ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

Visible Light-Induced Radical Cascade Difluoromethylation/Cyclization of Unactivated Alkenes: Access to CF_2H-Substituted Polycyclic Imidazoles

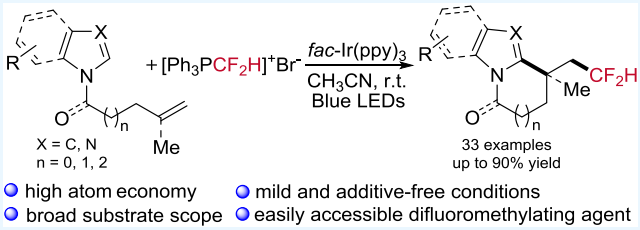
Sheng-Nan Lin,* Yuanyuan Deng, Hanxun Zhong, Liu-Liang Mao, Cong-Bin Ji, Xian-Hong Zhu, Xiaolan Zhang, and Bin-Miao Yang*

Cite This: *ACS Omega* 2024, 9, 28129−28143

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An efficient and mild protocol for the visible light-induced radical cascade difluoromethylation/cyclization of imidazoles with unactivated alkenes using easily accessible and bench-stable difluoromethyltriphenylphosphonium bromide as the precursor of the $-CF_2H$ group has been developed to afford CF_2H-substituted polycyclic imidazoles in moderate to good yields. This strategy, along with the construction of $Csp^3-CF_2H/C-C$ bonds, is distinguished by mild conditions, no requirement of additives, simple operation, and wide substrate scope. In addition, the mechanistic experiments have indicated that the difluoromethyl radical pathway is essential for the methodology.



INTRODUCTION

Organic fluorine-containing compounds have always played significant roles in the fields of medicine and agriculture,[1] as the incorporation of fluorine-containing moieties into candidate molecules often leads to significant changes in physicochemical properties and biological activities.[2] The synthesis of fluorine-containing compounds has become a hot topic in organic chemistry.[3] Notably, among diverse fluorine-containing groups, the difluoromethyl moiety (CF_2H), which acts as a lipophilic hydrogen bond donor beneficial for modulating the bioselectivity of bioactive molecules and serves as a lipophilic isostere for hydroxyl and thiol groups,[4] has attracted gradually increasing attention of drug developers[5] (Figure 1a). During the past few decades, a great deal of effort has been devoted to the development of methods for introducing CF_2H into organic molecules using various difluoromethylation-related reagents,[6] which involved nucleophilic,[7] electrophilic,[8] and radical pathways.[9] Up to now, numerous favorable methodologies for radical difluoromethylation with difluoromethyl precursors, such as $Zn(SO_2CF_2H)_2$,[10] HCF_2SO_2Cl,[11] HCF_2SO_2Na,[12] HCF_2COOH,[13] 2-[(difluoromethyl)sulfonyl]benzo[*d*]-thiazole,[14] *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine,[15] and *S*-(difluoromethyl)diaryl-sulfonium salt,[16] have been reported. However, these reagents were prepared from unreadily available starting materials through multiple-step reactions involving the usage of gaseous HCF_2Cl. As a result of these concerns, the method of photocatalytic radical difluoromethylation using difluoromethyltriphenylphosphonium bromide ($[Ph_3PCF_2H]^+Br^-$), which is a kind of fascinating CF_2H source with the advantages of strong air-stability and convenient preparation, has increasingly caught the attention of researchers.[17] Currently, the strategy of photocatalytic radical cascade cyclization for the synthesis of heterocyclic compounds has emerged as a promising methodology due to its efficiency and environmental friendliness.[18] Therefore, the development of protocols for visible light-induced radical cascade difluoromethylation/cyclization with $[Ph_3PCF_2H]^+Br^-$ to synthesize CF_2H-functionalized *N*-heterocyclic compounds is of great importance.[19]

The benzimidazole core is widely recognized as an important pharmacophore with biological activity.[20] Moreover, the tricyclic benzimidazole skeletons have been identified in a multitude of bioactive compounds and drugs[21] (Figure 1b). So far, the synthetic methods for polycyclic benzimidazole derivatives have been widely reported.[22] Among these approaches, the direct cyclization reaction of substituted benzimidazoles and alkenes for the synthesis of the tricyclic benzimidazoles is a promising and atom-economical strategy. The significant advancements in the protocols for radical cascade addition/cyclization of *N*-alkenoxyl 2-aryl benzimidazoles to synthesize functionalized polycyclic benzimidazoles,[23] especially those with various fluorine-containing groups,[24] have been achieved in recent years. In 2021, Guo and co-workers

Received: February 5, 2024
Revised: June 7, 2024
Accepted: June 11, 2024
Published: June 19, 2024

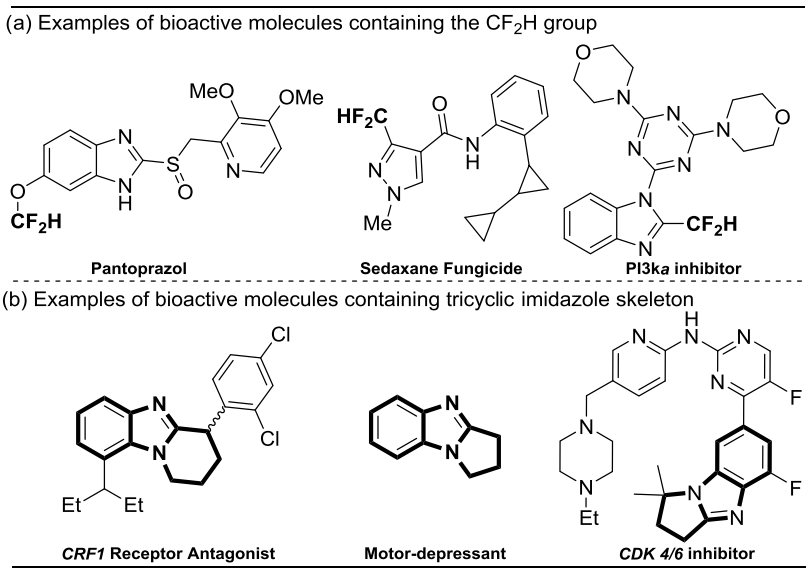
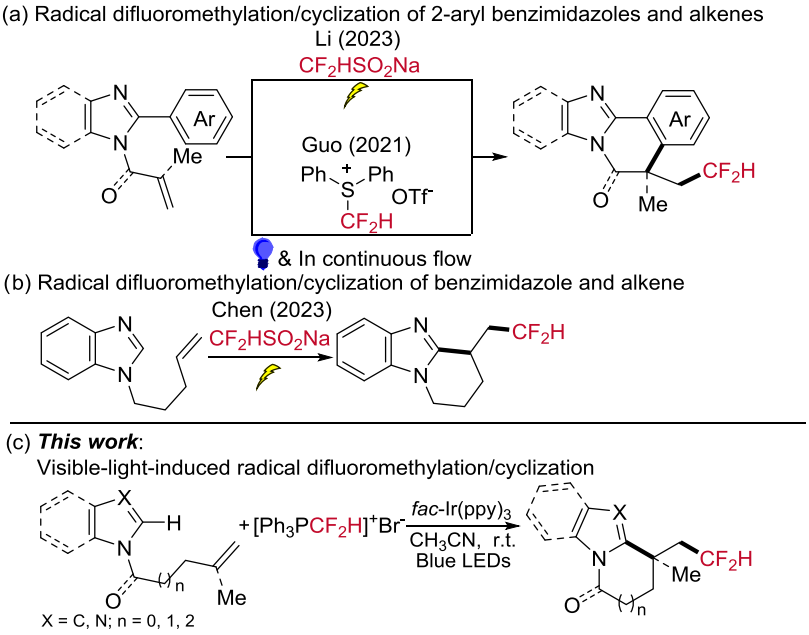


Figure 1. Representative bioactive molecules containing CF_2H or tricyclic benzimidazole core.

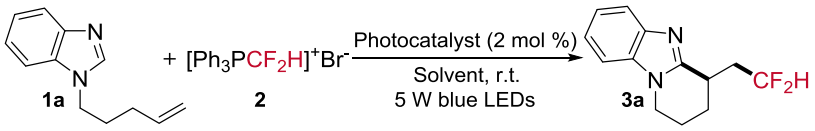
Scheme 1. Synthesis of Polycyclic Imidazoles from Imidazoles and Olefins



disclosed the synthesis of CF_2H-substituted polycyclic benzimidazoles via photocatalytic radical difluoromethylation/cyclization of *N*-alkenoxyl 2-aryl benzimidazoles in continuous flow.[25] In 2023, the synthesis of 5-(2,2-difluoroethyl)-5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline from *N*-alkenyl 2-aryl benzimidazole through the electrochemical radical process was reported by Li's group[26] (Scheme 1a). Notably, a variety of protocols for the cyclization of benzimidazoles with olefins at the C-2 position have been continuously developed. On the one hand, significant development has been made in the methods for catalyzed C−H activation and intramolecular cyclization of imidazoles with alkenes using diverse transition-metal catalysts, including [Pd],[27] [Rh],[28] [Ni],[29] and [Sc].[30] On the other hand, a series of methods for synthesizing substituted tricyclic benzimidazole derivatives with various functional groups, such as trifluoromethyl,[31] difluoroalkyl,[32] sulfonyl,[33] perfluoroalkyl,[34] and chloromethyl,[35] have been established, involving the strategy of radical cascade addition/cyclization of olefin-containing imidazoles. Although these methods have promising prospects, there is still a necessity to develop direct, mild, and efficient methodologies to synthesize highly functionalized polycyclic imidazoles with broad substrate scopes. Given the significance of the benzimidazole core and difluoromethyl group, it is beneficial to incorporate CF_2H into polycyclic benzimidazole skeletons for the synthesis of CF_2H-substituted *N*-heterocyclic benzimidazoles.[36] Regretfully, the methodologies for synthesizing difluoromethylated tricyclic imidazoles via direct radical cyclization of imidazoles with olefins have rarely been reported, only a limited number of substrates were reported by Chen's group[37] in 2023 (Scheme 1b). Above all, the development of effective methods to synthesize CF_2H-substituted tricyclic imidazoles via direct radical cascade addition/cyclization of imidazoles with olefins is still desirable.

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst	solvent	yield (%)[b]
1	*fac*-Ir(ppy)$_3$	CH_3CN	74
2	Ir(dFppy)$_2$(dtbbppy)(PF_6)	CH_3CN	62
3	Ir(dF(Me)ppy)$_2$(dtbbpy)(PF_6)	CH_3CN	55
4	Ir(dF(CF_3)ppy)$_2$(dtbbpy)(PF_6)	CH_3CN	40
5	Ru(bppy)$_3$Cl$_2$·6H_2O	CH_3CN	n.r.
6	[Mes-Acr$^+$]BF_4^-	CH_3CN	n.r.
7	4-CzIPN	CH_3CN	n.r.
8	Eosin B	CH_3CN	n.r.
9	Eosin Y	CH_3CN	n.r.
10	methylene blue	CH_3CN	n.r.
11	*fac*-Ir(ppy)$_3$	DMSO	68
12	*fac*-Ir(ppy)$_3$	DMF	37
13	*fac*-Ir(ppy)$_3$	DCM	50
14	*fac*-Ir(ppy)$_3$	toluene	n.r.
15[c]	*fac*-Ir(ppy)$_3$	CH_3CN	86 (83)
16[d]	*fac*-Ir(ppy)$_3$	CH_3CN–H_2O	84
17	—	CH_3CN	n.r.
18[e]	*fac*-Ir(ppy)$_3$	CH_3CN	n.r.

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), and photocatalyst (0.004 mmol) in solvent (2 mL) irradiated with 5 W blue LEDs at room temperature for 16 h under a N_2 atmosphere. n.r. no reaction, [b]Determined by crude ^{19}F NMR with (trifluoromethoxy)benzene as the internal standard. [c]In CH_3CN (1 mL). [d]In CH_3CN–H_2O (1 mL, v/v, 9:1). Isolated yields are given in parentheses. [e]No irradiation.

Considering the advantages of visible light-mediated radical cascade addition/cyclization reactions in the synthesis of functionalized polycyclic heterocyclic molecules, we envisioned a protocol for photocatalytic radical cascade difluoromethylation/cyclization of unactivated olefin-containing imidazoles with [Ph_3PCF_2H]$^+Br^-$ to synthesize CF_2H-substituted tricyclic imidazole derivatives (Scheme 1c).

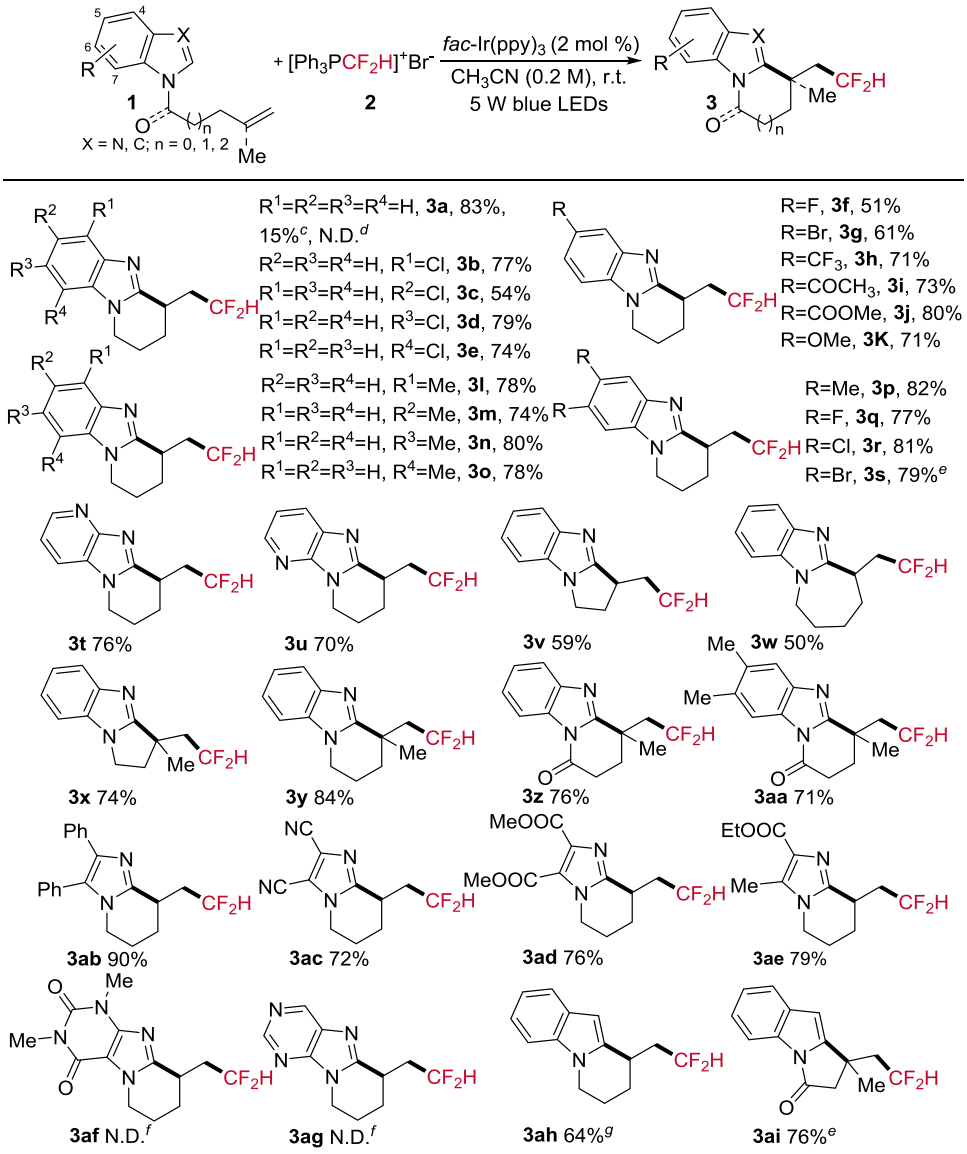
RESULTS AND DISCUSSION

In the initial phase of this study, the model reaction of 1-(pent-4-en-1-yl)-1*H*-benzo[*d*]imidazole (**1a**) and [Ph_3PCF_2H]$^+Br^-$ (**2**) was investigated to optimize the protocol conditions (Table 1, details in the Supporting Information). First, several frequently used photocatalysts were examined. We found that the common polypyridyl complexes of iridium (Table 1, entries 1−4) could facilitate this reaction. While other photocatalysts, such as Ru(bpy)$_3$Cl$_2$·6H_2O, [Mes-Acr$^+$]BF_4^-, 4-CzIPN, Eosin B, Eosin Y, and Methylene Blue, turned out to be ineffective for this transformation (Table 1, entry 5−10). Fortunately, *fac*-Ir(ppy)$_3$ was the most effective with the crude NMR yield of **3a** as high as 74% (Table 1, entry 1), probably due to the easy access to a stronger reducing excited state than other photocatalysts.[38] Subsequently, various solvents, such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dichloromethane (DCM), and toluene, were screened, and the results showed that the yield of **3a** was decreased to different degrees, especially with no reaction occurring when toluene was used as the solvent (Table 1, entries 11−14). Surprisingly, when the concentration of **1a** was doubled, the isolated yield of **3a** was notably increased to 83% (Table 1, entry 15). Meanwhile, the mixed solvent of CH_3CN and H_2O was also suitable for the protocol reaction conditions (Table 1, entry 16). In addition, control experiments verified that the presence of the photocatalyst and the irradiation of light were both indispensable for the method (Table 1, entries 17 and 18). Therefore, the optimized reaction conditions were established as follows: the reaction mixture of **1a** (0.2 mmol), **2** (0.3 mmol), and *fac*-Ir(ppy)$_3$ (2 mol %) in CH_3CN (1 mL) exposed to 5 W blue light-emitting diodes (LEDs) at room temperature for 16 h.

With the optimized conditions in hand, we have conducted the experiments to explore the scope of substrates (Table 2). First, we were pleased to find that the substituted *N*-alkenyl benzimidazoles bearing either electron-withdrawing groups (−F, −Cl, −Br, −CF_3, −$COCH_3$, and −COOMe) or electron-donating groups (−OMe and −Me) on the aromatic ring could be transformed into the expected six-membered tricyclic benzimidazoles in moderate to satisfactory yields (**3b−o**, 51−80%). The substrates containing halogen groups (−F, −Cl, −Br) on the benzene ring were compatible with this protocol, smoothly affording the desired products in 51−79% yields (**3b−g**), thereby allowing further functionalization. The substrates with electron-withdrawing groups (−CF_3, −$COCH_3$, and −COOMe) or electron-donating groups (−OMe and −Me) at the 5-position of the benzimidazole skeleton exhibited higher reactivity than those with halogen groups (−F, −Cl, −Br) at the same position (**3h**, **3i**, **3j**, **3k**, **3m** vs **3c**, **3f**, **3g**). When comparing the electron-withdrawing groups (−$COCH_3$ and −COOMe) and electron-donating groups (−OMe) at the same position, we found that substrates containing electron-withdrawing groups (−$COCH_3$ and −COOMe) exhibited higher reactivity (**3i**, **3j** vs **3k**). Specially, the substrate with the −COOMe group was tolerated with the optimized conditions, yielding the target product **3j** in up to 80% yield. The substrate with the methyl group at the 4-position of the benzimidazole ring was successfully transformed into the corresponding product **3l** in a slightly

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

Table 2. Substrate Scope of the Protocol[a,b]



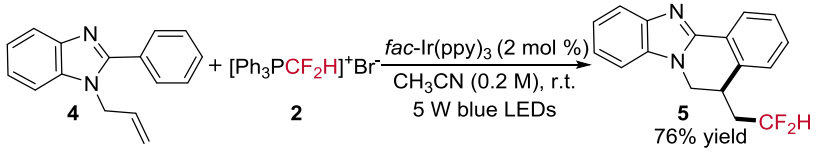
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), and *fac*-Ir(ppy)$_3$ (0.004 mmol) in CH_3CN (1 mL) irradiated with 5 W blue LEDs at room temperature for 16 h under a N_2 atmosphere. [b]Isolated yields. [c]**2a** as the difluoromethylation reagent. [d]**2b** or **2c** as the difluoromethylation reagent. [e]Irradiation for 24 h. [f]N.D. = not detected. [g]Pyridine as an additive.

decreased yield of 78%, indicating that the reaction proceeded smoothly without probable interference from steric hindrance. Subsequently, 5,6-disubstituted *N*-alkenyl benzimidazoles, such as -dimethyl, -difluoro, -dichloro, and -dibromo, were also suitable for this methodology, generating the expected products in good yields (**3p**−**s**, 77−82%). Then, we turned our attention to the substrates containing 4- or 7-azobenzimidazole motif (**1t** and **1u**), and the anticipated products (**3t** and **3u**) were obtained in 76 and 70% yields, respectively. When it comes to the construction of five-membered cyclized benzimidazoles, the transformation of **1v** to **3v** under the optimized conditions proceeded smoothly with a considerable yield of 59%, and a similar situation applied to the construction of seven-membered cyclized benzimidazole (**3w**) with an acceptable yield of 50%. Considering the modification of the alkene moiety, we installed the methyl group into the olefin motif along with the improvement of radical stability, and the corresponding products (**3x** and **3y**) were obtained in good yields of 74 and 84%, respectively. Furthermore, *N*-alkenoxyl substrates were effectively transformed into the relative products in moderate yields (**3z**, 76%; **3aa**, 71%). Finally, when we focused on substrates with a single imidazole ring, we found that the radical cascade difluoromethylation/cyclization reaction of unactivated olefin-containing imidazoles could occur smoothly to yield CF_2H-substituted bicyclic imidazoles with moderate to excellent yields (**3ab**, 90%; **3ac**, 72%; **3ad**, 76%; **3ae**, 79%).

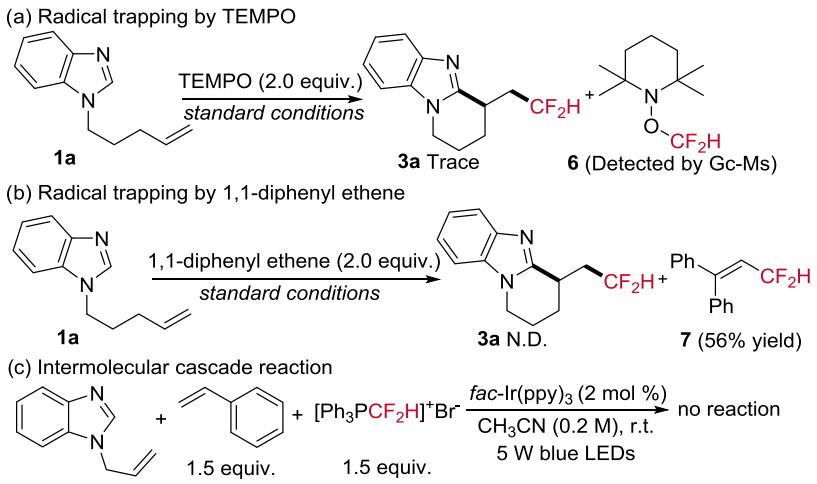
To broaden the application of this strategy, other fluorine sources, such as HCF_2SO_2Cl (**2a**), $BTSO_2CF_2H$ (**2b**), and hypervalent iodine(III) difluoromethylation reagent (**2c**), were investigated. Regretfully, none of these fluorine sources could facilitate the efficient generation of **3a** under standard conditions. Subsequently, *N*-alkenyl theophylline (**1af**) and *N*-alkenyl purine (**1ag**) were evaluated; however, both substrates could not be transformed into the corresponding products (**3af** and **3ag**) under the optimal conditions with the

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

Scheme 2. Construction of the CF_2H-Containing Benzimidazole-dihydroisoquinoline



Scheme 3. Control Experiments



remaining raw materials. These results possibly indicated that the electronic effects of substrates, which were probably related to the introduction of the ***N*** moiety into the substrates (**3ag** vs **3u**; **3af** vs **3ad**) along with the changes due to induction or conjugation of ***N*** moiety, were incompatible with the protocol reaction conditions. We attempted to synthesize appealing CF_2H-substituted tricyclic indoles under the optimized conditions. Encouragingly, both *N*-alkenyl indole (**1ah**) and *N*-alkenoxyl indole (**1ai**) were suitable for this protocol, affording the desired products with synthetically useful yields (**3ah**, 64%; **3ai**, 76%). When the optimized conditions were applied to the construction of the CF_2H-containing benzimidazole-dihydroisoquinoline skeleton, the tetracyclic product (**5**) was prepared from *N*-alkenyl 2-phenyl benzimidazole (**4**) in an isolated yield of 76% (Scheme 2). In order to investigate the potential synthetic utility of this methodology, the scale-up model reaction for the gram-scale preparation of **3a** was performed with an isolated yield of 74% (1.05 g, details in the SI). This outcome confirmed the appropriateness of the protocol for the large-scale preparation of CF_2H-containing ring-fused imidazoles.

To gain insight into the mechanism of this protocol, the control experiments were carried out. Initially, the template reaction under the standard conditions was investigated by adding the radical scavenger 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO, 2.0 equiv), demonstrating that only a trace amount of **3a** was detected, and radical-trapping adduct TEMPO−CHF_2 (**6**) was detected by gas chromatography−mass spectrometry (GC-MS) (Scheme 3a). It was noticeable that the transformation from **1a** to **3a** was significantly inhibited. Moreover, when 1,1-diphenylethylene was employed as a radical scavenger (2.0 equiv), **3a** was not detected and the coupling compound **7** was isolated in a yield of 56% (Scheme 3b), indicating that the generation of **3a** was completely suppressed. The results of radical-trapping experiments confirmed that the model procedure involved an indispensable CF_2H-radical pathway. The intermolecular cascade reaction using N-substituted benzoimidazole and styrene as the substrates under the optimized conditions were investigated; however, the desired reaction did not occur (Scheme 3c). Subsequently, a series of Stern−Volmer fluorescence-quenching experiments were conducted on *fac*-Ir(ppy)$_3$ with **1a** or **2a** as the additive, and the results demonstrated that the excited state $[Ir^{3+}]^*$ was more dramatically quenched by **2a** than by **1a**, indicating that the initial step of protocol reaction mainly involved the oxidative quenching of $[Ir^{3+}]^*$ by **2a** (Figure 2). The light on−off experiment showed that the absence of light irradiation no longer resulted in the generation of **3a** (Figure 3), indicating that the process of CF_2H radical addition/cyclization was probably related to the photocatalytic mechanism. Furthermore, the low apparent quantum yield (0.81, details in the SI) indicated that the predominant pathway access to **3a** was unlikely to be a radical chain propagation process.

On the basis of the above mechanistic studies and previous related literature,[19] we proposed a plausible reaction mechanism for this approach (Scheme 4, taking the reaction of **1a** with **2** as an example). First, the photocatalyst $[Ir^{3+}]$ was activated via irradiation with visible light to give an excited species $[Ir^{3+}]^*$, which subsequently participated in the reduction of $[Ph_3PCF_2H]^+Br^-$ to generate the CF_2H radical and the $[Ir^{4+}]$ complex through a single-electron transfer (SET) process. Next, this resultant radical was added to the terminal alkene of **1a** to generate radical intermediate **I**, which immediately underwent conversion into intermediate **II** through an intramolecular radical addition/cyclization process. Simultaneously, the oxidation of intermediate **II** by $[Ir^{4+}]$ occurred to form the carbocation intermediate **III** through a SET process along with the regeneration of $[Ir^{3+}]$ for the subsequent catalytic cycle. Ultimately, the carbocation intermediate **III** underwent deprotonation to afford **3a**.

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

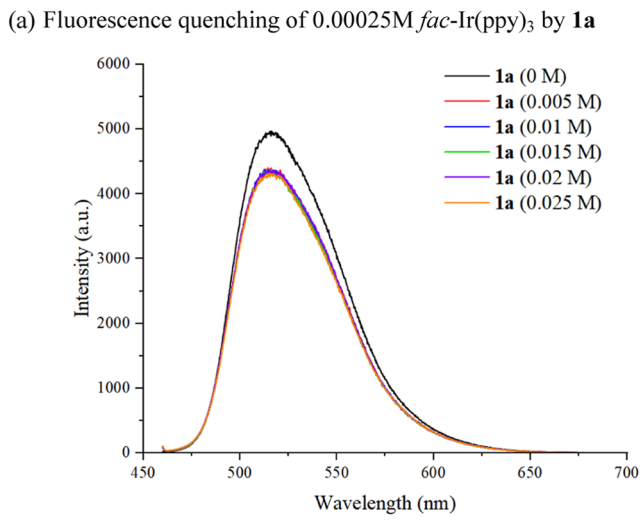


Figure 2. Stern−Volmer Fluorescence-quenching experiments.

CONCLUSIONS

In summary, an efficient and straightforward protocol for visible light-induced radical cascade difluoromethylation/cyclization of unactivated olefin-containing imidazoles with bench-stable and easily accessible $[Ph_3PCF_2H]^+Br^-$ has been developed to afford CF_2H-substituted ring-fused imidazoles in moderate to excellent yields. Significantly, this strategy also applied to the synthesis of CF_2H-containing tetrahydropyrido-[1,2-*a*]indole, dihydropyrrolo[1,2-*a*]indol-3-one, and benzimidazole-dihydroisoquinoline. Additionally, this methodology was practical along with the features of simple operation, mild conditions, absence of additives, and commendable functional group compatibility.

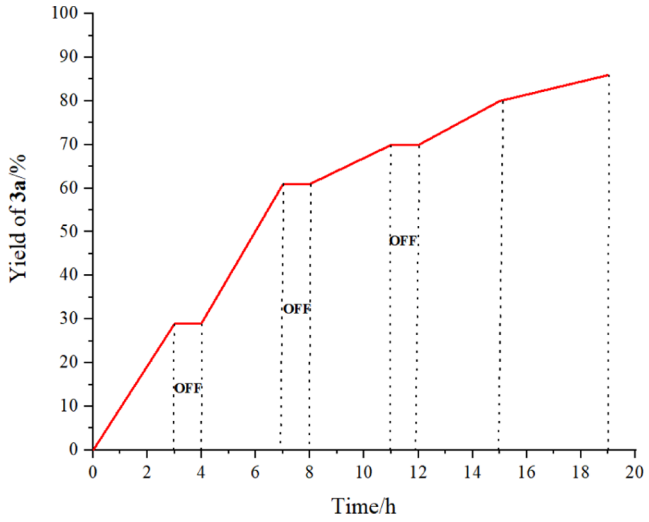


Figure 3. Light on/off experiment.

EXPERIMENTAL SECTION

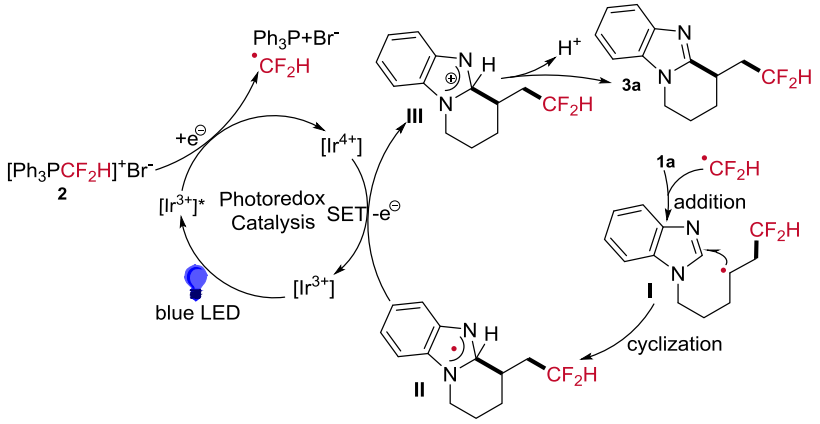
General Information. Unless otherwise noted, all reactions were carried out in flame-dried glassware under N_2. All solvents were purified and dried according to standard methods prior to use. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer in deuterated solvents. ^1H NMR chemical shifts are reported in ppm with the internal tetramethylsilane (TMS) signal at 0.0 ppm as a standard. The data are being reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, brs = broad singlet, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded in a deuterated solvent. Chemical shifts are reported in ppm with the internal solvent signal as a standard. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as the external standard. GC-MS measurements were conducted on a Shimadzu QP2010SE instrument. High-resolution mass spectrometry (HRMS) was performed on a Waters GCT-TOF spectrometer.

General Procedure for the Synthesis of Products 3a−ai, 5 (3a as an Example). To a 10 mL sealed tube equipped with a rubber septum and a magnetic stirring bar, **1a** (0.2 mmol), 2 (0.3 mmol), and *fac*-Ir(ppy)$_3$ (0.004 mmol) were added. The tube was evacuated and backfilled with N_2 three times, and CH_3CN (1.0 mL) was added. The mixture was stirred and irradiated with 5 W blue LEDs for 16 h at room temperature. After the reaction was completed (monitored by thin-layer chromatography (TLC)), the crude mixture was purified directly by flash column chromatography on silica gel using petroleum ether and ethyl acetate (10:1−5:1, v/v) as the eluent to give the desired products **3a**.

*4-(2,2-Difluoroethyl)-1,2,3,4-tetrahydrobenzo[4,5]-imidazo[1,2-a]pyridine (**3a**).* Colorless oil (39 mg, 83% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^1H NMR (400 MHz,

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

Scheme 4. Proposed Mechanism



$CDCl_3$) δ 7.73−7.69 (m, 1H), 7.30−7.21 (m, 3H), 6.39 (tdd, J = 56.8, 5.5, 3.8 Hz, 1H), 4.19−4.14 (m, 1H), 3.98−3.91 (m, 1H), 3.32−3.24 (m, 1H), 2.82−2.67 (m, 1H), 2.32−2.00 (m, 4H), 1.78−1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 142.7, 134.7, 122.4, 122.2, 119.2, 116.9 (t, J = 239.0 Hz), 109.1, 42.5, 38.1 (t, J = 21.4 Hz), 31.4 (dd, J = 6.3, 5.2 Hz), 27.6, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.05−114.03) (m, 1F), −(117.20−118.21) (m, 1F); HRMS (electrospray ionization (ESI), m/z) [M + H$^+$] calcd for $C_{13}H_{15}F_2N_2$: 237.1198, found 237.1197. The spectral data were in accordance with the literature.[37]

*6-Chloro-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3b**).* Colorless oil (42 mg, 77% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.26 (m, 1H), 7.21−7.14 (m, 2H), 6.38 (tdd, J = 56.6, 5.4, 3.7 Hz, 1H), 4.21−4.16 (m, 1H), 4.02−3.96 (m, 1H), 3.38−3.31 (m, 1H), 2.93−2.77 (m, 1H), 2.36−2.03 (m, 4H), 1.82−1.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 139.9, 135.8, 124.0, 122.7, 122.3, 116.9 (t, J = 239.2 Hz), 107.9, 42.8, 38.0 (t, J = 21.3 Hz), 31.39 (dd, J = 6.8, 4.6 Hz), 27.3, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.24 (ddt, J = 284.1, 56.5, 15.0 Hz, 1F), −(117.10−118.11) (m, 1F); HRMS (ESI, m/z) [M + H$^+$] calcd for $C_{13}H_{14}ClF_2N_2$: 271.0809, found 271.0807.

*7-Chloro-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3c**).* Pale yellow oil (29 mg, 54% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.69 (m, 1H), 7.22−7.21 (m, 2H), 6.39 (tdd, J = 56.7, 5.5, 3.7 Hz, 1H), 4.22−4.17 (m, 1H), 4.01−3.94 (m, 1H), 3.35−3.28 (m, 1H), 2.82−2.67 (m, 1H), 2.36−2.04 (m, 4H), 1.82−1.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 143.6, 133.4, 128.0, 122.7, 119.2, 116.8 (t, J = 240.0 Hz), 109.8, 42.7, 38.1 (t, J = 21.5 Hz), 31.5 (dd, J = 6.5, 4.8 Hz), 27.5, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.10−114.08) (m, 1F), −(117.37−118.38) (m, 1F); HRMS (ESI, m/z) [M + H$^+$] calcd for $C_{13}H_{14}ClF_2N_2$: 271.0809, found 271.0806.

*8-Chloro-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3d**).* Colorless oil (43 mg, 79% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.22 (dd, J = 8.6, 1.9 Hz, 1H), 6.39 (tdd, J = 56.8, 5.5, 3.8 Hz, 1H), 4.17−4.12 (m, 1H), 3.97−3.90 (m, 1H), 3.32−3.25 (m, 1H), 2.81−2.65 (m, 1H), 2.34−2.02 (m, 4H), 1.80−1.69 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 141.3, 135.4, 127.9, 122.9, 120.0, 116.8 (t, J = 239.2 Hz), 109.3, 42.6, 38.0 (t, J = 21.5 Hz), 31.4 (dd, J = 7.0, 4.8 Hz), 27.5, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.61 (ddt, J = 284.0, 56.7, 15.2 Hz, 1F), −(117.39−118.40) (m, 1F); HRMS (ESI, m/z) [M + H$^+$] calcd for $C_{13}H_{14}ClF_2N_2$: 271.0809, found 271.0808.

*9-Chloro-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3e**).* Colorless oil (40 mg, 74% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.5, 1.6 Hz, 1H), 7.17−7.11 (m, 2H), 6.38 (tdd, J = 56.7, 5.55, 3.8 Hz, 1H), 4.87−4.81 (m, 1H), 4.39−4.32 (m, 1H), 3.33−3.26 (m, 1H), 2.82−2.66 (m, 1H), 2.31−2.00 (m, 4H), 1.77−1.67 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 144.7, 131.1, 123.6, 122.9, 118.1, 116.8 (t, J = 239.2 Hz), 116.3, 45.6, 38.3 (t, J = 21.5 Hz), 31.8 (dd, J = 6.8, 5.0 Hz), 26.9, 22.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.12−114.10) (m, 1F), −(117.32−118.33) (m, 1F); HRMS (ESI, m/z) [M + H$^+$] calcd for $C_{13}H_{14}ClF_2N_2$: 271.0809, found 271.0807.

*4-(2,2-Difluoroethyl)-7-fluoro-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3f**).* Colorless oil (26 mg, 51% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 9.5, 2.4 Hz, 1H), 7.20 (dd, J = 8.7, 4.6 Hz, 1H), 6.99 (td, J = 9.1, 2.4 Hz, 1H), 6.39 (tdd, J = 56.8, 5.4, 3.8 Hz, 1H), 4.20−4.15 (m, 1H), 4.00−3.93 (m, 1H), 3.33−3.26 (m, 1H), 2.81−2.66 (m, 1H), 2.34−2.03 (m, 4H), 1.79−1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (d, J = 236.8 Hz), 154.8, 143.0 (d, J = 12.7 Hz), 131.3, 116.8 (t, J = 239.0 Hz), 110.3 (d, J = 26.2 Hz), 109.2 (d, J = 10.4 Hz), 105.0 (d, J = 24.2 Hz), 42.6, 38.0 (t, J = 21.4 Hz), 31.4 (dd, J = 6.6, 4.8 Hz), 27.3, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.11−114.09) (m, 1F), −(117.33−118.34) (m, 1F), −(120.83−120.89) (m, 1F); HRMS (ESI, m/z) [M + H$^+$] calcd for $C_{13}H_{14}F_3N_2$: 255.1104, found 255.1101.

*7-Bromo-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3g**).* White solid (38 mg, 61% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 1.5 Hz, 1H), 7.33−7.30 (m, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.38 (tdd, J = 56.8, 5.3, 3.9 Hz, 1H), 4.18−4.13 (m, 1H), 3.97−3.90 (m, 1H), 3.30−3.23 (m, 1H), 2.78−2.63 (m, 1H), 2.33−2.02 (m, 4H), 1.78−1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 144.0, 133.7, 125.2,

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

122.1, 116.8 (t, J = 239.2 Hz), 115.3, 110.3, 42.6, 38.1 (t, J = 21.5 Hz), 31.4 (dd, J = 6.6, 4.8 Hz), 27.4, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.10−114.08) (m, 1F), −(117.38−118.38) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{14}BrF_2N_2$: 315.0303, found 315.0303; mp 104.5−105.7 °C.

*4-(2,2-Difluoroethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (**3h**).* White solid (43 mg, 71% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 6.42 (tdd, J = 56.7, 5.6, 3.6 Hz, 1H), 4.28−4.23 (m, 1H), 4.02 (td, J = 11.6, 4.8 Hz, 1H), 3.37−3.30 (m, 1H), 2.82−2.67 (m, 1H), 2.38−2.27 (m, 2H), 2.26−2.06 (m, 2H), 1.83−1.77 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 142.2, 136.7, 125.0 (q, J = 272.8 Hz), 124.9 (q, J = 32.1 Hz), 119.2 (q, J = 3.7 Hz), 116.9 (q, J = 4.0 Hz), 116.7 (t, J = 239.2 Hz), 109.5, 42.8, 38.1 (t, J = 21.6 Hz), 31.51 (dd, J = 6.8, 4.6 Hz), 27.5, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.58 (s, 3F), −113.64 (ddt, J = 284.1, 56.5, 14.6 Hz, 1F), −(117.50−118.51) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{14}F_5N_2$: 305.1072, found 305.1069; mp 86.5−87.9 °C.

*1-(4-(2,2-Difluoroethyl)-1,2,3,4-tetrahydrobenzo[4,5]-imidazo[1,2-a]pyridin-7-yl)ethan-1-one (**3i**).* White solid (41 mg, 73% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 1.2 Hz, 1H), 7.97 (dd, J = 8.5, 1.6 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 6.43 (tdd, J = 56.8, 5.6, 3.7 Hz, 1H), 4.29−4.24 (m, 1H), 4.02 (td, J = 11.7, 4.8 Hz, 1H), 3.37−3.30 (m, 1H), 2.84−2.69 (m, 1H), 2.67 (s, 3H), 2.38−2.07 (m, 4H), 1.83−1.74 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 155.5, 142.2, 138.0, 132.3, 122.6, 120.9, 116.7 (t, J = 239.1 Hz), 109.1, 42.8, 38.1 (t, J = 21.5 Hz), 31.54 (dd, J = 6.6, 4.8 Hz), 27.5, 26.8, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.11−114.09) (m, 1F), −(117.45−118.46) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{15}H_{17}F_2N_2O$: 279.1304, found 279.1301; mp 110.5−111.4 °C.

*Methyl-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine-7-carboxylate (**3j**).* White solid (47 mg, 80% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.99 (dd, J = 8.4, 1.3 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 6.42 (tdd, J = 56.8, 5.5, 3.7 Hz, 1H), 4.26−4.21 (m, 1H), 4.04−3.97 (m, 1H), 3.94 (s, 3H), 3.36−3.28 (m, 1H), 2.83−2.67 (m, 1H), 2.37−2.05 (m, 4H), 1.82−1.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 155.2, 142.2, 137.9, 124.4, 123.8, 121.4, 116.7 (t, J = 239.0 Hz), 108.7, 52.1, 42.7, 38.0 (t, J = 21.6 Hz), 31.4 (dd, J = 6.6, 4.8 Hz), 27.3, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.08−114.07) (m, 1F), −(117.45−118.46) (dt, J = 260.0, 18.9 Hz, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{15}H_{17}F_2N_2O_2$: 295.1253, found 295.1250; mp 113.2−114.5 °C.

*4-(2,2-Difluoroethyl)-7-methoxy-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3k**).* White solid (38 mg, 71% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 2.3 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.89 (dd, J = 8.7, 2.3 Hz, 1H), 6.40 (tdd, J = 56.8, 5.6, 3.8 Hz, 1H), 4.18−4.13 (m, 1H), 3.98−3.90 (m, 1H), 3.85 (s, 3H), 3.32−3.25 (m, 1H), 2.82−2.66 (m, 1H), 2.33−2.02 (m, 4H), 1.79−1.69 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 153.5, 143.3, 129.3, 116.9 (t, J = 239.0 Hz), 112.1, 109.4, 101.7, 55.9, 42.5, 38.2 (t, J = 21.5 Hz), 31.3 (dd, J = 6.6, 4.8 Hz), 27.5, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.03−114.02) (m, 1F), −(117.24−118.25) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2O$: 267.1304, found 267.1303; mp 122.5−123.8 °C.

*4-(2,2-Difluoroethyl)-6-methyl-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3l**).* Colorless oil (39 mg, 78% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.09 (m, 2H), 7.06−7.05 (m, 1H), 6.48 (tdd, J = 56.9, 5.8, 3.6 Hz, 1H), 4.18−4.13 (m, 1H), 3.99−3.92 (m, 1H), 3.36−3.29 (m, 1H), 2.81−2.65 (m, 1H), 2.64 (s, 3H), 2.32−2.01 (m, 4H), 1.80−1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 142.1, 134.4, 129.4, 122.8, 122.2, 117.2 (t, J = 238.8 Hz), 106.5, 42.6, 38.5 (t, J = 21.3 Hz), 31.4 (dd, J = 7.1, 4.5 Hz), 27.7, 21.8, 16.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(112.75−113.73) (m, 1F), −(117.32−118.33) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2$: 251.1354, found 251.1355.

*4-(2,2-Difluoroethyl)-7-methyl-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3m**).* Colorless oil (37 mg, 74% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.19−7.17 (m, 1H), 7.08−7.06 (m, 1H), 6.38 (tdd, J = 56.8, 5.4, 3.8 Hz, 1H), 4.20−4.14 (m, 1H), 3.99−3.92 (m, 1H), 3.33−3.26 (m, 1H), 2.83−2.67 (m, 1H), 2.47 (s, 3H), 2.33−2.02 (m, 4H), 1.80−1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 143.0, 132.8, 132.1, 123.7, 119.1, 117.0 (t, J = 239.0 Hz), 108.6, 42.5, 38.2 (t, J = 21.3 Hz), 31.4 (dd, J = 6.5, 4.9 Hz), 27.6, 21.8, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.02−114.00) (m, 1F), −(117.16−118.16) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2$: 251.1355, found 251.1353.

*4-(2,2-Difluoroethyl)-8-methyl-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3n**).* Colorless oil (40 mg, 80% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 1H), 7.08−7.06 (m, 2H), 6.38 (tdd, J = 56.8, 5.4, 3.9 Hz, 1H), 4.16−4.10 (m, 1H), 3.94−3.87 (m, 1H), 3.29−3.22 (m, 1H), 2.81−2.64 (m, 1H), 2.48 (s, 3H), 2.30−1.99 (m, 4H), 1.76−1.66 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 140.7, 134.9, 132.2, 123.8, 118.7, 116.9 (t, J = 239.0 Hz), 109.1, 42.4, 38.1 (t, J = 21.3 Hz), 31.4 (dd, J = 6.4, 5.0 Hz), 27.6, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.03−114.01) (m, 1F), −(117.16−118.17) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2$: 251.1355, found 251.1353.

*4-(2,2-Difluoroethyl)-9-methyl-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3o**).* Colorless oil (39 mg, 78% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.37 (tdd, J = 56.8, 5.3, 4.0 Hz, 1H), 4.66−4.61 (m, 1H), 4.36−4.30 (m, 1H), 3.36−3.28 (m, 1H), 2.87−2.73 (m, 1H), 2.72 (s, 3H), 2.31−2.02 (m, 4H), 1.78−1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 143.0, 133.7, 124.8, 122.3, 121.3, 117.3, 117.0 (t, J = 239.0 Hz), 45.4, 38.3 (t, J = 21.3 Hz), 31.8 (dd, J = 6.6, 4.8 Hz), 27.1, 22.5, 18.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(112.99−113.98) (m, 1F), −(117.13−118.13) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2$: 251.1355, found 251.1354.

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

*4-(2,2-Difluoroethyl)-7,8-dimethyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (**3p**).* White solid (43 mg, 82% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.04 (s, 1H), 6.36 (tdd, J = 56.9, 5.5, 3.9 Hz, 1H), 4.13−4.08 (m, 1H), 3.92−3.85 (m, 1H), 3.27−3.20 (m, 1H), 2.79−2.63 (m, 1H), 2.36 (d, J = 6.1 Hz, 6H), 2.28−1.97 (m, 4H), 1.74−1.64 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 141.3, 133.3, 131.2, 131.1, 119.3, 117.0 (t, J = 239.9 Hz), 109.3, 42.4, 38.2 (t, J = 21.3 Hz), 31.4 (dd, J = 6.5, 4.9 Hz), 27.6, 21.8, 20.5, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.01−113.99) (m, 1F), −(117.07−118.08) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{15}H_{19}F_2N_2$: 265.1511, found 265.1510; mp 161.0−162.2 °C.

*4-(2,2-Difluoroethyl)-7,8-difluoro-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (**3q**).* White solid (42 mg, 77% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 10.6, 7.2 Hz, 1H), 7.07 (dd, J = 9.6, 6.9 Hz, 1H), 6.39 (tdd, J = 56.8, 5.4, 3.8 Hz, 1H), 4.16−4.11 (m, 1H), 3.94 (td, J = 11.4, 4.8 Hz, 1H), 3.32−3.25 (m, 1H), 2.79−2.64 (m, 1H), 2.35−2.04 (m, 4H), 1.80−1.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (d, J = 2.3 Hz), 149.0 (dd, J = 15.1, 1.2 Hz), 146.6 (d, J = 15.6 Hz), 137.8 (dd, J = 10.5, 1.1 Hz), 129.9 (d, J = 10.6 Hz), 116.7 (t, J = 239.0 Hz), 106.6 (d, J = 19.3 Hz), 97.1 (d, J = 22.3 Hz), 42.7, 38.0 (t, J = 21.5 Hz), 31.4 (dd, J = 6.7, 4.8 Hz), 27.3, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.65 (ddt, J = 283.9, 56.6, 15.0 Hz, 1F), −(117.46−118.47) (m, 1F), −(142.47−142.57) (m, 1F), −(143.74−143.84) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{13}F_4N_2$: 273.1010, found 273.1007; mp 108.5−109.5 °C.

*7,8-Dichloro-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (**3r**).* White solid (49 mg, 81% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.35 (s, 1H), 6.39 (tdd, J = 56.8, 5.5, 3.7 Hz, 1H), 4.16−4.11 (m, 1H), 3.92 (td, J = 11.4, 4.7 Hz, 1H), 3.31−3.23 (m, 1H), 2.78−2.62 (m, 1H), 2.34−2.03 (m, 4H), 1.79−1.69 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 142.1, 134.0, 126.3, 126.2, 120.5, 116.7 (t, J = 239.1 Hz), 110.5, 42.8, 38.0 (t, J = 21.6 Hz), 31.5 (dd, J = 6.6, 4.8 Hz), 27.4, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.65 (ddt, J = 283.9, 56.6, 14.9 Hz, 1F), −(117.50−118.51) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{13}Cl_2F_2N_2$: 305.0418, found 305.0418; mp 101.3−102.7 °C.

*7,8-Dibromo-4-(2,2-difluoroethyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (**3s**).* White solid (62 mg, 79% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.57 (s, 1H), 6.39 (tdd, J = 56.7, 5.5, 3.7 Hz, 1H), 4.16−4.11 (m, 1H), 3.96−3.89 (m, 1H), 3.31−3.24 (m, 1H), 2.78−2.62 (m, 1H), 2.35−2.03 (m, 4H), 1.79−1.69 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 143.0, 134.9, 123.7, 117.5, 117.3, 116.6 (t, J = 239.2 Hz), 113.7, 42.7, 37.9 (t, J = 21.6 Hz), 31.4 (dd, J = 6.6, 4.7 Hz), 27.3, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.64 (ddt, J = 284.0, 56.6, 14.9 Hz, 1F), −(117.50−118.50) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{13}Br_2F_2N_2$: 394.9388, found; 394.9389, mp 115.4−116.7 °C.

*9-(2,2-Difluoroethyl)-6,7,8,9-tetrahydroimidazo[1,2-a:4,5-b′]dipyridine (**3t**).* Colorless oil (36 mg, 76% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 4.8, 1.5 Hz, 1H), 7.62 (dd, J = 8.0, 1.5 Hz, 1H), 7.17 (dd, J = 8.0, 4.8 Hz, 1H), 6.58 (tdd, J = 56.9, 6.0, 3.4 Hz, 1H), 4.26−4.21 (m, 1H), 4.00 (td, J = 11.4, 4.6 Hz, 1H), 3.37−3.30 (m, 1H), 2.81−2.65 (m, 1H), 2.36−2.27 (m, 2H), 2.26−2.07 (m, 2H), 1.82−1.72 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 155.5, 144.6, 126.7, 117.3, 116.9, 116.8 (t, J = 238.7 Hz), 42.4, 38.1 (t, J = 21.7 Hz), 31.4 (dd, J = 7.4, 4.4 Hz), 27.4, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(112.97−113.20) (m, 1F), −(118.16−119.18) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{12}H_{14}F_2N_3$: 238.1151, found 238.1150.

*6-(2,2-Difluoroethyl)-6,7,8,9-tetrahydroimidazo[1,2-a:5,4-b′]dipyridine (**3u**).* Colorless oil (33 mg, 70% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 4.8, 1.2 Hz, 1H), 7.97 (dd, J = 8.0, 1.2 Hz, 1H), 7.22 (dd, J = 8.0, 4.8 Hz, 1H), 6.41 (tdd, J = 56.8, 5.4, 3.8 Hz, 1H), 4.48−4.42 (m, 1H), 4.10−4.02 (m, 1H), 3.37−3.30 (m, 1H), 2.84−2.68 (m, 1H), 2.38−2.03 (m, 4H), 1.84−1.74 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 147.8, 143.4, 134.9, 126.6, 118.5, 116.7 (t, J = 239.1 Hz), 41.6, 38.0 (t, J = 21.5 Hz), 31.6 (dd, J = 6.5, 4.8 Hz), 27.5, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.16−114.15) (m, 1F), −(117.37−118.38) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{12}H_{14}F_2N_3$: 238.1151, found 238.1152.

*3-(2,2-Difluoroethyl)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (**3v**).* Colorless oil (26 mg, 59% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 1H), 7.34−7.29 (m, 1H), 7.26−7.21 (m, 2H), 6.26 (tdd, J = 56.2, 5.5, 3.3 Hz, 1H), 4.20−4.14 (m, 1H), 4.06−4.00 (m, 1H), 3.55−3.47 (m, 1H), 3.02−2.94 (m, 1H), 2.67−2.52 (m, 1H), 2.50−2.41 (m, 1H), 2.24−2.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 148.5, 132.3, 122.3, 122.0, 119.8, 116.1 (t, J = 239.5 Hz), 109.7, 42.0, 37.2 (t, J = 21.3 Hz), 33.8, 30.7 (dd, J = 7.0, 4.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.93 (ddt, J = 284.1, 55.9, 14.3 Hz, 1F), −(117.45−118.46) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{12}H_{13}F_2N_2$: 223.1042, found 223.1040.

*6-(2,2-Difluoroethyl)-7,8,9,10-tetrahydro-6H-benzo[4,5]-imidazo[1,2-a]azepine (**3w**).* Colorless oil (25 mg, 50% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (m, 1H), 7.29−7.20 (m, 3H), 6.49−6.18 (m, 1H), 4.41−4.36 (m, 1H), 3.97−3.91 (m, 1H), 3.23−3.17 (m, 1H), 3.02−2.86 (m, 1H), 2.26−1.94 (m, 4H), 1.89−1.78 (m, 1H), 1.58−1.46 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 142.1, 135.7, 122.3, 121.8, 119.5, 116.9 (t, J = 239.2 Hz), 108.8, 44.0, 37.7 (t, J = 21.8 Hz), 34.5 (dd, J = 7.9, 4.0 Hz), 32.9, 29.6, 28.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.52−114.49) (m, 1F), −(118.14−119.16) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2$: 251.1355, found 251.1354.

*3-(2,2-Difluoroethyl)-3-methyl-2,3-dihydro-1H-benzo[d]-pyrrolo[1,2-a]imidazole (**3x**).* Colorless oil (35 mg, 74% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 1H), 7.33−7.27 (m, 1H), 7.25−7.20 (m, 2H), 6.03 (tt, J = 56.0, 4.8 Hz, 1H), 4.12−4.03 (m, 2H),

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

2.79−2.72 (m, 1H), 2.54−2.48 (m, 1H), 2.44−2.23 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 148.4, 132.1, 122.3, 122.0, 119.9, 116.1 (t, J = 240.1 Hz), 109.8, 42.9 (t, J = 20.8 Hz), 41.0, 40.7, 37.3 (dd, J = 5.9, 4.6 Hz), 25.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(111.91−112.93) (m, 1F), −(113.24−114.24) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{15}F_2N_2$: 237.1198, found 237.1198.

*4-(2,2-Difluoroethyl)-4-methyl-1,2,3,4-tetrahydrobenzo-[4,5]imidazo[1,2-a]pyridine (**3y**).* Colorless oil (42 mg, 84% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.72 (m, 1H), 7.32−7.24 (m, 3H), 6.10 (tt, J = 56.2, 4.6 Hz, 1H), 4.17−4.12 (m, 1H) 4.06−4.00 (m, 1H), 2.54−2.34 (m, 2H), 2.22−2.09 (m, 3H), 1.94−1.89 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 142.7, 134.5, 122.5, 122.3, 119.4, 116.7 (t, J = 242.4 Hz), 109.3, 44.8 (t, J = 20.6 Hz), 42.7, 34.6 (t, J = 5.1 Hz), 33.8, 27.8, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(110.43−111.44) (m, 1F), −(111.94−112.94) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{17}F_2N_2$: 251.1354, found 251.1357.

*4-(2,2-Difluoroethyl)-4-methyl-3,4-dihydrobenzo[4,5]-imidazo[1,2-a]pyridin-1(2H)-one (**3z**).* Colorless oil (40 mg, 76% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.24 (m, 1H), 7.73−7.69 (m, 1H), 7.41−7.36 (m, 2H), 6.19 (tt, J = 55.9, 4.6 Hz, 1H), 3.04−2.90 (m, 2H), 2.55−2.44 (m, 2H), 2.36−2.29 (m, 1H), 2.13−2.07 (m, 1H), 1.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 158.6, 142.4, 131.5, 125.6, 125.5, 119.8, 116.0 (t, J = 239.0 Hz), 115.7, 43.2 (t, J = 21.4 Hz), 34.3 (t, J = 5.1 Hz), 32.4, 30.4, 25.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ −(110.62−111.63) (m, 1F), −(111.68−112.69) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{15}F_2N_2O$: 265.1147, found 265.1147.

*4-(2,2-Difluoroethyl)-4,7,8-trimethyl-3,4-dihydrobenzo-[4,5]imidazo[1,2-a]pyridin-1(2H)-one (**3aa**).* White solid (42 mg, 71% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.45 (s, 1H), 6.17 (tt, J = 56.0, 4.6 Hz, 1H), 3.00−2.86 (m, 2H), 2.52−2.41 (m, 2H), 2.37 (d, J = 7.7 Hz, 6H), 2.33−2.25 (m, 1H), 2.10−2.04 (m, 1H), 1.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 157.7, 140.8, 134.7, 134.4, 129.8, 119.9, 116.1 (t, J = 239.0 Hz), 115.9, 43.2 (t, J = 21.5 Hz), 34.2 (t, J = 5.1 Hz), 32.5, 30.3, 25.4, 20.5, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(110.58−111.59) (m, 1F), −(111.63−112.64) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{16}H_{19}F_2N_2O$: 293.1460, found 293.1458; mp 127.9−128.8 °C.

*8-(2,2-Difluoroethyl)-2,3-diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (**3ab**).* White solid (61 mg, 90% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 5:1−1:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.38 (m, 5H), 7.34−7.31 (m, 2H), 7.20−7.16 (m, 2H), 7.13−7.09 (m, 1H), 6.57 (tdd, J = 57.2, 6.2, 3.3 Hz, 1H), 3.74−3.59 (m, 2H), 3.23−3.16 (m, 1H), 2.75−2.60 (m, 1H), 2.24−2.02 (m, 3H), 1.96−1.85 (m, 1H), 1.72−1.62 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 136.8, 134.8, 131.1, 130.7, 129.0, 128.5, 128.2, 127.7, 126.8, 126.3, 117.3 (t, J = 238.6 Hz), 43.9, 38.9 (t, J = 21.1 Hz), 30.9 (dd, J = 7.5, 4.0 Hz), 27.8, 22.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(112.63−113.60) (m, 1F), −(117.73−118.70) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{21}H_{21}F_2N_2$: 339.1668, found 339.1665; mp 153.1−154.1 °C.

*8-(2,2-Difluoroethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]-pyridine-2,3-dicarbonitrile (**3ac**).* Colorless oil (34 mg, 72% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 5:1−1:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (tdd, J = 56.4, 5.6, 3.4 Hz, 1H), 4.26−4.21 (m, 1H), 4.05−3.98 (m, 1H), 3.19−3.12 (m, 1H), 2.64−2.48 (m, 1H), 2.36−2.25 (m, 2H), 2.18−2.01 (m, 2H), 1.76−1.65 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 121.9, 116.0 (t, J = 239.7 Hz), 111.9, 111.6, 108.1, 45.5, 37.6 (t, J = 22.0 Hz), 31.1 (dd, J = 7.0, 4.4 Hz), 26.8, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.41−114.39) (m, 1F), −(118.09−119.10) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{11}H_{11}F_2N_4$: 237.0947, found 237.0944.

*Dimethyl-8-(2,2-difluoroethyl)-5,6,7,8-tetrahydroimidazo-[1,2-a]pyridine-2,3-dicarboxylate (**3ad**).* White solid (46 mg, 76% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 5:1−1:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (tdd, J = 56.6, 5.2, 4.0 Hz, 1H), 4.37−4.32 (m, 1H), 4.09−4.02 (m, 1H), 3.90 (d, J = 5.3 Hz, 6H), 3.19−3.12 (m, 1H), 2.78−2.62 (m, 1H), 2.27−1.90 (m, 4H), 1.72−1.63 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 160.5, 149.6, 136.3, 124.0, 116.5 (t, J = 239.3 Hz), 52.4, 52.3, 45.6, 37.9 (t, J = 21.3 Hz), 30.9 (dd, J = 6.3, 5.0 Hz), 26.5, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.12−114.10) (m, 1F), −(117.13−118.13) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{17}F_2N_2O_4$: 303.1151, found 303.1150; mp 82.0−83.5 °C.

*3-Ethyl-8-(2,2-difluoroethyl)-3-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (**3ae**).* Colorless oil (43 mg, 79% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 5:1−1:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44−6.12 (m, 1H), 4.47−4.40 (m, 1H), 4.34−4.28 (m, 2H), 4.09−4.01 (m, 1H), 3.14−3.06 (m, 1H), 2.68−2.51 (m, 1H), 2.46−2.45 (m, 3H), 2.19−1.86 (m, 4H), 1.67−1.57 (m, 1H), 1.40−1.35 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 149.6, 147.0, 118.4, 116.7 (t, J = 239.0 Hz), 60.0, 45.6, 38.1 (t, J = 21.2 Hz), 30.8 (t, J = 5.6 Hz), 26.6, 21.8, 15.6, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.16−114.16) (m, 1F), −(117.21−118.22) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{13}H_{19}F_2N_2O_2$: 273.1410, found 273.1406.

*1-(2,2-Difluoroethyl)-1-methyl-1,2-dihydro-3H-pyrrolo-[1,2-a]indol-3-one (**3ah**).* Colorless oil (30 mg, 64% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7, 1H), 7.27 (d, J = 8.1, 1H), 7.19−7.14 (m, 1H), 7.12−7.08 (m, 1H), 6.28 (s, 1H), 6.05 (tt, J = 56.5, 4.7 Hz, 1H), 4.19−4.13 (m, 1H), 3.96−3.89 (m, 1H), 3.32−3.24 (m, 1H), 2.57−2.41 (m, 1H), 2.26−1.97 (m, 4H), 1.69−1.59 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 136.5, 127.9, 121.0, 120.1, 120.0, 116.7 (t, J = 239.2 Hz), 108.9, 97.6, 42.2, 39.2 (t, J = 20.8 Hz), 30.0 (t, J = 5.8 Hz), 27.3, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(113.68−114.68) (m, 1F), −(115.21−116.21) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{16}F_2N$: 236.1245, found 236.1245.

*1-(2,2-Difluoroethyl)-1-methyl-1,2-dihydro-3H-pyrrolo-[1,2-a]indol-3-one (**3ai**).* Colorless oil (38 mg, 76% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 10:1−5:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 1H), 7.54−7.52 (m, 1H), 7.34−7.26 (m, 2H), 6.33 (s, 1H), 5.85 (tt, J = 55.8, 4.8 Hz, 1H), 3.23 (d, J = 18.2 Hz, 1H), 2.93 (d, J = 18.2 Hz, 1H), 2.42−2.23 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6,

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

149.7, 134.9, 130.3, 124.5, 124.2, 121.1, 116.0 (t, J = 239.8 Hz), 114.1, 99.6, 49.2, 44.6 (t, J = 20.7 Hz), 35.3 (t, J = 5.2 Hz), 28.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −(112.49−113.49) (m, 1F), −(113.59−114.60) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{14}H_{14}F_2NO$: 250.1038, found 250.1036.

*5-(2,2-Difluoroethyl)-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**5**).* Colorless oil (43 mg, 76% yield); purified by silica gel column chromatography (hexanes/ethyl acetate mixtures 5:1−1:1 (v/v)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35−8.32 (m, 1H), 7.87−7.82 (m, 1H), 7.50−7.42 (m, 2H), 7.40−7.28 (m, 4H), 5.78 (tdd, J = 56.2, 3.5, 3.1 Hz, 1H), 4.46 (dd, J = 12.8, 2.2 Hz, 1H), 4.32−4.27 (m, 1H), 3.60−3.55 (m, 1H), 2.22−1.96 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 144.1, 136.6, 134.9, 130.6, 128.6, 127.9, 126.3, 126.0, 123.1, 122.8, 119.9, 115.9 (t, J = 239.7 Hz), 109.1, 44.8, 37.9 (t, J = 21.2 Hz), 33.2 (dd, J = 6.5, 3.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −(115.22−116.20) (m, 1F), −(117.13−118.15) (m, 1F); HRMS (ESI, m/z) [M + H^+] calcd for $C_{17}H_{15}F_2N_2$: 285.1198, found 285.1199. The spectral data were in accordance with the literature.[26]

General Procedure for Gram-Scale Synthesis of 3a. To a 100 mL sealed tube equipped with a rubber septum and a magnetic stirring bar, **1a** (6.0 mmol), **2** (9.0 mmol), and *fac*-Ir(ppy)$_3$ (0.12 mmol) were added. The tube was evacuated and backfilled with N_2 three times, and CH_3CN (30 mL) was added. The mixture was stirred and irradiated with 5 W blue LEDs at room temperature. After the reaction was completed (monitored by TLC), the crude mixture was purified directly by flash column chromatography on silica gel using petroleum ether and ethyl acetate (10:1−5:1, v/v) as the eluent to obtain **3a** in 74% yield (1.05 g, colorless oil).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c01177.

Optimization details; general procedure for the synthesis of **1a**−**ai**, **4**; character data for **1i** and **1k**; character data for **3a**−**ai**, **5**; scale-up reaction; preliminary mechanistic studies; and NMR spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Sheng-Nan Lin − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China;* orcid.org/0009-0006-4004-5782; Email: 307192@sru.edu.cn

Bin-Miao Yang − *Joint School of National University of Singapore and Tianjin University, Fuzhou 350207, China*; Email: bmyang@tjufz.org.cn

Authors

Yuanyuan Deng − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China*

Hanxun Zhong − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China*

Liu-Liang Mao − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China;* orcid.org/0000-0001-7208-0757

Cong-Bin Ji − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China*

Xian-Hong Zhu − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China*

Xiaolan Zhang − *College of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c01177

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for the financial support from the National Natural Science Foundation of China (22201205), the Science and Technology Special Foundation of Shangrao (2022YF020 and 2022YF026), and the Technology Research Projects of the Education Department of Jiangxi Province (GJJ2201818).

■ REFERENCES

(1) For selected reviews: (a) Chandra, G.; Singh, D. V.; Mahato, G. K.; Patel, S. Fluorine-a Small Magic Bullet Atom in the Drug Development: Perspective to FDA Approved and COVID-19 Recommended Drugs. *Chem. Pap.* **2023**, *77*, 4085−4106. (b) Jeschke, P. Recent Developments in Fluorine-containing Pesticides. *Pest Manage. Sci.* **2024**, *80*, 3065.

(2) (a) Melnykov, K. P.; Nazar, K.; Smyrnov, O.; Skreminskyi, A.; Pavlenko, S.; Klymenko-Ulianov, O.; Shishkina, S.; Volochnyuk, D. M.; Grygorenko, O. O. Mono- and Difluorinated Saturated Heterocyclic Amines for Drug Discovery: Systematic Study of Their Physicochemical Properties. *Chem.—Eur. J.* **2023**, *29*, No. e202301383. (b) Kawagoe, F.; Mototani, S.; Yasuda, K.; Mano, H.; Takeuchi, A.; Saitoh, H.; Sakaki, T.; Kittaka, A. Synthesis of New 26,27-Difluoro- and 26,26,27,27-Tetrafluoro-25-hydroxyvitamin D_3: Effects of Terminal Fluorine Atoms on Biological Activity and Half-life. *Chem. Pharm. Bull.* **2023**, *71*, 717−723. (c) Staroń, J.; Pietruś, W.; Bugno, R.; Kurczab, R.; Satała, G.; Warszycki, D.; Lenda, T.; Wantuch, A.; Hogendorf, A. S.; Hogendorf, A.; Duszyńska, B.; Bojarski, A. J. Tuning the Activity of Known Drugs via the Introduction of Halogen Atoms, a Case Study of SERT Ligands-Fluoxetine and Fluvoxamine. *Eur. J. Med. Chem.* **2021**, *220*, No. 113533. (d) Johnson, B. M.; Shu, Y.-Z.; Zhuo, X.; Meanwell, N. A. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem.* **2020**, *63*, 6315−6386.

(3) For selected reviews: (a) Lin, D.; Coe, M.; Krishnamurti, V.; Ispizua-Rodriguez, X.; Surya Prakash, G. K. Recent Advances in Visible Light-Mediated Radical Fluoro-alkylation, -alkoxylation, -alkylthiolation, -alkylselenolation, and -alkylamination. *Chem. Rec.* **2023**, *23*, No. e202300104. (b) Purushotam; Bera, A.; Banerjee, D. Recent Advances on Non-precious Metal-catalysed Fluorination, Difluoromethylation, Trifluoromethylation, and Perfluoroalkylation of N-heteroarenes. *Org. Biomol. Chem.* **2023**, *21*, 9298−9315. (c) Chen, N.; Lei, J.; Wang, Z.; Liu, Y.; Sun, K.; Tang, S. Construction of Fluoro-containing Heterocycles Mediated by Free Radicals. *Chin. J. Org. Chem.* **2022**, *42*, 1061−1084. (d) Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; Am Ende, C. W.; Trabanco, A. A.; Gouverneur, V. Late-stage Difluoromethylation: Concepts, Developments and Perspective. *Chem. Soc. Rev.* **2021**, *50*, 8214−8247.

(4) (a) Chen, M.; Cui, Y.; Chen, X.; Shang, R.; Zhang, X. C-F Bond Activation Enables Synthesis of Aryl Difluoromethyl Bicyclopentanes as Benzophenone-type Bioisosteres. *Nat. Commun.* **2024**, *15*, No. 419. (b) Zafrani, Y.; Sod-Moriah, G.; Yeffet, D.; Berliner, A.; Amir, D.;

Marciano, D.; Elias, S.; Katalan, S.; Ashkenazi, N.; Madmon, M.; Gershonov, E.; Saphier, S. CF_2H, a Functional Group-Dependent Hydrogen-Bond Donor: Is It a More or Less Lipophilic Bioisostere of OH, SH, and CH_3? *J. Med. Chem.* **2019**, *62*, 5628−5637. (c) Zheng, B.; D'Andrea, S. V.; Sun, L.-Q.; Wang, A. X.; Chen, Y.; Hrnciar, P.; Friborg, J.; Falk, P.; Hernandez, D.; Yu, F.; Sheaffer, A. K.; Knipe, J. O.; Mosure, K.; Rajamani, R.; Good, A. C.; Kish, K.; Tredup, J.; Klei, H. E.; Paruchuri, M.; Ng, A.; Gao, Q.; Rampulla, R. A.; Mathur, A.; Meanwell, N. A.; McPhee, F.; Scola, P. M. Potent Inhibitors of Hepatitis C Virus NS3 Protease: Employment of a Difluoromethyl Group as a Hydrogen-Bond Donor. *ACS Med. Chem. Lett.* **2018**, *9*, 143−148. (d) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. CF_2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325−9332. (e) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60*, 797−804.

(5) (a) Ali, S.; Zhou, J. Highlights on U.S. FDA-approved Fluorinated Drugs over the Past Five Years (2018−2022). *Eur. J. Med. Chem.* **2023**, *256*, No. 115476. (b) Wang, Y.; Liu, Y.; Ge, T.; Tang, J.; Wang, S.; Gao, Z.; Chen, J.; Xu, J.; Gong, P.; Zhao, Y.; Liu, J.; Hou, Y. Based on 2-(Difluoromethyl)-1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (ZSTK474), Design, Synthesis and Biological Evaluation of Novel PI3Kα Selective Inhibitors. *Bioorg. Chem.* **2023**, *130*, No. 106211. (c) Kataria, A.; Stolow, E.; Hubbard, H. Pantoprazole-induced Acute Hepatocellular and Cholestatic Hepatitis. *Postgrad. Med. J.* **2022**, *98*, 11−12. (d) Tong, Z.; Chu, Y.; Wen, H.; Li, B.; Dong, X.; Sun, M.; Meng, D.; Wang, M.; Gao, T.; Duan, J. Stereoselective Bioactivity, Toxicity and Degradation of Novel Fungicide Sedaxane with Four Enantiomers under Rice-wheat Rotation Mode. *Ecotoxicol. Environ. Saf.* **2022**, *241*, No. 113784.

(6) For selected reviews: (a) Shi, L.; An, D.; Mei, G.-J. Difluoromethylation of Heterocycles via a Radical Process. *Org. Chem. Front.* **2022**, *9*, 4192−4208. (b) Kisukuri, C. M.; Fernandes, V. A.; Delgado, J. A. C.; Häring, A. P.; Paixão, M. W.; Waldvogel, S. R. Electrochemical Installation of CFH_2-, CF_2H-, CF_3-, and Perfluoroalkyl Groups into Small Organic Molecules. *Chem. Rec.* **2021**, *21*, 2502−2525. (c) Levi, N.; Amir, D.; Gershonov, E.; Zafrani, Y. Recent Progress on the Synthesis of CF_2H-Containing Derivatives. *Synthesis* **2019**, *51*, 4549−4567.

(7) (a) Zhao, H.; Gu, Y.; Shen, Q. [(SIPr)Ag(CF_2H)]: a Shelf-Stable, Versatile Difluoromethylation Reagent. *Chem. Rec.* **2023**, *23*, No. e202300124. (b) Liu, A.; Ni, C.; Xie, Q.; Hu, J. Transition-Metal-Free Controllable Single and Double Difluoromethylene Formal Insertions into C-H Bonds of Aldehydes with $TMSCF_2Br$. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202217088. (c) You, Y.; Chen, Y.; You, C.; Wang, J.; Weng, Z. Synthesis of 3-(Tri/Difluoromethyl)-1H-1,2,4-Triazol-5(4H)-ones via the Cyclization of Hydrazinecarboxamides with Ri/Difluoroacetic Anhydride. *Org. Biomol. Chem.* **2019**, *17*, 9343−9347.

(8) For selected reviews: (a) Qin, W.; Chen, J.; Xiong, W.; Liu, G. Recent Advance in Development and Application of Electrophilic Difluoromethylating Reagents. *Chin. J. Org. Chem.* **2020**, *40*, 3177−3195. For selected examples: (b) Gu, Y.-Q.; Long, H.-X.; Zhang, D.-D.; Ruan, M.-F.; Liu, G.-K. Difluoromethyl Phenoxathiinium Salt: a New General and Versatile Difluoromethylating Reagent with Divergent $\bullet CF_2H$, CF_2H^+, and:CF_2 Reactivities. *Sci. China Chem.* **2024**, *67*, 953−962. (c) Wang, Y.; Wang, S.; Qiu, P.; Fang, L.; Wang, K.; Zhang, Y.; Zhang, C.; Zhao, T. Asymmetric α-Electrophilic Difluoromethylation of β-Keto Esters by Phase Transfer Catalysis. *Org. Biomol. Chem.* **2021**, *19*, 4788−4795.

(9) For selected reviews: (a) Laishram, R. D.; Chen, J.; Fan, B. Progress in Visible Light-Induced Difluroalkylation of Olefins. *Chem. Rec.* **2021**, *21*, 69−86. (b) Koike, T. Frontiers in Radical Fluoromethylation by Visible-Light Organic Photocatalysis. *Asian J. Org. Chem.* **2020**, *9*, 529−537. (c) Koike, T.; Akita, M. Recent Progress in Photochemical Radical Di- and Mono-fluoromethylation. *Org. Biomol. Chem.* **2019**, *17*, 5413−5419. For selected examples: (d) Tagami, T.; Mitani, Y.; Kawamura, S.; Sodeoka, M. Catalytic Difluoromethylation of Alkenes with Difluoroacetic Anhydride: Reactivity of Fluorinated Diacyl Peroxides and Radicals. *Adv. Synth. Catal.* **2023**, *365*, 3637−3647. (e) Xie, F.; Han, F.; Yan, Y.; Li, H.; Hao, J.; Jing, L.; Han, P. Difluoromethylation-Carboxylation and -Deuteration of Alkenes Triggered by Electroreduction of Difluoromethyltriphenylphosphonium Bromide. *J. Org. Chem.* **2023**, *88*, 17134−17143. (f) Du, W.; Luo, Q.; Wei, Z.; Wang, X.; Ni, C.; Hu, J. Switching from 2-pyridination to Difluoromethylation: Ligand-enabled Nickel-catalyzed Reductive Difluoromethylation of Aryl Iodides with Difluoromethyl 2-pyridyl Sulfone. *Sci. China Chem.* **2023**, *66*, 2785−2790. (g) Cai, A.; Yan, W.; Zeng, X.; Zacate, S. B.; Chao, T.-H.; Krause, J. A.; Cheng, M.-J.; Liu, W. Copper-catalyzed Carbo-difluoromethylation of Alkenes via Radical Relay. *Nat. Commun.* **2021**, *12*, No. 3272. (h) Xu, H.-H.; Song, J.; Xu, H.-C. Electrochemical Difluoromethylation of Electron-Deficient Alkenes. *ChemSusChem* **2019**, *12*, 3060−3063. (i) Zhang, M.; Lin, J.-H.; Xiao, J.-C. Photocatalyzed Cyanodifluoromethylation of Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 6079−6083. (j) Lin, Q.-Y.; Xu, X.-H.; Zhang, K.; Qing, F.-L. Visible-Light-Induced Hydrodifluoromethylation of Alkenes with a Bromodifluoromethylphosphonium Bromide. *Angew. Chem., Int. Ed.* **2016**, *55*, 1479−1483.

(10) (a) Garrido-Castro, A. F.; Gini, A.; Maestro, M. C.; Alemán, J. Unlocking the Direct Photocatalytic Difluoromethylation of C = N Bonds. *Chem. Commun.* **2020**, *56*, 3769−3772. (b) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. A New Reagent for Direct Difluoromethylation. *J. Am. Chem. Soc.* **2012**, *134*, 1494−1497.

(11) (a) Lei, Z.; Wei, S.; Zhou, L.; Zhang, Z.; Lopez, S. E.; Dolbier, W. R. Photocatalytic Difluoromethylarylation of Unactivated Alkenes via a (Hetero)aryl Neophyl-like Radical Migration. *Org. Biomol. Chem.* **2022**, *20*, 5712−5715. (b) Wei, S.; Le, S.; Lei, Z.; Zhou, L.; Zhang, Z.; Dolbier, W. R. Difluoromethylarylation of Alpha, Beta-unsaturated Amides via a Photocatalytic Radical Smiles Rearrangement. *Org. Biomol. Chem.* **2022**, *20*, 2064−2068. (c) Vytla, D.; Kaliyaperumal, K.; Velayuthaperumal, R.; Shaw, P.; Gautam, R.; Mathur, A.; Roy, A. Visible-Light-Promoted Radical Cyclization of N-Arylvinylsulfonamides: Synthesis of CF_3/CHF_2/CH_2CF_3-Containing 1,3-Dihydrobenzo[c]isothiazole 2,2-Dioxide Derivatives. *Synthesis* **2022**, *54*, 667−682. (d) Zhang, Z.; Martinez, H.; Dolbier, W. R. Photoredox Catalyzed Intramolecular Fluoroalkylarylation of Unactivated Alkenes. *J. Org. Chem.* **2017**, *82*, 2589−2598. (e) Zhang, Z.; Tang, X.; Thomoson, C. S.; Dolbier, W. R. Photoredox-Catalyzed Intramolecular Aminodifluoromethylation of Unactivated Alkenes. *Org. Lett.* **2015**, *17*, 3528−3531.

(12) (a) Zheng, J.; Xu, Y.; Song, S.; Huang, L.; Cao, D.; Zhong, A.; Yang, J.; Chen, D. Direct 1,6-Difluoromethylation of 3-Methyl-4-nitro-5-styryl Isoxazoles by Photoredox-Promoted Radical Addition. *J. Org. Chem.* **2023**, *88*, 10206−10211. (b) Chen, X.; Geng, Y.; Liu, B.; Zhu, Y.; Zou, D.; Wu, Y.; Wu, Y. Photochemical Difluoromethylation of Alkynes: Synthesis of CF_2H-substituted Seven-membered Dioxodibenzothiazepines and Dibenzazepines. *Org. Chem. Front.* **2023**, *10*, 1968−1974. (c) Chen, X.; Jiang, J.; Huang, X.-J.; He, W.-M. Electrochemical Oxidative Radical Cascade Reactions for the Synthesis of Difluoromethylated Benzoxazines. *Org. Chem. Front.* **2023**, *10*, 3898−3902. (d) Luan, S.; Castanheiro, T.; Poisson, T. Electrochemical Difluoromethylation of Electron-Rich Olefins. *Org. Lett.* **2023**, *25*, 1678−1682. (e) Liu, F.; Lv, L.; Ma, Y.; L, Z. Copper-Catalyzed Radical Difluoromethylation-Peroxidation of Alkenes: Synthesis of β-Difluoromethyl Peroxides. *Asian J. Org. Chem.* **2022**, *11*, No. e202200393. (f) Zhang, D.; Cai, J.; Du, J.; Wang, Q.; Yang, J.; Geng, R.; Fang, Z.; Guo, K. Electrochemical-Oxidation-Promoted Direct N-ortho-Selective Difluoromethylation of Heterocyclic N-Oxides. *Org. Lett.* **2022**, *24*, 1434−1438. (g) Dai, P.; Li, C.; Li, Y.; Zhu, Y.; Teng, P.; Gu, Y.-C.; Zhang, W.-H. Direct Difluoromethylation of Heterocycles through Photosensitized Electron Transfer. *Eur. J. Org. Chem.* **2022**, *2022*, No. e202100896. (h) Zhang, Y.; Ma, C.; Struwe, J.; Feng, J.; Zhu, G.; Ackermann, L. Electrooxidative Dearomatization of Biaryls: Synthesis of Tri- and Difluoromethylated Spiro[5.5]trienones. *Chem. Sci.* **2021**, *12*, 10092−10096.

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

(13) (a) Qi, X.-K.; Yao, L.-J.; Zheng, M.-J.; Zhao, L.; Yang, C.; Guo, L.; Xia, W. Photoinduced Hydrodifluoromethylation and Hydromethylation of Alkenes Enabled by Ligand-to-Iron Charge Transfer Mediated Decarboxylation. *ACS Catal.* **2024**, *14*, 1300−1310. (b) Bian, K.-J.; Lu, Y.-C.; Nemoto, D.; Kao, S.-C.; Chen, X.; West, J. G. Photocatalytic Hydrofluoroalkylation of Alkenes with Carboxylic Acids. *Nat. Chem.* **2023**, *15*, 1683−1692. (c) Wang, J.; Luo, Z.; Wu, Y.; Tang, Y.; Yang, X.; Tsui, G. C. Copper-Catalyzed Visible-Light-Induced Allylic Difluoromethylation of Unactivated Alkenes Using Difluoroacetic Acid. *Org. Lett.* **2023**, *25*, 1045−1049. (d) Gui, Q.-W.; Teng, F.; Li, Z.-C.; Xiong, Z.-Y.; Jin, X.-F.; Lin, Y.-W.; Cao, Z.; He, W.-M. Visible-Light-Initiated Tandem Synthesis of Difluoromethylated Oxindoles in 2-MeTHF under Additive-, Metal Catalyst-, External Photosensitizer-free and Mild Conditions. *Chin. Chem. Lett.* **2021**, *32*, 1907−1910. (e) Tung, T. T.; Christensen, S. B.; Nielsen, J. Difluoroacetic Acid as a New Reagent for Direct C-H Difluoromethylation of Heteroaromatic Compounds. *Chem.—Eur. J.* **2017**, *23*, 18125−18128.

(14) (a) Shi, L.; Li, T.; Zhang, W.; Hu, W.; Zhu, X.; Lu, Y.; Mei, G.-J. Visible-Light Induced Photocatalyst-free Difluoromethylation of Quinoxalinones with Difluorosulfones. *Green Synth. Catal.* **2023**. (b) Zhang, B.; Wang, J. Acyldifluoromethylation Enabled by NHC-Photoredox Cocatalysis. *Org. Lett.* **2022**, *24*, 3721−3725. (c) Trump, L.; Lemos, A.; Jacq, J.; Pasau, P.; Lallemand, B.; Mercier, J.; Genicot, C.; Luxen, A.; Lemaire, C. Development of a General Automated Flow Photoredox ^{18}F-Difluoromethylation of N-Heteroaromatics in an AllinOne Synthesizer. *Org. Process Res. Dev.* **2020**, *24*, 734−744. (d) Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X.-Q.; Song, M.-P. Visible-light-Mediated Radical Oxydifluoromethylation of Olefinic Amides for the Synthesis of CF_2H-Containing Heterocycles. *Chem. Commun.* **2016**, *52*, 13413−13416.

(15) (a) Briand, M.; Thai, L. D.; Bourdreux, F.; Vanthuyne, N.; Moreau, X.; Magnier, E.; Anselmi, E.; Dagousset, G. Remote Radical Trifluoromethylation: a Unified Approach to the Selective Synthesis of γ-Trifluoromethyl α,β-Unsaturated Carbonyl Compounds. *Org. Lett.* **2022**, *24*, 9375−9380. (b) Selmi-Higashi, E.; Zhang, J.; Cambeiro, X. C.; Arseniyadis, S. Synthesis of α-Difluoromethyl Aryl Ketones through a Photoredox Difluoromethylation of Enol Silanes. *Org. Lett.* **2021**, *23*, 4239−4243. (c) Nakayama, Y.; Ando, G.; Abe, M.; Koike, T.; Akita, M. Keto-Difluoromethylation of Aromatic Alkenes by Photoredox Catalysis: Step-Economical Synthesis of α-CF_2H-Substituted Ketones in Flow. *ACS Catal.* **2019**, *9*, 6555−6563. (d) Noto, N.; Koike, T.; Akita, M. Diastereoselective Synthesis of CF_3- and CF_2H-Substituted Spiroethers from Aryl-Fused Cycloalkenylalkanols by Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7064−7071.

(16) (a) Zhao, Y.-S.; Huang, S.-J.; Gu, Y.-Q.; Liu, G.-K. Visible-light Photoredox-catalyzed Radical Aryldifluoromethylation of N-arylacrylamides with S-(difluoromethyl)sulfonium Salt. *Org. Biomol. Chem.* **2023**, *21*, 4013−4017. (b) Qin, W.-B.; Xiong, W.; Li, X.; Chen, J.-Y.; Lin, L.-T.; Wong, H. N. C.; Liu, G.-K. Visible-Light-Driven Difluoromethylation of Isocyanides with S-(Difluoromethyl)-diarylsulfonium Salt: Access to A Wide Variety of Difluoromethylated Phenanthridines and Isoquinolines. *J. Org. Chem.* **2020**, *85*, 10479−10487. (c) Liu, G.-K.; Qin, W.-B.; Li, X.; Lin, L.-T.; Wong, H. N. C. Difluoromethylation of Phenols and Thiophenols with the S-(Difluoromethyl)sulfonium Salt: Reaction, Scope, and Mechanistic Study. *J. Org. Chem.* **2019**, *84*, 15948−15957. (d) Noto, N.; Koike, T.; Akita, M. Metal-free Di- and Tri-fluoromethylation of Alkenes Realized by Visible-light-induced Perylene Photoredox Catalysis. *Chem. Sci.* **2017**, *8*, 6375−6379.

(17) For selected reviews: (a) Feng, J.; Jia, X.; Zhang, S.; Lu, K.; Cahard, D. State of Knowledge in Photoredox-catalysed Direct Difluoromethylation. *Org. Chem. Front.* **2022**, *9*, 3598−3623. For selected examples: (b) Wu, Q.; Zhang, N.; Gong, X.; Ren, M.; Xu, Y.; Chen, Y. Transition Metal-free Photocatalytic Radical Annulation of 2-Cyanoaryl Acrylamides with Difluoromethyl Radicals to Assemble 4-Amino-quinolinone Derivatives. *Green Chem.* **2023**, *25*, 6188−6193. (c) Fang, Y.; Liu, C.; Tang, J.; Pei, Z.; Chen, Z. Visible-Light Photocatalytic Synthesis of Difluoromethylated Selenides from Selenosulfonates through a Radical Process. *J. Org. Chem.* **2023**, *88*, 12658−12667. (d) Li, P.; Liu, Q.; Sun, D.-Q.; Chen, X.-Y. Catalytic Charge Transfer Complex Enabled Difluoromethylation of Enamides with Difluoromethyltriphenylphosphonium Bromide. *Org. Biomol. Chem.* **2022**, *20*, 7599−7603. (e) Zhu, T.-H.; Zhang, Z.-Y.; Tao, J.-Y.; Zhao, K.; Loh, T.-P. Regioselective and Stereoselective Difluoromethylation of Enamides with Difluoromethyltriphenylphosphonium Bromide via Photoredox Catalysis. *Org. Lett.* **2019**, *21*, 6155−6159. (f) Heine, N. B.; Studer, A. Radical Difluoromethylation of Thiols with (Difluoromethyl)triphenylphosphonium Bromide. *Org. Lett.* **2017**, *19*, 4150−4153. (g) Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. Photoredox-Catalyzed Bromodifluoromethylation of Alkenes with (Difluoromethyl)triphenylphosphonium Bromide. *Org. Lett.* **2016**, *18*, 2419−2422.

(18) For selected reviews: (a) Oueis, E.; Elkadi, M.; Rios, R. Visible-Light-Driven Cyclizations. *Adv. Synth. Catal.* **2024**, *366*, 635. (b) Kumar, P. V.; Aravindraj, K.; Madhumitha, G.; Roopan, S. M. Recent Advances in the Light-assisted Synthesis of Ring Junction Nitrogen Heterocycles. *Curr. Org. Chem.* **2023**, *27*, 997−1009. (c) Liu, H.; Wang, L.; Yu, J.-T. Radical Cascade Cyclization of Alkene-Tethered Compounds: Versatile Approach towards Ring-Fused Polycyclic Structures. *Asian J. Org. Chem.* **2023**, *12*, No. e202300101. (d) Cai, Z.; Trienes, S.; Liu, K.; Ackermann, L.; Zhang, Y. Radical Cascade Cyclization of 1,n-Enynes under Photo/Electrochemical Conditions. *Org. Chem. Front.* **2023**, *10*, 5735−5745. (e) Samanta, A.; Debnath, S.; Mondal, P. P.; Maity, S. Visible Light Induced Difunctional Hetero-Annulation of Unsaturated C-C Bonds. *Adv. Synth. Catal.* **2023**, *365*, 3182−3210. (f) Srivastava, V.; Singh, P. K.; Singh, P. P. Recent Advances of Visible-light Photocatalysis in the Functionalization of Organic Compounds. *J. Photochem. Photobiol., C* **2022**, *50*, No. 100488. (g) Liao, J.; Yang, X.; Ouyang, L.; Lai, Y.; Huang, J.; Luo, R. Recent Advances in Cascade Radical Cyclization of Radical Acceptors for the Synthesis of Carbo- and Heterocycles. *Org. Chem. Front.* **2021**, *8*, 1345−1363. (h) Xu, G.-Q.; Xu, P.-F. Visible Light Organic Photoredox Catalytic Cascade Reactions. *Chem. Commun.* **2021**, *57*, 12914−12935. (i) Lemos, A.; Lemaire, C.; Luxen, A. Progress in Difluoroalkylation of Organic Substrates by Visible Light Photoredox Catalysis. *Adv. Synth. Catal.* **2019**, *361*, 1500−1537. For selected examples: (j) Zhao, P.; Wang, L.; Guo, X.; Chen, J.; Liu, Y.; Wang, L.; Ma, Y. Visible Light-Driven α-Diazoketones as Denitrogenated Synthons: Synthesis of Fluorinated N-Heterocycles via Multicomponent Cyclization Reactions. *Org. Lett.* **2023**, *25*, 3314−3318. (k) Yuan, J.; Shen, L.; Guo, N.; Yin, Y.; Yang, P.; Yang, L.; Xiao, Y.; Zhang, S. Visible-Light-Induced Cascade Cyclization of 1-Acryloyl-2-cyanoindole: Access of Difluoroalkylated Pyrrolo[1,2-a]indolediones. *J. Org. Chem.* **2023**, *88*, 16598−16608. (l) Zhao, S.; Zhu, P.; Xu, B.; Ling, S.; Zhang, L.; Sun, F.-G. Visible-Light-Induced Intermolecular Trifluoromethyl Heteroarylation of Vinyl Ethers for the Syntheses of β-Trifluoromethyl Alkyl Thiochromones. *J. Org. Chem.* **2023**, *88*, 9283−9292. (m) Li, Y.-H.; Huang, A.-X.; Zhang, F.-Y.; Sun, K.; Yu, B. Visible-light-induced Photocatalyst-free Activation of Alkynyl Triflones for Trifluoromethylalkynylation of Unactivated 1,6-Dialkenes. *Green Chem.* **2023**, *25*, 6009−6013. (n) Liu, H.; Fan, X.; Hu, J.; Ma, T.; Wang, F.; Yang, J.; Li, D. Visible-Light-Enabled Ph_3P/LiI-Promoted Tandem Radical Trifluoromethylation/Cyclization/Iodination of 1,6-Enynes with Togni's Reagent. *J. Org. Chem.* **2022**, *87*, 12877−12889.

(19) (a) Zhang, J.; Selmi-Higashi, E.; Zhang, S.; Jean, A.; Hilton, S. T.; Cambeiro, X.-T.; Arseniyadis, S. Synthesis of CHF_2-Containing Heterocycles through Oxy-difluoromethylation Using Low-Cost 3D Printed PhotoFlow Reactors. *Org. Lett.* **2024**, *26*, 2877. (b) Qu, H.; Yuan, J.; Feng, Z.; Guo, N.; Yin, Y.; Yang, L.; Xiao, Y.; Qu, L. Visible-Light-Promoted Difluoromethylation/Cyclization of 1-Acryloyl-2-cyanoindole for Construction of Difluoromethylated Pyrrolo[1,2-a]indolediones. *Adv. Synth. Catal.* **2024**, *366*, 1158−1164. (c) Mao, L.-L.; Zhou, A.-X.; Zhu, X.-H.; Peng, H.; Quan, L.-X.; Wan, J.-P.; Yang, S.-D. Visible-Light-Mediated Tandem Difluoromethylation/Cyclization of Alkenyl Aldehydes toward CF_2H-Substituted Chro-

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

man-4-one Derivatives. *J. Org. Chem.* **2022**, *87*, 12414−12423. (d) Wang, H.; Huang, Y.; Wu, Q.; Lu, J.; Xu, Y.-L.; Chen, Y.-Y. Visible-Light-Promoted bis(Difluoromethylation)/Cyclization of 2-Vinyloxy Arylalkynes to Prepare Benzofuran Derivatives. *J. Org. Chem.* **2022**, *87*, 13288−13299. (e) Chen, X.; Liu, B.; Pei, C.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. Visible-Light-Induced Radical Difluoromethylation/Cyclization of Unactivated Alkenes: Access to CF_2H-Substituted Quinazolinones. *Org. Lett.* **2021**, *23*, 7787−7791.

(20) For selected reviews: (a) Venugopal, S.; Kaur, B.; Verma, A.; Wadhwa, P.; Magan, M.; Hudda, S.; Kakoty, V. Recent Advances of Benzimidazole as Anticancer agents. *Chem. Biol. Drug Des.* **2023**, *102*, 357−376. (b) Guo, Y.; Hou, X.; Fang, H. Recent Applications of Benzimidazole as a Privileged Scaffold in Drug Discovery. *Mini-Rev. Med. Chem.* **2021**, *21*, 1367−1379. (c) Brishty, S. R.; Hossain, M. J.; Khandaker, M. U.; Faruque, M. R. I.; Osman, H.; Rahman, S. M. A. A Comprehensive Account on Recent Progress in Pharmacological. Activities of Benzimidazole Derivatives. *Front. Pharmacol.* **2021**, *12*, No. 762807. (d) Beltran-Hortelano, I.; Alcolea, V.; Font, M.; Pérez-Silanes, S. The Role of Imidazole and Benzimidazole Heterocycles in Chagas Disease: A Review. *Eur. J. Med. Chem.* **2020**, *206*, No. 112692.

(21) (a) Kojima, T.; Mochizuki, M.; Takai, T.; Hoashi, Y.; Morimoto, S.; Seto, M.; Nakamura, M.; Kobayashi, K.; Sako, Y.; Tanaka, M.; Kanzaki, N.; Kosugi, Y.; Yano, T.; Aso, K. Discovery of 1,2,3,4-Tetrahydropyrimido[1,2-a]benzimidazoles as Novel Class of Corticotropin Releasing Factor 1 Receptor Antagonists. *Bioorg. Med. Chem.* **2018**, *26*, 2229−2250. (b) Wang, Y.; Liu, W.-J.; Yin, L.; Li, H.; Chen, Z.-H.; Zhu, D.-X.; Song, X.-Q.; Cheng, Z.-Z.; Song, P.; Wang, Z.; Li, Z.-G. Design and Synthesis of 4-(2,3-dihydro-1H-benzo[d]-pyrrolo[1,2-a]imidazol-7-yl)-N-(5-(piperazin-1-ylmethyl)pyridine-2-yl)pyrimidin-2-amine as a Highly Potent and Selective Cyclin-dependent Kinases 4 and 6 Inhibitors and the Discovery of Structure-activity Relationships. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 974−978. (c) Charlson, A. J.; Harington, J. S. The Anti-inflammatory and Analgesic Activity of Some Benzimidazoles, and Their Ability to Protect Erythrocytes from Hemolysis by Silica Powder. *Carbohydr. Res.* **1975**, *43*, 383−387.

(22) For selected reviews: (a) Twardy, D. J.; Wheeler, K. A.; Török, B.; Dembinski, R. Recent Advances in the Synthesis of Isoquinoline-Fused Benzimidazoles. *Molecules* **2022**, *27*, 2062−2078. (b) Sweeney, M.; Conboy, D.; Mirallai, S. I.; Aldabbagh, F. Advances in the Synthesis of Ring-Fused Benzimidazoles and Imidazobenzimidazoles. *Molecules* **2021**, *26*, 2684−2712. For selected examples: (c) Li, A.; Li, C.; Yang, T.; Yang, Z.; Liu, Y.; Li, L.; Tang, K.; Zhou, C. Electrochemical Synthesis of Benzo[d]imidazole via Intramolecular $C(sp^3)$-H Amination. *J. Org. Chem.* **2023**, *88*, 1928−1935. (d) Yi, X.; Zhao, Z.; Wang, M.; Yu, W.; Chang, J. Synthesis of 1,2-Fused/Disubstituted Benzimidazoles and Benzimidazolium Salts by I_2-Mediated sp^3 C-H Amination. *Org. Lett.* **2022**, *24*, 8703−8708. (e) He, Y.-T.; Mao, Y.-J.; Hao, H.-Y.; Xu, Z.-Y.; Lou, S.-J.; Xu, D.-Q. Cu-Catalyzed Regioselective C-H Alkylation of Benzimidazoles with Aromatic Alkenes. *Org. Lett.* **2020**, *22*, 8250−8255. (f) Coyle, R.; Fahey, K.; Aldabbagh, F. Barton Esters for Initiator-free Radical Cyclisation with Heteroaromatic Substitution. *Org. Biomol. Chem.* **2013**, *11*, 1672−1682.

(23) (a) Upreti, G. C.; Singh, T.; Khanna, K.; Singh, A. Pd-Catalyzed Photochemical Alkylative Functionalization of C = C and C = N Bonds. *J. Org. Chem.* **2023**, *88*, 4422−4433. (b) Meher, P.; Samanta, R. K.; Mannaa, S.; Murarka, S. Visible Light Photoredox-catalyzed Arylative Cyclization to Access Benzimidazo[2,1-a]-isoquinolin-6(5H)-ones. *Chem. Commun.* **2023**, *59*, 6092−6095. (c) Tan, Z.; Jiang, Y.; Xu, K.; Zeng, C. Electrophotoredox/cerium-catalyzed Unactivated Alkanes Activation for the Sustainable Synthesis of Alkylated Benzimidazo-fused Isoquinolinones. *J. Catal.* **2023**, *417*, 473−480. (d) Zhang, L.; Chen, P.; Bai, S. Decarboxylative Alkylarylation of Alkenes with $PhI(O_2CR)_2$ to Access Benzimidazo-[2,1-a]isoquinolin-6(5H)-ones Catalyzed by a Low-valent Divanadium Complex. *Mol. Catal.* **2022**, *522*, No. 112200. (e) Pan, Y.-L.; Gong, X.-M.; Hao, R.-R.; Zeng, S.-X.; Shen, Z.-R.; Huang, W.-H. The Synthesis of Anticancer Sulfonated Indolo[2,1-a]isoquinoline and Benzimidazo[2,1-a]isoquinolin-6(5H)-ones Derivatives via a Free Radical Cascade Pathway. *RSC Adv.* **2022**, *12*, 9763−9772. (f) Zhao, P.; Wang, Y.; Wang, X.; Zhuang, D.; Yan, R. Synthesis of Benzimidazo[2,1-a]isoquinoline and Indolo[2,1-a]isoquinoline Derivatives via Copper-Catalyzed Silylation/Methylation of 2-Arylindoles and 2-Arylbenzimidazoles. *J. Org. Chem.* **2022**, *87*, 9056−9068. (g) Li, Z.; Cao, Y.; Chen, L.; Rong, D.; Huang, G.; Xie, Y. Copper-catalyzed Radical Cascade Cyclization: Synthesis of Benzylated Benzimidazo-[2,1-a]isoquinoline-6(5H)-ones. *Tetrahedron Lett.* **2022**, *122*, No. 132952. (h) Tang, L.; Ouyang, Y.; Sun, K.; Yu, B. Visible-light-promoted Decarboxylative Radical Cascade Cyclization to Acylated Benzimidazo/indolo[2,1-a]isoquinolin-6(5H)-ones in Water. *RSC Adv.* **2022**, *12*, 19736−19740. (i) Li, J.-Z.; Mei, L.; Cai, X.-E.; Zhang, C.-C.; Cao, T.-T.; Huang, X.-J.; Liu, Y.-L.; Wei, W.-T. Transition-Metal-Free Radical Cyclization of 2-Arylbenzoimidazoles with Unactivated Alkanes via $C(sp^3)$-H Functionalizations in Aqueous Media. *Adv. Synth. Catal.* **2022**, *364*, 2080−2085. (j) Liu, J.; Huang, H.-L.; Wang, C.; Li, Y.; Li, H.; Hu, H.; He, S.; Tang, H.; Gao, F. Visible-light-driven Cascade Radical Cyclization toward the Synthesis of α-Carbonyl Alkyl-substituted Benzimidazo[2,1-a]isoquinolin-6(5H)-one Derivatives. *RSC Adv.* **2021**, *11*, 29372−29375. (k) Tang, Y.; Li, M.; Huang, H.; Wang, F.; Hu, X.; Zhang, X. Iron-Catalyzed Oxidative Radical Alkoxycarbonylation of Activated Alkenes with Carbazates toward Alkoxycarbonylated Benzimidazo-[2,1-a]isoquinolin-6(5H)-ones. *Synlett* **2021**, *32*, 1219−1222. (l) Li, H.-C.; Sun, K.; Li, X.; Wang, S.-Y.; Chen, X.-L.; He, S.-Q.; Qu, L.-B.; Yu, B. Metal-Free Photosynthesis of Alkylated Benzimidazo[2,1-a]isoquinoline-6(5H)-ones and Indolo[2,1-a]isoquinolin-6(5H)-ones in PEG-200. *J. Org. Chem.* **2021**, *86*, 9055−9066. (m) Yuan, Y.; Zheng, Y.; Xu, B.; Liao, J.; Bu, F.; Wang, S.; Hu, J.-G.; Lei, A. Mn-Catalyzed Electrochemical Radical Cascade Cyclization toward the Synthesis of Benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one Derivatives. *ACS Catal.* **2020**, *10*, 6676−6681. (n) Wang, X.; Li, G.; Sun, K.; Zhang, B. Peroxide-Induced Radical Relay Carbocyclization towards Polycyclic Benzimidazole[2,1-a]isoquinolines. *Chin. J. Org. Chem.* **2020**, *40*, 913−921. (o) Sun, K.; Li, G.; Li, Y.; Yu, J.; Zhao, Q.; Zhang, Z.; Zhang, G. Oxidative Radical Relay Functionalization for the Synthesis of Benzimidazo[2,1-a]iso-quinolin-6(5H)-ones. *Adv. Synth. Catal.* **2020**, *362*, 1947−1954. (p) Boora, R.; Ravi kumar, G.; Subba Reddy, B. V. Metal-free Oxidative Acylation/cyclization of N-Methacryloyl-2-phenylbenzoimidazole with Aryl Aldehydes: an Easy Access to Benzimidazo[2,1-a]isoquinolin-6(5H)-ones. *Org. Biomol. Chem.* **2019**, *17*, 9627−9630. (q) Sun, K.; Li, S.-J.; Chen, X.-L.; Liu, Y.; Huang, X.-Q.; Wei, D.-H.; Qu, L.-B.; Zhao, Y.-F.; Yu, B. Silver-catalyzed Decarboxylative Radical Cascade Cyclization toward Benzimidazo[2,1-a]isoquinolin-6(5H)-ones. *Chem. Commun.* **2019**, *55*, 2861−2864.

(24) (a) Chen, D.; Yang, X.; Wang, D.; Li, Y.; Shi, L.; Liang, D. Electrophotocatalytic Tri- or Difluoromethylative Cyclization of Alkenes. *Org. Chem. Front.* **2023**, *10*, 2482−2490. (b) Sui, K.; Leng, Y.; Wu, Y. Synthesis of Difluoroarymethyl-Substituted Benzimidazo-[2,1-a]isoquinolin-6(5H)-ones under Mild Conditions. *ACS Omega* **2023**, *8*, 7517−7528. (c) Zhang, C.; Yu, Z.; Ding, Y.; Shi, Y.; Xie, Y. Metal-free Electrochemistry Promoted Radical Cascade Cyclization to Access CF_3-Containing Benzimidazo[2,1-a]isoquinolin-6(5H)-ones. *Org. Biomol. Chem.* **2023**, *21*, 6715−6718. (d) Chen, Z.; Huang, X.; Sun, J.; Liu, Y.; Li, Z. Metal-free Cascade Radical Cyclization of N-Methylacrylyl-2-phenylbenzimidazole: Construction of Aryldifluoro-methylated Benzimidazole[2,1-a]iso-Quinoline-6(5H)-ketone. *Asian J. Org. Chem.* **2022**, *11*, No. e202200255. (e) Guo, Y.; Huang, P.-F.; Liu, Y.; He, B.-H. Visible-light-induced Acylation/cyclization of Active Alkenes: Facile Access to Acylated Isoquinolinones. *Org. Biomol. Chem.* **2022**, *20*, 3767−3778. (f) Sun, K.; Li, G.; Guo, S.; Zhang, Z.; Zhang, G. Copper-Catalyzed Radical Cascade Cyclization for Synthesis of CF_3-Containing Tetracyclic Benzimidazo[2,1-a]iso-quinolin-6(5H)-ones. *Org. Biomol. Chem.* **2021**, *19*, 375−378. (g) Liu, L.; Yang, D.-Y.; He, Y.-H.; Guan, Z. Redox-Neutral Photocatalytic Radical Cascade Cyclization for the Synthesis of CH_2CN/CF_2COOEt/CF_3-Containing Benzo[4,5]imidazo[2,1-a]-isoquinolin-

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143

6(5H)-one Derivatives. *J. Org. Chem.* **2020**, *85*, 11892−11901. (h) Zeng, F.-L.; Sun, K.; Chen, X.-L.; Yuan, X.-Y.; He, S.-Q.; Liu, Y.; Peng, Y.-Y.; Qu, L.-B.; Lv, Q.-Y.; Yu, B. Metal-Free Visible-Light Promoted Radical Cyclization to Access Perfluoroalkyl-Substituted Benzimidazo[2,1-a]isoquinolin-6(5H)-ones and Indolo[2,1-a]-isoquinolin-6(5H)-ones. *Adv. Synth. Catal.* **2019**, *361*, 5176−5181.

(25) Yuan, X.; Duan, X.; Cui, Y.-S.; Sun, Q.; Qin, L.-Z.; Zhang, X.-P.; Liu, J.; Wu, M.-Y.; Qiu, J.-K.; Guo, K. Visible-Light Photocatalytic Tri- and Difluoroalkylation Cyclizations: Access to a Series of Indole[2,1-a]isoquinoline Derivatives in Continuous Flow. *Org. Lett.* **2021**, *23*, 1950−1954.

(26) Lv, Y.; Dai, J.-Y.; Zhao, Z.-X.; Liu, J.; Li, Z.-W.; Lu, C.-H.; Zhang, Y.-F.; Liu, W.-D.; Li, J.-S. Electrochemical Synthesis of 5-Trifluoroethyl Dihydrobenzimidazo[2,1-a]isoquinolines from Pendent Unactivated Alkenes via Radical Relay. *Tetrahedron Lett.* **2023**, *119*, No. 154410.

(27) Wu, X.; Xiao, G.; Ding, Y.; Zhan, Y.; Zhao, Y.; Chen, R.; Loh, T.-P. Palladium-Catalyzed Intermolecular Polarity-Mismatched Addition of Unactivated Alkyl Radicals to Unactivated Alkenes. *ACS Catal.* **2020**, *10*, 14107−14116.

(28) (a) Lu, M.; Xu, W.; Ye, M. Phosphine Oxide-Promoted Rh(I)-Catalyzed C-H Cyclization of Benzimidazoles with Alkenes. *Molecules* **2023**, *28*, No. 736. (b) Tsai, A. S.; Wilson, R. M.; Harada, H.; Bergman, R. G.; Ellman, J. A. Rhodium Catalyzed Enantioselective Cyclization of Substituted Imidazoles via C-H Bond Activation. *Chem. Commun.* **2009**, *26*, 3910−3912. (c) Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrasso, P. V.; Bergman, R. G.; Ellman, J. A. Synthesis of Potent Bicyclic Bisarylimidazole c-Jun *N*-Terminal Kinase Inhibitors by Catalytic C-H Bond Activation. *J. Am. Chem. Soc.* **2007**, *129*, 490−491. (d) Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. Microwave-Assisted C−H Bond Activation: A Rapid Entry into Functionalized Heterocycles. *Org. Lett.* **2003**, *5*, 2131−2134. (e) Tan, K. L.; Bergman, R. G.; Ellman, J. A. Annulation of Alkenyl-Substituted Heterocycles via Rhodium-Catalyzed Intramolecular C-H Activated Coupling Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 2685−2686.

(29) (a) Liu, Z.-J.; Li, J.-F.; Zhang, F.-P.; Xu, X.-T.; Ye, M. Catalyst-Controlled Nickel-Catalyzed Intramolecular endo-Selective C-H Cyclization of Benzimidazoles with Alkenes. *Org. Lett.* **2023**, *25*, 353−357. (b) Loup, J.; Müller, V.; Ghorai, D.; Ackermann, L. Enantioselective Aluminum-Free Alkene Hydroarylations through C-H. Activation by a Chiral Nickel/JoSPOphos Manifold. *Angew. Chem., Int. Ed.* **2019**, *58*, 1749−1753. (c) Wang, Y.-X.; Qi, S.-L.; Luan, Y.-X.; Han, X.-W.; Wang, S.; Chen, H.; Ye, M. Enantioselective Ni-Al Bimetallic Catalyzed exo-Selective C-H Cyclization of Imidazoles with Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 5360−5364.

(30) Lou, S.-J.; Mo, Z.; Nishiura, M.; Hou, Z. Construction of All-Carbon Quaternary Stereocenters by Scandium-Catalyzed Intramolecular C-H Alkylation of Imidazoles with 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 1200−1205.

(31) (a) Zhou, Q.-H.; Dai, J.-Y.; Zhao, W.-J.; Zhong, X.-Y.; Liu, C.-Y.; Luo, W.-W.; Li, Z.-W.; Li, J.-S.; Liu, W.-D. Photocatalytic Synthesis of Azaheterocycle-fused Piperidines and Pyrrolidines via Tandem Difunctionalization of Unactivated Alkenes. *Org. Biomol. Chem.* **2023**, *21*, 3317−3322. (b) Ma, R.; Ren, Y.; Deng, Z.; Wang, K.-H.; Wang, J.; Huang, D.; Hu, Y.; Lv, X. Visible Light Promotes Cascade Trifluoromethylation/Cyclization, Leading to Trifluoromethylated Polycyclic Quinazolinones, Benzimidazoles and Indoles. *Molecules* **2022**, *27*, No. 8389. (c) Lin, S.; Cui, J.; Chen, Y.; Li, Y. Copper-Catalyzed Direct Cycloaddition of Imidazoles and Alkenes to Trifluoromethylated Tricyclic Imidazoles. *J. Org. Chem.* **2021**, *86*, 15768−15776.

(32) Lin, S.-N.; Chen, Y.; Luo, X.-D.; Li, Y. Sustainable Cascades to Difluoroalkylated Polycyclic Imidazoles. *Eur. J. Org. Chem.* **2021**, *2021*, 4485−4489.

(33) Sun, B.; Tian, H.-X.; Ni, Z.-G.; Huang, P.-Y.; Ding, H.; Li, B.-Q.; Jin, C.; Wu, C.-L.; Shen, R.-P. Photocatalyst-, Metal- and Additive-free Regioselective Radical Cascade Sulfonylation/cyclization of Benzimidazole Derivatives with Sulfonyl Chlorides Induced by Visible Light. *Org. Chem. Front.* **2022**, *9*, 3669−3676.

(34) Guo, Z.; Chen, X.; Xue, Y.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. Cu-Catalyzed C-H Perfluoroalkylation/Cyclization of Unactivated Alkenes: Synthesis of Perfluoroalkylated Tricyclimidazoles. *Adv. Synth. Catal.* **2022**, *364*, 4231−4236.

(35) (a) Liu, Y.; Li, Z.; Yang, L.; Li, S.; Chen, Z. Photochemically Induced Chloromethylation/Cyclization of Benzimidazole Derivatives with CCl_4/$CHCl_3$. *Org. Biomol. Chem.* **2023**, *21*, 8690−8694. (b) Wu, Y.; Liu, H.; Liu, L.; Yu, J.-T. Metal-free Polychloromethylation/cyclization of Unactivated Alkenes towards Ring-fused Tricyclic Indolones and Benzoimidazoles. *Org. Biomol. Chem.* **2023**, *21*, 7079−7084.

(36) Zhao, X.; Verma, R.; Sridhara, M. B.; Sharath Kumar, K. S. Fluorinated Azoles as Effective Weapons in Fight Against Methicillin-resistance Staphylococcus Aureus (MRSA) and Its SAR Studies. *Bioorg. Chem.* **2024**, *143*, No. 106975.

(37) Chen, Z.; Li, Z.; Li, S.; Qian, G.; Sun, Y. Electrochemically Mediated Fluoroalkylation/Cyclization of Unactivated Alkenes: Synthesis of Polycyclic Benzimidazoles Containing a CF_3 group. *New J. Chem.* **2023**, *47*, 11465−11470.

(38) (a) Becker, M. R.; Wearing, E. R.; Schindler, C. S. Synthesis of Azetidines via Visible-Light-Mediated Intermolecular [2 + 2] Photocycloaddition. *Nat. Chem.* **2020**, *12*, 898−905. (b) Ran, Y.; Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. Visible Light Induced Oxydifluoromethylation of Styrenes with Difluoromethyltriphenylphosphonium Bromide. *J. Org. Chem.* **2016**, *81*, 7001−7007. (c) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. Advances in Photocatalysis: A Microreview of Visible Light Mediated Ruthenium and Iridium Catalyzed Organic Transformations. *Org. Process Res. Dev.* **2016**, *20*, 1156−1163. (d) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166. (e) Shaw, M.-H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898−6926. (f) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363.

https://doi.org/10.1021/acsomega.4c01177
ACS Omega 2024, 9, 28129−28143