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ARTICLE

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

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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 difluoromethyl group (CF_2H) into drug molecules has matured, efficient installation of their deuterated counterparts (CF_2D) remains a formidable challenge in medicinal chemistry. This study reports a novel (deuterio)difluoromethyl imidazolate reagent **IMDN-SO_2CF_2X** (X=D, H), which successfully constructs 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 (KIE), 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 development[11] (Figure 1A).

Recently, the difluoromethyl group (CF_2H) has attracted significant attention owing to its unique biochemical and physicochemical properties[12-16] (Figure 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] the deuterated counterpart 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 (Figure 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 radical remains challenging, primarily due to the lack of universal synthesis methods.[48-51]

Conventional methods for generating deuteriodifluoromethyl radical ($\cdot CF_2D$) 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] deuterated Sodium difluoromethylsulfonate (CF_2DSO_2Na) reported by Li's research group. Although this reagent can

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generate ·CF_2D radicals through metal catalysis and selectively modify the **C2** position of indole compounds,[51] its substrate applicability remains limited (Figure 1C).

Fluorosulfonyl difluoroacetic acid methyl ester (**$FSO_2CF_2CO_2Me$**, 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 remains a significant challenge.

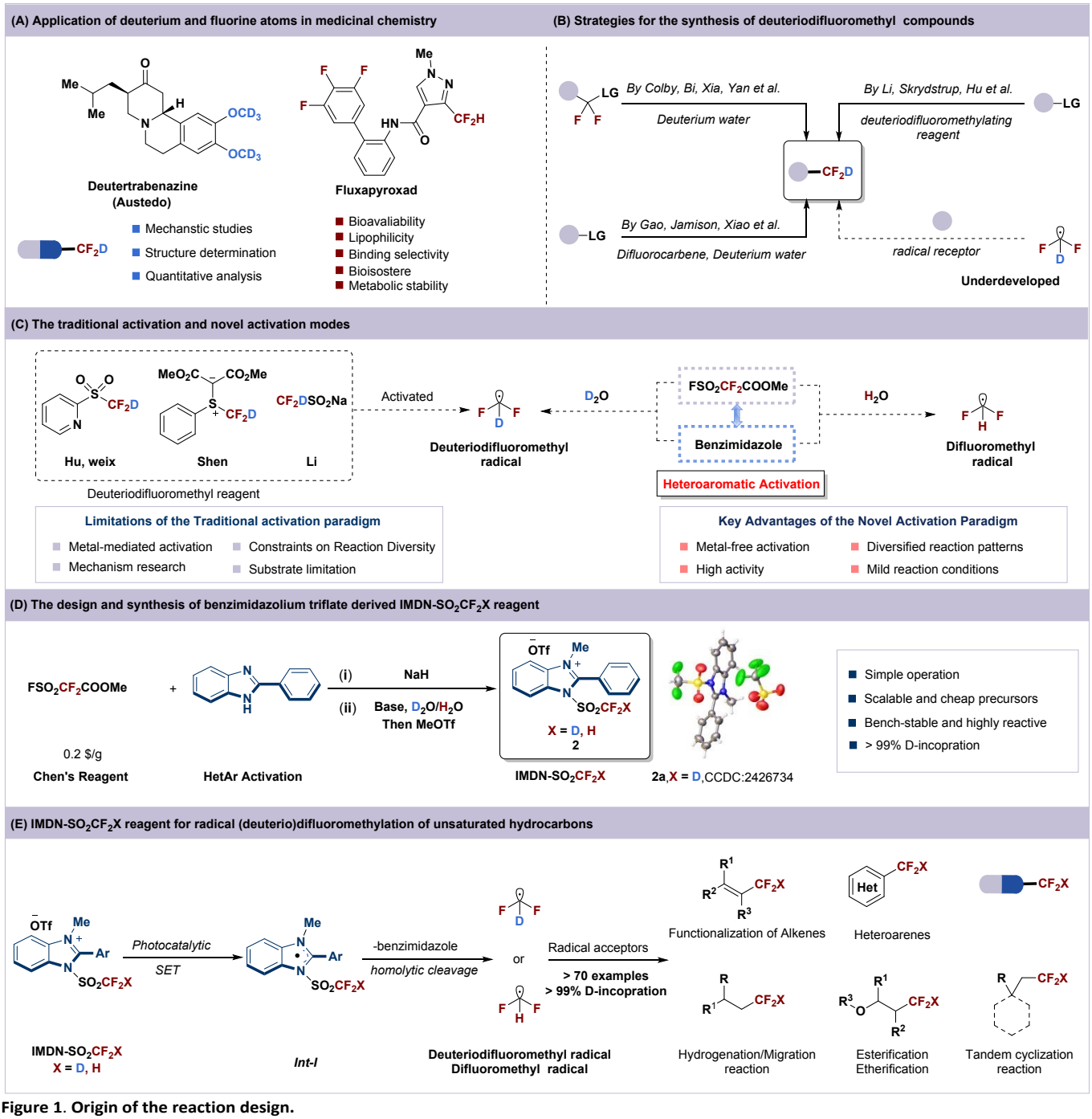

Figure 1. Origin of the reaction design.

Therefore, we attempted to combine Chen's reagent with imidazole to construct a benzimidazolium fluorosulfonate salt 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),[56] this cationic complex undergoes SET process to generate deuteriodifluoromethyl radical or difluoromethyl radical.

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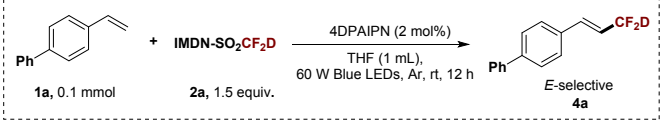
Herein, we developed a versatile imidazole salt reagent (**IMDN-SO$_2$CF$_2$X**, X = D/H; **2a**, **2b**) with high reactivity, practicality, and air stability (Figure 1D). This reagent enables: Radical-mediated stereoselective difluoromethylation and deuteriodifluoromethylation of olefins, difluoromethylation of heteroaromatic hydrocarbons (both deuterated and non-deuterated), functionalization of α,β-unsaturated olefins with CF_2D/CF_2H groups. Additionally, it provides a general platform for synthesizing (deuterio)difluoromethylated architectures (Figure 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-SO$_2$CF$_2$D**, **2a**, $E_{1/2}^{red}$ = 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 in this condition. We then conducted control experiments to verify the necessity of 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, 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, Supplementary Table 4-7).

Table 1 Optimization of the reaction conditions



Entry	variation fom the above conditions	Conversion[a]	Yield of 4a[b]
1	standard condition	90%	71%
2	w/o photocatalyst	< 5%	0
3	In the darkness	< 5%	0
4	**18 h instead of 12 h**	**> 95%**	**75%(70%)[c]**
5	4CzIPN instead of 4DPAIPN	< 5%	Trace
6	*fac*-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; [c]GC yield with dodecane as the internal standard. [c] Isolated yield.

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-SO$_2$CF$_2$X** 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**-**4e**), but also showing excellent performance for complex alkenes containing ester and amino groups (**4k**-**4r**). 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**-**4j**), achieving high levels of yield and deuterium incorporation. Notably, isomerization of the alkene was observed in product **4g**. Moreover, natural products derivatized olefin involving menthol, cholesterol and bexarotene can also be tolerated under the mild photocatalytic conditions and obtained the corresponding alkenyl (deuterio)difluoromethylation products in moderate yields (**4q**-**4s**). 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 quinoxalinone derivatives, quinolinone derivatives, and benzofuran derivatives were also compatible and generated the desired products (**5a–5d**) in moderate to good yields (62–85%). Moreover, this strategy enables efficient functionalization of heteroaromatic 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 β-CF_2D/CF_2H carbonyls and related compounds (**7a**-**7g**) 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

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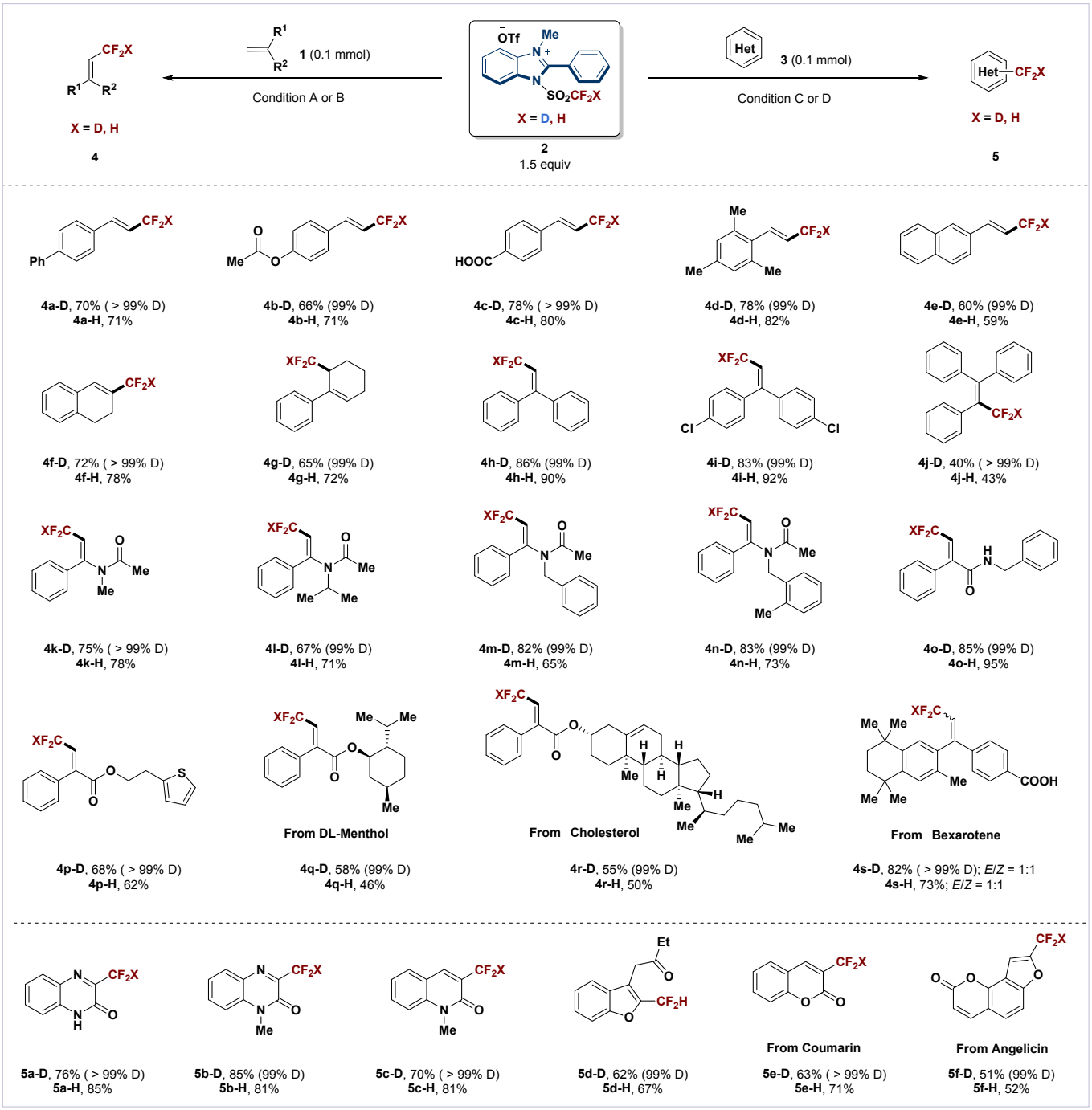
deuterated variant required longer reaction times. However, certain substrates showed notable differences in yield and selectivity, likely due to their inherent structural properties.

After the applicability of **IMDN-SO$_2$CF$_2$X** (X = D/H; **2a**, **2b**) for (deuterio)difluoromethylation in olefinic and heteroaromatic substrates was demonstrated, its reactivity was systematically evaluated under photocatalytic conditions. As shown in Scheme 3, the three-component reaction of 4-phenylstyrene, **IMDN-SO$_2$CF$_2$X** 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,



Scheme 1. Substrate scope of the olefins and heteroaromatic. 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.

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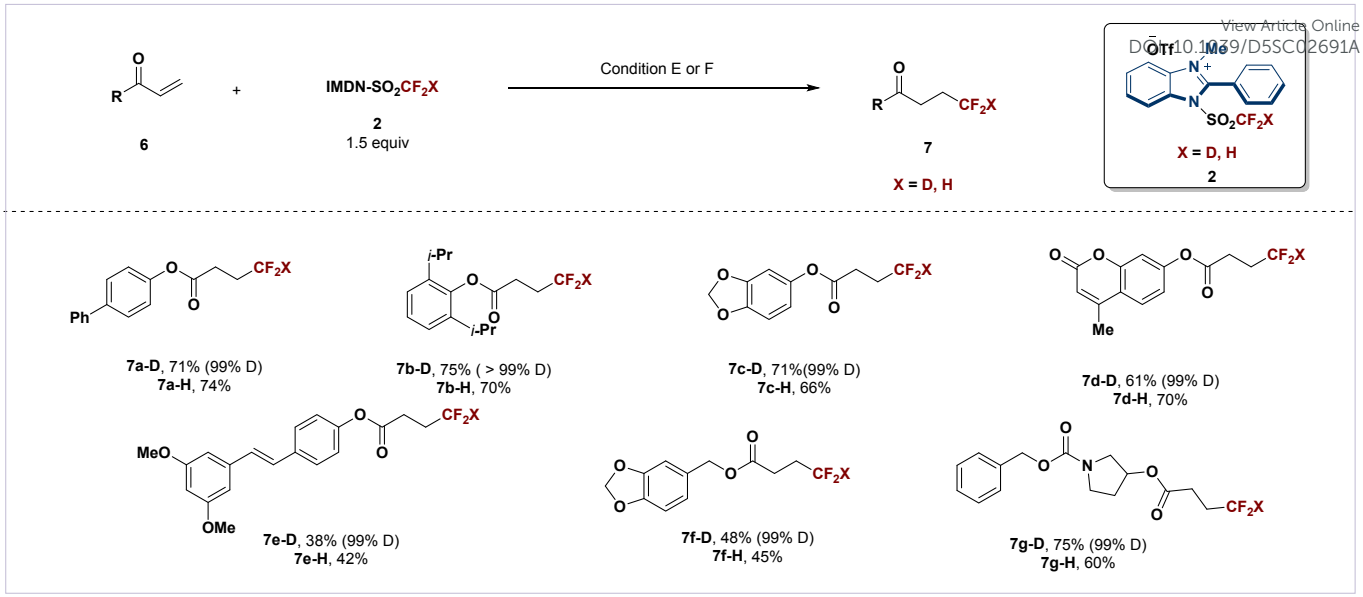
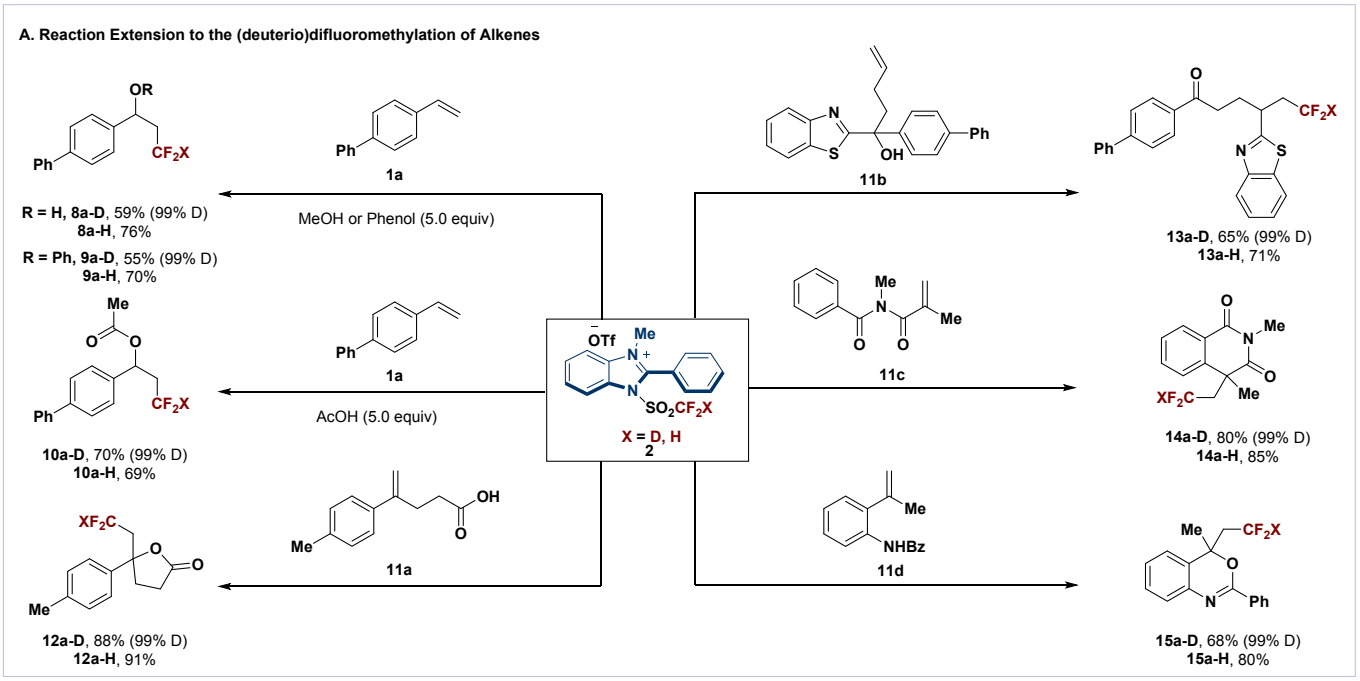


Scheme 2. Substrate scope of the α,β-unsaturated olefins Condition E: alkynes **6** (0.10 mmol), **2a** (1.5 equiv.), Cyclohexa-1,4-diene (2.5 equiv.), 4DPAIPN (2 mol%) in 2-Me-THF (1.0 mL) under Ar and 90 W Blue LEDs for 24 h. Condition F: alkynes **6** (0.10 mmol), **2b** (1.5 equiv.), Cyclohexa-1,4-diene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

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-SO$_2$CF$_2$X** (X = D/H; **2a**, **2b**) reagent for synthetic applications in the radical functionalization of olefins.

It is gratifying to note that **IMDN-SO$_2$CF$_2$X 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-CF$_2$D 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 $MgCl_2$ additive, the ring-opened



Scheme 3. Extension of experiments

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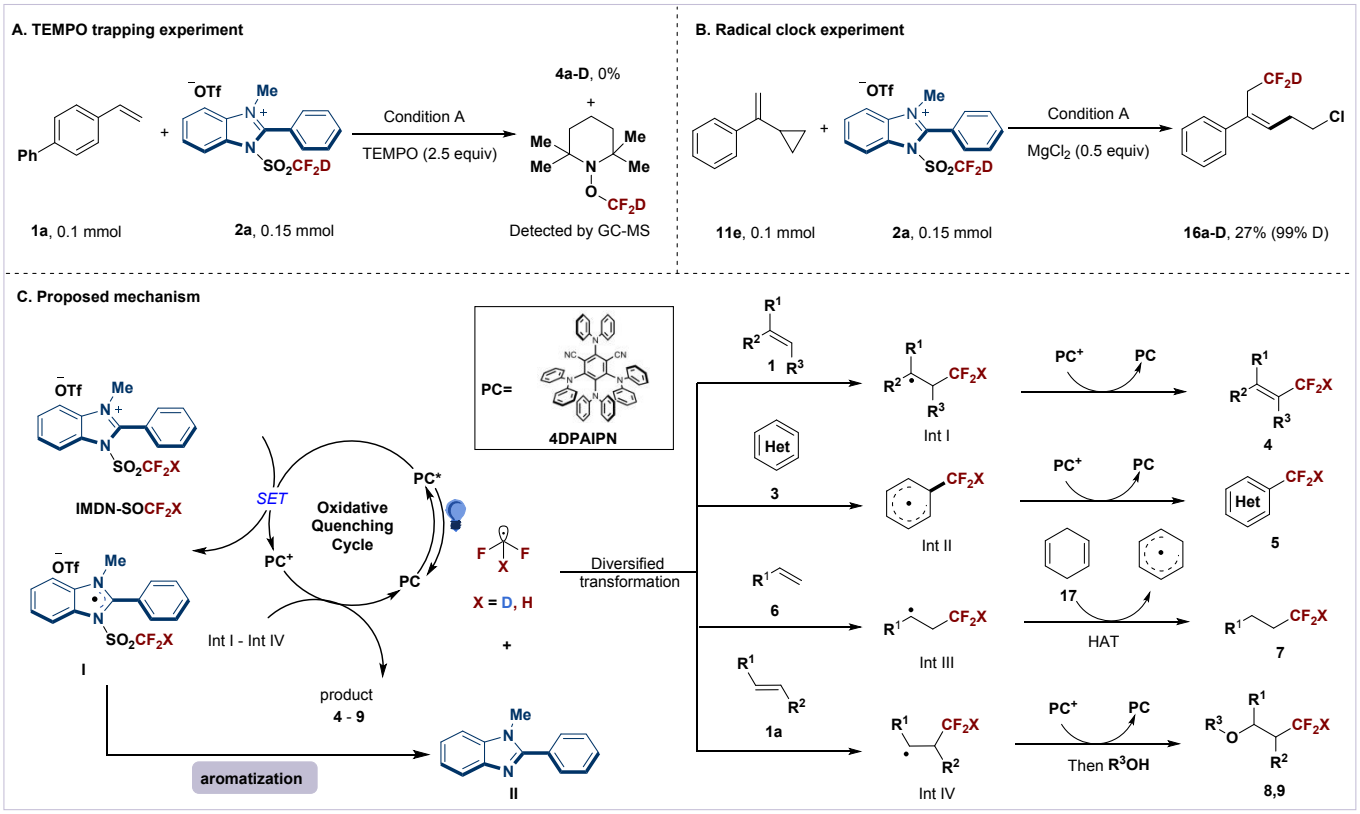
product **16a-D** can be obtained in 27% (99% D-incopration) isolated yield (Scheme 4B). This result indicated the potential involvement of deuteriodifluoromethyl radical (·CF_2D) in the reaction.

From the above mechanistic experiments, we speculate on the possible mechanism of the reaction (Scheme 4C): First, under the irradiation, the cationic **IMDN-SO_2CF_2X** reagent **2** can be reduced by excited state photocatalyst (PC*) to generate (deuterio)difluoromethyl radical. Then the addition of (deuterio)difluoromethyl radical to the unsaturated hydrocarbons (**1**, **3**, **6**) furnishes radical intermediate I-IV. Then the intermediate I-II was oxidized by PC^+ to undergo hydrogen eliminated to get the corresponding product (**4**, **5**) and regenerate PC. The intermediate III followed by 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 product (**8**, **9**).



Scheme 4. Study of reaction mechanisms

Experimental

General Procedure for the synthesis of products (4a-4s)-D. Condition A: Under argon, to a solution of 4DPAIPN (2 mol%), and **IMDN-SO_2CF_2D** reagent **2a** (0.15 mmol, 1.5 equiv.) in dried THF (Tetrahydrofuran) (1.0 mL) was added corresponding alkenes **1** (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs 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-4s)-H. Condition B: Under argon, to a solution of 4DPAIPN (2 mol%), and **IMDN-SO_2CF_2H** reagent **2b** (0.15 mmol, 1.5 equiv.) in dried THF (Tetrahydrofuran) (1.0 mL) was added corresponding alkenes **1** (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs 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-5f)-D. Condition C: Under argon, to a solution of 4DPAIPN (2 mol%), and **IMDN-SO_2CF_2D** reagent **2a** (0.15 mmol, 1.5 equiv.) in dried IA (Isopropyl acetate) (1.0 mL) was added corresponding heterocyclic compounds **3** (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs 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 product (5a-5f)-H. Condition D: Under argon, to a solution of 4DPAIPN (2 mol%), and **IMDN-SO_2CF_2H** reagent **2b** (0.15 mmol, 1.5 equiv.) in dried IA (Isopropyl acetate) (1,0 mL) was added corresponding heterocyclic compounds **3** (0.1 mmol) at room temperature. After that, the tube was exposed to a 60 W blue LEDs 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 product (7a-7g)-D. Condition E: Under argon, to a solution of 4DPAIPN (2 mol%), and **IMDN-SO_2CF_2D** 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) was added corresponding alkenes **6** (0.1 mmol) at room temperature. After that, the tube was exposed to a 90 W blue LEDs 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 product (7a-7g)-D. Condition F: Under argon, to a solution of 4DPAIPN (2 mol%), **IMDN-SO_2CF_2H** 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) was added corresponding alkenes **6** (0.1 mmol) at room temperature. After that, the tube was exposed to a 90 W blue LEDs 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-SO_2CF_2X** (X = D/H; **2a**, **2b**). A key design feature of this radical deuteriodifluoromethylation/difluoromethylation reagent is the cationic nature, which favors the stepwise formation of deuteriodifluoromethyl/difluoromethyl radical ($\cdot CF_2D$/$\cdot CF_2H$) 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.

Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

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Author Contributions

C. S. conducted all experiments and characterized the novel compounds. Y. W., W. Z., C. S. designed the experiments. C. S., W. Z., 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.

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The authors confirm that the data supporting the findings of this study are available within thearticle as its supplementary materials.