Electronic Supplementary Information (ESI)

Hypervalent phenyl-λ^3-iodane-mediated *para*-selective aromatic fluorination of 3-phenylpropyl ethers

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General Information. IR spectra were recorded on JASCO FT/IR-420 spectrometers. ^{1}H NMR and ^{13}C NMR spectra were obtained on either a JEOL JNM-AL300, JNM-AL400, or Bruker AV400 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield from internal Me_4Si. Mass spectra (MS) were obtained on either a JEOL-JMS-SX102A, JEOL JMS-T100GC, Waters LCT Premier, or SHIMADZU Model GCMS-QP 505 spectrometer. Preparative thin-layer chromatography (TLC) was carried out on precoated plates of silica gel (MERCK, silica gel F-254). Kieselgel 60 (Merck, 230-400 mesh) was used for column chromatography. Melting points were determined with a Yanaco micro melting points apparatus and are uncorrected.

Substrate. Hydroxy(phenyl)-λ^3-iodane·18-crown-6 complex **3** was prepared from iodosylbenzene according to a literature method.[1] Methyl ethers **6**, **12**, and **17d-g**, ethyl ether **17a**, and propyl ether **17b** were prepared from the corresponding alcohols by alkylation using Me_2SO_4, Et_2SO_4, and *n*-Pr_2SO_4, respectively.[2] *t*-Butyl ether **17c** was prepared according to a literature procedure.[3]

General Procedure for *p*-Fluorination of 3-Phenylpropyl Ethers with Hydroxy(phenyl)-λ^3-iodane·18-crown-6 Complex 3. A Typical Example (Table 2, entry 3). To a stirred suspension of hydroxyl-λ^3-iodane·18C6 complex **3** (136 mg, 0.24 mmol) in dichloromethane (3 mL) was added 3-phenylpropyl methyl ether (**6**) (11.9 mg, 0.079 mmol), H_2O (0.71 μL, 0.040 mmol), and BF_3-Et_2O (30.2 μL, 0.24 mmol) under nitogen, and the mixture was heated at 45 °C for 6 h. The reaction mixture was poured into cold water and extracted with dichloromethane four times. Combined organic phase was dried over Na_2SO_4, filtered, and concentrated under an aspirator vacuum at -10 to 0 °C to give a yellow oil. ^{1}H NMR analysis (reference: 1,1,2,2-tetrachloroethane) showed the formation of 3-(4-fluorophenyl)propyl methyl ether (**7**) (80%), [4-(3-methoxypropyl)phenyl](phenyl)(tetrafluoroborato)-λ^3-iodane (**5b**) (16%), and 1,4-benzoquinone (4%). The yellow crude oil was extracted with pentane five times by decantation at room temperature to give a pentane solution and an oily residue. The pentane solution was purified by silica gel column chromatography using pentane-dichloromethane to give a colorless oil of *p*-fluorobenzene **7** (7.8 mg, 59%),[3] contaminated with a trace amount of methyl ether **6**: IR (neat) 2927, 2868, 2829, 1601, 1510, 1452, 1387, 1221, 1157, 1119, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.9 Hz, $^4J_{HF}$ = 5.6 Hz, 2H), 6.96 (t, J = 8.9 Hz, 2H), 3.37 (t, J = 6.1 Hz, 2H), 3.34 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 1.91-1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (d, $^1J_{CF}$ = 242.9 Hz), 137.5 (d, $^4J_{CF}$ = 3.1 Hz), 129.8 (d, $^3J_{CF}$ = 7.4 Hz), 115.0 (d, $^2J_{CF}$ = 20.4 Hz), 71.7, 58.6, 31.5, 31.4; MS *m/z* (relative intensity) 168 (6%, M^+), 136 (95), 135 (100), 110 (12), 109 (60), 83 (13), 57 (6);

HRMS *m/z* calcd for $C_{10}H_{13}FO$ (M^+) 168.0950, found 168.0947.

The oily residue was dissolved in dichloromethane and washed with a saturated aqueous solution of KBr. Organic phase was concentrated under an aspirator vacuum to give an oil, which was washed five times with hexane and diethyl ether by decantation to afford [4-(3-methoxypropyl)phenyl](phenyl)(bromo)-λ^3-iodane as an oil. The diaryl(bromo)-λ^3-iodane was dissolved in dichloromethane and washed ten times with a saturated aqueous solution of $NaBF_4$ to give diaryl(tetrafluoroborato)-λ^3-iodane **5b**: a yellow oil; IR (neat) 3091, 3062, 2933, 2868, 1581, 1564, 1469, 1444, 1406, 1282, 1184, 1160-900, 841, 781, 742, 681, 652, 521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.61 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.46 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 3.35 (t, *J* = 6.2 Hz, 2H), 3.32 (s, 3H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.90-1.79 (m, 2H); HRMS (ESI, positive) *m/z* calcd for $C_{16}H_{18}IO$ [$(M\text{-}BF_4)^+$] 353.0402, found 353.0414. The structure of diaryl-λ^3-iodane **5b** was determined by spectroscopic comparison with an authentic sample, prepared from the reaction 4-(3-methoxypropyl)phenylboronic acid with (diacetoxyiodo)benzene according to the literature method.[5]

4-(4-Fluorophenyl)butyl Methyl Ether (13c): a colorless oil; IR (neat) 2933, 2862, 2827, 1601, 1510, 1458, 1387, 1221, 1157, 1120, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.8 Hz, $^4J_{HF}$ = 5.3 Hz, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 3.38 (t, *J* = 6.2 Hz, 2H), 3.32 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.71-1.52 (m, 4H); MS *m/z* (relative intensity) 182 (9%, M^+), 150 (14), 135 (9), 122 (100), 109 (36), 83 (8); HRMS *m/z* calcd for $C_{11}H_{15}FO$ (M^+) 182.1107, found 182.1114.

[4-(Methoxymethyl)phenyl](phenyl)(tetrafluoroborato)-λ^3-iodane (14a): colorless needles (recrystallized from dichloromethane-hexane); mp 116-116.5 °C; IR (KBr) 3087, 2927, 2835, 1562, 1469, 1446, 1410, 1286, 1186, 1170-950, 924, 812, 798, 760, 692, 654, 613, 571, 555, 540, 528 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.10 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.75 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.57 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.52 (s, 2H), 3.39 (s, 3H); HRMS (ESI, positive) *m/z* calcd for $C_{14}H_{14}IO$ [$(M\text{-}BF_4)^+$] 325.0089, found 325.0086.

[4-(2-Methoxyethyl)phenyl](phenyl)(tetrafluoroborato)-λ^3-iodane (14b): colorless needles (recrystallized from dichloromethane-hexane); mp 120-120.2 °C; IR (KBr) 3089, 3059, 2997, 2929, 2848, 1566, 1473, 1446, 1404, 1383, 1282, 1259, 1213, 1200-930, 914, 841, 810, 771, 733, 677, 654, 596, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.0 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.63 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.48 (dd, *J* = 8.3, 7.5 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.32 (s, 3H), 2.91 (t, *J* = 6.4 Hz, 2H); HRMS (ESI, positive) *m/z* calcd for $C_{15}H_{16}IO$ [$(M\text{-}BF_4)^+$] 339.0246, found 339.0235.

[4-(4-Methoxybutyl)phenyl](phenyl)(tetrafluoroborato)-λ^3-iodane (14c): a yellow oil; IR (neat) 3089, 3060, 2929, 2862, 1579, 1564, 1471, 1444, 1402, 1186, 1170-930, 831, 741, 681, 652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.63 (tt, *J* = 7.6, 1.3 Hz, 1H), 7.48 (dd, *J* = 8.6, 7.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 3.37 (t, *J* = 6.1 Hz, 2H), 3.31 (s, 3H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.73-1.53 (m, 4H); HRMS (ESI, positive) *m/z* calcd for $C_{17}H_{20}IO$ [$(M\text{-}BF_4)^+$] 367.0559, found 367.0566.

[2-(Methoxymethyl)phenyl](phenyl)(tetrafluoroborato)-λ^3-iodane (15a): colorless needles (recrystallized from dichloromethane-hexane); mp 140.2-140.8 °C; IR (KBr) 3089, 3001, 2937, 2833,

1564, 1466, 1444, 1385, 1282, 1217, 1188, 1169, 1160-960, 947, 931, 744, 683, 646, 523 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.12 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.87 (tt, *J* = 7.8, 1.3 Hz, 1H), 7.67 (dd, *J* = 8.3, 7.8 Hz, 2H), 7.59 (dt, *J* = 1.1, 7.3 Hz, 1H), 7.50 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.19 (dd, *J* = 8.5, 1.1 Hz, 1H), 4.80 (s, 2H), 3.66 (s, 3H); HRMS (ESI, positive) *m/z* calcd for $C_{14}H_{14}IO$ $[(M\text{-}BF_4)^+]$ 325.0089, found 325.0091.

[2-(2-Methoxyethyl)phenyl](phenyl)(tetrafluoroborato)-λ³-iodane (15b): a yellow oil; IR (neat) 3085, 3059, 2927, 1564, 1471, 1442, 1381, 1284, 1160-940, 823, 742, 681, 644 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.10 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.78 (tt, *J* = 7.2, 1.3 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.66-7.56 (m, 4H), 7.35-7.28 (m, 1H), 3.64 (t, *J* = 5.3 Hz, 2H), 3.34 (s, 3H), 3.22 (t, *J* = 5.3 Hz, 2H); HRMS (ESI, positive) *m/z* calcd for $C_{15}H_{16}IO$ $[(M\text{-}BF_4)^+]$ 339.0246, found 339.0234.

3-(4-Fluorophenyl)propyl Ethyl Ether (18a): a colorless oil; IR (neat) 2976, 2933, 2862, 1601, 1510, 1454, 1377, 1352, 1223, 1157, 1111, 822, 748, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.8 Hz, $^4J_{HF}$ = 5.4 Hz, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 3.46 (q, *J* = 7.4 Hz, 2H), 3.40 (t, *J* = 7.4 Hz, 2H), 2.66 (t, *J* = 7.4 Hz, 2H), 1.93-1.82 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H); MS *m/z* (relative intensity) 182 (2%, M^+), 137 (9), 136 (100), 135 (96), 110 (12), 109 (58), 83 (13), 59 (9); HRMS *m/z* calcd for $C_{11}H_{15}FO$ (M^+) 182.1107, found 182.1110.

3-(4-Fluorophenyl)propyl Propyl Ether (18b): a colorless oil; IR (neat) 2933, 2858, 1601, 1510, 1456, 1375, 1223, 1157, 1119, 1049, 1018, 822, 748, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 9.0 Hz, $^4J_{HF}$ = 5.4 Hz, 2H), 6.96 (t, *J* = 9.0 Hz, 2H), 3.40 (t, *J* = 6.5 Hz, 2H), 3.36 (t, *J* = 6.5 Hz, 2H), 2.67 (t, *J* = 7.8 Hz, 2H), 1.93-1.82 (m, 2H), 1.65-1.54 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); MS *m/z* (relative intensity) 196 (1%, M^+), 137 (10), 136 (100), 135 (77), 110 (11), 109 (65), 83 (10); HRMS *m/z* calcd for $C_{12}H_{17}FO$ (M^+) 196.1264, found 196.1259.

3-(4-Fluorophenyl)-1-methylpropyl Methyl Ether (18d): a colorless oil; IR (neat) 2970, 2927, 2856, 2821, 1601, 1510, 1454, 1373, 1221, 1136, 1088, 827, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.8 Hz, $^4J_{HF}$ = 5.4 Hz, 2H), 6.96 (t, *J* = 8.8 Hz, 2H), 3.36-3.23 (m, 1H), 3.32 (s, 3H), 2.74-2.56 (m, 2H), 1.86-1.75 (m, 1H), 1.73-1.62 (m, 1H), 1.16 (d, *J* = 6.0 Hz, 3H); MS *m/z* (relative intensity) 182 (1%, M^+), 151 (8), 150 (72), 136 (9), 135 (89), 110 (10), 109 (76), 83 (14), 59 (100); HRMS *m/z* calcd for $C_{11}H_{15}FO$ (M^+) 182.1107, found 182.1101.

2,2-Dimethyl-3-(4-fluorophenyl)propyl Methyl Ether (18e): a colorless oil; IR (neat) 2958, 2925, 2870, 1606, 1510, 1479, 1394, 1363, 1223, 1194, 1157, 1111, 1009, 966, 841, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 9.0 Hz, $^4J_{HF}$ = 5.6 Hz, 2H), 6.95 (t, *J* = 9.0 Hz, 2H), 3.34 (s, 3H), 2.95 (s, 2H), 2.54 (s, 2H), 0.87 (s, 6H); MS *m/z* (relative intensity) 196 (8%, M^+), 164 (26), 149 (11), 135 (7), 110 (10), 109 (74), 88 (5), 87 (100), 86 (13), 83 (12), 71 (6), 57 (6), 56 (6), 55 (75); HRMS *m/z* calcd for $C_{12}H_{17}FO$ (M^+) 196.1264, found 196.1265.

3-(4-Fluorophenyl)-2-(methoxymethyl)propyl Methyl Ether (18f): a colorless oil; IR (neat) 2981, 2924, 2875, 2810, 1601, 1510, 1479, 1450, 1390, 1221, 1157, 1111, 968, 850, 818, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 8.8 Hz, $^4J_{HF}$ = 5.5 Hz, 2H), 6.96 (t, *J* = 8.8 Hz, 2H), 3.32 (s, 6H), 3.30 (d, *J* = 5.7 Hz, 4H), 2.66 (d, *J* = 7.2 Hz, 2H), 2.13-2.02 (m, 1H); MS *m/z* (relative intensity) 212 (0.4%, M^+), 180 (32), 148 (17), 147 (12), 139 (42), 136 (14), 135 (100), 133 (14), 123 (6), 122 (65), 115 (9), 110

(12), 109 (77), 83 (17), 71 (62); HRMS *m/z* calcd for $C_{12}H_{17}FO_2$ (M^+) 212.1213, found 212.1219.

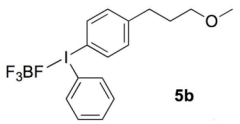
3-(4-Fluorophenyl)-2-(methoxymethyl)-2-methylpropyl Methyl Ether (18g): a colorless oil; IR (neat) 2978, 2925, 2875, 2812, 1604, 1508, 1479, 1458, 1394, 1364, 1223, 1196, 1157, 1109, 968, 843, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, J = 8.8 Hz, $^4J_{HF}$ = 5.7 Hz, 2H), 6.95 (t, J = 8.8 Hz, 2H), 3.34 (s, 6H), 3.08 (s, 4H), 2.59 (s, 2H), 0.82 (s, 3H); MS *m/z* (relative intensity) 226 (0.7%, M^+), 150 (10), 149 (53), 147 (10), 140 (9), 139 (81), 135 (29), 131 (22), 122 (9), 121 (39), 117 (15), 110 (10), 109 (100), 91 (42), 87 (12), 85 (59), 83 (14), 72 (51), 71 (12), 55 (14); HRMS *m/z* calcd for $C_{13}H_{19}FO_2$ (M^+) 226.1369, found 226.1397.

Reaction of *n*-Propylbenzene with Hydroxy-λ³-iodane·18C6 Complex 3 (Scheme 3). To a stirred suspension of hydroxyl-λ³-iodane·18C6 complex **3** (123 mg, 0.22 mmol) in dichloromethane (2.5 mL) was added BF_3-Et_2O (27.4 μL, 0.22 mmol) and then *n*-propylbenzene (8.6 mg, 0.072 mmol) at room temperature under argon and the mixture was heated at 45 ºC for 5 h. The reaction mixture was poured into water and extracted with dichloromethane four times. The combined organic phase was filtered and concentrated under aspirator vacuum to give an oil, which was washed several times with hexane and then with diethyl ether by decantation at room temperature to give a 1.4:1 mixture (35 mg, 81%) of [4-(propyl)phenyl](phenyl)(tetrafluoroborato)-λ³-iodane and 18C6. Recrystallization from dichloromethane-ether gave 2:1 complex **8** as colorless plates: mp 120-121 ºC; IR (KBr) 3054, 2892, 1578, 1565, 1471, 1441, 1401, 1354, 1287, 1252, 1220-900, 837, 738, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.4, 1.1 Hz, 4H), 7.91 (d, J = 8.8 Hz, 4H), 7.65 (tt, J = 7.0, 1.1 Hz, 2H), 7.50 (dd, J = 8.4, 7.0 Hz, 4H), 7.31 (d, J = 8.8 Hz, 4H), 3.67 (s, 24H), 2.64 (t, J = 7.7 Hz, 4H), 1.64 (sext, J = 7.7 Hz, 4H), 0.94 (t, J = 7.7 Hz, 6H). Anal. Calcd for $C_{42}H_{56}B_2F_8I_2O_6$: C, 46.52; H, 5.21. Found: C, 46.23; H, 5.34.

Reaction of 4-Propylphenol with Hydroxy-λ³-iodane·18C6 Complex 3. To a stirred suspension of hydroxyl-λ³-iodane·18C6 complex **3** (19.9 mg, 0.035 mmol) in dichloromethane-d_2 (584 μL) was added a solution of 4-propylphenol (1.6 mg, 0.012 mmol) in dichloromethane-d_2 (16 μL) at room temperature under argon, and the mixture was stirred for 10 min at room temperature. ^1H NMR analysis showed the formation of *p*-benzoquinone in 24% yield.

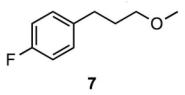
References

1) M. Ochiai, K. Miyamoto, M. Shiro, T. Ozawa and K. Yamaguchi, *J. Am. Chem. Soc*., 2003, **125**, 13006.
2) T. Miyakoshi, M. Nakajima, H. Omichi and S. Saito, *Nippon Kagaku Kaishi,* 1985, **5**, 986.
3) S. W. Wright, D. L. Hageman, A. S. Wright and L. D. McClure, *Tetrahedron Lett*., 1997, **38**, 7345.
4) M. S. Chambers, S. C. Hobbs and L. J. Street, *PCT Int. Appl*., 1997, WO 9717338.
5) M. Ochiai, M. Toyonari, T. Sueda and Y. Kitagawa, *Tetrahedron Lett*., 1996, **37**, 8421.



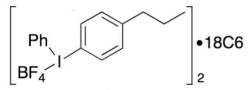
5b

^{1}H NMR, 400 MHz, $CDCl_3$



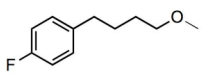
7

^{1}H NMR, 400 MHz, $CDCl_3$



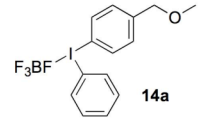
8

^{1}H NMR, 400 MHz, $CDCl_3$



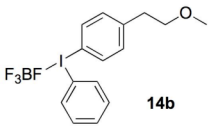
13c

^{1}H NMR, 400 MHz, $CDCl_3$



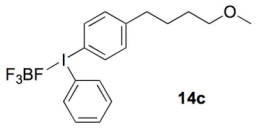
14a

^{1}H NMR, 400 MHz, CD_3CN



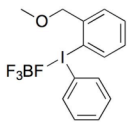
14b

^{1}H NMR, 400 MHz, $CDCl_3$



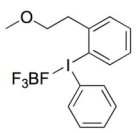
14c

^{1}H NMR, 400 MHz, $CDCl_3$



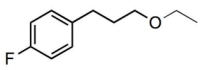
15a

^{1}H NMR, 400 MHz, CD_2Cl_2



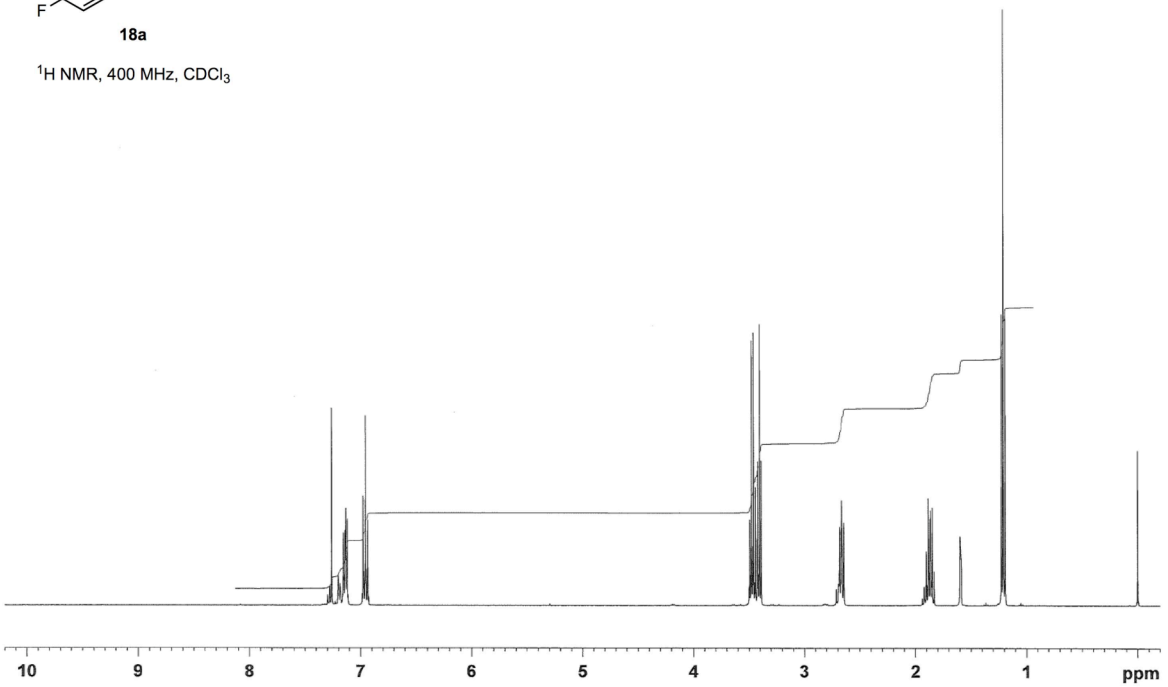
15b

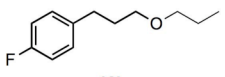
^{1}H NMR, 400 MHz, CD_3CN



18a

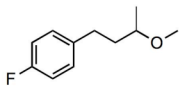
^{1}H NMR, 400 MHz, $CDCl_3$





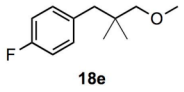
18b

^{1}H NMR, 400 MHz, $CDCl_3$



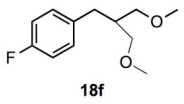
18d

^{1}H NMR, 400 MHz, $CDCl_3$



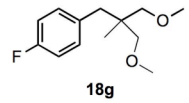
18e

^{1}H NMR, 400 MHz, $CDCl_3$



18f

^{1}H NMR, 400 MHz, $CDCl_3$



18g

^{1}H NMR, 400 MHz, $CDCl_3$