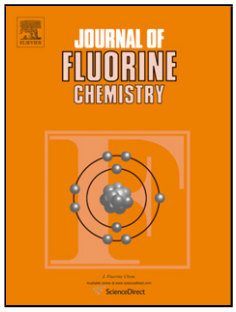

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Direct Access to 2-Difluoromethyl Indoles via Photoredox Catalysis

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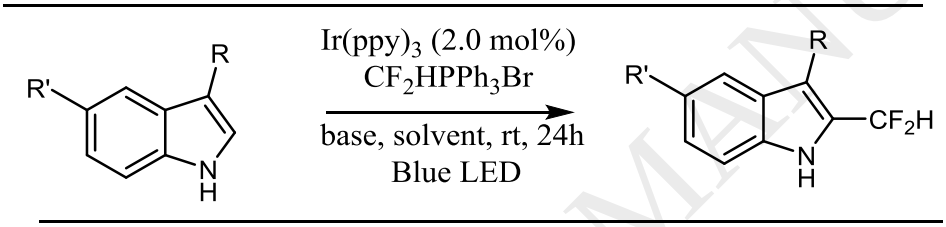
Graphical abstract



Highlights

CF_2HPh_3PBr is a very effective source of difluoromethyl radicals under photoredox catalysis.

Direct difluoromethylation of 3-substituted indoles at the 2-position has been accomplished for the first time.

fac-Ir(ppy)$_3$ is the most effective photoredox catalyst for difluoromethylation of indoles using CF_2HPh_3PBr as the radical precursor.

Abstract

A visible-light mediated approach to radical difluoromethylation of 3- and 3,5-substituted indoles was investigated using a readily synthesized difluoromethyl source, CF_2HPPh_3Br. Direct

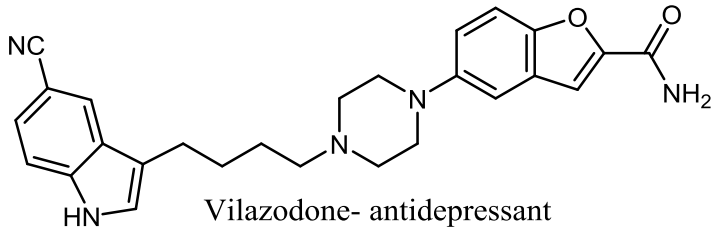
difluoromethylation of indoles in the two position is a rare feat in the literature. The reactions were conducted at room temperature, using $Ir(ppy)_3$ as photocatalyst in acetone, to afford the 2-difluoromethyl indoles in relatively low to moderate yields.

1. Introduction

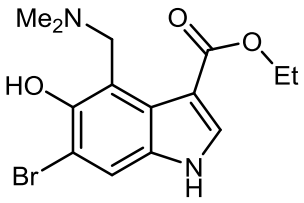
Inspired by the enhancement of properties such as lipophilicity, bioavailability, and metabolic stability, chemists have developed numerous methodologies to install fluoroalkyl moieties, especially the trifluoromethyl and difluoromethyl groups [1]. These enhancements are being explored in fields like pharmaceuticals, agrochemicals, and even novel materials. The expansion of possibilities for realizing direct trifluoromethylation has increased significantly within the last two decades, especially with respect to aromatic and hetero-aromatic substrates [2]. The CF_2H group has also seen impressive development, but the need for more general methods to access a similar breadth of compounds as seen for trifluoromethylation is apparent. The CF_2H group is especially popular as it has hydrogen bonding capabilities, similar to an alcohol or amine, while still bestowing beneficial pharmacological properties like other perfluoroalkyl groups [3]. The desire to install different fluoroalkyl groups into heterocyclic structures has been the goal of many recent publications [4].

Indoles are a class of heterocycles that are widely present in bioactive natural products, as well as pharmaceuticals (Figure 1), as a result of established activities like aiding with central nervous and cardiovascular system diseases, antimitotic therapies, anti-inflammatory, antidepressant, as well as being an effective option for the treatment of infections caused by various bacteria and viruses [5]. Additionally, indole derivatives containing fluorine atoms, trifluoromethyl groups, or other fluoroalkyl groups have shown promise in their own right as potent pharmaceuticals. Direct and indirect access to 2- and 3-CF_3 indole derivatives has been accomplished using a variety of copper-mediated, transition

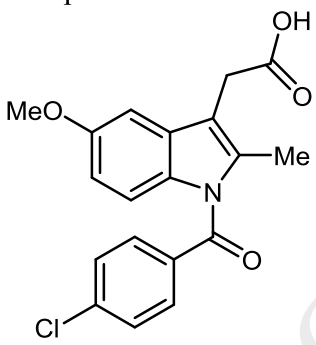
Figure 1. Representative pharmaceutical indole derivatives. Adapted from Ref. 5.



Vilazodone- antidepressant



Arbidol- used to target certain viruses



Indomethacin- nonsteroidal anti-inflammatory drug

metal catalyzed, and photoredox catalyzed approaches [6,7]. Installing a variety of fluoroalkyl groups into the indole substructure has also been accomplished using a copper mediated approach [8]. However, reports for the generation of difluoromethyl indoles are significantly less prevalent in the literature, especially on 3-substituted indoles bearing an unprotected nitrogen. One difficulty in utilizing previously established fluoroalkylation strategies for analogous difluoromethylation reactions is that the reactivity of the intermediates necessary to accomplish the desired products have different properties [9]. Copper complexes that are suitable for generating relatively stable and isolatable "$CuCF_3$" intermediates are more challenging to generate for "$CuCF_2H$", with only three reports being available [7d, 10]. Additionally, the CF_2H radical is relatively nucleophilic as compared to other CF_2R radicals, like the CF_3, CF_2CO_2Et, CF_2CF_2R, and CF_2Cl (11). As a result, predicting the regiochemistry by using the same method to generate each fluoroalkyl radical can be difficult. Excluding pathways that involve direct fluorination of a carbonyl group to gain access to the $–CF_2R$ moiety, the options are relatively limited (Figure 2).

In 2004, Konno and coworkers demonstrated the intermolecular annulation of 2-iodoanilines with internal alkynes bearing CF_3 and CF_2H groups to furnish 2- and 3-fluoroalkyl indoles using

different Pd catalysts to control the regiochemistry (Figure 2, a) [12]. Next, in 2007 Wang *et al.* first synthesized 2-benzyl bromide *N*-aryl difluoromethyl imidoyl chlorides in order to access the 2-CF_2H indoles via an intramolecular Grignard attack (Figure 2, b) [13]. Two separate reports of direct ethoxycarbonyldifluoromethylation of alkenes and heterocycles were reported by Lin *et al.* in 2013, and then by Jung in 2014, both using photoredox catalysis with bromodifluoroethylacetate (Figure 2, c) [14, 15]. While neither group focused on indoles, there were several examples synthesized by both groups, especially 3-Me indole. Further utilization of the bromodifluoroethylacetate as a precursor to the difluoromethyl group was achieved by Guan *et al.* in 2015 via a $Pd(PPh_3)_4$ catalyzed approach using XantPhos as a ligand for regioselective ethoxycarbonyl-difluoromethylation of several electron-rich 3- and 5-substituted indoles (Figure 2, d) [16]. Copper catalyzed methods were then developed by the Shi group, with the utilization of *N*-substituted indoles for regiocontrol being a novel strategy (Figure 2, e) [17]. Based on our recent publications related to the pairing of photoredox catalysis and fluoroalkylation, and the need for the development of direct difluoromethylation strategies, we sought to take advantage of the mild reaction conditions provided by a photoredox strategy with respect to synthesizing 2-CF_2H indoles [18]. This work is, to the best of our knowledge, the first report of direct regioselective difluoromethylation of indoles using photoredox catalysis.

Figure 2. Previous methodologies to synthesize –CF_2R indoles.

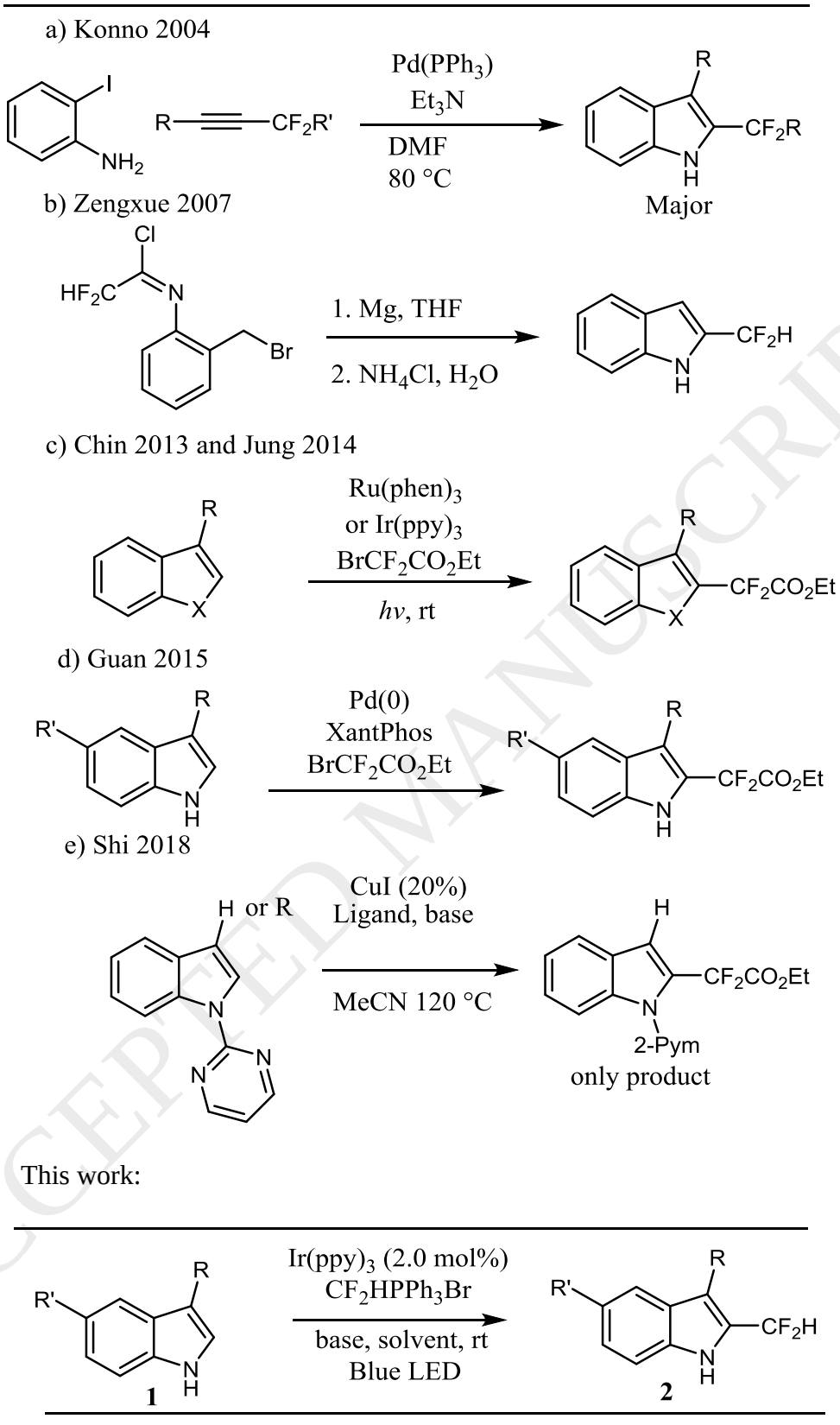
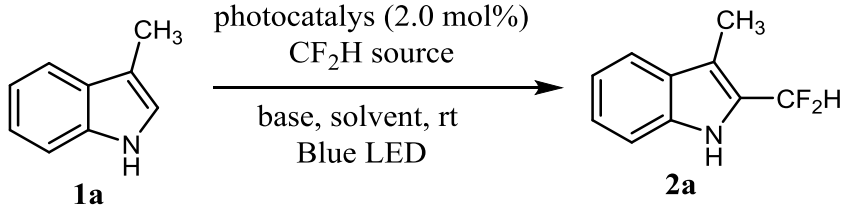


Table 1. Optimization of reaction conditions. Reaction were done using a 0.2 mmol scale relative to **1a**, with 2.0 equivalents of CF_2H source, 2.0 mol% of catalyst, 2.0 equivalents of additive, and 2 mL

of solvent, unless otherwise noted, during 24 h. Yield were calculated using trifluorotoluene as internal standard in the crude ^{19}F-NMR spectrum.



1a **2a**

Entry	CF_2H Source	Catalyst	Solvent	Additive	Yield [a] (%)
1	CF_2HSO_2Cl	**3a**	MeCN	K_2CO_3	34
2	CF_2HSO_2BOT	**3a**	MeCN	K_2CO_3	trace
3	CF_2HPPh_3Br	**3a**	MeCN	K_2CO_3	39
4	CF_2HPPh_3Br	**3b**	MeCN	K_2CO_3	32
5	CF_2HPPh_3Br	**3c**	MeCN	K_2CO_3	6
6	CF_2HPPh_3Br	**3d**	MeCN	K_2CO_3	trace
7	CF_2HPPh_3Br	**3e**	MeCN	K_2CO_3	20
8	CF_2HPPh_3Br	**3f**	MeCN	K_2CO_3	25
9	CF_2HPPh_3Br	**3a**	DMF	K_2CO_3	27
10	CF_2HPPh_3Br	**3a**	DMSO	K_2CO_3	14
11	CF_2HPPh_3Br	**3a**	Dioxane	K_2CO_3	28
12	CF_2HPPh_3Br	**3a**	DCE	K_2CO_3	trace
13	CF_2HPPh_3Br	**3a**	Acetone	K_2CO_3	44
14	CF_2HPPh_3Br	**3a**	Acetone	Na_2CO_3	39
15	CF_2HPPh_3Br	**3a**	Acetone	Na_2HPO_4	33
16	CF_2HPPh_3Br	**3a**	Acetone	K_2HPO_4	28
17	CF_2HPPh_3Br	**3a**	Acetone	KOAc	23
18	CF_2HPPh_3Br	**3a**	Acetone	H_2O	37
19	CF_2HPPh_3Br	**3a**	Acetone	$NaHCO_3$	53
20	CF_2HPPh_3Br	**3a**	Acetone	$CuBr_2$ (20%)	trace
21	CF_2HPPh_3Br	**3a**	Acetone	Et_3N	trace

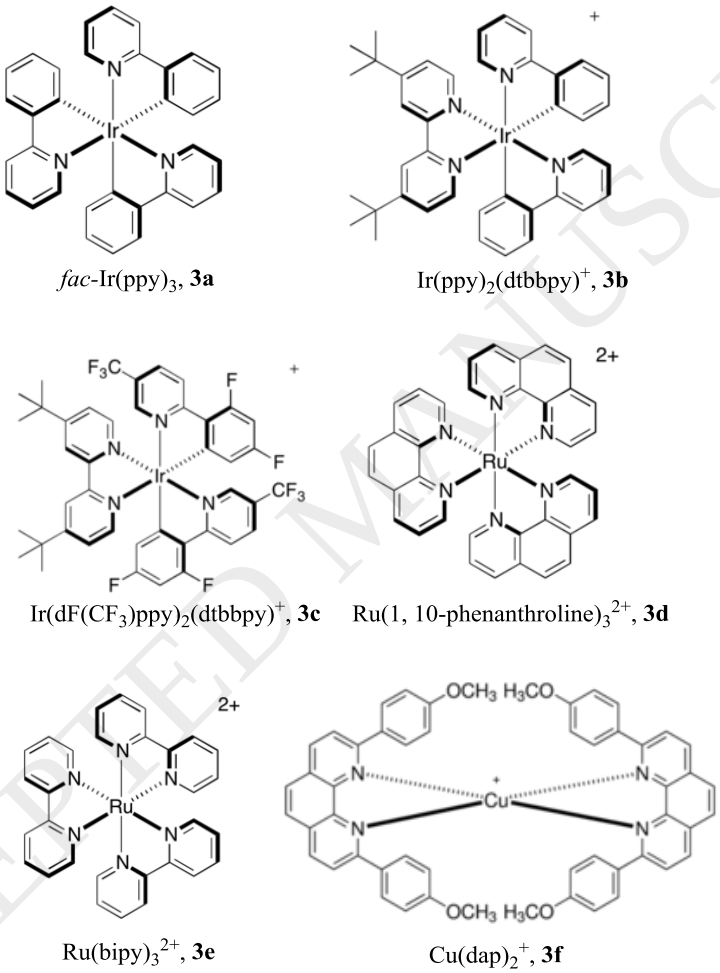
[a] Isolated yield

2. Results and Discussion

Initially, we sought to determine which difluoromethyl radical source would be suitable for the regioselective difluoromethylation of indoles using photoredox catalysis. To this end, we tested three common -CF_2H radical precursors, CF_2HSO_2Cl, difluoromethyl sulfonyl benzothiazole (CF_2HSO_2BOT), and difluoromethyl triphenylphosphonium bromide (CF_2HPPh_3Br) [19]. To our

tentative satisfaction we detected the desired 2-CF_2H indole using either CF_2HSO_2Cl or CF_2HPPh_3Br in 34% and 39% yields, respectively, using 3-Me indole as the standard substrate with $Ir(ppy)_3$ (**3a**), Na_2CO_3 as an additive, and acetonitrile as solvent (Table 3, Entries 1 and 3). Next, we subjected the discovery

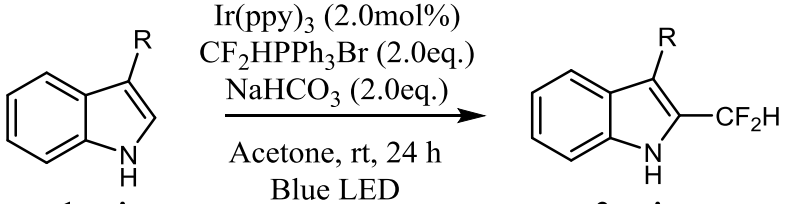
Figure 3. Photocatalysts tested.



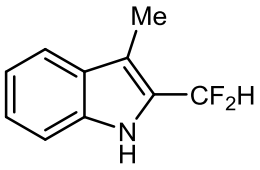
to an optimization protocol by varying the photocatalyst, solvent, and additive. The alternative photocatalysts (**3b-f**, Figure 3) that were screened proved ineffective (Table 3, entries 4-8), providing little to no reactivity in most cases. $Ir(ppy)_3$ (**3a**) was determined to be the best option moving forward (Entries 3, 13,14,18, 19). Then a variety of solvents like DCE, DMF, DMSO and acetone (Entries 9-

13) were evaluated, and only acetone showed an improvement in yield (entry 13, 44%). Having an optimized photocatalyst and solvent combination, we then examined the effectiveness of different additives on the course of the reaction (Entries 14-21). Using a weak base like $NaHCO_3$ proved beneficial to the reaction, giving our best yields yet at 53%, suggesting the phosphonium may be sensitive to stronger bases. Using an organic base like Et_3N, or a cocatalyst like $Cu(OA_C)_2$ did not improve or help the reaction with trace product being formed in both cases (Entries 20-21). Satisfied with our optimized conditions we then wanted to expand the substrate scope, starting with varying the substituent in the 3-position (Figure 4). Our standard substrate 3-Me indole, **1a**, gave the corresponding 2-CF_2H indole, **2a**, in 53% yield according to the crude ^{19}F-NMR. Subsequent substrates were tested with differing *para*-substituted phenyl groups in the 3-position, with only halogens, and methoxy derivatives giving moderate to good yields (compounds **2b** through **2e**). Phenyl groups with strong *para*-EWG were not well tolerated under these conditions and consequently were not extensively screened, but 3-(4-nitrophenyl) indole (**1f**) was found to yield 17% of the desired product by NMR analysis (**2f**). When the substituent was an electron-withdrawing group, like in the 3-carboxyaldehyde indole case, the observed yield was appreciably lower at 35% (**2g**). Switching the substituent to a heteroatom like in 3-(4-chlorophenyl)thio-indole, **1h**, also did not improve the yield, giving only 28% of the product (**2h**). Finally, with no modification to the indole structure we found **1i** to react well with high conversion at 53%, however this resulted in a mixture of products (ratio of 1.2:1; 3-CF_2H:2-CF_2H respectively) with the desired compound being the minor product, making its isolation challenging (compound **2i**). Overall, the reaction works best with electron-rich substituents in the 3-position, and tolerates a variety of substituents, albeit in relatively low yields.

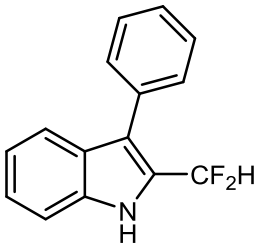
Figure 4. Substrate scope 3-substituted indoles.



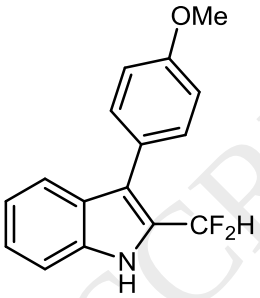
1a - i **2a - i**



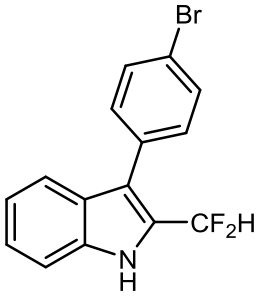
2a
53% (39%)



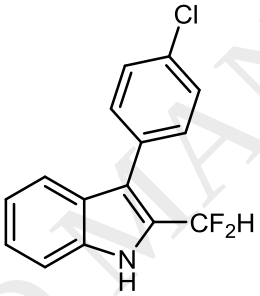
2b
56% (45%)



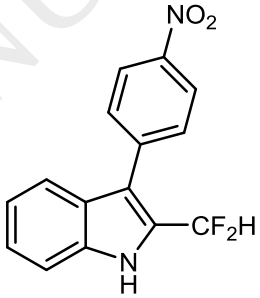
2c
58% (47%)



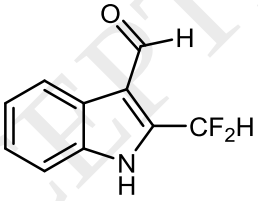
2d
67% (39%)



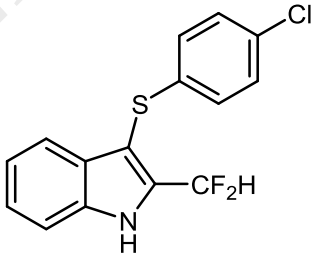
2e
56% (37%)



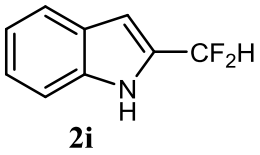
2f
17% (15%)



2g
35% (31%)



2h
28% (22%)



2i
53% conversion 1.2 : 1
(15% for 2-CF_2H)

Crude yields were calculated by ^{19}F-NMR, using trifluorotoluene as an internal standard. Isolated yields in parentheses.

Next, we explored the impact of varying the substituent on the phenyl portion of the indole structure, with an emphasis on position 5 (Figure 5). Interestingly, the yield of 3-phenyl-5-methoxy indole (**1j**) have a lower yield than anticipated (37%, compound **2j**). This could possibly be due to the increased basicity of the indole thus interfering with the generation of the CF_2H radical by reacting counterproductively with the phosphonium. Substrates **1k** and **1l** gave the corresponding 2-CF_2H indole in moderate yields of 49% (**2k**) and 43% (**2l**) respectively. Finally, substrate **1m** bearing 4,6-dichloro-3-phenyl indole, also worked well with a similar yield observed as other halogen containing substrates (42%, **2m**). Interestingly, the 5-nitro-3-phenyl indole, **1n**, afforded much better conversion when compared to the 3-*para*-nitrophenyl indole, **1g** (17% vs. 50% conversion). However, **2n** was produced alongside a byproduct (not isolated), allowing for only 24% of **2n** to be isolated. Overall, the substituents on the benzene-portion of the indole work best when they are not strongly donating or withdrawing electrons, with problems of regioselectivity arising from highly EWGs and reactivity with EDGs. Protecting groups on the indole nitrogen were not extensively screened, however *N*-Ac-3-Me indole, **1o**, provided the desired compound (**2o**) in 56% yield, suggesting that other similarly withdrawing protecting groups, like Tos, Boc, and Bz, could be tolerated if desired (Figure 6).

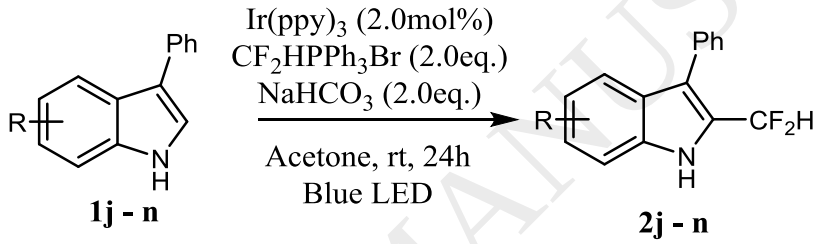
A comment on the generally mediocre yields obtained in this study is appropriate: Unreacted stating material was observed, but not isolated in most cases (one example: 5-Fluoro-3-Ph indole could be seen in the crude ^{1}HNMR very clearly, and in a similar concentration as the major product, **2k**). The vast majority of the conversion for the reaction is into the desired compound, with trace amounts of other regioisomers being present. There are some tarlike by-products produced can be observed stuck on the column during purification.

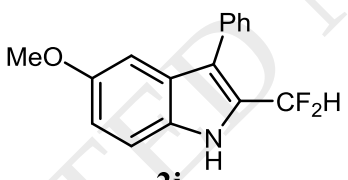
2.1. Mechanism

A plausible reaction mechanism for photoredox mediated radical addition to indoles is well established in the literature (Figure 7). First, the photocatalyst is excited by visible light irradiation (A)

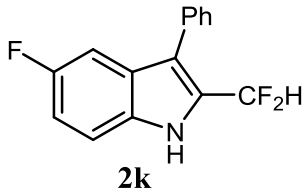
whereby it reduces the difluoromethyl triphenylphosphonium via a single-electron transfer process (SET) generating the CF_2H radical, and triphenyl phosphine as a byproduct (B). The CF_2H radical can then add regioselectively (C) to the 2-position of the starting indole (**1**), forming a highly stabilized radical (**4**). The photocatalyst can then be regenerated by SET transfer (D) from the intermediate tertiary radical (**4**), thus oxidizing the indole to the corresponding cation (**5**). Finally, the cationic intermediate can be deprotonated (E) to afford the 2-CF_2H indole (**2**).

Figure 5. Substrates tested with differing substituents on the phenyl ring of the indole skeleton. Crude yields calculated using ^{19}F-NMR and trifluorotoluene as an internal standard. Isolated yields in parentheses.

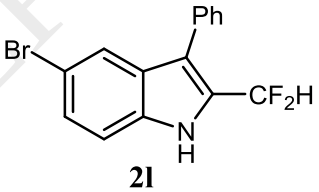




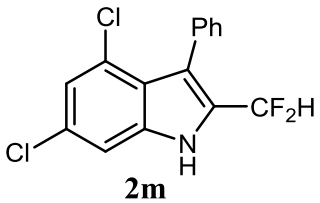
2j
37% (24%)



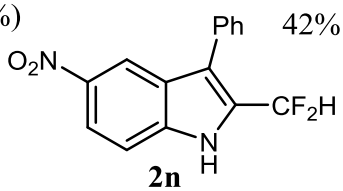
2k
49% (42%)



2l
43% (37%)



2m
42% (33%)



2n
50% conversion; 3:2 mixture
(24% isolated for 2-CF_2H)

Figure 6. *N*-Ac-3-Me indole example. Crude yields calculated using ^{19}F-NMR and trifluorotoluene as an internal standard. Isolated yields in parentheses.

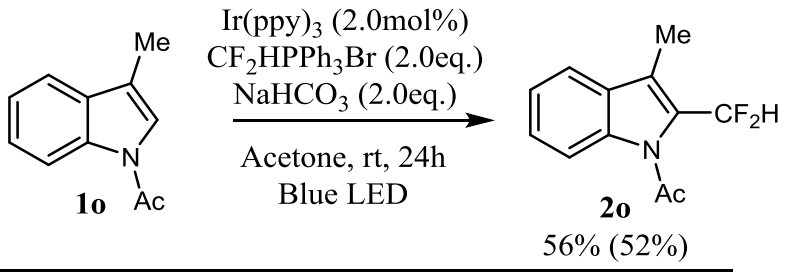
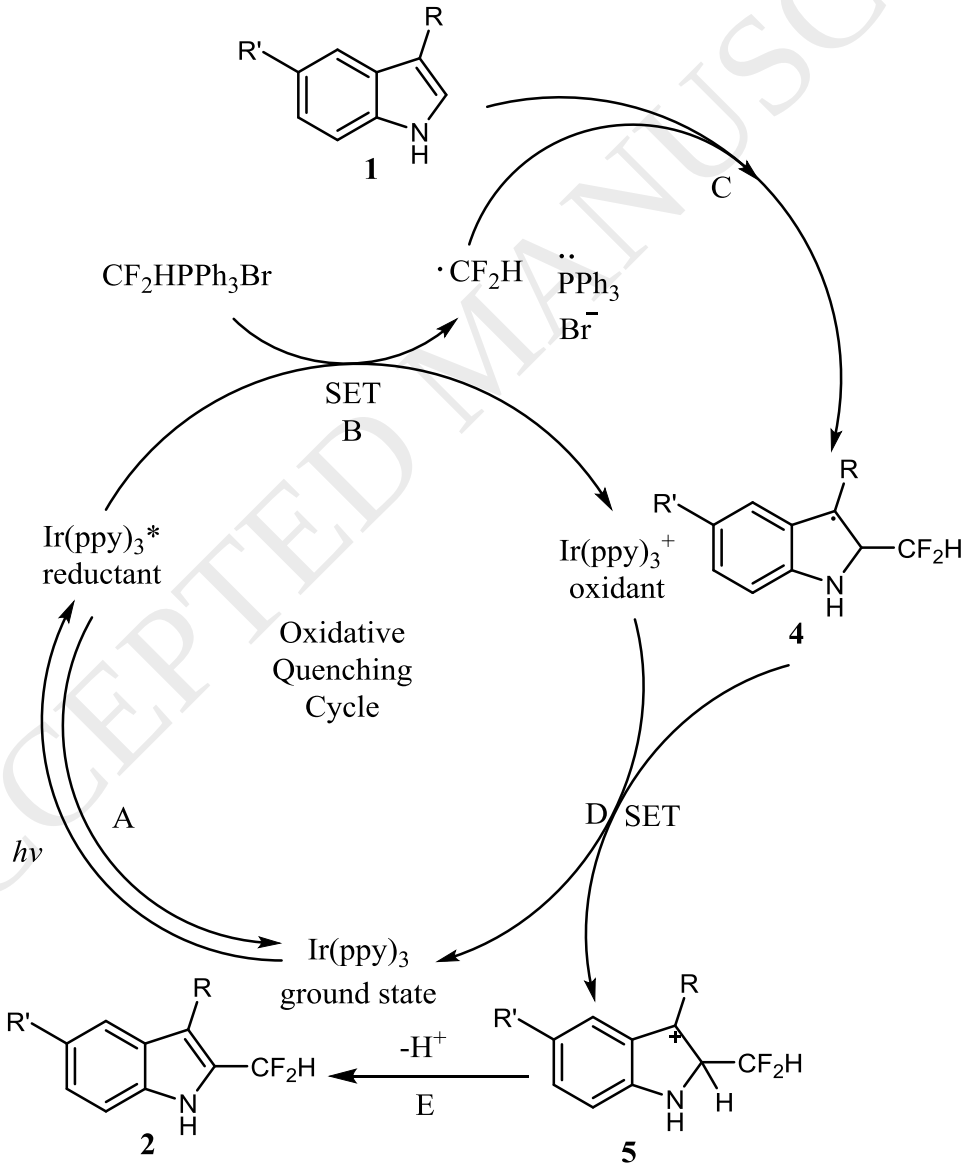
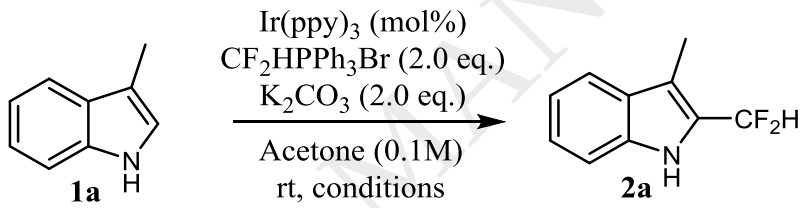


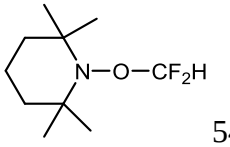
Figure 7. Plausible mechanism for the photoredox difluoromethylation of indoles.



Several experiments were conducted to increase our confidence in the proposed reaction mechanism (Table 2). First, we conducted the reaction in complete darkness, resulting in no reaction occurring (entry 1). Then, we added TEMPO, a radical scavenger, and the corresponding TEMPO-CF_2H adduct could be detected in the ^{19}F-NMR crude material (54%), as well as small amounts of product **2a** (entry 2). We also tested the reaction by irradiating the reagents without photocatalyst, which afforded no product, however the difluoromethyl source mostly decomposed (entry 3). These results indicate that the proposed mechanism is both reasonable, and highly likely given the need for photocatalyst, visible light irradiation, and the formation of the TEMPO-CF_2H product which is formed primarily by trapping the CF_2H radical.

Table 2. Mechanistic investigations. Yields were calculated using the crude ^{19}F-NMR spectrum and trifluorotoluene as an internal standard.



Entry	$Ir(ppy)_3$	conditions	yield **2a** (%)
1	2.0 %	no light, 48h	0
2	2.0%	TEMPO (2.0 equiv.) Blue LED, 24h	21  54
3	0.0%	Blue LED, 24h	0

3. Conclusion

In conclusion, we have developed the first report of photoredox mediated regioselective direct difluoromethylation of 3- and 3, 5- substituted indoles. This methodology is useful as it does not require any protecting or directing groups on the indole nitrogen. Additionally, the reaction utilizes the easily synthesized CF_2HPPh_3Br, does not require expensive additives, and uses benign solvents as well as

ambient temperature. This reaction also represents a late stage functionalization of easily synthesized substrates to afford the corresponding 2-CF_2H indoles, which is beneficial when compared to other routes the 2-CF_2H indoles that require multistep synthesis of substrates, high reaction temperatures, high catalyst loading, and can require the formation of the difluoromethyl unit post-reaction. Moderate yields, and lacking generality in terms of substrate electronics and substitution patterns are both drawbacks, but the possibility of improving this protocol has been established.

4. Experimental

NMR spectra were obtained either in $CDCl_3$ or $DMSO_{d6}$ using TMS as the internal standard for ^1H (300 MHz or 500 MHz as indicated) and ^{13}C NMR (75 MHz), and $CFCl_3$ for ^{19}F NMR (282 MHz). Reagents were purchased at commercial quality (Oakwood) and were used without further purification. CF_2HPPh_3Br [20] and 3-arylindoles [21] were prepared according to the literature. Blue LED was bought from FEIT Electric (16 W, 120 VAC, 60 Hz, 130 mA). High resolution mass spectrometric measurements were performed by the University of Florida Department of Chemistry Mass Spectrometry Services, using an Agilent 6220 Time-of-Flight (TOF) instrument.

General procedure for the photoredox direct synthesis of 2-difluoromethyl indoles (**2a - o**):

To an oven-dried 17 × 60 mm (8 mL) borosilicate vial equipped with a magnetic stirrer were added the corresponding indole (0.1 mmol), *fac*-$Ir(ppy)_3$ (1.3 mg, 0.002 mmol, 0.02 equiv) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv). To this mixture were added 1 mL acetone, and CF_2HPPh_3Br (78 mg, 0.2 mmol, 2 equiv) under a blanket of nitrogen. The vial was sealed, and stirred under blue LED light at room temperature for 24 h. After this time, the solvent was removed in vacuo, and the residue purified by column chromatography on silica gel eluting with hexanes/ethyl acetate. The Rf values of the products are between 0.15 and 0.25 using 1% EtOAc/ hexanes and evolving to about 10% EtOAc/ hexanes.

4.1. 2-Difluoromethyl)-3-methyl-1H-indole (**2a**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (bs, 1H), 7.61 (d, J = 8 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 6.94 (t, J = 51.2 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 133.6, 128.7, 128.1, 124.2, 119.9, 119.7, 109.9 (t, J_{C-F} = 234.6 Hz), 111.5, 8.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.7 (d, J = 54.4 Hz, 2F). HRMS (-ESI-TOF): m/z Calcd. for [$C_{10}H_9F_2N$]: 181.0703. Found: 180.0627 [M-H]$^-$.

4.2. 2-Difluoromethyl)-3-phenyl-1H-indole (**2b**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (bs, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.55-7.41 (m, 6H), 7.48 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.79 (t, J = 54 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 132.5, 129.6, 128.9, 127.4, 126.4, 124.7, 120.9, 120.6, 111.8, 110.7 (t, J_{C-F} = 233Hz),. ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.3 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_{11}F_2N$]: 243.0860. Found: 242.0789 [M-H]$^-$.

4.3. 2-Difluoromethyl)-3-(4-methoxyphenyl)-1H-indole (**2c**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.46 (m, 3H), 7.35 (t, J = 8.1 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H) 7.06 (d, J = 8.7 Hz, 2H), 6.78 (t, J = 54 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 135.7, 130.7, 126.6, 125.4, 124.8, 124.6, 114.4, 111.7, 110.2 (t, J_{C-F} = 233 Hz), 55.4 (s). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.2 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{16}H_{13}F_2NO$]: 273.0965. Found: 272.0896 [M-H]$^-$.

4.4. 3-(4-Bromophenyl)-2-(difluoromethyl)-1H-indole (**2d**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 7.65 (m, 3H), 7.38 (m, 4H), 7.22 (t, J = 7.5 Hz, 1H), 6.75 (t, J = 54 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 132.1, 131.5, 131.2, 126.2, 124.9, 121.6, 121.2, 120.3, 111.9, 109.9 (t, J_{C-F} = 234 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.3 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_{10}BrF_2N$]: 320.9965. Found: 319.9893 [M-H]$^-$.

4.5. 3-(4-Chlorophenyl)-2-(difluoromethyl)-1H-indole (**2e**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.47 (m, 5H), 7.37 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.76 (t, J = 54 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 133.5, 131.1, 130.8, 129.1, 126.3, 124.9, 121.1, 120.3, 118.7, 111.9, 109.9 (t, J_{C-F} = 234 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.3 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_{10}ClF_2N$]: 277.0470. Found: 276.0407 [M-H]$^-$.

4.7. 2-(Difluoromethyl)-3-(4-nitrophenyl)-1H-indole (**2f**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (bs, 1H), 8.37 (d, J = 9 Hz, 2H), 7.74-7.67 (m, 3H), 7.53 (d, J = 8.1 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.27 (dt, J = 8.1, 1.2 Hz, 1H), 6.78 (t, J = 53.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.9, 135.6, 132.1, 130.0, 125.8, 125.2, 124.3, 121.8, 120.0, 111.4, 109.5 (t, J_{C-F} = 235 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.5 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_9F_2N_2O_2$]: 288.0710. Found: 287.0649 [M-H]$^-$.

4.8. 2-(Difluoromethyl)-1H-indole-3-carbaldehyde (**2g**). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.94 (bs, 1H), 10.23 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 53.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.39-7.26 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 185.3, 138.1, 136.2, 125.4, 124.9, 123.5, 121.8, 116.1, 113.4, 109.9 (t, J_{C-F} = 236 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (d, J = 53.9 Hz, 2F). (+ESI-TOF): m/z Calcd. for [$C_{10}H_7F_2NO$]: 195.0496. Found: 196.0595 [M+H]$^+$.

4.9. 3-((4-Chlorophenyl)thio)-2-(difluoromethyl)-1H-indole (**2h**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (bs, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.24-7.13 (m, 3H), 7.1 (t, J = 53.7 Hz, 1H), 7.0-6.9 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 133.7, 131.4, 129.0, 128.6, 127.7, 125.3, 121.8, 120.3, 112.2, 111.1, 109.0 (t, J_{C-F} = 283 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.7 (d, J = 53.6, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_{10}ClF_2NS$]: 309.0191. Found: 308.0130 [M-H]$^-$.

4.10. 2-(Difluoromethyl)-1H-indole (**2i**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (bs, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 8.1 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.84 (t, $J_{H\text{-}F}$ = 55.5 Hz, 1H), 6.76 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 130.0 (t, $J_{C\text{-}C\text{–}F}$ = 24.2 Hz, *C*-CF_2H), 126.9, 124.1, 121.6, 120.6, 111.6, 110.5 (t, $J_{C\text{–}F}$ = 233.4 Hz, CF_2H), 103.9 (t, $J_{CH=C\text{-}C\text{–}F}$ = 6.9 Hz, *C*H=C-CF_2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5 (d, J = 55.3 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_9H_7F_2N$]: 167.0547. Found: 166.0479 [M-H]$^-$.

4.11. 2-(Difluoromethyl)-5-methoxy-3-phenyl-1H-indole (**2j**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (bs, 1H), 7.66-7.36 (m, 7H), 7.12 (d, J = 9 Hz, 1H), 6.86 (t, J = 53.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 132.7, 130.8, 129.5, 128.9, 127.3, 126.8, 126.4 (t, $J_{C\text{-}C\text{–}F}$ = 22.4 Hz), 119.7, 115.5, 112.7, 110.0 (t, $J_{C\text{-}F}$ = 234 Hz), 101.5, 55.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.2 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{16}H_{13}F_2NO$]: 273.0965. Found: 272.0888 [M-H]$^-$.

4.12. 2-(Difluoromethyl)-5-fluoro-3-phenyl-1H-indole (**2k**).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (bs, 1H), 7.55-7.47 (m, 4H), 7.45-7.35 (m, 3H), 7.12 (dt, J = 8.7, 1.8 Hz, 1H), 6.78 (t, J = 53.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.7, 162.2, 130.3, 129.4, 129.0, 128.3, 127.6, 117.0 (d, J = 27.7 Hz), 113.4 (d, J = 8.8 Hz), 109.0 (t, $J_{C\text{-}F}$ = 230 Hz, CF_2H), 106.5 (d, J = 24 Hz), 105.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.6 (d, J = 53.6 Hz, 2F), -122.6 (td, 9, 4.5 Hz, 1F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_{10}F_3N$]: 261.0765. Found: 260.0699 [M-H]$^-$.

4.13. 5-Bromo-2-(difluoromethyl)-3-phenyl-1H-indole (**2l**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (bs, 1H), 7.85 (s, 1H), 7.54-7.34 (m, 7H), 6.76 (t, J = 53.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.6, 163.9, 162.7, 130.4, 129.6, 129.0, 128.4, 127.8, 123.2, 117.3, 113.9, 113.3, 109.7 (t, $J_{C\text{-}F}$ = 230 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.7 (d, J = 53.6, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_{10}BrF_2N$]: 320.9965. Found: 319.9895 [M-H]$^-$.

4.14. 4,6-Dichloro-2-(difluoromethyl)-3-phenyl-1H-indole (**2m**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (bs, 1H), 7.46-7.29 (m, 6H), 7.14 (d, J = 3 Hz, 1H), 6.49 (t, J = 53.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.6, 131.5, 131.3, 130.9, 130.1, 127.9, 127.7, 127.5, 127.0, 125.6, 122.4, 121.9, 110.5, 109.4 (t, J_{C-F} = 234.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.8 (d, J = 53.6 Hz, 2F). (-ESI-TOF): m/z Calcd. for [$C_{15}H_9Cl_2F_2N$]: 311.0080. Found: 310.0005 $[M-H]^-$.

4.15. 2-(Difluoromethyl)-5-nitro-3-phenyl-1H-indole (**2n**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (bs, 1H), 8.69 (s, 1H), 8.26 (d, J = 9 Hz, 1H), 7.59. ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 144.4, 129.6, 129.3, 128.4, 128.3, 126.0, 120.1, 118.2, 112.0, 109.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.4 (d, J = 53.3 Hz, 2F). (+ESI-TOF): m/z Calcd. for [$C_{15}H_{10}F_2N_2O_2$]: 288.0710. Found: 289.0792 $[M+H]^+$.

4.16. 1-(2-(Difluoromethyl)-3-methyl-1H-indol-1-yl)ethan-1-one (**2o**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.31 (m, 5H), 2.82 (s, 3H), 2.47 (t, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 135.3, 130.6, 128.5, 126.4, 123.3, 122.4, 120.4, 114.4, 111.4 (t, J_{C-F} = 239 Hz), 27.2, 9.28. ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.7 (d, J = 53.9 Hz, 2F). (+ESI-TOF): m/z Calcd. for [$C_{12}H_{11}F_2NO$]: 223.0809. Found: 246.0710 $[M+Na]^+$.

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