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Visible light induced hydrodifluoromethylation of alkenes derived from oxindoles with (difluoromethyl)triphenylphosphonium bromide

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ABSTRACT

A visible light induced hydrodifluoromethylation of alkenes derived from oxindoles with (difluoromethyl)triphenylphosphonium bromide was developed. This reaction delivers a series of previously unknown difluoromethylated oxindoles containing C—CF_2H quaternary centers in moderate to excellent yields. The resulting CF_2H-containing oxindoles are potentially useful in drug discovery.

1. Introduction

The indolin-2-one (oxindole) frame is commonly found in natural compounds as well as in biological active compounds [1]. Especially, the 3-substituted oxindoles are widely recognized as valuable synthetic intermediates [2]. On the other hand, the incorporation of fluorine atom(s) and fluorine-containing groups into organic molecules has a significant influence on the lipophilicity, metabolic stability, and bioavailability of compounds [3]. Given the biological importance of fluorinated functional groups and oxindole scaffolds, the fluorinated oxindoles have many applications in drug development [4]. Over the last decade, there has been continuous interest in the preparation of oxindoles bearing fluorinated functional groups at the 3-position. Up to now, numerous synthetic methods have been developed for the preparation fluorinated oxindoles, such as 3-fluoro-2-oxindoles [5], 3,3-difluoro-2-oxindoles [6], 3-trifluoromethyl-2-oxindoles [7], 3-difluoroalkyl-2-oxindoles [8], and 3-monofluoroalkyl-2-oxindoles [9].

The difluoromethyl moiety (CF_2H) is an intriguing structural motif that has special biological properties [10]. Additionally, it is proposed to act as a hydrogen bond donor and thus a surrogate for hydroxyl or thiol groups [11]. Recently, a variety of methods have been developed for the direct introduction of CF_2H into organic compounds [12,13]. However, the synthesis of difluoromethylated oxindoles remains limited. In 2014, the groups of Dolbier [14a], Wang [14b,c], and Tan [14d] independently reported the photoredox- or transition-metal-catalyzed radical difluoromethylation/cyclization of *N*-arylacrylamides for the construction of difluoromethylated oxindoles with different CF_2H sources (Scheme 1a). Although these methods are efficient, the substrates are limited to the disubtituted terminal alkenes. Thus, the development of new synthetic methods of difluoromethylated oxindoles is highly desirable.

Very recently, our group disclosed that bromodifluoromethylphosphonium bromide was used as a CF_2H radical precursor for the difunctionalization-type difluoromethylation reactions of alkenes under visible light photoredox conditions [15]. To further extend the application of difluoromethylphosphonium salts, we became interested in the incorporation of CF_2H into oxindoles (Scheme 1b). This protocol affords a series of difluoromethylated oxindoles containing C—CF_2H quaternary centers, which are difficult to access by existing methods.

2. Results and discussion

We initiated our exploration by investigating the difluoromethylation of 3-(propan-2-ylidene)indolin-2-one (**1a**) with several difluoromethylphosphonium salts (**2a–d**) in the presence of $Ir(ppy)_3$ (3 mol%) under visible-light irradiation (Table 1). To our disappointment, no desired product was obtained using difluoromethylphosphonium salts **2a–c** (entries 1–3). In contrast, difluoromethylphosphonium bromide (**2d**) could promote this reaction, giving the difluoromethylated product **3a** in 33% yield (entry 4). We envisioned that the bromide anion probably acted as a reductive quencher in the catalytic cycle of this reaction. Thus, we investigated different additives, including tetra-*n*-butylammonium iodide (TBAI), diisopropylethylamine (DIPEA), NaI, and KI (entries 5–8). Among them, KI was

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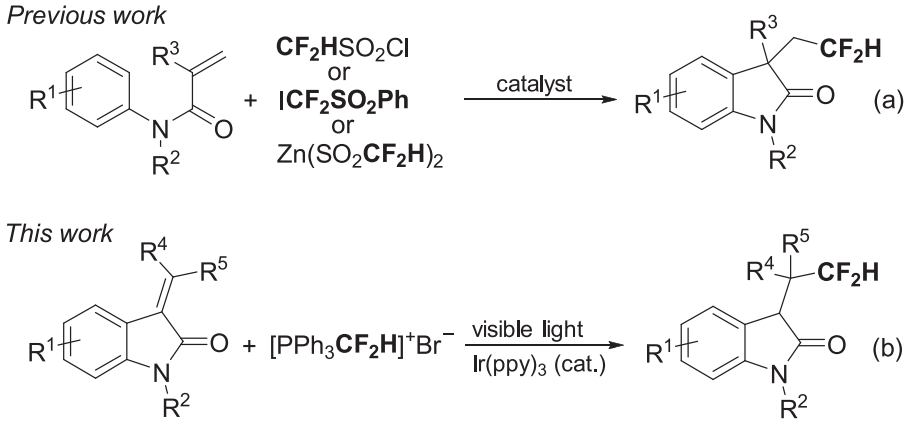
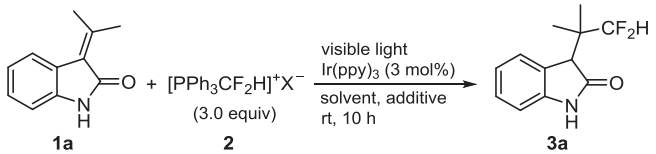


Scheme 1. Synthesis of difluoromethylated oxindoles.

Table 1
Optimization of reaction conditions.[a]



Entry	2 (X)	Solvent	Additive	Yield (%)[b]
1	**2a** (PF_6)	DMF	–	0
2	**2b** (BF_4)	DMF	–	0
3	**2c** (OTf)	DMF	–	0
4	**2d** (Br)	DMF	–	33
5	**2d** (Br)	DMF	TBAI	72
6	**2d** (Br)	DMF	DIPEA	50
7	**2d** (Br)	DMF	NaI	75
8	**2d** (Br)	DMF	KI	77
9	**2d** (Br)	DCE	KI	84
10	**2d** (Br)	EA	KI	0
11	**2d** (Br)	THF	KI	89
12	**2d** (Br)	CH_3CN	KI	96
13[c]	**2d** (Br)	CH_3CN	KI	71
14[d]	**2d** (Br)	CH_3CN	KI	85
15[e]	**2d** (Br)	CH_3CN	KI	0
16[f]	**2d** (Br)	CH_3CN	KI	94
17[g]	**2d** (Br)	CH_3CN	KI	0
18[h]	**2d** (Br)	CH_3CN	KI	0

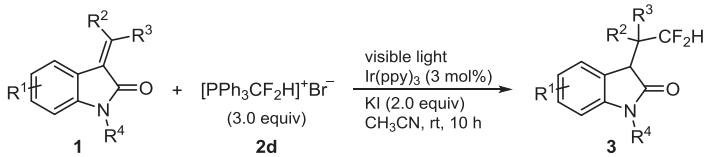
[a] Reaction conditions: **1a** (0.2 mmol), difluoromethyltriphenylphosphonium salt (0.6 mmol), $Ir(ppy)_3$ (0.006 mmol), additive (0.4 mmol), solvent (2.0 mL), visible light, rt, under N_2.
[b] Yields were determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard.
[c] Difluoromethyltriphenylphosphonium bromide (0.4 mmol).
[d] $Ir(ppy)_3$ (0.002 mmol) was added.
[e] Without degassing.
[f] H_2O (0.6 mmol) was added.
[g] Without $Ir(ppy)_3$.
[h] No light.

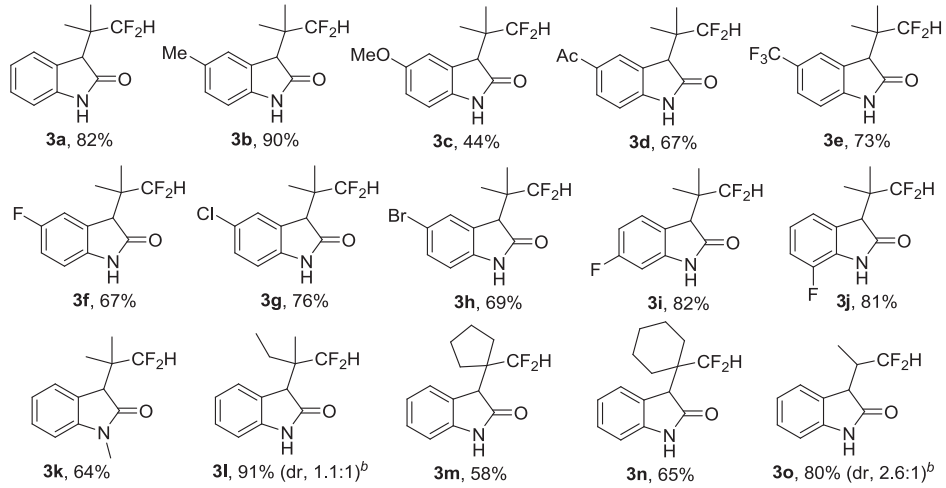
superior to other additives, affording **3a** in 77% yield (entry 8). Subsequent variation of the solvent led to the discovery that CH_3CN was an excellent solvent for this reaction (entries 9–12). Decreasing the amount of **2d** or $Ir(ppy)_3$ resulted in lower yields (entries 13 and 14). Notably, **1a** was not converted at all without the degassing of the reaction system, which signified that rigorous exclusion of oxygen is necessary for this reaction (entry 15). Furthermore, the presence of water did not affect the reaction (entry 16). Finally, the control experiments showed that both the photocatalyst and visible light were indispensable for this transformation (entries 17 and 18).

With the optimized reaction conditions in hand (Table 1, entry 12), the substrate scope of this transformation was investigated. As shown in Table 2, a series of oxindole-derived alkenes (**1b–o**) with different substituents and substitution patterns underwent the hydrodifluoromethylation to afford the corresponding products (**3b–o**) in moderate to excellent yields. The substrates with either electron-donating (**1b** and **1c**) or electron-withdrawing substituents (**1d** and **1e**) were suitable substrates. Moreover, different halide substitutions on the oxindole ring (**1f–j**) were well tolerated, and the corresponding adducts were obtained in high yields. When compound **1k** with methyl as the *N*-protecting group was subjected to the reaction, slightly lower yield was obtained. Finally, this photocatalytic protocol presented herein was easily extended to other polysubstituted oxindole-derived alkenes (**1l–1o**). The structure of these hydrodifluoromethylated products were confirmed by the X-ray crystallographic analysis of **3g** (see the Supporting information).

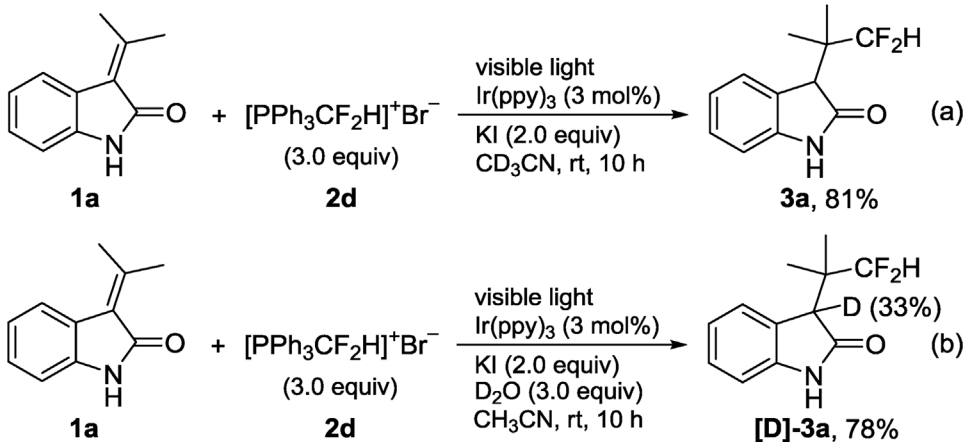
To gain insight into the reaction mechanism, the isotopic labeling experiments were conducted under standard reaction conditions. When

Table 2
Scope of substrates.[a]





[a]Reaction conditions: **1a** (0.5 mmol), difluoromethyltriphenylphosphonium salt (1.5 mmol), $Ir(ppy)_3$ (0.015 mmol), KI (1.0 mmol), CH_3CN (5.0 mL), visible light, rt, under N_2, 10 h, isolated yields.
[b]dr ratio was determined by ^{19}F NMR spectroscopy.



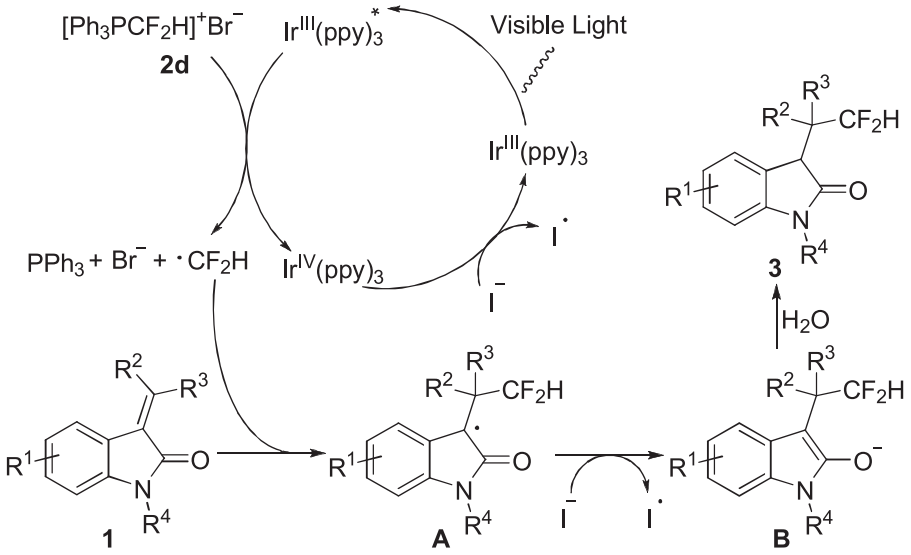
Scheme 2. Isotopic mechanistic experiments.

the reaction of **1a** was performed in CD_3CN, we did not observe any incorporation of the deuterium into product **3a** (Scheme 2a). In contrast, the reaction in the presence of D_2O (3.0 equiv) provided deuterated product **[D]-3a** in 78% yield with a deuterium content of 33% (Scheme 2b). These results indicated that the hydrogen atom probably originates from trace amount of water in the reaction system.

On the basis of the above results and previous reports, a plausible mechanism for this hydrodifluoromethylation is depicted in Scheme 3. First, irradiation with visible light excites $Ir^{III}(ppy)_3$ into $*Ir^{III}(ppy)_3$. Then, oxidation of $*Ir^{III}(ppy)_3$ by difluoromethylphosphonium **2d** affords $Ir^{IV}(ppy)_3$ and CF_2H radical [15]. Subsequently, the addition of CF_2H radical to alkenes **1** generates radical intermediate **A**, which is reduced by iodide anion to give enolate anion **B** [16]. Finally, protonation of enol anion **B** with H_2O affords the desired product **3**. On the other hand, reduction of $Ir^{IV}(ppy)_3$ by iodide anion regenerates the ground-state photocatalyst $Ir^{III}(ppy)_3$ [17].

3. Conclusion

In conclusion, we have developed a hydrodifluoromethylation of alkenes derived from oxindoles with (difluoromethyl)triphenylphosphonium bromide under photoredox catalysis. This photocatalytic protocol enables access to a variety of difluoromethylated oxindoles containing C−CF_2H quaternary centers in moderate to excellent yields. Efforts are in progress towards the application of this protocol to synthesize biologically active compounds.



Scheme 3. Proposed reaction mechanism.

4. Experimental section

4.1. General information

^{1}H NMR (TMS as the internal standard), ^{19}F NMR, and ^{13}C NMR spectra were recorded on a Agilent 400 MHz spectrometer, Bruker AM 400 MHz/500 MHz or VARIAN400 MHz spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS data using ESI were obtained on a Thermo Fisher Scientific LTQ FTICR-MS. All reagents were used as received from commercial sources without further purification or prepared as described in references. Substrates **1a** [18], **1g** [19], **1h** [20], **1l** [20], **1m** [21], **1n** [22], and **1o** [23] are all known compounds.

4.2. General procedure for the synthesis of 3-(propan-2-ylidene)indolin-2-one

A 50 mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar was charged with indolin-2-one (10.0 mmol), ethanol (10 mL), acetone (7.3 mL, 0.1 mmol, 10.0 equiv), benzylamine (0.33 mL, 3.0 mmol, 0.3 equiv), and acetic acid (0.17 mL, 3.0 mmol, 0.3 equiv). Then, the reaction mixture was heated under reflux for 2 h. The precipitation was filtered off and washed with cold PE (10 mL). The obtained product was dried for 30 min and used without further purification.

4.2.1. 5-Methyl-3-(propan-2-ylidene)indolin-2-one (1b)

Brown solid, mp 215–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.32 (s, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 2.62 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 155.2, 137.4, 130.8, 128.0, 124.6, 124.5, 123.4, 109.2, 25.4, 23.3, 21.6. IR (thin film) ν 2918, 2848, 1697, 1646, 1629, 1614, 655 cm^{-1}; MS (ESI): m/z 188 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{14}NO^+$: 188.1070; Found: 188.1069.

4.2.2. 5-Methoxy-3-(propan-2-ylidene)indolin-2-one (1c)

Yellow solid, mp 202–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.10 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.73 (dd, J = 8.4, 2.3 Hz, 1H), 3.80 (s, 3H), 2.61 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 155.8, 154.9, 133.6, 125.3, 123.5, 111.7, 111.6, 109.4, 56.0, 25.2, 23.2. IR (thin film) ν 2919, 1693, 1627, 1481, 678, 668, 653 cm^{-1}; MS (ESI): m/z 204 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{14}NO_2^+$: 204.1019; Found: 204.1017.

4.2.3. 5-Acetyl-3-(propan-2-ylidene)indolin-2-one (1d)

White solid, mp 219–221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.17 (s, 1H), 7.85 (dd, J = 8.1, 1.2 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 2.64 (s, 3H), 2.60 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 170.2, 158.4, 143.7, 131.5, 129.6, 124.6, 123.7, 122.3, 108.9, 26.5, 25.7, 23.5. IR (thin film) ν 2919, 2849, 1674, 1658, 1646, 1469, 668, 655 cm^{-1}; MS (ESI): m/z 216 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{13}H_{14}NO_2^+$: 216.1019; Found: 216.1017.

4.2.4. 3-(Propan-2-ylidene)-5-(trifluoromethyl)indolin-2-one (1e)

White solid, mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.35 (s, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 2.62 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 158.2, 144.0 (d, J = 2.0 Hz), 138.2, 125.2, 122.8, 120.8 (q, J = 255.78 Hz), 120.6, 117.6, 109.8, 25.4, 23.5. IR (thin film) ν 1691, 1621, 1241, 1220, 1194, 1151, 688, 652 cm^{-1}; MS (ESI): m/z 258 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{11}FNO_2^+$: 258.0736; Found: 258.0734.

4.2.5. 5-Fluoro-3-(propan-2-ylidene)indolin-2-one (1f)

Yellow solid, mp 217–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.24 (dd, J = 9.9, 2.3 Hz, 1H), 6.93 (td, J = 9.2, 2.5 Hz, 1H), 6.72 (dd, J = 8.5, 4.8 Hz, 1H), 2.45 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.5, 157.5 (d, J = 234.3 Hz), 156.2, 136.6, 124.5 (d, J = 8.9 Hz), 122.6 (d, J = 2.7 Hz), 113.6 (d, J = 23.2 Hz), 110.9 (d, J = 26.3 Hz), 109.4 (d, J = 8.5 Hz), 24.7, 22.4. IR (thin film) ν 2919, 2849, 1689, 1646, 1632, 668 cm^{-1}; MS (ESI): m/z 192 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{11}H_{11}FNO^+$: 192.0819; Found: 192.0818.

4.2.6. 6-Fluoro-3-(propan-2-ylidene)indolin-2-one (1i)

White solid, mp 193–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 7.41 (dd, J = 8.5, 5.6 Hz, 1H), 6.66 (ddd, J = 9.9, 8.7, 2.5 Hz, 1H), 6.54 (dd, J = 9.2, 2.5 Hz, 1H), 2.41 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.7, 161.7 (d, J = 244.4 Hz), 153.6 (d, J = 2.5 Hz), 142.0 (d, J = 12.1 Hz), 124.8 (d, J = 9.6 Hz), 121.8, 120.0 (d, J = 2.7 Hz), 106.9 (d, J = 22.2 Hz), 96.9 (d, J = 26.3 Hz), 24.7, 22.2. IR (thin film) ν 2919, 2849, 1689, 1646, 1632, 668 cm^{-1}; MS (ESI): m/z 192 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{11}H_{11}FNO^+$: 192.0819; Found: 192.0823.

4.2.7. 7-Fluoro-3-(propan-2-ylidene)indolin-2-one (1j)

White solid, mp 212–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.04–6.98 (m, 1H), 6.87 (td, J = 8.1, 5.2 Hz, 1H), 2.45 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 156.4, 146.2 (d, J = 241.4 Hz), 127.3 (d, J = 12.8 Hz), 126.6 (d, J = 4.8 Hz), 122.3 (d, J = 3.5 Hz), 121.5 (d, J = 6.0 Hz), 119.6 (d, J = 2.9 Hz), 114.3 (d, J = 17.0 Hz), 24.9, 22.4. IR (thin film) ν 2919, 2849, 1686, 1658, 1621, 716 cm^{-1}; MS (ESI): m/z 192 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{11}H_{11}FNO^+$: 192.0819; Found: 192.0818.

4.2.8. 1-Methyl-3-(propan-2-ylidene)indolin-2-one (1k)

Yellow solid, mp 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.7 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.22 (s, 3H), 2.61 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 154.8, 142.2, 127.6, 123.7, 123.4, 122.8, 121.7, 107.6, 25.7, 25.3, 23.3. IR (thin film) ν 2919, 2849, 1696, 1632, 1469, 1338, 746, 668 cm^{-1}; MS (ESI): m/z 188 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{14}NO^+$: 188.1070; Found: 188.1069.

4.3. General procedure for the synthesis of 3-(1,1-difluoro-2-methylpropan-2-yl)indolin-2-one

A 25 mL Schlenk flask equipped with a rubber septum and a magnetic stir bar was charged with $Ir(ppy)_3$ (9.8 mg, 0.015 mmol, 3 mol %), substrates (**1a–1o**) (0.5 mmol, 1.0 equiv.), KI (165.0 mg, 1.0 mmol, 2.0 equiv.), $[PPh_3CF_2H]^+Br^-$ (589.8 mg, 1.5 mmol, 3.0 equiv.), and CH_3CN (5.0 mL). The flask was sealed with 3 M vinyl electrical tape. The mixture was degassed three times by the freeze-pump-thaw procedure. The flask was placed at a distance of 5 cm from the blue LEDs. The mixture was stirred at room temperature under nitrogen atmosphere and irradiated by blue LEDs for 10 h. After the reaction was complete, the reaction mixture was concentrated under vacuum and the crude product was purified by column chromatography on silica gel to give the products (**3a–3o**).

4.3.1. 3-(1,1-Difluoro-2-methylpropan-2-yl)indolin-2-one (3a)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–17/1) as the eluent, compound **3a** was obtained as a light brown solid (92.6 mg, 82%), mp 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.27 (dd, J = 21.3, 7.1 Hz, 2H), 7.02 (t, J = 7.1 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.37 (t, J = 57.0 Hz, 1H), 3.54 (s, 1H), 1.23 (s, 3H), 1.02 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.30 (dd, J = 278.2, 56.4 Hz, 1F), −132.72 (dd, J = 274.5, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 142.6, 128.7, 126.4, 125.9, 122.3, 118.2 (t, J = 246.4 Hz), 110.3, 51.0, 41.4 (t, J = 19.1 Hz), 17.7, 17.2. IR (thin film) ν 3181, 2919, 1700, 1618, 1473, 1237, 1077, 1046, 755, 671 cm^{-1}; MS (ESI): m/z 226 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{14}F_2NO^+$: 226.1038; Found: 226.1037.

4.3.2. 3-(1,1-Difluoro-2-methylpropan-2-yl)-5-methylindolin-2-one (3b)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–10/1) as the eluent, compound **3b** was obtained as a white solid (107.8 mg, 90%), mp 193–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.11 (s, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.38 (t, J = 57.1 Hz, 1H), 3.50 (s, 1H), 2.34 (s, 3H), 1.23 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.48 (dd, J = 274.5, 56.4 Hz, 1F), −132.80 (dd, J = 274.5, 56.4 Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 140.0, 131.8, 129.0, 127.3, 126.0, 118.3 (t, J = 245.7 Hz), 109.7, 51.0, 41.4 (t, J = 19.1 Hz), 21.4, 17.7, 17.2. IR (thin film) ν 3357, 2919, 2849, 1698, 1658, 1632, 1469 cm^{-1}; MS (ESI): m/z 238 $(M-H)^-$; HRMS (ESI) m/z: $[M-H]^-$ Calculated for $C_{13}H_{14}F_2NO^-$: 238.1049; Found: 238.1045.

4.3.3. 3-(1,1-Difluoro-2-methylpropan-2-yl)-5-methoxyindolin-2-one (3c)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–10/1) as the eluent, compound **3c** was obtained as a brown solid (56.1 mg, 44%), mp 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 6.90 (s, 1H), 6.79 (m, 2H), 6.38 (t, J = 57.1 Hz, 1H), 3.77 (s, 3H), 3.49 (s, 1H), 1.22 (s, 3H), 1.00 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.14 (dd, J = 278.2, 56.4 Hz, 1F), −132.82 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 155.5, 136.0, 127.3, 118.2 (t, J = 246.4 Hz), 114.2, 112.8, 110.3, 55.9, 51.4, 41.4 (t, J = 19.2 Hz), 17.6, 17.2. IR (thin film) ν 2922, 1698, 1490, 1471, 1216, 1080, 1051, 1036, 804 cm^{-1}; MS (ESI): m/z 256 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{13}H_{16}F_2NO_2^+$: 256.1144; Found: 256.1142.

4.3.4. 5-Acetyl-3-(1,1-difluoro-2-methylpropan-2-yl)indolin-2-one (3d)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–10/1) as the eluent, compound **3d** was obtained as a white solid (89.9 mg, 67%), mp 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.94 (s, 1H), 7.91 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.31 (t, J = 56.8 Hz, 1H), 3.56 (s, 1H), 2.56 (s, 3H), 1.25 (s, 3H), 1.01 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −130.75 (dd, J = 278.2, 56.4 Hz, 1F), −132.52 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 178.9, 147.0, 131.9, 130.6, 126.4, 117.9 (t, J = 245.3 Hz), 109.7, 50.7, 41.6 (t, J = 19.2 Hz), 26.5, 17.8, 17.4. IR (thin film) ν 2922, 1719, 1613, 1359, 1258, 1083, 1054, 825, 544 cm^{-1}; MS (ESI): m/z 268 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{14}H_{16}F_2NO_2^+$: 268.1144; Found: 268.1143.

4.3.5. 3-(1,1-Difluoro-2-methylpropan-2-yl)-5-(trifluoromethyl)indolin-2-one (3e)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3e** was obtained as a pale brown solid (107 mg, 73%), mp 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.13 (s, 1H), 7.09 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.27 (t, J = 56.9 Hz, 1H), 3.50 (s, 1H), 1.18 (s, 3H), 0.96 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.54 (s, 3F), −130.92 (dd, J = 278.2, 56.4 Hz, 1F), −132.69 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 144.4 (d, J = 1.9 Hz), 141.2, 127.3, 122.1, 120.7 (q, J = 257.6 Hz), 120.5, 118.0 (t, J = 245.4 Hz), 110.6, 51.3 (d, J = 3.8 Hz), 41.6 (t, J = 19.2 Hz), 17.7 (dd, J = 6.1, 4.0 Hz), 17.5 (dd, J = 5.1, 2.0 Hz). IR (thin film) ν 3180, 2984, 1711, 1489, 1198, 1153, 1081, 1050, 830, 673 cm^{-1}; MS (ESI): m/z 332 $(M+K)^+$; HRMS (ESI) m/z: $[M+K]^+$ Calculated for $C_{13}H_{12}F_5KNO_2^+$: 332.0471; Found: 332.0468.

4.3.6. 3-(1,1-Difluoro-2-methylpropan-2-yl)-5-fluoroindolin-2-one (3f)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3f** was obtained as a light gray solid (81.1 mg, 67%), mp 143–145 °C. ^{1}H NMR (400 MHz, $CCDl_3$) δ 9.55 (s, 1H), 7.10–6.83 (m, 3H), 6.37 (t, J = 56.9 Hz, 1H), 3.55 (s, 1H), 1.25 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.47 to −120.52 (m, 1F), −131.09 (dd, J = 278.2, 56.4 Hz, 1F), −132.70 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 158.8 (d, J = 240.4 Hz), 138.5 (d, J = 2.0 Hz), 127.4 (d, J = 9.1 Hz), 118.0 (t, J = 43.4 Hz), 115.2 (d, J = 23.2 Hz), 114.4 (d, J = 25.3 Hz), 110.7 (d, J = 8.3 Hz), 51.5, 41.5 (t, J = 19.2 Hz), 17.7, 17.3. IR (thin film) ν 2920, 2850, 1699, 1658, 1486, 1078, 1047, 777, 674 cm^{-1}; MS (ESI): m/z 244 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{13}F_3NO^+$: 244.0944; Found: 244.0942.

4.3.7. 5-Chloro-3-(1,1-difluoro-2-methylpropan-2-yl)indolin-2-one (3g)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3g** was obtained as a white solid (98.7 mg, 76%), mp 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.33–7.22 (m, 2H), 6.87 (d,

J = 8.2 Hz, 1H), 6.35 (t, J = 56.9 Hz, 1H), 3.55 (s, 1H), 1.25 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.08 (dd, J = 278.2, 56.4 Hz, 1F), −132.71 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 141.0, 128.8, 127.8, 127.6, 126.8, 117.9 (t, J = 245.4 Hz), 111.1, 51.1, 41.6 (t, J = 19.2 Hz), 17.8, 17.4. IR (thin film) ν 2920, 2850, 1679, 1479, 1238, 1083, 1053, 817, 665 cm^{-1}; MS (ESI) m/z 260 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{13}ClF_2NO^+$: 260.0648; Found: 260.0646.

4.3.8. 5-Bromo-3-(1,1-difluoro-2-methylpropan-2-yl)indolin-2-one (3h)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3h** was obtained as a pale yellow solid (105.3 mg, 69%), mp 205–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.41 (t, J = 9.1 Hz, 2H), 6.82 (d, J = 8.2 Hz, 1H), 6.33 (t, J = 56.9 Hz, 1H), 3.55 (s, 1H), 1.24 (s, 3H), 1.03 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.06 (dd, J = 278.2, 56.4 Hz, 1F), −132.66 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2, 141.4, 131.7, 129.6, 128.0, 117.9 (t, J = 246.4 Hz), 115.1, 111.5, 41.6 (t, J = 19.1 Hz), 17.8, 17.4. IR (thin film) ν 2919, 1695, 1614, 1475, 1316, 1235, 1084, 1051, 884 cm^{-1}; MS (ESI): m/z 304 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{13}BrF_2NO^+$: 304.0143; Found: 304.0143.

4.3.9. 3-(1,1-Difluoro-2-methylpropan-2-yl)-6-fluoroindolin-2-one (3i)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–10/1) as the eluent, compound **3i** was obtained as a white solid (99.7 mg, 82%), mp 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.17 (dd, J = 8.3, 5.2 Hz, 1H), 6.70–6.58 (m, 2H), 6.24 (t, J = 56 Hz, 1H), 3.44 (s, 1H), 1.14 (s, 3H), 0.96 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.68 to −111.74 (m, 1F), −131.12 (dd, J = 278.2, 56.4 Hz, 1F), −132.47 (dd, J = 278.2, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 163.2 (d, J = 247.5 Hz), 143.8 (d, J = 11.1 Hz), 127.5 (d, J = 9.1 Hz), 121.2 (d, J = 3.0 Hz), 120.6 (t, J = 245.4 Hz), 108.8 (d, J = 22.2 Hz), 98.8 (d, J = 27.3 Hz), 50.6 (q, J = 3.4 Hz), 41.5 (t, J = 19.2 Hz), 17.7 (dd, J = 5.1, 4.0 Hz), 17.3 (dd, J = 5.1, 2.0 Hz). IR (thin film) ν 1709, 1627, 1503, 1465, 1337, 1082, 1056, 844, 787 cm^{-1}; MS (ESI): m/z 244 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{13}F_3NO^+$: 244.0944; Found: 244.0942.

4.3.10. 3-(1,1-Difluoro-2-methylpropan-2-yl)-7-fluoroindolin-2-one (3j)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3j** was obtained as a brown solid (98.7 mg, 81%), mp 179–181 °C; ^{1}H NMR (400 MHz, $CCDl_3$) δ 8.48 (s, 1H), 7.34 (s, 1H), 7.14–6.93 (m, 2H), 6.33 (t, J = 56.9 Hz, 1H), 3.60 (s, 1H), 1.23 (s, 3H), 1.05 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.29 (dd, J = 278.2, 56.4 Hz, 1F), −132.69 (dd, J = 278.2, 56.4 Hz, 1F), −113.79 to −111.83 (m, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 147.1 (d, J = 244.4 Hz), 129.7 (d, J = 12.2 Hz), 128.5 (d, J = 3.0 Hz), 122.9 (d, J = 6.1 Hz), 122.2 (d, J = 3.0 Hz), 118.0 (t, J = 236.3 Hz), 115.8 (d, J = 8.1 Hz), 51.2, 41.6 (t, J = 19.3 Hz), 17.7, 17.3. IR (thin film) ν 2919, 2849, 1707, 1644, 1470, 1216, 1081, 1048, 771 cm^{-1}; MS (ESI): m/z 244 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{13}F_3NO^+$: 244.0944; Found: 244.0942.

4.3.11. 3-(1,1-Difluoro-2-methylpropan-2-yl)-1-methylindolin-2-one (3k)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (30/1–20/1) as the eluent, compound **3k** was obtained as a yellow solid (76.8 mg, 64%), mp 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (ddd, J = 5.5, 3.8, 0.7 Hz, 2H), 7.05 (td, J = 7.6, 1.0 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.39 (t, J = 56.0 Hz, 1H), 3.50 (s, 1H), 3.18 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −131.39 (dd, J = 274.5, 56.4 Hz, 1F), −132.92 (dd, J = 274.5, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 145.2, 128.7, 126.2, 125.2, 122.3, 118.3 (t, J = 245.4 Hz), 108.3, 50.3 (t, J = 3.0 Hz), 41.4 (t, J = 19.2 Hz), 26.1, 17.7 (dd, J = 5.3, 3.6 Hz), 17.2 (dd, J = 5.4, 2.3 Hz). IR (thin film) ν 2920, 1705, 1611, 1494, 1347, 1080, 1051, 752, 665 cm^{-1}; MS (ESI): m/z 240 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{13}H_{16}F_2NO^+$: 240.1194; Found: 240.1192.

4.3.12. 3-(1,1-Difluoro-2-methylbutan-2-yl)indolin-2-one (3l)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3l** was obtained as a pale yellow solid (110.2 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.32–7.20 (m, 2H), 7.01 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.23 (t, J = 60.0 Hz, 0.52H), 6.19 (t, J = 56.6 Hz, 0.48), 3.69 (s, 0.48H), 3.62 (s, 0.52H), 1.95–1.86 (m, 0.96H), 1.71–1.51 (m, 1.04H), 1.27 (s, 1.44H), 1.06 (s, 1.56H), 1.06 (t, J = 7.7 Hz, 0.96H), 0.88 (t, J = 7.8 Hz, 1.04H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −125.87 (dd, J = 274.5, 56.4 Hz, 0.47F), −128.22 (dd, J = 274.5, 56.4 Hz, 0.53F), −129.08 (dd, J = 274.5, 56.4 Hz, 0.53F), −130.47 (dd, J = 274.5, 56.4 Hz, 0.47F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7 (dd, J = 18.8, 9.6 Hz), 142.4 (dd, J = 6.9, 3.7 Hz), 128.6 (d, J = 2.7 Hz), 126.3 (d, J = 12.5 Hz), 126.0, 122.3 (d, J = 4.2 Hz), 121.9, 121.4, 119.4, 119.0, 117.0, 116.5, 110.1 (t, J = 3.6 Hz), 49.6, 48.9, 44.4 (dt, J = 35.5, 17.9 Hz), 25.0 (dd, J = 7.4, 4.2 Hz), 17.0 (dd, J = 6.3, 1.6 Hz), 15.6 (t, J = 4.5 Hz), 9.1 (d, J = 3.2 Hz), 8.6. IR (thin film) ν 3216, 2971, 1704, 1619, 1472, 1333, 1084, 1061, 752, 672 cm^{-1}; MS (ESI): m/z 240 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{13}H_{16}F_2NO^+$: 240.1194; Found: 240.1193.

4.3.13. 3-(1-(Difluoromethyl)cyclopentyl)indolin-2-one (3m)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3m** was obtained as a light red solid (72.4 mg, 58%), mp 138–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.05–6.98 (m, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.25 (t, J = 57.4 Hz, 1H), 3.60 (s, 1H), 2.15–2.02 (m, 2H), 1.97–1.87 (m, 1H), 1.77–1.63 (m, 2H), 1.62–1.45 (m, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −125.36 (dd, J = 274.5, 56.4 Hz, 1F), −129.85 (dd, J = 274.5, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 142.2, 128.7, 126.5, 125.8, 122.4, 118.5 (t, J = 245.4 Hz), 110.2, 52.2 (t, J = 18.7 Hz), 50.2, 31.2 (d, J = 4.8 Hz), 29.4 (d, J = 4.5 Hz), 26.4, 26.3. IR (thin film) ν 2925, 1704, 1319, 1472, 1230, 1099, 1062, 750, 672 cm^{-1}; MS (ESI): m/z 252 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{14}H_{16}F_2NO^+$: 252.1194; Found: 252.1193.

4.3.14. 3-(1-(Difluoromethyl)cyclohexyl)indolin-2-one (3n)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (20/1–15/1) as the eluent, compound **3n** was obtained as a white solid (86.3 mg, 65%), mp 209–211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.30–7.18 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.1 Hz, 1H), 5.51 (t, J = 56.3 Hz, 1H), 3.76 (s, 1H), 2.51 (d, J = 12.4 Hz, 1H), 2.09 (d, J = 10.0 Hz, 1H), 1.92 (s, 1H), 1.78–1.58 (m, 6H), 1.49–1.41 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −125.68 (dd, J = 274.5, 56.4 Hz, 1F), −128.08 (dd, J = 274.5, 56.4 Hz, 1F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 142.0, 128.4, 126.7, 126.2, 122.0, 119.0 (t, J = 247.5 Hz), 109.9, 45.6, 28.0 (d, J = 3.9 Hz), 26.2, 25.8, 21.3, 21.2. IR (thin film) ν 2921, 2861, 1706, 1619, 1474, 1060, 1043, 746, 635 cm^{-1}; MS (ESI): m/z 266 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{15}H_{18}ONF_2^+$: 266.1351; Found: 266.1350.

4.3.15. 3-(1,1-Difluoropropan-2-yl)indolin-2-one (3o)

After purification by silica gel column chromatography using petroleum ether/ethyl acetate (30/1–15/1) as the eluent, compound **3o** was obtained as a yellow solid (84.5 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 0.37H), 8.61 (s, 0.63H), 7.30–7.23 (m, 2H), 7.08–7.05 (m, 1H), 6.93–6.92 (m, 1H), 6.23 (dt, J = 48.2, 7.8 Hz, 0.63H), 6.02

(dt, J = 44.8, 6.4 Hz, 0.37H), 3.78–3.75 (m, 1H), 2.88–2.77 (m, 0.37H), 2.70–2.60 (m, 0.63H), 0.96 (d, J = 4.8 Hz, 1.89H), 0.87 (d, J = 7.8 Hz, 1.11H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.43 (dd, J = 274.5, 56.4 Hz, 0.74F), −120.50 (dd, J = 274.5, 56.4 Hz, 0.26F), −121.77 (dd, J = 274.5, 56.4 Hz, 0.26F), −121.81 (dd, J = 274.5, 56.4 Hz, 0.74F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 178.3, 142.1, 142.0, 128.6, 127.0, 126.0, 125.7, 124.0, 122.9, 122.7, 118.1 (t, J = 244.4 Hz), 117.7 (t, J = 242.4 Hz), 110.2, 110.1, 46.3, 46.1, 39.8 (t, J = 20.2 Hz), 38.9 (t, J = 20.2 Hz), 38.7, 9.8, 9.0. IR (thin film) ν 3227, 1710, 1620, 1486, 1471, 1224, 1060, 751, 670 cm^{-1}; MS (ESI): m/z 212 $(M+H)^+$; HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{11}H_{12}F_2NO^+$: 212.0881; Found: 212.0880.

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