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可见光诱导 2-芳基吲哚与二氟甲基亚磺酸钠二氟甲基化/环化反应

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摘要 二氟甲基化合物广泛存在于天然产物、生物活性分子和药物中. 此研究发展了一种可见光诱导 2-芳基吲哚结构的二氟甲基化/环化反应合成吲哚[2,1-*a*]异喹啉酮衍生物. 该反应使用廉价、易于处理的二氟甲基亚磺酸钠(HCF_2SO_2Na)为二氟甲基来源, 各种二氟甲基基取代吲哚[2,1-*a*]异喹啉酮衍生物以中等到良好的收率获得. 机理验证实验表明, 该反应可能经历了自由基历程.

关键词 二氟甲基化合物; 可见光; 2-芳基吲哚; 二氟甲基化/环化

Photoinduced Difluoromethylation/Cyclization of 2-Aryl Indoles with HCF_2SO_2Na

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Abstract Difluoromethyl compounds are widely found in natural products, bioactive molecule and pharmaceuticals. A visible-light induced difluoromethylation/cyclization of 2-aryl indoles is described to construct indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives using the inexpensive and easy-to-handle HCF_2SO_2Na as an HCF_2 sources. Diverse difluoromethylated indolo[2,1-*a*]isoquinolines were readily obtained in moderate to good yields. Mechanistic studies demonstrate that the reaction may involve a radical process.

Keywords difluoromethyl compounds; visible-light; 2-aryl indoles; difluoromethylation/cyclization

1 Introduction

The introduction of difluoromethyl group (HCF_2) into organic molecules can not only improve chemical, physical properties and physiological activity of the parent molecule, but also affect their binding affinity, metabolic stability, membrane permeability and bioactivity.[1-3] Hence, the synthesis of difluoromethylated compounds has attracted increasing attention in drug design and life science industry. Over the past decade, a series of HCF_2 reagents, such as HCF_2SO_2Cl,[4] HCF_2X,[5] $TMSCF_2H$,[6] HCF_2COOH,[7] $CF_2HSO_2NHNHBoc$,[8] $(HCF_2CO)_2O$,[9] difluoromethyl sulfones,[10] HCF_2SO_2Na[11] and Ph_2SCF_2HOTf[12] have been well developed as an effective HCF_2 source to construct diverse difluoromethylated compounds (Scheme 1a). Despite significant progresses in difluoromethylation have been achieved, a convenient and sustainable process for construction of complex molecules containing the CF_2H group is still limited.

As an important class of nitrogen-containing heterocycles, indole[2,1-*a*]isoquinoline framework is commonly found in biologically active natural products, organic synthetic intermediates, pharmaceuticals and functional materials.[13] Recently, 2-aryl indole structures have become an important starting materials for the efficient construction of functional indole[2,1-*a*]isoquinoline derivatives. These efforts predominantly relied on a cyclization strategy chiefly employing a radical as initiator, and a variety of functionalities, such as $PhSO_2$,[14a-14b] RCO,[14c-14d] RS,[14e] RSi[14f] and POR_2[14] have been successfully added to C=C bond of 2-aryl indoles. In this context, the synthesis of difluoromethylated indole[2,1-*a*]isoquinolines has gained

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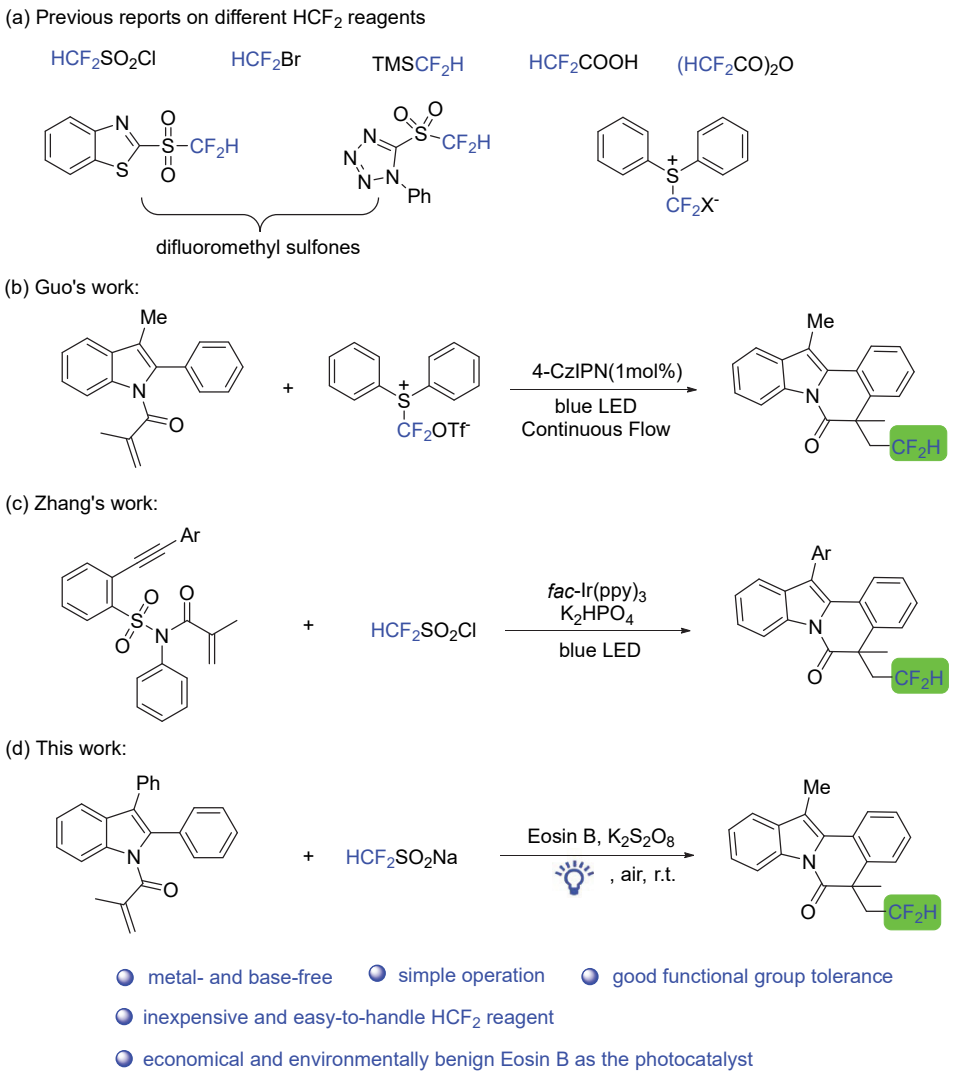
wide attention from chemists. For example, in 2021, Guo *et al*.[12] reported a photocatalyzed fluoroalkylation/cyclization reaction for constructing a series of tri- or difluoromethylated indole[2,1-*a*]isoquinoline derivatives by using Ph_2S-CF_2HBF_4 reagents as the CF_2H sources under continuous flow conditions (Scheme 1b). After that, Zhang *et al*.[4b] developed a photocatalytic difluoromethylation of conjugated arylsulfonylated amides using HCF_2SO_2Cl as the CF_2H radical source to construct *β*-difluoromethyl amide and heterocyclic scaffolds (Scheme 1c). However, some drawbacks such as the use of high costs of metal catalysts, complicated multistep syntheses of HCF_2 reagents and/or harsh reaction conditions are yet to be addressed in those reported reactions. Therefore, it is highly desirable to develop new, convenient methods for the synthesis of difluoromethylated indole[2,1-*a*]isoquinoline derivatives from readily available and inexpensive starting materials. With this in mind and our ongoing interests in radical cyclization reactions,[15] we considered using our previously reported organic-dye catalyst/visible-light system and HCF_2SO_2Na as an inexpensive and easy-to-handle fluorine sources, maybe realize the difluoromethylation/cyclization to access diverse difluoromethylated indole[2,1-*a*]isoquinolines. We herein report an alternatively visible-light-mediated organic-dye-catalyzed difluoromethylation of 2-aryl-indoles with HCF_2SO_2Na, furnishing a variety of indolo[2,1-*a*]isoquinolines under mild conditions (Scheme 1d). Compared with previous work, this strategy exhibits several advantages, such as the use of the inexpensive, easy-to-handle and commercially available HCF_2SO_2Na as an HCF_2 sources, metal- and base-free, economical and environmentally benign Eosin B as the photocatalyst and simple operation, thus makes the present methodology more attractive and practical.

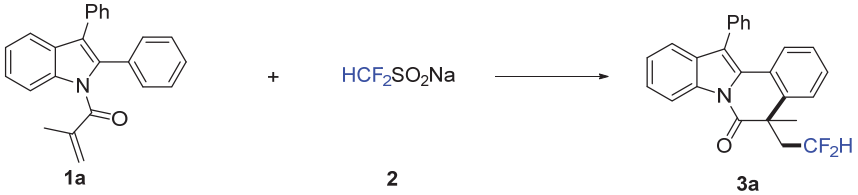
2 Results and discussion

Initially, 1-(2,3-diphenyl-1*H*-indol-1-yl)-2-methylprop-2-en-1-one (**1a**) and HCF_2SO_2Na (**2**) were chosen as the model substrates to optimize various reaction parameters in the presence of $K_2S_2O_8$ as oxidant and a photo-catalyst (Table 1). After extensive investigation of various photo-



Scheme 1 Diverse HCF_2 reagents and synthesis of difluoromethylated indolo[2,1-*a*]isoquinolines

Table 1 Optimization of reaction conditions[a]



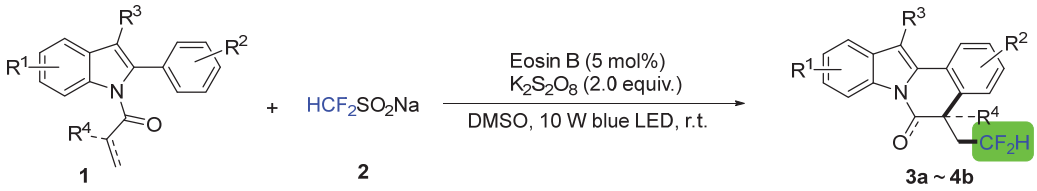
Entry	Organic dye	Oxidant	Solvent	Yield[b]/%
1	Fluorescein	$K_2S_2O_8$	DMSO	38
2	Rose Bengal	$K_2S_2O_8$	DMSO	64
3	**Eosin B**	**$K_2S_2O_8$**	**DMSO**	**70**
4	Na_2-EosinY	$K_2S_2O_8$	DMSO	49
5	$Ru(bpy)_3(Cl)_2$•$6H_2O$	$K_2S_2O_8$	DMSO	62
6	Eosin B	$(NH_4)_2S_2O_8$	DMSO	55
7	Eosin B	$Na_2S_2O_8$	DMSO	58
8[c]	Eosin B	TBHP	DMSO	29
9	Eosin B	$K_2S_2O_8$	DMF	49
10	Eosin B	$K_2S_2O_8$	CH_3CN	Trace
11	Eosin B	$K_2S_2O_8$	DCE	54
12	Eosin B	$K_2S_2O_8$	THF	5
13[d]	Eosin B	$K_2S_2O_8$	DMSO	58
14[e]	Eosin B	$K_2S_2O_8$	DMSO	18
15	—	$K_2S_2O_8$	DMSO	46
16[f]	Eosin B	$K_2S_2O_8$	DMSO	Trace

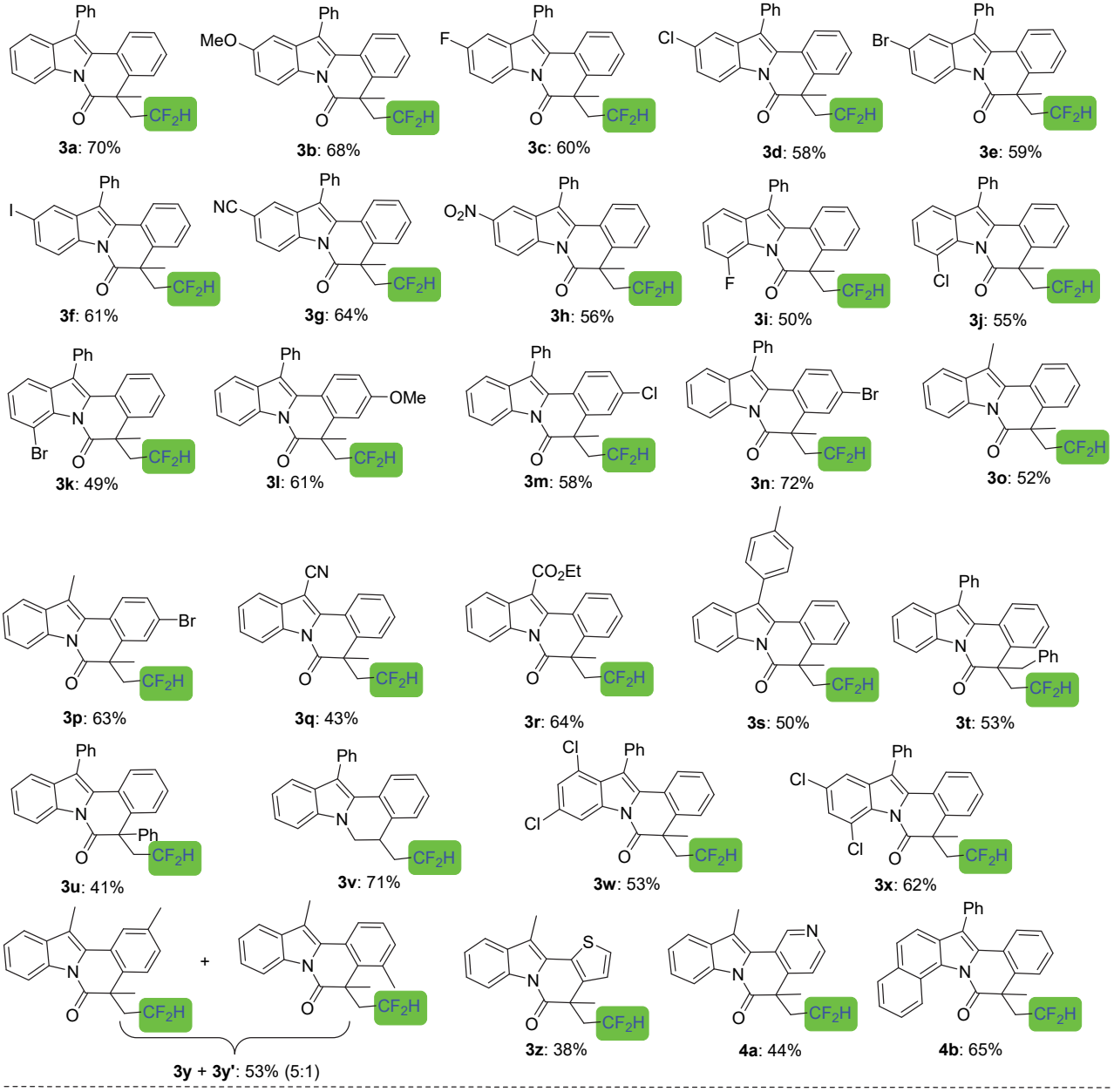
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), organic dye catalyst (5 mol%), oxidant (0.4 mmol, 2.0 equiv.) and solvent (2.5 mL) were stirred under 10 W blue LED (460～465 nm) irradiation at room temperature under air for 10 h. [b] Isolated yield. [c] TBHP (70% solution in water). [d] 2 mol% of Eosin B was used. [e] Under 3 W blue LED (460～465 nm) irradiation. [f] Without 10 W blue LED (460～465 nm) irradiation.

catalysts, such as fluorescein, rose bengal, Na_2-Eosin $Ru(bpy)_3Cl_2$•$6H_2O$, it was delighted to find that Eosin B was the optimal choice and the yield of target product **3a** is 70% (Table 1, Entries 1～5). Next, the effect of oxidants on the reaction was investigated. A series of other oxidants including $(NH_4)_2S_2O_8$, $Na_2S_2O_8$ and *t*-butyl hydroperoxide (TBHP) were explored and gave no positive results than $K_2S_2O_8$ (Table 1, Entries 6～8). Additionally, several solvents, such as *N*,*N*-dimethylformamide (DMF), CH_3CN, dichloroethane (DCE) and tetrahydrofuran (THF) were tested, but no better yield was obtained (Table 1, Entries 9～12). Decreasing the loading of photo-catalyst Eosin B to 2 mol% or performing the reaction under **3w** blue light-emitting diode (LED) irradiation could lead to a decrease of the yield of **3a** (Table 1, Entries 13, 14). Notably, the reaction could occur smoothly under catalyst-free condition, which might due to the generation of $SO_4^{-\bullet}$ radical anion from $K_2S_2O_8$ under LED irradiation (Table 1, Entry 15).[16] Finally, a control experiment was carried out in the dark, and the result showed that no product **3a** formed in the absence of visible-light, suggesting that visible-light was critical for this difluoromethylation reaction (Table 1, Entry 16).

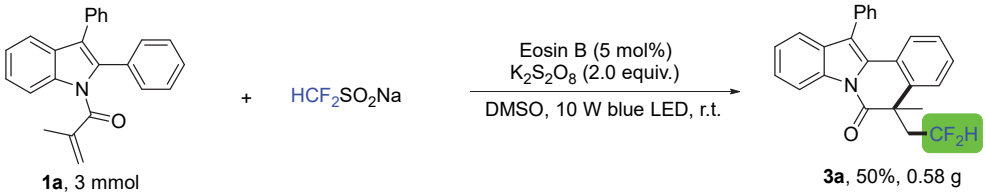
With the optimized reaction conditions in hand, the substrate scope of this transformation was investigated. As shown in Table 2, a series of substituted 2-aryl-indoles (**1**) with electron-donating (MeO) or electron-withdrawing groups (halo, CN, NO_2) at *para*-, or *ortho*-position of indole-ring were well tolerated with HCF_2SO_2Na, and the desired products (**3b**～**3k**) were provided in moderate to good yields (49%～68%). To our delight, the cascade reaction was also not sensitive to the electronic nature of the R^2 substituents on the aromatic ring, and both electron-donating and electron-withdrawing substituted substrates accommodated well with this protocol, providing target products **3l**～**3n** in good yields. Next, a wide range of substituents at R^3 position were evaluated. A series of synthetically useful functional groups including CH_3, CN, CO_2Et and tolyl can be well-tolerated under the standard conditions to give the target products **3o**～**3s**. When the methyl group at R^4 position was replaced by benzyl or phenyl, the reaction also showed high reaction efficiency, furnishing the desired products **3t** and **3u** in moderate yield. Especially, 2-aryl indole bearing an unactivated alkene was also well tolerated under the standard conditions, giving the desired product **3v** in 71% yield. Substrates containing two substituents on the phenyl ring were also compatible in this reaction as well to generate corresponding products in 53% and 62% yields (**3w** and **3x**). To investigate the regioselectivity of the transformation, a *meta*-methyl substituted 2-aryl indole derivative was treated with HCF_2SO_2Na, as expected, two regioisomers (**3y** and **3y'**) were generated in a total yield of 53% with the ratio of 5∶1. Finally, this protocol could be applied to hetero aryl and naphthalene substituted 2-aryl indole, giving the corresponding indolo-[2,1-*α*]isoquinolines **3z**～**4b** in 38%～65% yields. To verify the scalability of the present reaction, a 3.0 mmol scale reaction of **1a** was carried out under the standard conditions,

Table 2 Substrate scope of 2-aryl indoles[a,b]





Gram-scale synthesis of **3a**:



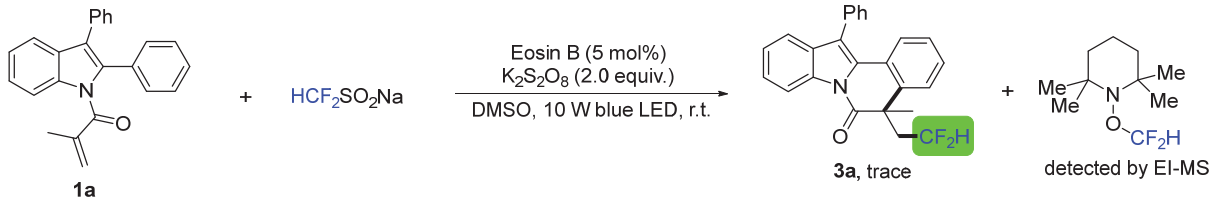
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), Eosin B (5 mol%), $K_2S_2O_8$ (0.4 mmol, 2.0 equiv.) and DMSO (2.5 mL) were stirred under 10 W blue LED (460～465 nm) irradiation at room temperature under air for 10 h. [b] Isolated yield.

affording **3a** in a 50% yield, suggesting that this reaction could be readily scalable.

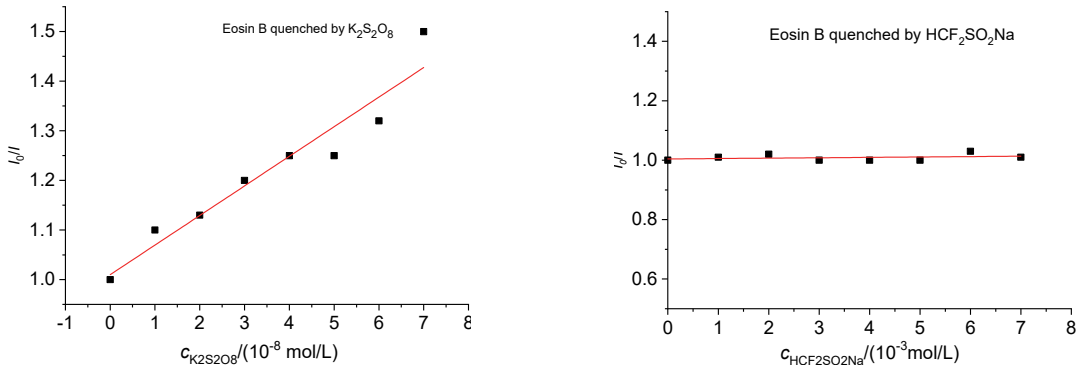
To gain insight into the reaction mechanism, a series of control experiments were conducted. First, the reaction was completely inhibited in the presence of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl, a radical scavenger) and only a trace amount of product **3a** was detected. Moreover, the TEMPO-CF_2H adduct was detected by EI-MS, indicating that CF_2H radical might involved in this transformation (Scheme 2a). Second, Stern-Volmer fluorescence quenching experiments were conducted. The Stern-Volmer studies between Eosin B and $K_2S_2O_8$ revealed that the excited photocatalyst Eosin B* could be quenched by $K_2S_2O_8$ with a good linear relationship, in which a single electron transfer (SET) process might be involved. While when HCF_2SO_2Na solution added to the Eosin B under visible-light condition, no obvious decrease in the emission intensity can be observed, ruling out the the possibility of difluoromethyl radical (HCF_2•) was generated by the excited photocatalyst Eosin B* (Scheme 2b).

Based on the above experiments and previous reports,[4,11,14] a plausible mechanism for current photocatalytic difluoromethylation/cyclization is depicted in Scheme 3. Upon visible-light irradiation, photocatalyst Eosin B absorbs the light energy and become excited species Eosin B*, which next undergoes a single electron transfer (SET) process with $K_2S_2O_8$ to generate sulfate radical anion ($SO_4^{-\bullet}$). Next, the HCF_2 radical **A** (HCF_2•) can be generated from HCF_2SO_2Na by the oxidation with the assistance of $SO_4^{-\bullet}$, followed by release of SO_2. Then the addition of HCF_2• to the C=C bond of **1a** affords radical intermediate **B**, which subsequently undergoes an intramolecular cyc-

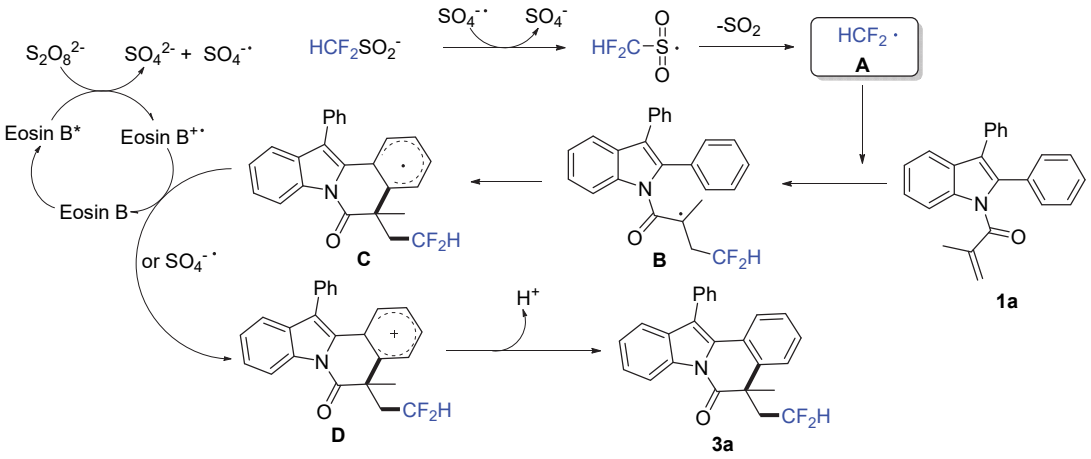
(a) Radical inhibition experiments



(b) Stern-Volmer fluorescence quenching experiment



Scheme 2 Mechanistic studies



Scheme 3 Proposed reaction mechanism

lization to give radical intermediate **C**. Finally, the radical intermediate **C** undergoes another single electron transfer (SET) oxidation by Eosin $B^{+\bullet}$ or $SO_4^{-\bullet}$ to form the cation intermediate **D**, which occurs deprotonation to generate the expected product **3a**.

3 Conclusions

In summary, we have developed an efficient and sustainable visible-light induced difluoromethylation/cyclization of 2-aryl indoles to construct indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives. Compared with previous work, this strategy exhibits several advantages, such as the use of the inexpensive, easy-to-handle and commercially available HCF_2SO_2Na as an HCF_2 sources, metal- and base-free, and economical and environmentally benign Eosin B as the photocatalyst. With the optimal conditions, a variety of diverse valuable difluoromethylated indolo[2,1-*a*]isoquinolines were readily obtained in moderate to good yields. Meanwhile, this protocol was applicable to a gram scale synthesis, which further showcased its potential applications in the future.

4 Experimental section

4.1 General information

All reagents and solvents were purchased from commercial suppliers and used without purifications. Thin-layer chromatography (TLC) was performed on silica gel plates (200～300 mesh) using UV light (254/365 nm) for detection and column chromatography was performed on silica gel (200～300 mesh). The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 ℃ in $CDCl_3$ at 400 and 100 MHz, respectively, with TMS as the internal standard. All reactions were performed on the photoreaction instrument (WP-TEC-1020SL), which are purchased from WATTCAS, China. Fluorescence spectra were performed on a F-7000 spectrophotometer (Hitachi Ltd., Japan) with excitation and emission lit widths of 10 nm.

4.2 General procedure for the synthesis of difluoromethylated indolo[2,1-*a*]isoquinolines

To a stirred solution of 2-aryl indole (0.2 mmol) in dimethyl sulfoxide (DMSO) (2.5 mL) were added Eosin B (5 mol%) HCF_2SO_2Na (0.4 mmol) and $K_2S_2O_8$ (0.4 mmol). The resulting mixture was stirred in air under a 10 W blue LEDs (460～465 nm) and irradiated for 10 h. The temperature was maintained at 20～25 ℃ when the LED light was on. After the reaction was complete, the reaction mixture was diluted with a brine solution (25 mL) and extracted with EtOAc (30 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography to afford the desired products **3a**～**4b**.

5-(2,2-Difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]-isoquinolin-6(5*H*)-one (**3a**):[4b,12] Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J=8.3 Hz, 1H), 7.54～7.28 (m, 8H), 7.18 (d, J=24.5 Hz, 3H), 6.96 (t, J=7.7 Hz, 1H), 5.68～5.29 (m, 1H), 2.99 (ddd, J=27.2, 13.0, 5.8 Hz, 1H), 2.60～2.38 (m, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.71, 136.64, 134.26, 133.89, 132.30, 130.15, 129.30, 128.97, 128.54, 128.20, 127.24,126.15, 126.13, 125.65, 125.06, 124.74, 120.83, 119.55, 116.69, 115.4 (t, J=238.0 Hz), 113.05, 44.9 (t, J=4.0 Hz), 44.75 (d, J=22.0 Hz), 29.87; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.71 (m, 1F), −115.09 (m, 1F).

5-(2,2-Difluoroethyl)-10-methoxy-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3b**):[4b] Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (d, J=9.0 Hz, 1H), 7.66～7.21 (m, 8H), 7.02 (d, J=13.3 Hz, 2H), 6.72 (s, 1H), 5.78～5.36 (m, 1H), 3.78 (s, 3H), 3.07 (q, J=29.4, 16.0 Hz, 1H), 2.56 (q, J=17.2, 14.7 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.30, 157.48, 136.82, 133.96, 133.45, 130.16, 129.69, 129.40, 128.91, 128.50, 128.24, 127.22, 126.20, 125.58, 125.08, 120.67, 117.60, 115.47 (t, J=239.0 Hz), 114.32, 102.37, 55.74, 44.89 (t, J=5.0 Hz), 44.76 (t, J=22.0 Hz), 29.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.78 (d, J=293.0 Hz, 1F), −115.15 (d, J=290.0 Hz, 1F).

5-(2,2-Difluoroethyl)-10-fluoro-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3c**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (dd, J=9.0, 4.7 Hz, 1H), 7.63～7.38 (m, 7H), 7.31 (t, J=7.7 Hz, 1H), 7.08 (dt, J=20.4, 7.8 Hz, 2H), 6.94 (d, J=6.1 Hz, 1H), 5.73～5.37 (m, 1H), 3.08 (dt, J=21.7, 14.1 Hz, 1H), 2.56 (dt, J=22.0, 12.5 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.59, 160.58 (d, J=240.0 Hz), 136.87, 133.69 (d, J=8.0 Hz), 133.43, 130.53 (d, J=8.0 Hz), 130.07, 129.47, 128.91, 128.46, 127.37, 126.23, 125.78, 124.77, 120.39, 117.96, 117.87, 115.40 (t, J=238.0 Hz), 113.66 (d, J=25.0 Hz), 105.42, 105.18, 44.84 (t, J=6.0 Hz), 44.77 (t, J=22.0 Hz), 29.94; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.86 (d, J=286.0 Hz, 1F), −115.35 (d, J=289.0 Hz, 1F), −117.37 (s, 1F). HRMS (ESI) calcd for $C_{25}H_{19}F_3NO$ 406.1419, found 406.1415.

10-Chloro-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3d**):[4b] White solid. m.p. 114～115 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, J=8.2 Hz, 1H), 7.69～7.20 (m, 10H), 7.07 (d, J=7.8 Hz, 1H), 5.79～5.35 (m, 1H), 3.10 (q, J=18.5, 16.9 Hz, 1H), 2.74～2.46 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.68, 136.79, 133.68, 133.23, 132.55, 130.49, 130.23, 130.07, 129.47, 128.96, 128.48, 127.38, 126.20, 126.12, 125.79, 124.66, 119.91, 119.16, 117.75, 115.33 (t, J=239.0 Hz), 112.94, 44.87 (t, J=4.0 Hz), 44.76 (t, J=22.0 Hz), 29.87; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.89 (d, J=290.0 Hz, 1F), −115.39 (d, J=290.0 Hz, 1F).

10-Bromo-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3e**): White solid. m.p. 138～139 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, J=8.7 Hz, 1H), 7.62～7.16 (m, 10H), 6.97 (t, J=7.7 Hz, 1H), 5.46 (t, J=56.0 Hz, 1H), 2.97 (dd, J=29.6, 12.0 Hz, 1H), 2.48 (dd, J=25.1, 10.9 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.68, 135.78, 133.09, 132.17, 131.89, 129.08, 129.05, 128.45, 127.94, 127.81, 127.46,

126.35, 125.16, 124.77, 123.59, 121.16, 118.76, 117.22, 117.12, 114.29 (t, J=239.0 Hz), 43.87 (q, J=4.0 Hz), 43.75 (t, J=22.0 Hz), 28.81; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.88 (d, J=290.0 Hz, 1F), −115.41 (d, J=290 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}BrF_2NO$ 466.0618, found 466.0620.

5-(2,2-Difluoroethyl)-10-iodo-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3f**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (dd, J=99.5, 8.4 Hz, 1H), 7.79～7.36 (m, 8H), 7.34～7.20 (m, 2H), 7.04 (d, J=8.1 Hz, 1H), 5.79～5.33 (m, 1H), 3.08 (dt, J=21.1, 7.2 Hz, 1H), 2.72～2.40 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.75, 136.80, 134.58, 130.16, 130.09, 129.76, 129.49, 129.31, 128.96, 128.49, 128.31, 127.38, 126.14, 125.80, 124.74, 119.56, 118.46, 116.70, 115.32 (t, J=238.0 Hz), 89.14, 44.90 (t, J=4.0 Hz), 44.77 (t, J=21.0 Hz), 44.68, 29.84; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.90 (q, J=60.0 Hz, 1F), −115.40 (q, J=113.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}IF_2NO$ 514.0479, found 514.0477.

5-(2,2-Difluoroethyl)-5-methyl-6-*oxo*-12-phenyl-5,6-dihydroindolo[2,1-*a*]isoquinoline-10-carbonitrile (**3g**):[4b] White solid. m.p. 228～229 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (t, J=7.6 Hz, 1H), 8.19～7.32 (m, 10H), 7.12 (p, J=7.8 Hz, 1H), 5.55 (t, J=56.0 Hz, 1H), 3.36～2.99 (m, 1H), 2.82～2.45 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.13, 136.75, 136.06, 132.58, 132.55, 131.13, 130.03, 129.67, 129.51, 129.08, 128.85, 127.62, 126.29, 126.05, 124.25, 119.85, 119.39, 117.64, 115.26 (t, J=239.0 Hz), 108.20, 45.12 (t, J=4.0 Hz), 44.83 (t, J=22.0 Hz), 29.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −115.05 (d, J=293.0 Hz, 1F), −115.65 (d, J=293.0 Hz, 1F).

5-(2,2-Difluoroethyl)-5-methyl-10-nitro-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3h**): Pale yellow solid. m.p. 196～197 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (dt, J=9.4, 5.2 Hz, 1H), 8.47～8.07 (m, 2H), 7.85～7.34 (m, 8H), 7.31～7.06 (m, 1H), 5.90～5.33 (m, 1H), 3.27～3.00 (m, 1H), 2.75～2.50 (m, 1H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.16, 145.23, 137.23, 136.72, 132.64, 132.43, 131.87, 130.03, 129.74, 129.60, 128.93, 127.76, 127.67, 126.28, 126.11, 124.20, 121.19, 120.59, 116.97, 115.64, 115.2 (t, J=238.0 Hz), 45.06 (t, J=5.0 Hz), 44.77 (d, J=21.0 Hz), 29.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.7 (d, J=293.0 Hz, 1F), −116.1 (d, J=293.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}F_2N_2O_3$ 433.1364, found 433.1361.

5-(2,2-Difluoroethyl)-8-fluoro-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3i**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78～7.27 (m, 9H), 7.26～7.00 (m, 3H), 5.65 (t, J=55.7 Hz, 1H), 3.04 (ddt, J=27.6, 19.2, 10.6 Hz, 1H), 2.59 (p, J=16.4 Hz, 1H), 1.98～1.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.11, 150.43 (d, J=254.0 Hz), 137.27, 136.36, 133.50, 131.15, 130.17, 129.42, 128.90, 128.41, 127.29, 126.04 (d, J=3.0 Hz), 125.66, 125.58, 124.99, 121.00, 115.53, 115.50, 115.38 (t, J=239.0 Hz), 113.46 (d, J=22.0 Hz), 45.58 (d, J=5.0 Hz), 44.85 (t, J=21.0 Hz), 29.20; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −109.90 (s, 1F), −114.54 (s, 2F). HRMS (ESI) calcd for $C_{25}H_{19}F_3NO$ 406.1419, found 406.1415.

8-Chloro-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3j**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14～7.15 (m, 11H), 7.04 (t, J=7.5 Hz, 1H), 5.74 (t, J=58.5 Hz, 1H), 3.20～2.87 (m, 1H), 2.75～2.46 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.80, 137.83, 136.28, 133.31, 132.46, 130.22, 129.43, 128.98, 128.45, 127.81, 127.33, 126.22, 125.93, 125.67, 125.34, 122.14, 120.40, 118.39, 115.44 (t, J=244.0 Hz), 46.10 (t, J=5.0 Hz), 44.46 (t, J=22.0 Hz), 28.66; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −113.81 (d, J=290.0 Hz, 1F), −113.95 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}ClF_2NO$ 422.1123, found 422.1120.

8-Bromo-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3k**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99～6.96 (m, 12H), 5.76 (t, J=49.8 Hz, 1H), 3.21～2.88 (m, 1H), 2.75～2.42 (m, 1H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.58, 137.82, 136.56, 134.93, 134.22, 133.25, 132.59, 131.10, 130.23, 129.94, 129.43, 128.99, 128.47, 127.32, 126.28, 125.96, 125.37, 120.29, 118.98, 115.47 (t, J=239.0 Hz), 109.74, 65.57, 46.19 (t, J=4.0 Hz), 44.21 (t, J=22.0 Hz), 28.82; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −113.81 (d, J=290.0 Hz, 1F), −114.03 (d, J=282.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}BrF_2NO$ 466.0618, found 466.0620.

5-(2,2-Difluoroethyl)-3-methoxy-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3l**): Pale yellow solid. m.p. 147～148 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (t, J=7.7 Hz, 1H), 7.76～7.19 (m, 9H), 6.92 (d, J=23.0 Hz, 1H), 6.62 (d, J=8.2 Hz, 1H), 5.87～5.41 (m, 1H), 3.80 (s, 3H), 3.08 (s, 1H), 2.69～2.40 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.62, 159.74, 138.68, 134.14, 134.09, 132.53, 130.33, 129.32, 129.22, 128.11, 127.33, 125.65, 124.72, 119.21, 119.01, 118.05, 116.60, 115.46 (t, J=239.0 Hz), 112.85, 111.93, 55.40, 45.13 (t, J=4.0 Hz), 44.82 (t, J=22.0 Hz), 29.86; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.63(d, J=293.0 Hz, 1F), −114.98 (d, J=293.0 Hz, 1F). HRMS (ESI) calcd for $C_{26}H_{22}F_2NO_2$ 418.1619, found 418.1621.

3-Chloro-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3m**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (d, J=8.3 Hz, 1H), 7.52～7.19 (m, 10H), 6.93 (d, J=8.8 Hz, 1H), 5.81～5.27 (m, 1H), 3.10～2.88 (m, 1H), 2.54～2.32 (m, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.92, 137.60, 133.27, 133.24, 132.47, 131.11, 129.02, 128.38, 127.37, 127.07, 126.71, 125.85, 125.37, 125.26, 123.88, 122.61, 120.27, 118.63, 115.65, 114.12 (t, J=240.0 Hz), 43.95 (t, J=5.0 Hz), 43.62 (t, J=23.0 Hz), 28.66; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.66 (d, J=293.0 Hz, 1F), −114.79 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}ClF_2NO$ 422.1123, found 422.1120.

3-Bromo-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3n**): White solid. m.p. 152～153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (d, J=8.3 Hz, 1H), 7.66～7.38 (m, 7H), 7.36～7.26 (m, 3H), 7.17

(d, J=8.7 Hz, 1H), 5.82～5.44 (m, 1H), 3.06 (qd, J=15.2, 14.8, 5.7 Hz, 1H), 2.66～2.40 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.91, 138.82, 134.29, 133.49, 132.14, 130.62, 130.02, 129.42, 129.24, 128.42, 128.12, 127.02, 126.45, 124.93, 124.07, 122.43, 121.44, 119.69, 116.70, 115.15 (t, J=239.0 Hz), 44.88 (t, J=5.0 Hz), 44.66 (t, J=21.0 Hz), 29.74; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.70 (d, J=293.0 Hz, 1F), −114.84 (d, J=293.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{19}BrF_2NO$ 466.0618, found 466.0620.

5-(2,2-Difluoroethyl)-5,12-dimethylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3o**): White solid. m.p. 165～166 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, J=7.7 Hz, 1H), 7.96 (d, J=7.4 Hz, 1H), 7.51 (d, J=7.3 Hz, 1H), 7.47～7.11 (m, 5H), 5.44 (t, J=54.6 Hz, 1H), 3.07～2.88 (m, 1H), 2.57 (s, 3H), 2.53～2.34 (m, 1H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.29, 135.48, 133.25, 131.39, 128.16, 126.96, 126.63, 125.41, 125.18, 124.93, 124.35, 123.37, 117.43, 115.72, 114.43 (t, J=239.0 Hz), 113.91, 43.80 (t, J=4.0 Hz), 43.73 (t, J=22.0 Hz), 28.84, 10.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.78 (d, J=290.0 Hz, 1F), −115.18 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{20}H_{18}F_2NO$ 326.1356, found 326.1353.

3-Bromo-5-(2,2-difluoroethyl)-5,12-dimethylindolo-[2,1-*a*]isoquinolin-6(5*H*)-one (**3p**): White solid. m.p. 116～117 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (q, J=8.6, 6.6 Hz, 1H), 7.96～7.64 (m, 2H), 7.61～7.41 (m, 3H), 7.36～7.24 (m, 1H), 5.76～5.28 (m, 1H), 3.04～2.82 (m, 1H), 2.53 (s, 3H), 2.40 (d, J=16.1 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.53, 138.69, 134.31, 132.27, 130.97, 129.60, 128.37, 126.74, 126.31, 125.19, 124.61, 121.82, 118.62, 116.77, 115.63, 115.20 (t, J=239.0 Hz), 44.79 (t, J=4Hz), 44.74 (t, J=22.0 Hz), 29.81, 11.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.70 (d, J=290 Hz, 1F), −114.87 (d, J=290 Hz, 1F). HRMS (ESI) calcd for $C_{20}H_{17}BrF_2NO$ 404.0462, found 404.0460.

5-(2,2-Difluoroethyl)-5-methyl-6-*oxo*-5,6-dihydroindolo[2,1-*a*]isoquinoline-12-carbonitrile (**3q**): White solid. m.p. 105～106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98～8.40 (m, 2H), 7.92～7.19 (m, 6H), 5.47 (t, J=55.8 Hz, 1H), 3.28～3.00 (m, 1H), 2.69 (d, J=39.0 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.65, 162.07, 140.17, 137.69, 131.51, 128.97, 128.73, 127.43, 126.46, 126.08, 125.78, 122.36, 119.26, 117.18, 115.41, 114.92 (t, J=241.0 Hz), 45.19 (t, J=4.0 Hz), 44.86 (t, J=21 Hz), 30.45; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −115.45 (m, 1F), −115.91 (m, 1F). HRMS (ESI) calcd for $C_{20}H_{15}F_2N_2O$ 337.1152, found 337.1148.

Ethyl 5-(2,2-difluoroethyl)-5-methyl-6-*oxo*-5,6-dihydroindolo[2,1-*a*]isoquinoline-12-carboxylate (**3r**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (dd, J=42.0, 8.0 Hz, 2H), 7.95 (d, J=7.7 Hz, 1H), 7.82～7.31 (m, 5H), 5.56 (t, J=55.9 Hz, 1H), 4.78～4.36 (m, 2H), 3.19～2.87 (m, 1H), 2.71～2.40 (m, 1H), 1.75 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.11, 165.65, 137.53, 136.07, 134.25, 130.34, 128.94, 128.34, 127.67, 126.53, 125.83, 125.34, 123.60, 121.14, 116.54, 115.14 (t, J=238.0 Hz), 110.97, 61.43, 45.34 (t, J=4.0 Hz), 44.65 (t, J=22.0 Hz), 29.05, 14.37; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.62 (d, J=290.0 Hz, 1F), −115.00 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{22}H_{20}F_2NO_3$ 384.1411, found 384.1410.

5-(2,2-Difluoroethyl)-5-methyl-12-(*p*-tolyl)indolo[2,1-*a*]isoquinolin-6(5H)-one (**3s**):[4b] Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (t, J=9.1 Hz, 1H), 7.77～7.21 (m, 10H), 7.16～6.98 (m, 1H), 5.57 (t, J=56.0 Hz, 1H), 3.12 (s, 1H), 2.61 (s, 1H), 2.49 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.69, 137.96, 136.61, 134.28, 132.45, 130.74, 130.03, 129.98, 128.89, 128.46, 127.22, 126.11, 126.08, 125.67, 125.21, 124.70, 120.91, 119.62, 116.68, 115.46 (t, J=239.0 Hz), 44.94 (t, J=4.0 Hz), 44.66 (t, J=21.0 Hz), 29.84, 21.45; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.71 (d, J=290.0 Hz, 1F), −115.08 (d, J=290 Hz, 1F).

5-Benzyl-5-(2,2-difluoroethyl)-12-phenylindolo[2,1-*a*]-isoquinolin-6(5*H*)-one (**3t**): White solid. m.p. 123～124 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (t, J=9.0 Hz, 1H), 7.81～6.73 (m, 15H), 6.53 (s, 2H), 5.68 (t, J=55.9 Hz, 1H), 3.79～3.37 (m, 2H), 3.07 (d, J=12.5 Hz, 1H), 2.96～2.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.36, 134.20, 133.92, 133.78, 133.70, 131.91, 129.95, 129.38, 129.06, 128.67, 128.15, 127.97, 127.52, 127.20, 127.04, 126.95, 126.33, 125.90, 125.42, 124.54, 119.27, 116.54, 115.55 (t, J=239.0 Hz), 51.37, 51.11 (t, J=3.0 Hz), 41.99 (t, J=21.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.47 (d, J=290.0 Hz, 1F), −114.99 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{31}H_{24}F_2NO$ 464.1826, found 464.1822.

5-(2,2-Difluoroethyl)-5,12-diphenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3u**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J=8.3 Hz, 1H), 7.57～7.03 (m, 11H), 6.98～6.82 (m, 2H), 6.71 (t, J=7.6 Hz, 2H), 6.44 (d, J=7.5 Hz, 2H), 5.79～5.42 (m, 1H), 3.47 (d, J=12.6 Hz, 1H), 2.99 (d, J=12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.34, 133.19, 132.90, 132.76, 132.69, 130.90, 128.93, 128.36, 128.04, 127.65, 127.12, 126.94, 126.50, 126.17, 126.01, 125.93, 125.31, 124.88, 124.39, 123.52, 119.28, 118.25, 115.52, 114.53 (t, J=239.0 Hz), 50.34 (q, J=3.0 Hz), 40.98 (t, J=22.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.50 (d, J=290.0 Hz, 1F), −115.03 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{30}H_{22}F_2NO$ 450.1669, found 450.1666.

5-(2,2-Difluoroethyl)-12-phenyl-5,6-dihydroindolo[2,1-*a*]isoquinoline (**3v**): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71～7.34 (m, 7H), 7.32～6.94 (m, 6H), 6.03～5.65 (m, 1H), 4.49 (d, J=12.4 Hz, 1H), 4.16 (d, J=13.0 Hz, 1H), 3.48 (s, 1H), 2.25～1.91 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.99, 135.43, 135.37, 130.47, 129.64, 129.44, 129.11, 128.87, 128.81,128.39, 128.09, 127.53, 127.49, 126.84, 126.62, 122.70, 120.26, 119.73, 116.35 (t, J=238.0 Hz), 108.72, 44.60 (t, J=5.0 Hz), 37.03 (t, J=24.0 Hz), 29.72; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −116.07 (d, J=282.0 Hz, 1F), −116.84 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{24}H_{20}F_2N$ 360.1564, found 360.1560.

9,11-Dichloro-5-(2,2-difluoroethyl)-5-methyl-12-phenyl-indolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3w**): Pale yellow solid. m.p. 56～57 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 7.63～7.35 (m, 6H), 7.35～7.20 (m, 2H), 7.12 (d, J=8.2 Hz, 1H), 7.00 (t, J=7.7 Hz, 1H), 5.51 (td, J=56.0, 6.9 Hz, 1H), 3.18～2.97 (m, 1H), 2.67～2.42 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.90, 136.55, 135.37, 134.00, 131.55, 130.91, 130.83, 130.61, 129.06, 128.98, 128.93, 128.48, 127.50, 127.00, 126.66, 126.33, 126.12, 125.97, 124.46, 119.86, 115.74, 115.26 (t, J=238.0 Hz), 44.94 (t, J=3.0 Hz), 44.86 (t, J=21.0 Hz), 30.03; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −115.12 (d, J=290.0 Hz, 1F), −115.75 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{25}H_{18}Cl_2F_2NO$ 456.0734, found 456.0731.

8,10-Dichloro-5-(2,2-difluoroethyl)-5-methyl-12-phenylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3x**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75～7.27 (m, 9H), 7.16 (s, 1H), 7.10～6.98 (m, 1H), 5.70 (t, J=56.2 Hz, 1H), 3.15～2.88 (m, 1H), 2.73～2.47 (m, 1H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.68, 137.88, 137.03, 133.75, 132.66, 130.87, 130.15, 129.60, 129.39, 128.74, 127.47, 127.38, 126.25, 126.08, 124.94, 122.72, 119.67, 118.09, 115.34 (t, J=239.0 Hz), 46.07 (t, J=5.0 Hz), 44.44 (t, J=22.0 Hz), 28.68; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.03 (d, J=20.1 Hz, 2F). HRMS (ESI) calcd for $C_{25}H_{18}Cl_2F_2NO$ 456.0734, found 456.0731.

5-(2,2-Difluoroethyl)-2,5,12-trimethylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3y**) and 5-(2,2-difluoroethyl)-4,5,12-trimethylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (**3y'**): Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (d, J=7.9 Hz, 1H), 8.00 (s, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.47～7.33 (m, 4H), 5.54 (tt, J=56.0, 4.5 Hz, 1H), 3.03 (qd, J=14.5, 5.9 Hz, 1H), 2.67 (s, 3H), 2.49 (ddd, J=33.6, 14.2, 3.7 Hz, 1H), 1.71 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.80, 134.92, 134.31, 133.70, 132.13, 128.85, 127.99, 127.93, 127.78, 126.47, 125.00, 124.60, 118.73, 116.78, 116.14, 115.24 (t, J=241.0 Hz), 65.58, 44.62 (t, J=5.0 Hz), 44.40 (t, J=20 Hz), 29.96, 11.51; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.77 (m, 1F), −114.84 (m, 1F). HRMS (ESI) calcd for $C_{21}H_{20}F_2NO$ 340.1513, found 340.1515.

4-(2,2-Difluoroethyl)-4,11-dimethylthieno[2',3':3,4]pyrido[1,2-*a*]indol-5(4*H*)-one (**3z**): Pale yellow solid. m.p. 128～129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, J=6.5 Hz, 1H), 8.28 (d, J=7.9 Hz, 1H), 7.66 (d, J=5.2 Hz, 1H), 7.45 (s, 2H), 7.14 (d, J=5.3 Hz, 1H), 5.53 (t, J=50.9 Hz, 1H), 3.04 (dt, J=13.8, 6.9 Hz, 1H), 2.51 (q, J=15.8, 15.1 Hz, 1H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.64, 172.49, 144.31, 137.77, 134.57, 131.84, 127.41, 126.99, 126.19, 125.22, 123.31, 120.89, 117.21, 114.88 (t, J=245.0 Hz), 44.97 (t, J=7.0 Hz), 44.83 (t, J=22.0 Hz), 29.72, 29.47; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −115.35 (d, J = 15.5 Hz). HRMS (ESI) calcd for $C_{18}H_{16}F_2NOS$ 332.0921, found 332.0918.

5-(2,2-Difluoroethyl)-5,12-dimethylindolo[2,1-*a*][2,7]-naphthyridin-6(5*H*)-one (**4a**): Pale yellow solid. m.p. 128～129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.78 (d, J=12.1 Hz, 1H), 8.70 (d, J=44.4 Hz, 2H), 8.32 (d, J=12.5 Hz, 1H), 7.75～7.37 (m, 3H), 5.82～5.42 (m, 1H), 3.09 (d, J=25.1 Hz, 2H), 1.76 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.60, 172.26, 156.61, 151.16, 135.55, 134.53, 128.43, 127.50, 126.31, 122.96, 120.89, 119.49, 118.49, 117.73, 115.36 (t, J=238.0 Hz), 48.11, 42.83 (t, J=4.0 Hz), 42.26 (t, J=21.0 Hz), 29.49; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −115.31 (d, J=290.0 Hz, 1F), −116.22 (d, J=290.0 Hz, 1F). HRMS (ESI) calcd for $C_{19}H_{17}F_2N_2O$ 327.1309, found 27.1307.

5-(2,2-Difluoroethyl)-5-methyl-14-phenylbenzo[6,7]indolo[2,1-*a*]isoquinolin-6(5*H*)-one (**4b**): White solid. m.p. 90～91 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (d, J=8.9 Hz, 1H), 7.87 (dd, J=26.2, 8.6 Hz, 2H), 7.75～7.51 (m, 5H), 7.37 (dd, J=19.4, 8.2 Hz, 3H), 7.29～7.16 (m, 2H), 7.12 (d, J=8.2 Hz, 1H), 7.00 (t, J=7.8 Hz, 1H), 5.57 (tdd, J=56.1, 6.7, 3.4 Hz, 1H), 3.26～2.98 (m, 1H), 2.70～2.45 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.56, 136.62, 136.17, 131.83, 131.77, 130.41, 130.20, 130.05, 130.00, 128.77, 128.60, 128.52, 127.99, 127.55, 127.35, 127.08, 126.08, 126.02, 125.56, 125.41, 125.17, 124.77, 123.57, 122.34, 116.28, 115.42(t, J=239.0 Hz), 45.08 (t, J=3.0 Hz), 44.86 (t, J=21.0 Hz), 29.95; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.80 (d, J=290.0 Hz, 1F), −115.26 (d, J = 290.0 Hz, 1F). HRMS (ESI) calcd for $C_{29}H_{22}F_2NO$ 438.1669, found 438.1667.

Supporting Information Copies of ^{1}H NMR and ^{13}C NMR spectra of the products **3a**～**4b**. The Supporting Information is available free of charge *via* the Internet at http://sioc-journal.cn/.

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