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Friedel–Crafts Fluoroacetylation of Indoles with Fluorinated Acetic Acids for the Synthesis of Fluoromethyl Indol-3-yl Ketones under Catalyst- and Additive-Free Conditions

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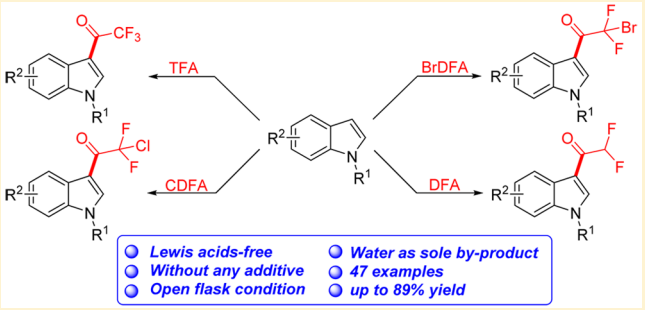
Supporting Information

ABSTRACT: A simple and efficient protocol for the fluoroacetylation of indoles is reported. The reaction uses fluorinated acetic acids as the fluoroacetylation reagents to synthesize diverse fluoromethyl indol-3-yl ketones in good yields under catalyst- and additive-free conditions. In addition, the only byproduct is water in this transformation. The synthetic utility of this reaction was also demonstrated by the concise synthesis of α-(trifluoromethyl)(indol-3-yl)methanol and indole-3-carboxylic acid.

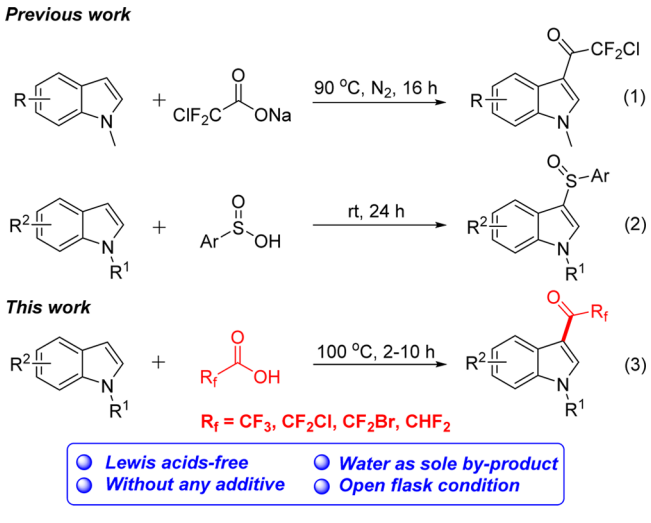


INTRODUCTION

Increased attention is being focused on organofluorine chemistry because the incorporation of fluorine-containing groups into organic molecules can dramatically alter physical, chemical, and biological properties such as binding affinity, metabolic stability, and lipophilicity.[1] In recent years, a number of highly effective methods have been developed for the incorporation of fluorine atoms or fluoromethyl groups into organic molecules.[2,3] Among numerous fluoromethyl-containing compounds, indolyl fluoromethyl ketones are an important structural motif of many biologically active compounds[4] and intermediates for the synthesis of other fluoromethyl-substituted compounds.[5] Traditional methods for the preparation of indolyl fluoromethyl ketones largely involve either Friedel–Crafts acylation (strong electrophiles in combination with reactive Lewis acids)[6] or oxidation of α-fluoromethyl alcohols (multistep conversions).[7] A general, efficient method for the preparation of indolyl fluoromethyl ketones from easily available reagents is highly desirable.[8]

Recently, 3-chlorodifluoroacylation of *N*-alkylindoles for the synthesis of indolyl chlorodifluoromethyl ketones through an elegant self-activation of sodium chlorodifluoroacetate has been developed by Greaney and Williams (Scheme 1, eq 1).[9] However, approaches to the ready preparation of diverse indolyl fluoromethyl ketones, such as indolyl trifluoromethyl ketones, indolyl bromodifluoromethyl ketones, and indolyl difluoromethyl ketones, are still urgently needed and remain a significant challenge. More recently, an electrophilic sulfenylation of indoles with arylsulfinic acids in water under catalyst- and additive-free conditions has been developed by Wang and co-workers (Scheme 1, eq 2).[10] To the best of our knowledge, Friedel–Crafts acylation with carboxylic acids under catalyst- and additive-free conditions has never been reported.[11] Inspired by Greaney and Wang's results, we envisaged that the fluoroacetylation of indoles may occur by using fluorinated acetic acids as the fluoroacetylation reagents. In this paper, we report a Friedel–Crafts fluoroacetylation of indoles with commercially available fluorinated acetic acids for the synthesis of indolyl fluoromethyl ketones under catalyst- and additive-free conditions (Scheme 1, eq 3). Moreover, water is the sole byproduct in this transformation. This process not only

Scheme 1. Acylation Reactions of Indoles



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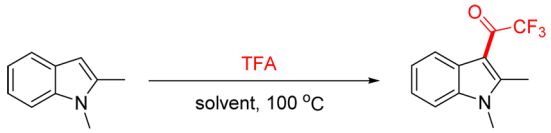
addresses the issues of corrosion (without addition of Lewis acids as catalysts during the reaction) but also circumvents the problems of strict exclusion of moisture (insensitive to water and air). This method also provides a facile and convenient method for the construction of a C−COR_f bond.

RESULTS AND DISCUSSION

To explore the fluoroacetylation, the reaction of 1,2-dimethylindole (**1a**) and trifluoroacetic acid (TFA) was conducted as a model reaction. Gratifyingly, the desired 3-trifluoroacetylated indole **2a** was observed in 8% yield when CH_3CN was employed as the solvent (Table 1, entry 1). This result encouraged us to optimize the reaction conditions. Screening of various solvents, such as CH_2Cl_2, 1,4-dioxane, CH_3OH, CH_3NO_2, toluene, *N*,*N*-dimethylformamide (DMF), and 1,2-dichloroethane (DCE), suggested that DCE was the optimal solvent for the transformation (Table 1, entries 2−8). Extra trifluoroacetic acid was added to the reaction mixture to enhance the protonation of the trifluoroacetic acid to the trifluoroacetyl cation intermediate.[10,11a] We found that increasing the amount of TFA enhanced the reaction, with 3 equiv providing a 89% isolated yield of **2a** (Table 1, entry 9). Further increases or decreases in the reaction temperature resulted in lower yields (Table 1, entries 10 and 11).

Table 1. Optimization of Reaction Conditions[a]

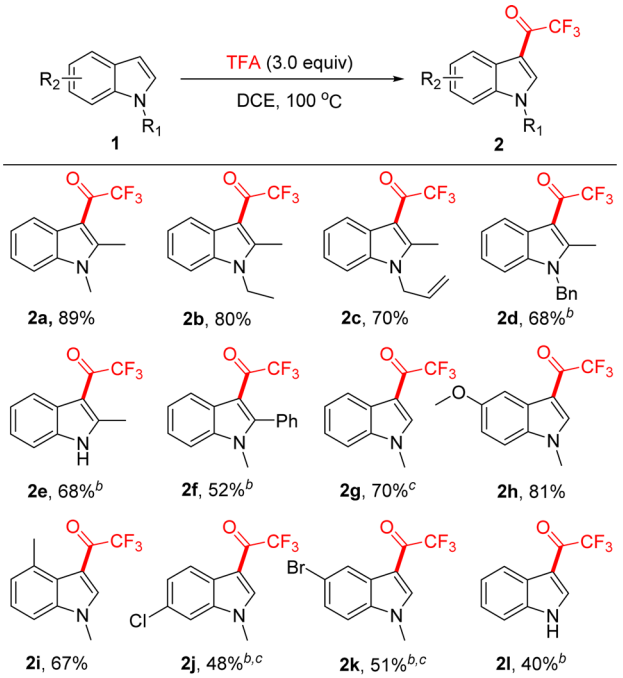


entry	solvent	T (°C)	yield (%)[b]
1	CH_3CN	100	8
2[c]	CH_2Cl_2	100	42
3	1,4-dioxane	100	0
4[c]	CH_3OH	100	0
5	CH_3NO_2	100	0
6	toluene	100	54
7	DMF	100	0
8[c]	DCE	100	57
9[c,d]	**DCE**	**100**	**89**
10[c,d]	DCE	120	72
11[d]	DCE	80	73

[a]Reaction conditions unless specified otherwise: **1a** (0.2 mmol), TFA (2.0 equiv), solvent (2.0 mL), 3 h in air. [b]Isolated yield. [c]The reaction mixture was refluxed in an oil bath. [d]TFA (3.0 equiv).

With the optimized conditions in hand, we next investigated the substrate scope of the reaction (Table 2). The 2-methylindoles with *N*-methyl, *N*-ethyl, *N*-allyl, and *N*-benzyl were smoothly converted to the trifluoromethyl ketones in good to high yields (**2a**−**d**). However, 2-phenyl-substituted *N*-methylindole gave the corresponding trifluoromethyl ketone **2f** in 52% yield, likely due to steric hindrance of the phenyl group. When *N*-methylindole was used as substrate, the corresponding trifluoromethyl ketone **2g** was obtained in 70% yields.[12] It is noteworthy that the *N*-methylindoles bearing electron-donating groups or electron-withdrawing groups, such as methoxyl, methyl, chloro, and bromo groups on the aromatic rings, reacted with trifluoroacetic acid to afford the corresponding trifluoroacetylated products in moderate to good yields (**2h**−**k**). In comparison with electron-donating groups, indoles substituted with electron-withdrawing groups afforded modestly lower yields presumably because of the reduced nucleophilicity. It is notable that the free (N−H) indoles worked under the standard conditions and gave the desired 3-trifluoroacetylindoles in good yields (**2e**,**l**). Unfortunately, no reaction occurred when *N*-Ac indole, *N*-Boc indole, *N*-Ts indole, or 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine were employed as substrates.

Table 2. Trifluoroacetylation of Various Indoles[a]



[a]Reaction conditions unless specified otherwise: indoles (0.2 mmol), TFA (3.0 equiv), DCE (2.0 mL), reflux in a 100 °C oil bath, 3−10 h in air. Isolated yields are given. [b]TFA (5.0 equiv). [c]Toluene was used as solvent.

In comparison to TFA, chlorodifluoroacetic acid (CDFA) has been reported to undergo ready decarboxylation to form difluoromethylene or chlorodifluoromethyl radicals, which were used in situ for difluoromethylation or chlorodifluoromethylation.[13] However, chlorodifluoroacetic acid has not been reported to directly provide the chlorodifluoroacetyl group. Encouraged by our previous success, we were prompted to attempt the straightforward chlorodifluoroacetylation reaction of indoles with chlorodifluoroacetic acid under our optimized conditions.

A wide range of indoles bearing substituents on the aromatic rings and nitrogen atom were investigated, and the results are summarized in Table 3. 2-Methyl-*N*-methylindole, 2-methyl-*N*-benzylindole, and 2-methylindole afforded the desired chlorodifluoroacetylated products in good yields (**3a**,**d**,**e**). In addition, 1-methyl-2-phenyl-1*H*-indole was well tolerated and the corresponding product **3f** was obtained in 68% yield. *N*-Methylindoles bearing methoxyl and methyl groups on the carbon skeleton showed good reactivity in the generation of the desired chlorodifluoromethyl ketones (**3h**,**i**,**m**,**n**). It is important to note that methyl 1-methyl-1*H*-indole-6-carboxylate gave the corresponding chlorodifluoromethyl ketone **3o** in 38% yield. Furthermore, *N*-ethylindole, *N*-allylindole, *N*-propargy-

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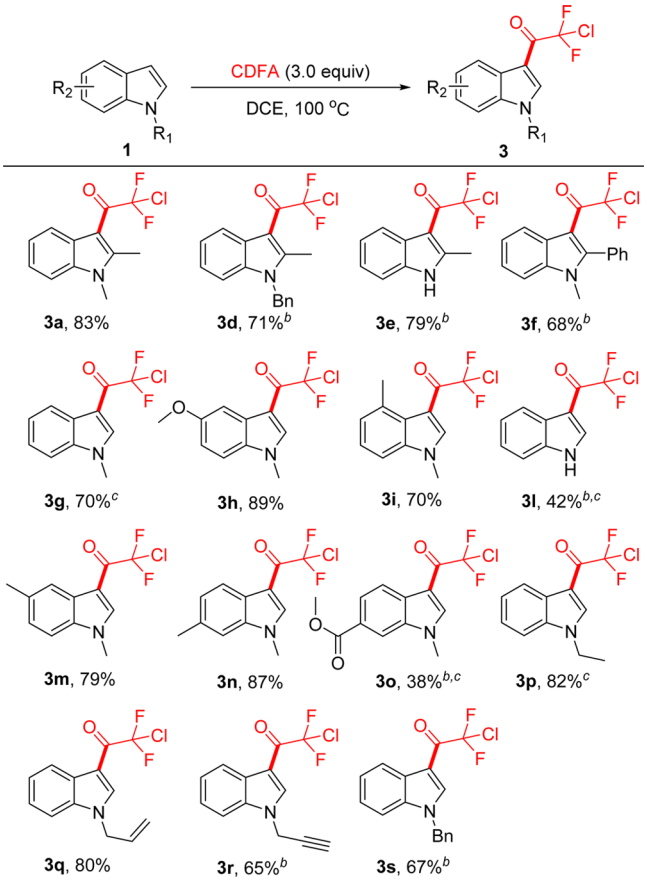
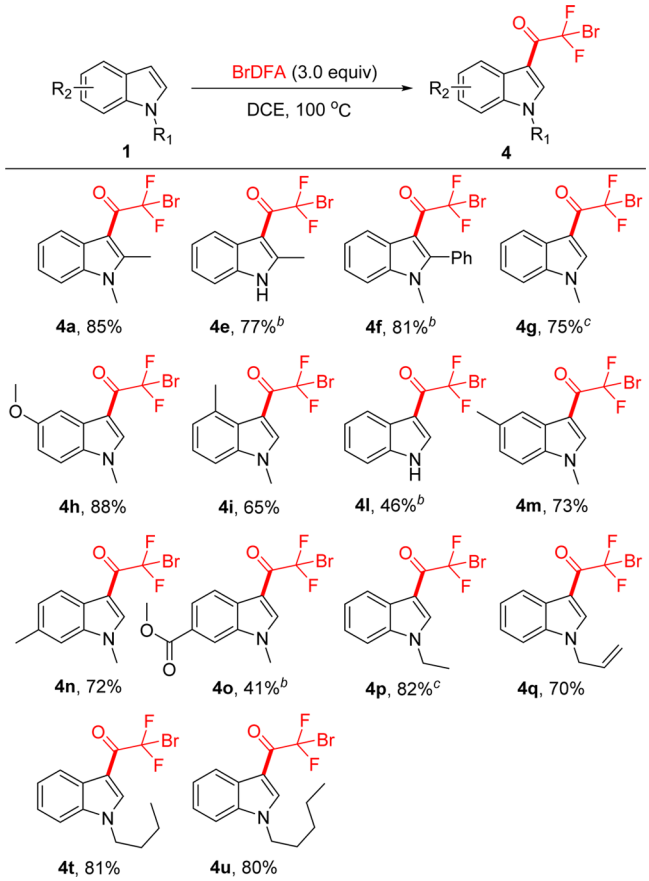
Table 3. Chlorodifluoroacetylation of Various Indoles[a]



[a]Reaction conditions unless specified otherwise: indoles (0.2 mmol), CDFA (3.0 equiv), DCE (2.0 mL), reflux in a 100 °C oil bath, 2−10 h in air. Isolated yields are given. [b]CDFA (5.0 equiv). [c]Toluene was used as solvent.

Table 4. Bromodifluoroacetylation of Various Indoles[a]



[a]Reaction conditions unless specified otherwise: indoles (0.2 mmol), BrDFA (3.0 equiv), DCE (2.0 mL), reflux in a 100 °C oil bath, 2−10 h in air. Isolated yields are given. [b]BrDFA (5.0 equiv). [c]Toluene was used as solvent.

lindole, and *N*-benzylindole proved to be suitable substrates and offered the desired products in 65−82% yields (**3p**−**s**).

We next focused on the bromodifluoroacetylation of indoles because the $BrCF_2COR$ moiety can serve as a CF_2 radical precursor[14] and there have been no reports of the preparation of bromodifluoromethyl indol-3-yl ketones. Satisfactorily, bromodifluoroacetic acid (BrDFA) was also applicable to this reaction and afforded the bromodifluoromethyl ketones in good to high yields (Table 4). Notably, indoles bearing methyl or phenyl substitution at the C-2 position reacted with BrDFA to give the corresponding bromodifluoromethyl ketones in 77−85% yields (**4a**,**e**,**f**). *N*-Methylindoles bearing methoxyl and methyl groups on the aromatic rings performed smoothly in the reaction to produce the desired 3-bromodifluoroacetyl indoles in 65−88% yields (**4h**,**i**,**m**,**n**). When NH indole was used, the 3-bromodifluoroacetylated product **4l** was generated in 46% yield. Furthermore, a methoxycarbonyl group was well tolerated and the corresponding product **4o** was obtained in 41% yield. Finally, different substituent groups on the indole nitrogen were studied. C_2−C_5 alkyl groups, such as ethyl, allyl, butyl, and pentyl groups, afforded the corresponding bromodifluoromethyl ketones in 70−82% yields (**4p**,**q**,**t**,**u**).

To further expand the scope of the fluoroacetylation reaction, we turned our attention to difluoroacetylation of indoles with difluoroacetic acid (DFA), since the difluoromethyl ketones display good biological and reactive activities.[15] Pleasingly, in this difluoroacetylation protocol, a series of indoles reacted with difluoroacetic acid to produce the desired difluoromethyl indol-3-yl ketones in 26−76% yields (Table 5).

To demonstrate the synthetic utility of the trifluoroacetylation reaction, several examples are illustrated in Scheme 2. First, direct reduction of **2g** using $NaBH_4$ smoothly gave 2,2,2-trifluoro-1-(1-methyl-1*H*-indol-3-yl)ethanol (**6**) in 85% yield. This has been shown to be a vital intermediate for the synthesis of highly active cell death inhibitors and 1-trifluoromethylated cyclopenta[*b*]indole alkaloids.[16] Under the simple hydrolysis conditions, **2g** was easily transformed into *N*-methylindole-3-carboxylic acid (**7**), which has been widely applied in various pharmaceutical and organic syntheses.[17] Furthermore, **2a** could be used to synthesize the photochromic fulgimide **8** and fulgide **9**. These results are particularly useful as optical switches in information storage devices and biological sensors owing to a reversible change between two thermally stable states with different structures and colors.[18]

On the basis of the above results, a plausible reaction mechanism for this trifluoroacetylation reaction is proposed (Scheme 3). First, the reaction was initiated by a protonation of trifluoroacetic acid to form species **A** under acidic conditions. The intermediate **A** underwent a dehydration to release trifluoroacetyl cation **B**. Subsequently, electrophilic addition of trifluoroacetyl cation **B** to 1,2-dimethylindole (**1a**) gave

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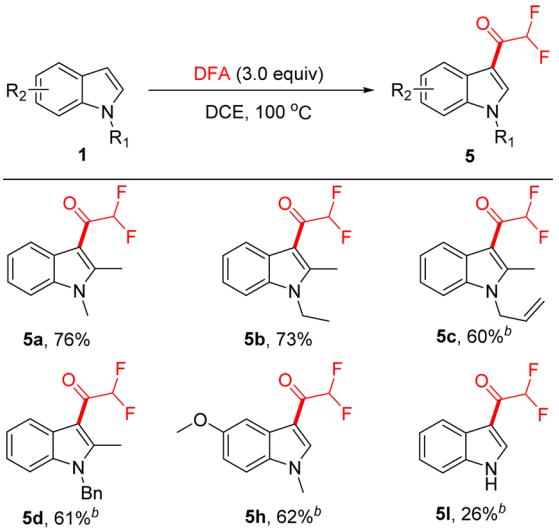
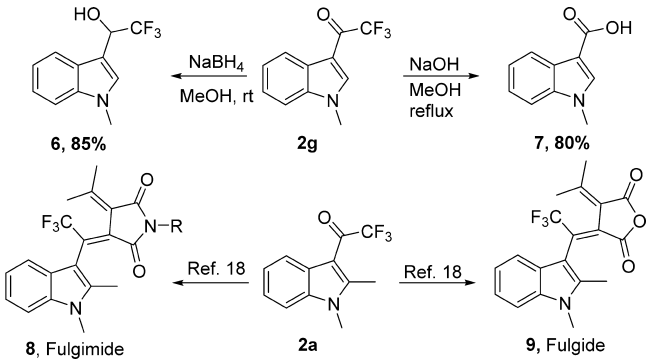
Table 5. Difluoroacetylation of Indoles[a]

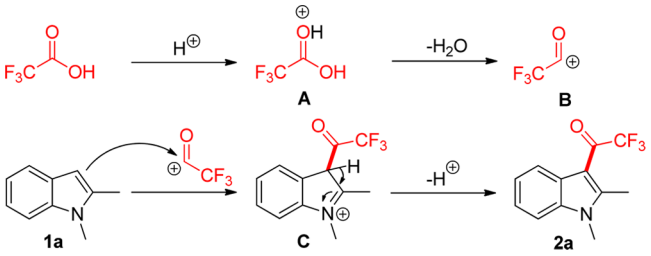


[a]Reaction conditions unless specified otherwise: indoles (0.2 mmol), DFA (3.0 equiv), DCE (2.0 mL), reflux in a 100 °C oil bath, 4–9 h in air. Isolated yields are given. [b]DFA (5.0 equiv).

Scheme 2. Synthetic Utility of Trifluoromethyl Indol-3-yl Ketones



Scheme 3. Plausible Reaction Mechanism



indole iminium ion **C**. Finally, deprotonation from **C** afforded the trifluoromethyl indol-3-yl ketone **2a**. Reactions of chlorodifluoroacetic acid, bromodifluoroacetic acid, and difluoroacetic acid with indoles were explained as following a similar mechanistic pathway.

CONCLUSION

In summary, we have developed a simple and efficient methodology for trifluoro-, chlorodifluoro-, bromodifluoro-, and difluoroacetylation of indoles using commercially available trifluoroacetic acid, chlorodifluoroacetic acid, bromodifluoroacetic acid, and difluoroacetic acid as the fluoroacetylating reagents under catalyst- and additive-free conditions. The new approach displays a powerful method for the direct construction of diverse fluoromethyl indol-3-yl ketones. In addition, water is the sole byproduct in this transformation. The unique transformation is complementary for the traditional Friedel–Crafts acylation and has significant potential for application to a series of organic syntheses. Detailed mechanistic and further scope studies of this fluoroacetylation are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Coupling constants, *J*, are reported in hertz (Hz). All products were characterized by HRMS (ESI-TOF-Q); copies of their ^{1}H, ^{13}C, and ^{19}F NMR spectra are provided in the Supporting Information. Preparative TLC was performed on TLC plates, analytical thin-layer chromatography was performed on 10–25 μm silica gel GF254, and visualization was carried out with UV light. Flash column chromatography was performed with SiO_2 (silica gel 200–300 mesh). Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. All of the *N*-substituted indoles were prepared according to literature procedures.[19]

Typical Procedure for Synthesis of Trifluoromethyl Indol-3-yl Ketones 2. Indoles (0.2 mmol) and trifluoroacetic acid (3 equiv) were refluxed in a 100 °C oil bath in 2 mL of DCE in an air atmosphere, and the progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction mixture was cooled to room temperature. Water (2 × 5 mL) was added, the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine, and the solvent was removed on a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc 20/1–15/1) to afford the corresponding products **2**.

1-(1,2-Dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (***2a***)*:*[9] pink solid (42.8 mg, 89%, mp 108–109 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04–8.02 (m, 1 H), 7.30–7.27 (m, 3 H), 3.68 (s, 3 H), 2.73 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0 (q, J_{CF} = 35.6 Hz), 150.2, 136.7, 125.0, 123.1, 121.5, 120.6 (q, J_{CF} = 4.3 Hz), 117.2 (q, J_{CF} = 288.0 Hz), 109.7, 107.6, 29.7, 12.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −74.3 (s, 3 F); HRMS calcd (ESI) *m*/*z* for $C_{12}H_{10}F_3NNaO$ $[M + Na]^+$ 264.0607, found 264.0612.

1-(1-Ethyl-2-methyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (***2b***)*:* yellow oil (40.9 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05–8.03 (m, 1 H), 7.34–7.32 (m, 1 H), 7.31–7.26 (m, 2 H), 4.20–4.15 (m, 2 H), 2.74 (s, 3 H), 1.37 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2 (q, J_{CF} = 35.6 Hz), 149.5, 135.7, 125.2, 123.1, 123.1, 120.9 (q, J_{CF} = 4.6 Hz), 117.2 (q, J_{CF} = 288.1 Hz), 109.8, 107.8, 38.2, 14.3, 12.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −74.3 (s, 3 F); HRMS calcd (ESI) *m*/*z* for $C_{13}H_{12}F_3NNaO$ $[M + Na]^+$ 278.0763, found 278.0754.

1-(1-Allyl-2-methyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (***2c***)*:* yellow oil (40 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.06 (d, *J* = 7.2 Hz, 1 H), 7.33–7.28 (m, 3 H), 5.97–5.89 (m, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 4.89 (d, *J* = 17.2 Hz, 1 H), 4.79–4.80 (m, 2 H), 2.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4 (q, J_{CF} = 35.7 Hz), 150.0, 136.2, 130.7, 125.1, 123.3, 123.2, 120.9 (q, J_{CF} = 4.4 Hz), 117.5, 117.1 (q, J_{CF} = 288.1 Hz), 110.0, 108.1, 45.4, 12.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −74.4 (s, 3 F); HRMS calcd (ESI) *m*/*z* for $C_{14}H_{12}F_3NNaO$ $[M + Na]^+$ 290.0763, found 290.0751.

1-(1-Benzyl-2-methyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (***2d***)*:* white solid (45.5 mg, 68%, mp 112–113 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 7.6 Hz, 1 H), 7.31–7.23 (m, 6 H), 7.00 (d, *J* = 6.4 Hz, 2 H), 5.38 (s, 2 H), 2.73 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.5 (q, J_{CF} = 35.7 Hz), 150.1, 136.6, 135.0, 129.1, 128.0, 125.8, 125.1, 123.4, 123.3, 120.9 (q, J_{CF} = 4.4 Hz), 117.1 (q, J_{CF} =

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288.1 Hz), 110.2, 108.3, 46.7, 13.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −74.3 (s, 3 F); HRMS calcd (ESI) m/z for $C_{18}H_{14}F_3NNaO$ $[M + Na]^+$ 340.0920, found 340.0914.

*2,2,2-Trifluoro-1-(2-methyl-1H-indol-3-yl)ethan-1-one (**2e**):*[7] white solid (30.9 mg, 68%, mp 149−151 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.92−7.90 (m, 1 H), 7.48−7.47 (m, 1 H), 7.26−7.23 (m, 2 H), 2.70 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.6 (q, J_{CF} = 34.7 Hz), 150.6, 135.2, 125.7, 123.1, 122.8, 120.0 (q, J_{CF} = 3.3 Hz), 117.1 (q, J_{CF} = 288.5 Hz), 112.1, 106.6, 15.1; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −73.8 (s, 3 F); HRMS calcd (ESI) m/z for $C_{11}H_8F_3NNaO$ $[M + Na]^+$ 250.0450, found 250.0442.

*2,2,2-Trifluoro-1-(1-methyl-2-phenyl-1H-indol-3-yl)ethan-1-one (**2f**):* yellow solid (31.5 mg, 52%, mp 87−89 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33−8.31 (m, 1 H), 7.53−7.48 (m, 3 H), 7.40−7.35 (m, 5 H), 3.51 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.8 (q, J_{CF} = 36.0 Hz), 149.6, 136.8, 130.3, 130.1, 129.7, 128.2, 126.3, 124.1, 123.8, 121.8 (q, J_{CF} = 1.9 Hz), 116.5 (q, J_{CF} = 288.1 Hz), 110.2, 108.8, 31.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −72.5 (s, 3 F); HRMS calcd (ESI) m/z for $C_{17}H_{12}F_3NNaO$ $[M + Na]^+$ 326.0763, found 326.0767.

*2,2,2-Trifluoro-1-(1-methyl-1H-indol-3-yl)ethan-1-one (**2g**):*[7] colorless solid (31.6 mg, 70%, mp 101−103 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40−8.37 (m, 1 H), 7.89 (s, 1 H), 7.39−7.36 (m, 3 H), 3.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7 (q, J_{CF} = 34.5 Hz), 138.4 (q, J_{CF} = 4.9 Hz), 137.3, 126.9, 124.6, 123.9, 122.4, 117.1 (q, J_{CF} = 289.3 Hz), 110.2, 109.3, 34.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −72.2 (s, 3 F); HRMS calcd (ESI) m/z for $C_{11}H_8F_3NNaO$ $[M + Na]^+$ 250.0450, found 250.0453.

*3,3′-(2,2,2-Trifluoro-1-(1-methyl-1H-indol-2-yl)ethane-1,1-diyl)-bis(1-methyl-1H-indole) (**2g′**):* red solid, mp 276−277 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.23 (m, 6 H), 7.14−7.10 (m, 3 H), 6.97 (s, 3 H), 6.87−6.84 (m, 3 H), 3.70 (s, 9 H); HRMS calcd (ESI) m/z for $C_{29}H_{23}F_3N_3$: $[M - H]^+$ 470.1839, found 470.1821.

*2,2,2-Trifluoro-1-(5-methoxy-1-methyl-1H-indol-3-yl)ethan-1-one (**2h**):* colorless solid (41.7 mg, 81%, mp 93−95 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 2.0 Hz, 1 H), 7.83 (s, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.00 (dd, J = 2.4, 2.0 Hz, 1H), 3.90 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5 (q, J_{CF} = 34.4 Hz), 157.3, 138.0 (q, J_{CF} = 4.9 Hz), 132.0, 127.9, 117.1 (q, J_{CF} = 289.3 Hz), 114.6, 110.9, 108.9, 103.8, 55.7, 34.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −72.2 (s, 3 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}F_3NNaO_2$ $[M + Na]^+$ 280.0556, found 280.0555.

*1-(1,4-Dimethyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (**2i**):* colorless solid (32.1 mg, 67%, mp 110−112 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 1 H), 7.27 (t, J = 8.0 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.12 (d, J = 7.2 Hz, 1 H), 3.86 (s, 3 H), 2.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7 (q, J_{CF} = 33.4 Hz), 139.5 (q, J_{CF} = 5.4 Hz), 138.2, 133.7, 125.8, 125.5, 124.6, 117.6 (q, J_{CF} = 290.8 Hz), 110.3, 107.6, 34.0, 23.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −70.3 (s, 3 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}F_3NNaO$ $[M + Na]^+$ 264.0607, found 264.0608.

*1-(6-Chloro-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (**2j**):* colorless solid (25.1 mg, 48%, mp 135−137 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 8.8 Hz, 1 H), 7.89 (s, 1 H), 7.39 (d, J = 1.6 Hz, 1 H), 7.34 (dd, J = 2.0 Hz, 2.0 Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7 (q, J_{CF} = 34.9 Hz), 138.7 (q, J_{CF} = 4.8 Hz), 137.8, 130.7, 125.3, 124.5, 123.5, 116.9 (q, J_{CF} = 289.1 Hz), 110.4, 109.4, 34.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −72.4 (s, 3 F); HRMS calcd (ESI) m/z for $C_{11}H_7ClF_3NNaO$ $[M + Na]^+$ 284.0060, found 284.0054.

*1-(5-Bromo-1-methyl-1H-indol-3-yl)-2,2,2-trifluoroethan-1-one (**2k**):* colorless solid (31.1 mg, 51%, mp 178−180 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (s, 1 H), 7.85 (s, 1 H), 7.42 (d, J = 8.8 Hz, 1 H), 7.21 (d, J = 4.8 Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5 (q, J_{CF} = 35.0 Hz), 138.8 (q, J_{CF} = 4.9 Hz), 135.9, 128.3, 127.5, 124.9, 117.6, 116.8 (q, J_{CF} = 289.1 Hz), 111.5, 108.7, 34.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −72.5 (s, 3 F); HRMS calcd (ESI) m/z for $C_{11}H_7BrF_3NNaO$ $[M + Na]^+$ 327.9555, found 327.9552.

*2,2,2-Trifluoro-1-(1H-indol-3-yl)ethan-1-one (**2l**):*[6] white solid (17.2 mg, 40%, mp 153−155 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.75 (s, 1 H), 8.49 (s, 1 H), 8.20 (d, J = 5.6 Hz, 1 H), 7.60 (d, J = 6.4 Hz, 1 H), 7.36−7.30 (m, 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.0 (q, J_{CF} = 33.6 Hz), 137.6 (q, J_{CF} = 4.8 Hz), 136.7, 125.8, 124.4, 123.5, 121.2, 117.0 (q, J_{CF} = 289.8 Hz), 113.1, 108.9; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −71.3 (s, 3 F); HRMS calcd (ESI) m/z for $C_{10}H_6F_3NNaO$ $[M + Na]^+$ 236.0294, found 236.0286.

Typical Procedure for Synthesis of Chlorodifluoromethyl Indol-3-yl Ketones 3. Indoles (0.2 mmol) and chlorodifluoroacetic acid (3 equiv) were refluxed in a 100 °C oil bath in 2 mL of DCE in an air atmosphere, and the progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction mixture was cooled to room temperature. Water (2 × 5 mL) was added, the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine, and the solvent was removed on a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc 20/1−15/1) to afford the corresponding products **3**.

*2-Chloro-1-(1,2-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one (**3a**):*[9] red solid (42.7 mg, 83%, mp 95−96 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 4.8 Hz, 1 H), 7.31−7.28 (m, 3 H), 3.70 (s, 3 H), 2.76 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0 (t, J_{CF} = 30.0 Hz), 150.7, 136.8, 124.8, 123.0, 122.9, 121.7 (t, J_{CF} = 5.4 Hz), 121.0 (t, J_{CF} = 301.7 Hz), 109.7, 106.9, 30.0, 13.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}ClF_2NNaO$ $[M + Na]^+$ 280.0311, found 280.0305.

*1-(1-Benzyl-2-methyl-1H-indol-3-yl)-2-chloro-2,2-difluoroethan-1-one (**3d**):*[9] yellow solid (47.5 mg, 71%, mp 102−104 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 8.4 Hz, 1 H), 7.32−7.23 (m, 6 H), 7.01−6.99 (m, 2 H), 5.38 (s, 2 H), 2.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4 (t, J_{CF} = 30.1 Hz), 150.6, 136.7, 135.1, 129.1, 128.0, 125.8, 124.9, 123.3, 123.1, 121.9 (t, J_{CF} = 5.5 Hz), 121.0 (t, J_{CF} = 302.0 Hz), 110.2, 107.5, 46.8, 13.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −62.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{18}H_{14}ClF_2NNaO$ $[M + Na]^+$ 356.0624, found 356.0612.

*2-Chloro-2,2-difluoro-1-(2-methyl-1H-indol-3-yl)ethan-1-one (**3e**):* white solid (38.5 mg, 79%, mp 109−111 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.66 (s, 1 H), 7.93−7.91 (m, 1 H), 7.48−7.46 (m, 1 H), 7.25−7.23 (m, 2 H), 2.71 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.1 (t, J_{CF} = 29.4 Hz), 150.6, 134.7, 124.9, 122.5, 122.1, 120.3 (t, J_{CF} = 4.4 Hz), 120.2 (t, J_{CF} = 300.7 Hz), 111.6, 105.0, 15.3; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −62.2 (s, 2 F); HRMS calcd (ESI) m/z for $C_{11}H_8ClF_2NNaO$ $[M + Na]^+$ 266.0155, found 266.0145.

*2-Chloro-2,2-difluoro-1-(1-methyl-2-phenyl-1H-indol-3-yl)ethan-1-one (**3f**):* white solid (43.7 mg, 68%, mp 71−73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28−8.26 (m, 1 H), 7.51 (d, J = 6.0 Hz, 3 H), 7.41−7.36 (m, 5 H), 3.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.4 (t, J_{CF} = 30.5 Hz), 149.9, 136.9, 130.9, 130.1, 129.6, 128.3, 126.0, 123.9, 123.5, 122.3 (t, J_{CF} = 3.3 Hz), 120.8 (t, J_{CF} = 302.6 Hz), 110.2, 107.9, 31.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −61.0 (s, 2 F); HRMS calcd (ESI) m/z for $C_{17}H_{12}ClF_2NNaO$ $[M + Na]^+$ 342.0468, found 342.0454.

*2-Chloro-2,2-difluoro-1-(1-methyl-1H-indol-3-yl)ethan-1-one (**3g**):*[9] off-white solid (34.2 mg, 70%, mp 94−96 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40−8.38 (m, 1 H), 7.92 (s, 1 H), 7.38−7.35 (m, 3 H), 3.87 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2 (t, J_{CF} = 28.8 Hz), 138.1 (t, J_{CF} = 6.8 Hz), 137.1, 127.2, 124.4, 123.8, 122.5, 120.8 (t, J_{CF} = 302.9 Hz), 110.1, 107.8, 33.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.5 (s, 2 F); HRMS calcd (ESI) m/z for $C_{11}H_8ClF_2NNaO$ $[M + Na]^+$ 266.0155, found 266.0151.

*2-Chloro-2,2-difluoro-1-(5-methoxy-1-methyl-1H-indol-3-yl)-ethan-1-one (**3h**):*[9] white solid (48.6 mg, 89%, mp 85−87 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90−7.88 (m, 2 H), 7.27 (d, J = 10.8 Hz, 1 H), 7.00 (dd, J = 1.6, 2.0 Hz, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1 (t, J_{CF} = 28.7 Hz), 157.3, 137.8 (t, J_{CF} = 6.8 Hz), 132.0, 128.3, 120.9 (t, J_{CF} = 303.0 Hz), 114.6, 110.9, 107.5, 103.8, 55.7, 34.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}ClF_2NNaO_2$ $[M + Na]^+$ 296.0260, found 296.0257.

*2-Chloro-1-(1,4-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one (**3i**):* white solid (36.0 mg, 70%, mp 128−130 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (s, 1 H), 7.26 (t, J = 7.6 Hz,, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 7.11 (d, J = 7.2 Hz, 1 H), 3.85 (s, 3 H), 2.84 (s, 3 H); ^{13}C

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NMR ($CDCl_3$, 100 MHz) δ 175.5 (t, J_{CF} = 27.7 Hz), 139.1 (t, J_{CF} = 7.3 Hz), 138.0, 133.8, 125.9, 125.8, 124.6, 121.5 (t, J_{CF} = 304.4 Hz), 108.9, 107.6, 34.1, 23.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −58.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}ClF_2NNaO$ $[M + Na]^+$ 280.0311, found 280.0300.

2-Chloro-2,2-difluoro-1-(1H-indol-3-yl)ethan-1-one ***(3l):*** yellow solid (19.3 mg, 42%, mp 150−152 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.67 (s, 1 H), 8.48−8.46 (m, 1 H), 8.20−8.18 (m, 1 H), 7.60−7.58 (m, 1 H), 7.36−7.31 (m, 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.7 (t, J_{CF} = 28.2 Hz), 137.2 (t, J_{CF} = 6.7 Hz), 136.5, 126.1, 124.2, 123.4, 121.1, 120.6 (t, J_{CF} = 302.8 Hz), 113.0, 107.3; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −60.0 (s, 2 F); HRMS calcd (ESI) m/z for $C_{10}H_6ClF_2NNaO$ $[M + Na]^+$ 251.9998, found 251.9995.

2-Chloro-1-(1,5-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(3m):*** yellow solid (40.7 mg, 79%, mp 118−120 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1 H), 7.87 (s, 1 H), 7.24 (s, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 3.84 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1 (t, J_{CF} = 28.7 Hz), 138.0 (t, J_{CF} = 6.9 Hz), 135.5, 133.7, 127.5, 125.9, 122.3, 120.9 (t, J_{CF} = 303.2 Hz), 109.7, 107.4, 33.9, 21.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}ClF_2NNaO$ $[M + Na]^+$ 280.0311, found 280.0299.

2-Chloro-1-(1,6-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(3n):*** off-white solid (44.8 mg, 87%, mp 114−116 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1 H), 7.87 (s, 1 H), 7.25 (d, J = 8.4 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 3.85 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1 (t, J_{CF} = 28.7 Hz), 138.0 (t, J_{CF} = 6.8 Hz), 135.5, 133.7, 127.5, 125.9, 122.3, 120.9 (t, J_{CF} = 303.1 Hz), 109.7, 107.4, 33.9, 21.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}ClF_2NNaO$ $[M + Na]^+$ 280.0311, found 280.0307.

Methyl 3-(2-chloro-2,2-difluoroacetyl)-1-methyl-1H-indole-6-carboxylate ***(3o):*** yellow solid (22.9 mg, 38%, mp 159−160 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (d, J = 8.4 Hz, 1 H), 8.14 (s, 1 H), 8.06−8.03 (m, 2 H), 3.97 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1 (t, J_{CF} = 29.2 Hz), 167.2, 140.1 (t, J_{CF} = 6.7 Hz), 136.8, 130.9, 126.3, 124.7, 122.3, 120.7 (t, J_{CF} = 302.9 Hz), 112.2, 108.0, 52.3, 34.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −61.0 (s, 2 F); HRMS calcd (ESI) m/z for $C_{13}H_{10}ClF_2NNaO_3$ $[M + Na]^+$ 324.0209, found 324.0204.

2-Chloro-1-(1-ethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(3p):*** off-white solid (42.1 mg, 82%, mp 76−77 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44−8.41 (m, 1 H), 7.99 (s, 1 H), 7.45−7.37 (m, 3 H), 4.31−4.25 (m, 2 H), 1.60−1.56 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1 (t, J_{CF} = 28.7 Hz), 136.5 (t, J_{CF} = 6.9 Hz), 136.3, 127.5, 124.3, 123.8, 122.7, 120.9 (t, J_{CF} = 303.1 Hz), 110.2, 107.9, 42.3, 15.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}ClF_2NNaO$ $[M + Na]^+$ 280.0311, found 280.0301.

1-(1-Allyl-1H-indol-3-yl)-2-chloro-2,2-difluoroethan-1-one ***(3q):*** yellow oil (43.0 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42−8.41 (m, 1 H), 7.97 (s, 1 H), 7.39−7.35 (m, 3 H), 6.07−5.97 (m, 1 H), 5.35 (d, J = 10.4 Hz, 1 H), 5.22 (d, J = 17.2 Hz, 1 H), 4.81 (d, J = 5.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3 (t, J_{CF} = 29.0 Hz), 137.1 (t, J_{CF} = 6.8 Hz), 136.6, 131.2, 127.4, 124.4, 123.9, 122.6, 120.8 (t, J_{CF} = 303.0 Hz), 119.4, 110.5, 108.2, 49.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.5 (s, 2 F); HRMS calcd (ESI) m/z for $C_{13}H_{10}ClF_2NNaO$ $[M + Na]^+$ 292.0311, found 292.0300.

2-Chloro-2,2-difluoro-1-(1-(prop-2-yn-1-yl)-1H-indol-3-yl)ethan-1-one ***(3r):*** white solid (34.5 mg, 65%, mp 69−70 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43−8.40 (m, 1 H), 8.13 (t, J = 1.6 Hz, 1 H), 7.48−7.46 (m, 1 H), 7.45−7.38 (m, 2 H), 4.95 (d, J = 2.8 Hz, 2 H), 2.59 (t, J = 2.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.4 (t, J_{CF} = 29.0 Hz), 136.4 (t, J_{CF} = 7.0 Hz), 136.1, 127.5, 124.7, 124.2, 122.8, 120.8 (t, J_{CF} = 303.0 Hz), 110.1, 108.5, 76.1, 75.3, 37.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.7 (s, 2 F); HRMS calcd (ESI) m/z for $C_{13}H_8ClF_2NNaO$ $[M + Na]^+$ 290.0155, found 290.0157.

1-(1-Benzyl-1H-indol-3-yl)-2-chloro-2,2-difluoroethan-1-one ***(3s):*** yellow solid (42.6 mg, 67%, mp 86−88 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (d, J = 8.0 Hz, 1 H), 8.00 (s, 1 H), 7.35−7.30 (m, 6 H), 7.16 (d, J = 6.0 Hz, 2 H), 5.37 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.4 (t, J_{CF} = 29.0 Hz), 137.5 (t, J_{CF} = 6.8 Hz), 136.7, 134.8, 129.1, 128.4, 127.5, 126.9, 124.6, 123.9, 122.7, 120.8 (t, J_{CF} = 303.1 Hz), 110.7, 108.3, 51.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −60.5 (s, 2 F); HRMS calcd (ESI) m/z for $C_{17}H_{12}ClF_2NNaO$ $[M + Na]^+$ 342.0468, found 342.0456.

Typical Procedure for Synthesis of Bromodifluoromethyl Indol-3-yl Ketones 4. Indoles (0.2 mmol) and bromodifluoroacetic acid (3 equiv) were refluxed in a 100 °C oil bath in 2 mL of DCE in an air atmosphere, and the progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction mixture was cooled to room temperature. A saturated sodium bicarbonate solution (5 mL) and water (5 mL) were added, the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine, and the solvent was removed on a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc 20/1−15/1) to afford the corresponding products **4**.

2-Bromo-1-(1,2-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(4a):*** off-white solid (51.2 mg, 85%, mp 114−115 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08−8.06 (m, 1 H), 7.32−7.27 (m, 3 H), 3.69 (s, 3 H), 2.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7 (t, J_{CF} = 27.1 Hz), 150.8, 136.8, 124.6, 123.0, 122.9, 122.2 (t, J_{CF} = 5.7 Hz), 115.0 (t, J_{CF} = 315.6 Hz), 109.7, 106.5, 30.0, 13.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −58.6 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}BrF_2NNaO$ $[M + Na]^+$ 323.9806, found 323.9804.

2-Bromo-2,2-difluoro-1-(2-methyl-1H-indol-3-yl)ethan-1-one ***(4e):*** yellow solid (44.1 mg, 77%, mp 163−165 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.64 (s, 1 H), 7.95−7.93 (m, 1 H), 7.48 (d, J = 8.8 Hz, 1 H), 7.28−7.24 (m, 2 H), 2.72 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.7 (t, J_{CF} = 26.7 Hz), 151.0, 135.2, 125.2, 122.9, 122.4, 121.2 (t, J_{CF} = 4.7 Hz), 114.5 (t, J_{CF} = 313.3 Hz), 112.0, 105.1, 16.0; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −59.6 (s, 2 F); HRMS calcd (ESI) m/z for $C_{11}H_8BrF_2NNaO$ $[M + Na]^+$ 309.9650, found 309.9650.

2-Bromo-2,2-difluoro-1-(1-methyl-2-phenyl-1H-indol-3-yl)ethan-1-one ***(4f):*** white solid (59.1 mg, 81%, mp 92−93 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27−8.25 (m, 1 H), 7.51 (d, J = 5.6 Hz, 3 H), 7.40−7.37 (m, 5 H), 3.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.0 (t, J_{CF} = 27.5 Hz), 149.9, 137.0, 131.0, 130.0, 129.6, 128.4, 125.9, 123.8, 123.4, 122.5 (t, J_{CF} = 3.5 Hz), 114.9 (t, J_{CF} = 316.6 Hz), 110.3, 107.4, 31.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −57.2 (s, 2 F); HRMS calcd (ESI) m/z for $C_{17}H_{12}BrF_2NNaO$ $[M + Na]^+$ 385.9963, found 385.9961.

2-Bromo-2,2-difluoro-1-(1-methyl-1H-indol-3-yl)ethan-1-one ***(4g):*** red solid (43.2 mg, 75%, mp 118−120 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41−8.38 (m, 1 H), 7.95 (s, 1 H), 7.38−7.36 (m, 3 H), 3.89 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8 (t, J_{CF} = 26.0 Hz), 138.1 (t, J_{CF} = 6.9 Hz), 137.1, 127.3, 124.4, 123.8, 122.6, 114.4 (t, J_{CF} = 316.6 Hz), 110.1, 107.2, 34.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.8 (s, 2 F); HRMS calcd (ESI) m/z for $C_{11}H_8BrF_2NNaO$ $[M + Na]^+$ 309.9650, found 309.9647.

2-Bromo-2,2-difluoro-1-(5-methoxy-1-methyl-1H-indol-3-yl)-ethan-1-one ***(4h):*** white solid (55.5 mg, 88%, mp 116−118 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89−7.88 (m, 2 H), 7.27−7.25 (m, 1 H), 6.99 (dd, J = 2.4, 2.4 Hz, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8 (t, J_{CF} = 25.9 Hz), 157.3, 137.8 (t, J_{CF} = 8.0 Hz), 132.0, 128.4, 114.7, 114.6 (t, J_{CF} = 316.7 Hz), 111.0, 106.9, 103.8, 55.7, 34.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.7 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}BrF_2NNaO_2$ $[M + Na]^+$ 339.9755, found 339.9751.

2-Bromo-1-(1,4-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(4i):*** white solid (38.9 mg, 65%, mp 125−126 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (s, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.2 Hz, 1 H), 3.85 (s, 3 H), 2.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1 (t, J_{CF} = 24.9 Hz), 139.0 (t, J_{CF} = 7.6 Hz), 138.0, 133.8, 125.9, 125.8, 124.6, 115.1 (t, J_{CF} = 318.2 Hz), 108.4, 107.6, 34.1, 22.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −54.7 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}BrF_2NNaO$ $[M + Na]^+$ 323.9806, found 323.9801.

2-Bromo-2,2-difluoro-1-(1H-indol-3-yl)ethan-1-one ***(4l):*** yellow solid (25.4 mg, 46%, mp 163−165 °C); ^{1}H NMR (DMSO-d_6, 400

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MHz) δ 12.64 (s, 1 H), 8.47−8.45 (m, 1 H), 8.20−8.18 (m, 1 H), 7.60−7.58 (m, 1 H), 7.35−7.29 (m, 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.8 (t, J_{CF} = 25.5 Hz), 137.1 (t, J_{CF} = 6.9 Hz), 136.5, 126.2, 124.2, 123.3, 121.2, 114.2 (t, J_{CF} = 315.3 Hz), 113.0, 106.8; ^{19}F NMR (DMSO-d_6, 376 MHz) δ −57.4 (s, 2 F); HRMS calcd (ESI) m/z for $C_{10}H_6BrF_2NNaO$ $[M + Na]^+$ 295.9493, found 295.9496.

2-Bromo-1-(1,5-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(4m)****:* yellow solid (43.8 mg, 73%, mp 99−101 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1 H), 7.89 (s, 1 H), 7.25 (d, J = 8.4 Hz, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 3.84 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7 (t, J_{CF} = 26.0 Hz), 138.0 (t, J_{CF} = 7.3 Hz), 135.5, 133.7, 127.6, 125.9, 122.3, 114.5 (t, J_{CF} = 316.8 Hz), 109.7, 106.8, 34.0, 21.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.6 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}BrF_2NNaO$ $[M + Na]^+$ 323.9806, found 323.9804.

2-Bromo-1-(1,6-dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(4n)****:* yellow solid (43.5 mg, 72%, mp 106−108 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1 H), 7.89 (s, 1 H), 7.26 (d, J = 8.4 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 3.85 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7 (t, J_{CF} = 25.7 Hz), 138.0 (t, J_{CF} = 7.2 Hz), 135.5, 133.7, 127.6, 125.9, 122.4, 114.5 (t, J_{CF} = 316.9 Hz), 109.7, 106.8, 34.0, 21.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.6 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}BrF_2NNaO$ $[M + Na]^+$ 323.9806, found 323.9806.

Methyl 3-(2-bromo-2,2-difluoroacetyl)-1-methyl-1H-indole-6-carboxylate ***(4o)****:* yellow solid (28.6 mg, 41%, mp 157−159 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (dd, J = 3.2, 3.2 Hz, 1 H), 8.13 (s, 1 H), 8.07−8.03 (m, 2 H), 3.97 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7 (t, J_{CF} = 26.3 Hz), 167.1, 140.0 (t, J_{CF} = 6.8 Hz), 136.7, 130.9, 126.2, 124.7, 122.3, 114.2 (t, J_{CF} = 316.5 Hz), 112.2, 107.4, 52.3, 34.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −57.3 (s, 2 F); HRMS calcd (ESI) m/z for $C_{13}H_{10}BrF_2NNaO_3$ $[M + Na]^+$ 367.9704, found 367.9700.

2-Bromo-1-(1-ethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(4p)****:* off-white solid (49.2 mg, 82%, mp 69−71 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42−8.40 (m, 1 H), 8.01 (s, 1 H), 7.43−7.40 (m, 1 H), 7.39−7.35 (m, 2 H), 4.28−4.23 (m, 2 H), 1.56 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7 (t, J_{CF} = 25.9 Hz), 136.5 (t, J_{CF} = 7.2 Hz), 136.3, 127.6, 124.3, 123.8, 122.7, 114.5 (t, J_{CF} = 316.7 Hz), 110.2, 107.3, 42.3, 15.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.7 (s, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{10}BrF_2NNaO$ $[M + Na]^+$ 323.9806, found 323.9806.

1-(1-Allyl-1H-indol-3-yl)-2-bromo-2,2-difluoroethan-1-one ***(4q)****:* brown oil (43.6 mg, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42−8.40 (m, 1 H), 7.99 (s, 1 H), 7.40−7.33 (m, 3 H), 6.07−5.97 (m, 1 H), 5.35 (d, J = 10.4 Hz, 1 H), 5.22 (d, J = 17.2 Hz, 1 H), 4.81 (d, J = 5.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.9 (t, J_{CF} = 26.1 Hz), 137.1 (t, J_{CF} = 7.1 Hz), 136.6, 131.2, 127.5, 124.4, 123.8, 122.7, 119.4, 114.4 (t, J_{CF} = 316.7 Hz), 110.5, 107.6, 49.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.8 (s, 2 F); HRMS calcd (ESI) m/z for $C_{13}H_{10}BrF_2NNaO$ $[M + Na]^+$ 335.9806, found 335.9805.

2-Bromo-1-(1-butyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(4t)****:* yellow oil (53.0 mg, 81%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43−8.40 (m, 1 H), 7.98 (s, 1 H), 7.42−7.35 (m, 3 H), 4.19 (t, J = 7.2 Hz, 2 H), 1.92−1.85 (m, 2 H), 1.39−1.34 (m, 2 H), 0.99−0.95 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8 (t, J_{CF} = 25.9 Hz), 137.2 (t, J_{CF} = 7.1 Hz), 136.5, 127.5, 124.3, 123.7, 122.7, 114.5 (t, J_{CF} = 316.9 Hz), 110.3, 107.2, 47.4, 31.7, 20.0, 13.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.7 (s, 2 F); HRMS calcd (ESI) m/z for $C_{14}H_{14}BrF_2NNaO$ $[M + Na]^+$ 352.0119, found 352.0116.

2-Bromo-2,2-difluoro-1-(1-pentyl-1H-indol-3-yl)ethan-1-one ***(4u)****:* brown oil (54.8 mg, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35−8.32 (m, 1 H), 7.89 (s, 1 H), 7.33−7.26 (m, 3 H), 4.10 (t, J = 7.2 Hz, 2 H), 1.85−1.78 (m, 2 H), 1.27−1.22 (m, 4 H), 0.81 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8 (t, J_{CF} = 25.8 Hz), 137.2 (t, J_{CF} = 7.1 Hz), 136.5, 127.5, 124.3, 123.7, 122.7, 114.5 (t, J_{CF} = 316.9 Hz), 110.3, 107.2, 47.6, 29.3, 28.8, 22.1, 13.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −56.6 (s, 2 F); HRMS calcd (ESI) m/z for $C_{15}H_{16}BrF_2NNaO$ $[M + Na]^+$ 366.0276, found 366.0273.

Typical Procedure for Synthesis of Difluoromethyl Indol-3-yl Ketones 5. Indoles (0.2 mmol) and difluoroacetic acid (3 equiv) were refluxed in a 100 °C oil bath in 2 mL of DCE in an air atmosphere, and the progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction mixture was cooled to room temperature. Water (2 × 5 mL) was added, the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine, and the solvent was removed on a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc 20/1−15/1) to afford the corresponding products **5**.

1-(1,2-Dimethyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(5a)****:* white solid (33.9 mg, 76%, mp 82−84 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96−7.93 (m, 1 H), 7.33−7.28 (m, 3 H), 6.38 (t, J_{HF} = 54.0 Hz, 1 H), 3.71 (s, 3 H), 2.77 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (t, J_{CF} = 24.4 Hz), 148.9, 136.7, 125.2, 122.9, 122.9, 120.6 (t, J_{CF} = 3.0 Hz), 110.2 (t, J_{CF} = 248.6 Hz), 109.8, 109.4, 29.7, 12.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −125.6 (d, J_{HF} = 54.1 Hz, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{11}F_2NNaO$ $[M + Na]^+$ 246.0701, found 246.0690.

1-(1-Ethyl-2-methyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(5b)****:* yellow oil (35.6 mg, 73%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, J = 4.8 Hz, 1 H), 7.35−7.34 (m, 1 H), 7.29−7.27 (m, 2 H), 6.39 (t, J_{HF} = 54.0 Hz, 1 H), 4.22−4.16 (m, 2 H), 2.77 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.7 (t, J_{CF} = 24.7 Hz), 148.0, 135.7, 125.5, 122.9, 122.8, 120.8 (t, J_{CF} = 3.4 Hz), 110.5 (t, J_{CF} = 249.1 Hz), 109.8, 109.7, 38.1, 14.5, 12.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −125.6 (d, J_{HF} = 54.1 Hz, 2 F); HRMS calcd (ESI) m/z for $C_{13}H_{13}F_2NNaO$ $[M + Na]^+$ 260.0857, found 260.0847.

1-(1-Allyl-2-methyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(5c)****:* yellow oil (29.7 mg, 60%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.0 Hz, 1 H), 7.30−7.24 (m, 3 H), 6.39 (t, J_{HF} = 54.0 Hz, 1 H), 5.91−5.86 (m, 1 H), 5.18 (d, J = 10.4 Hz, 1 H), 4.84 (d, J = 17.2 Hz, 1 H), 4.72−4.71 (m, 2 H), 2.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.9 (t, J_{CF} = 24.6 Hz), 148.5, 136.2, 130.9, 125.3, 123.0, 120.8 (t, J_{CF} = 3.1 Hz), 117.4, 110.4 (t, J_{CF} = 248.9 Hz), 110.1, 109.8, 45.3, 12.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −125.5 (d, J_{HF} = 54.1 Hz, 2 F); HRMS calcd (ESI) m/z for $C_{14}H_{13}F_2NNaO$ $[M + Na]^+$ 272.0857, found 272.0850.

1-(1-Benzyl-2-methyl-1H-indol-3-yl)-2,2-difluoroethan-1-one ***(5d)****:* orange solid (36.6 mg, 61%, mp 93−95 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, J = 7.6 Hz, 1 H), 7.30−7.22 (m, 6 H), 6.99−6.97 (m, 1 H), 6.41 (t, J_{HF} = 54.0 Hz, 1 H), 5.35 (s, 2 H), 2.73 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.0 (t, J_{CF} = 24.8 Hz), 148.6, 136.6, 135.2, 129.0, 127.9, 125.8, 125.4, 123.2, 123.1, 120.9 (t, J_{CF} = 3.3 Hz), 110.5 (t, J_{CF} = 249.2 Hz), 110.3, 110.1, 46.6, 13.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −125.5 (d, J_{HF} = 53.8 Hz, 2 F); HRMS calcd (ESI) m/z for $C_{18}H_{15}F_2NNaO$ $[M + Na]^+$ 322.1014, found 322.1010.

2,2-Difluoro-1-(5-methoxy-1-methyl-1H-indol-3-yl)ethan-1-one ***(5h)****:* white solid (29.8 mg, 62%, mp 124−126 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 1 H), 7.89 (s, 1 H), 7.26 (d, J = 3.2 Hz, 1 H), 6.99 (dd, J = 2.8, 2.4 Hz, 1 H), 6.10 (t, J_{HF} = 54.4 Hz, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6 (t, J_{CF} = 24.9 Hz), 157.1, 137.7 (t, J_{CF} = 7.0 Hz), 132.0, 127.8, 114.4, 112.0 (t, J_{CF} = 252.2 Hz), 110.7, 110.0, 103.7, 55.7, 33.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −120.1 (d, J_{HF} = 54.1 Hz, 2 F); HRMS calcd (ESI) m/z for $C_{12}H_{11}F_2NNaO_2$ $[M + Na]^+$ 262.0650, found 262.0640.

2,2-Difluoro-1-(1H-indol-3-yl)ethan-1-one ***(5l)****:* off-white solid (10.0 mg, 26%, mp 130−132 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.42 (s, 1 H), 8.48 (d, J = 2.4 Hz, 1 H), 8.18 (dd, J = 2.4, 1.6 Hz, 1 H), 7.55 (dd, J = 1.6, 2.0 Hz, 1 H), 7.31−7.25 (m, 2 H), 6.84 (t, J_{HF} = 53.6 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.8 (t, J_{CF} = 23.4 Hz), 136.5, 136.5 (t, J_{CF} = 3.7 Hz), 125.5, 123.9, 122.8, 121.1, 112.7, 111.6, 109.4 (t, J_{CF} = 244.9 Hz); ^{19}F NMR (DMSO-d_6, 376 MHz) δ −123.8 (d, J_{HF} = 53.8 Hz, 2 F); HRMS calcd (ESI) m/z for $C_{10}H_7F_2NNaO$ $[M + Na]^+$ 218.0388, found 218.0383.

2,2,2-Trifluoro-1-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (6). A 10 mL round-bottom flask was charged with 2,2,2-trifluoro-1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (**2g**; 45.4 mg, 0.2 mmol), $NaBH_4$ (15.1 mg, 0.4 mmol), methanol (3 mL), and a magnetic stirring bar. The reaction mixture was stirred at room temperature. The progress of the

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reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction mixture was extracted with ethyl acetate (20 mL) and water (10 mL), the organic layers were washed with saturated brine, and the solvent was removed on a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc 15/1) to afford the corresponding product **6** (38.9 mg, 85%) as a yellow oil:[16a] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.0 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.22−7.16 (m, 2 H), 5.27 (s, 1 H); 3.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.8, 128.2, 126.2, 124.8 (q, J_{CF} = 280.3 Hz), 122.4, 120.1, 119.2, 109.6, 107.8, 67.3 (q, J_{CF} = 33.3 Hz), 32.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −77.8 (s, 3 F); HRMS calcd (ESI) m/z for $C_{11}H_{10}F_3NNaO$ $[M + Na]^+$ 252.0607, found 252.0614.

1-Methyl-1*H*-indole-3-carboxylic Acid (7). A 10 mL round-bottom flask was charged with 2,2,2-trifluoro-1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (**2g**; 45.4 mg, 0.2 mmol), NaOH (5 M, 1.2 mL), ethanol (0.4 mL), and a magnetic stirring bar. The reaction mixture was refluxed for 4 h and then cooled to room temperature, and H_2O (10 mL) was added. The layers were separated, and the organic layer was extracted with 1 M aqueous NaOH (10 mL). The combined aqueous phases were acidified to pH 1 with 12 M aqueous HCl and extracted with ethyl acetate (2 × 10 mL), and the solvent was evaporated. The product was purified by silica gel chromatography (petroleum ether/EtOAc 5/1) to afford the corresponding product **7** (28.4 mg, 80%) as a white solid (mp 182−184 °C):[20] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.04−8.03 (m, 2 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.27−7.19 (m, 2 H), 3.85 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.7, 137.0, 136.1, 126.4, 122.2, 121.3, 120.7, 110.6, 106.2, 33.0; HRMS calcd (ESI) m/z for $C_{10}H_9NNaO_2$ $[M + Na]^+$ 198.0525, found 198.0528.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00580.

^{1}H, ^{13}C, and ^{19}F NMR spectra for the products (PDF)

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Notes

The authors declare no competing financial interest.

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