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Silver-Catalyzed Difluoroamidation of Activated Alkenes for the Construction of Difluorinated 3,3-Disubstituted Oxindoles

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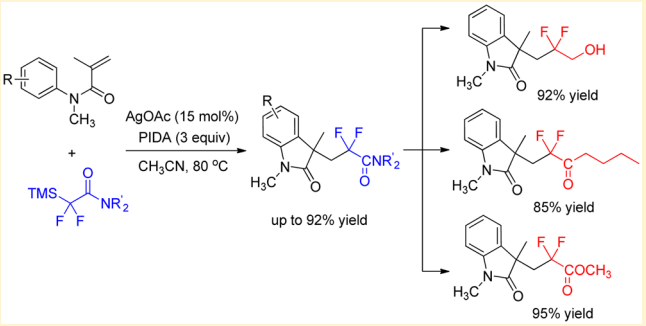
Supporting Information

ABSTRACT: A AgOAc catalyzed difunctionalization of activated alkenes through a difluoroamidic radical addition to afford difluoroamidated 3,3-disubstituted oxindoles has been developed. Various functional groups were well tolerated. Moreover, the product could be efficiently derived to the corresponding difluorofunctionalized alcohol, ketone, and ester in high yields. The mechanistic studies revealed that a radical pathway was involved in the transformation.

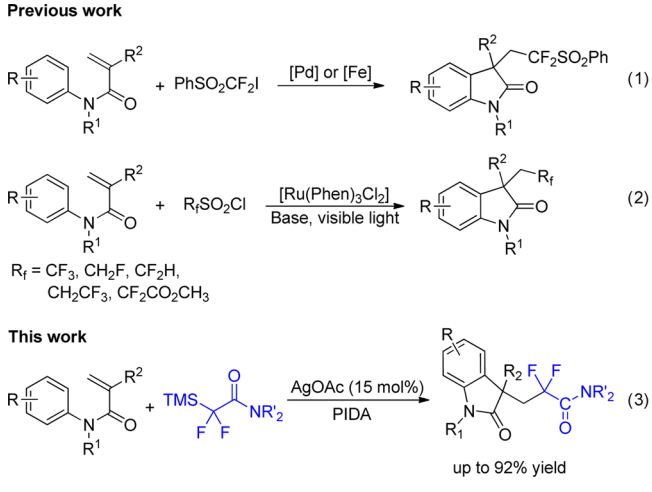


In the past few decades, fluorinated organic compounds have attracted extensive attention due to their excellent lipophilicity, metabolic stability, and bioavailability. With these advantages, fluorine-containing molecules are widely applied to pharmaceuticals, agrochemicals, and materials science.[1]

Oxindoles and their derivatives are a large class of *N*-heterocycles, which play important roles in the structural library design and drug discovery.[2] Therefore, the preparation of oxindoles with diversified functional groups has become an important part of organic synthetic chemistry. In recent years, a variety of 3,3-disubstituted oxindoles have been synthesized via the functionalization of alkenes, such as phosphorylation, nitration, azidation, carbonylation, alkylation, hydroxylation, sulfinylation, etc.[3] Recently, methods for the construction of CF_3-containing 3,3-disubstituted oxindoles have been well studied by several groups.[4] However, literatures about the preparation of CF_2-containing 3,3-disubstituted oxindoles were relatively limited.

The difluoromethylene group (CF_2) has unique properties in biochemistry and drug discovery, which was commonly used as bioisostere for ethereal oxygen atom or lipophilic hydrogen-bond donor.[5] Therefore, the introduction of CF_2-containing motifs into oxindoles would significantly affect their bioactivities. In 2012, Wang and co-workers disclosed a radical addition/cyclization cascade reaction of activated alkenes for the synthesis of difluoromethylated 3,3-disubstituted oxindoles using Pd catalyst or Fe catalyst (Scheme 1, eq 1).[6] Recently, Dolbier's group reported a Ru-catalyzed and visible-light-induced method to construct CF_2-containing 3,3-disubstituted oxindoles using fluoroalkylsulfonyl chlorides as fluorinating reagents (eq 2), etc.[7] Up to now, CF_2SO_2−containing reagents were incorporated into the oxindole skeletons due to their relatively higher reactivity than other difluoromethylation regeants. However, the further functionalization of CF_2SO_2R group could be problematic. Very recently, Hartwig and Zhang reported a serial of works of transition metal catalyzed cross-coupling of Csp^2 with difluoromethylenyl carbonyl compounds.[8,9] In contrast, the construction of (Csp^3-CF_2-COX) (X = OR or NR_2) was not well developed.[10] Difluoromethylated carbonyl compounds have been proven to be qualified precursors for a series of difluoromethylated analogues, and had

Scheme 1. Preparation of CF_2-Containing 3,3-Disubstituted Oxindoles



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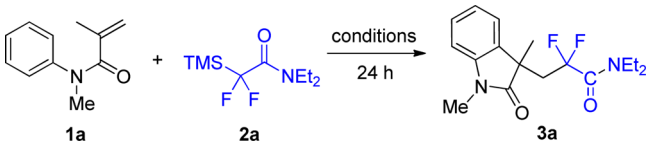
been successfully introduced to different kinds of bioactive molecules.[8,9] Nevertheless, the synthesis of Csp^3-CF_2-carbonyl substituted compounds, especially for the preparation of biologically interesting difluoroalkylated oxindoles, has not been documented and still remains a challenge. Herein, we report a novel method for the construction of difluoroamidated 3,3-disubstituted oxindoles by using AgOAc as catalyst. It is worth noting that the product could be smoothly derivatized to difluorofunctionalized alcohol, ketone, and ester in excellent yields. The preliminary mechanistic study indicated the involvement of a radical pathway in this transformation.

Initially, we chose *N*-methyl-*N*-phenyl-methacrylamide **1a** as the model substrate and *N*,*N*-diethyl-α,α-difluoro-α-(TMS)-acetamide **2a** as the difluoroamidation reagent in the presence of catalytic amount of $Cu(OAc)_2$. Fortunately, when the reaction was carried out in dry MeCN under an argon atmosphere at 80 °C, 23% yield of the desired difluoroamidated 3,3-disubstituted oxindole **3a** was obtained (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	oxidant	solvent	yield[b]
1	$Cu(OAc)_2$		MeCN	23
2	$Cu(OAc)_2$	TBHP	MeCN	29
3[c]	$Cu(OAc)_2$	TBHP	DMAc	41
4	AgOAc		MeCN	11
5	AgOAc	$Na_2S_2O_8$	MeCN	trace
6	AgOAc	BQ	MeCN	0
7	AgOAc	TBHP	MeCN	0
8	AgOAc	DDQ	MeCN	0
9	AgOAc	O_2(1 atm)	MeCN	0
10	AgOAc	BPO	MeCN	trace
11	AgOAc	$KMnO_4$	MeCN	20
12	AgOAc	MnO_2	MeCN	0
13	AgOAc	PIDA	MeCN	73
14[d]	AgOAc	PIDA	MeCN	85
15[d,e]	AgOAc	PIDA	MeCN	87
16[c,d,e]	AgOAc	PIDA	DMF	54
17[d,e,f]	AgOAc	PIDA	toluene	0

[a]All reactions were carried out by using **1a** (0.1 mmol), **2a** (2.0 equiv), catalyst (20 mol%), oxidant (2.0 equiv), solvent (1 mL), under argon, and stirred at 80 °C for 24 h, except as noted. [b]Yields were detected by GC. [c]At 140 °C. [d]3.0 equiv of PIDA was used. [e]15 mol% of AgOAc was used. [f]At 100 °C.

Other copper catalysts, such as CuI, CuCl, CuBr, $CuCl_2$, or $Cu(OTf)_2$, only gave trace amount of the product. Among the oxidants tested, $Na_2S_2O_8$, PIDA, BPO, MnO_2, $KMnO_4$, and O_2 (1 atm) showed negative results, whereas TBHP gave a slightly better yield (29%, entry 2, see the Supporting Information for details). Although the solvent screening led to an increase of the yield, the efficiency of the catalytic system still not satisfying at this stage (entry 3). We then switched the catalyst to silver salts, such as $AgNO_3$, Ag_2CO_3, AgOAc, and Ag_2O. The results revealed that AgOAc was the most effective catalyst for this transformation (entry 4). A series of oxidants were subsequently investigated, and PIDA was found to be the best oxidant which improving the yield of **3a** to 73% (entries 5−13). Better still, 3 equiv of oxidant gave the desired product with 85% yield (entry 14). Thankfully, when the catalytic charge of AgOAc was reduced to 15 mol%, the yield of **3a** was increased to 87% (entry 15). Finally, other solvents, such as DMF and toluene, could not provide a better yield for this reaction (entries 16 and 17, see the Supporting Information for details).

To explore the substrate scope of the reaction, various substituted acrylamides were investigated under the optimized reaction conditions (Table 1, entry 15). As shown in Table 2, substrates with different functional groups on the nitrogen atom, such as alkyl, aryl, benzyl, or Boc provided good yields of the desired products (**3a**−**3d**). Both electron-withdrawing and electron-donating groups at the para-position of the aryl ring gave good results (**3e**−**3j**). *Ortho*-substituted *N*-arylacrylamides such as methyl and methoxyl produced the desired products in 74% and 72% yields, respectively (**3k** and **3l**). Yet regrettably, when the *ortho*-position of acrylamide was substituted by halogen, the yield of product was moderate (**3m**). As expected, substituent group at the meta-position of the phenyl ring gave a mixture of regioselective isomers in 90% yield (**3n**:**3n′** = 1.9:1). To our delight, a variety of α-substituted alkenes with different functional groups, such as phthalimide, ether, benzyl, or ester, all went through the desired reaction smoothly under standard conditions and provided the corresponding oxindoles **3o**−**3r** in good yields. Furthermore, the acrylamide bearing phenyl group at the α-position gave the corresponding product in moderate yield (**3s**). It should be noted that when other difluoro reagents, namely α-TMS-difluoroacetate and α-Br-difluoroacetate, were tested under the established conditions, the cyclization products were observed in less than 5%.

We then evaluated the reactivities of *N*-methyl-*N*-phenyl-methacrylamide **1a** with different α-(TMS)acetamides **2** under optimized conditions. Both piperidinyl amide and morpholinyl amide were suitable substrates for this reaction, furnishing the desired products in excellent yields (Table 3, **4a** and **4b**). Nevertheless, when the six-membered cycloamide was replaced by a five-membered one, **4c** was isolated in 68% yield.

To further illustrate the synthetic utility of the current methodology, we extended the reaction to other type of substrate. When *N*-methyl-*N*-phenyl-methbutylamide **5** was applied in the reaction under basic conditions, a six-member-ring product **6** was isolated in 87% yield (Scheme 2).

Carboxylic acid derivatives, such as esters and amides, could be frequently transformed from one form to another. They are also feasible to be reduced to their homologous alcohols. The resonance stability of the amide bond makes amides poor electrophiles normally,[11] but the two fluorine atoms on the α carbon of α,α-difluoroacetamide increased their electrophilicity and promoted the transformation between different type of difluorine carboxylic acid derivatives. When the difluoroamidation product **4b** was treated with sodium borohydride, it was smoothly reduced and forming the corresponding alcohol **7** in excellent yield (Scheme 3). The reaction between **4b** and *n*-butyllithium also proceeded successfully to give the α,α-difluoro ketone **8** in 85% yield. Although the α-silyldifluoroacetates failed to provide the difluoroacetated oxindole, the difluorofunctionalized ester **9** (cannot be synthesized by the reaction of α-TMS-difluoroacetate and *N*-methyl-*N*-phenyl-methacrylamide) could be obtained in very good yield from the corresponding amide.

In order to gain some mechanistic insight, several radical trapping experiments were carried out (Scheme 4). Under the standard conditions, when 2,2,6,6-tetramethylpiperidin-1-oxyl

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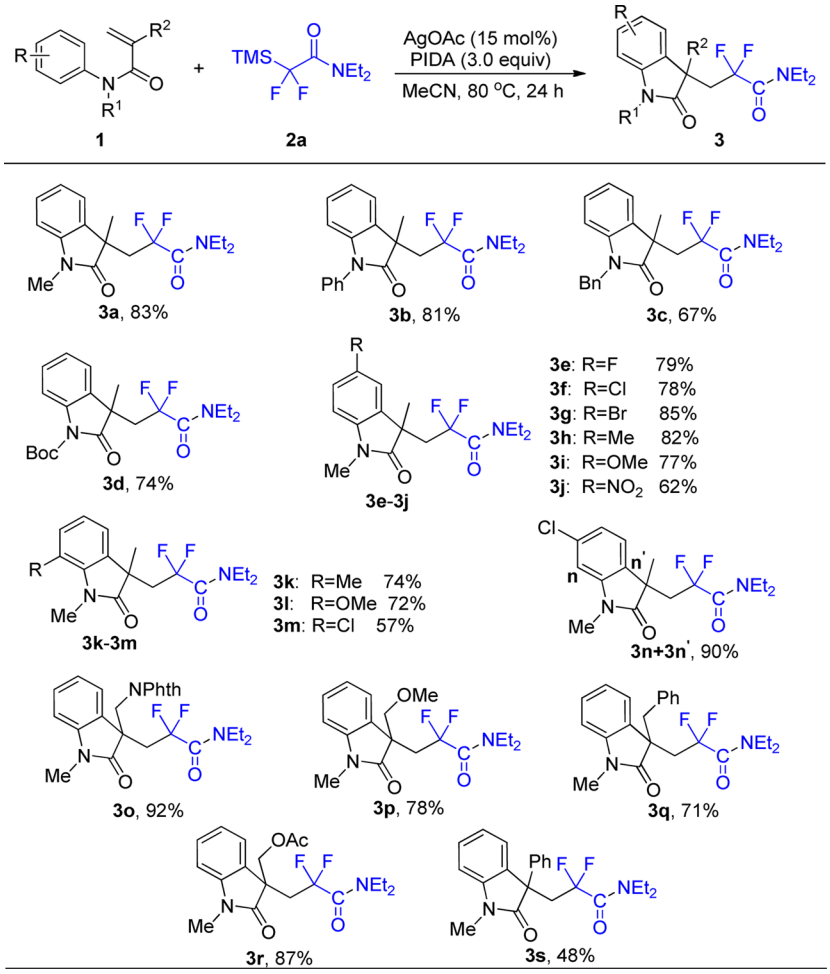
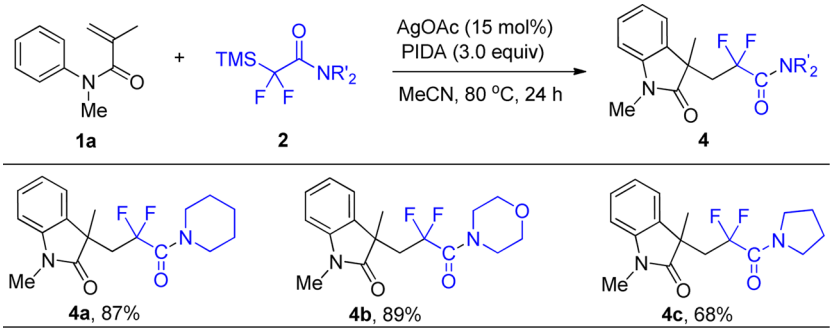
Table 2. Scope of Acrylamides[a,b]



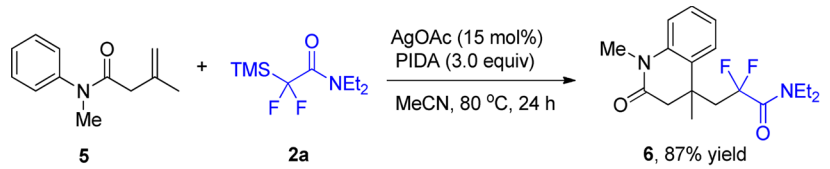
[a]All reactions were carried out by using 0.2 mmol of **1**, 0.4 mmol of **2a**, 0.03 mmol of AgOAc, 0.6 mmol of PIDA, 2 mL of MeCN, and stirred at 80 °C for 24 h under argon atmosphere. [b]Isolated yields.

Table 3. Scope of α,α-Difluoro-α-(TMS)amides[a,b]



[a]All reactions were carried out by using 0.2 mmol of **1a**, 0.4 mmol of **2**, 0.03 mmol of AgOAc, 0.6 mmol of PIDA, 2 mL of MeCN, and stirred at 80 °C for 24 h under argon atmosphere. [b]Isolated yields.

Scheme 2. Six-Member-Ring Product



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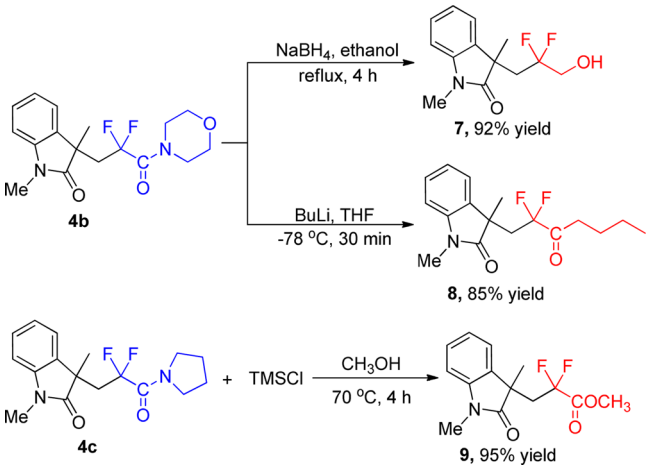
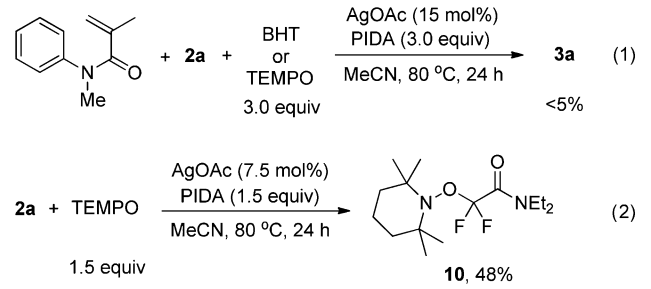
Scheme 3. Synthetic Utilities of the Current Method



Scheme 4. Mechanistic Study for Radical Formation



(TEMPO, 3.0 equiv) or 2,6-di-*tert*-butyl-4-methylphenol (BHT, 3.0 equiv) was added to the reaction, the yield of **3a** decreased dramatically (eq 1, Scheme 4). The result suggested that a radical pathway might be involved. To further clarify the formation of radical intermediate in the system, a reaction was carried out in the absent of alkene substrate. To our delight, the radical trapping product **10** was isolated in 48% yield (eq 2, Scheme 4). The results prove the involvement of the difluoroacetamided radical in this reaction.

On the basis of our experimental results and previous reports,[3d,12] a plausible mechanism was proposed in Scheme 5. Initially, α,α-difluoro-α-(TMS)acetamide **2a** is desilylated to a trimethylsilyl radical and an intermediate **A** by Ag^{I}. A single ligand exchange between PIDA and intermediate **A** would generate intermediate **B** and difluoroacetamidated radical **C**. Then, the radical attacks **1a** to give the alkyl radical **E**, which subsequently undergoes an intromolecular radical cyclization to form the intermediate **F**. The radical **F** is oxidized to a cation **G** by the oxidative hypervalent iodide **D**. The final elimination of H^+ results in the desired difluoroamidated product **3a**.

In summary, we have reported a novel and efficient protocol for the preparation of difluoroamidated 3,3-disubstituted oxindoles using AgOAc as the catalyst. Moreover, the product could be efficiently transformed to the corresponding difluorofunctionalized alcohol, ketone, and ester in excellent yields.

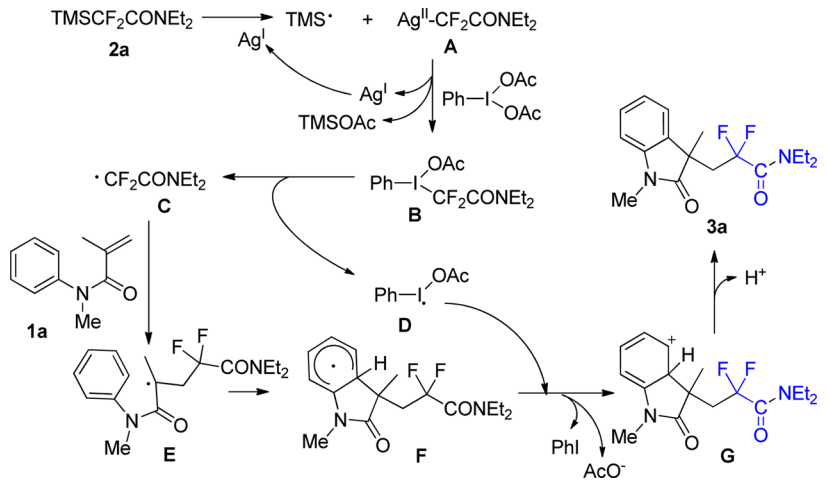
EXPERIMENTAL SECTION

General. Unless noted otherwise, all reactions were carried out under an argon atmosphere. All solvents were purified and dried according to standard methods prior to use. Reactions were monitored by thin layer chromatography (TLC) and column chromatography purifications were carried out using silica gel GF254. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on 300, 75, and 282 MHz instruments, respectively. Data are presented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet) and coupling constant in Hertz (Hz). Gas chromatography (GC) was equipped with a split-mode capillary injection system and flame ionization detectors. High-resolution mass spectra (HRMS) were obtained by ESI (TOF) ionization sources. The amides **1a**–**1r**, **5**,[3a] and α,α-difluoro-α-trimethylsilyl acetamides[8a] were prepared according to the previous reported literatures. All other reagents were commercially available.

General Procedure for the Synthesis of 3 and 4. To a 25 mL of Schlenk tube was added *N*-arylacrylamide **1** (0.2 mmol), AgOAc (0.03 mmol, 5.0 mg), and PIDA (0.6 mmol, 193.2 mg). Then, air was withdrawn and backfilled with Ar. α,α-Difluoro-α-(trimethylsilyl)-acetamide **2** (0.4 mmol, 89.2 mg) and MeCN (2 mL) were added by syringes. The mixture was stirred at 80 °C for 24 h. After the reaction was completed (detected by TLC), the mixture was quenched with water (1 mL), extracted with dichloromethane, dried over sodium sulfate, concentrated in vacuo, and purified by column chromatography (dichloromethane/ethyl acetate = 25:1–10:1) to afford the product **3** or **4**.

*3-(1,3-Dimethyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3a**).* Yellow solid (53.8 mg, 83%, mp 95–96 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J = 6.7 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 3.34–3.14 (m, 7H), 3.08–2.82 (m, 2H), 1.40

Scheme 5. Proposed Mechanism



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(s, 3H), 1.03 (dt, J = 17.1, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 162.2 (t, J = 28.5 Hz), 142.9, 132.1, 127.8, 124.0, 122.1, 118.3 (t, J = 256.7 Hz), 108.0, 44.5, 41.70 (t, J = 6.4 Hz), 41.66, 40.9 (t, J = 22.2 Hz), 26.3, 26.1, 14.0, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.9 (d, J = 277.5 Hz), −98.9 (d, J = 277.4 Hz). HRMS (ESI): $C_{17}H_{23}F_2N_2O_2$ $[M + H]^+$ calcd: 325.1722, found: 325.1733.

*N,N-Diethyl-2,2-difluoro-3-(3-methyl-2-oxo-1-phenylindolin-3-yl)propanamide (**3b**).* White solid (62.5 mg, 81%, mp 147−148 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.50 (m, 2H), 7.40 (dd, J = 10.3, 4.4 Hz, 3H), 7.33 (d, J = 7.3 Hz, 1H), 7.19 (td, J = 7.7, 1.2 Hz, 1H), 7.07 (td, J = 7.5, 0.9 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 3.41−3.17 (m, 4H), 3.15−2.90 (m, 2H), 1.52 (s, 3H), 1.09−1.00 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 162.3 (t, J = 28.4 Hz), 142.9, 134.7, 131.8, 129.5, 127.9, 127.8, 126.6, 124.4, 122.6, 118.4 (t, J = 255.4 Hz), 109.3, 44.7, 41.8 (t, J = 6.5 Hz), 41.7, 41.4 (t, J = 22.1 Hz), 26.5, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.5 (d, J = 277.4 Hz), −98.5 (d, J = 277.5 Hz). HRMS (ESI): $C_{22}H_{25}F_2N_2O_2$ $[M+H]^+$ calcd: 387.1879, found: 387.1892.

*3-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3c**).* Yellow solid (53.6 mg, 67%, mp 124−125 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 6H), 7.14 (td, J = 7.7, 1.1 Hz, 1H), 7.00 (td, J = 7.6, 0.7 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 5.04 (d, J = 15.7 Hz, 1H), 4.84 (d, J = 15.6 Hz, 1H), 3.33−3.16 (m, 4H), 3.11−2.88 (m, 2H), 1.45 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 162.2 (t, J = 28.3 Hz), 141.9, 135.9, 132.0, 128.5, 127.7, 127.4, 127.3, 124.0, 122.1, 118.2 (t, J = 255.2 Hz), 109.0, 44.5 (d, J = 2.6 Hz), 43.7, 41.67, 41.66 (t, J = 6.3 Hz), 40.7 (t, J = 22.2 Hz), 26.6, 14.0, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.4 (d, J = 277.2 Hz), −98.6 (d, J = 277.2 Hz). HRMS (ESI): $C_{23}H_{27}F_2N_2O_2$ $[M+H]^+$ calcd: 401.2035, found: 401.2051.

*tert-Butyl-3-(3-(diethylamino)-2,2-difluoro-3-oxopropyl)-3-methyl-2-oxoindoline-1-carboxylate (**3d**).* Yellow solid (60.7 mg, 74%, mp 112−113 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 1H), 7.33−7.26 (m, 2H), 7.15 (t, J = 7.3 Hz, 1H), 3.33−3.16 (m, 4H), 3.12−2.81 (m, 2H), 1.65 (s, 9H), 1.45 (s, 3H), 1.03 (dt, J = 16.2, 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 162.0 (t, J = 28.3 Hz), 149.4, 138.7, 130.8, 128.1, 124.1, 124.0, 118.1 (t, J = 257.1 Hz), 115.0, 84.2, 45.0, 41.69 (t, J = 6.2 Hz), 41.66 (t, J = 21.9 Hz), 41.66, 28.0, 27.2, 14.0, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.1 (d, J = 280.2 Hz), −98.2 (d, J = 280.2 Hz). HRMS (ESI): $C_{21}H_{29}F_2N_2O_4$ $[M+H]^+$ calcd: 411.2090, found: 411.2103.

*N,N-Diethyl-2,2-difluoro-3-(5-fluoro-1,3-dimethyl-2-oxoindolin-3-yl)propanamide (**3e**).* Yellow solid (54.0 mg, 79%, mp 79−80 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (ddd, J_{H-F} = 20.0 Hz, J = 8.6, 2.5 Hz, 2H), 6.78 (dd, J = 8.4, 4.2 Hz, 1H), 3.36−3.17 (m, 7H), 3.09−2.79 (m, 2H), 1.40 (s, 3H), 1.09−1.00 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 162.1 (t, J = 28.4 Hz), 159.0 (d, J = 240.0 Hz), 138.8, 133.8 (d, J = 8.1 Hz), 118.2 (t, J = 256.8 Hz), 114.1 (d, J = 23.5 Hz), 112.2 (d, J = 24.9 Hz), 108.4 (d, J = 8.2 Hz), 45.0 (d, J = 1.8 Hz), 41.73 (t, J = 6.5 Hz), 41.69, 40.8 (t, J = 22.3 Hz), 26.5, 26.0, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.8 (d, J = 277.8 Hz), −98.8 (d, J = 277.8 Hz), −121.1 (s). HRMS (ESI): $C_{17}H_{22}F_3N_2O_2$ $[M+H]^+$ calcd: 343.1628, found: 343.1641.

*3-(5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3f**).* Yellow solid (55.8 mg, 78%, mp 107−108 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.24 (m, 2H), 6.79−6.76 (m, 1H), 3.36−3.15 (m, 7H), 3.08−2.76 (m, 2H), 1.39 (s, 3H), 1.04 (dt, J = 17.4, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 162.1 (t, J = 28.4 Hz), 141.5, 133.8, 127.8, 127.6, 124.6, 118.2 (t, J = 256.8 Hz), 108.9, 44.8, 41.73 (t, J = 6.1 Hz), 41.72, 40.9 (t, J = 22.3 Hz), 26.5, 26.0, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.2. HRMS (ESI): $C_{17}H_{22}ClF_2N_2O_2$ $[M+H]^+$ calcd: 359.1332, found: 359.1343.

*3-(5-Bromo-1,3-dimethyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3g**).* Yellow solid (68.3 mg, 85%, mp 96−97 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.38 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 3.37−3.15 (m, 7H), 3.08−2.80 (m, 2H), 1.39 (s, 3H), 1.04 (dt, J = 18.3, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 162.0 (t, J = 28.1 Hz), 142.0, 134.2, 130.7, 127.4, 118.2 (t, J = 255.4 Hz), 114.9, 109.4, 44.7, 41.72, 41.71 (t, J = 6.3 Hz), 40.9 (t, J = 22.3 Hz), 26.4, 26.0, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.6 (d, J = 278.4 Hz), −98.7 (d, J = 278.4 Hz). HRMS (ESI): $C_{17}H_{22}BrF_2N_2O_2$ $[M+H]^+$ calcd: 403.0827, found: 403.0840.

*N,N-Diethyl-2,2-difluoro-3-(1,3,5-trimethyl-2-oxoindolin-3-yl)-propanamide (**3h**).* Yellow solid (55.4 mg, 82%, mp 85−86 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 7.9 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 3.35−3.14 (m, 7H), 3.05−2.80 (m, 2H), 2.33 (s, 3H), 1.38 (s, 3H), 1.03 (dt, J = 16.8, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 162.3 (t, J = 28.5 Hz), 140.5, 132.1, 131.6, 128.1, 124.8, 118.2 (t, J = 256.5 Hz), 107.7, 44.5, 41.7 (t, J = 6.3 Hz), 41.6, 40.8 (t, J = 22.2 Hz), 26.3, 26.2, 21.1, 14.0, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.0 (d, J = 276.6 Hz), −99.0 (d, J = 276.7 Hz). HRMS (ESI): $C_{18}H_{25}F_2N_2O_2$ $[M+H]^+$ calcd: 339.1879, found: 339.1893.

*N,N-Diethyl-2,2-difluoro-3-(5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)propanamide (**3i**).* Yellow oil (54.5 mg, 77%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 2.1 Hz, 1H), 6.83−6.75 (m, 2H), 3.80 (s, 3H), 3.36−3.15 (m, 7H), 3.07−2.79 (m, 2H), 1.39 (s, 3H), 1.04 (dt, J = 13.8, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 162.2 (t, J = 28.4 Hz), 155.6, 136.3, 133.4, 118.2 (t, J = 256.8 Hz), 112.2, 111.3, 108.2, 55.7, 44.9, 41.7 (t, J = 6.3 Hz), 41.6, 40.7 (t, J = 22.1 Hz), 26.4, 26.2, 14.0, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.9 (d, J = 277.2 Hz), −99.0 (d, J = 277.2 Hz). HRMS (ESI): $C_{18}H_{25}F_2N_2O_3$ $[M+H]^+$ calcd: 355.1828, found: 355.1844.

*3-(1,3-Dimethyl-5-nitro-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3j**).* Yellow solid (45.8 mg, 62%, mp 138−139 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, J = 8.6, 2.2 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 3.32−2.84 (m, 9H), 1.47 (s, 3H), 1.05 (q, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 161.7 (t, J = 28.2 Hz), 148.6, 143.2, 133.0, 125.3, 119.9, 118.1 (t, J = 257.1 Hz), 107.7, 44.5, 41.64 (t, J = 6.2 Hz), 41.57, 40.9 (t, J = 22.2 Hz), 26.8, 25.9, 14.0, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.8 (d, J = 278.8 Hz), −98.7 (d, J = 278.9 Hz). HRMS (ESI): $C_{17}H_{22}F_2N_3O_4$ $[M+H]^+$ calcd: 370.1573, found: 370.1587.

*N,N-Diethyl-2,2-difluoro-3-(1,3,7-trimethyl-2-oxoindolin-3-yl)-propanamide (**3k**).* Yellow solid (50.0 mg, 74%, mp 108−109 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 7.1 Hz, 1H), 7.00 (d, J = 6.9 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 3.52 (s, 3H), 3.35−3.14 (m, 4H), 3.07−2.77 (m, 2H), 2.59 (s, 3H), 1.37 (s, 3H), 1.04 (dt, J = 12.1, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 162.3 (t, J = 28.5 Hz), 140.6, 132.7, 131.5, 122.0, 121.8, 119.5, 118.2 (t, J = 256.6 Hz), 43.9, 41.7 (d, J = 6.4 Hz), 41.6, 41.0 (t, J = 22.1 Hz), 29.7, 26.6, 19.1, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.9 (d, J = 276.7 Hz), −99.0 (d, J = 276.7 Hz). HRMS (ESI): $C_{18}H_{25}F_2N_2O_2$ $[M+H]^+$ calcd: 339.1879, found: 339.1892.

*N,N-Diethyl-2,2-difluoro-3-(7-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)propanamide (**3l**).* Yellow solid (51.0 mg, 72%, mp 73−74 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01−6.96 (m, 1H), 6.86 (dd, J = 12.7, 8.0 Hz, 2H), 3.86 (s, 3H), 3.51 (s, 3H), 3.36−3.15 (m, 4H), 2.92 (ddt, J_{H-F} = 30.8, 23.2 Hz, J = 13.2 Hz, 2H), 1.37 (s, 3H), 1.05 (dt, J = 10.6, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 162.3 (t, J = 28.5 Hz), 145.2, 133.8, 130.6, 122.6, 118.1 (t, J = 255.0), 116.6, 111.5, 55.8, 44.5, 41.7 (d, J = 6.3 Hz), 41.6, 41.0 (t, J = 21.9 Hz), 29.6, 26.4, 14.1, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.0 (d, J = 276.4 Hz), −99.3 (d, J = 276.5 Hz). HRMS (ESI): $C_{18}H_{25}F_2N_2O_3$ $[M+H]^+$ calcd: 355.1828, found: 355.1841.

*3-(7-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3m**).* Yellow solid (40.8 mg, 57%, mp 81−82 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, J = 14.3, 7.7 Hz, 2H), 6.95 (t, J = 7.8 Hz, 1H), 3.61 (s, 3H), 3.30−3.15 (m, 4H), 3.05−2.79 (m, 2H), 1.39 (s, 3H), 1.05 (dd, J = 15.9, 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 162.0 (t, J = 28.4 Hz), 138.8, 134.9, 130.1, 122.9, 122.5, 118.1 (t, J = 257.0 Hz), 115.3, 44.3, 41.7 (t, J = 6.4 Hz), 41.6, 41.1 (t, J = 22.2 Hz), 29.7, 26.5, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.7 (d, J = 278.1 Hz), −98.8 (d, J = 278.2 Hz). HRMS (ESI): $C_{17}H_{22}ClF_2N_2O_2$ $[M+H]^+$ calcd: 359.1332, found: 359.1345.

*3-(4-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3n**). 3-(6-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3n′**) **3n:3n′** = 1.9:1.* Yellow solid (64.4 mg, 90%, mp 103−104 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.17 (m, 1H), 7.04−6.99 (m, 1H), 6.87−6.79 (m, 1H), 3.39−2.79 (m, 9H), 1.53 (s, 2H), 1.38 (s, 1H), 1.12−1.00 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 178.8, 162.0 (t, J = 28.2

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Hz), 144.5, 144.0, 133.5, 131.1, 131.1, 130.3, 129.1, 128.6, 124.9, 123.3, 121.9, 118.1 (t, J = 255.2 Hz), 117.9 (t, J = 255.0 Hz), 108.7, 106.6, 45.4, 45.3, 44.2, 41.7−41.4 (m), 41.3, 40.7 (t, J = 22.1 Hz), 39.0 (t, J = 21.4 Hz), 26.5, 26.4, 26.0, 22.7, 14.0, 12.13, 12.07. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.8 (d, J = 277.8 Hz), −98.9 (d, J = 277.9 Hz), −99.9 (d, J = 274.7 Hz), −102.1 (d, J = 274.9 Hz). HRMS (ESI): $C_{17}H_{22}ClF_2N_2O_2$ $[M+H]^+$ calcd: 359.1332, found: 359.1348.

*3-(3-((1,3-Dioxoisoindolin-2-yl)methyl)-1-methyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3o**).* Colorless oil (86.3 mg, 92%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 5.2, 3.1 Hz, 2H), 7.69 (dd, J = 5.2, 3.0 Hz, 2H), 7.26 (dd, J = 9.8, 4.8 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 3.98 (q, J = 14.0 Hz, 2H), 3.32−3.13 (m, 9H), 1.01 (dt, J_{H-F} = 22.3 Hz, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 167.8, 162.0 (t, J = 28.4 Hz), 143.5, 134.0, 131.5, 128.7, 127.5, 125.3, 123.4, 121.9, 118.1 (t, J = 255.3 Hz), 108.1, 48.8, 44.5, 41.70, 41.69 (t, J = 6.3 Hz), 38.2 (t, J = 22.3 Hz), 26.5, 14.0, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.6. HRMS (ESI): $C_{25}H_{26}F_2N_3O_4$ $[M+H]^+$ calcd: 470.1886, found: 470.1901.

*N,N-Diethyl-2,2-difluoro-3-(3-(methoxymethyl)-1-methyl-2-oxoindolin-3-yl)propanamide (**3p**).* Yellow solid (55.2 mg, 78%, mp 87−88 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 3.62 (d, J = 8.7 Hz, 1H), 3.45 (d, J = 8.7 Hz, 1H), 3.29−2.84 (m, 12H), 1.03 (dt, J = 18.0, 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 162.1 (t, J = 28.3 Hz), 143.7, 129.1, 128.1, 125.2, 122.0, 118.6 (d, J = 256.8 Hz), 107.8, 77.2, 59.5, 49.7, 41.7 (t, J = 6.3 Hz), 41.6, 36.9 (t, J = 22.3 Hz), 26.4, 14.0, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.0 (d, J = 277.1 Hz), −98.0 (d, J = 277.1 Hz). HRMS (ESI): $C_{18}H_{25}F_2N_2O_3$ $[M+H]^+$ calcd: 355.1828, found: 355.1843.

*3-(3-Benzyl-1-methyl-2-oxoindolin-3-yl)-N,N-diethyl-2,2-difluoropropanamide (**3q**).* Yellow solid (56.8 mg, 71%, mp 129−130 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.16 (m, 2H), 7.09−6.98 (m, 4H), 6.75 (d, J = 6.5 Hz, 2H), 6.55 (d, J = 7.7 Hz, 1H), 3.35−2.99 (m, 8H), 2.93 (s, 3H), 1.02 (dt, J_{H-F} = 26.4 Hz, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 162.3 (t, J = 28.4 Hz), 143.4, 134.3, 130.0, 129.0, 127.9, 127.3, 126.6, 125.1, 121.6, 118.3 (d, J = 256.7 Hz), 107.6, 50.3, 45.5, 41.7, 41.7 (t, J = 6.3 Hz), 39.7 (t, J = 22.1 Hz), 25.8, 14.0, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.3. HRMS (ESI): $C_{23}H_{27}F_2N_2O_2$ $[M+H]^+$ calcd: 401.2035, found: 401.2048.

*(3-(3-(Diethylamino)-2,2-difluoro-3-oxopropyl)-1-methyl-2-oxoindolin-3-yl)methyl acetate(**3r**).* White solid (66.5 mg, 87%, mp 134−135 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 10.3, 4.4 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 4.42 (d, J = 10.7 Hz, 1H), 4.07 (d, J = 10.7 Hz, 1H), 3.35−3.17 (m, 7H), 3.14−2.92 (m, 2H), 1.94 (s, 3H), 1.03 (dt, J = 17.4, 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 170.1, 161.9 (t, J = 28.3 Hz), 143.6, 128.6, 127.6, 125.2, 122.2, 118.4 (t, J = 257.3 Hz), 108.0, 67.7, 48.4, 41.6, 41.6 (t, J = 6.3 Hz), 36.8 (t, J = 22.3 Hz), 26.4, 20.5, 14.0, 12.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.5. HRMS (ESI): $C_{19}H_{25}F_2N_2O_4$ $[M+H]^+$ calcd: 383.1777, found: 383.1789.

*N,N-Diethyl-2,2-difluoro-3-(1-methyl-2-oxo-3-phenylindolin-3-yl)propanamide (**3s**).* White solid (37.1 mg, 48%, mp 109−110 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 7H), 7.10 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 3.64−3.13 (m, 9H), 1.03 (dt, J_{H-F} = 22.1 Hz, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 162.2 (t, J = 28.5 Hz), 143.8, 139.8, 129.9, 128.6, 128.4, 127.5, 126.7, 126.5, 122.1, 118.2 (t, J = 257.4 Hz), 108.2, 52.3, 41.77, 41.76 (t, J = 6.4 Hz), 41.1 (t, J = 21.8 Hz), 26.6, 14.1, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.7. HRMS (ESI): $C_{22}H_{25}F_2N_2O_2$ $[M+H]^+$ calcd: 387.1879, found: 387.1886.

*3-(2,2-Difluoro-3-oxo-3-(piperidin-1-yl)propyl)-1,3-dimethylindolin-2-one (**4a**).* White solid (58.5 mg, 87%, mp 95−96 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (ddd, J = 8.4, 5.8, 1.9 Hz, 2H), 7.06 (td, J = 7.5, 0.9 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 3.47−3.40 (m, 4H), 3.24 (s, 3H), 3.12−2.72 (m, 2H), 1.63−1.42 (m, 6H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 161.1 (t, J = 28.2 Hz), 142.8, 132.2, 127.8, 123.7, 122.1, 118.2 (t, J = 255.1 Hz), 108.0, 46.6 (t, J = 6.8 Hz), 44.5 (d, J = 2.8 Hz), 44.4, 40.8 (t, J = 21.8 Hz), 26.3, 26.23, 26.15, 25.4, 24.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.7 (d, J = 276.9 Hz), −99.0 (d, J = 276.9 Hz). HRMS (ESI): $C_{18}H_{23}F_2N_2O_2$ $[M+H]^+$ calcd: 337.1722, found: 337.1736.

*3-(2,2-Difluoro-3-morpholino-3-oxopropyl)-1,3-dimethylindolin-2-one (**4b**).* Yellow oil (60.2 mg, 89%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 3.65−3.48 (m, 8H), 3.24 (s, 3H), 3.13−2.73 (m, 2H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 161.4 (t, J = 28.8 Hz), 142.8, 132.0, 128.0, 123.7, 122.2, 118.0 (t, J = 256.4 Hz), 108.1, 66.5, 46.2 (t, J = 6.5 Hz), 44.39, 44.35, 43.3, 40.6 (t, J = 21.5 Hz), 26.3, 26.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.6 (d, J = 278.9 Hz), −98.8 (d, J = 278.9 Hz). HRMS (ESI): $C_{17}H_{21}F_2N_2O_3$ $[M+H]^+$ calcd: 339.1515, found: 339.1526.

*3-(2,2-Difluoro-3-oxo-3-(pyrrolidin-1-yl)propyl)-1,3-dimethylindolin-2-one (**4c**).* yellow oil (43.8 mg, 68%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J = 7.6 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 3.43−3.24 (m, 6H), 3.08−2.82 (m, 3H), 1.84−1.58 (m, 4H), 1.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 161.7 (t, J = 29.1 Hz), 143.0, 131.4, 128.0, 124.1, 122.1, 117.6 (dd, J = 255.6, 250.8 Hz), 107.9, 47.5, 46.4 (dd, J = 8.8, 5.1 Hz), 44.5, 44.4, 40.8 (dd, J = 23.7, 21.7 Hz), 26.4, 25.9, 22.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.5 (d, J = 272.7 Hz), −103.4 (d, J = 272.7 Hz). HRMS (ESI): $C_{17}H_{21}F_2N_2O_2$ $[M+H]^+$ calcd: 323.1566, found: 323.1579.

*3-(1,4-Dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)-N,N-diethyl-2,2-difluoropropanamide (**6**).* To a 25 mL of Schlenk tube was added **5** (0.2 mmol), AgOAc (0.03 mmol, 5.0 mg), and PIDA (0.6 mmol, 193.2 mg). Then, air was withdrawn and backfilled with Ar. *N*,*N*-diethyl-α,α-difluoro-α-(trimethylsilyl)acetamide **2a** (0.4 mmol, 89.2 mg) and MeCN (2 mL) were added by syringes. The mixture was stirred at 80 °C. After the reaction was completed (detected by TLC), the mixture was quenched with water, extracted with dichloromethane, dried over sodium sulfate, concentrated in vacuo, and purified by column chromatography (petroleum ether/ethyl acetate = 3:1) to afford the product **6** (0.174 mmol, 58.8 mg, 87% yield) as a faint yellow solid, mp 124−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 2H), 7.10−7.00 (m, 2H), 3.53−3.39 (m, 5H), 3.29 (q, J = 7.1 Hz, 2H), 2.87 (d, J = 16.0 Hz, 1H), 2.63−2.36 (m, 3H), 1.56 (s, 3H), 1.13 (dt, J_{H-F} = 19.0 Hz, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 162.5 (t, J = 28.9 Hz), 139.2, 133.0, 127.8, 125.0, 123.1, 119.7 (t, J = 256.9 Hz), 115.1, 44.1, 41.8 (t, J = 6.4 Hz), 41.6, 41.0 (t, J = 21.8 Hz), 34.6, 29.4, 25.6, 14.2, 12.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ −96.1 (d, J = 277.7 Hz), −98.0 (d, J = 277.8 Hz). HRMS (ESI): $C_{18}H_{25}F_2N_2O_2$ $[M+H]^+$ calcd: 339.1879, found: 339.1892.

*3-(2,2-Difluoro-3-hydroxypropyl)-1,3-dimethylindolin-2-one (**7**).* In a 25 mL round flask, difluoroamidated oxindole **4b** (0.275 mmol, 93 mg), sodium borohydride (4.125 mmol, 156 mg), a magnetic stirring bar, and ethanol (10 mL) were added. The resulting suspension was refluxed for 4 h with stirring. The mixture was cooled to room temperature, carefully quenched with aqueous HCl (3 M), and extracted with diethyl ether. Ether fraction was concentrated in vacuo and purified by column chromatography (petroleum ether/ethyl acetate = 2:1) to afford the product 7 (0.253 mmol, 64.5 mg, 92% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 11.2, 4.4 Hz, 2H), 7.12−7.07 (m, 1H), 6.90−6.87 (m, 1H), 3.49−3.34 (m, 3H), 3.23 (s, 3H) 2.85−2.68 (m, 1H), 2.52 (ddd, J_{H-F} = 19.6 Hz, J = 15.2, 13.6 Hz, 1H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 142.4, 132.4, 128.1, 123.3, 122.6, 122.1 (t, J = 242.7 Hz), 108.4, 63.9 (t, J = 32.2 Hz), 44.9 (t, J = 2.8 Hz), 39.5 (t, J = 23.6 Hz), 26.4, 26.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.9 (d, J = 254.2 Hz), −105.2 (d, J = 254.2 Hz). HRMS (ESI): $C_{13}H_{16}F_2NO_2$ $[M+H]^+$ calcd: 256.1144, found: 256.1155.

*3-(2,2-Difluoro-3-oxoheptyl)-1,3-dimethylindolin-2-one (**8**).* To a 10 mL of round-bottom flask was added difluoroamidated oxindole **4b** (0.434 mmol, 146.7 mg), THF (2 mL), and a magnetic stirring bar. The mixture was then evacuated and backfilled with Ar. The flask was cooled to −78 °C and butyl lithium (1.6 M in hexanes, 0.56 mL) was added dropwise. The reaction was stirred at this temperature for 30 min. The mixture was warmed to room temperature, quenched with H_2O, and extracted with diethyl ether. The organic phase was dried over sodium sulfate, concentrated in vacuo, and purified by column chromatography (petroleum ether/ethyl acetate = 8:1) to afford the

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product **8** (0.369 mmol, 114 mg, 85% yield, mp 53−54 °C) as a faint yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.26 (m, 1H), 7.11−7.00 (m, 2H), 6.87 (d, J = 7.8 Hz, 1H), 3.24 (s, 3H), 2.92−2.69 (m, 2H), 2.35−2.23 (m, 1H), 1.81−1.68 (m, 1H), 1.44−1.09 (m, 7H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1 (dd, J = 33.6, 27.6 Hz), 179.2, 143.2, 131.0, 128.3, 124.5, 122.2, 116.7 (dd, J = 256.6, 251.3 Hz), 108.1, 44.2 (d, J = 5.5 Hz), 39.6 (dd, J = 24.3, 21.5 Hz), 35.5, 26.3, 25.4, 24.2, 21.7, 13.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ −97.5 (d, J = 280.9 Hz), −110.2 (d, J = 280.9 Hz). HRMS (ESI): $C_{17}H_{22}F_2NO_2$ $[M+H]^+$ calcd: 310.1613, found: 310.1622.

*Methyl 3-(1,3-Dimethyl-2-oxoindolin-3-yl)-2,2-difluoropropanoate (**9**).* A 25 mL Schlenk tube was charged with difluoroamidated oxindole **4c** (0.35 mmol, 112.7 mg), methanol (3 mL), and a magnetic stirring bar. At 0 °C, Me_3SiCl (0.67 mL) was added and the mixture was stirred at 70 °C for 4 h. The reaction was quenched with H_2O and extracted with diethyl ether. The organic phase was dried over sodium sulfate, concentrated in vacuo, and purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford the product **9** (0.33 mmol, 93 mg, 95% yield, mp 99−100 °C) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.28 (m, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 3.56 (s, 3H), 3.24 (s, 3H), 2.88−2.69 (m, 2H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 163.8 (t, J = 32.2 Hz), 143.3, 130.5, 128.6, 123.7, 122.1, 114.5 (dd, J = 255.3, 248.6 Hz), 108.4, 53.2, 44.3 (d, J = 5.6 Hz), 41.2 (dd, J = 24.6, 22.4 Hz), 26.3, 25.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.2 (d, J = 267.4 Hz), −106.4 (d, J = 267.5 Hz). HRMS (ESI): $C_{14}H_{16}F_2NO_3$ $[M+H]^+$ calcd: 284.1093, found: 284.1103.

*N,N-Diethyl-2,2-difluoro-2-((2,2,6,6-tetramethylpiperidin-1-yl)-oxy)acetamide (**10**).* Colorless oil (29.4 mg, 48%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (q, J = 7.0 Hz, 2H), 3.43 (q, J = 7.1 Hz, 2H), 1.63−1.53 (m, 5H), 1.26−1.16 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$) δ159.7 (t, J = 37.4 Hz), 116.7 (t, J = 273.9 Hz), 61.0, 41.7, 40.7, 40.2, 33.7 (t, J = 4.3 Hz), 20.9, 16.9, 14.2, 12.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.4. HRMS (ESI): $C_{15}H_{29}F_2N_2O_2$ $[M+H]^+$ calcd: 307.2192, found: 307.2200.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01013.

Optimization of reaction conditions, mechanistic study, ^{1}H and ^{13}C NMR spectra for the products, and single crystal data of **3q** (PDF)

X-ray crystallography data for **3q**(CIF)

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Notes

The authors declare no competing financial interest.

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