Bromotriphenylphosphonium Salt Promoted One-Pot Cyclization to 2-Fluoroalkyl-Substituted Indoles

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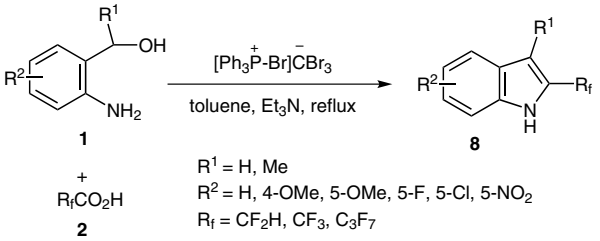
Abstract: 2-Fluoroalkyl-substituted indoles were prepared in moderate to excellent yields through bromotriphenylphosphonium salt promoted ring formation with fluorine-containing carboxylic acids in the presence of triethylamine in toluene at reflux temperature. A range of 2-fluoroalkyl-substituted indole derivatives can be conveniently prepared.

Key words: cyclization, fluoroalkyl, indole, one-pot reaction, ylides

Indole has been known for thousands of years, and the indole group has been found in many natural products, and employed as a synthetic intermediate for the preparation of numerous heterocyclic compounds. Molecules containing the heterocyclic indole group constitute one of the most important classes of compounds in organic chemistry.[1] Among those, the fluoroalkyl-substituted indole derivatives have received wide attention from both synthetic and pharmaceutical viewpoints for a long time because of the wide potential bioactivities of such derivatives.[2] Until now, a number of synthetic methods have been established for the construction of the indole ring skeleton.[3] Although these approaches are efficient, most of the cyclization conditions have drawbacks in that they use harmful solvents, involve complex reaction systems, or produce low yields.

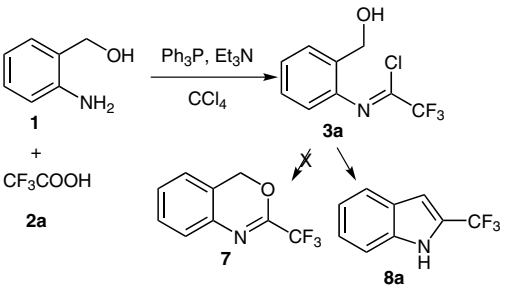
Chlorotriphenylphosphonium carbon trichloride ($[Ph_3P^+Cl]CCl_3^-$), which is easily generated in situ by the reaction of triphenylphosphane with carbon tetrachloride, serves as a chlorination reagent that can be used to transform alcohols and carboxylic acid derivatives into the corresponding chlorides,[4] acyl chlorides, or imidoyl chlorides.[5] However, the overuse of carbon tetrachloride in these processes raised great environmental concern. Therefore, the development of a general, reliable, and environmentally friendly method for the construction of such nitrogen-containing bicyclic systems remains an important issue in organic synthesis.

Herein, we disclose a one-pot cyclization of 2-aminobenzyl alcohols with fluorine-containing carboxylic acids in the presence of triethylamine and bromotriphenylphosphonium salt, which is generated in situ by the reaction of triphenylphosphane with carbon tetrabromide in toluene at reflux temperature. This process provides a convenient modular, scalable, and well-suited approach for the direct synthesis of various 2-fluoroalkyl-substituted indole compounds in one step (Scheme 1).



Scheme 1 Synthesis of 2-fluoroalkyl-substituted indoles

Hao and co-workers reported the synthesis of 2-fluoroalkyl-substituted indoles through Grignard cyclization of either fluorinated *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides or *N*-[2-(chloroalkyl)phenyl]imidoyl chlorides,[6] which were simply prepared according to Uneyama's procedure.[7] By using this method, they also reported the synthesis of fluorine-containing benzoxazole [8] and indoline derivatives[9] from 2-aminophenol or 2-aminophenethyl alcohol. In this case, we wondered whether the fluoroalkyl-substituted benzene-fused six-membered-ring compound 2-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazine (**7**) could be obtained by using 2-aminobenzyl alcohol in the above procedure. However, the cyclized 2-trifluoromethylindole (**8a**) was instead obtained in 55% yield (Scheme 2).



Scheme 2 Synthesis of **8a** instead of **7**

Carbon tetrachloride was used in this process as both the reactant and solvent, and although it was evident that the overuse of carbon tetrachloride represents a serious environmental problem, the reactions provided reasonable results. To overcome this problem, carbon tetrabromide was

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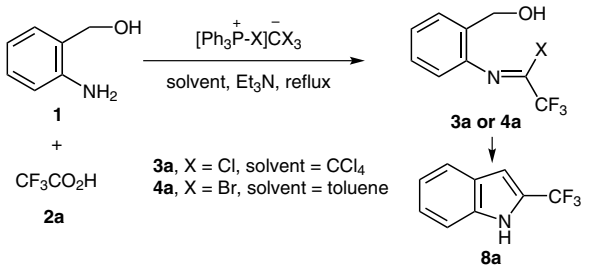
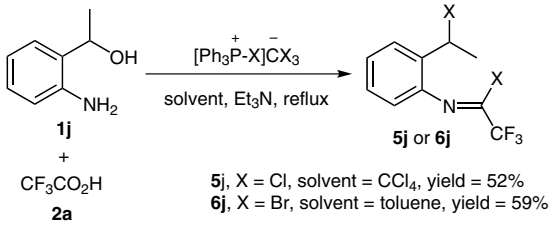
used as a substitute for carbon tetrachloride as the reactant with the use of toluene as the solvent. The reaction went to completion in the presence of carbon tetrabromide (3 equiv) in toluene. Furthermore, the reactant performed better and the yield reached 65%.

It was clear that during the model reaction with trifluoroacetic acid, the imidoyl halide intermediate *N*-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl halide **3a** or **4a** was formed at the initial stage, the intermediate gradually disappeared and the cyclized product **8a** was obtained as the final product (Scheme 3).



Scheme 3 Synthesis of the intermediate **3a** or **4a** and 2-trifluoromethylindole (**8a**)



Scheme 4 Synthesis of **5j** or **6j**

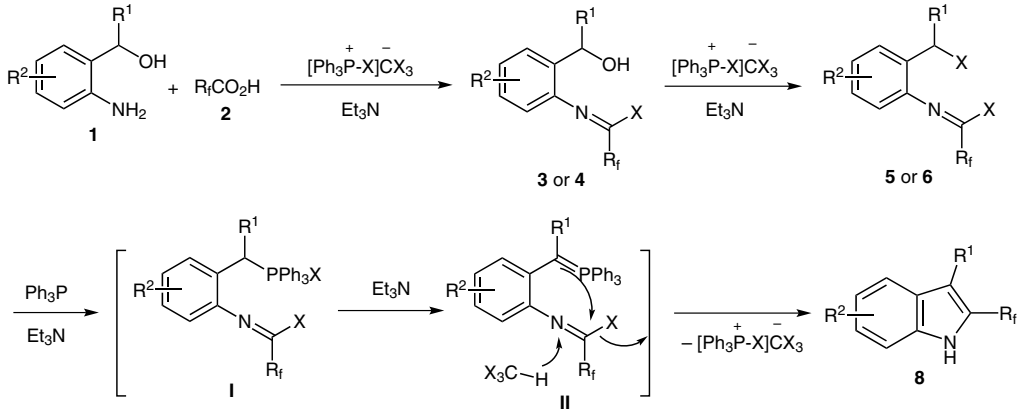
Further study of the mechanism revealed that decreasing the quantity of triethylamine that was used in this reaction to one-third of normal dosage could effectively prevent the subsequent cyclization from reaching completion. Thus, the intermediate **3a** or **4a** was successfully isolated as a major and stable compound from the reaction mixture. The further cyclization of **3a** or **4a** could not be achieved when these compounds were treated with an equivalent of base, such as triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or potassium carbonate, in dichloromethane or carbon tetrachloride at ambient temperature or at reflux temperature. In contrast to previous reports, the further cyclization of **3a** or **4a** could be achieved only in the presence of triphenylphosphine, carbon tetrachloride or carbon tetrabromide, and triethylamine.[8,9]

All imidoyl halide intermediates, such as **3a** or **4a**, were clearly detected in all examined cases and formed indole compounds except using 1-(2-aminophenyl)ethanol (**1j**) as the starting material, which formed *N*-[2-(1-haloethyl)phenyl]-2,2,2-trifluoroacetimidoyl halide **5j** or **6j** instead of the corresponding indole compound (Scheme 4).

The intermediate *N*-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl halide **3** or **4**, which could be detected, formed the intermediate *N*-[2-(halomethyl)phenyl]-2,2,2-trifluoroacetimidoyl halide **5** or **6** in the presence of $[Ph_3P^+X]CX_3^-$ and triethylamine. We reasoned that the excess triphenylphosphine attacked **5** or **6** and formed a phosphonium salt **I**, which then reacted with triethylamine to give ylide **II**. The latter was very active and unstable and, once formed, can undergo immediate cyclization to form **8** (Scheme 5). Because **3j** is a secondary alkyl halide, formation of the phosphonium salt intermediate **I** is difficult, which is presumably why we failed to obtain the corresponding indole.

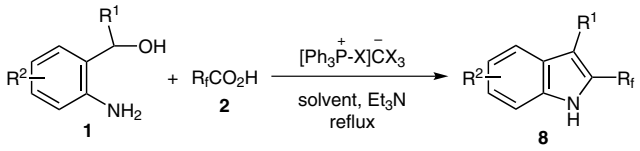
Although details of the mechanism of the reaction remain to be fully clarified, a range of 2-fluoroalkyl-substituted indoles with different fluorine-containing carboxylic acids and 2-aminobenzyl alcohols (Table 1) were prepared in moderate to excellent yields by using this procedure. Most of the starting 2-aminobenzyl alcohols are commercially available. For specific structure demands, the desired product can also be simply prepared by the reduction of 2-aminobenzoic acid or 2-nitrobenzoic acid.[10]

It was found that the yields of **8** were affected by the electronic nature of the substituent group R^2 on the benzene ring. Without substituent group (R^2 = H) or with an electron-donating group, such as a methoxy group, the prod-



Scheme 5 Postulated mechanisms for the transformation of 2-aminobenzyl alcohols **1** into indoles **8**

Table 1 Synthesis of 2-Fluoroalkyl-Substituted Indole



Entry	R^1	R^2	R_f	**8**	Yield of **8** (%)[a] X = Cl[b]	X = Br[c]
1	H	H	CF_3	**8a**	55	65
2	H	H	CF_2H	**8b**	47	56
3	H	H	C_3F_7	**8c**	62	72
4	H	4-OMe	CF_3	**8d**	73	80
5	H	4-F	CF_3	**8e**	55	64
6	H	4-Cl	CF_3	**8f**	49	55
7	H	4-NO_2	CF_3	**8g**	41	51
8	H	5-OMe	CF_3	**8h**	66	77
9	H	5-OMe	C_3F_7	**8i**	67	76

[a] Isolated yield.
[b] CCl_4 as solvent.
[c] Toluene as solvent.

ucts are obtained in good yields, whereas with an electron-deficient substituent, such as NO_2, the yields decreased to moderate. When the side-chain contained a substituent group, such as R^1 = Me, the reaction did not occur. The bromotriphenylphosphonium salt system was, in all cases, more efficient.

In conclusion, a unique and concise one-pot synthesis of 2-fluoroalkyl-substituted indoles from 2-aminobenzyl alcohols and fluorine-containing carboxylic acids has been developed. This new approach provides an efficient, scalable, low-cost, and direct access to the biologically important indoles.

All reagents were of analytical grade and were used without further purification. All melting points were recorded with a WRS-1A or WRS-1B digital melting-point apparatus without correction. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ with a Bruker AV-500 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in ppm downfield from TMS; chemical shifts for ^{13}C NMR spectra are reported in ppm relative to internal $CDCl_3$ (δ = 77.0 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in ppm downfield from external fluorotrichloromethane ($CFCl_3$). Infrared spectra (IR) were recorded with a VATAR 370 FT-IR spectrophotometer. Elemental analyses were carried out with a VARIO EL111 elemental analyzer.

_N_-[2-(Hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl Chloride (3a); Typical Procedure[6]

To a 200-mL three-necked, round-bottomed flask equipped with a condenser and a magnetic stir bar was added Ph_3P (7.86 g, 30 mmol), Et_3N (1.4 mL, 10 mmol), CCl_4 (40 mL, 419 mmol), and carboxylic acid (10 mmol) at 0 °C under a nitrogen atmosphere and the solution was then stirred for 10 min. 2-Aminobenzyl alcohol **1a** (10 mmol) was then added to the reaction mixture. Once the addition was complete, the reaction mixture was heated to reflux for 2 h. After cooling, the solvent was removed by rotary evaporator, the residue was carefully washed three times with hexane–EtOAc (10:1), and the precipitate was removed by filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by column chromatography (hexane–EtOAc, 10:1), to give the product **3a**.

Yield: 1.26 g (53%); off-white solid; mp 100–101 °C.

^{1}H NMR (500 MHz): δ = 8.43 (br, 1 H), 7.91 (d, J = 8.0 Hz, 1 H, Ar-H), 7.45 (m, 1 H), 7.37 (dd, J = 7.5, 1.5 Hz, 1 H), 7.27 (m, 1 H), 4.63 (s, 2 H).

^{13}C NMR (125 MHz): δ = 155.2 (q, $^2J_{C-F}$ = 37.5 Hz, C-CF_3), 133.7, 130.7, 130.3, 128.6, 127.6, 124.1, 115.8 (q, $^1J_{C-F}$ = 286.7 Hz, CF_3), 43.7 (Ar-CH_2OH).

^{19}F NMR (470 MHz): δ = 75.86 (s, 3 F).

Synthesis of _N_-[2-(Hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl Bromide (4a); General Procedure

A 100-mL, three-necked flask equipped with a condenser was charged with Ph_3P (2.20 g, 8.4 mmol), Et_3N (0.28 g, 2.8 mmol), CBr_4 (2.79 g, 8.4 mmol), and fluorine-containing carboxylic acid (2.8 mmol) in toluene (25.0 mL) at 0 °C under a nitrogen atmosphere and the solution was stirred for 10 min. 2-Aminobenzyl alcohol **1a** (2.8 mmol) was then added to the reaction mixture. Once the addition was complete, the reaction mixture was heated to reflux for 2 h. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed three times with hexane–EtOAc (10:1), and the precipitate was removed by filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by column chromatography (hexane–EtOAc, 10:1) to offer the product **4a**.

Yield: 442 mg (56%); off-white solid; mp 112–113 °C.

^{1}H NMR (500 MHz): δ = 8.75 (br, 1 H), 7.92 (d, J = 8.0 Hz, 1 H, Ar-H), 7.44 (m, 1 H), 7.37 (dd, J = 7.5, 1.5 Hz, 1 H), 7.26 (m, 1 H), 4.65 (s, 2 H).

^{13}C NMR (125 MHz): δ = 154.5 (q, $^2J_{C-F}$ = 37.5 Hz, C-CF_3), 133.8, 130.6, 130.3, 128.7, 127.1, 124.3, 114.7 (q, $^1J_{C-F}$ = 286.7 Hz, CF_3), 43.5 (Ar-CH_2OH).

^{19}F NMR (470 MHz): δ = 75.15 (s, 3 F).

MS (EI, 70 eV): m/z (%) = 281.0 (100) [M^+], 283.0 (98), 263.9 (76), 265.9 (74), 196.0 (50), 198.0 (48), 106 (25).

HRMS: m/z [M^+] calcd for $C_9H_7BrF_3NO$: 280.9663; found: 280.9659.

Synthesis of 2-Fluoroalkyl-Substituted Indoles

General Procedure 1

To a 200-mL three-necked, round-bottomed flask equipped with a condenser was added Ph_3P (7.86 g, 30 mmol), Et_3N (4.2 mL, 30 mmol), CCl_4 (40 mL, 419 mmol), and carboxylic acid (10 mmol) at 0 °C under a nitrogen atmosphere and the solution was then stirred for 10 min. 2-Aminobenzyl alcohol **1** (10 mmol) was added to the reaction mixture. Once the addition was complete, the reaction mixture was heated to reflux for 3–12 h. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed three times with hexane–EtOAc (4:1), and the precipitate was removed by filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by column chromatography (hexane–EtOAc, 4:1) to give the product.

General Procedure 2

A 100-mL, three-necked flask equipped with a condenser was charged with Ph_3P (2.20 g, 8.4 mmol), Et_3N (0.85 g, 8.4 mmol), CBr_4 (2.79 g, 8.4 mmol), and fluorine-containing carboxylic acid (2.8 mmol) in toluene (25.0 mL) at 0 °C under a nitrogen atmosphere and the solution was then stirred for 10 min. 2-Aminobenzyl

alcohol **1** (2.8 mmol) was added to the reaction mixture. Once the addition was complete, the reaction mixture was heated to reflux for 1–3 h. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed three times with hexane–EtOAc (4:1), and the precipitate was removed by filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by column chromatography (hexane–EtOAc, 4:1) to give the product.

_N_-[2-(1-Chloroethyl)phenyl]-2,2,2-trifluoroacetimidoyl Chloride (5j)

Obtained by following Procedure 1 from 1-(2-aminophenyl)ethanol (1.37 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol).

Yield: 1.40 g (52%); colorless oil.

IR (neat): 2980, 1697 (C=N), 1486, 1288, 1209, 1165, 951, 765 cm^{-1}.

^1H NMR (500 MHz): δ = 7.65 (dd, J = 7.5, 2.0 Hz, 1 H), 7.40–7.31 (m, 2 H, Ar-H), 6.95 (dd, J = 7.5, 1.2 Hz, 1 H), 5.29 (q, J = 7.0 Hz, 1 H), 2.15 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz): δ = 141.1, 134.9, 134.2 (q, $^2J_{C–F}$ = 42.9 Hz, *C*-CF_3), 128.8, 127.7, 126.5, 119.2, 116.7 (q, $^1J_{C–F}$ = 275.8 Hz, CF_3), 43.1, 26.1 (Ar-CHBr*C*H_3).

^{19}F NMR (470 MHz): δ = –71.60 (s, 3 F).

MS (EI, 70 eV): *m*/*z* (%) = 269.0 (100) [M^+], 271.0 (63), 201.0 (68), 203.0 (43), 131 (45).

HRMS: *m*/*z* [M^+] calcd for $C_{10}H_8Cl_2F_3N$: 268.9986; found: 268.9982.

Anal. Calcd for $C_{10}H_8Cl_2F_3N$: C, 44.47; H, 2.99; N, 5.19. Found: C, 44.50; H, 3.01; N, 5.21.

_N_-[2-(1-Bromoethyl)phenyl]-2,2,2-trifluoroacetimidoyl Bromide (6j)

Obtained by following Procedure 2 from 1-(2-aminophenyl)ethanol (384 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 593 mg (59%).

IR (neat): 2960, 1689, 1488, 1278, 1215, 1150, 953, 778 cm^{-1}.

^1H NMR (500 MHz): δ = 7.65 (dd, J = 7.5, 2.0 Hz, 1 H), 7.41–7.31 (m, 2 H, Ar-H), 6.94 (dd, J = 7.5, 1.2 Hz, 1 H), 5.38 (q, J = 7.0 Hz, 1 H), 2.34 (d, J = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz): δ = 141.3, 134.8, 134.1 (q, $^2J_{C–F}$ = 42.9 Hz, *C*-CF_3), 128.7, 127.5, 126.5, 119.2, 116.7 (q, $^1J_{C–F}$ = 275.8 Hz, CF_3), 46.2, 27.0.

^{19}F NMR (470 MHz): δ = –71.70 (s, 3 F).

MS (EI, 70 eV): *m*/*z* (%) = 358.9 [M^+] (100.0), 356.8 (51), 360.9 (49), 290.9 (57), 288.9 (30), 292.9 (29), 131 (45).

HRMS: *m*/*z* [M^+] calcd for $C_{10}H_8Br_2F_3N$: 356.8976; found: 356.8965.

2-Trifluoromethylindole (8a)[6]

Obtained by following Procedure 1 from 2-aminobenzyl alcohol (1.23 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol), or by following Procedure 2 from 2-aminobenzyl alcohol (345 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 1.02 g (55%; Procedure 1), 337 mg (65%; Procedure 2); light-yellow solid; mp 107–108 °C.

IR (neat): 3389 (NH), 2921, 1375, 1306, 1168, 1103, 940, 818, 754 cm^{-1}.

^1H NMR (500 MHz): δ = 8.31 (br, 1 H, NH), 7.66 (d, J = 8.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 6.92 (s, 1 H).

^{13}C NMR (125 MHz): δ = 136.1, 126.5, 125.7 (q, $^2J_{C–F}$ = 38.8 Hz, *C*-CF_3), 124.8, 122.1, 121.2 (q, $^1J_{C–F}$ = 266.2 Hz, CF_3), 121.1, 111.7, 104.3 (q, $^3J_{C–F}$ = 3.3 Hz, *C*H=C-CF_3).

^{19}F NMR (470 MHz): δ = –60.50 (s, 3 F).

Anal. Calcd for $C_9H_6F_3N$: C, 58.38; H, 3.27; N, 7.57. Found: C, 58.40; H, 3.31; N, 7.55.

2-Difluoromethylindole (8b)[6]

Obtained by following Procedure 1 from 2-aminobenzyl alcohol (1.23 g, 10 mmol) and 2,2-difluoroacetic acid (0.96 g, 10 mmol) or by following Procedure 2 from 2-aminobenzyl alcohol (345 mg, 2.8 mmol) and 2,2-difluoroacetic acid (269 mg, 2.8 mmol).

Yield: 0.78 g (47%; Procedure 1), 262 mg (56%; Procedure 2); yellow solid; mp 56–58 °C.

IR (neat): 3395 (NH), 2924, 1621, 1371, 1069, 1015, 810, 750 cm^{-1}.

^1H NMR (500 MHz): δ = 8.31 (br, 1 H, NH), 7.65 (d, J = 8.0 Hz, 1 H, Ar-H), 7.35 (d, J = 8.0 Hz, 1 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 6.82 (t, $J_{H–F}$ = 54.5 Hz, 1 H, CF_2H), 6.73 (d, $J_{H–F}$ = 2.0 Hz, 1 H, C*H*=C-CF_2H).

^{13}C NMR (125 MHz): δ = 136.2, 130.0 (t, $^2J_{C–F}$ = 24.2 Hz, *C*-CF_2H), 126.9, 124.1, 121.6, 120.6, 111.6, 110.5 (t, $^1J_{C–F}$ = 233.4 Hz, CF_2H), 103.9 (t, $^3J_{C–F}$ = 6.9 Hz, *C*H=C-CF_2H).

^{19}F NMR (470 MHz): δ = –109.83 (d, $J_{F–H}$ = 54.9 Hz, 2 F).

Anal. Calcd for $C_9H_7F_2N$: C, 64.67; H, 4.22; N, 8.38. Found: C, 64.66; H, 4.19; N, 8.35.

2-Heptafluoropropylindole (8c)[11]

Obtained by following Procedure 1 from 2-aminobenzyl alcohol (1.23 g, 10 mmol) and heptafluorobutyric acid (2.14 g, 10 mmol) or by following Procedure 2 from 2-aminobenzyl alcohol (345 mg, 2.8 mmol) and heptafluorobutyric acid (600 mg, 2.8 mmol).

Yield: 1.77 g (62%; Procedure 1); 575 mg (72%; Procedure 2); yellow solid; mp 63–64 °C.

IR (neat): 3308, 2953, 1628, 1548, 1459, 1343, 1232, 1080, 814, 760 cm^{-1}.

^1H NMR (500 MHz): δ = 8.32 (br, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.35 (m, 1 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 6.87 (s, 1 H).

^{13}C NMR (125 MHz): δ = 136.1, 127.5, 124.9, 121.5, 120.1, 119.3 (t, $J_{C–C–F}$ = 28.1 Hz), 117.9 (qt, $J_{C–F}$ = 286.2 Hz, $J_{C–C–F}$ = 33.8 Hz), 116.6 (m), 114.1 (tt, $J_{C–F}$ = 253.1 Hz, $J_{C–C–F}$ = 31.9 Hz), 111.5, 109.0 (m).

^{19}F NMR (470 MHz): δ = –80.20 (t, J = 9.4 Hz, 3 F), –109.60 (q, J = 9.4 Hz, 2 F), –126.70 (s, 2 F).

Anal. Calcd for $C_{11}H_6F_7N$: C, 46.33; H, 2.12; N, 4.91. Found: C, 46.36; H, 2.09; N, 4.85.

6-Methoxy-2-trifluoromethylindole (8d)[12]

Obtained by following Procedure 1 from 2-amino-4-methoxyphenyl methanol (1.53 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol) or by following Procedure 2 from 2-amino-4-methoxyphenyl methanol (428 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 1.57 g (73%; Procedure 1), 482 mg (80%; Procedure 2); colorless solid; mp 88–90 °C.

IR (neat): 3302 (NH), 2959, 1599, 1560, 1254, 1174, 1117, 1001 cm^{-1}.

^1H NMR (500 MHz): δ = 8.28 (br, 1 H, NH), 7.48 (d, J = 8.5 Hz, 1 H), 7.10 (d, J = 2.5 Hz, 1 H), 6.89 (dd, J = 9.0, 2.5 Hz, 1 H), 6.86 (s, 1 H, C*H*=C-CF_3), 3.85 (s, 3 H).

^{13}C NMR (125 MHz): δ = 158.2, 137.3, 126.2 (q, $^2J_{C–F}$ = 38.4 Hz, *C*-CF_3), 122.7, 121.2 (q, $^1J_{C–F}$ = 265.9 Hz, CF_3), 119.7, 111.6, 104.3 (q, $^3J_{C–F}$ = 3.3 Hz, *C*H=C-CF_3), 94.8, 55.7 (Ar-O*C*H_3).

^{19}F NMR (470 MHz): δ = –60.45 (s, 3 F).

Anal. Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51; O, 7.44. Found: C, 55.86; H, 3.77; N, 6.45; O, 7.46.

6-Fluoro-2-trifluoromethylindole (8e)[6]
Obtained by following Procedure 1 from 2-amino-4-fluorophenyl methanol (1.41 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol) or by following Procedure 2 from 2-amino-4-fluorophenyl methanol (395 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 1.12 g (55%; Procedure 1), 364 mg (64%; Procedure 2); yellow viscous liquid; mp 125 °C (dec.).

IR (neat): 3457 (NH), 2938, 1566, 1305, 1249, 1169, 831 cm^{-1}.

^1H NMR (500 MHz): δ = 8.38 (br, 1 H, NH), 7.57 (dd, *J* = 8.8, 5.2 Hz, 1 H), 7.06 (m, 1 H), 6.96 (m, 1 H), 6.88 (s, 1 H, CH=C-CF_3).

^{13}C NMR (125 MHz): δ = 161.1 (d, $^1J_{C–F}$ = 240.0 Hz), 136.2 (d, $^3J_{C–F}$ = 12.5 Hz), 126.2 (q, $^2J_{C–F}$ = 39.2 Hz, *C*-CF_3), 123.2 (d, $^3J_{C–F}$ = 10.0 Hz), 122.9, 121.1 (q, $^1J_{C–F}$ = 265.8 Hz, *C*F_3), 110.2 (d, $^2J_{C–F}$ = 25.0 Hz), 104.3 (q, $^3J_{C–F}$ = 3.3 Hz, *C*H=C-CF_3), 97.8 (d, $^2J_{C–F}$ = 26.2 Hz).

^{19}F NMR (470 MHz): δ = –60.56 (s, 3 F, CF_3), –116.7 (m, 1 F, Ar-F).

Anal. Calcd for $C_9H_5F_4N$: C, 53.21; H, 2.48; N, 6.90. Found: C, 53.17; H, 2.50; N, 6.91.

6-Chloro-2-trifluoromethylindole (8f)[6]
Obtained by following Procedure 1 from 2-amino-4-chlorophenyl methanol (1.58 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol) or by following Procedure 2 from 2-amino-4-chlorophenyl methanol (441 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 1.08 g (49%; Procedure 1), 338 mg (55%; Procedure 2); yellow viscous liquid; mp 147 °C (dec.).

IR (neat): 3425 (NH), 1554, 1416, 1357, 1310, 1125, 922, 826 cm^{-1}.

^1H NMR (500 MHz): δ = 8.40 (br, 1 H, NH), 7.56 (d, *J* = 8.5 Hz, 1 H), 7.43–7.16 (m, 2 H, Ar-H), 6.91 (s, 1 H, CH=C-CF_3).

^{13}C NMR (125 MHz): δ = 136.3, 130.8, 126.2 (q, $^2J_{C–F}$ = 38.8 Hz, *C*-CF_3), 124.8, 122.7, 122.1, 120.6 (q, $^1J_{C–F}$ = 266.3 Hz, CF_3), 111.5, 103.8 (q, $^3J_{C–F}$ = 3.5 Hz, *C*H=C-CF_3).

^{19}F NMR (470 MHz): δ = –60.61 (s, 3 F).

Anal. Calcd for $C_9H_5ClF_3N$: C, 49.23; H, 2.30; N, 6.38. Found: C, 49.35; H, 2.28; N, 6.40.

6-Nitro-2-trifluoromethylindole (8g)[13]
Obtained by following Procedure 1 from 2-amino-4-nitrophenyl methanol (1.68 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol) or by following Procedure 2 from 2-amino-4-nitrophenyl methanol (470 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 943 mg (41%; Procedure 1), 328 mg (51%; Procedure 2); yellow solid; mp 143–144 °C.

IR (neat): 3380 (NH), 1654, 1515, 1456, 1300, 1025, 927, 835 cm^{-1}.

^1H NMR (500 MHz): δ = 8.45 (br, 1 H, NH), 8.26 (d, *J* = 8.5 Hz, 1 H), 7.50–7.55 (m, 2 H), 6.95 (s, 1 H, C*H*=C-CF_3).

^{13}C NMR (125 MHz): δ = 140.3, 138.8, 127.9 (q, $^2J_{C–F}$ = 38.6 Hz, *C*-CF_3), 123.7, 122.7, 122.1, 120.8 (q, $^1J_{C–F}$ = 266.3 Hz, CF_3), 118.5, 102.4 (q, $^3J_{C–F}$ = 3.5 Hz, *C*H=C-CF_3).

^{19}F NMR (470 MHz): δ = –60.81 (s, 3 F).

Anal. Calcd for $C_9H_5F_3N_2O_2$: C, 46.97; H, 2.19; N, 12.17; O, 13.90. Found: C, 46.92; H, 2.17; N, 12.18; O, 13.93.

5-Methoxy-2-trifluoromethyl Indole (8h)[6]
Obtained by following Procedure 1 from 2-amino-5-methoxyphenyl methanol (1.53 g, 10 mmol) and 2,2,2-trifluoroacetic acid (1.14 g, 10 mmol) or by following Procedure 2 from 2-amino-5-methoxyphenyl methanol (428 mg, 2.8 mmol) and 2,2,2-trifluoroacetic acid (320 mg, 2.8 mmol).

Yield: 1.42 g (66%; Procedure 1), 464 mg (77%; Procedure 2); yellow solid; mp 50–51 °C.

IR (neat): 3402 (NH), 2949, 1559, 1461, 1224, 1174, 1117, 801 cm^{-1}.

^1H NMR (500 MHz): δ = 8.30 (br, 1 H, NH), 7.33 (d, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 2.5 Hz, 1 H), 7.00 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.84 (s, 1 H, C*H*=C-CF_3), 3.86 (s, 3 H, Ar-OCH_3).

^{13}C NMR (125 MHz): δ = 154.7, 131.3, 127.1, 126.2 (q, $^2J_{C–F}$ = 38.4 Hz, *C*-CF_3), 121.2 (q, $^1J_{C–F}$ = 265.9 Hz, *C*F_3), 115.6, 112.4, 103.8 (q, $^3J_{C–F}$ = 3.3 Hz, *C*H=C-CF_3), 102.7, 55.5 (Ar-O*C*H_3).

^{19}F NMR (470 MHz): δ = –60.45 (s, 3 F).

Anal. Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51; O, 7.44. Found: C, 55.85; H, 3.76; N, 6.48; O, 7.56.

5-Methoxy-2-heptafluoropropylindole (8i)[6]
Obtained by following Procedure 1 from 2-amino-5-methoxyphenyl methanol (1.53 g, 10 mmol) and heptafluorobutyric acid (2.14 g, 10 mmol) or by following Procedure 2 from 2-amino-5-methoxyphenyl methanol (428 mg, 2.8 mmol) and heptafluorobutyric acid (600 mg, 2.8 mmol).

Yield: 2.11 g (67%; Procedure 1), 670 mg (76%; Procedure 1); yellow solid; mp 44–45 °C.

IR (neat): 3318 (NH), 2956, 1545, 1450, 1345, 1232, 1181, 967, 790 cm^{-1}.

^1H NMR (500 MHz): δ = 8.52 (br, 1 H, NH), 7.27 (d, *J* = 9.0 Hz, 1 H), 7.10 (d, *J* = 2.0 Hz, 1 H), 6.99 (dd, *J* = 8.8, 2.3 Hz, 1 H), 6.87 (s, 1 H, C*H*=C-C_3F_7), 3.84 (s, 3 H).

^{13}C NMR (125 MHz): δ = 155.1, 132.0, 127.5, 124.4 (t, $^2J_{C–F}$ = 29.4 Hz, *C*-C_3F_7), 118.0 (qt, $^1J_{C–F}$ = 286.2 Hz, $^2J_{C–F}$ = 33.8 Hz, $CF_2CF_2CF_3$), 116.1, 112.8 (tt, $^1J_{C–F}$ = 251.9 Hz, $^2J_{C–F}$ = 31.2 Hz, $CF_2CF_2CF_3$), 112.7, 108.8 (m, CF_2CF_2-CF_3), 106.0 (t, ^3J = 5.0 Hz, *C*H=C-C_3F_7), 102.7, 55.8 (Ar-O*C*H_3).

^{19}F NMR (470 MHz): δ = –80.20 (t, *J* = 9.4 Hz, 3 F, $CF_2CF_2CF_3$), –109.47 (q, *J* = 9.4 Hz, 2 F, $CF_2CF_2CF_3$), –126.70 (s, 2 F, $CF_2CF_2CF_3$).

Anal. Calcd for $C_{12}H_8F_7NO$: C, 45.73; H, 2.56; N, 4.44; O, 5.08. Found: C, 45.75; H, 2. 60; N, 4.42; O, 5.11.

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