct a benzimidazolium fluorosulfonate reagent. The positive charge of the resulting benzimidazolium fluorosulfonate can be delocalized on both nitrogens. By the homolytic cleavage of the weak N–S bond (BDE ≈ 70 kcal mol^{–1}),⁵⁶ this cationic complex undergoes the SET process to generate a deuteriodifluoromethyl radical or difluoromethyl radical.

Herein, we developed a versatile imidazole salt reagent (IMDN-SO₂CF₂X, X = D/H; 2a, 2b) with high reactivity, practicality, and air stability (Fig. 1D). This reagent enables radical-mediated stereoselective difluoromethylation and



deuteriodifluoromethylation of olefins, difluoromethylation of heteroaromatic hydrocarbons (both deuterated and non-deuterated), and functionalization of α,β -unsaturated olefins with $\text{CF}_2\text{D}/\text{CF}_2\text{H}$ groups. Additionally, it provides a general platform for synthesizing (deuterio)difluoromethylated architectures (Fig. 1E).

Results and discussion

Our initial investigation began with 4-vinylbiphenyl **1a** as the model substrate (Table 1). After extensive screening of reaction conditions, we found that when using 1.5 equiv. of benzimidazolium sulfonate reagent (**IMDN-SO₂CF₂D**, **2a**, $E_{1/2}^{\text{red}} = 0.732$ V vs. SCE), 2 mol% of 4DPAIPN, and 1.0 equiv. of 4-vinylbiphenyl in THF (tetrahydrofuran) (1.0 mL) under irradiation with 60 W blue LEDs (entry 1), the (*E*)- CF_2D -alkene product **4a** could be obtained in 71% GC yield and the conversion of **1a** was 90% and no (*Z*)- CF_2D -alkene products were observed under these conditions. We then conducted control experiments to verify the necessity of the light source and photocatalyst in the reaction (entries 2 and 3). The results showed that without either the light source or the photocatalyst, the reaction did not proceed, and the starting material remained largely unconsumed. Subsequently, by screening reaction times, we found that upon extending the reaction time to 18 hours, the starting material was fully consumed and the GC yield was 75% (with an isolated yield of 70%) (entry 4). Building on these findings, we then optimized the photocatalysts and solvents separately. When the photocatalyst was replaced with 4CZIPN, only trace amounts of product were formed (entry 5); when *fac*-Ir(ppy)₃ was used as a photocatalyst, **1a** had a great conversion (>95%) with a GC yield of 41%, (entry 6). For solvent screening: DME (1,2-dimethoxyethane) provided >95% conversion and 47% GC yield (entry 7); 2-Me-THF(2-methyltetrahydrofuran) improved conversion to >95% and 70% GC yield (entry 8). Notably, when

the solvent was switched to MeCN (entry 9), the reaction barely occurred, yielding only trace products (as illustrated in SI, SI Tables 4–7).

With the optimized reaction conditions in hand, we next examined the generality of this transformation with different alkenes and heteroarenes. Using 2 mol% of 4DPAIPN and **IMDN-SO₂CF₂X** salt **2** (1.5 equiv.) at ambient temperature, a range of alkenes underwent radical (deuterio)difluoromethylation with high efficiency. As shown in Scheme 1, this strategy has demonstrated broad applicability, not only effectively acting on simple mono-substituted alkenes (**4a–e**), but also showing excellent performance for complex alkenes containing ester and amino groups (**4k–r**). The experimental results indicate that these substrates can all complete the reaction with good yields, high selectivity, and high deuterium incorporation rates. Furthermore, this method also exhibits excellent applicability to di- and tri-substituted alkenes (**4f–j**), achieving high levels of yield and deuterium incorporation. Notably, isomerization of the alkene was observed in product **4g**. Moreover, natural product derivatized olefin involving menthol, cholesterol and bexarotene can also be tolerated under the mild photocatalytic conditions and the corresponding alkenyl (deuterio)difluoromethylation products are obtained in moderate yields (**4q–s**). Notably, for product **4s**, the *E/Z* ratio is 1 : 1, which may arise from the symmetric steric environment imposed by the two phenyl rings.

Heteroaryl- CF_2H , as a key structural motif in drug development, has attracted significant interest. By variation of the reaction conditions, we extended this radical (deuterio)difluoromethylation protocol to heteroarenes. This method developed herein enables efficient deuterated and non-deuterated difluoromethylation of diverse aromatic compounds (Scheme 1). Heteroarene derivatives such as quinoxaline derivatives, quinolinone derivatives, and benzofuran derivatives were also compatible and generated the desired products (**5a–d**) in moderate to good yields (62–85%). Moreover, this strategy enables efficient functionalization of hetero-aromatic drug molecules (coumarin and angelicin) *via* direct radical (deuterio)difluoromethylation, achieving moderate yields under mild conditions (**5e, 5f**).

By modifying the reaction conditions, including the light source, catalyst, and other parameters, we extended this radical (deuterio)difluoromethylation protocol to acrylates. As shown in Scheme 2, electron-deficient acrylates were compatible with this transformation, affording $\beta\text{-CF}_2\text{D}/\text{CF}_2\text{H}$ carbonyls and related compounds (**7a–g**) in moderate yields. Notably, the method consistently provides 99% deuterium incorporation across diverse heteroaromatic substrates.

In the substrate scope investigation, it was observed that most substrates exhibited comparable yields and selectivity between deuteriodifluoromethylation and difluoromethylation, though the deuterated variant required longer reaction times. However, certain substrates showed notable differences in yield and selectivity, likely due to their inherent structural properties.

After the applicability of **IMDN-SO₂CF₂X** (X = D/H; **2a, 2b**) for (deuterio)difluoromethylation in olefinic and heteroaromatic substrates was demonstrated, its reactivity was systematically

Table 1 Optimization of the reaction conditions

Entry	Variation from the above conditions	Conversion ^a	Yield of 4a ^b
1	Standard conditions	90%	71%
2	W/o photocatalyst	<5%	0
3	In darkness	<5%	0
4	18 h instead of 12 h	>95%	75%(70%) ^c
5	4CZIPN instead of 4DPAIPN	<5%	Trace
6	<i>fac</i> -Ir(ppy) ₃ instead of 4DPAIPN	>95%	41%
7	DME instead of THF	>95%	47%
8	2-Me-THF instead of THF	>95%	70%
9	MeCN instead of THF	<5%	Trace

^a Yield determined by gas chromatography (GC) using dodecane as an internal standard. ^b GC yield with dodecane as the internal standard.

^c Isolated yield.





Scheme 1 Substrate scope of olefins and heteroaromatic compounds. Condition A: alkynes **1** (0.10 mmol), **2a** (1.5 equiv.), 4DPAIPN (2 mol%) in THF (1.0 mL) under Ar and 60 W blue LEDs for 18 h. Condition B: alkynes **1** (0.10 mmol), **2b** (1.5 equiv.), 4DPAIPN (2 mol%) in THF (1.0 mL) under Ar and 60 W blue LEDs for 12 h. Condition C: alkynes **3** (0.10 mmol), **2a** (1.5 equiv.), 4DPAIPN (2 mol%) in IA (isopropyl acetate) (1.0 mL) under Ar and 60 W blue LEDs for 18 h. Condition D: alkynes **3** (0.10 mmol), **2b** (1.5 equiv.), 4DPAIPN (2 mol%) in IA (isopropyl acetate) (1.0 mL) under Ar and 60 W blue LEDs for 12 h.

evaluated under photocatalytic conditions. As shown in Scheme 3, the three-component reaction of 4-phenylstyrene, **IMDN-SO₂CF₂X** reagent **2**, and oxygen nucleophile reagents (methanol, phenol, and acetic acid) obtained good yields of β-methoxy compound **8a**, β-phenoxy compound **9a**, and β-acetate compound **10a**. In addition, the 5-heteroaromatic-substituted alkene **11b** undergoes (deuterio)difluoromethylation, followed by migration of the heteroaromatic group to the distal end, to afford the corresponding ketone product **13**, in high yield.

Under photocatalytic conditions, substrates **11c**, **11d**, and **11a** undergo distinct radical-initiated tandem cyclization reactions, affording isoquinoline-1,3-dione **14**; 1,3-benzoxazine **15**; and lactone **12** in 68–91% yields, respectively. These reactions and radical-polar crossover transformations highlight the significant potential of the **IMDN-SO₂CF₂X** (X = D/H; **2a**, **2b**) reagent for synthetic applications in the radical functionalization of olefins.



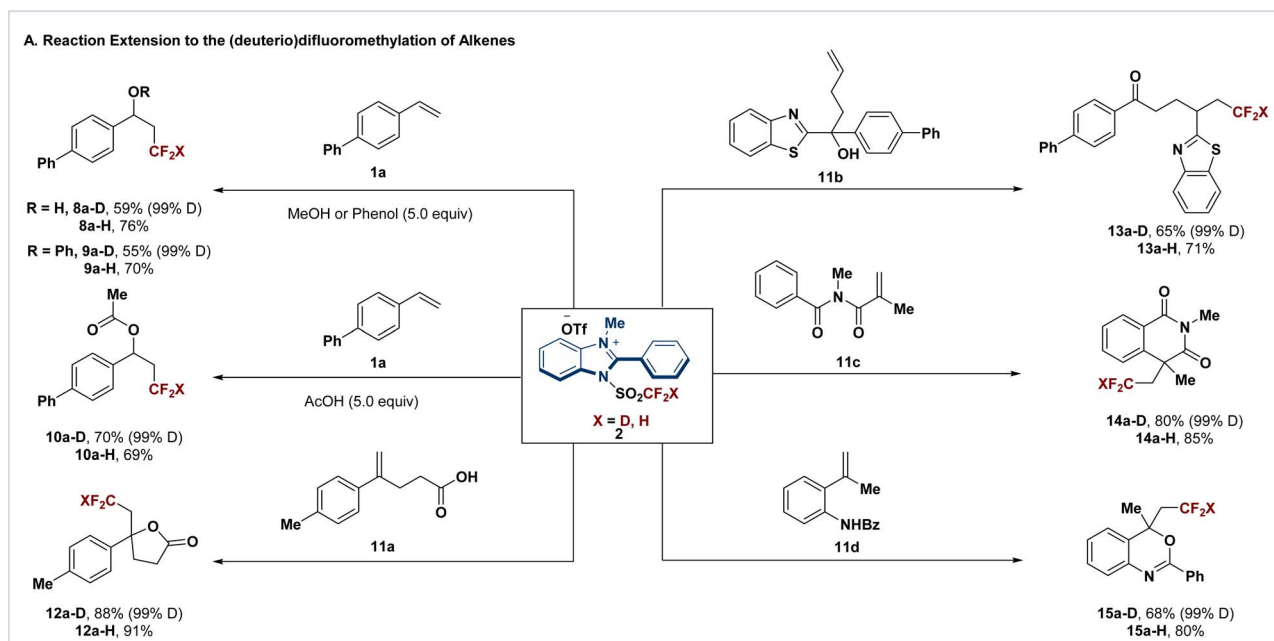
Scheme 2 Substrate scope of the α,β -unsaturated olefins Condition E: alkynes **6** (0.10 mmol), **2a** (1.5 equiv.), cyclohexa-1,4-diene (2.5 equiv.), 4DPAIPN (2 mol%) in 2-Me-THF (1.0 mL) under Ar and 90 W blue LEDs for 24 h. Condition F: alkynes **6** (0.10 mmol), **2b** (1.5 equiv.), cyclohexa-1,4-diene (2.5 equiv.), 4DPAIPN (2 mol%) in 2-Me-THF (1.0 mL) under Ar and 90 W blue LEDs for 24 h.

It is gratifying to note that **IMDN-SO₂CF₂X** reagent **2** demonstrates good to excellent yields and selectivity for (deuterio)difluoromethylation across diverse reaction types. It also shows favorable performance in the modification of bioactive molecule derivatives through (deuterio)difluoromethylation. Based on its robust performance in various reactions, this reagent holds significant potential for future applications in the synthesis of pharmaceutical molecules.

To probe the reaction mechanism, we performed a series of mechanism-validation experiments. First, 2.5 equiv. of TEMPO were added to the baseline reaction system (Scheme 4A). This

addition significantly suppressed the reaction progress. Concurrently, the TEMPO-CF₂D adduct was identified *via* GC-MS analysis, indicating the involvement of radical intermediates. The radical clock experiment was carried out using cyclopropyl styrene **11e**. Under the standard conditions with the MgCl₂ additive, the ring-opened product **16a-D** can be obtained in 27% (99% D-incorporation) isolated yield (Scheme 4B). This result indicated the potential involvement of the deuteriodifluoromethyl radical ($\cdot$ CF₂D) in the reaction.

From the above mechanistic experiments, we speculate the possible mechanism of the reaction (Scheme 4C): first, under



Scheme 3 Extension of experiments.





Scheme 4 Study of reaction mechanisms.

irradiation, the cationic **IMDN-SO₂CF₂X** reagent **2** can be reduced by the excited state photocatalyst (PC*) to generate the (deuterio)difluoromethyl radical. Then the addition of the (deuterio)difluoromethyl radical to the unsaturated hydrocarbons (**1**, **3**, and **6**) furnishes radical intermediates I–IV. Then the intermediates I–II were oxidized by PC⁺ to undergo hydrogen elimination to get the corresponding product (**4** and **5**) and regenerate PC. The intermediate III undergoes hydrogen atom transfer with cyclohexa-1,4-diene **17** to furnish the product **7**. On the other hand, the intermediate IV was oxidized by PC⁺ and then attacked by appropriate nucleophiles to provide the 1,2-difunctionalized products (**8** and **9**).

Experimental

General procedure for the synthesis of products (4a–s)-D

Condition A. Under argon, to a solution of 4DPAIPN (2 mol%) and **IMDN-SO₂CF₂D** reagent **2a** (0.15 mmol, 1.5 equiv.) in dried THF (tetrahydrofuran) (1.0 mL) corresponding alkene **1** was added (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LED for about 18 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of products (4a–s)-H

Condition B. Under argon, to a solution of 4DPAIPN (2 mol%) and **IMDN-SO₂CF₂H** reagent **2b** (0.15 mmol, 1.5

equiv.) in dried THF (tetrahydrofuran) (1.0 mL) corresponding alkene **1** (0.1 mmol) was added at room temperature. After that, the tube was exposed to a 60 W blue LED for about 12 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of products (5a–f)-D

Condition C. Under argon, to a solution of 4DPAIPN (2 mol%) and **IMDN-SO₂CF₂D** reagent **2a** (0.15 mmol, 1.5 equiv.) in dried IA (isopropyl acetate) (1.0 mL) corresponding heterocyclic compound **3** (0.1 mmol) was added at room temperature. After that, the tube was exposed to a 60 W blue LED for about 18 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of products (5a–f)-H

Condition D. Under argon, to a solution of 4DPAIPN (2 mol%) and **IMDN-SO₂CF₂H** reagent **2b** (0.15 mmol, 1.5 equiv.) in dried IA (isopropyl acetate) (1.0 mL) corresponding heterocyclic compound **3** (0.1 mmol) was added at room temperature. After that, the tube was exposed to a 60 W blue LED for about 12 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of products (7a–g)-D

Condition E. Under argon, to a solution of 4DPAIPN (2 mol%), IMDN-SO₂CF₂D reagent **2a** (0.15 mmol, 1.5 equiv.) and cyclohexa-1,4-diene (0.25 mmol, 2.5 equiv.) in dried 2-Me-THF (2-methyltetrahydrofuran) (1.0 mL) corresponding alkene **6** (0.1 mmol) was added at room temperature. After that, the tube was exposed to a 90 W blue LED for about 24 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired products.

General procedure for the synthesis of products (7a–g)-D

Condition F. Under argon, to a solution of 4DPAIPN (2 mol%) and IMDN-SO₂CF₂H reagent **2b** (0.15 mmol, 1.5 equiv.) and cyclohexa-1,4-diene (0.25 mmol, 2.5 equiv.) in dried 2-Me-THF (2-methyltetrahydrofuran) (1.0 mL) corresponding alkene **6** (0.1 mmol) was added at room temperature. After that, the tube was exposed to a 90 W blue LED for about 24 h until the reaction was completed as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired products.

Conclusions

In summary, we have described an air-stable redox-active imidazolium fluorosulfonate reagent IMDN-SO₂CF₂X (X = D/H; **2a**, **2b**). A key design feature of this radical deuteriodifluoromethylation/difluoromethylation reagent is its cationic nature, which favors the stepwise formation of a deuteriodifluoromethyl/difluoromethyl radical ($\cdot$ CF₂D/ $\cdot$ CF₂H) *via* a SET reduction process under photocatalytic conditions. Radical scavenger experiments and radical clock experiments collectively confirm that the reaction proceeds *via* a radical mechanism. This reservoir of deuteriodifluoromethyl/difluoromethyl radicals can engage with diverse heteroarenes and olefins, yielding a diverse array of functionalized deuteriodifluoromethylation and difluoromethylation compounds. Further study of this highly reactive and bench-stable solid reagent is underway in our laboratory.

Author contributions

C. S. conducted all experiments and characterized the novel compounds. Y. W., W. Z., and C. S. designed the experiments. C. S., W. Z., and Y. W. wrote the manuscript. Y. P. was responsible for funding application. Y. S., H. L., Z. W., Y. L., M. H., Z. Z., J. L., and A. L. contributed to the analysis and interpretation of the data.

Conflicts of interest

There are no conflicts to declare.

Data availability

Crystallographic data for **2a** has been deposited at the CCDC under 2426734 and can be obtained from <https://doi.org/10.5517/ccdc.csd.cc2mg6r2>.⁶² Crystallographic data for **2b** has been deposited at the CCDC under 2432449 and can be obtained from <https://doi.org/10.5517/ccdc.csd.cc2mn53l>.⁶³

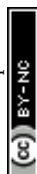
Data for this article, including the preparation of reagents, the reaction procedures, and the NMR data and mass spectrometry data of compounds are available at supplementary information. See DOI: <https://doi.org/10.1039/d5sc02691a>.

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