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Synthesis of Difluoroarymethyl-Substituted Benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones under Mild Conditions

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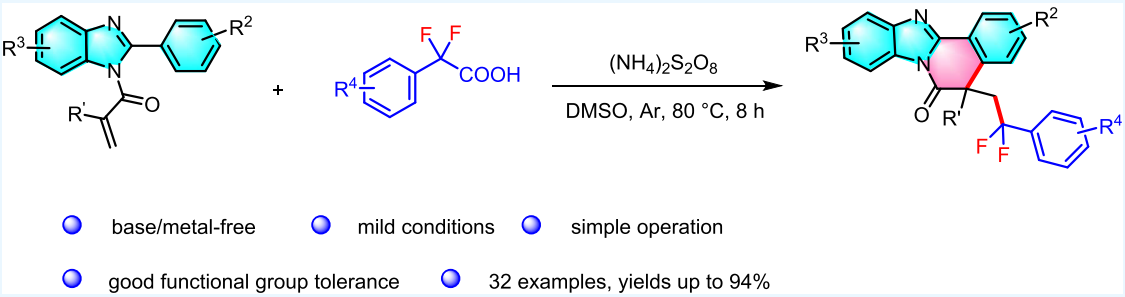

ABSTRACT: A highly efficient method for synthesis of difluoroarymethyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones using 2-arylbenzoimidazoles with *α*,*α*-difluorophenylacetic acid as reaction substrates has been developed through radical cascade cyclization. The advantage of this strategy lies in excellent functional group tolerance to generate the corresponding products in good yields under base- and metal-free conditions.

INTRODUCTION

Benzimidazo-fused polycyclic motifs, especially benzimidazo-isoquinolin-6(5*H*)-one derivatives, are important N-heterocyclic moieties, which have been frequently found in natural products and pharmaceuticals.[1,2] This kind of polycyclic compound also exhibited an amazingly wide spectrum of biological properties, including anti-inflammatory,[3] antidiabetic,[4] antitumor,[5] and anti-HIV-1 properties (Figure 1).[6] Therefore, a great number of synthetic methods have been developed for the preparation of various functionalized novel benzimidazo-isoquinolin-6(5*H*)-one compounds, such as condensation and metal-free-catalyzed cross-couplings.[7,8] Recently, radical cascade cyclization has emerged as a powerful strategy for assembling these frameworks because of its simplicity, efficiency, and atom economy.[9−11] In 2019, Yu and co-workers realized the construction of benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones *via* silver-catalyzed decarboxylative radical cascade cyclization (Scheme 1a).[12] At the same time, Guan's laboratory has devoted effort to the development of photocatalysis radical cascade cyclization reaction toward the preparation of benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones (Scheme 1b).[13] In addition, Li and co-workers reported a facile cascade cyclization reaction for the construction of carbamoylated benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones.[14] Moreover, Pan's group constructed the indolo[2,1-*a*]-isoquinolin derivatives *via* metal-free radical cascade cyclization.[15] Recently, Chen's group published a similar type of work.[16] Despite these achievements, the development of an efficient method for the novel benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives is still highly desirable and valuable.

On the other hand, fluorine-containing compounds, as the most important organic compounds, have been widely presented in the fields of pharmaceutical, chemical, agrochemical, and materials science.[17] Among these fluorine-containing groups, the benzylic difluoromethylene groups ($ArCF_2$) are versatile and valuable moieties for the development of potential pharmaceuticals owing to their unique stability, and an isosteric property as an ethereal oxygen atom or a carbonyl group, as well as a lipophilic hydrogen-bond donor.[18] In recent years, the decarboxylative radical difluoromethylation reaction has usually been considered one of the most efficient methods for the preparation of C−CF_2 bonds.[19] In addition, *α*,*α*-difluoroarylacetic acids have received particular interest due to their beneficial properties, such as easy to store and accessible building blocks for the construction of fluorinated compounds.[20]

In this context, the preparation of $ArCF_2$-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones is an attractive task. With our ongoing interest in radical chemistry, we, herein, designed metal-free and base-free-catalyzed radical

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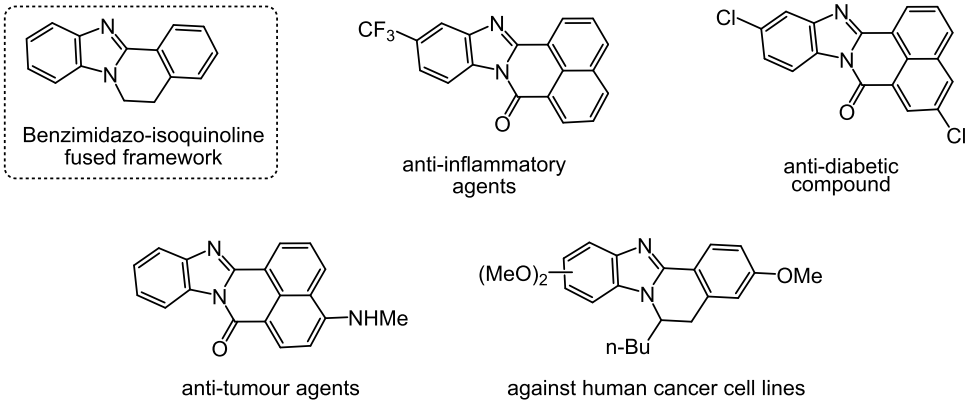
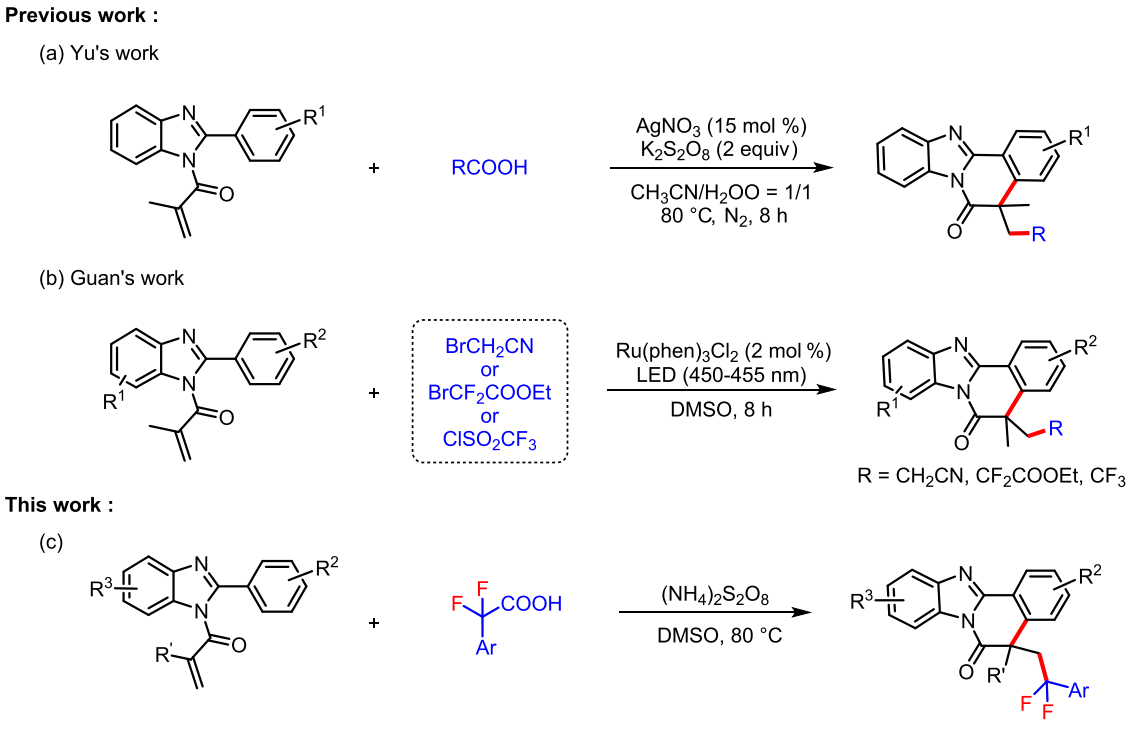


Figure 1. Selected examples containing a benzimidazo-isoquinolin-6(5*H*)-one unit.

Scheme 1. Synthesis of Benzimidazo-Isoquinoline Fused Frameworks



cascade cyclization for the construction of difluoroarymethyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones (Scheme 1c).

RESULTS AND DISCUSSION

Initially, we examined the feasibility of the oxidative coupling reaction of *N*-methacryloyl-2-phenylbenzoimidazole **1a** with *α*,*α*-difluorophenylacetic acid **2a** using $(NH_4)_2S_2O_8$ as an oxidant (Table 1). To our delight, the desired product **3aa** was obtained in 89% yield using 3.0 equiv of $(NH_4)_2S_2O_8$ as an oxidant in dimethyl sulfoxide (DMSO) at 80 °C under an Ar atmosphere (Table 1, entry 1). The structure of **3aa** was unambiguously confirmed by nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS). Based on this result, different control experiments were carried out to evaluate the factors that influence reaction efficiency. Other conditions, such as catalysts, oxidants, the loading of oxidants, solvents, the molar ratio of reactants, temperatures, and times, were further conducted. It is extraordinarily effective with the Ag(I)−peroxydisulfate combination in many decarboxylative and related oxidative transformations.[21] Therefore, we tried different silver carbonates as the catalyst for this transformation. Nevertheless, the yield of **3aa** could not be improved but decreased slightly when the typical $AgNO_3$ or Ag_2CO_3 was employed (Table 1, entries 2 and 3). Next, various oxidants were tested, and the results showed that $(NH_4)_2S_2O_8$ turned out to be the most effective oxidant (Table 1, entries 4−8), especially, the reaction could not proceed without it. In addition, we evaluated the effect of the loading of the oxidant on the reaction. The results showed that 3.0 equiv of $(NH_4)_2S_2O_8$ was the optimal one (Table S1, entries 1−5). Subsequently, the equivalent ratios of **1a** and **2a** were examined. When the equivalent ratio was 1.5:1, the best yield could be gained (Table S2, entries 1−5). Screening of the temperature revealed that 80 °C was the optimal one, increasing or decreasing the temperature showed a negative effect (Table S3, entries 1−5). It is possible that the reaction produced other byproducts under high temperatures and lower

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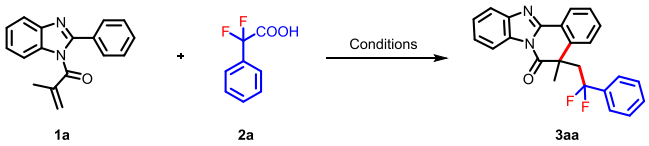
Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	time (h)	yield[b] (%)
1	$(NH_4)_2S_2O_8$	DMSO	12	89
2[c]	$(NH_4)_2S_2O_8$	DMSO	12	81
3[d]	$(NH_4)_2S_2O_8$	DMSO	12	84
4	$K_2S_2O_8$	DMSO	12	32
5[e]	TBHP	DMSO	12	nr
6	DTBP	DMSO	12	nr
7	TBPB	DMSO	12	nr
8		DMSO	12	nr
9	$(NH_4)_2S_2O_8$	DMSO	8	94
10	$(NH_4)_2S_2O_8$	DMSO	6	87
11	$(NH_4)_2S_2O_8$	DMSO	4	59
12[f]	$(NH_4)_2S_2O_8$	DMSO	8	78

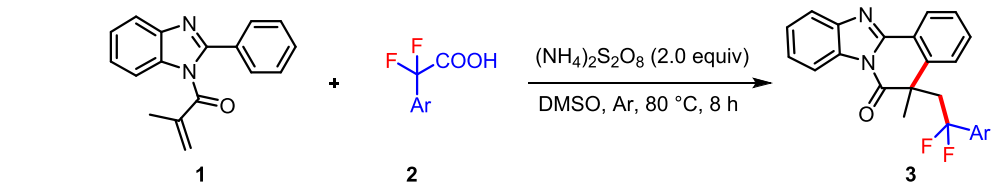
[a]Reaction conditions: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), oxidant (0.6 mmol, 3.0 equiv), and solvent (2.0 mL) was allowed to stir at 80 °C for T h under an Ar atmosphere. [b]Isolated yield. [c]10 mol % $AgNO_3$ was used. [d]10 mol % Ag_2CO_3 was used. [e]70% *tert*-butyl hydroperoxide (TBHP) in H_2O. [f]Under air. nr: no reaction.

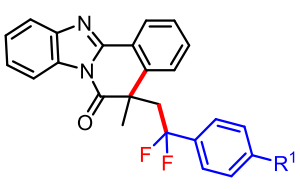
oxidation activity under the lower temperature, thus reducing the yield of the desired products. Several other solvents were tried in the reaction (Table S4, entries 1−9), and it was found that none of them had a good effect. The results indicated that DMSO is the best solvent. Finally, the effect of reaction time was also investigated, and the results showed that 8 h was the optimal time (Table 1, entries 9−11). Unfortunately, a slightly decreased yield was obtained when the reaction was exposed to air (Table 1, entry 12). After rigorous experiments, the optimal conditions were established as follows: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), $(NH_4)_2S_2O_8$ (0.6 mmol, 3.0 equiv), and DMSO (2 mL) at 80 °C for 8 h under an Ar atmosphere.

Having identified the optimal conditions, we further explored the applicability of this reaction. First, the suitability of a series of *α*,*α*-difluoroarylacetic acids **2** was investigated (Scheme 2). As anticipated, substrates **2** with electron-donating or electron-withdrawing substituents on the phenyl rings could react well with **1a**, affording products in moderate to good yields (46−94%). In general, *α*,*α*-difluoroarylacetic acids bearing electron-donating groups showed better reactivity than those attached with electron-withdrawing groups. To our delight, electron-withdrawing substituents, such as F, Br, and CN, at the para position, proved to be well-tolerated under the standard conditions to afford the corresponding difluorobenzyl benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones in good yields (56−75%). Br atom at the meta or ortho position led to a slight drop in yields (**3ak**, **3an**), which might be caused by the low stability of the difluoromethyl radicals and steric hindrance. Notably, when 2,2-difluoro-2-(naphthalen-1-yl)-acetic acid **2o** and 2,2-difluoro-2-(thiophen-2-yl)acetic acid **2p** were employed, the transformation could also proceed smoothly, and the products (**3ao**, **3ap**) were obtained in (74%, 39%) yields, respectively. Gratifyingly, aliphatic difluoroacetic acid and *α*,*α*-difluoropropanoic acid **2q** could also react well to deliver the desired product **3aq** (62%) under the current reaction conditions.

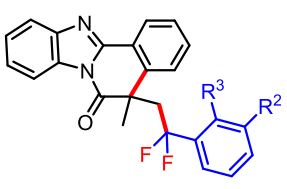
Encouraged by the above results, we then examined the scope of *N*-methacryloyl-2-phenylbenzoimidazole **1** (Scheme 3). Pleasingly, *N*-methacryloyl-2-arylbenzoimidazoles bearing different substituents on the aromatic ring also could react well

Scheme 2. Substrate Scope with Difluoroarylacetic Acid[a,b]

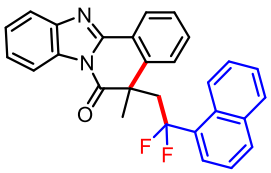




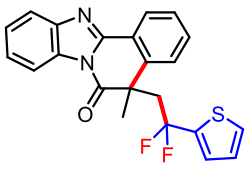
3aa, R^1 = H, 94%
3ab, R^1 = Me, 79%
3ac, R^1 = Et, 91%
3ad, R^1 = OMe, 84%
3ae, R^1 = F, 75%
3af, R^1 = Br, 77%
3ag, R^1 = CN, 56%
3ah, R^1 = Ph, 82%



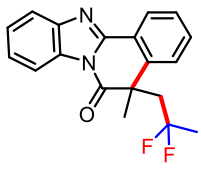
3ai, R^2= Me, R^3 = H, 77%
3aj, R^2 = OMe, R^3 = H, 79%
3ak, R^2 = Br, R^3 = H, 42%
3al, R^2 = H, R^3 = Me, 71%
3am, R^2 = H, R^3 = OMe, 73%
3an, R^2 = H, R^3 = Br, 46%



3ao, 74%



3ap, 39%



3aq, 62%

[a]Reaction conditions: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol. 1.0 equiv), and $(NH_4)_2S_2O_8$ (0.6 mmol, 2.0 equiv) in DMSO (2.0 mL) at 80 °C for 8 h under an Ar atmosphere. [b]Isolated yield.

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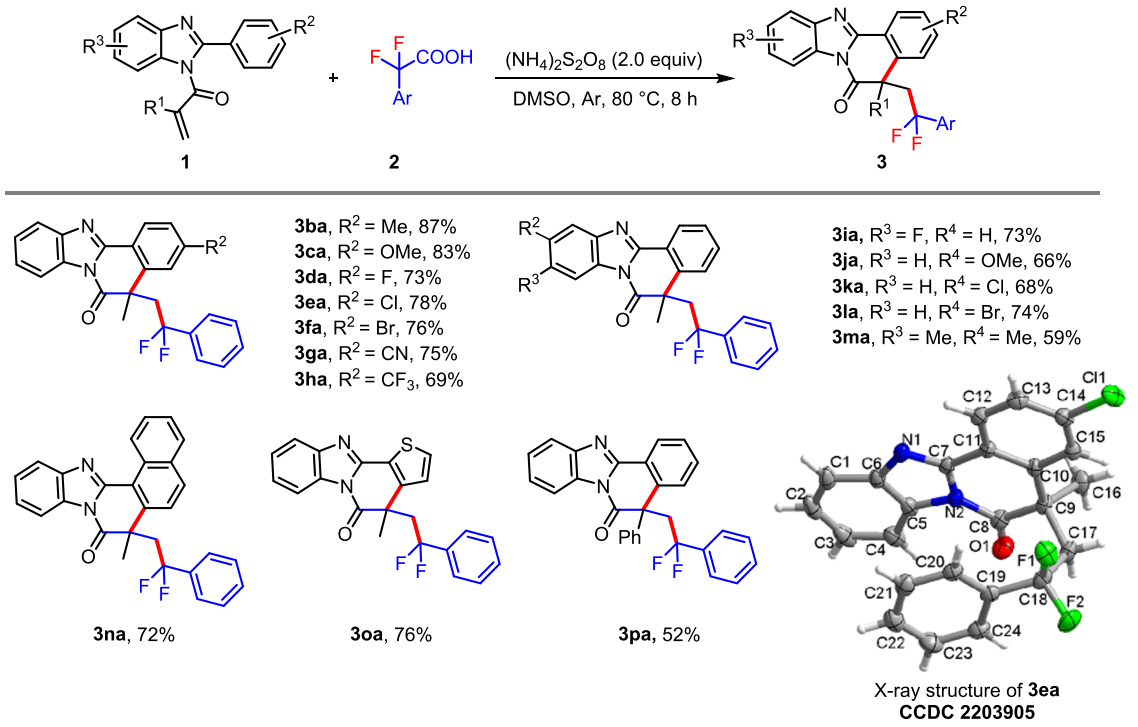
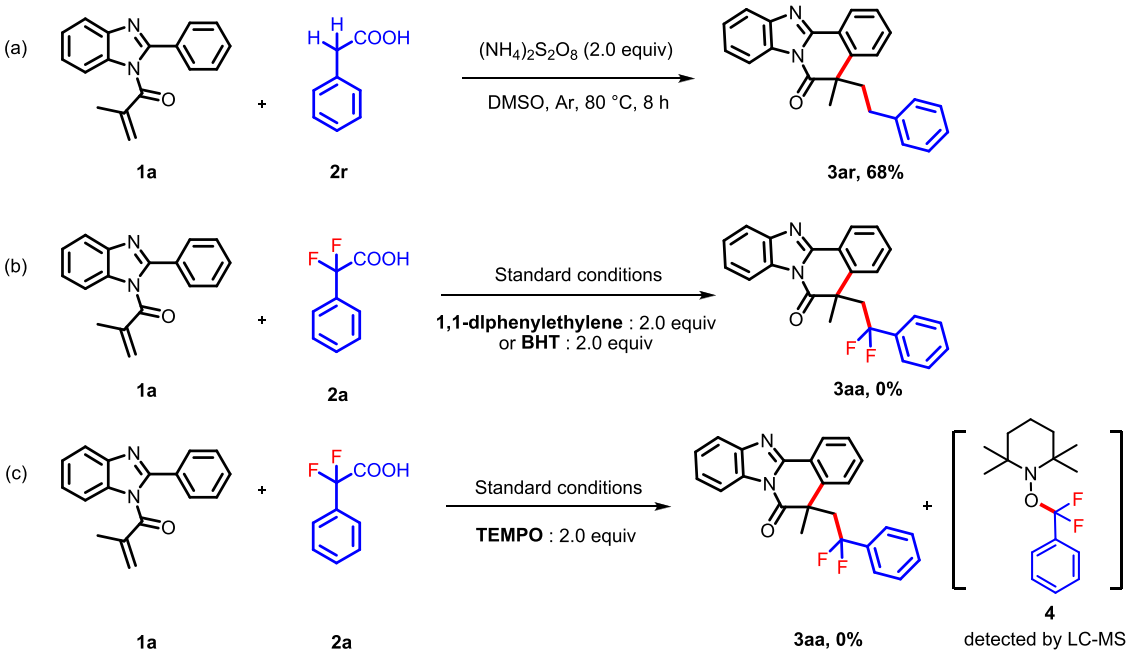
Scheme 3. Substrate Scope with 2-Arylbenzoimidazoles[a,b]



[a]Reaction conditions: **1a** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), and $(NH_4)_2S_2O_8$ (0.6 mmol, 2.0 equiv) in DMSO (2.0 mL) at 80 °C for 8 h under an Ar atmosphere. [b]Isolated yield.

Scheme 4. Control Experiments[a,b]



[a]Reaction conditions: (a) **1a** (0.3 mmol, 1.5 equiv), **2r** (0.2 mmol, 1.0 equiv), and $(NH_4)_2S_2O_8$ (0.6 mmol, 2.0 equiv) in DMSO (2.0 mL) at 80 °C for 8 h under an Ar atmosphere. (b) **2r** was changed to **2a**, 1,1-dlphenylethylene (2.0 equiv) or BHT (2.0 equiv) was used. (c) **2r** was changed to **2a**, TEMPO (2.0 equiv) was used. [b]Isolated yield.

with **2a** to give the corresponding target products (**3ba**-**3ma**) in good yields (59−87%). Benzimidazole derivatives with an electron-donating group or an electron-withdrawing group at different positions of the 2-phenyl moiety in substrate **1** readily could react, providing the desired benzimidazo[2,1-*a*]-isoquinolin-6(5*H*)-ones **3** in moderate to good yields. This transformation also proceeded well when the ortho-substituted or meta-substituted 2-phenyl ring benzimidazole derivatives were employed, affording the corresponding products (**3ia**−**3la**, 66−74%) in a relatively high yield. The results showed

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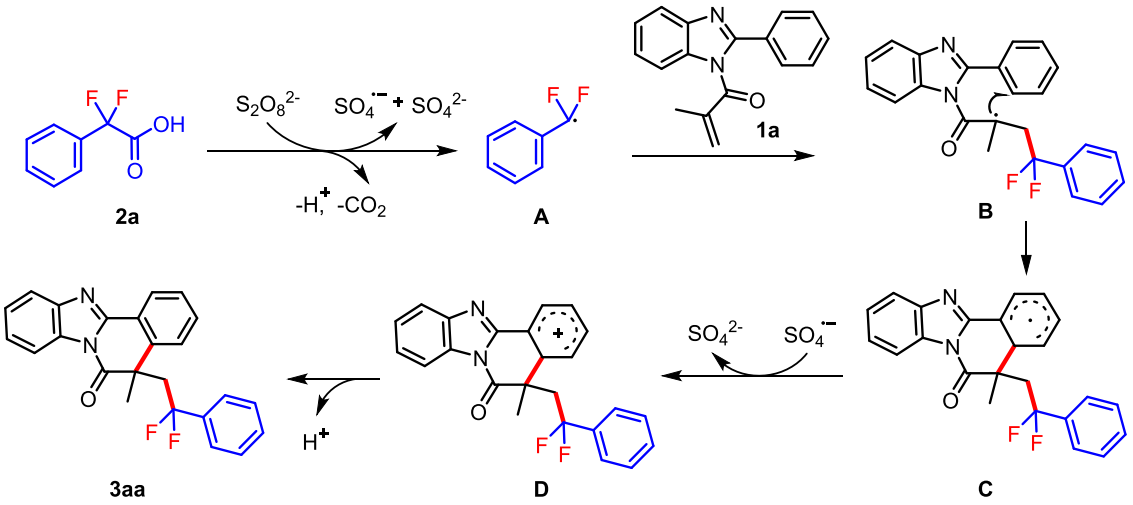
Scheme 5. Plausible Mechanism of Reaction between 1a and 2a[a]



[a]Reaction conditions: (a) 1a (0.3 mmol, 1.5 equiv), 2a (0.2 mmol, 1.0 equiv), and $(NH_4)_2S_2O_8$ (0.6 mmol, 2.0 equiv) in DMSO (2.0 mL) at 80 °C for 8 h under an Ar atmosphere. A, B were the radicals produced in the reaction. C, D were the intermediates produced in the reaction. 3aa was the desired product.

that the reaction was not affected by the steric hindrance of the substrate. When the benzene ring of benzimidazole was substituted with 4,5-di(Me), it could also react well to give the corresponding products (**3ma**) in satisfactory yield (59%). To our great delight, it could also accomplish this transformation in the presence of a naphthyl group or a thienyl group on the 2-phenyl ring of benzimidazole derivatives, the cyclization products were isolated in good yields (**3na**, **3oa**). Specifically, when *N*-phenylacryloyl-2-phenylbenzoimidazole **1p** was employed as the corresponding product **3pa** was obtained in 52% yield. Among all of the new synthetic products, the structure of **3ea** was further confirmed by X-ray crystallography.

To gain further insight into the reaction mechanism, several control experiments were carried out. First, the oxidative decarboxylation reaction of *N*-methacryloyl-2-phenylbenzoimi dazole **1a** with phenylacetic acid **2r** could proceed under standard conditions (Scheme 4a). These results indicate that the CF_2 group of α,α-difluorophenylacetic acid has little influence on the transformation process, and corresponding products **3ar** can be obtained in a relatively high yield (68%). When the radical scavengers 2,2,6,6-tetramethylpiperidin-1-yl-oxidanyl (TEMPO) and 2,6-di-*tert*-butyl-butyl-4-methylphenol (BHT) were added to the optimized reactions of **1a** and **2a**, respectively, the desired product **3aa** was not observed (Scheme 4b,c). Instead, the generation of a TEMPO adduct **4** was detected by liquid chromatography−mass spectrometry (LC-MS). This result indicates that a radical pathway might be engaged in.

Based on the above experimental results as well as previous literature reports,[22] a plausible reaction pathway is proposed (Scheme 5). Initially, in the presence of $(NH_4)_2S_2O_8$, a radical intermediate **A** is generated from α,α-difluorophenylacetic acid **2a** *via* a decarboxylation process, with the release of carbon dioxide. Next, the intermediate **A** attacks the alkenyl moiety in substrate **1a** to deliver a more stable tertiary radical **B**. Subsequently, intramolecular cyclization of radical **B** occurs quickly to form intermediate **C**. Finally, intermediate **C** undergoes SET oxidation to produce the corresponding carbocation **D**, followed by deprotonation to give the product **3aa**.

CONCLUSIONS

In summary, we developed an efficient and simple synthesis scheme for the construction of difluoroarymethyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones through direct decarboxylative coupling of 2-arylbenzoimidazoles with α,α-difluorophenylacetic acid. Remarkably, the merits of this method make this reaction particularly beneficial for further transformation with the wide reactant scope under the transition-metal-free and base-free conditions. Moreover, mechanistic studies confirmed that difluoroarylmethylation occurs *via* a radical mechanism. Further synthetic application of this strategy is ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and were used as received. All air- and moisture-sensitive manipulations were performed using oven-dried glassware (120 °C for a minimum of 15 h), including standard Schlenk techniques under an atmosphere of argon. Flash column chromatography was performed using 100−200 mesh silica gel. Analytical thin-layer chromatography was performed using glass plates precoated with silica gel (GF254). Visualization was done by ultraviolet fluorescence (λ = 254 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. Melting points were measured using a WC-1 microscopic apparatus and were uncorrected. X-ray analysis was performed with a single-crystal X-ray diffractometer (Gemini E) purchased from Agilent. The mass spectra were indicated by GC-MS (Thermo Fisher Scientific DSQ II). High-resolution mass spectrometry (HRMS) data were obtained on an Agilent Technologies 1290−6540 UHPLC/accurate mass quadrupole time-of flight (Q-TOF) LC/MS using ESI as an ion source. Measured values were reported to 4 decimal places of the calculated value.

General Procedure for the Construction of 3aa−3aq and 3ba−3oa. To a 25 mL oven-dried Schlenk tube containing a magneton were added **1** (0.3 mmol, 1.5 equiv),

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2 (0.2 mmol, 1.0 equiv), $(NH_4)_2S_2O_8$ (0.6 mmol, 3.0 equiv), DMSO (2mL). Then, the mixture was charged with Ar and stirred at 80 °C. After 8 h, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1∼5/1) to get the desired products **3aa**−**3ar** and **3ba**−**3oa**.

*5-(2,2-Difluoro-2-phenylethyl)-5-methylbenzo[4,5]-imidazo[2,1-a]isoquinolin-6(5H)-one (**3aa**).* White solid (yield 72.97 mg, 94%), mp 102−103 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.50−8.43 (m, 1H), 8.27−8.20 (dd, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.48−7.33 (m, 5H), 7.08−6.96 (m, 5H), 3.58−3.41 (m, 1H), 3.02−2.88 (m, 1H), 1.66 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.4, 149.2, 143.6, 139.2, 135.3 (t, J_{C-F} = 26.3 Hz), 131.1, 130.9, 129.3 (t, J_{C-F} = 2.0 Hz), 127.7, 127.5, 126.8, 125.5, 125.4, 125.1, 124.4 (t, J_{C-F} = 6.1 Hz), 123.5, 122.1, 121.1, 119.4, 118.6, 115.4, 49.2 (t, J_{C-F} = 27.3 Hz), 45.3 (t, J_{C-F} = 3.0 Hz), 30.9. ^{19}F NMR (376 MHz, chloroform-*d*) δ −89.29 (d, J = 248.5 Hz, 1F), −90.76 (d, J = 248.5 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{18}F_2N_2O$ $[M + H]^+$ 389.1460, found: 389.1462.

*5-(2,2-Difluoro-2-(p-tolyl)ethyl)-5-methylbenzo[4,5]-imidazo[2,1-a]isoquinolin-6(5H)-one (**3ab**).* White solid (yield 63.54 mg, 79%), mp 156−157 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.52−8.44 (m, 1H), 8.17−8.12 (m, 1H), 7.82−7.75 (m, 1H), 7.59−7.47 (m, 3H), 7.44−7.34 (m, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.0 Hz, 2H), 3.57−3.42 (m, 1H), 3.09−2.97 (m, 1H), 1.87 (s, 3H), 1.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.5, 149.3, 143.5, 140.0, 139.3, 131.7 (t, J_{C-F} = 26.3 Hz), 131.2, 131.0, 128.3, 127.7, 127.2, 125.5, 125.2, 124.7 (q, J_{C-F} = 6.1 Hz), 123.8, 122.3, 121.3, 119.4, 118.9, 115.45, 49.4 (t, J_{C-F} = 26.3 Hz), 49.1, 45.5 (d, J_{C-F} = 5.1Hz), 31.4, 20.5. ^{19}F NMR (376 MHz, chloroform-*d*) δ −84.89 (d, J = 247.8 Hz, 1F), −92.82 (d, J = 247.8 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O$ $[M + H]^+$ 403.1617, found: 403.1618.

*5-(2-(4-Ethylphenyl)-2,2-difluoroethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ac**).* White solid (yield 75.74 mg, 91%), mp 130−131 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.48−8.44 (m, 1H), 8.21−8.08 (m, 1H), 7.84−7.72 (m, 1H), 7.55−7.45 (m, 3H), 7.42−7.33 (m, 2H), 6.91 (d, J = 8.0Hz, 2H), 6.82 (d, J = 8.0Hz, 2H), 3.59−3.45 (m, 1H), 3.12−2.94 (m, 1H), 2.22 (q, J = 8.0 Hz, 2H), 1.69 (s, 3H), 0.93 (t, J = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.4, 149.2, 146.0 (t, J_{C-F} = 2.0 Hz), 143.5, 139.2, 132.1 (t, J_{C-F} = 26.3 Hz), 131.1, 130.9, 127.6, 127.1 (d, J_{C-F} = 8.1 Hz), 125.5 (t, J_{C-F} = 5.1 Hz), 125.1, 124.7 (t, J_{C-F} = 6.1 Hz), 123.7, 122.2, 121.3 (d, J_{C-F} = 2.0 Hz), 119.4, 118.9, 115.4, 49.2 (q, J_{C-F} = 27.3 Hz), 45.5 (d, J_{C-F} = 5.1 Hz), 31.4, 27.8, 14.5. ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.64 (d, J = 247.8 Hz, 1F), −91.68 (d, J = 247.4 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{26}H_{22}F_2N_2O$ $[M + H]^+$ 417.1773, found: 417.1769.

*5-(2,2-Difluoro-2-(4-methoxyphenyl)ethyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ad**).* White solid (yield 70.25 mg, 84%), mp 141−142 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.47−8.44 (m, 1H), 8.16−8.11 (m, 1H), 7.80−7.74 (m, 1H), 7.55−7.45 (m, 3H), 7.44−7.34 (m, 2H), 6.89 (d, J = 8.0 Hz, 2H), 6.43 (d, J = 8.0 Hz, 2H), 3.57−3.40 (m, 1H), 3.38 (s, 3H), 3.08−2.88 (m, 1H), 1.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.6, 160.5, 149.5, 143.8, 139.6, 131.3 (d, J_{C-F} = 16.2 Hz), 127.9, 127.4, 127.3, 127.0, 126.8, 126.5 (t, J_{C-F} = 6.1 Hz), 125.7, 125.4, 124.0, 122.5, 121.6, 119.6, 119.1, 115.7, 113.2, 54.9, 49.7 (dd, J_{C-F} = 26.3Hz, 4.0 Hz), 45.7 (d, J_{C-F} = 5.1 Hz), 31.5. ^{19}F NMR (376 MHz, chloroform-*d*) δ −83.63 (d, J = 247.8 Hz, 1F), −91.86 (d, J = 247.8 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O_2$ $[M + H]^+$ 419.1566, found: 419.1567.

*5-(2,2-Difluoro-2-(4-fluorophenyl)ethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ae**).* White solid (yield 60.92 mg, 75%), mp 118−119 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.49−8.43 (m, 1H), 8.27−8.14 (m, 1H), 7.84−7.78 (m, 1H), 7.53−7.37 (m, 5H), 7.08−7.00 (m, 2H), 6.74 (t, J = 8.0 Hz, 2H), 3.57−3.44 (m, 1H), 3.07−2.94 (m, 1H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.4, 164.3, 161.8, 149.2, 143.6, 139.1, 131.0 (d, J_{C-F} = 2.0 Hz), 127.8, 126.9 (t, J_{C-F} = 3.0 Hz), 126.8 (q, J_{C-F} = 3.0 Hz), 126.6, 125.7 (t, J_{C-F} = 11.1 Hz), 125.3, 123.3, 122.2, 120.8, 119.5, 118.4, 115.3, 115.0, 114.8, 49.4 (t, J_{C-F} = 28.3 Hz), 45.4 (q, J_{C-F} = 2.0 Hz), 31.1 ^{19}F NMR (376 MHz, chloroform-*d*) δ −87.93 (d, J = 250.0 Hz, 1F), −90.13 (d, J = 250.9 Hz, 1F), −110.75 (s, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}F_3N_2O$ $[M + H]^+$ 407.1366, found: 407.1368.

*5-(2-(4-Bromophenyl)-2,2-difluoroethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3af**).* White solid (yield 71.77 mg, 77%), mp 146−147 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.48−8.43 (m, 1H), 8.21−8.15 (m, 1H), 7.84−7.77 (m, 1H), 7.50−7.49 (m, 2H), 7.48−7.40 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 3.55−3.42 (m, 1H), 3.06−2.94 (m, 1H), 1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.4, 149.1, 143.6, 139.0, 134.2 (t, J_{C-F} = 26.3 Hz), 131.1,131.0, 127.8, 127.0, 126.3 (t, J_{C-F} = 6.1 Hz), 125.6, 125.5, 124.3 (t, J_{C-F} = 2.0 Hz), 123.2, 122.2, 120.8, 119.6, 118.4, 115.3, 49.2 (q, J_{C-F} = 27.3 Hz), 45.4 (q, J_{C-F} = 2.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-*d*) δ −88.25 (d, J = 250.42 Hz, 1F), −91.67 (d, J = 250.42 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}BrF_2N_2O$ $[M + H]^+$ 467.0565, found: 467.0564.

*4-(1,1-Difluoro-2-(5-methyl-6-oxo-5,6-dihydrobenzo[4,5]-imidazo[2,1-a]isoquinolin-5-yl)ethyl)benzonitrile (**3ag**).* White solid (yield 46.27 mg, 56%), mp 169−170 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.50−8.43 (m, 1H), 8.18−8.12 (m, 1H), 7.85−7.80 (m, 1H), 7.52−7.40 (m, 5H), 7.34 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 3.50 (m, 1H), 3.03 (m, 1H), 1.73 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.5, 149.2, 143.8, 139.9 (t, J_{C-F} = 26.3 Hz), 139.0, 131.8, 131.4, 131.1, 128.3, 127.1, 126.4, 126.0, 125.9, 125.7 (t, J_{C-F} = 6.1 Hz), 123.0, 122.5, 120.5, 120.0, 118.1, 117.5, 115.5, 113.8 (d, J_{C-F} = 2.0 Hz), 49.3 (t, J_{C-F} = 26.3 Hz), 45.6 (q, J_{C-F} = 2.0 Hz), 31.3. ^{19}F NMR (376 MHz, chloroform-*d*) δ −89.18 (d, J = 253.0 Hz, 1F),

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−92.46 (d, J = 250.4 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{17}F_2N_3O$ $[M + H]^+$ 414.1413, found: 414.1427.

*5-(2-([1,1′-Biphenyl]-4-yl)-2,2-difluoroethyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ah**).* White solid (yield 76.12 mg, 82%), mp 186−187 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.50−8.44 (m, 1H), 8.19−8.14 (m, 1H), 7.78−7.72 (m, 1H), 7.55−7.47 (m, 3H), 7.37−7.28 (m, 5H), 7.24−7.16 (m, 4H), 7.08 (d, J = 8.0 Hz, 2H), 3.66−3.52 (m, 1H), 3.15−3.04 (m, 1H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.7, 149.5, 143.8, 142.9 (d, J_{C-F} = 2.0 Hz), 139.8, 139.5, 134.0 (t, J_{C-F} = 27.3 Hz), 131.3 (d, J_{C-F} = 8.1 Hz), 128.6, 128.0, 127.7, 127.4, 127.1, 126.7, 125.8 (d, J_{C-F} = 2.0 Hz), 125.6, 125.4 (t, J_{C-F} = 7.1 Hz), 124.0, 122.6, 121.5, 119.8, 119.1, 115.6, 49.5 (t, J_{C-F} = 26.3 Hz), 45.8 (d, J_{C-F} = 4.0 Hz), 31.7. ^{19}F NMR (376 MHz, chloroform-d) δ −86.88 (d, J = 248.5 Hz, 1F), −91.20 (d, J = 248.9 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{30}H_{22}F_2N_2O$ $[M + H]^+$ 465.1773, found: 465.1779.

*5-(2,2-Difluoro-2-(m-tolyl)ethyl)-5-methylbenzo[4,5]-imidazo[2,1-a]isoquinolin-6(5H)-one (**3ai**).* Yellow oily liquid (yield 61.93 mg, 77%), purified by column chromatography with petroleum ether/ethyl acetate (8:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.55−8.43 (m, 1H), 8.26−8.13 (m, 1H), 7.88−7.72 (m, 1H), 7.56−7.33 (m, 5H), 6.93 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 3.59−3.42 (m, 1H), 3.10−2.92 (m, 1H), 2.07 (s, 3H), 1.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.5, 149.3, 143.6, 139.3, 137.6, 135. 0(t, J_{C-F} = 25.3 Hz), 131.2, 130.9, 130.2 (t, J_{C-F} = 2.0 Hz), 127.7 (t, J_{C-F} = 4.0 Hz), 127.0, 125.5 (d, J_{C-F} = 14.1 Hz), 125.2, 125.2 (t, J_{C-F} = 6.1Hz), 123.7, 122.3, 121.9 (t, J_{C-F} = 6.1 Hz), 121.2, 119.4, 118.8, 115.5, 49.4 (q, J_{C-F} = 28.3 Hz), 45.5 (q, J_{C-F} = 2.0 Hz), 31.24, 20.8. ^{19}F NMR (376 MHz, chloroform-d) δ −87.43 (d, J = 247.8 Hz, 1F), −91.4 (d, J = 247.4 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O$ $[M + H]^+$ 403.1617, found: 403.1617.

*5-(2,2-Difluoro-2-(3-methoxyphenyl)ethyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3aj**).* White solid (yield 66.07 mg, 79%), mp 102−103 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.54−8.43 (m, 1H), 8.27−8.18 (m, 1H), 7.84−7.72 (m, 1H), 7.58−7.32 (m, 5H), 6.96 (t, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.75−6.42 (m, 2H), 3.5 (s, 3H), 3.57−3.42 (m, 1H), 3.11−2.91 (m, 1H), 1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.5, 158.8, 149.3, 143.6, 139.3, 136.6 (t, J_{C-F} = 26.3 Hz), 131.1 (d, J_{C-F} = 18.2 Hz), 129.0, 127.7, 127.0, 125.6 (d, J_{C-F} = 6.1 Hz), 125.2, 123.4, 122.3, 121.0, 119.4, 118.5, 116.9 (t, J_{C-F} = 6.1 Hz), 115.5, 115.0 (d, J_{C-F} = 2.0 Hz), 110.2 (t, J_{C-F} = 7.1 Hz), 54.8, 49.3 (t, J_{C-F} = 28.3 Hz), 45.5 (q, J_{C-F} = 2.0 Hz), 31.2. ^{19}F NMR (376 MHz, chloroform-d) δ −87.84 (d, J = 247.4 Hz, 1F), −91.37 (d, J = 247.8 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O_2$ $[M + H]^+$ 419.1566, found: 419.1564.

*5-(2-(3-Bromophenyl)-2,2-difluoroethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ak**).* Yellow oily liquid (yield 39.15 mg, 42%), purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.52−8.44 (m, 1H), 8.29−8.18 (m, 1H), 7.88−7.76 (m, 1H), 7.59−7.32 (m, 5H), 7.22−7.10 (m, 2H), 7.01−6.88 (m, 2H), 3.57−3.42 (m, 1H), 3.06−2.95 (m, 1H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.7, 149.4, 144.0, 139.2, 137.7 (t, J_{C-F} = 26.3 Hz), 132.9 131.4, 131.3, 129.7, 128.3 (t, J_{C-F} = 7.1 Hz), 127.2, 126.1, 126.0, 125.7, 123.6 (t, J_{C-F} = 6.1 Hz), 123.1, 122.6, 122.4, 120.6, 119.9, 115.8, 49.5 (t, J_{C-F} = 27.3 Hz), 45.7 (t, J_{C-F} = 3.0 Hz), 31.4. ^{19}F NMR (376 MHz, chloroform-d) δ −89.60 (d, J = 250.8 Hz, 1F), −90.64 (d, J = 250.4 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}BrF_2N_2O$ $[M + H]^+$ 467.0565, found: 467.0567.

*5-(2,2-Difluoro-2-(o-tolyl)ethyl)-5-methylbenzo[4,5]-imidazo[2,1-a]isoquinolin-6(5H)-one (**3al**).* White solid (yield 57.10 mg, 71%), mp 126−127 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.52−8.43 (m, 1H), 8.21−8.16 (m, 1H), 7.82−7.75 (m, 1H), 7.54−7.45 (m, 3H), 7.44−7.32 (m, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.92−6.81 (m, 1H), 6.78−6.68 (m, 2H), 3.64−3.344 (m, 1H), 3.12−2.83 (m, 1H), 2.37 (s, 3H), 1.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.4, 149.5, 143.9, 139.7, 135.6 (d, J_{C-F} = 4.0 Hz), 133.4 (t, J_{C-F} = 24.0 Hz), 131.4 (d, J_{C-F} = 31.3 Hz), 129.6, 127.9, 127.1, 125.8 (d, J_{C-F} = 3.0 Hz), 125.3 (d, J_{C-F} = 3.0 Hz), 125.1 (t, J_{C-F} = 9.1 Hz), 124.5, 122.5, 122.1, 119.67, 115.6, 48.3 (d, J_{C-F} = 27.3 Hz), 45.6 (d, J_{C-F} = 4.0 Hz), 31.5, 20.0 (t, J_{C-F} = 3.0 Hz). ^{19}F NMR (376 MHz, chloroform-d) δ −86.91 (d, J = 251.9 Hz, 1F), −89.30 (d, J = 251.9 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O$ $[M + H]^+$ 403.1617, found: 403.1615.

*5-(2,2-Difluoro-2-(2-methoxyphenyl)ethyl)-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3am**).* White solid (yield 61.89 mg, 73%), mp 159−160 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.41−8.32 (m, 1H), 8.21−8.17 (m, 1H), 7.81−7.76 (m, 1H), 7.42−7.32 (m, 5H), 6.99−6.84 (m, 1H), 6.67−6.52 (m, 2H), 6.46−6.32 (m, 1H), 3.86 (s, 3H), 3.77−3.52 (m, 1H), 3.34−3.12 (m, 1H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.7, 156.6 (t, J_{C-F} = 5.0 Hz), 149.7, 143.9, 139.8, 131.4, 131.0, 127.9, 127.2, 125.8 (t, J_{C-F} = 9.1 Hz), 125.6, 125.4, 123.2 (q, J_{C-F} = 9.1 Hz), 122.8, 122.6, 120.7, 120.1, 119.7, 118.3, 115.8, 111.3, 55.7, 47.7 (q, J_{C-F} = 26.3 Hz), 45.7 (q, J_{C-F} = 4.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-d) δ −88.02 (d, J = 253.8 Hz, 1F), −88.87 (d, J = 253.0 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O_2$ $[M + H]^+$ 419.1566, found: 419.1569.

*5-(2-(2-Bromophenyl)-2,2-difluoroethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3an**).* Colorless oily liquid (yield 42.88 mg, 46%), purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.54−8.37 (m, 1H), 8.32−8.21 (m, 1H), 7.88−7.77 (m, 1H), 7.49−7.32 (m, 6H), 6.99−6.72 (m, 3H), 3.77−3.54 (m, 1H), 3.49−3.33 (m, 1H), 1.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.4, 158.8, 149.2, 143.6, 139.2, 136.5(t, J_{C-F} = 26.3 Hz), 134.2, 130.9 (t, J_{C-F} = 19.2 Hz), 128.9, 127.6, 126.9, 125.5 (q, J_{C-F} = 11.1 Hz), 125.1, 123.3, 122.2, 120.9, 119.4 (d, J_{C-F} = 3.0 Hz), 118.5, 116.8(t, J_{C-F} = 6.1 Hz), 115.4 (d, J_{C-F} = 11.1 Hz), 114.9 (t, J_{C-F} = 2.0 Hz), 110.1 (t, J_{C-F} = 7.1 Hz), 49.2 (t, J_{C-F} = 27.3 Hz), 45.4 (q, J_{C-F} = 2.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-d) δ −87.25 (d, J = 255.7 Hz, 1F), −91.09 (d, J = 255.7 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}BrF_2N_2O$ $[M + H]^+$ 467.0565, found: 467.0589.

*5-(2,2-Difluoro-2-(naphthalen-1-yl)ethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ao**).* White solid

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(yield 62.92 mg, 74%), mp 115−116 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.45−8.42 (m, 1H), 8.09 (d, J = 8.0Hz, 1H), 8.04−7.93 (m, 1H), 7.84−7.76 (m, 1H), 7.69−7.66 (m, 1H), 7.62−7.56 (m, 1H), 7.51−7.28 (m, 8H), 6.97 (t, J = 1.2 Hz, 1H), 3.86−3.74 (m, 1H), 3.34−3.12 (m, 1H), 1.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.0, 149.2, 143.5, 139.1, 133.5, 131.0, 130.7 (t, J_{C-F} = 3.0 Hz), 130.4, 130.2, 128.8(t, J_{C-F} = 3.0 Hz), 128.6, 127.6, 126.7 (d, J_{C-F} = 8.1 Hz), 125.6 (t, J_{C-F} = 7.1 Hz), 125.4, 125.1, 124.3, 124.1 (t, J_{C-F} = 4.0 Hz), 123.8, 123.5 (t, J_{C-F} = 10.1 Hz), 122.1, 121.8, 119.3, 115.4, 48.7 (t, J_{C-F} = 26.3 Hz), 45.4 (t, J_{C-F} = 3.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-*d*) δ −85.24 (d, J = 253.4 Hz, 1F), −87.57 (d, J = 253.4 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{28}H_{20}F_2N_2O$ [M + H]$^+$ 439.1617, found: 439.1622.

*5-(2,2-Difluoro-2-(thiophen-2-yl)ethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ap**).* Yellow oily liquid (yield 30.74 mg, 39%), purified by column chromatography with petroleum ether/ethyl acetate (6:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.51−8.42 (m, 1H), 8.35−8.25 (m, 1H), 7.84−7.77 (m, 1H), 7.53−7.37 (m, 5H), 7.16−7.11 (m, 1H), 6.90−6.84 (m, 1H), 6.78−6.62 (m, 1H), 3.72−3.54 (m, 1H), 3.19−3.02 (m, 1H), 1.75 (s, 3H).^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.7, 149.6, 144.0, 139.5, 138.0 (t, J_{C-F} = 31.3 Hz), 131.3 (t, J_{C-F} = 26.3 Hz), 127.9, 127.2 (t, J_{C-F} = 2.0 Hz), 127.0, 126.6 (t, J_{C-F} = 6.1 Hz), 125.9 (d, J_{C-F} = 5.1 Hz), 125.5, 122.4, 122.1, 119.7 (d, J_{C-F} = 4.0 Hz), 117.3, 115.7, 49.7 (t, J_{C-F} = 26.3 Hz), 45.7 (t, J_{C-F} = 2.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-*d*) δ −79.30 (dd, J = 312.1 Hz, 255.7 Hz, 1F), −84.28 (dd, J = 627.9 Hz, 255.7 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{22}H_{16}F_2N_2OS$ [M + H]$^+$ 395.1024, found: 395.1024.

*(S)-5-(2,2-Difluoropropyl)-5-methylbenzo[4,5]imidazo-[2,1-a]isoquinolin-6(5H)-one (**3aq**).* Colorless oily liquid (yield 40.47 mg, 62%), purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.58−8.48 (m, 1H), 8.40−8.31 (m, 1H), 7.87−7.78 (m, 1H), 7.59−7.40 (m, 5H), 3.23 (m, 1H), 2.82−2.56 (m, 1H), 1.72 (s, 3H), 1.33 (t, J = 18.8 Hz, 3H). ^{13}C{1H} NMR (101 MHz, chloroform-*d*) δ 172.18, 149.62, 144.08, 140.0, 131.4 (d, J_{C-F} = 23.2 Hz), 127.9, 126.7, 126.0, 125.9, 125.5, 124.9, 122.5(d, J_{C-F} = 17.2 Hz), 120.2, 119.8, 115.7, 48.3 (t, J_{C-F} = 24.2 Hz), 45.6 (t, J_{C-F} = 3.0 Hz), 31.0, 24.7 (t, J_{C-F} = 27.3 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −86.2 (d, J = 7.5 Hz, 2F). HRMS (ESI) m/z: calcd for $C_{19}H_{16}F_2N_2O$ [M + H]$^+$ 327.3541, found: 327.3546.

*(S)-5-Methyl-5-phenethylbenzo[4,5]imidazo[2,1-a]-isoquinolin-6(5H)-one (**3ar**).* Yellow oily liquid (yield 47.93 mg, 68%), purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.57−8.48 (m, 1H), 8.35−8.28 (m, 1H), 7.84−7.80 (m, 1H), 7.67−7.59 (m, 1H), 7.55−7.49 (m, 2H), 7.48−7.32 (m, 2H), 7.16−7.05 (m, 2H), 7.03−6.97 (m, 1H), 6.95−6.89 (m, 2H), 2.86−2.75 (m, 1H), 2.35−2.16 (m, 3H), 1.74 (s, 3H). ^{13}C{1H} NMR (101 MHz, chloroform-*d*) δ 172.9, 149.7, 144.0, 141.3, 140.2, 132.0, 131.3, 128.2, 128.1, 127.8, 126.0, 126.0, 126.0, 125.8, 125.5, 123.2, 119.7, 115.7, 49.2, 44.2, 31.6, 29.4.

*5-(2,2-Difluoro-2-phenylethyl)-3,5-dimethylbenzo[4,5]-imidazo[2,1-a]isoquinolin-6(5H)-one (**3ba**).* White solid (yield 69.97 mg, 87%), mp 132−133 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.32 (d, J = 8.0 Hz, 1H), 8.23−8.20 (m, 1H), 7.81−7.75 (m, 1H), 7.44−7.38 (m, 2H), 7.28−7.24(m, 1H), 7.16 (s, 1H), 7.08−7.02 (m, 5H), 3.58−3.47 (m, 1H), 3.06−2.96 (m, 1H), 2.38 (s, 3H), 1.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.7, 149.5, 143.7, 141.5, 139.1, 135.5 (t, J_{C-F} = 26.3 Hz), 131.1, 129.3 (t, J_{C-F} = 2.0 Hz), 128.8, 127.7, 127.4, 125.5, 124.9, 124.4 (t, J_{C-F} = 6.1Hz), 123.6, 121.1, 119.6, 119.2, 118.7, 115.4, 49.2 (t, J_{C-F} = 28.3 Hz), 45.4 (t, J_{C-F} = 3.0 Hz), 31.2, 21.6. ^{19}F NMR (376 MHz, chloroform-*d*) δ −89.12 (d, J = 249.7 Hz, 1F), −90.75 (d, J = 249.7 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O$ [M + H]$^+$ 403.1617, found: 403.1625.

*5-(2,2-Difluoro-2-phenylethyl)-3-methoxy-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ca**).* Colorless oily liquid (yield 69.41 mg, 83%), purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.38 (d, J = 8.0 Hz, 1H), 8.22−8.17 (m, 1H), 7.78−7.72 (m, 1H), 7.77−7.74 (m, 2H), 7.10−6.98 (m, 6H), 6.87 (d, J = 4.0 Hz, 1H), 3.86 (s, 3H), 3.59−3.46 (m, 1H), 3.03−2.92 (m, 1H), 1.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.5, 161.8, 149.4, 143.7, 141.2, 135.5 (t, J_{C-F} = 26.3 Hz), 131.0, 129.3 (t, J_{C-F} = 2.0 Hz), 127.8, 127.5, 125.5, 124.7, 124.4 (t, J_{C-F} = 6.1 Hz), 123.5, 121.1, 119.0, 118.7, 115.3, 115.2, 113.6, 112.5, 55.2, 49.4 (t, J_{C-F} = 27.3 Hz), 45.6(t, J_{C-F} = 3.0 Hz), 31.3. ^{19}F NMR (376 MHz, chloroform-*d*) δ −89.62 (d, J = 248.9 Hz, 1F), −90.50 (d, J = 249.3 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O_2$ [M + H]$^+$ 419.1566, found: 419.1566.

*5-(2,2-Difluoro-2-phenylethyl)-3-fluoro-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3da**).* White solid (yield 59.29 mg, 73%), mp 134−135 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.46 (m, 1H), 8.25−8.18 (m, 1H), 7.81−7.73 (m, 1H), 7.46−7.33 (m, 2H), 7.22−7.15 (m, 1H), 7.14−7.02 (m, 6H), 3.61−3.44 (m, 1H), 3.02−2.86 (m, 1H), 1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.30, 165.9, 163.4, 148.9, 143.9, 142.4 (d, J_{C-F} = 8.1 Hz), 135.7 (t, J_{C-F} = 26.3 Hz), 131.4, 130.0 (t, J_{C-F} = 2.0 Hz), 128.4 (t, J_{C-F} = 9.1 Hz), 126.1, 125.6, 124.8 (t, J_{C-F} = 6.1Hz), 123.8, 121.4, 119.8, 119.1 (d, J_{C-F} = 2.0 Hz), 118.9, 116.3, 116.1, 115.8, 114.3, 114.1, 49.8 (t, J_{C-F} = 27.3 Hz), 46.0 (q, J_{C-F} = 2.0 Hz), 31.4. ^{19}F NMR (376 MHz, chloroform-*d*) δ −90.12 (d, J = 248.9 Hz, 1F), −90.98 (d, J = 249.3 Hz, 1F), −107.02 (s, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}F_3N_2O$ [M + H]$^+$ 407.1366, found: 407.1366.

*3-Chloro-5-(2,2-difluoro-2-phenylethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ea**).* White solid (yield 62.42 mg, 78%), mp 136−137 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.38 (d, J = 8.0 Hz, 1H), 8.26−8.20 (m, 1H), 7.82−7.76 (m, 1H), 7.47−7.36 (m, 4H), 7.15−7.02 (m, 5H), 3.59−3.45 (m, 1H), 3.01−2.88(m, 1H), 1.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.4, 149.0, 144.2, 141.5, 137.9, 135.9(t, J_{C-F} = 25.3 Hz), 131.7, 130.2 (t, J_{C-F} = 2.0 Hz), 128.9, 128.5, 127.8, 127.6, 126.4, 126.1, 125.0 (t, J_{C-F} = 6.1Hz), 124.1, 121.6 (d, J_{C-F} = 15.1Hz), 120.2, 119.2, 116.1, 50.2, 49.9 (t, J_{C-F} = 27.3 Hz), 46.1 (t, J_{C-F} = 3.0 Hz), 31.5. ^{19}F NMR (376 MHz, chloroform-*d*chloroform-*d*) δ −89.58 (d, J = 250.0 Hz,

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1F), −91.02 (d, J = 249.7 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}ClF_2N_2O$ $[M + H]^+$ 423.1070, found: 423.1073.

*3-Bromo-5-(2,2-difluoro-2-phenylethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3fa**).* White solid (yield 70.84 mg, 76%), mp 147−148 °C, purified by column chromatography with petroleum ether/ethyl acetate (8:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.31 (d, J = 12.0 Hz, 1H), 8.26−8.20 (m, 1H), 7.83−7.76 (m, 1H), 8.01−7.56 (m, 1H), 7.53 (d, J = 4.0 Hz, 1H), 7.48−7.38 (m, 2H), 7.14−7.06 (m, 5H), 3.61−3.47 (m, 1H), 8.26−8.20 (m, 1H), 1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 170.8, 148.4, 143.6, 141.0, 135.3 (t, J_{C-F} = 25.3 Hz), 131.1(d, J_{C-F} = 8.1 Hz), 130.1, 129.6 (t, J_{C-F} = 2.0 Hz), 127.9, 127.0, 125.8, 125.5 (t, J_{C-F} = 11.1 Hz), 124.4 (t, J_{C-F} = 6.1 Hz), 123.4, 121.3, 121.0, 119.5, 118.5, 115.5, 49.3 (t, J_{C-F} = 27.3 Hz), 45.4 (t, J_{C-F} = 3.0 Hz), 30.9. ^{19}F NMR (376 MHz, chloroform-d) δ −89.29 (d, J = 250.0 Hz, 1F), −91.25 (d, J = 249.7 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}BrF_2N_2O$ $[M + H]^+$ 467.0565, found: 467.0581.

*5-(2,2-Difluoro-2-phenylethyl)-5-methyl-6-oxo-5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline-3-carbonitrile (**3ga**).* White solid (yield 61.97 mg, 75%), mp 196−197 °C, purified by column chromatography with petroleum ether/ethyl acetate (5:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.55 (d, J = 8.0 Hz, 1H), 8.30−8.25 (m, 1H), 7.87−7.80 (m, 1H), 7.74−7.67 (m, 2H), 7.51−7.43 (m, 2H), 7.18−7.06 (m, 5H), 3.66−3.48 (m, 1H), 3.06−2.72 (m, 1H), 1.74 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 170.3, 147.3, 143.6, 140.1, 135.3 (t, J_{C-F} = 26.3 Hz), 131.2 (d, J_{C-F} = 4.0 Hz), 130.7, 129.8 (t, J_{C-F} = 2.0 Hz), 128.09, 126.3, 126.3, 126.2 (d, J_{C-F} = 3.0 Hz), 124.35(t, J_{C-F} = 6.1 Hz), 123.4, 121.0, 120.1, 118.6, 117.8, 115.7, 114.2, 49.3 (t, J_{C-F} = 27.3 Hz), 45.5 (t, J_{C-F} = 2.0 Hz), 30.7. ^{19}F NMR (376 MHz, chloroform-d) δ −89.58 (d, J = 249.7 Hz, 1F), −91.66 (d, J = 249.7 Hz). HRMS (ESI) m/z: calcd for $C_{25}H_{17}F_2N_3O$ $[M + H]^+$ 414.1413, found: 414.1392.

*5-(2,2-Difluoro-2-phenylethyl)-5-methyl-3-(trifluoromethyl)benzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ha**).* White solid (yield 62.95 mg, 69%), mp 125−126 °C, purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.57 (d, J = 8.0 Hz, 1H), 8.30−8.24 (m, 1H), 7.85−7.81 (m, 1H), 7.71−7.63 (m, 2H), 7.50−7.40 (m, 2H), 7.11−7.03 (m, 5H), 3.64−3.50 (m, 1H), 3.09−2.96 (m, 1H), 1.74 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 170.7, 147.8, 143.6, 139.8, 135.2 (t, J_{C-F} = 26.3 Hz), 132.5 (q, J_{C-F} = 32.3 Hz), 131.2, 129.6 (t, J_{C-F} = 2.0 Hz), 128.0, 126.2, 125.9 (d, J_{C-F} = 2.0 Hz), 125.5, 124.7, 124.5 (t, J_{C-F} = 3.0 Hz), 124.4 (t, J_{C-F} = 6.1 Hz), 124.0 (q, J_{C-F} = 4.0 Hz), 123.4, 122.0, 121.0, 119.9, 118.6, 115.6, 49.3 (t, J_{C-F} = 27.3 Hz), 45.6 (t, J_{C-F} = 3.0 Hz), 30.8. ^{19}F NMR (376 MHz, chloroform-d) δ −62.83 (s, 3F), −89.07 (d, J = 250.4 Hz, 1F), −91.33 (d, J = 250.0 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{17}F_5N_2O$ $[M + H]^+$ 457.1334, found: 457.1343.

*5-(2,2-Difluoro-2-phenylethyl)-1-fluoro-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ia**).* White solid (yield 59.29 mg, 73%), mp 161−162 °C, purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.27−8.19 (m, 1H), 7.95−7.86 (m, 1H), 7.50−7.39 (m, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.25−7.17 (m, 1H), 7.12−7.03 (m, 5H), 3.62−3.44 (m, 1H), 3.10−2.88 (m, 1H), 1.73 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.6, 162.0, 159.4, 146.1 (d, J_{C-F} = 8.1 Hz), 144.6 (d, J_{C-F} = 3.0 Hz), 142.5, 136.0 (t, J_{C-F} = 26.3 Hz), 132.2 (d, J_{C-F} = 9.1 Hz), 130.8 (d, J_{C-F} = 2.0 Hz), 130.2 (t, J_{C-F} = 2.0 Hz), 128.6, 126.39 (d, J_{C-F} = 5.1 Hz), 125.08(t, J_{C-F} = 6.1 Hz), 124.14, 123.58(d, J_{C-F} = 3.0 Hz), 121.7, 120.9, 119.3, 116.1 (t, J_{C-F} = 14.1 Hz), 112.4 (d, J_{C-F} = 10.1 Hz), 50.4(d, J_{C-F} = 27.3 Hz), 46.0 (q, J_{C-F} = 2.0 Hz), 32.02. ^{19}F NMR (376 MHz, chloroform-d) δ −89.53 (d, J = 249.3 Hz, 1F), −91.13 (d, J = 248.9 Hz, 1F), −107.45 (s, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}F_3N_2O$ $[M + H]^+$ 407.1366, found: 407.1367.

*5-(2,2-Difluoro-2-phenylethyl)-9-methoxy-5-methylbenzo[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ja**).* Yellowish oily liquid (yield 55.20 mg, 66%), purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.42−8.36 (m, 1H), 7.78 (d, J = 4.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.48−7.41 (m, 3H), 7.15−7.02 (m, 6H), 3.92 (s, 3H), 3.38−3.42 (m, 1H), 3.09−2.95 (m, 1H),1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 172.0, 158.4, 148.4, 138.9, 138.1, 135.7 (t, J_{C-F} = 26.3 Hz), 132.2, 130.7, 129.64, 127.9 (d, J_{C-F} = 17.2 Hz), 127.1, 125.3, 124.8 (t, J_{C-F} = 7.1 Hz), 123.81, 122.7, 121.4, 120.1, 118.9, 114.8, 99.5, 55.9, 49.6 (t, J_{C-F} = 27.3 Hz), 45.7 (d, J_{C-F} = 3.0 Hz), 31.4. ^{19}F NMR (376 MHz, chloroform-d) δ −89.51 (d, J = 248.9 Hz, 1F), −90.93 (d, J = 248.9 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{25}H_{20}F_2N_2O_2$ $[M + H]^+$ 419.1566, found: 419.1565.

*9-Chloro-5-(2,2-difluoro-2-phenylethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ka**).* White solid (yield 57.41 mg, 68%), mp 148−149 °C, purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.45−8.42 (m, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 4.0 Hz, 1H), 7.57−7.45 (m, 3H), 7.36−7.33 (m, 1H), 7.14−6.99 (m, 5H), 3.57−3.44 (m, 1H), 3.08−2.97 (m, 1H), 1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.4, 150.5, 144.7, 139.5, 135.3 (t, J_{C-F} = 26.3 Hz), 131.4, 131.1, 129.7, 129.5 (t, J_{C-F} = 2.0 Hz), 127.8 (d, J_{C-F} = 3.0 Hz), 127.0, 125.7, 125.3, 124.5 (t, J_{C-F} = 6.1Hz), 123.5, 121.8, 121.1, 119.4, 118.6, 116.1, 49.4 (t, J_{C-F} = 27.3 Hz), 45.5 (t, J_{C-F} = 2.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-d) δ −88.87 (d, J = 248,5 Hz, 1F), −91.36 (d, J = 248.5 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}ClF_2N_2O$ $[M + H]^+$ 423.1070, found: 423.1074.

*9-Bromo-5-(2,2-difluoro-2-phenylethyl)-5-methylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3la**).* White solid (yield 68.98 mg, 74%), mp 104−105 °C, purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-d) δ 8.44−8.42(m, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 4.0 Hz, 1H), 7.56−7.44 (m, 4H), 7.12−7.01 (m, 5H), 3.56−3.43 (m, 1H), 3.08−2.96 (m, 1H), 1.71 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-d) δ 171.4, 150.3, 145.0, 139.5, 135.2 (t, J_{C-F} = 25.3 Hz), 131.4, 130.1, 129.5 (t, J_{C-F} = 2.0 Hz), 128.0, 127.8 (d, J_{C-F} = 2.0 Hz), 127.0, 125.7, 124.5 (t, J_{C-F} = 7.1 Hz), 123.5, 122.4, 121.8, 121.1, 118.6, 116.5, 49.4 (t, J_{C-F} = 28.3 Hz), 45.5 (q, J_{C-F} = 2.0 Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-d) δ −88.91 (d, J = 248.9 Hz, 1F), −91.35 (d, J = 248.9 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{24}H_{17}BrF_2N_2O$ $[M + H]^+$ 467.0565, found: 467.0584.

*5-(2,2-Difluoro-2-phenylethyl)-5,9,10-trimethylbenzo-[4,5]imidazo[2,1-a]isoquinolin-6(5H)-one (**3ma**).* White solid (yield 49.11 mg, 59%), mp 181−182 °C, purified by column chromatography with petroleum ether/ethyl acetate (7:1) as

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the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.46−8.36 (m, 1H), 8.03 (s, 1H), 7.56 (s, 1H), 7.48−7.40 (m, 3H), 7.17−7.02 (m, 5H), 3.61−3.44 (m, 1H), 3.08−2.92 (m, 1H), 2.42 (d, J = 4.0 Hz, 6H), 1.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.6, 148.6, 142.2, 139.1, 135.7 (t, J_{C-F} = 26.3 Hz), 134.6 (d, J_{C-F} = 3.0 Hz), 130.6, 129.5 (t, J_{C-F} = 9.1 Hz), 127.9, 127.6, 126.9, 125.4, 124.5 (t, J_{C-F} = 6.1 Hz), 123.6, 122.5, 121.2, 119.7, 118.8, 115.8, 49.4 (t, J_{C-F} = 28.3 Hz), 45.5 (t, J_{C-F} = 2.0 Hz), 31.2, 29.5, 20.3 (t, J_{C-F} = 2.0 Hz). ^{19}F NMR (376 MHz, chloroform-*d*) δ −90.19 (d, J = 248.5 Hz, 1F), −90.10 (d, J = 248.5 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{26}H_{22}F_2N_2O$ $[M + H]^+$ 417.1773, found: 417.1773.

*7-(2,2-Difluoro-2-phenylethyl)-7-methylbenzo[h]benzo-[4,5]imidazo[2,1-a]isoquinolin-8(7H)-one (**3na**).* White solid (yield 63.08 mg, 72%), mp 137−138 °C, purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.54 (d, J = 12 Hz, 1H), 8.31 (m, 1H), 7.98−7.88 (m, 3H), 7.85−7.81 (m, 1H), 7.67−7.63 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.50−7.41 (m, 2H), 7.09−6.95 (m, 5H), 3.60−3.42 (m, 1H), 3.12−2.82 (m, 1H), 1.78 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 171.7, 149.5, 143.8, 140.1, 135.3 (t, J_{C-F} = 26.3 Hz), 132.6, 131.7, 130.1 (d, J_{C-F} = 12.1 Hz), 129.4 (t, J_{C-F} = 2.0 Hz), 128.4, 128.17, 127.97, 127.73, 126.68, 125.52(d, J_{C-F} = 4.0 Hz), 124.53(t, J_{C-F} = 6.1 Hz), 123.7, 123.6, 121.2, 119.8, 118.7, 117.6, 115.6, 49.2 (t, J_{C-F} = 27.3 Hz), 45.8 (q, J_{C-F} = 2.0Hz), 31.1. ^{19}F NMR (376 MHz, chloroform-*d*) δ −89.28 (d, J = 248.5 Hz, 1F), −91.48 (d, J = 248.2 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{28}H_{20}F_2N_2O$ $[M + H]^+$ 439.1617, found: 439.1612.

*4-(2,2-Difluoro-2-phenylethyl)-4-methylbenzo[4,5]-imidazo[1,2-a]thieno[2,3-c]pyridin-5(4H)-one (**3oa**).* Yellow oily liquid (yield 59.90 mg, 76%), purified by column chromatography with petroleum ether/ethyl acetate (7:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.17−8.13 (m, 1H), 7.75−7.71 (m, 1H), 7.48 (d, J = 4.0 Hz, 1H), 7.42−7.32 (m, 2H), 7.07 (d, J = 4.0 Hz, 4H), 7.03−6.99 (m, 2H), 3.52−3.39 (m, 1H), 2.94−2.83 (m, 1H), 1.63 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 172.0, 146.1, 145.1, 143.5, 135.0 (t, J_{C-F} = 26.3 Hz), 130.5, 130.1, 129.5 (t, J_{C-F} = 2.0 Hz), 127.8, 126.0, 125.5, 125.1, 124.5 (t, J_{C-F} = 6.1 Hz), 123.4 (d, J_{C-F} = 5.1 Hz), 121.0 119.3, 118.5, 114.9, 49.2 (t, J_{C-F} = 27.3 Hz), 45.40 (t, J_{C-F} = 2.0 Hz), 29.88. ^{19}F NMR (376 MHz, chloroform-*d*) δ −89.65 (d, J = 248.9 Hz, 1F), −91.19 (d, J = 249.3 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{22}H_{16}F_2N_2OS$ $[M + H]^+$ 395.1024, found: 395.1020.

*5-(2,2-Difluoro-2-phenylethyl)-5-phenylbenzo[4,5]-imidazo[2,1-a]isoquinolin-6(5H)-one (**3pa**).* Yellow oily liquid (yield 46.82 mg, 52%), purified by column chromatography with petroleum ether/ethyl acetate (6:1) as the eluent. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.58−8.51 (m, 1H), 8.16−8.11 (m, 1H), 7.84−7.78 (m, 1H), 7.57−7.42 (m, 1H), 7.46−7.33 (m, 2H), 7.38−7.31 (m, 1H), 7.29−7.21 (m, 3H), 7.19−7.09 (m, 8H), 4.29−4.11 (m, 1H), 3.48−3.33 (m, 1H). ^{13}C{^{1}H}NMR (101 MHz, chloroform-*d*) δ 169.9, 149.7, 144.0, 142.5, 139.3, 136.0 (t, J_{C-F} = 26.3 Hz),131.5, 131.2, 129.7 (d, J_{C-F} = 5.1 Hz), 129.0, 128.2 (t, J_{C-F} = 9.1 Hz), 126.9, 125.9, 125.6 (t, J_{C-F} = 5.1 Hz), 124.8 (t, J_{C-F} = 7.1 Hz), 124.1, 123.7, 121.7, 119.7, 115.8, 53.5, 47.4 (t, J_{C-F} = 27.3 Hz), 29.7.^{19}F NMR (376 MHz, chloroform-*d*) δ −88.60 (d, J = 248.9 Hz, 1F), −89.68 (d, J = 248.9 Hz, 1F). HRMS (ESI) m/z: calcd for $C_{29}H_{20}F_2N_2O$ $[M + H]^+$ 451.1617, found: 451.1612.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures; mechanistic experiments; characterization data; and NMR spectra (PDF)

Data_202208148 (CIF)

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This manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Xie, L. Y.; Peng, S.; Fan, T. G.; Liu, Y. F.; Sun, M.; Jiang, L. L.; Wang, X. X.; Cao, Z.; He, W. M. Metal-free C3-alkoxycarbonylation of quinoxalin-2(1*H*)-ones with carbazates as ecofriendly ester sources. *Sci. China: Chem.* **2019**, *62*, 460−464. (b) Sun, K.; Wang, S. N.; Feng, R. R.; Zhang, Y. X.; Wang, X.; Zhang, Z. G.; Zhang, B. Copper-Catalyzed Radical Selenodifluoromethylation of Alkenes: Access to CF_2-Containing γ-Lactams. *Org. Lett.* **2019**, *21*, 2052−2055. (c) Liu, X. C.; Sun, K.; Lv, Q. Y.; Chen, X. L.; Sun, Y. Q.; Peng, Y. Y.; Qu, L. B.; Yu, B. Silver-mediated radical phosphorylation/cyclization of *N*-allylbenzamides to access phosphoryl-substituted dihydroisoquinolones. *New J. Chem.* **2019**, *43*, 12221−12224. (d) Peng, Y.; Feng, C. T.; Li, Y. Q.; Chen, F. X.; Xu, K. Exploring the ring-opening reactions of imidazo[1,5-*a*]quinolines for the synthesis of imides under photochemical conditions. *Org. Biomol. Chem.* **2019**, *17*, 6570−6573.

(2) (a) Lygin, A. V.; de Meijere, A. Isocyanides in the Synthesis of Nitrogen Heterocycles. *Angew. Chem.-Int. Ed.* **2010**, *49*, 9094−9124. (b) Guo, X. X.; Gu, D. W.; Wu, Z. X.; Zhang, W. B. Copper-Catalyzed

C-H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 1622−1651. (c) Wu, B.; Yoshikai, N. Recent developments in synthetic methods for benzo[b]heteroles. *Org. Biomol. Chem.* **2016**, *14*, 5402−5416. (d) Xie, W. L.; Wu, Y. Q.; Zhang, J. A.; Mei, Q. H.; Zhang, Y. H.; Zhu, N.; Liu, R. Z.; Zhang, H. L. Design, synthesis and biological evaluations of novel pyridone-thiazole hybrid molecules as antitumor agents. *Eur. J. Med. Chem.* **2018**, *145*, 35−40.

(3) (a) Sun, K.; Si, Y. F.; Chen, X. L.; Lv, Q. Y.; Peng, Y. Y.; Qu, L. B.; Yu, B. Synthesis of Phosphoryl-Substituted Benzimidazo [2,1-*a*]isoquinolin-6(5*H*)-ones from 2-Arylbenzoimidazoles and Diarylphosphine Oxides. *Asian J. Org. Chem.* **2019**, *8*, 2042−2045. (b) Deady, L. W.; Rodemann, T. Reduced benzimidazo 2,1-a isoquinolines. Synthesis and cytotoxicity studies. *Aust. J. Chem.* **2001**, *54*, 529−534.

(4) Alam, K.; Hong, S. W.; Oh, K. H.; Park, J. K. Divergent C-H Annulation for Multifused N-Heterocycles: Regio- and Stereospecific Cyclizations of N-Alkynylindoles. *Angew. Chem.-Int. Ed.* **2017**, *56*, 13387−13391.

(5) Chou, Y. C.; Chen, R. L.; Lai, Z. S.; Song, J. S.; Chao, Y. S.; Shen, C. K. J. Pharmacological Induction of Human Fetal Globin Gene in Hydroxyurea-Resistant Primary Adult Erythroid Cells. *Mol. Cell. Biol.* **2015**, *35*, 2541−2553.

(6) Patil, N. T.; Yamamoto, Y. Coinage Metal-Assisted Synthesis of Heterocycles. *Chem. Rev.* **2008**, *108*, 3395−3442.

(7) (a) Kato, J.-y.; Ito, Y.; Ijuin, R.; Aoyama, H.; Yokomatsu, T. Novel Strategy for Synthesis of Substituted Benzimidazo[1,2-*a*]quinolines. *Org. Lett.* **2013**, *15*, 3794−3797. (b) Raji Reddy, C.; Burra, A. G. [4+2]-Annulation of MBH-Acetates of Acetylenic Aldehydes with Imidazoles/Benzimidazoles To Access Imidazo[1,2-*a*]pyridines/Benzimidazo[1,2-*a*]pyridines. *J. Org. Chem.* **2019**, *84*, 9169−9178.

(8) (a) Mai, S. Y.; Luo, Y. X.; Huang, X. Y.; Shu, Z. H.; Li, B. N.; Lan, Y.; Song, Q. L. Diversity-oriented synthesis of imidazo[2,1-a]isoquinolines. *Chem. Commun.* **2018**, *54*, 10240−10243. (b) Pereira, K. C.; Porter, A. L.; DeBoef, B. Intramolecular arylation of benzimidazoles via Pd(II)/Cu(I) catalyzed cross-dehydrogenative coupling. *Tetrahedron Lett.* **2014**, *55*, 1729−1732. (c) Yuan, Y.; Zheng, Y. F.; Xu, B. Z.; Liao, J. P.; Bu, F. X.; Wang, S. C.; Hu, J. G.; Lei, A. W. Mn-Catalyzed Electrochemical Radical Cascade Cyclization toward the Synthesis of Benzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5*H*)-one Derivatives. *ACS Catal.* **2020**, *10*, 6676−6681. (d) Liang, R. X.; Yang, R. Z.; Liu, R. R.; Jia, Y. X. Palladium-catalyzed asymmetric dearomative alkenylation of indoles through a reductive-Heck reaction. *Org. Chem. Front.* **2018**, *5*, 1840−1843.

(9) (a) Yang, Y. Z.; Zhou, B.; Zhu, X. M.; Deng, G. B.; Liang, Y.; Yang, Y. Palladium-Catalyzed Synthesis of Triphenylenes via Sequential C-H Activation and Decarboxylation. *Org. Lett.* **2018**, *20*, 5402−5405. (b) Huang, M. H.; Hao, W. J.; Li, G. G.; Tu, S. J.; Jiang, B. Recent advances in radical transformations of internal alkynes. *Chem. Commun.* **2018**, *54*, 10791−10811. (c) Liu, K. J.; Jiang, S.; Lu, L. H.; Tang, L. L.; Tang, S. S.; Tang, H. S.; Tang, Z. L.; He, W. M.; Xu, X. H. Bis(methoxypropyl) ether-promoted oxidation of aromatic alcohols into aromatic carboxylic acids and aromatic ketones with O_2 under metal-free and base-free conditions. *Green Chem.* **2018**, *20*, 3038−3043.

(10) (a) 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(5*H*)-ones and Indolo-[2,1-*a*]isoquinolin-6(5H)-ones. *Adv. Synth. Catal.* **2019**, *361*, 5176−5181. (b) Liu, J.; Huang, H. L.; Wang, C.; Li, Y. H.; Li, H. Q.; Hu, H. G.; He, S. P.; Tang, H.; Gao, F. Visible-light-driven cascade radical cyclization toward the synthesis of α-carbonyl alkyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives. *RSC Adv.* **2021**, *11*, 29372−29375. (c) Sun, K.; Li, G. F.; Guo, S.; Zhang, Z. G.; Zhang, G. S. Copper-catalyzed radical cascade cyclization for synthesis of CF_3-containing tetracyclic benzimidazo[2,1-*a*]iso-quinolin-6(5*H*)-ones. *Org. Biomol. Chem.* **2021**, *19*, 375−378. (d) Kong, R.; Fu, T. F.; Yang, R. H.; Chen, D. N.; Liang, D. Q.; Dong, Y.; Li, W. L.; Wang, B. L. 4-Nitroanisole Facilitates Proton Reduction: Visible Light-Induced Oxidative Aryltrifluoromethylation of Alkenes with Hydrogen Evolution. *ChemCatChem* **2021**, *13*, 2952−2958.

(11) (a) Li, J.; Hao, W. J.; Zhou, P.; Zhu, Y. L.; Wang, S. L.; Tu, S. J.; Jiang, B. Oxidative bicyclization of N-tethered 1,7-enynes toward polycyclic 3,4-dihydroquinolin-2(1*H*)-ones via site-selective decarboxylative C(sp^3)-H functionalization. *RSC Adv.* **2017**, *7*, 9693−9703. (b) 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. (c) Tang, L. L.; Ouyang, Y. J.; Sun, K.; Yu, B. Visible-light-promoted decarboxylative radical cascade cyclization to acylated benzimidazo/indolo[2,1-a]isoquinolin-6(5*H*)-ones in water. *RSC Adv.* **2022**, *12*, 19736−19740. (d) Zhu, H. L.; Zeng, F. L.; Chen, X. L.; Sun, K.; Li, H. C.; Yuan, X. Y.; Qu, L. B.; Yu, B. Acyl Radicals from alpha-Keto Acids: Metal-Free Visible-Light-Promoted Acylation of Heterocycles. *Org. Lett.* **2021**, *23*, 2976−2980.

(12) 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(5*H*)-ones. *Chem. Commun.* **2019**, *55*, 2861−2864.

(13) 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-6(5*H*)-One Derivatives. *J. Org. Chem.* **2020**, *85*, 11892−11901.

(14) Liu, Q.; Wang, L.; Liu, J.; Ruan, S. C.; Li, P. H. Facile synthesis of carbamoylated benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones *via* radical cascade cyclization under metal-free conditions. *Org. Biomol. Chem.* **2021**, *19*, 3489−3496.

(15) Hu, X. Y.; Xu, H. F.; Chen, Q.; Pan, Y. L.; Chen, J. Z. Synthesis of indolo[2,1-*a*]isoquinoline derivatives *via* metal-free radical cascade cyclization. *Org. Biomol. Chem.* **2021**, *19*, 10376−10384.

(16) Chen, Z. W.; Huang, X. X.; Sun, J.; Liu, Y. M.; Li, Z. W. Metal-free Cascade Radical Cyclization of *N*-Methylacrylyl-2-phenylbenzimidazole: Construction of Aryldifluoromethylated Benzimidazole[2,1-*a*]iso-Quinoline-6(5*H*)-ketone. *Asian J. Org. Chem.* **2022**, *11*, No. e202200255.

(17) (a) Huang, M. H.; Hao, W. J.; Jiang, B. Recent Advances in Radical-Enabled Bicyclization and Annulation/1,*n*-Bifunctionalization Reactions. *Chem.-Asian J.* **2018**, *13*, 2958−2977. (b) Zhang, S.; Li, L. J.; Zhang, J. J.; Zhang, J. Q.; Xue, M. Y.; Xu, K. Electrochemical fluoromethylation triggered lactonizations of alkenes under semi-aqueous conditions. *Chem. Sci.* **2019**, *10*, 3181−3185.

(18) (a) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. Remarkably selective iridium catalysts for the elaboration of aromatic C-H bonds. *Science.* **2002**, *295*, 305−308. (b) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. A *meta*-selective C-H borylation directed by a secondary interaction between ligand and substrate. *Nat. Chem.* **2015**, *7*, 712−717.

(19) (a) Chen, Z. W.; Bai, X.; Sun, J.; Xu, Y. C. Fe(III)-Catalyzed Decarboxylative C3-Difluoroarylmethylation of Coumarins with α, α-Difluoroarylacetic Acids. *J. Org. Chem.* **2020**, *85*, 7674−7682. (b) Yang, X. Y.; Liu, J.; Gao, Y. H.; Wang, L.; Zhang, Y. C.; Li, P. H. Photo-Driven Radical Addition/Cyclization of Biaryl Vinyl Ketones with CF_3SO_2Na and $ArCF_2CO_2K$ without an External Photocatalyst. *Asian J. Org. Chem.* **2022**, *11*, No. e202200269. (c) Wan, W.; Li, J. L.; Ma, G. B.; Chen, Y. R.; Jiang, H. Z.; Deng, H. M.; Hao, J. Ag(I)-Catalyzed oxidative decarboxylation of difluoroacetates with activated alkenes to form difluorooxindoles. *Org. Biomol. Chem.* **2017**, *15*, 5308−5317. (d) Xie, X. J.; Zhang, Y. F.; Hao, J.; Wan, W. Ag-Catalyzed minisci C-H difluoromethylarylation of N-heteroarenes. *Org. Biomol. Chem.* **2020**, *18*, 400−404.

(20) Mei, W. Q.; Kong, Y. L.; Yan, G. B. Synthetic applications of α, α-difluoroarylacetic acids and salts *via* decarboxylative functionalization. *Org. Chem. Front.* **2021**, *8*, 5516−5530.

https://doi.org/10.1021/acsomega.2c06689
ACS Omega 2023, 8, 7517−7528

(21) (a) Duncton, M. A. J. Minisci reactions: Versatile CH-functionalizations for medicinal chemists. *MedChemComm* **2011**, *2*, 1135−1161. (b) Mandal, S.; Bera, T.; Dubey, G.; Saha, J.; Laha, J. K. Uses of $K_2S_2O_8$ in Metal-Catalyzed and Metal-free Oxidative Transformations. *ACS Catal.* **2018**, *8*, 5085−5144. (c) Liu, W.; Hu, Y. Q.; Hong, X. Y.; Li, G. X.; Huang, X. B.; Gao, W. X.; Liu, M. C.; Xia, Y. Z.; Zhou, Y. B.; Wu, H. Y. Direct synthesis of 3-acylbenzothiophenes *via* the radical cyclization of 2-alkynylthioanisoles with α-oxocarboxylic acids. *Chem. Commun.* **2018**, *54*, 14148−14151.

(22) (a) Hong, G. F.; Yuan, J. W.; Fu, J. H.; Pan, G. Y.; Wang, Z. W.; Yang, L. R.; Xiao, Y. M.; Mao, P.; Zhang, X. M. Transition-metal-free-free decarboxylative C3-difluoroarylmethylation of quinoxalin-2(1*H*)-ones with α, α-difluoroarylacetic acids. *Org. Chem. Front.* **2019**, *6*, 1173−1182. (b) Yuan, J. W.; Yin, Q. Y.; Yang, L. R.; Mai, W. P.; Mao, P.; Xiao, Y. M.; Qu, L. B. Iron-catalyzed regioselective direct coupling of aromatic aldehydes with coumarins leading to 3-aroyl coumarins. *RSC Adv.* **2015**, *5*, 88258−88265. (c) Chen, Z. W.; Sun, J.; Ke, Z. W.; Huang, X. X.; Li, Z. W. Silver-catalyzed stereoselective C-4 arylthiodifluoromethylation of coumarin-3-carboxylic acids *via* a double decarboxylative strategy. *Org. Chem. Front.* **2022**, *9*, 757−763. (d) Yang, B.; Xu, X. H.; Qing, F. L. Synthesis of Difluoroalkylated Arenes by Hydroaryldifluoromethylation of Alkenes with α, α-Difluoroarylacetic Acids under Photoredox Catalysis. *Org. Lett.* **2016**, *18*, 5956−5959. (e) Li, X.; Li, S. Y.; Sun, S. Y.; Yang, F.; Zhu, W. G.; Zhu, Y.; Wu, Y. S.; Wu, Y. J. Direct Decarboxylative Alkynylation of α, α-Difluoroarylacetic Acids under Transition Metal-Free Conditions. *Adv. Synth. Catal.* **2016**, *358*, 1699−1704.

https://doi.org/10.1021/acsomega.2c06689
ACS Omega 2023, 8, 7517−7528