Supplementary Material for Chemical Communications

Hydroamination/Heck reaction sequence for a highly regioselective one-pot synthesis of indoles using 2-chloroaniline

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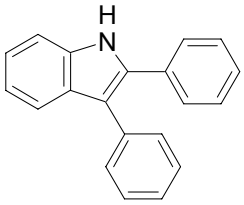
Supporting Information

Experimental Section

$TiCl_4$-mediated reactions were carried out on a 1.5-5.0 mmol scale under N_2 using pre-dried glassware. Chemicals were obtained from Aldrich, Fluka, Lancaster, Merck and Acros, and were used without further purification. Amines were distilled under N_2, and stored over molecular sieves (4 Å).

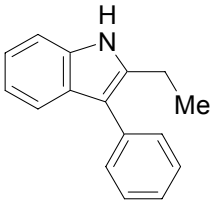
Representative Procedure:



2,3-Diphenylindole (S-1); Table 2, entry 1:

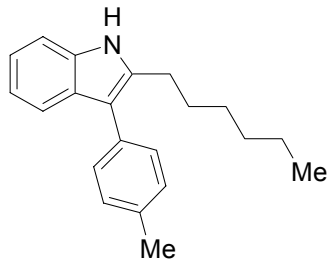
2-Chloroaniline (610 mg, 4.76 mmol) and tolan (1.02 g, 5.70 mmol) were added to a solution of $TiCl_4$ (0.05 mL, 0.47 mmol) and *t*-$BuNH_2$ (0.30 mL, 2.86 mmol) in toluene (5 mL) and the resulting mixture was stirred for 20 h at 105 °C. The solvent was partially removed and KO*t*-Bu (1.60 g, 14.0 mmol), HIPrCl (**4**) (202 mg, 0.48 mmol) and $Pd(OAc)_2$ (106 mg, 0.48 mmol) were added. The mixture was stirred at 105 °C for 24 h. CH_2Cl_2 (75 mL) and aqueous HCl (2N, 50 mL) were added to the cold

suspension. The separated aqueous phase was washed with CH_2Cl_2 (2 x 75 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). Drying with $MgSO_4$ and purification by column chromatography (silica gel, *n*-pentane/Et_2O 20/1→10/1→4/1) yielded 2,3-diphenylindole (974 mg, 76%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (s, br, 1H), 7.67 (d, 1H, *J* = 7.8 Hz), 7.45-7.12 (m, 13 H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): δ 135.9 (C_q), 135.1 (C_q), 134.1 (C_q), 132.7 (C_q), 130.2 (C_q), 128.8 (C_q), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 126.2 (CH), 122.7 (CH), 120.4 (CH), 119.7 (CH), 115.2 (CH), 110.9 (CH). MS (EI) *m/z* (relative intensity) 269 (100) [M^+], 254 (4), 239 (5), 165 (11), 134 (6), 127 (4). HR-MS (EI) *m/z* calcd for $C_{20}H_{15}N$ 269.1204, found 269.1198.



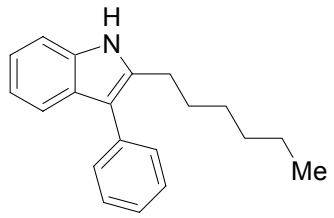
2-Ethyl-3-phenylindole (S-2); Table 1, entry 4:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 2-phenyl-1-butyne (195 mg, 2.00 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-2** (192 mg, 57 %) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→20/1→10/1) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): *δ* 7.87 (s, br, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.47-7.37 (m, 4 H), 7.27-7.23 (m, 2H), 7.15-7.06 (m, 2 H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (75 MHz, DEPT, $CDCl_3$): *δ* 137.2 (C_q), 135.5 (C_q), 135.1 (C_q), 129.6 (CH), 128.5 (CH), 127.9 (C_q), 125.9 (CH), 121.6 (CH), 119.9 (CH), 118.9 (CH), 113.9 (C_q), 110.4 (CH), 19.7 (CH_2), 14.3 (CH_3). IR (KBr, cm^{-1}): 3404 (s), 3055 (m), 2970 (m), 2931 (w), 1601 (m), 1459 (s), 1460 (s), 772 (m), 752 (m), 703 (m). MS *m/z* (relative intensity) 221 ([M^+] 100), 206 (98), 179 (15), 102 (5). HR-MS (EI) *m/z* calcd for $C_{16}H_{15}N$ 221.1204, found 221.1182.



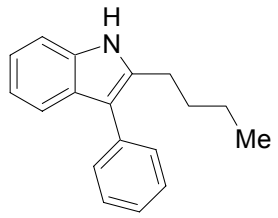
2-*n*-Hexyl-3-(4-methylphenyl)-indole (S-3); Table 2, entry 2:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-(4-methylphenyl)-1-n-octyne (300 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-3** (354 mg, 81%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1) as a yellow oil. Ratio of regioisomers: 9/81/10 (GC). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.95 (s, br, 1H), 7.65-7.62 **(**m, 1H), 7.42-7.09 (m, 7H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.44 (s, 3H), 1.70 (tt, *J* = 7.8, 7.8 Hz, 2H), 1.39-1.41 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): 135.9 (C_q), 135.4 (C_q), 135.2 (C_q), 132.4 (C_q), 129.5 (CH), 129.2 (CH), 128.1 (C_q), 121.4 (CH), 119.8 (CH), 118.9 (CH), 114.3 (C_q), 110.3 (CH), 31.6 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 21.2 (CH_3), 14.0 (CH_3). IR (KBr, cm^{-1}): 3408 (s), 3052 (w), 2926 (s) 2955 (vs), 2857 (s), 1511 (m), 1460 (vs), 1330 (w), 819 (m), 744 (s). MS (EI) *m/z* (relative intensity) 291 (55) [M^+], 234 (11), 220 (100), 205 (36), 178 (7). HR-MS (EI) *m/z* calcd for $C_{21}H_{25}N$ 291.1987, found 291.1975.



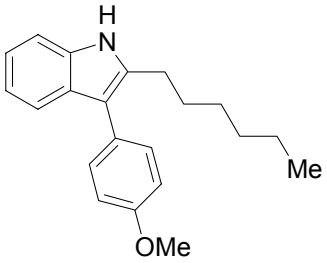
2-*n*-Hexyl-3-phenylindole (S-4), Table 2, entry 3:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-phenyl-1-n-octyne (244 mg, 1.31 mmol), HIPrCl (**4**) (57 mg, 0.13 mmol) and $Pd(OAc)_2$ (29 mg, 0.13 mmol), **S-4** (295 mg, 81%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→20/1) as a yellow oil. Ratio of regioisomers: 7/86/7 (GC). ^{1}H NMR ($CDCl_3$, DEPT, 300 MHz): 7.92 (s, br, 1H), 7.66-7.63 (m, 1H), 7.51-7.43 (m, 4H), 7.33-7.28 (m, 2H), 7.21-7.08 (m, 2H), 2.83 (t, *J* = 7.8 Hz, 2H), 1.67 (tt, *J* = 7.8, 7.8 Hz, 2H), 1.36-1.23 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 136.1 (C_q), 135.5 (C_q), 135.2 (C_q), 129.6 (CH), 128.4 (CH), 127.9 (C_q), 125.8 (CH), 121.5 (CH), 119.8 (CH), 118.9 (CH), 114.4 (C_q), 110.3 (CH), 31.5 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3). IR (KBr, cm^{-1}): 3409 (s), 3057 (w), 2955 (s), 2927 (vs), 2856 (m), 1496 (m), 1460 (vs), 772 (m), 744 (s), 702 (s). MS (EI) *m/z* (relative intensity) 277 (48) [M^+], 206 (100), 179 (9). HR-MS (EI) *m/z* calcd for $C_{20}H_{23}N$ 277.1830, found 277.1839.



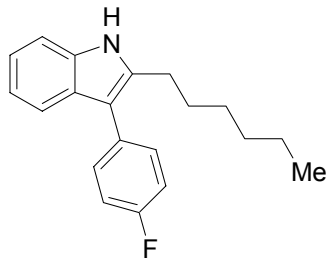
2-*n*-Butyl-3-phenylindole (S-5); Table 2, entry 4:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-phenyl-1-n-hexyne (237 mg, 1.5 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-5** (303 mg, 81%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→20/1→10/1) as a yellow oil. Ratio of regioisomers: 8/85/7 (GC). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.95 (s, br, 1H), 7.73-7.69 (m, 1H), 7.59-7.49 (m, 4H), 7.39-7.35 (m, 2H), 7.26-7.15 (m, 2H), 2.89 (t, J = 7.8 Hz, 2H), 1.71 (tt, J = 7.8, 7.8 Hz, 2H), 1.49-1.36 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 136.0 (C_q), 135.5 (C_q), 135.2 (C_q), 129.6 (CH), 128.4 (CH), 127.9 (C_q), 125.8 (CH), 121.5 (CH), 119.8 (CH), 118.9 (CH), 114.4 (C_q), 110.3 (CH), 32.0 (CH_2), 26.1 (CH_2), 22.5 (CH_2), 13.8 (CH_3). IR (KBr, cm^{-1}): 3409 (s), 3057 (w), 2957 (m), 2928 (m), 1496 (m), 1460 (vs), 771 (m), 744 (s), 702 (s). MS (EI) *m/z* (relative intensity) 249 (43) [M^+], 206 (100), 23 (10). HR-MS (EI) *m/z* calcd for $C_{18}H_{19}N$ 249.1517, found 249.1525.



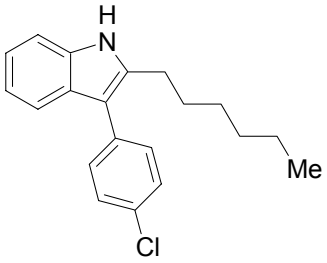
2-*n*-Hexyl-3-(4-methoxyphenyl)-indole (S-6); Table 2, entry 5:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-(4-methoxyphenyl)-1-n-octyne (324 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-6** (306 mg, 66%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→20/1→10/1) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): 7.97 (s, br, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.45-7.42 (m, 2H), 7.36-7.33 (m, 1H), 7.22-7.10 (m, 2H), 7.07-7.02 (m, 2H), 3.90 (s, 3H), 2.84 (t, J = 7.8 Hz, 2H), 1.70 (tt, J = 7.8, 7.8 Hz, 2H), 1.39-1.26 (m, 6H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): 157.9 (C_q), 135.8 (C_q), 135.8 (C_q), 135.1 (C_q), 130.7 (CH), 128.2 (C_q), 127.8 (C_q), 121.4 (CH), 119.7 (CH), 118.8 (CH), 113.9 (CH), 113.9 (C_q), 110.3 (CH), 55.3 (OCH_3), 31.5 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3). IR (KBr, cm^{-1}): 3406 (m), 3056 (w), 2955 (m), 2928 (m), 2856 (m), 1510 (vs), 1460 (s), 1243 (s), 1175 (m), 831 (m), 745 (m). MS (EI) *m/z* (relative intensity) 307 (90) [M^+], 250 (5), 236 (100), 220 (9), 205 (25), 192 (12). HR-MS (EI) *m/z* calcd for $C_{21}H_{25}NO$ 307.1936, found 307.1939.



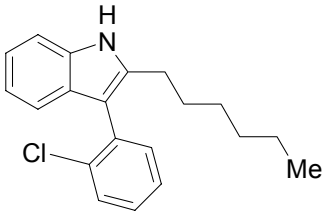
3-(4-Fluorophenyl)-2-*n*-hexylindole (S-7), Table 2, entry 6:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-(4-fluorophenyl)-1-n-octyne (306 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-7** (329 mg, 74%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→20/1→10/1) as a yellow oil. Ratio of regioisomers: 5/95/0 (GC). ^{1}H NMR ($CDCl_3$, 300 MHz): 7.98 (s, br, 1H), 7.60-7.57 (m, 1H), 7.47-7.42 (m, 2H), 7.37-7.34 (m, 1H), 7.22-7.10 (m, 4 H), 2.83 (t, *J* = 7.7 Hz, 2H), 1.69 (tt, *J* = 7.7, 7.7 Hz, 2H), 1.41-1.24 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): 161.4 (d, *J* = 244 Hz, C_q), 136.1 (C_q), 135.1 (C_q), 131.4 (d, *J* = 2.9 Hz, C_q), 131.1 (d, *J* = 7.6 Hz, CH), 128.0 (C_q), 121.6 (CH), 120.0 (CH), 118.6 (CH), 115.3 (d, *J* = 21.1 Hz, CH), 113.5 (C_q), 110.4 (CH), 31.5 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3). ^{19}F-NMR ($CDCl_3$, 375 MHz): δ –115.9 (tt, *J* = 9.2, 5.7 Hz). IR (KBr, cm^{-1}): 3404 (w), 3056 (m), 3956 (m), 2928 (s), 2857 (m), 1507 (vs), 1460 (s), 1222 (m), 1156 (m), 835 (m), 745 (m). MS (EI) *m/z* (relative intensity) 295 (50) [M^+], 238 (9), 224 (100), 197 (11), 177 (2). HR-MS (EI) *m/z* calcd for $C_{20}H_{22}FN$ 295.1736, found 295.1732.



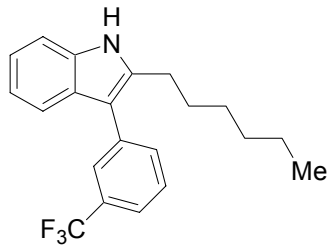
3-(4-Chlorophenyl)-2-*n*-hexylindole (S-8), Table 2, entry 7:

Following the general procedure using 2-bromoaniline (258 mg, 1.50 mmol), 1-(4-chlorophenyl)-1-octyne (331 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-8** (312 mg, 67%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→15/1) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): 8.00 (s, br, 1H), 7.60-7.57 (m, 1H), 7.43 (m, 4H), 7.37-7-34 (m, 1H), 7.22-7.10 (m, 2H), 2.83 (t, J = 7.8 Hz, 2H), 1.69 (tt, J = 7.8, 7.8 Hz, 2H), 1.40-1.23 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): 136.6 (C_q), 135.6 (C_q), 134.4 (C_q), 132.0 (C_q), 131.2 (CH), 129.0 (CH), 128.1 (C_q), 122.1 (CH), 120.5 (CH), 119.0 (CH), 113.7 (C_q), 110.8 (CH), 31.9 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 26.7 (CH_2), 22.9 (CH_2), 14.4 (CH_3). IR (KBr, cm^{-1}): 3403 (m), 3055 (w), 2955 (m), 2927 (s), 2856 (m), 1493 (vs), 1460 (s), 1090 (m), 1014 (m), 820 (m), 744 (m). MS (EI) *m/z* (relative intensity) 311 (61) [M^+], 254 (10), 240 (48), 205 (100), 130 (4). HR-MS (EI) *m/z* calcd for $C_{20}H_{22}NCl$ 311.1441, found 311.1417.



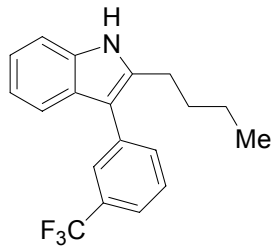
3-(2-Chlorophenyl)-2-*n*-hexylindole (S-9), Table 2, entry 8:

Following the general procedure using 2-bromoaniline (258 mg, 1.50 mmol), 1-(2-chlorophenyl)-1-octyne (331 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-9** (214 mg, 46%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→20/1→10/1) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): 8.01 (s, br, 1H), 7.57-7.54 (m, 1H), 7.44-7.41 (m, 1H), 7.38-7-32 (m, 4H), 7.20 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H), 7.12 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 2.76-2.66 (m, 2H), 1.71-1.59 (m, 2H), 1.33-1.21 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): 137.0 (C_q), 135.0 (C_q), 135.0 (C_q), 134.2 (C_q), 133.1 (CH), 129.7 (CH), 128.2 (C_q), 128.1 (CH), 126.4 (CH), 121.4 (CH), 119.7 (CH), 119.2 (CH), 112.1 (C_q), 110.4 (CH), 31.5 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 26.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3). IR (KBr, cm^{-1}): 3409 (s), 3058 (m), 2928 (s), 2857 (s), 1479 (s), 1462 (m), 1434 (m), 1332 (m), 1066 (m), 1036 (m), 820 (m), 741 (m). MS (EI) *m/z* (relative intensity) 311 (52) [M^+], 254 (12), 240 (49), 217 (14), 205 (100), 130 (4). HR-MS (EI) *m/z* calcd for $C_{20}H_{22}NCl$ 311.1441, found 311.1444.



2-*n*-Hexyl-3-(3-trifluoromethylphenyl)-indole (S-10), Table 2, entry 9:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-(3-trifluoromethylphenyl)-1-n-octyne (382 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-10** (422 mg, 82%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→20/1→10/1) as a yellow oil. Ratio of regioisomers: 4/93/3 (GC). ^{1}H NMR ($CDCl_3$, 300 MHz): 8.04 (s, br, 1H), 7.78-7.77 (m, 1H), 7.71-7.67 (m, 1H), 7.63-7.57 (m, 3H), 7.39-7.36 (m, 1H), 7.22 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H), 7.16 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H), 2.86 (t, *J* = 7.8 Hz, 2H), 1.72 (tt, *J* = 7.8, 7.8 Hz, 2H), 1.39-1.24 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, DEPT, 75 MHz): 136.6 (C_q), 136.4 (C_q), 135.2 (C_q), 132.7 (CH), 130.4 (q, *J* = 32.0 Hz, C_q), 128.9 (CH), 127.6 (C_q), 126.2 (q, *J* = 3.7 Hz, CH), 124.3 (q, *J* = 272 Hz, C_q), 122.5 (q, *J* = 3.7 Hz, CH), 121.9 (CH), 120.3 (CH), 118.5 (CH), 113.2 (C_q), 110.5 (CH), 31.5 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3). ^{19}F-NMR (CDCl3, 375 MHz): δ –61.4 (s). IR (KBr, cm^{-1}): 3405 (m), 3060 (w), 2958 (m), 2929 (s), 2858 (m), 1461 (s), 1323 (s), 1306 (s), 1166 (s), 1127 (vs), 1073 (s), 804 (m). MS (EI) *m/z* (relative intensity) 345 (50) [M^+], 288 (15), 274 (100), 254 (6), 204 (17). HR-MS (EI) *m/z* calcd for $C_{21}H_{22}F_3N$ 345.1704, found 345.1695.



2-*n*-Butyl-3-(3-trifluoromethylphenyl)-indole (S-11), Table 2, entry 10:

Following the general procedure using 2-chloroaniline (191 mg, 1.50 mmol), 1-(3-trifluoromethylphenyl)-1-n-hexyne (339 mg, 1.50 mmol), HIPrCl (**4**) (64 mg, 0.15 mmol) and $Pd(OAc)_2$ (34 mg, 0.15 mmol), **S-11** (398 mg, 84%) was obtained after purification by column chromatography (SiO_2, *n*-pentane/Et_2O 50/1→30/1→15/1) as a yellow solid. Ratio of regioisomers: 3/96/3 (GC). ^{1}H NMR ($CDCl_3$, 300 MHz): 8.03 (s, br, 1H), 7.79 (m, 1H), 7.72-7.69 (m, 1H), 7.65-7.58 (m, 3H), 7.38 (d, J = 6.3 Hz, 1H), 7.26-7.15 (m, 2H), 2.86 (t, J = 7.6 Hz, 2H), 1.71 (tt, J = 7.6, 7.6 Hz, 2H), 1.41 (tq, J = 7.6, 7.6 Hz, 2H), 0.93 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 136.6 (C_q), 136.4 (C_q), 135.2 (C_q), 132.7 (CH), 130.4 (q, J = 32.0 Hz, C_q), 128.9 (CH), 127.6 (C_q), 126.1 (q, J = 3.8 Hz, CH), 124.3 (q, J = 272 Hz, C_q), 122.5 (q, J = 3.8 Hz, CH), 121.9 (CH), 120.3 (CH), 118.4 (CH), 113.2 (C_q), 110.5 (CH), 31.9 (CH_2), 26.0 (CH_2), 22.4 (CH_2), 13.7 (CH_3). ^{19}F-NMR ($CDCl_3$, 375 MHz): δ –61.4 (s). IR (KBr, cm^{-1}): 3411 (s), 3366 (s), 3060 (w), 2955 (m), 2928 (m), 2863 (m), 1460 (m), 1326 (m), 1308 (m), 1163 (m), 1124 (s), 1073 (m), 802 (m), 747 (m), 702 (m). MS (EI) *m/z* (relative intensity) 317 (46) [M^+], 274 (100), 254 (6), 204 (22), 178 (6). HR-MS (EI) *m/z* calcd for $C_{19}H_{18}F_3N$ 317.1391, found 317.1411.