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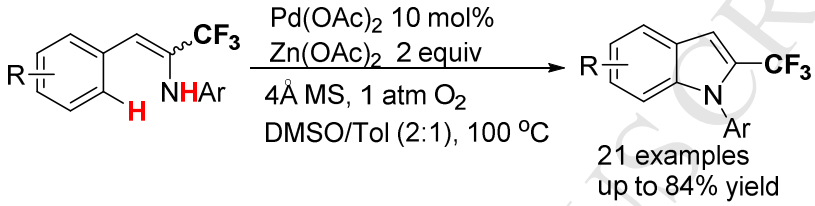

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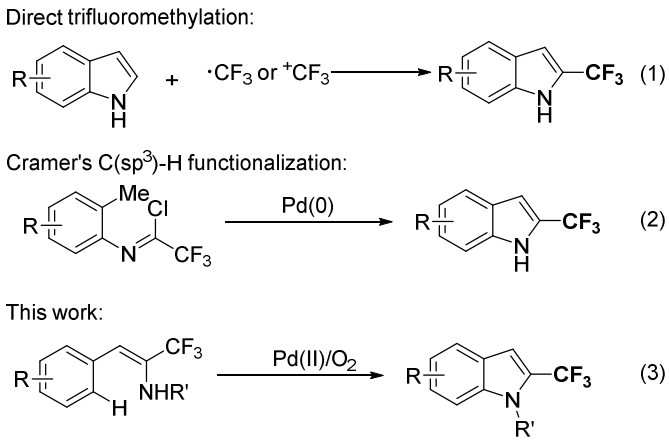
ABSTRACT

A new palladium-catalyzed C-H amination of aryl enamines for the synthesis of trifluoromethylated indoles is established. The attractive features of this transformation are the use of atom-economical O_2 as the oxidant and easily prepared enamines as substrates. A variety of pharmaceutically important 2-trifluoromethyl indoles can be targeted in moderate to good yields with good functional compatibility.

1. Introduction

The indole scaffold is an essential structural motif in biologically active compounds and natural products,[1] and considerable efforts have been devoted towards the development of efficient methods for the preparation of their derivatives.[2] Whereas the synthesis of trifluoromethylated indoles was relatively less reported,[3] although the incorporation of a trifluoromethyl group into organic molecules frequently enhances their biological activity and has become a powerful and widely used strategy in drug discovery.[4] For instance, 2-trifluoromethylindoles are widely used as core structures in many pharmaceuticals, including general anesthesia inducer,[5] tyrosine kinase inhibitor[6] and antitumor compounds.[7] Traditionally, the direct trifluoromethylation of indole with trifluoromethyl radical (such as CF_3SO_2Na, CF_3I) or electrophilic trifluoromethylating reagent (Togni's or Umemoto's reagent) is the commonly used method, which suffers poor regioselectivity or/and low yields (Scheme 1, eq.1).[8] Recently, some cyclization strategies have also been developed for the preparation of 2-trifluoromethylindoles, which involves the effective transformation of synthons bearing a CF_3 group at the appropriate position.[9] In 2016, Cramer group reported the synthesis of 2-trifluoromethylindoles from palladium-catalyzed cyclization of *N*-(*o*-toyl)-trifluoroacetimidoyl chlorides through C(sp^3)-H functionalization of toluene moiety (eq.2).[10] Inspired by some intramolecular aryl C-H amination reactions,[11] we envisioned whether CF_3-containing enamine, a type of versatile building blocks,[12] could participate in a similar aryl C-H amination reaction. Herein, we report an intramolecular palladium-catalyzed C-H oxidative amination of enamines using molecular oxygen as the terminal oxidant, affording 2-trifluoromethylindoles in moderate to good yields (eq.3).

Scheme 1. The synthesis of 2-trifluoromethylindoles



2. Results and discussion

We initiated our study by testing the intramolecular C-H amination of N-(3,3,3-trifluoro-1-phenylprop-1-en-2-yl)aniline **1a** to optimize the reaction conditions (Table 1). Firstly, substrate **1a** was treated with 10 mol% $Pd(OAc)_2$ under oxygen atmosphere (1 atm) in

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DMSO at 100 °C, the desired product **2a** was isolated in 26% yield (entry 1). To enhance the reaction yield, the solvent effect was investigated. We found that toluene provided the similar yield (entry 2), but only trace amount of product were observed in DMF or DCE (entries 3 and 4). To our delight, the combination of DMSO and toluene as cosolvent afforded better results. A 68% yield was obtained when the reaction was carried out in DMSO/toluene (2:1) (entry 6). Subsequently, some oxidants were tested, including $Cu(OAc)_2$, $K_2S_2O_8$, $PhI(OAc)_2$ and Di-tert-butyl peroxide (DTBP), but all gave low yields (entries 7-10). Considering that metal acetates could promote some C-H activation reactions,[13] we attempted to add 2 equiv of metal acetates, such as CsOAc, KOAc, NaOAc and $Zn(OAc)_2$ (entries 11-14). We were please to find that the reaction afford product **2a** in 84% yield in the presence of 2 equiv of $Zn(OAc)_2$ (entry 14). A lower yield was observed when the reaction was conducted at 80 °C (entry 15).

Table 1. Screening of conditions [a]

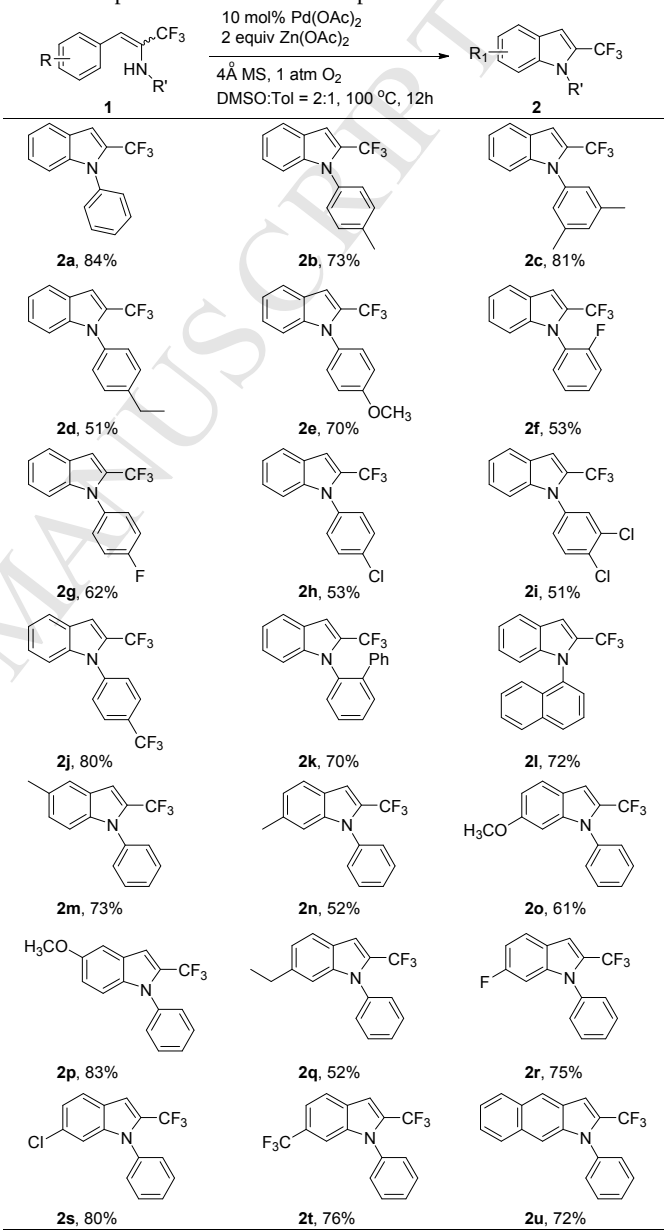
[redacted]

Entry	Oxidant	Additive	Solvent	Yield (%)
1	O_2	-	DMSO	26
2	O_2	-	Toluene	24
3	O_2	-	DMF	Trace
4	O_2	-	DCE	Trace
5	O_2	-	DMSO/Tol(1:1)	48
6	O_2	-	DMSO/Tol(2:1)	68
7	$Cu(OAc)_2$	-	DMSO/Tol(2:1)	21
8	$K_2S_2O_8$	-	DMSO/Tol(2:1)	24
9	$PhI(OAc)_2$	-	DMSO/Tol(2:1)	21
10	DTBP	-	DMSO/Tol(2:1)	23
11	O_2	CsOAc	DMSO/Tol(2:1)	23
12	O_2	KOAc	DMSO/Tol(2:1)	20
13	O_2	NaOAc	DMSO/Tol(2:1)	70
14	O_2	$Zn(OAc)_2$	DMSO/Tol(2:1)	84
15[b]	O_2	$Zn(OAc)_2$	DMSO/Tol(2:1)	55

[a] Reaction conditions: **1a** (0.2 mmol), 4Å MS (0.4 g), additive (2 equiv) in solvent (3 mL) under O_2 atmosphere (1 atm) at 100 °C for 12 h. Isolated yields.
[b] At 80 °C.

With the optimal reaction conditions in hand, we began to investigate substrate scope of the C-H amination and the results were shown in Table 2. Initially, we tested a variety of N-aryl enamines, and results demonstrated that the reaction conditions were compatible with both electron-donating and electron-withdrawing aryl moieties. For example, methyl, ethyl and methoxyl substituted N-phenyl enamines afforded products **2b**-**2e** in 51-81% yields. Fluoro and chloro substituted N-phenyl enamines gave products **2f**-**2i** in 51-62% yields. Interestingly, the electron-deficient CF_3-containing enamine **1j** was also suitable substrate to produce indole **2j** in 80% yield. Moreover, N-biphenyl and N-naphthyl indole **2k** and **2l** were obtained in 70% and 72% yields, respectively. Unfortunately, our efforts to furnish N-alkyl and N-acryl enamines failed, possibly due to their poor stability. Next, the substituent effect of R group was examined. Similarly, methyl, ethyl and methoxyl substituted in indoles **2m**-**2q** in 52-83% yields. For substrate **1m** and **1p**, only 6-position C-H amination product **2m** and **2p** were isolated owing to the steric hindrance of *meta*-substituents. 6-Fluoro and 6-chloro indole **2r** and **2s** were obtained in 75% and 80% yields, respectively. 2,6-ditrifluoromethyl indole **2t** was obtained in 76% yield. As expected, trifluoromethylated benzoindole **2u** could also be prepared in 72% yield by this palladium-catalyzed C-H amination.

Table 2. Exploration of substrate scope [a]



[a] Reaction conditions: 1 (0.2 mmol), $Pd(OAc)_2$ (10 mol %), 4Å MS (0.4 g) and $Zn(OAc)_2$ (0.4 mmol) in DMSO : Tol = 2 : 1 (3 mL) under 1 atm O_2 at 100 °C for 12 h. Isolated yields.

Since the CF_3-containing enamines were prepared from the palladium-catalyzed amination of β-chlorostyrenes with anilines, we attempted to develop a one-pot method for this indole synthesis from β-chlorostyrenes with anilines. However, direct combination of the β-chlorostyrenes amination[12a] with the above C-H amination reaction conditions did not work to afford indole. After a series of trials, we found that indole **2a** could be isolated in 39% yield by adding 2 equiv of HOAc to the cooled down mixture of β-chloro styrene

amination, following with the optimal C-H amination (Scheme 2). Thus, 2-trifluoromethyl indoles could be easily prepared through this one-pot reaction of β-chlorostyrenes with anilines, albeit in a moderate yield.

Scheme 2. One-pot synthesis of 2-trifluoromethylindole

Scheme 3. Possible mechanism

Base on the previously reported mechanism and our observed results,[14] a plausible mechanism for the Pd-catalyzed C-H amination was proposed as outlined in Scheme 3. Firstly, with the coordination of $Pd(OAc)_2$ and N atom in substrate **1a**, a divalent palladium intermediate **A** is formed by removing an acetic acid. Then, intramolecular elimination of another acetic acid produces palladacycle **B**. Subsequent C-N reductive elimination affords the indole product **2a** and Pd(0) species, which undergo oxidation by O_2 to regenerate catalytic $Pd(OAc)_2$.

3. Conclusion

In summary, we have developed a palladium-catalyzed intramolecular C-H amination strategy for the synthesis of 2-trifluoromethylindoles using O_2 as oxidant. In the presence of $Pd(OAc)_2$, $Zn(OAc)_2$ and 1 atm O_2, a range of N-aryl enamines underwent the palladium-catalyzed C-H amination to afford 2-trifluoromethylindoles in moderate to good yields. It is noteworthy that we also developed a one-pot reaction for the synthesis 2-trifluoromethyl indoles from β-chlorostyrenes and anilines, albeit in a moderate yield. The present process provided a new optional method for the synthesis of trifluoromethyl-containing indoles from simple starting materials.

4. Experimental section

4.1. General

Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. ^{19}F NMR spectra were recorded on a 500MHz spectrometer (470 MHz for ^{19}F) and are reported relative to the $CDCl_3$ as the internal standard. High resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometry. All reactions were conducted using standard Schlenk techniques. Melting points were measured on an X4 melting point apparatus and were uncorrected. Column chromatography was performed using EM silica gel 60 (300-400 mesh).

4.2. Typical experimental procedure for the synthesis of 1-phenyl-2-(trifluoromethyl)-1H-indole derivatives 2a–2u

To a flame-dried Schlenk tube with a magnetic stirring bar was charged 1 (52.7 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol %), $Zn(OAc)_2$ (73.4 mg, 2 eq), 4 Å MS (400 mg) in DMSO (2 mL) and toluene (1 mL) under O_2 atmosphere (equipped with O_2 balloon). The reaction mixture was stirred at 100 °C for 12 hours. After the reaction was finished, the mixture was poured into ethyl acetate, which was washed with brine (2 x 15 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to afford the desired products **2a** - **2u**.

4.2.1 1-Phenyl-2-(trifluoromethyl)-1H-indole ***(2a)***:[9f] Pale yellow solid, m.p. 54-56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 6.5 Hz, 2H), 7.47-7.33 (m, 5H), 7.20-7.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 132.1, 130.0, 128.4, 127.6, 125.2, 121.7 (q, J_{C-F} = 267.5 Hz), 121.3, 121.2 (q, J_{C-F} = 37.5 Hz), 119.9, 118.7, 118.5, 111.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.78 (3F); LRMS (EI, 70 ev) m/z (%): 261 (M^+, 100), 242 (11), 192 (32), 184 (24).

4.2.2 1-p-Tolyl-2-(trifluoromethyl)-1H-indole ***(2b)***:[9f] Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.41-7.38 (m, 2H), 7.33-7.31 (m, 2H), 7.25 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 132.3, 130.8, 130.0, 128.4, 127.53, 127.45, 126.9, 121.7 (q, J_{C-F} = 267.5 Hz), 121.2 (q, J_{C-F} = 37.6 Hz), 120.3, 119.3, 111.3, 21.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.75 (3F); LRMS (EI, 70 ev) m/z (%): 275 (M^+, 100), 254 (11), 206 (22), 178 (7).

4.2.3 1-(3,5-Dimethylphenyl)-2-(trifluoromethyl)-1H-indole ***(2c)***: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.30 (m, 5H), 6.98 (s, 1H), 6.66 (s, 1H), 2.35 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 135.1, 134.0, 132.5, 130.8, 127.5, 124.6, 124.0, 121.7 (q, J_{C-F} = 267.5 Hz), 121.3 (q, J_{C-F} = 36.3 Hz), 120.4, 118.5, 109.1, 21.6, 19.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.00 (3F); LRMS (EI, 70 ev) m/z (%): 289 (M^+, 100), 274 (14), 254 (7), 234 (4), 220 (17), 204 (15); HRMS (ESI) Calcd for $C_{17}H_{15}F_3N^+$ ($[M + H]^+$) 290.1151, Found: 290.1150.

4.2.4 1-(4-Ethylphenyl)-2-(trifluoromethyl)-1H-indole ***(2d)***: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.45 (d, J = 7.5 Hz, 2H), 7.41-7.38 (m, 2H), 7.35-7.28 (m, 3H), 7.15 (d, J = 7.5 Hz, 1H), 2.64 (q, J = 7.5 Hz, 2H), 1.16 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 133.5, 132.4, 130.0, 128.4, 127.6, 127.5, 125.9, 121.7 (q, J_{C-F} = 267.5 Hz), 121.3 (q, J_{C-F} = 36.3 Hz), 119.6, 119.2, 111.5, 29.0, 16.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.76 (3F); LRMS (EI, 70 ev) m/z (%): 289 (M^+, 75), 275 (17), 274 (100), 254 (15), 234 (14); HRMS (ESI) Calcd for $C_{17}H_{15}F_3N^+$ ($[M + H]^+$) 290.1151, Found: 290.1156.

4.2.5 1-(4-Methoxyphenyl)-2-(trifluoromethyl)-1H-indole ***(2e)***:[9f] Yellow solid, m.p. 99-102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.45-7.41 (m, 4H), 7.34 (d, J = 7.0 Hz, 1H), 7.27 (d, J = 9.5 Hz, 1H), 6.96-6.95 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 155.3, 132.3, 130.1, 129.8, 128.4, 127.8, 127.5, 121.6 (q, J_{C-F} = 267.5 Hz), 121.8 (q, J_{C-F} = 37.5 Hz), 119.5, 116.3, 112.6, 101.6, 55.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.79 (3F); LRMS (EI, 70 ev) m/z (%): 291 (M^+, 100), 276 (23), 156 (6), 249 (21), 228 (13), 208 (20).

4.2.6 5,7-Dimethoxy-3-phenyl-2-((trifluoromethyl)thio)-1H-inden-1-one ***(2f)***: Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.44-7.39 (m, 4H), 7.35-7.32 (m, 2H), 7.04-6.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5 (d, J_{C-F} = 243.8 Hz), 131.6, 130.81, 130.77, 129.8, 128.5, 127.8, 123.8 (d, J_{C-F} = 15.0 Hz), 122.1 (q, J_{C-F} = 36.3 Hz), 121.6, 121.5, 121.3 (q, J_{C-F} = 267.5 Hz), 120.6, 109.6 (d, J_{C-F} = 15.0 Hz), 116.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.06 (3F), -134.50 (1F); LRMS (EI, 70 ev) m/z (%): 279 (M^+, 100), 258 (24), 239 (33), 208 (13), 183 (16); HRMS (ESI) Calcd for $C_{15}H_{10}F_4N^+$ ([M + H]$^+$) 280.0744, Found: 280.0743.

4.2.7 1-(4-Fluorophenyl)-2-(trifluoromethyl)-1H-indole ***(2g)***:[9f] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.41-7.38 (m, 4H), 7.33-7.29 (m, 2H), 7.20 (d, *J* = 9.5 Hz, 1H), 7.06-7.02 (m 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (d, J_{C-F} = 235.0 Hz), 131.7, 131.4, 129.7, 128.5, 127.81, 127.76, 121.6 (q, J_{C-F} = 36.3 Hz), 121.4 (q, J_{C-F} = 267.5 Hz), 119.9, 114.2 (d, J_{C-F} = 26.3 Hz), 112.7, 105.8 (d, J_{C-F} = 11.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.08 (3F), -121.89 (1F); LRMS (EI, 70 ev) m/z (%): 279 (M^+, 100), 258 (24), 239 (33), 208 (13), 183 (16).

4.2.8 1-(4-Chlorophenyl)-2-(trifluoromethyl)-1H-indole ***(2h)***:[9f] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.42-7.41 (m, 4H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.25-7.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 131.4, 129.8, 129.5, 128.5, 128.4, 127.9, 127.2, 125.7, 122.4 (q, J_{C-F} = 37.5 Hz), 121.3 (q, J_{C-F} = 267.5 Hz), 120.5, 112.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.08 (3F); LRMS (EI, 70 ev) m/z (%): 295 (M^+,100), 274 (7), 256 (10), 234 (14).

4.2.9 1-(3,4-Dichlorophenyl)-2-(trifluoromethyl)-1H-indole ***(2i)***: Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.70 (s, 1H), 7.58-7.55 (m, 1H), 7.50-7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 130.9, 129.7, 129.4, 128.6, 128.1, 127.0, 125.9, 122.9 (q, J_{C-F} = 36.3 Hz), 121.7, 121.4, 121.1 (q, J_{C-F} = 267.5 Hz), 120.9, 119.6, 113.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.25 (3F); LRMS (EI, 70 ev) m/z (%): 328 (M^+, 48), 311 (41), 294 (8), 292 (26); HRMS (ESI) Calcd for $C_{15}H_8Cl_2F_3NNa^+$ ([M + Na]$^+$) 351.9878, Found: 351.9881.

4.2.10 2-(Trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)-1H-indole ***(2j)***:[9f] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.84 (s, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.43-7.40 (m, 5H), 7.36-7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 131.1, 129.8, 128.7, 128.1, 126.0, 124.0 (q, J_{C-F} = 32.5 Hz), 123.8, 123.3 (q, J_{C-F} = 255.0 Hz), 122.9 (q, J_{C-F} = 37.5 Hz), 121.8, 121.3 (q, J_{C-F} = 267.5 Hz), 119.1, 112.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.14 (3F), -60.70 (3F); LRMS (EI, 70 ev) m/z (%): 329 (M^+, 100), 310 (12), 208 (13), 289 (20), 240 (18).

4.2.11 1-(Biphenyl-2-yl)-2-(trifluoromethyl)-1H-indole ***(2k)***: Pale yellow solid, m.p. 79-81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.65-7.56 (m, 7H), 7.49-7.37 (m, 5H), 7.29-7.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 133.0, 132.1, 129.9, 129.7, 129.5, 129.2, 128.4, 128.2, 128.0, 127.8, 127.6, 127.3, 126.4, 124.9, 121.9, 121.6 (q, J_{C-F} = 267.5 Hz), 121.5 (q, J_{C-F} = 37.5 Hz), 120.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.00 (3F); LRMS (EI, 70 ev) m/z (%): 337 (M^+, 100), 216 (9), 296 (18), 267 (10), 240 (12); HRMS (ESI) Calcd for $C_{21}H_{15}F_3N^+$ ([M + H]$^+$) 338.1151, Found: 338.1156.

4.2.12 1-(Naphthalen-1-yl)-2-(trifluoromethyl)-1H-indole ***(2l)***:[9f] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.59-7.54 (m, 2H), 7.53-7.48 (m, 3H), 7.47-7.41 (m, 3H), 7.37-7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2, 131.8, 130.3, 130.0, 129.0, 128.4, 127.6, 126.2, 125,5, 123.4, 122.4, 121.8 (q, J_{C-F} = 267.5 Hz), 121.6, 121.5, 120.0, 119.8, 119.7, 119.2 (q, J_{C-F} = 36.3 Hz), 118.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.02 (3F); LRMS (EI, 70 ev) m/z (%): 311 (M^+, 100), 290 (19), 271 (22), 240 (10), 215 (11).

4.2.13 5-Methyl-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2m)***: Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.29-7.24 (m, 4H), 7.14-7.10 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 135.0, 132.0, 130.6, 128.3, 127.4, 127.0, 125.1, 121.7 (q, J_{C-F} = 267.5 Hz), 121.2, 121.1 (q, J_{C-F} = 36.3 Hz), 120.0, 111.6, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.77 (3F); LRMS (EI, 70 ev) m/z (%): 275 (M^+, 100), 274 (7), 254 (6), 240 (24); HRMS (ESI) Calcd for $C_{16}H_{12}F_3NNa^+$ ([M + Na]$^+$) 298.0814, Found: 298.0809.

4.2.14 6-Methyl-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2n)***: Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.38-7.34 (m, 3H), 7.29-7.26 (m, 1H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.13-7.10 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 134.9, 129.7, 129.1, 129.0, 127.4, 125.1, 121.7 (q, J_{C-F} = 267.5 Hz), 121.66, 121.1, 121.0 (q, J_{C-F} = 36.3 Hz), 119.9, 111.6, 21.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.78 (3F); LRMS (EI, 70 ev) m/z (%): 275 (M^+, 100), 274 (7), 254 (6), 240 (24); HRMS (ESI) Calcd for $C_{16}H_{12}F_3NNa^+$ ([M + Na]$^+$) 298.0814, Found: 298.0810.

4.2.15 6-Methoxy-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2o)***: White solid, m.p. 151-153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41(s, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.38-7.37 (m, 3H), 7.29-7.26 (m, 1H), 7.12-7.10 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 135.0, 131.0, 127.6, 125.1, 124.4, 121.8 (q, J_{C-F} = 267.5 Hz), 121.2, 121.1, 120.7 (q, J_{C-F} = 37.5 Hz), 119.7, 114.0, 111.6, 55.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.89 (3F); LRMS (EI, 70 ev) m/z (%): 291 (M^+, 100), 272 (4), 208 (12); HRMS (ESI) Calcd for $C_{16}H_{13}F_3NO^+$ ([M + H]$^+$) 292.0944, Found: 292.0956.

4.2.16 5-Methoxy-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2p)***: Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.30-7.27 (m, 2H), 7.13-7.10 (m, 1H), 7.04-7.01 (m, 2H), 6.88 (d, *J* = 9 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 134.9, 133.4, 129.4, 127.3, 125.2, 122.5, 121.7 (q, J_{C-F} = 267.5 Hz), 121.3, 121.2 (q, J_{C-F} = 36.3 Hz), 115.5, 113.3, 111.7, 55.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.76 (3F); LRMS (EI, 70 ev) m/z (%): 291 (M^+, 100), 272 (4), 208 (12), 176 (5); HRMS (ESI) Calcd for $C_{16}H_{13}F_3NO^+$ ([M + H]$^+$) 292.0944, Found: 292.0941.

4.2.17 6-Ethyl-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2q)***: Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.37-7.36 (m, 3H), 7.29-7.26 (m, 1H), 7.23-7.22 (m, 2H), 7.13-7.10 (m, 1H), 2.65 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 135.0, 129.8, 129.3 127.9, 127.4, 125.1, 121.7 (q, J_{C-F} = 267.5 Hz), 121.2, 120.7 (q, J_{C-F} = 36.2 Hz), 120.0, 119.9, 111.6, 28.6, 15.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.77 (3F); LRMS (EI, 70 ev) m/z (%): 289 (M^+, 100), 275 (17), 274 (96), 234 (8), 204 (15), 137 (10); HRMS (ESI) Calcd for $C_{17}H_{15}F_3N^+$ ([M + H]$^+$) 290.1151, Found: 290.1159.

4.2.18 6-Fluoro-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2r)***: Yellow solid, m.p. 89-91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41

(s, 1H), 7.49 (s, 1H), 7.38-7.27 (m, 4H), 7.12-7.06 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (d, J_{C-F} = 245.0 Hz) ,134.9, 131.6, 128.2 (d, J_{C-F} = 21.3 Hz), 127.3, 125.2, 121.6 (q, J_{C-F} = 267.5 Hz), 121.4, 121.3 (q, J_{C-F} = 37.5 Hz), 120.8, 118.8, 115.4 (d, J_{C-F} = 22.5 Hz), 111.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.85 (3F), -114.62 (1F); LRMS (EI, 70 ev) m/z (%): 279 (M^+, 100), 258 (21), 239 (30), 232 (8), 208 (13); HRMS (ESI) Calcd for $C_{15}H_{10}F_4N^+$ ([M + H]$^+$) 280.0744, Found: 280.0752.

4.2.19 6-Chloro-1-phenyl-2-(trifluoromethyl)-1H-indole ***(2s)***: Pale yellow solid, m.p. 76-78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.46-7.44 (m, 5H), 7.39-7.36 (m, 1H), 7.23-7.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.9, 133.6, 131.2, 130.6, 128.7, 127.1, 125.3, 121.6 (q, J_{C-F} = 267.5 Hz), 121.3 (q, J_{C-F} = 36.3 Hz), 120.8, 118.5, 118.3, 111.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.81 (3F); LRMS (EI, 70 ev) m/z (%): 295 (M^+, 100), 241 (12), 240 (59), 183 (6); HRMS (ESI) Calcd for $C_{15}H_{10}ClF_3N^+$ ([M + H]$^+$) 296.0488, Found: 296.0487.

4.2.20 1-Phenyl-2,6-bis(trifluoromethyl)-1H-indole ***(2t)***: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.52-7.49 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.28-7.25 (m, 1H), 7.12-7.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 135.0, 130.2, 129.7 (q, J_{C-F} = 32.5 Hz), 127.0, 125.5, 125.4, 125.3, 124.3 (q, J_{C-F} = 270.0 Hz), 122.2 (q, J_{C-F} = 37.5 Hz), 121.5 (q, J_{C-F} = 267.5 Hz), 120.7, 118.3, 111.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ -56.80 (3F), -62.42 (3F); LRMS (EI, 70 ev) m/z (%): 329 (M^+, 100), 310 (13), 389 (7), 240 (60); HRMS (ESI) Calcd for $C_{16}H_{10}F_6N^+$ ([M + H]$^+$) 330.0712, Found: 330.0717.

4.2.21 1-Phenyl-2-(trifluoromethyl)-1H-benzo[f]indole ***(2u)***: Pale yellow solid, m.p. 99-101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.92-7.91 (m, 2H), 7.61-7.48 (m, 5H), 7.38-7.35 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.11-7.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.9, 133.6, 132.9, 129.6, 128.7, 128.5, 128.2, 126.2, 126.0, 125.8, 125.3, 125.1, 122.8 (q, J_{C-F} = 35.0 Hz), 121.6 (q, J_{C-F} = 267.5 Hz), 121.59, 121.2, 111.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.75 (3F); LRMS (EI, 70 ev) m/z (%): 311 (M^+, 100), 310 (16), 290 (8), 272 (10), 241 (66), 120 (24); HRMS (ESI) Calcd for $C_{19}H_{13}F_3N^+$ ([M + H]$^+$) 312.0995, Found: 312.1002.

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