JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b00580 • Publication Date (Web): 21 Apr 2016

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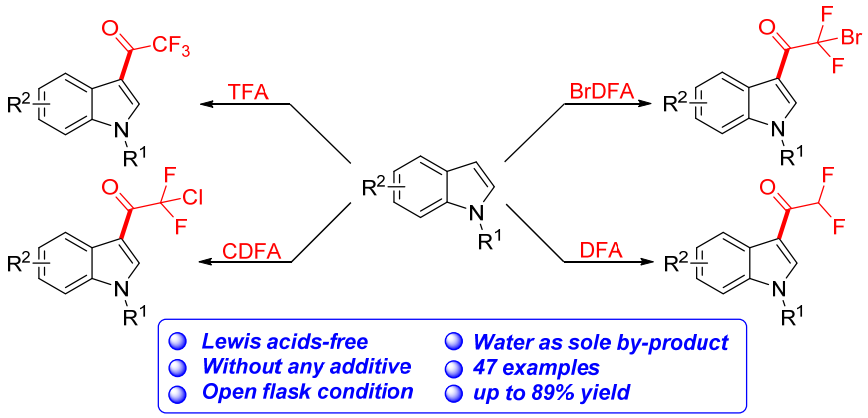


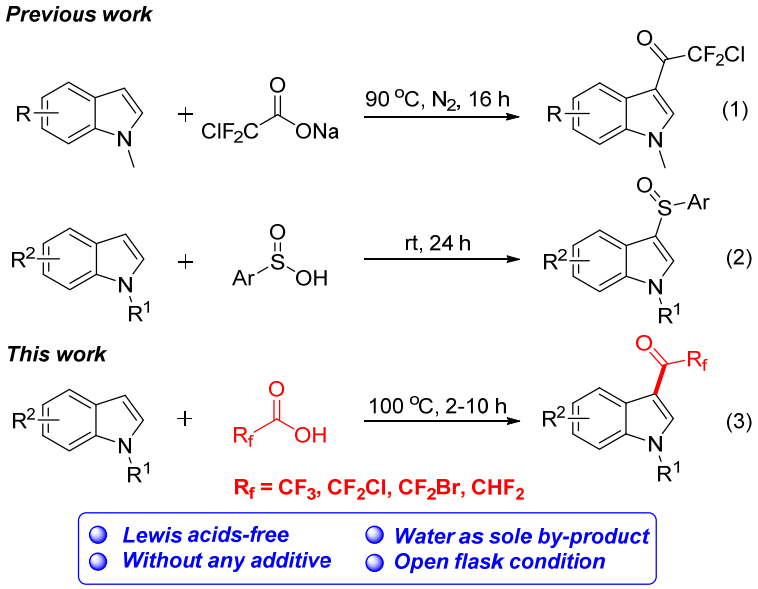
ABSTRACT: A simple and efficient protocol for the fluoroacetylation of indoles is reported. The reaction performs using fluorinated acetic acids as the fluoroacetylation reagents to synthesize diverse fluoromethyl indol-3-yl ketones in good yields under catalyst- and additive-free conditions. Also, the only by-product 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]

Scheme 1. Acylation Reactions of Indoles



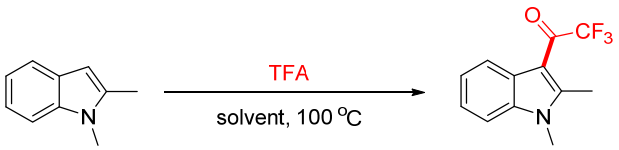
Recently, 3-chlorodifluoroacylation of *N*-alkylindoles for the synthesis of indolyl chlorodifluoromethyl ketones through an elegant self-activation of sodium chlorodifluoroacetate has been developed by Greaney and Williams (Scheme 1, eq 1).[9] However, the approachs for the ready preparation of diverse 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, the 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 by-product in this transformation. This process not only 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 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*-dimethyl formamide (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 to enhance the protonation the trifluoroacetic acid to trifluoroacetyl cation intermediate.[10,11a] We found that raising the equivalents of TFA enhanced the reaction, with 3 equiv providing a 89% isolated yield of **2a** (Table 1, entry 9). Further increasing or lowering the reaction temperature resulted in lower yields (Table 1, entries 10-11).

Table 1. Optimization of Reaction Conditions[a]



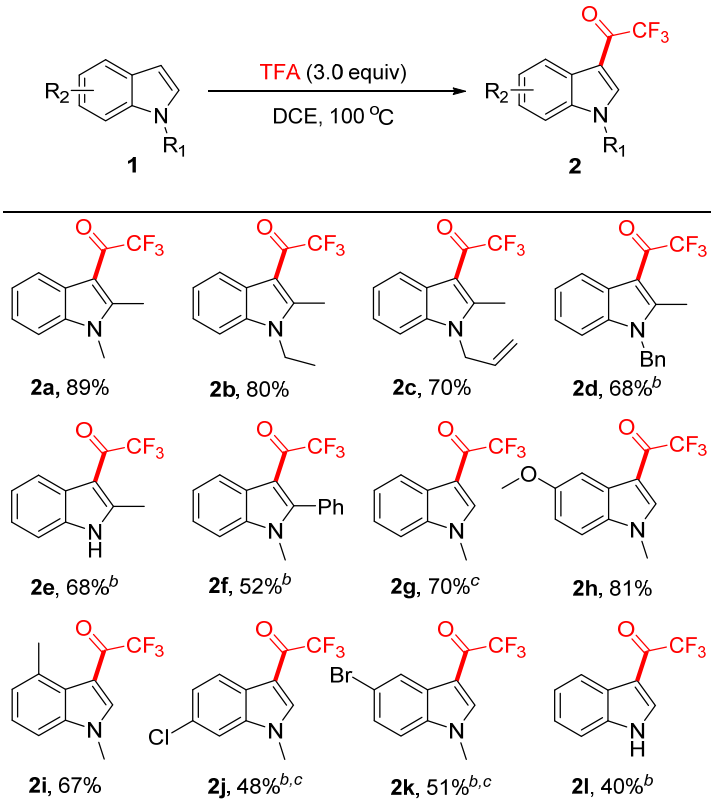
1a **2a**

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: **1a** (0.2 mmol), TFA (2.0 equiv), solvent (2.0 mL), 3 h under air. [b]Isolated yield. [c]The reaction was reflux in oil bath. [d]TFA (3.0 equiv).

Table 2. Trifluoroacetylation of Various Indoles[a]

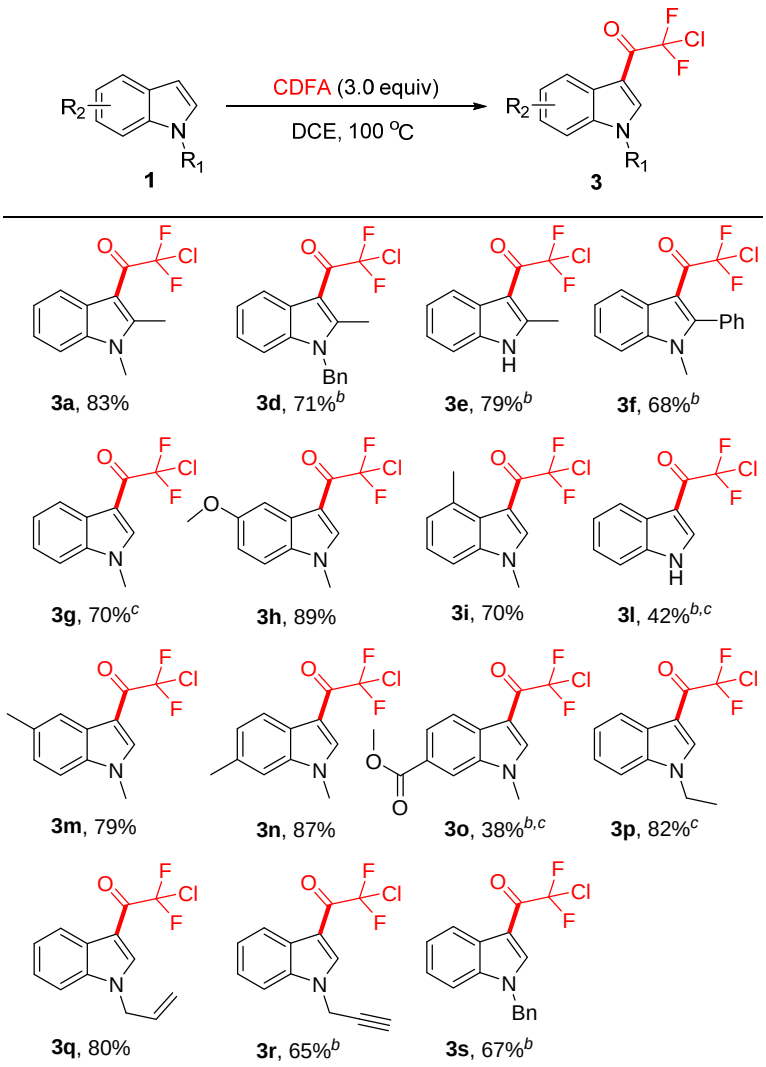


[a]Reaction conditions: indoles (0.2 mmol), TFA (3.0 equiv), DCE (2.0 mL), the reaction was reflux in a 100 °C oil bath, 3-10 h under air; isolated yields. [b]TFA (5.0 equiv). [c]Toluene was used as solvent.

With the optimized conditions in hand, we next investigated the substrate scope of the reaction (Table 2). The 2-methylindoles with *N*-methyl, ethyl, allyl, and benzyl were smoothly converted to the trifluoromethyl ketones in good to high yields (**2a-2d**). 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 was 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-2k**). Compared with electron-donating groups, electron-withdrawing groups substituted indoles afforded modestly lower yields presumably because of the reduced nucleophilicity. It was

notable that the free (N-H) indoles worked under the standard conditions and gave the desired 3-trifluoroacetylindoles in good yields (**2e** and **2l**). Unfortunately, no reaction occurred when *N*-Ac indole, *N*-Boc indole, *N*-Ts indole, or 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine was employed as the substrate.

Table 3. Chlorodifluoroacetylation of Various Indoles[a]



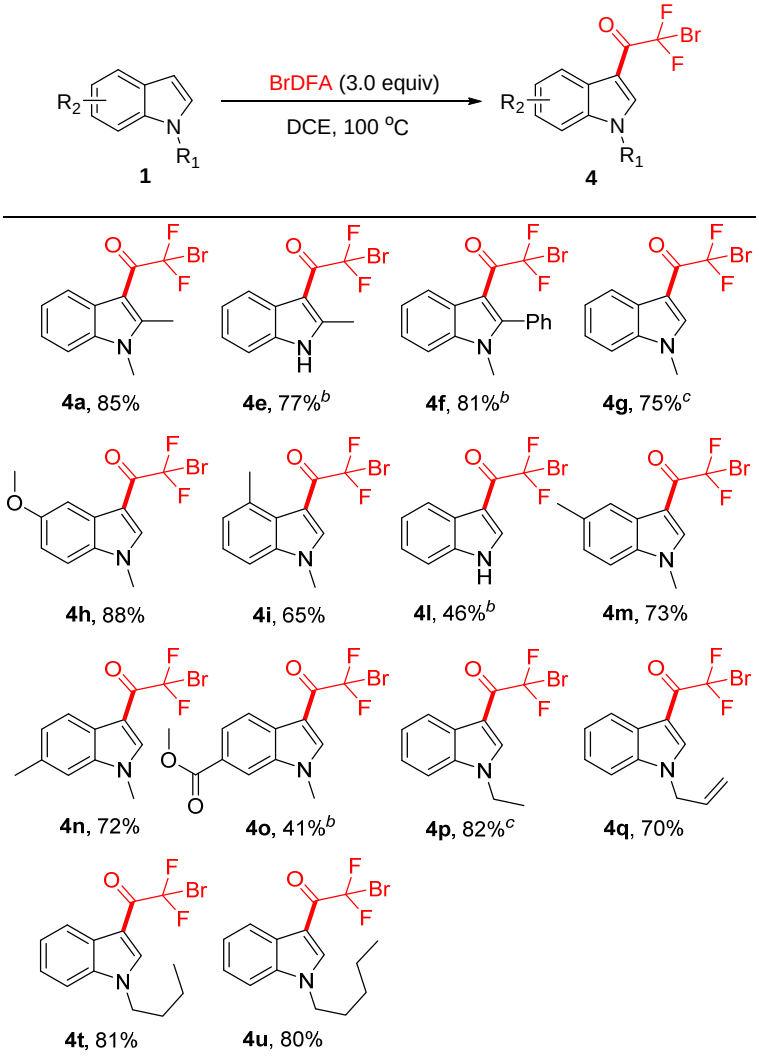
[a]Reaction conditions: indoles (0.2 mmol), CDFA (3.0 equiv), DCE (2.0 mL), the reaction was reflux in a 100 °C oil bath, 2-10 h under air; isolated yields. [b]CDFA (5.0 equiv). [c]Toluene was used as solvent.

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**, **3d**-**3e**). 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 on the carbon skeleton showed good reactivity in the generation of the desired chlorodifluoromethyl ketones (**3h**-**3i**, **3m**-**3n**). 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*-propargylindole, and *N*-benzylindole proved to be suitable substrates and offered the desired products in 65-82% yields (**3p**-**3s**).

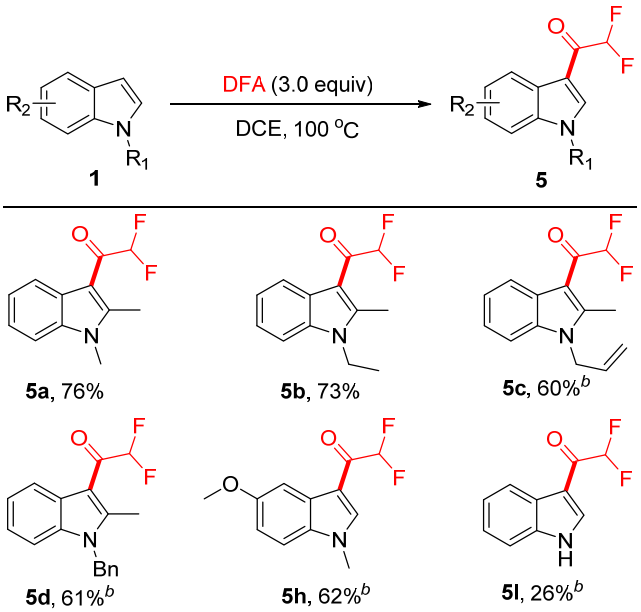
Table 4. Bromodifluoroacetylation of Various Indoles[a]



[a]Reaction conditions: indoles (0.2 mmol), BrDFA (3.0 equiv), DCE (2.0 mL), the reaction was reflux in a 100 °C oil bath, 2-10 h under air; isolated yields. [b]BrDFA (5.0 equiv). [c]Toluene was used as solvent.

We next focused on the bromodifluoroacetylation of indoles because the $BrCF_2COR$ moiety can serve as a CF_2 radical precursor[14] and there are 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**, **4e-4f**). *N*-Methylindoles bearing methoxyl and methyl on the aromatic rings performed smoothly in the reaction to produce the desired 3-bromodifluoroacetyl indoles in 65-88% yields (**4h-4i**, **4m-4n**). When NH indole was used, a 3-bromodifluoroacetylated product **4l** was generated in 46% yield. Furthermore, methoxycarbonyl group was well tolerated and the corresponding product **4o** was obtained in 41% yield. Finally, the different substitution groups on the indole nitrogen were studied. The C_2-C_5 alkyl groups, such as ethyl, allyl, butyl, and pentyl groups, afforded corresponding bromodifluoromethyl ketones in 70-82% yields (**4p-4q**, **4t-4u**).

Table 5. Difluoroacetylation of Indoles[a]

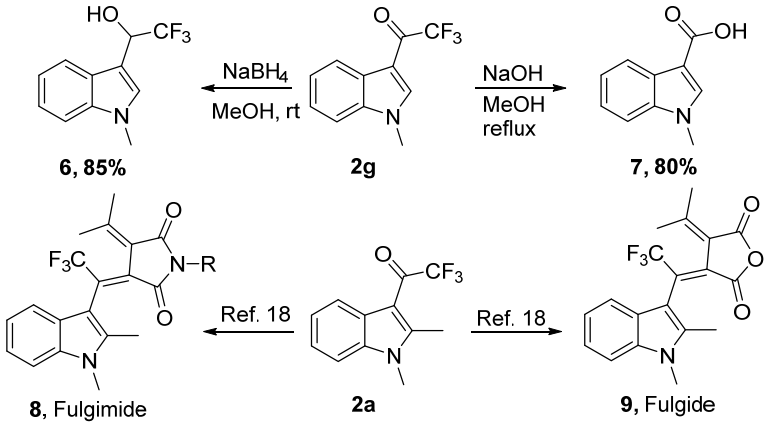


[a]Reaction conditions: indoles (0.2 mmol), DFA (3.0 equiv), DCE (2.0 mL), the reaction was reflux in a 100 °C oil bath, 4-9 h under air; isolated yields. [b]DFA (5.0 equiv).

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

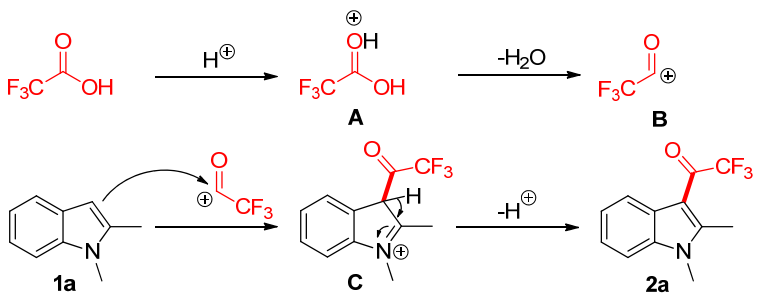
display good biological and reactive activities.[15] Pleasingly, in this difluoroacetylation protocol, a series of indoles reacted with difluoroacetic acid to produce the desired difluoromethyl indol-3-yl ketones in 26-76% yields (Table 5).

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



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-*1H*-indol-3-yl)ethanol **6** in 85% yield. This has been shown to be a vital intermediate for synthesis of high active Cell death inhibitor and 1-trifluoromethylated cyclopenta[*b*]indole alkaloids.[16] Under the simple hydrolysis conditions, **2g** was easily transformed into *N*-methylindole-3-carboxylic acid **7** that 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 reversible change between two thermally stable states with different structures and colors.[18]

Scheme 3. Plausible Reaction Mechanism



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 indole iminium ion **C**. Finally, deprotonation from **C** afforded 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 ketones. Also, water is the sole by-product 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 MHz), (100 MHz), and (376 MHz). 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 were reported in Hertz unit (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 Supporting Information. Preparative TLC was performed on TLC plate, analytical thin layer chromatography was performed on 10-25um silica gel GF254, 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 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 reflux at 100 ^{o}C oil bath in 2 mL of DCE under an air atmosphere, and progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction was cooled to room temperature. Water (2×5 mL) was added, and the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine and it was removed in a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc = 20:1-15:1) to afford 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} = 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 reflux at 100 ^{o}C oil bath in 2 mL of DCE under an air atmosphere, and progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction was cooled to room temperature.

Water (2×5 mL) was added, and the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine and it was removed in a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc = 20:1-15:1) to afford 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 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 (19.3mg, 42%, mp 150-152 °C); ^{1}H NMR (DMSO-*d*^{6}, 400 MHz): δ 12.67 (s, 1 H), 8.48-7.46 (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), 7.48-7.45 (m, 1 H), 7.46-7.38 (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 reflux at 100 ^{o}C oil bath in 2 mL of DCE under an air atmosphere, and progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction was cooled to room temperature. The saturated sodium bicarbonate solution (5 mL) and water (5 mL) was added, and the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine and it was removed in a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc = 20:1-15:1) to afford 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 -60.0 (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 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 reflux at 100 ^{o}C oil bath in 2 mL of DCE under an air atmosphere, and progress of the reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction was cooled to room temperature. Water (2×5 mL) was added, and the product was extracted with ethyl acetate (20 mL), the organic layers were washed with saturated brine and it was removed in a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc = 20:1-15:1) to afford 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 reaction was monitored by TLC. After completion of the reaction, as determined by TLC, the reaction was extracted with ethyl acetate (20 mL) and water (10 mL), the organic layers were washed with saturated brine and it was removed in a rotary evaporator. The product was purified by silica gel chromatography (petroleum ether/EtOAc = 15:1) to afford 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 aq. NaOH (10 mL). The combined aqueous phases were acidified to pH 1 with 12 M aq. HCl, 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 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.

Acknowledgement. This work was supported by generous grants from the National Natural Science Foundation of China (NSFC-21472147, 21272183).

Supporting Information. Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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