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Bench-stable azidodifluoromethyl imidazolium reagents unlock the synthetic potential of carbonimidic difluorides

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N-fluoroalkyl compounds are highly valuable in medicinal chemistry. While carbonimidic difluorides have been recognized as valuable intermediates for *N*-CF_3 compounds synthesis, their broader synthetic potential remains largely unexplored due to the limitations of current methodologies, particularly in expanding the scope of *N*-fluoroalkyl derivatives. Herein, we report the design and synthesis of azidodifluoromethyl imidazolium reagents that enable the in situ generation of carbonimidic difluorides. These intermediates undergo a series of controlled transformations, including chlorination, fluorination, monodefluorination, didefluorination, and subsequent derivatization of *N*-chlorodifluoromethyl compounds, providing an efficient strategy for the synthesis of structurally diverse *N*-fluoroalkane and amine derivatives.

The *N*-fluoroalkyl compounds have garnered increasing attention due to their distinctive physicochemical properties and broad applicability across pharmaceutical chemistry, agrochemicals, and materials science[1–6]. Notably, *N*-CF_3 and *N*-CF_2H motifs play a crucial role in the design of bioactive molecules, often enhancing metabolic stability, lipophilicity, and bioavailability. As illustrated in Fig. 1a, numerous bioactive molecules incorporate *N*-fluoroalkyl functionalities[7–11], underscoring their significance in drug discovery and development.

Carbonimidic difluorides play a pivotal role in current strategies for synthesizing *N*-CF_3 compounds[12–18]. However, existing approaches[19–28] for their synthesis and modification fail to fully exploit their synthetic potential. Typically, carbonimidic difluorides are prepared either by oxidation of isothiocyanates or isocyanides (Fig. 1, b)[29–33], or through chlorine-to-fluorine substitution from carbonimidic dichlorides[19,34–38]. The pioneering work of Schoenebeck[20–25], Wilson[26], Yi[27], and Tlili[28] has significantly advanced the application of carbonimidic difluorides in the synthesis of *N*-CF_3 compounds, introducing a series of one-pot transformations from isothiocyanates and AgF. Additionally, carbonimidic difluorides can be generated through defluorination of *N*-CF_3 compounds, which is often regarded as a side reaction[19,27]. Despite these advances, current methodologies predominantly rely on substituted amines as starting materials for functional group interconversion, often requiring harsh reaction conditions, highly toxic reagents, or excessive fluorine sources, thereby limiting their scope for broader and more versatile applications.

Notably, in 1967, the Ogden group reported a reaction that generated difluoromethylenimino radicals by reacting tetrafluoro-2,3-diaza-1,3-butadiene with hexafluoropropylene (Fig. 1, c)[39]. This process enables radical amination with polyfluoro-olefins to yield carbonimidic difluorides, offering a route to these compounds without requiring excess fluorine sources. However, limited by unstable difluoromethylenimino radical precursors and harsh activation conditions, the substrate scope of the reaction and related derivatization have not been fully explored. Follow-up studies on difluoromethylenimino radicals have not resolved these issues[40–42]. Thus, we aim to design a bench-stable reagent that can generate difluoromethylenimino radicals, synthesize carbonimidic difluorides under mild conditions, and produce a variety of *N*-fluoroalkyl derivatives in a one-pot process.

Inspired by the work of Schoenebeck[24] and Beier[14,43], we envisioned that an azidodifluoromethyl reagent containing a leaving group could undergo single-electron transfer (SET) upon photoexcitation (Fig. 1, d). This process would release difluoromethylenimino radicals, which then react with radical acceptors to generate carbonimidic difluorides in situ. Since this process does not require an excess fluorine source, the

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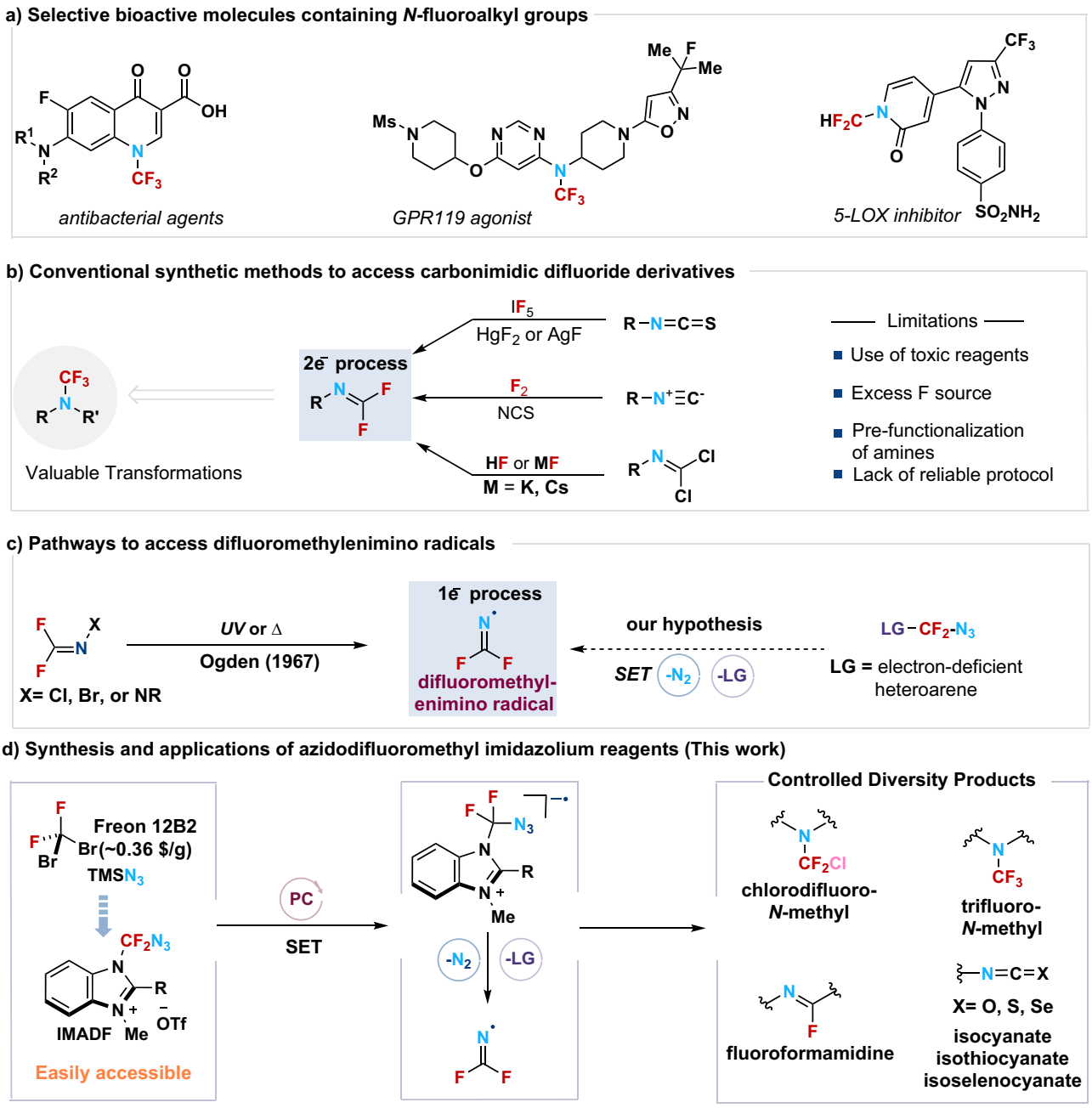

Fig. 1 | The importance of carbonimidic difluorides in synthesis and our design strategy. a Selective bioactive molecules with *N*-fluoroalkyl groups. **b** Conventional synthetic methods to access carbonimidic difluoride derivatives. **c** Pathways to access difluoromethylenimino radicals. **d** Synthesis and applications of azidodifluoromethyl imidazolium reagents.

carbonimidic difluorides can undergo further transformations such as chlorination (the AgF system is not compatible with chloride ions[20,26]), fluorination, monodefluorination, and didefluorination reactions, yielding the corresponding *N*-fluoroalkyl and amine compounds. Our previous work has established that imidazolium salts exhibit significant reactivity in the generation of fluorinated radicals[44–47]. In this work, we report the synthesis and application of bench-stable azidodifluoromethyl imidazolium reagents (**IMADF**s), with the aim of enabling the efficient synthesis of diverse *N*-fluoroalkyl compounds.

Results

Synthesis and reactivity study of IMADFs

Starting from CF_2Br_2, the compound undergoes two or three nucleophilic substitutions[48], yielding a series of **IMADF**s. In order to test the reactivity of these reagents, we designed a radical cyclization reaction using phenylvinylbenzoyl chloride for *N*-fluoroalkyl pyridone synthesis. The 2-pyridone scaffold is commonly found in pharmaceuticals and natural products[49–52]. *N*-fluoroalkyl-substituted 2-pyridones have been shown to enhance the biological activity of molecules[10,11]. In parallel, chlorodifluoromethyl groups are also widely used in bioactive molecules[53,54] and can be further modified to synthesize a variety of difluoromethylene derivatives[55–57]. We began our study with the reaction of 2-(1-phenylvinyl)benzoyl chloride (**1a**) and **IMADF-1** in anhydrous dichloromethane catalyzed by *fac*-Ir(ppy)$_3$ under 30 W blue LED irradiation. To our delight, the 2-(chlorodifluoromethyl)−4-phenylisoquinolin-1(2*H*)-one product (**2a**) was produced after 12 hours in a 30% yield (Table 1, entry 1). Next, we explored the use of different photocatalysts (entries 2-5) and found that Ir(piq)$_3$ improved the yield. Other

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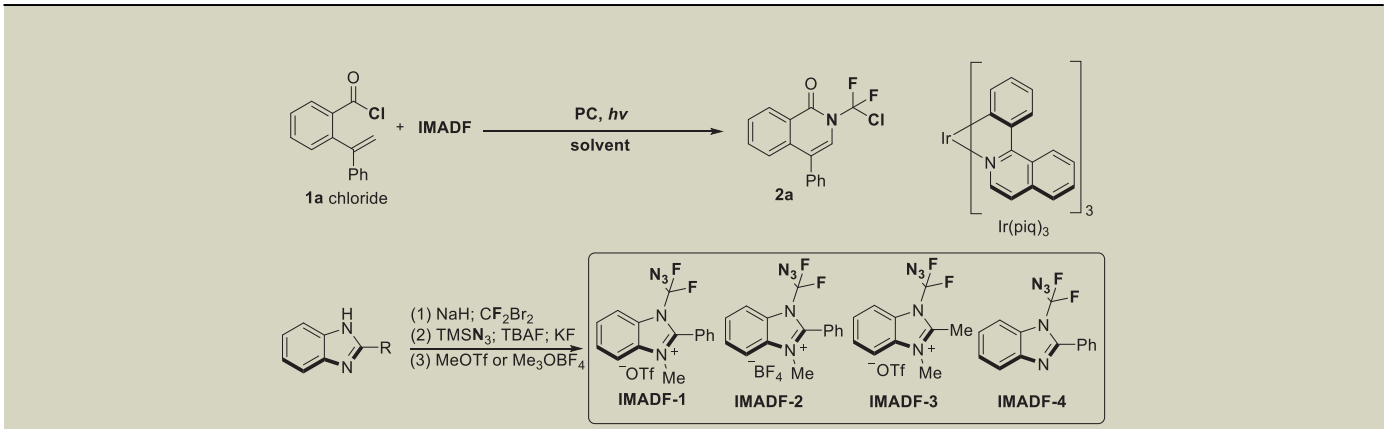
Table 1 | Optimization of the Reaction Conditions



Entry	PC (3%)	Solvent	Light intensity	Reagent	Yield[a] (isolated)
1	*fac*-Ir(ppy)$_3$	DCM (0.1 M)	30 W	**IMADF-1**	30%
s2	Ir(piq)$_3$	DCM (0.1 M)	30 W	**IMADF-1**	40%
3	Ir[dF(CF$_3$)ppy]$_2$(dtbpy)PF$_6$	DCM (0.1 M)	30 W	**IMADF-1**	<5%
4	Ir(Fppy)$_3$	DCM (0.1 M)	30 W	**IMADF-1**	26%
5	4CzIPN	DCM (0.1 M)	30 W	**IMADF-1**	13%
6	Ir(piq)$_3$	DCM (0.1 M)	30 W	**IMADF-2**	24%
7	Ir(piq)$_3$	DCM (0.1 M)	30 W	**IMADF-3**	13%
8	Ir(piq)$_3$	DCM (0.1 M)	30 W	**IMADF-4**	trace
9	Ir(piq)$_3$	DCM (0.05 M)	30 W	**IMADF-1**	55%
10	Ir(piq)$_3$	DCM (0.033 M)	30 W	**IMADF-1**	60%
11[b]	Ir(piq)$_3$	DCM (0.033 M)	30 W	**IMADF-1**	61%
12[b]	Ir(piq)$_3$	DCM (0.05 M)	30 W	**IMADF-1**	61%
13[b]	Ir(piq)$_3$	DCM (0.05 M)	60 W	**IMADF-1**	72%
14[b]	Ir(piq)$_3$	DCM (0.05 M)	90 W	**IMADF-1**	78% (72%)
15[b]	Ir(piq)$_3$	DCM (0.05 M)	–	**IMADF-1**	0%
16[b]	–	DCM (0.05 M)	90 W	**IMADF-1**	trace

Reaction conditions: **1a** (0.1 mmol), **IMADF** (0.15 mmol), **PC** (0.003 mmol), solvent, blue LED, 12 h under Ar.
DCM dichloromethane, *IMADF* azidodifluoromethyl imidazolium reagent, *PC* photocatalyst.
[a]GC-MS yield with n-dodecane as the internal standard.
[b]**1a** (0.2 mmol), **IMADF** (0.3 mmol), **PC** (0.006 mmol), solvent, blue LED, 12 h under Ar. Isolated yield in parentheses.

IMADFs were also tested (entries 6-8), with **IMADF-1** being the most effective. Considering that high concentrations might lead to the formation of various byproducts[20,35], we reduced the concentration, which significantly improved the yield (entries 9–12). Additionally, we observed that the yield varied with light intensity (entries 13–14), with the 90 W blue light source providing the best results, achieving a 78% GC yield and a 72% isolated yield for the target product. Control experiments confirmed that both the light source and the photocatalyst were essential for these transformations (entries 15 and 16).

With the optimal conditions established, the substrate scope of chlorodifluoromethylamination was examined (Fig. 2). A broad range of benzoyl chlorides (**1**) with electron-withdrawing and electron-donating substituents smoothly underwent these transformations to afford the corresponding products (**2b**-**2f**) in 53-84% yields. Other aromatic rings, such as naphthalene afforded the corresponding product (**2g**) in 68% yield. Heteroaromatic acyl chlorides also participated in the reaction, affording the corresponding *N*-chlorodifluoromethyl-2-pyridone in moderate to good yields, examples include substrates derived from thiophene (**2 h**), furan (**2i**), oxazole (**2j**), imidazole (**2k**), thiazole (**2 l**), pyridine (**2 m**). Other disubstituted and trisubstituted phenylvinylbenzoyl chlorides also demonstrated the feasibility of the reaction (**2n** and **2o**). Notably, monosubstituted alkenylbenzoyl chlorides also successfully yielded the target products in synthetically useful yields (**2p**-**2s**). To further demonstrate the potential of this protocol in medicinal chemistry, we synthesized 2-chlorodifluoromethyl-1(2*H*)-isoquinolone derivatives (**2t** and **2u**), which may function as bioisosteric building blocks for some drugs. Trotabresib, an oral potent inhibitor of bromodomain and extraterminal (BET) proteins, is used for the treatment of high-grade glioma[58]. Using our strategy, its *N*-CF_2Cl bioisostere was synthesized in 65% yield (**2v**). The mild conditions tolerated many functional groups, including halides (**2b, 2m, 2t, 2u**), ethers (**2f**), nitriles (**2c**), trifluoromethyl groups (**2d, 2s**), and sulfonyl groups (**2 v**). Through the employment of phenylvinylbenzoyl fluorides in the reaction, the corresponding *N*-CF_3 compounds were successfully synthesized. While the yield was less than ideal, the products were still obtained in synthetically useful quantities (**3a**-**3e, 3v**).

Carbonimidic difluorides not only underwent chlorination and fluorination reactions, but also tunable defluorination reactions (Fig. 3). When styrene was used as radical acceptor, the intermediate imine was stable enough to be detected in the reaction system (see SI for details). Subsequently, secondary amines were used as nucleophiles. The radical addition followed by selective defluorination of carbonimidic

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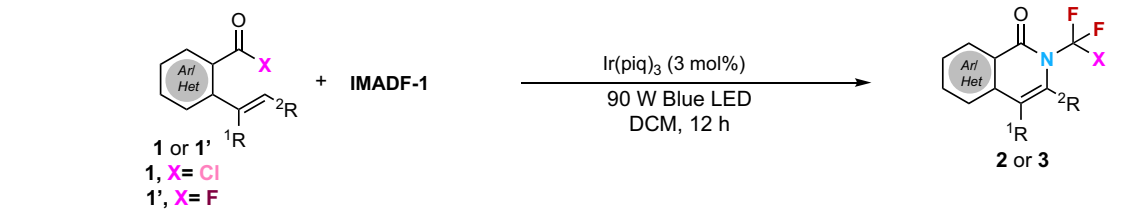

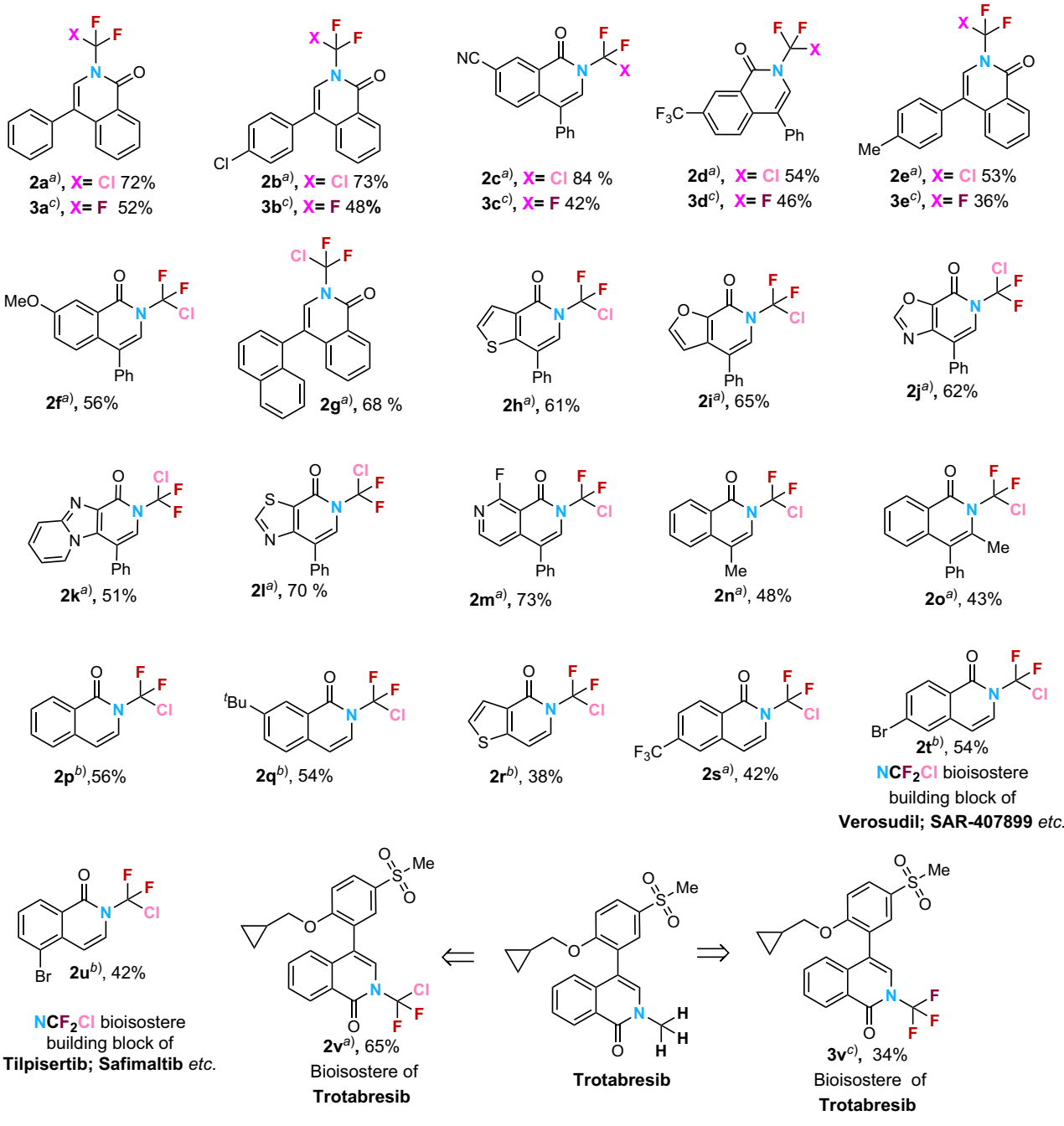

Fig. 2 | Substrate scope of chlorodifluoromethylamination[a,b] and trifluoromethylamination[c]. Reaction conditions: [a]**1a** (0.2 mmol in DCM), **IMADF-1** (0.3 mmol), $Ir(piq)_3$ (0.006 mmol), 90 W blue LED, 12 h under Ar. [b]Additional NaCl (0.2 mmol) was added to the reaction. [c]**1'a** (0.2 mmol in DCM), **IMADF-1** (0.3 mmol), $Ir(piq)_3$ (0.006 mmol), 4-pyrrolidinopyridine (0.02 mmol), 90 W blue LED, 12 h under Ar.

difluorides led to the corresponding fluoroformamidines. Such types of moieties have been less studied due to their limited approaches[59]. We applied our protocol to various styrene derivatives—including electron-withdrawing (**6b**), electron-donating (**6c**), disubstituted (**6a-6d**), trisubstituted (**6e**), and monosubstituted (**6f**)—affording the corresponding fluoroformamidines in 36%-83% yields. Besides morpholine, various nitrogen nucleophiles were evaluated in the monodefluorination reaction. Pyrrolidine (**6g**) and acyclic secondary amines (**6h, 6i**)

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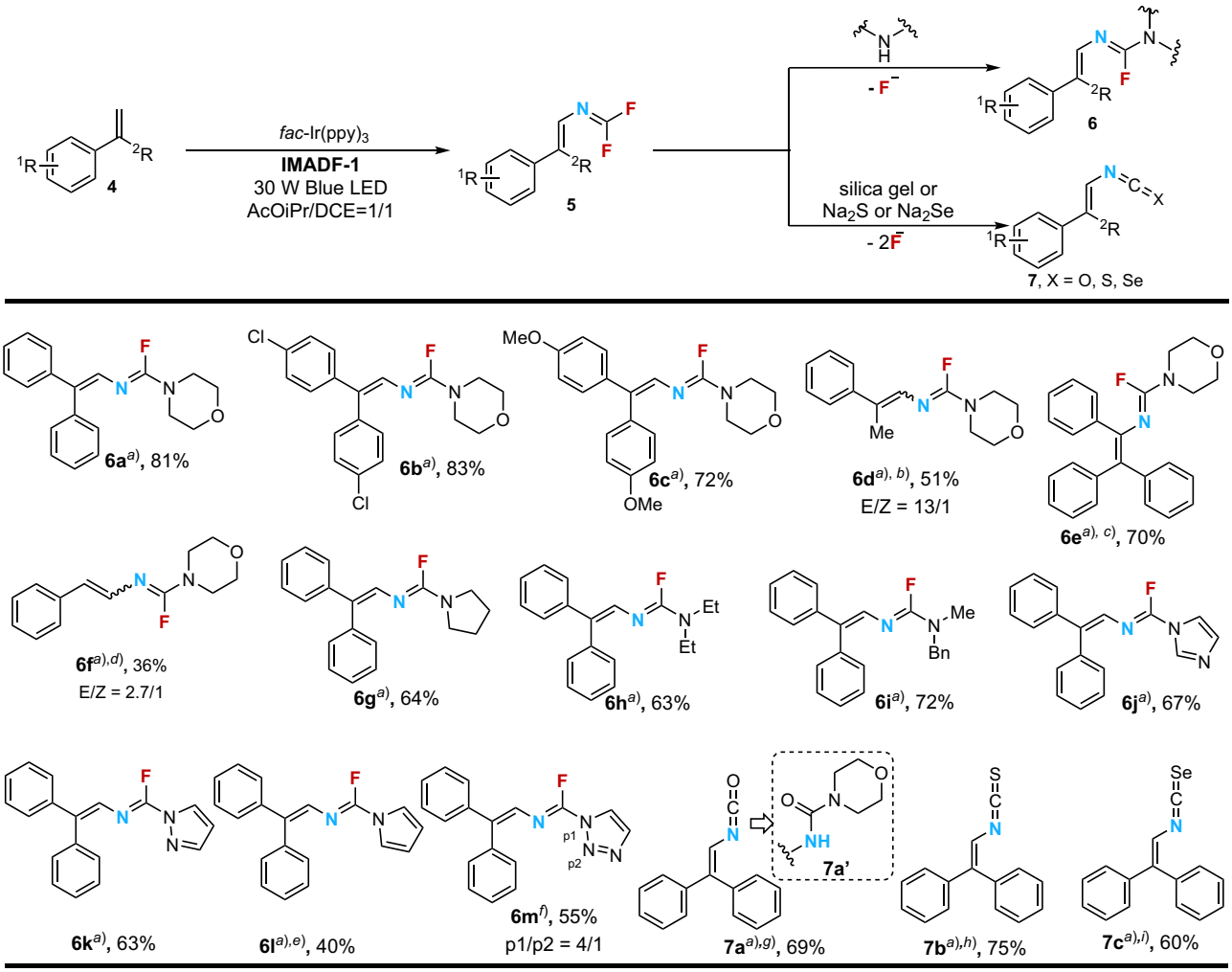

Fig. 3 | Substrate scope in the synthesis of carbonimidic difluorides and their defluorination reactions. Reaction conditions: [a]**4** (0.2 mmol), **IMADF-1** (0.3 mmol), *fac*-Ir(ppy)$_3$ (0.006 mmol), 30 W blue LED, 2 h under Ar, then added secondary amine (0.3 mmol), triethylamine (0.3 mmol). [b]The ratio of E/Z isomers was determined by NMR. [c]0.5 mmol **IMADF-1** was used and stirred for 5 h. [d] The ratio of E/Z isomers was determined through isolated yield. [e]pyrrole sodium salt as nucleophile. [f] The ratio of p1/p2 isomers was determined by NMR. [g]silica gel (200 mg) as nucleophile and corresponding urea **7a'** was isolated. [h]Na_2S (0.4 mmol) as nucleophile. [i]Na_2Se (0.4 mmol) as nucleophile.

underwent smooth transformation, affording fluoroformamidines in moderate to good yields. Additionally, azoles such as imidazole (**6j**), pyrazole (**6k**), pyrrole (**6l**) and 1,2,3-triazole (**6 m**) showed reactivity under the conditions, yielding analogous products in comparable yields. The defluorination could proceed further to produce isocyanate (**7a**), isothiocyanate (**7b**), and isoselenocyanate (**7c**), which are important synthons for amine derivatives.

Synthetic applications of 2a

To demonstrate the practical utility of this chlorodifluoromethylamination, a series of derivatizations were carried out (Fig. 4). A rapid chlorine-to-fluorine substitution was successfully achieved. Within 15 min, *N*-CF_2Cl (**2a**) was converted to *N*-CF_3 (**3a**) using KF as the fluorine source. The corresponding difluoromethyl (**8**) and difluoromethylene (**9**) compounds were also obtained via radical dechlorination in the presence of AIBN. These results demonstrate the potential of this protocol for late-stage diversification of fluorinated bioactive compounds.

Mechanistic studies

Based on our experimental results and precedents in the literature[24], a plausible mechanism for the chlorodifluoromethylamination reaction is proposed (Fig. 5). Initially, photoexcitation of Ir^{III} generates Ir^{III*}. This is followed by a single-electron transfer (SET) reduction of **IMADF-1** ($E_{1/2}^{red}$ = -1.05 V vs SCE; see SI for details) with Ir^{III*}, leading to the formation of radical **Int-1** and Ir^{IV} [Ir(piq)$_3$, $E_{1/2}^{IV/III*}$ = -1.42 V vs SCE, see SI

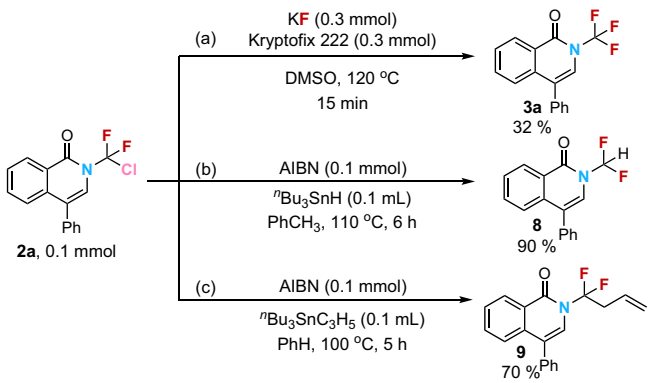

Fig. 4 | Synthetic applications. a Synthesis of **3a** via chlorine-to-fluorine substitution from **2a**. **b** Dechlorination followed by hydrogenation of **2a**. **c** Dechlorination followed by allylation of **2a**. AIBN: Azobisisobutyronitrile.

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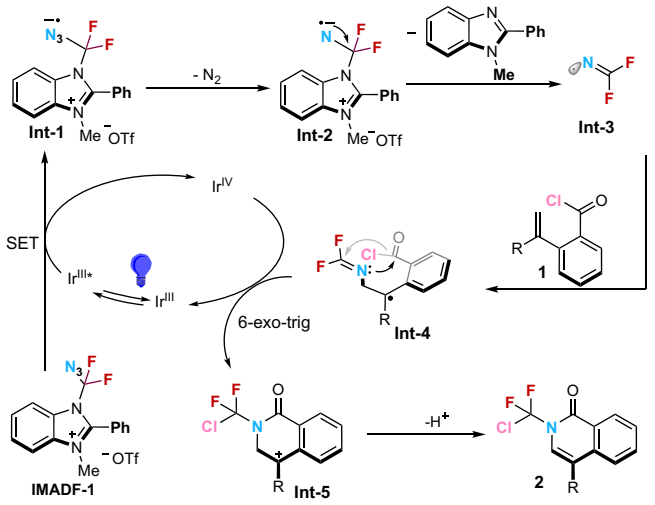

Fig. 5 | Proposed mechanism. Mechanistic proposal involving an SET pathway for the chlorodifluoromethylamination reaction.

for details]. Subsequently, the radical **Int-1** undergoes *N-N* bond cleavage to produce the radical **Int-2**. Next, the imidazole derivative is removed from **Int-2** yields **Int-3** (difluoromethylenimino radical), which then attacks styrene to furnish the radical **Int-4**. This intermediate could undergo an intramolecular ring closure reaction and be oxidized by Ir^{IV} to generate the cationic intermediate **Int-5**. Finally, deprotonation of **Int-5** results in the formation of *N*-CF_2Cl isoquinolone **2**.

To support the above mechanistic hypothesis, the control experiments were performed. Using diphenylethylene **4a** as a trapping agent, the difluoromethylenimino radical was captured, and the formation of adduct **5a** was confirmed by ^{19}F-NMR [δ -47.29 and δ -60.29 ppm], GC-MS (m/z = 243.1), HRMS [ESI (m/z) calcd for $C_{15}H_{12}F_2N$ $(M+H)^+$ 244.0932, found 244.0931] and IR (C = N: 1805.62 cm^{-1}) (Fig. 6a, see SI for details). Radical clock experiment using cyclopropane **10** and 2 equivalents of KF under the standard chlorodifluoromethylamination conditions resulted in the ring-opening product **11** (28% yield, Fig. 6b). When $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ ($E_{1/2}^{IV/III*}$ = -0.89 V vs SCE)[60] was employed as the photocatalyst, intramolecular cyclization product **12** was predominantly formed, with

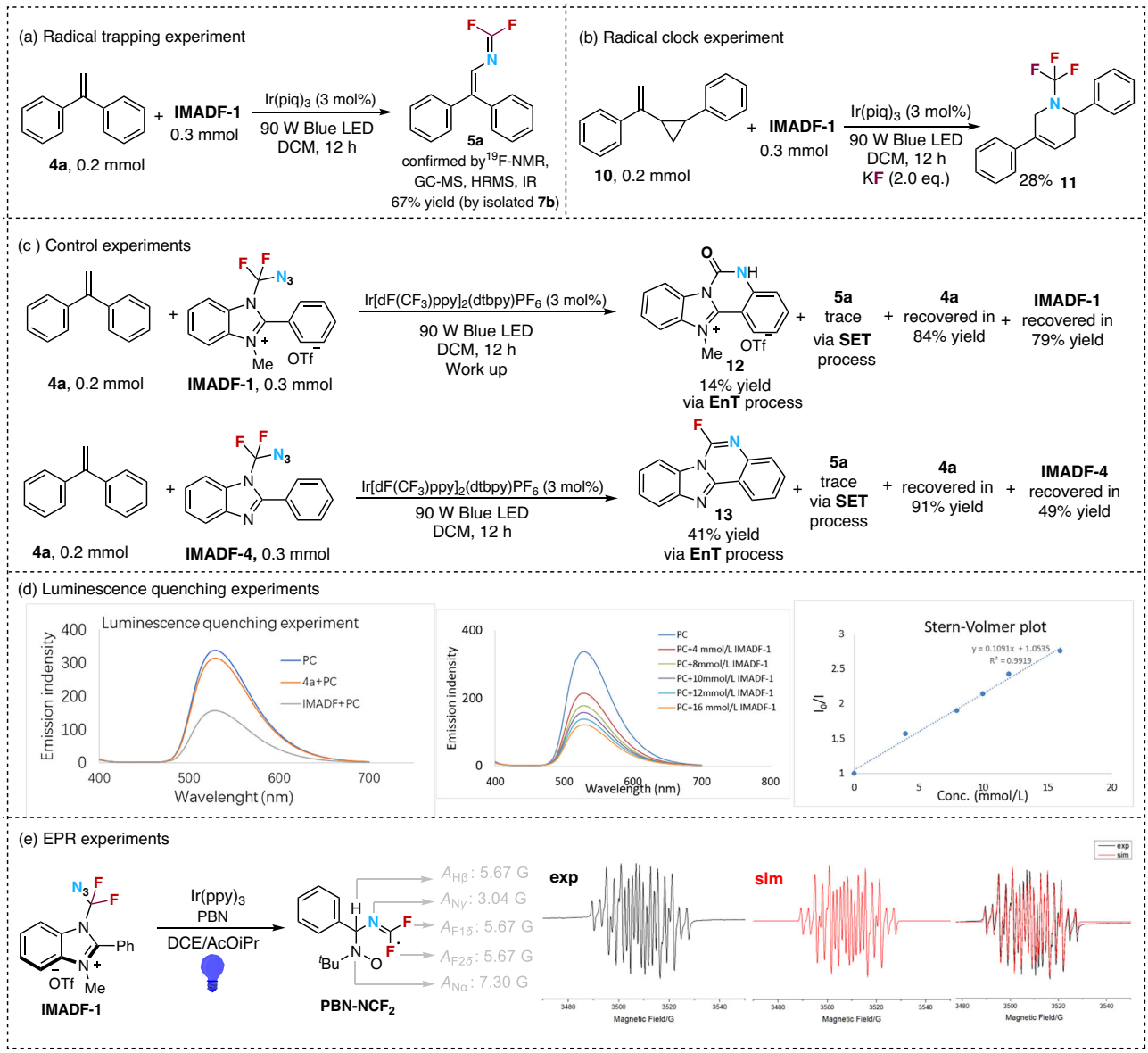

Fig. 6 | Mechanistic experiments. a Radical trapping experiment. **b** Radical clock experiment. **c** Control experiments. **d** Luminescence quenching experiments. **e** EPR experiments.

only trace amounts of the SET product **5a**. These results demonstrate that under photoexcitation conditions with weak reducing capacity, nitrene species are generated from cationic **IMADF-1** via an energy transfer (EnT) process (Fig. 6c)[24,61]. The consistently low yields (<5%) observed in both Table 1 (entry 3) and Supplementary Table 2 (entries 4-6) further support this mechanistic pathway. Additional experimental results demonstrate that the neutral **IMADF-4** can also undergo the EnT process, yielding the cyclized product **13** instead of **5a** (Fig. 6c). These results indicate that the SET process serves as the primary pathway for the chlorodifluoromethylamination reaction. Furthermore, the SET process exhibits a faster reaction rate compared to the EnT process. Luminescence quenching experiments reveal that the excited state photocatalyst (**PC***) is quenched by **IMADF-1**, involving an oxidative quenching catalytic cycle (Fig. 6d). Moreover, difluoromethylenimino radical was confirmed in the photolysis of **IMADF-1** via the Electron Paramagnetic Resonance (EPR) spectrum of **PBN** − **NCF_2** (Fig. 6e, hyperfine coupling constants: $A_{N\alpha} = 7.30$ G, $A_{H\beta} = 5.67$ G, $A_{N\gamma} = 3.04$ G, $A_{F1\delta} = A_{F2\delta} = 5.67$ G, $g = 2.0066$, see SI for details).

Discussion

In summary, we have successfully developed a highly reactive, bench-stable solid reagent capable of generating difluoromethylenimino radicals under visible-light catalysis. These radicals can then react with radical acceptors to form the corresponding carbonimidic difluorides. Through strategic substrate design, we programmed the synthesis of these compounds, enabling the subsequent preparation of various *N*-fluoroalkyl compounds and amine derivatives via chlorination, fluorination, and defluorination reactions (mono- and di-). We believe that this protocol will serve as a powerful tool for the preparation of valuable fluorinated amines. Ongoing studies of these reagents are underway in our laboratory.

Methods

General Procedure for Photocatalytic Chlorodifluoromethylamination, Trifluoromethylamination. Unless otherwise specified, all products were obtained using the following methods.

General procedure

Under argon, to an 8 mL flask was added $Ir(piq)_3$ (3 mol%), **IMADF-1** (0.3 mmol, 1.5 equiv.), 4 mL 0.05 M acyl chloride or acyl fluoride (in DCM) at room temperature. After that, the tube was exposed to a 90 W blue LED and stirred for 12 h until the reaction was completed as monitored by GC-MS analysis. The reaction mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel or preparative TLC to give the desired product **2** and **3**.

General Procedure for the Synthesis of Carbonimidic Difluorides and Their Defluorination.

General procedure

Under argon, *fac*-$Ir(ppy)_3$ (3 mol%) and **IMADF-1** (0.3–0.5 mmol, 1.5–2.5 equivalents) were added to an 8 mL flask. If **4** was solid, it was also added to the flask. A mixture of DCE and AcOiPr (1 mL each) was then added. If **4** was liquid, it was added directly to the flask at room temperature. The reaction mixture was exposed to a 30 W blue LED for 2–5 h, until completion, as monitored by GC-MS analysis. Next, the CH_3CN or THF solution of the nucleophile, along with TEA (triethylamine), was added to the reaction tube. The mixture was stirred at room temperature until the intermediate was fully consumed. Finally, the reaction mixture was evaporated under vacuum, and the residue was purified by column chromatography on silica gel or preparative TLC to yield the desired product.

Data availability

The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its Supplementary Information files, or from the corresponding author upon request. The X-ray structural data of **IMADF-1** is deposited in CCDC (No. 2333867 see Supplementary Table 1 for details). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

Y.W., W.Z., and Z.W. (王震) designed this project and analyzed the experiments. Z.W. (王震); Z.W. (王桢); J. L. and L.Y. carried out the experiments. X. G. conducted EPR experiments and data analysis. Z. W. (王震) and W.Z. wrote the manuscript. Y. P. and Y.W. directed the whole project.

Competing interests

The authors declare no competing interests.

Additional information

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