Synthesis of tertiary alkyl fluorides and chlorides by site-selective nucleophilic ring-opening reaction of α-aryl azetidinium salts

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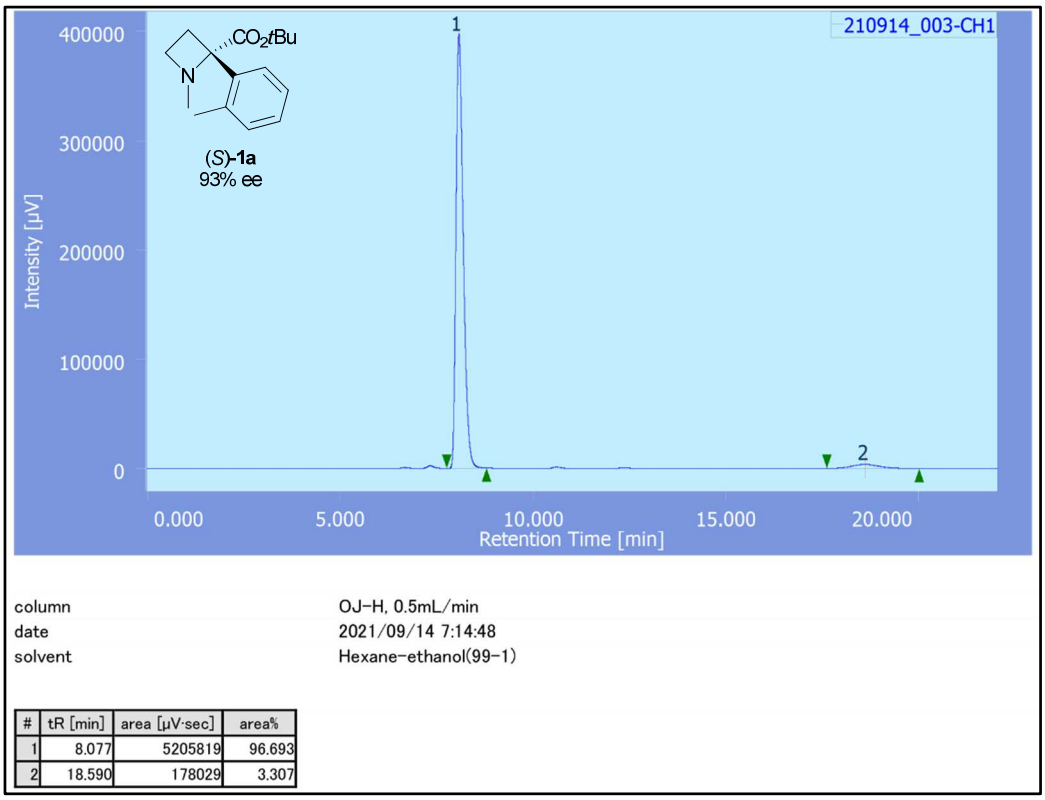
Electronic Supplementary Information

Contents:

1. HPLC chromatogram for determination of enantiomeric excess (ee)

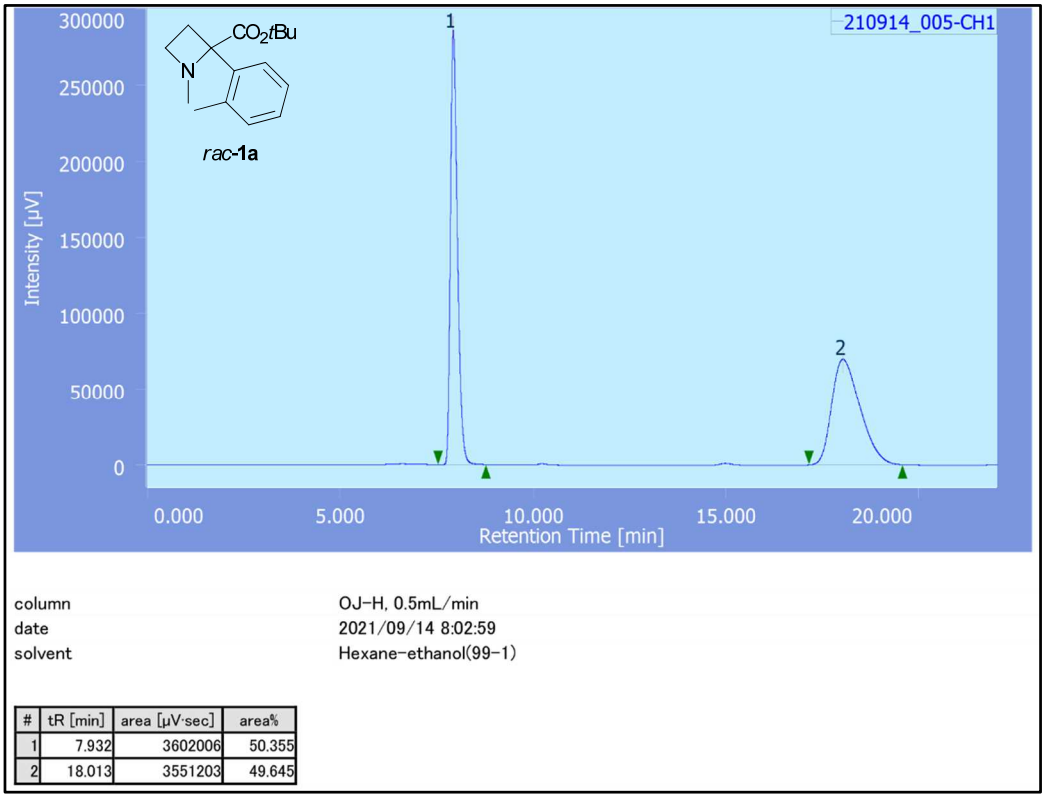
The ee were determined by HPLC analysis using chiral column in comparison with the racemic compounds.

(*S*)-**1a**: 93% ee, Daicel Chiralcel OJ-H column (25 cm), *n*-hexane/EtOH = 99/1 as the eluent, flow rate = 0.50 mL/min, t_R = 8.1 min for (*S*)-**1a** (96.7%) and 18.6 min for (*R*)-**1a** (3.3%).



column OJ-H, 0.5mL/min
date 2021/09/14 7:14:48
solvent Hexane-ethanol(99-1)

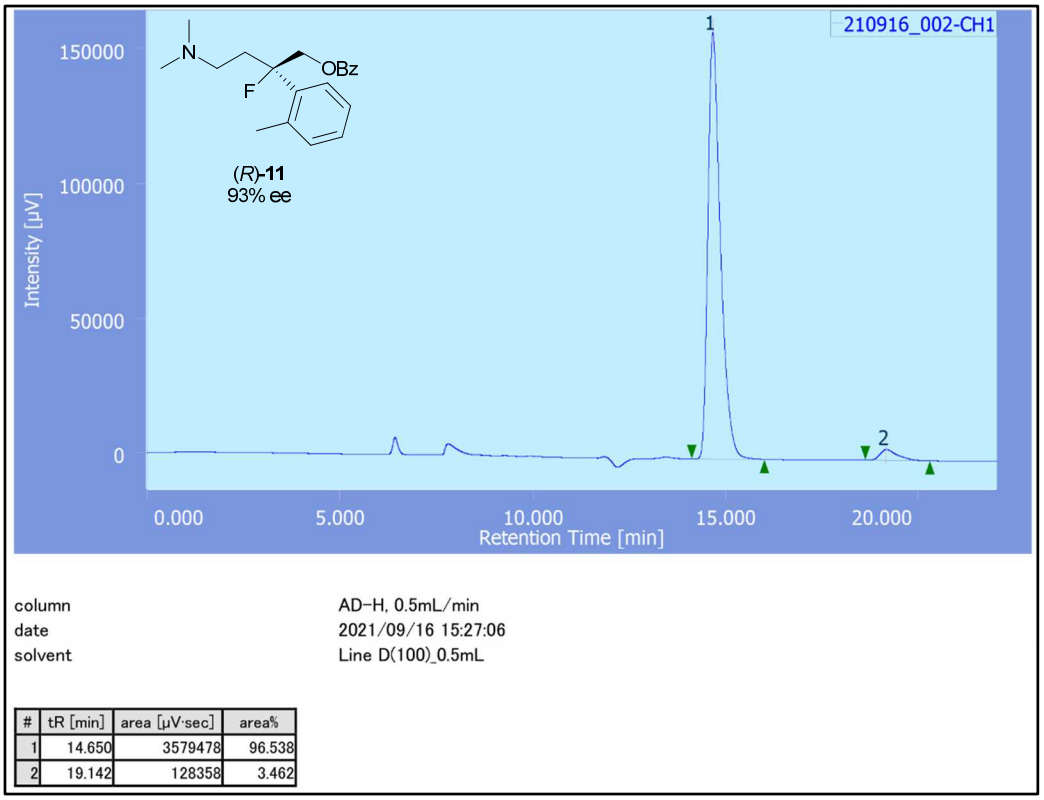
#	tR [min]	area [μV·sec]	area%
1	8.077	5205819	96.693
2	18.590	178029	3.307



column OJ-H, 0.5mL/min
date 2021/09/14 8:02:59
solvent Hexane-ethanol(99-1)

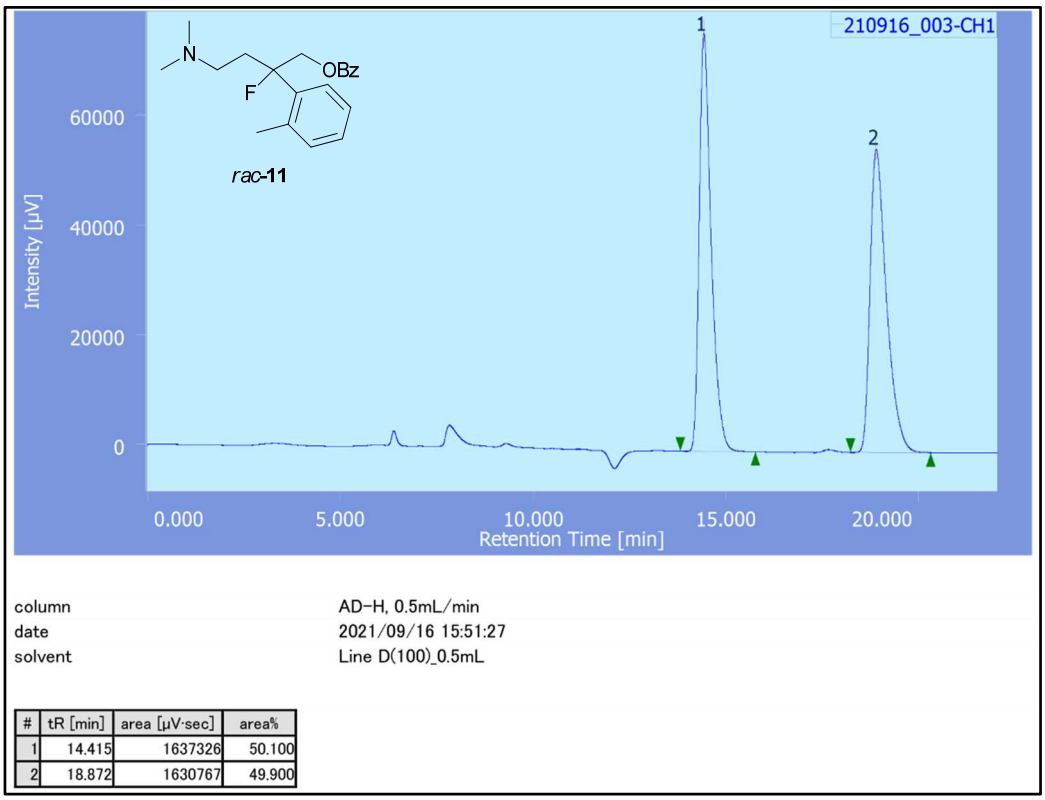
#	tR [min]	area [μV·sec]	area%
1	7.932	3602006	50.355
2	18.013	3551203	49.645

(*R*)-**11**: 93% ee, Daicel Chiralpak AD-H column (25 cm), *n*-hexane/EtOH/Et_2NH = 100/2/0.1 as the eluent, flow rate = 0.50 mL/min, t_R = 14.7 min for (*R*)-**11** (96.5%) and 19.1 min for (*S*)-**11** (3.5%).



column	AD-H, 0.5mL/min
date	2021/09/16 15:27:06
solvent	Line D(100)_0.5mL

#	tR [min]	area [μV·sec]	area%
1	14.650	3579478	96.538
2	19.142	128358	3.462

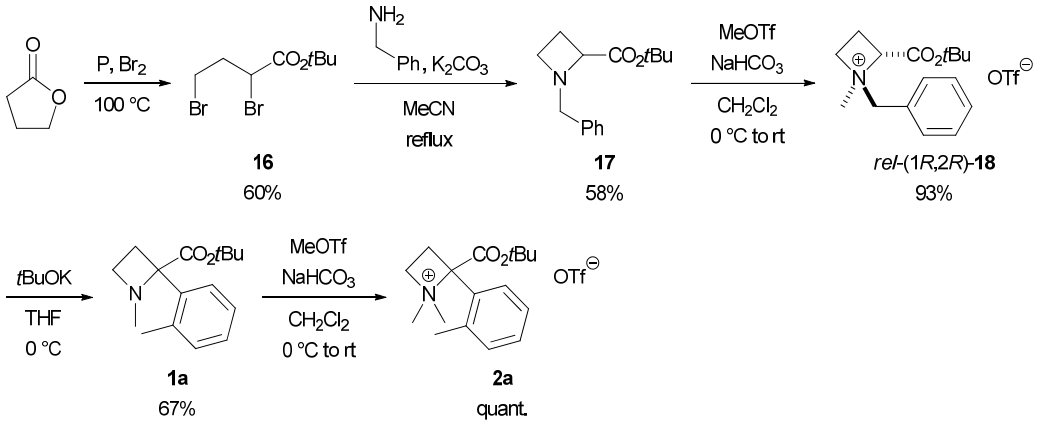


column	AD-H, 0.5mL/min
date	2021/09/16 15:51:27
solvent	Line D(100)_0.5mL

#	tR [min]	area [μV·sec]	area%
1	14.415	1637326	50.100
2	18.872	1630767	49.900

2. Preparation of substrates

2-1. Representative procedure for preparation of 2-(*tert*-butoxycarbonyl)-1,1-dimethyl-2-(*o*-tolyl)azetidin-1-ium trifluoromethanesulfonate (**2a**)[1]

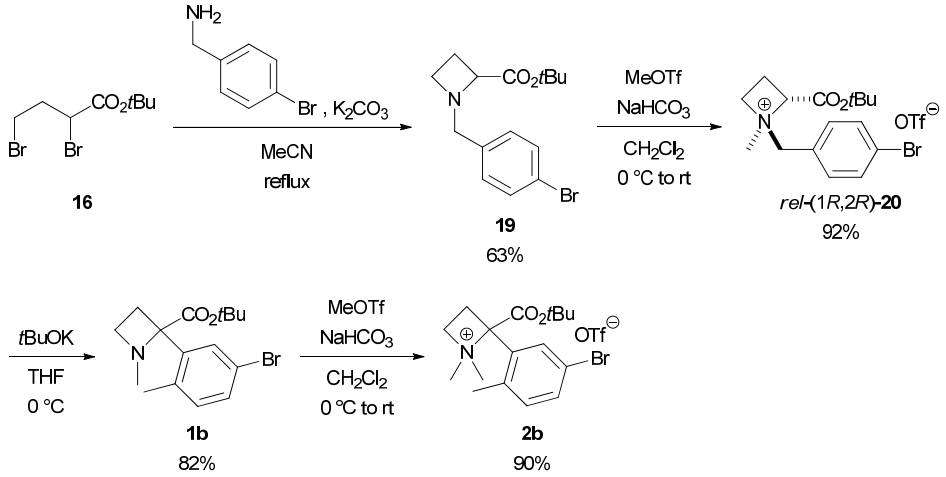


(Step 1) γ-Butyrolactone (6.0 mL, 78 mmol) and red-phosphorus (50 mg, 1.6 mmol) in a two-neck round-bottom flask was stirred at 100 °C under an Ar atmosphere. Br_2 (4.3 mL, 84 mmol) was added dropwise for 1 h to the mixture with stirring. The resulting mixture was cooled to room temperature and excess Br_2 was removed by flow of air. The residue was dissolved in CH_2Cl_2 (26 mL) and treated with *conc*. H_2SO_4 (0.4 mL). Isobutene gas (excess) was added to the solution in the reaction flask which equipped with a dry ice condenser. The solution was stirred for 2 days at room temperature. The resulting mixture was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaBr, dried over Na_2SO_4, and concentrated by evaporation. Purification of the residue by chromatography on silica gel (*n*-hexane/EtOAc = 30/1 to 20/1 as the eluent) gave *tert*-butyl 2,4-dibromobutanoate (**16**) (14.07 g, 60% yield) as a colourless oil. The product included impurities observed by ^1H NMR analysis. (Step 2) A mixture of benzylamine (276 μL, 2.53 mmol), **16** (764 mg, 2.53 mmol), and K_2CO_3 (1.05 g, 7.60 mmol) in MeCN (13 mL) was refluxed for 8 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated by evaporation and the residue was purified by chromatography on silica gel (*n*-hexane/EtOAc = 5/1 to 3/1 as the eluent) to obtain *tert*-butyl 1-benzylazetidine-2-carboxylate (**17**)[1] (360 mg, 58% yield) as a pale yellow oil. (Step 3) A mixture of **17** (360 mg, 1.46 mmol) and $NaHCO_3$ (0.37 g, 4.4 mmol) in CH_2Cl_2 (7.3 mL) was treated with methyl trifluoromethanesulfonate (0.25 mL, 2.2 mmol) at 0 °C and stirred for 1 h at room temperature. The mixture was concentrated by evaporation to ca. 1/2 volume and purified by chromatography on silica gel (CH_2Cl_2/MeOH = 15/1 to 6/1 as the eluent) to obtain *rel*-(1*R*,2*R*)-1-benzyl-2-(*tert*-butoxycarbonyl)-1-methylazetidin-1-ium trifluoromethanesulfonate [*rel*-(1*R*,2*R*)-**18**][1] (556 mg, 93% yield) as colourless crystals. (Step 4) A 1.0 M *t*BuOK THF solution (1.6 mL, 1.6 mmol) was added to a solution of *rel*-(1*R*,2*R*)-**18** (556 mg, 1.35 mmol) in THF (12 mL) at 0 °C under an Ar atmosphere. After stirring for 3 h at the same temperature, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ followed by brine. The solution was dried over Na_2SO_4 and concentrated by evaporation. Purification of the residue by chromatography on silica gel (*n*-

[1] E. Tayama, K. Watanabe and Y. Matano, *Eur. J. Org. Chem.*, 2016, 3631.

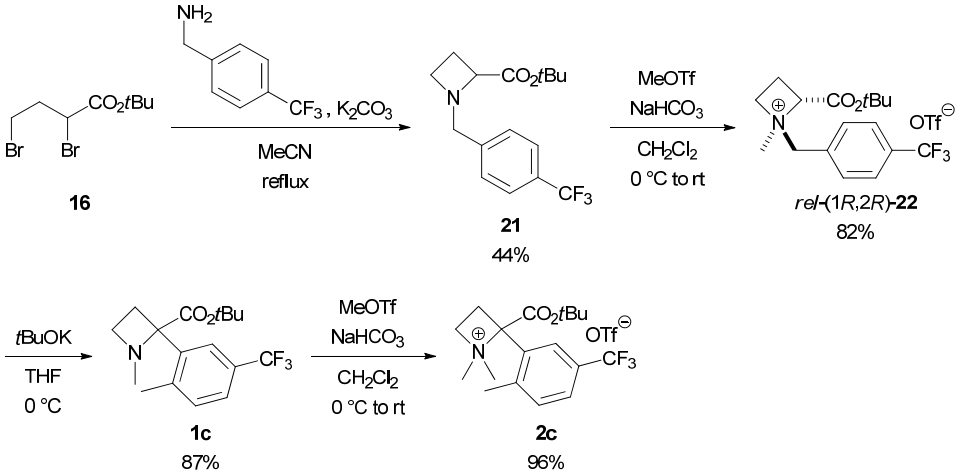
hexane/EtOAc = 10/1 to 6/1 as the eluent) gave *tert*-butyl 1-methyl-2-(*o*-tolyl)azetidine-2-carboxylate (**1a**)[1] (236 mg, 67% yield) as a colourless oil. (Step 5) A mixture of **1a** (678 mg, 2.59 mmol) and $NaHCO_3$ (0.66 g, 7.9 mmol) in CH_2Cl_2 (13 mL) was treated with methyl trifluoromethanesulfonate (0.59 mL, 5.2 mmol) at 0 °C and stirred for 3 h at room temperature. The mixture was concentrated by evaporation to ca. 1/2 volume and purified by chromatography on silica gel (CH_2Cl_2/MeOH = 15/1 to 7/1 as the eluent) to obtain **2a** (1.11 g, quant.) as colourless crystals, mp 119-121 °C. IR (ATR) ν_{max}/cm^{-1} 3076, 3041, 2979, 2940, 1728, 1459, 1395, 1371, 1302, 1254, 1225, 1145, 1105, 1078, 1030, 995, 969, 946, 856, 832, 770, 753, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.33 (3H, m, ArH), 7.29-7.23 (1H, m, ArH), 4.52 (1H, ddd, J = 10.6, 10.4, 9.4 Hz, 4-H), 4.27 (1H, ddd, J = 9.6, 9.4, 2.4 Hz, 4-H), 3.90 (1H, ddd, J = 12.4, 10.6, 9.6 Hz, 3-H), 3.63 (3H, s, NCH_3), 3.02-2.84 (1H, br m, 3-H), 2.97 (3H, s, NCH_3), 2.33 (3H, s, $ArCH_3$), 1.39 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 135.9, 132.5, 130.6, 129.7, 128.5, 126.9, 120.6 (q, J = 322 Hz), 86.8, 86.3, 62.7, 50.9, 50.7, 27.4, 27.1, 20.7; HRMS (ESI): calcd. for $C_{17}H_{26}NO_2$ [M – OTf]$^+$ 276.1958, found 276.1955.

2-2. 2-(5-Bromo-2-methylphenyl)-2-(*tert*-butoxycarbonyl)-1,1-dimethylazetidin-1-ium trifluoromethanesulfonate (**2b**)



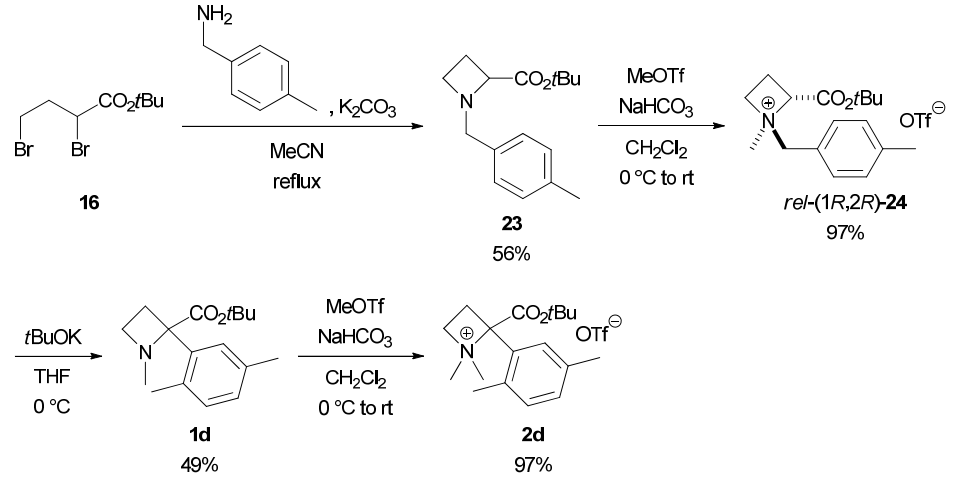
Prepared from **1b**[1] by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. Colourless gum; IR (ATR) ν_{max}/cm^{-1} 2980, 2938, 1731, 1461, 1397, 1372, 1250, 1224, 1141, 1095, 1075, 1029, 992, 942, 857, 831, 808, 791, 756, 724, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, J = 8.2, 2.0 Hz, ArH), 7.48 (1H, br s, ArH), 7.18 (1H, d, J = 8.2 Hz, ArH), 4.56 (1H, ddd, J = 10.6, 10.2, 9.6 Hz, 4-H), 4.31 (1H, ddd, J = 10.2, 9.3, 3.2 Hz, 4-H), 3.86 (1H, ddd, J = 12.9, 10.6, 9.3 Hz, 3-H), 3.64 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 2.95-2.80 (1H, br m, 3-H), 2.30 (3H, s, $ArCH_3$), 1.49 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.9, 135.4, 134.2, 133.7, 131.8, 131.2, 120.6 (q, J = 322 Hz), 120.3, 86.9, 85.8, 62.8, 51.1, 50.7, 27.4, 27.0, 20.4; HRMS (ESI): calcd. for $C_{17}H_{25}BrNO_2$ [M – OTf]$^+$ 354.1063; found 354.1058.

2-3. 2-(*tert*-Butoxycarbonyl)-1,1-dimethyl-2-(2-methyl-5-(trifluoromethyl)phenyl)azetidin-1-ium trifluoromethanesulfonate (**2c**)



Prepared from **1c**[1] by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. Colourless gum; IR (ATR) ν_{max}/cm^{-1} 3041, 2982, 2939, 1733, 1624, 1462, 1415, 1398, 1373, 1334, 1253, 1225, 1123, 1086, 1029, 997, 974, 942, 896, 863, 836, 795, 768, 756, 747, 731, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 8.0 Hz, ArH), 7.59 (1H, br s, ArH), 7.47 (1H, d, J = 8.0 Hz, ArH), 4.60 (1H, ddd, J = 10.0, 10.0, 10.0 Hz, 4-H), 4.27 (1H, ddd, J = 10.0, 10.0, 2.6 Hz, 4-H), 3.97 (1H, ddd, J = 12.0, 10.0, 10.0 Hz, 3-H), 3.65 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 2.95 (1H, br, 3-H), 2.43 (3H, s, $ArCH_3$), 1.40 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6, 140.9 (q, J = 1 Hz), 133.3, 130.9, 129.0 (q, J = 33 Hz), 127.1 (q, J = 4 Hz), 125.2, 123.4 (q, J = 273 Hz), 120.5 (q, J = 322 Hz), 87.0, 85.9, 62.8, 51.0, 50.7, 27.2, 26.8, 20.7; HRMS (ESI): calcd. for $C_{18}H_{25}F_3NO_2$ [M – OTf]$^+$ 344.1832; found 344.1819.

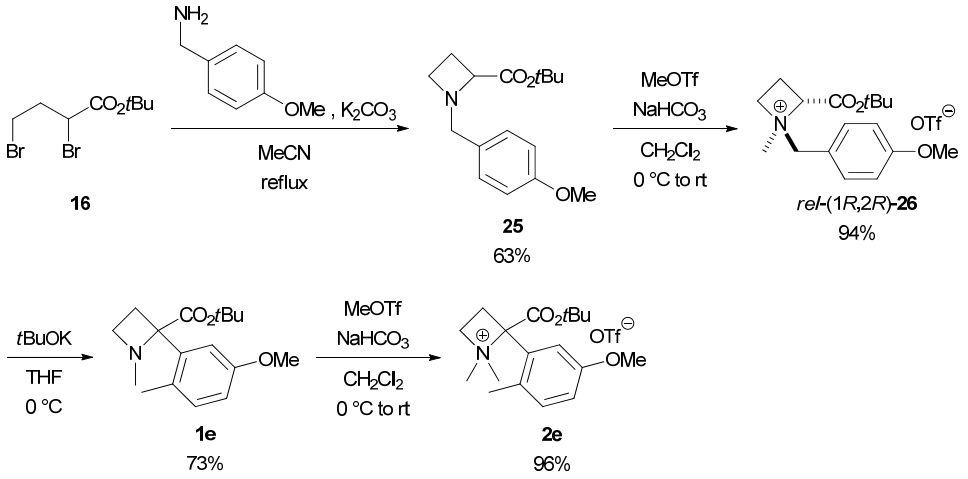
2-4. 2-(*tert*-Butoxycarbonyl)-2-(2,5-dimethylphenyl)-1,1-dimethylazetidin-1-ium trifluoromethanesulfonate (**2d**)



Prepared from **1d**[1] by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. Colourless crystals, mp 105-107 °C; IR (ATR) ν_{max}/cm^{-1} 2976, 2936, 1731, 1505, 1477, 1458, 1396, 1371, 1296, 1254, 1224, 1146, 1105, 1078, 1029, 982, 969, 958, 872, 847, 827, 794, 765, 755, 739, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (1H, br s, ArH), 7.19 (1H, d,

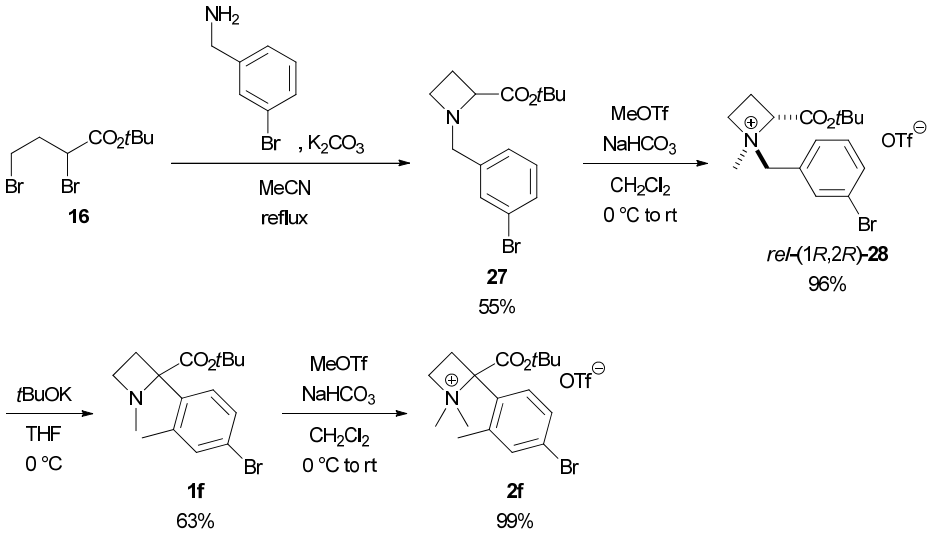
J = 8.0 Hz, ArH), 7.14 (1H, d, J = 8.0 Hz, ArH), 4.52 (1H, ddd, J = 10.0, 10.0, 9.4 Hz, 4-H), 4.28 (1H, ddd, J = 10.2, 9.4, 3.0 Hz, 4-H), 3.90 (1H, ddd, J = 12.0, 10.2, 10.0 Hz, 3-H), 3.63 (3H, s, NCH_3), 3.02-2.80 (1H, br m, 3-H), 2.95 (3H, s, NCH_3), 2.39 (3H, s, $ArCH_3$), 2.28 (3H, s, $ArCH_3$), 1.40 (9H, s, *t*Bu); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.6, 136.7, 132.7, 132.4, 131.4, 129.3, 129.1, 120.7 (q, J = 322 Hz), 86.8, 86.2, 62.5, 50.9, 50.6, 27.4, 27.0, 20.8, 20.2; HRMS (ESI): calcd. for $C_{18}H_{28}NO_2$ $[M - OTf]^+$ 290.2115; found 290.2110.

2-5. 2-(*tert*-Butoxycarbonyl)-2-(5-methoxy-2-methylphenyl)-1,1-dimethylazetidin-1-ium trifluoromethanesulfonate (**2e**)



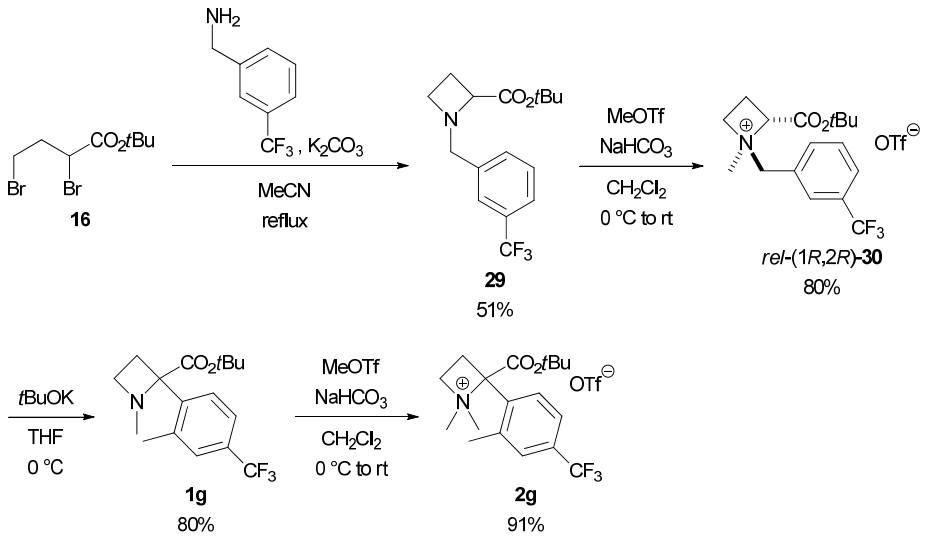
Prepared from **1e**[1] by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. Colourless crystals, mp 81-83 °C; IR (ATR) ν_{max}/cm^{-1} 3033, 2978, 2939, 1731, 1614, 1508, 1476, 1456, 1444, 1412, 1396, 1372, 1317, 1296, 1257, 1223, 1145, 1101, 1075, 1028, 971, 943, 844, 836, 820, 794, 769, 755, 739, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, d, J = 8.4 Hz, ArH), 6.96-6.88 (2H, m, ArH), 4.52 (1H, ddd, J = 10.2, 10.2, 9.4 Hz, 4-H), 4.26 (1H, ddd, J = 10.2, 9.4, 3.2 Hz, 4-H), 3.91 (1H, ddd, J = 12.0, 10.2, 10.2 Hz, 3-H), 3.85 (3H, s, OCH_3), 3.63 (3H, s, NCH_3), 2.96 (3H, s, NCH_3), 2.91-2.76 (1H, br m, 3-H), 2.25 (3H, s, $ArCH_3$), 1.41 (9H, s, *t*Bu); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 158.2, 133.6, 130.5, 127.5, 120.6 (q, J = 322 Hz), 116.0, 114.4, 86.4, 86.3, 62.4, 55.5, 50.9, 50.6, 27.4, 27.0, 19.8; HRMS (ESI): calcd. for $C_{18}H_{28}NO_3$ $[M - OTf]^+$ 306.2064; found 306.2060.

2-6. 2-(4-Bromo-2-methylphenyl)-2-(*tert*-butoxycarbonyl)-1,1-dimethylazetidin-1-ium trifluoromethanesulfonate (**2f**)



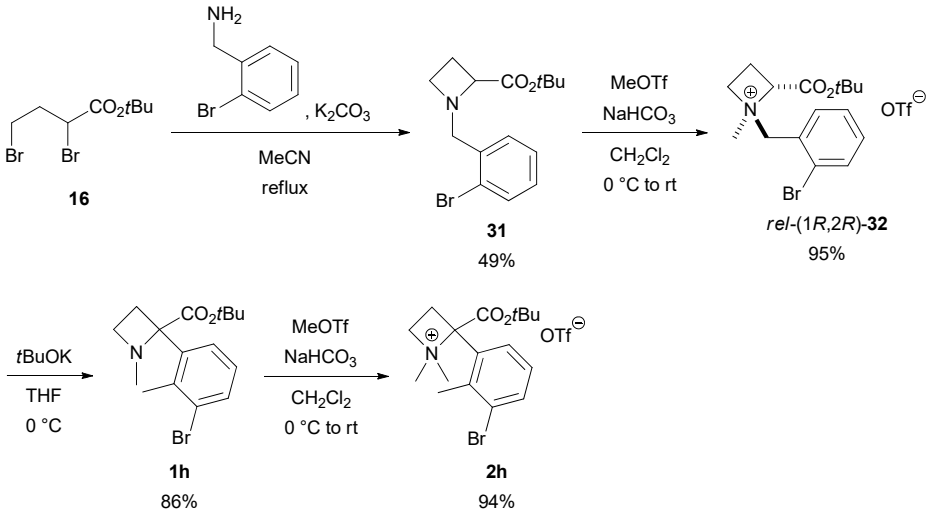
Prepared from *tert*-butyl 2-(4-bromo-2-methylphenyl)-1-methylazetidine-2-carboxylate (**1f**) by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. **1f**: colourless crystals, mp 133-135 °C; IR (ATR) ν_{max}/cm^{-1} 2972, 2931, 2854, 2829, 2780, 1712, 1591, 1564, 1474, 1442, 1392, 1367, 1254, 1237, 1207, 1159, 1123, 1085, 1053, 973, 955, 942, 910, 869, 840, 810, 768, 749, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, J = 8.0 Hz, ArH), 7.32 (1H, dd, J = 8.0, 1.8 Hz, ArH), 7.22 (1H, d, J = 1.8 Hz, ArH), 3.47 (1H, ddd, J = 8.6, 6.1, 2.5 Hz, 4-H), 3.32 (1H, ddd, J = 8.6, 8.2, 6.1 Hz, 4-H), 2.94 (1H, ddd, J = 10.5, 8.2, 2.5 Hz, 3-H), 2.46 (3H, s, NCH_3), 2.10 (1H, ddd, J = 10.5, 8.6, 8.6 Hz, 3-H), 2.05 (3H, s, $ArCH_3$), 1.43 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 141.8, 135.7, 132.8, 128.5, 127.0, 120.2, 81.9, 75.3, 52.0, 39.7, 28.9, 28.1, 18.8; HRMS (ESI): calcd. for $C_{16}H_{23}BrNO_2$ $[M + H]^+$ 340.0907, found 340.0902. **2f**: colourless gum; IR (ATR) ν_{max}/cm^{-1} 3034, 2980, 2937, 1731, 1590, 1561, 1466, 1397, 1372, 1250, 1224, 1142, 1098, 1079, 1028, 986, 941, 910, 857, 846, 825, 791, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, J = 8.6, 1.8 Hz, ArH), 7.42 (1H, d, J = 1.8 Hz, ArH), 7.35 (1H, d, J = 8.6 Hz, ArH), 4.50 (1H, ddd, J = 10.0, 10.0, 9.6 Hz, 4-H), 4.24 (1H, ddd, J = 9.6, 9.6, 2.8 Hz, 4-H), 3.99-3.84 (1H, br m, 3-H), 3.60 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 2.94-2.78 (1H, br m, 3-H), 2.31 (3H, s, $ArCH_3$), 1.41 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.7, 138.1, 134.9, 130.3, 129.8, 128.9, 124.7, 120.4 (q, J = 322 Hz), 86.6, 86.2, 62.6, 50.8, 50.5, 27.2, 26.8, 20.2; HRMS (ESI): calcd. for $C_{17}H_{25}BrNO_2$ $[M - OTf]^+$ 354.1063; found 354.1058.

2-7. 2-(*tert*-Butoxycarbonyl)-1,1-dimethyl-2-(2-methyl-4-(trifluoromethyl)phenyl)azetidin-1-ium trifluoromethanesulfonate (**2g**)



Prepared from *tert*-butyl 1-methyl-2-(2-methyl-4-(trifluoromethyl)phenyl)azetidine-2-carboxylate (**1g**) by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. **1g**: colourless crystals, mp 79-81 °C; IR (ATR) ν_{max}/cm^{-1} 3014, 2979, 2957, 2930, 2860, 2843, 2791, 1716, 1616, 1474, 1447, 1411, 1395, 1369, 1326, 1254, 1208, 1183, 1156, 1118, 1083, 998, 972, 956, 912, 894, 877, 844, 813, 771, 757, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 8.4 Hz, ArH), 7.46 (1H, d, J = 8.4 Hz, ArH), 7.32 (1H, s, ArH), 3.48 (1H, ddd, J = 8.6, 6.0, 2.6 Hz, 4-H), 3.36 (1H, ddd, J = 8.8, 8.2, 6.0 Hz, 4-H), 2.98 (1H, ddd, J = 10.5, 8.2, 2.6 Hz, 3-H), 2.49 (3H, s, NCH_3), 2.13 (3H, s, $ArCH_3$), 2.12 (1H, ddd, J = 10.5, 8.8, 8.6 Hz, 3-H), 1.43 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 146.5, 134.2, 128.7 (q, J = 32 Hz), 126.8 (q, J = 4 Hz), 125.7, 124.4 (q, J = 273 Hz), 122.4 (q, J = 4 Hz), 82.1, 75.5, 52.0, 39.6, 28.8, 28.0, 19.0; HRMS (ESI): calcd. for $C_{17}H_{23}F_3NO_2$ $[M + H]^+$ 330.1675, found 330.1666. **2g**: colourless gum; IR (ATR) ν_{max}/cm^{-1} 3048, 2982, 2939, 1733, 1469, 1410, 1373, 1335, 1252, 1225, 1123, 1092, 1029, 941, 914, 880, 829, 795, 768, 756, 741, 715; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.60 (2H, m, ArH), 7.52 (1H, s, ArH), 4.55 (1H, ddd, J = 10.0, 10.0, 9.5 Hz, 4-H), 4.23 (1H, ddd, J = 10.0, 9.5, 2.6 Hz, 4-H), 4.04-3.88 (1H, br m, 3-H), 3.62 (3H, s, NCH_3), 3.10-2.90 (1H, br m, 3-H), 3.02 (3H, s, NCH_3), 2.40 (3H, s, $ArCH_3$), 1.41 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.5, 137.2, 133.7, 132.1 (q, J = 33 Hz), 129.5, 128.9 (q, J = 4 Hz), 123.5 (q, J = 4 Hz), 123.4 (q, J = 271 Hz), 120.5 (q, J = 318 Hz), 87.0, 86.2, 63.1, 51.1, 50.8, 27.2, 27.1, 20.5; HRMS (ESI): calcd. for $C_{18}H_{25}F_3NO_2$ $[M - OTf]^+$ 344.1832; found 344.1817.

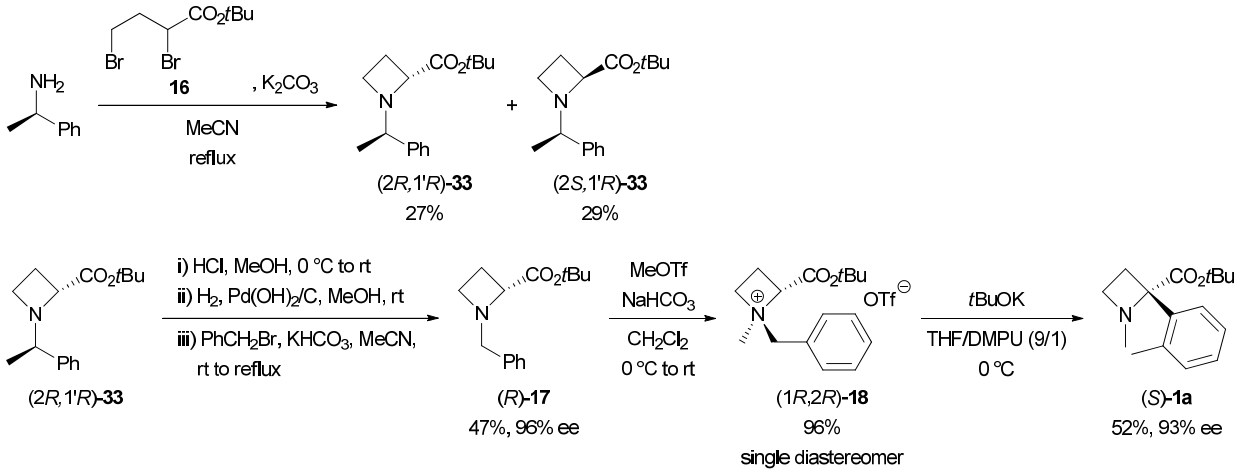
2-8. 2-(3-Bromo-2-methylphenyl)-2-(*tert*-butoxycarbonyl)-1,1-dimethylazetidin-1-ium trifluoromethanesulfonate (**2h**)



Prepared from *tert*-butyl 2-(3-bromo-2-methylphenyl)-1-methylazetidine-2-carboxylate (**1h**) by the same procedures with the preparation of **2a** shown in the representative procedure (2-1). The yields were shown in the above scheme. **1h**: yellow crystals, mp 42-44 °C; IR (ATR) ν_{max}/cm^{-1} 3002, 2971, 2933, 2860, 2837, 2788, 1713, 1593, 1560, 1458, 1433, 1393, 1366, 1279, 1253, 1210, 1195, 1159, 1149, 1126, 1088, 1055, 995, 971, 944, 909, 845, 822, 789, 771, 747, 717, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, dd, J = 8.0, 1.2 Hz, ArH), 7.43 (1H, dd, J = 8.0, 1.2 Hz, ArH), 7.06 (1H, dd, J = 8.0, 8.0 Hz, ArH), 3.46 (1H, ddd, J = 8.5, 6.0, 2.6 Hz, 4-H), 3.33 (1H, ddd, J = 8.8, 8.2, 6.0 Hz, 4-H), 2.96 (1H, ddd, J = 10.7, 8.2, 2.6 Hz, 3-H), 2.47 (3H, s, NCH_3), 2.14 (1H, ddd, J = 10.7, 8.8, 8.5 Hz, 3-H), 2.12 (3H, s, $ArCH_3$), 1.43 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.2, 144.8, 133.0, 130.8, 126.7, 125.8, 124.6, 81.9, 76.0, 51.7, 39.6, 29.3, 28.1, 19.1; HRMS (ESI): calcd. for $C_{16}H_{23}BrNO_2$ $[M + H]^+$ 340.0907, found 340.0902. **2h**: colourless gum; IR (ATR) ν_{max}/cm^{-1} 2980, 2936, 1731, 1635, 1562, 1467, 1436, 1397, 1372, 1251, 1224, 1141, 1073, 1029, 1003, 984, 942, 854, 830, 781, 757, 735, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 7.8 Hz, ArH), 7.51 (1H, d, J = 7.8 Hz, ArH), 7.28 (1H, dd, J = 7.8, 7.8 Hz, ArH), 4.57 (1H, ddd, J = 10.0, 9.7, 9.7 Hz, 4-H), 4.24 (1H, ddd, J = 9.7, 9.7, 2.8 Hz, 4-H), 3.96 (1H, ddd, J = 10.4, 10.0, 9.7 Hz, 3-H), 3.64 (3H, s, NCH_3), 3.03-2.77 (1H, br, 3-H), 2.94 (3H, s, NCH_3), 2.34 (3H, s, $ArCH_3$), 1.41 (9H, s, *t*Bu); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3, 135.5, 135.0, 131.7, 128.6, 128.1, 127.6, 120.6 (q, J = 322 Hz), 86.8, 86.5, 62.4, 51.1, 50.2, 27.5, 27.3, 21.5; HRMS (ESI): calcd. for $C_{17}H_{25}BrNO_2$ $[M - OTf]^+$ 354.1063; found 354.1059.

2-9. (*S*)-*tert*-Butyl 1-methyl-2-(*o*-tolyl)azetidine-2-carboxylate [(*S*)-**1a**][1]

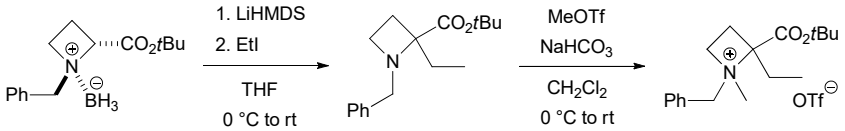
(*S*)-**1a** was prepared according to the slightly modified procedures reported by our group.[1]



(Step 1) A mixture of **16** (3.02 g, 10.0 mmol), (*R*)-1-phenylethylamine (1.27 mL, 10.0 mmol), and K_2CO_3 (4.15 g, 30.0 mmol) in MeCN (50 mL) was refluxed for 7 h. The resulting mixture was cooled to room temperature followed by filtered. The filtrate was concentrated by evaporation and the residue was purified by chromatography on silica gel [*n*-hexane/EtOAc = 15/1 to 5/1 as the eluent, R_f: (2*R*,1′*R*) > (2*S*,1′*R*)] to obtain (2*R*,1′*R*)-*tert*-butyl 1-(1′-phenylethyl)azetidine-2-carboxylate (2*R*,1′*R*)-**33** (718 mg, 27% yield) as a pale yellow oil and (2*S*,1′*R*)-*tert*-butyl 1-(1′-phenylethyl)azetidine-2-carboxylate (2*S*,1′*R*)-**33** (768 mg, 29% yield) as a pale yellow oil. (2*R*,1′*R*)-**33**: $[\alpha]^{24}_{589}$ +108.6 (*c* 1.0 in EtOH); (2*S*,1′*R*)-**33**: $[\alpha]^{24}_{589}$ –58.7 (*c* 1.0 in EtOH). (Step 2) A solution of (2*R*,1′*R*)-**33** (718 mg, 2.75 mmol) in MeOH (14 mL) was treated with a 4 M HCl cyclopentyl methyl ether (CPME) solution (0.83 mL, 3.3 mmol) at 0 °C. After stirring for 30 min at room temperature, the solution was concentrated by evaporation. A mixture of the residue and $Pd(OH)_2/C$ (Pd 20%, wetted with ca. 50% H_2O) (0.20 g) in MeOH (14 mL) was stirred for 3 days at room temperature under a H_2 atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated by evaporation. A mixture of the residue, benzyl bromide (327 μL, 2.75 mmol), and $KHCO_3$ (1.38 g, 13.8 mmol) in MeCN (14 mL) was stirred for 1 h at room temperature and refluxed for 0.5 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated by evaporation and the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 7/1 to 5/1 as the eluent) to obtain (*R*)-*tert*-butyl 1-benzylazetidine-2-carboxylate (*R*)-**17** (323 mg, 47% yield) as a colourless oil. 96% ee [determined by HPLC analysis: Daicel Chiralcel OJ-H column (25 cm), *n*-hexane/2-PrOH = 99/1 as the eluent, flow rate = 0.50 mL/min, t_R = 11.8 min for (*R*)-**17** (97.9%) and 14.4 min for (*S*)-**17** (2.1%)]. $[\alpha]^{24}_{589}$ +86.2 (*c* 1.0 in EtOH). (Step 3) A mixture of (*R*)-**17** (323 mg, 1.31 mmol, 96% ee) and $NaHCO_3$ (0.33 g, 3.9 mmol) in CH_2Cl_2 (6.6 mL) was treated with methyl trifluoromethanesulfonate (0.22 μL, 1.96 mmol) at 0 °C and stirred for 1 h at room temperature. The resulting mixture was concentrated by evaporation to ca. 1/2 volume and purified by chromatography on silica gel (CH_2Cl_2/MeOH = 15/1 to 6/1 as the eluent) to obtain (1*R*,2*R*)-1-benzyl-2-(*tert*-butoxycarbonyl)-1-methylazetidin-1-ium trifluoromethanesulfonate (1*R*,2*R*)-**18** (516 mg, 96% yield) as a colourless gum. $[\alpha]^{24}_{589}$ +28.6 (*c* 1.0 in EtOH). (Step 4) A solution of (1*R*,2*R*)-**18** (516 mg, 1.25 mmol) in

THF (10 mL) and DMPU[2] (1.3 mL) was treated with a 1 M *t*BuOK THF solution (1.5 mL, 1.5 mmol) at 0 °C under an Ar atmosphere. After stirring for 3 h at the same temperature, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with *n*-hexane. The combined extracts were washed with saturated aqueous $NaHCO_3$ followed by brine. The solution was dried over Na_2SO_4 and concentrated by evaporation. Purification by chromatography on silica gel (*n*-hexane/EtOAc = 10/0 to 10/1 as the eluent) gave (*S*)-**1a** (171 mg, 52% yield) as a colourless oil. 93% ee [determined by HPLC analysis: Daicel Chiralcel OJ-H column (25 cm), *n*-hexane/EtOH = 99/1 as the eluent, flow rate: 0.50 mL/min, *t*R = 8.1 min for (*S*)-**1a** (96.7 %) and 18.6 min for (*R*)-**1a** (3.3 %)]. $[a]^{23}_{589}$ –165.2 (*c* 1.0 in EtOH).

2-10. 1-Benzyl-2-(*tert*-butoxycarbonyl)-2-ethyl-1-methylazetidin-1-ium trifluoromethanesulfonate (**12**)



rel-(1*R*,2*R*)-**34** → **35** 48% → **12** quant., almost single diastereomer

(Step 1) A solution of *rel*-((1*R*,2*R*)-1-benzyl-2-(*tert*-butoxycarbonyl)azetidin-1-ium-1-yl)trihydroborate[3] [*rel*-(1*R*,2*R*)-**34**] (346 mg, 1.32 mmol) in THF (7.5 mL) was treated with a 1.0 M LiHMDS solution in THF (3.2 mL, 3.2 mmol) at 0 °C under an Ar atmosphere. The solution was stirred for 30 min at 0 °C and treated with iodoethane (275 μL, 3.42 mmol) at the same temperature. The mixture was allowed to warm at room temperature and stirred for 3 h. The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ followed by brine. The solution was dried over Na_2SO_4 and concentrated by evaporation. The residue was purified by chromatography on silica gel (*n*-hexane/EtOAc = 20/1, 10/1 to 5/1 as the eluent) to obtain *tert*-butyl 1-benzyl-2-ethylazetidine-2-carboxylate (**35**) (176 mg, 48% yield) as a coluorless oil. IR (ATR) ν_{max}/cm^{-1} 3087, 3062, 3028, 3004, 2967, 2931, 2877, 2828, 2799, 1716, 1602, 1495, 1476, 1455, 1391, 1366, 1338, 1312, 1248, 1227, 1175, 1140, 1028, 1004, 946, 908, 849, 828, 799, 732, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (4H, m, Ph), 7.24-7.17 (1H, m, Ph), 3.75 (1H, d, *J* = 12.8 Hz, C*H*$_2$Ph), 3.67 (1H, d, *J* = 12.8 Hz, C*H*$_2$Ph), 3.14 (1H, ddd, *J* = 8.3, 6.3, 5.9 Hz, 4-H), 3.07 (1H, ddd, *J* = 8.3, 6.3, 5.9 Hz, 4-H), 2.51 (1H, dddd, *J* = 10.7, 8.3, 5.9, 0.6 Hz, 3-H), 2.01-1.86 (2H, m, 3-H and C*H*$_2$CH$_3$), 1.83 (1H, dq, *J* = 13.2, 7.5 Hz, C*H*$_2$CH$_3$), 1.50 (9H, s, *t*Bu), 0.87 (3H, dd, *J* = 7.5, 7.5 Hz, CH$_2$C*H*$_3$); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.7, 138.9, 128.5, 128.1, 126.7, 80.5, 72.9, 55.8, 49.4, 28.1, 26.5, 25.4, 8.0; HRMS (ESI): calcd. for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1958, found 276.1952. (Step 2) A mixture of **35** (92 mg, 0.33 mmol) and $NaHCO_3$ (84 mg, 1.0 mmol) in CH_2Cl_2 (1.7 mL) was treated with methyl trifluoromethanesulfonate (74 μL, 0.65 mmol) at 0 °C and stirred for 2 h at room temperature. The mixture was concentrated by evaporation to ca. 1/2 volume and purified by chromatography on silica gel (CH_2Cl_2/MeOH = 20/1 to 10/1 as the eluent) to obtain **12** (146 mg, quant.) as a colourless gum. The product **12** was obtained as an almost single diastereomer. The relative stereochemistry of **12** was not determined. IR (ATR) ν_{max}/cm^{-1} 3040, 2981, 2942, 2887, 1733,

[2] Addition of DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone] improve the yield of the Sommelet–Hauser rearrangement product: E. Tayama, K. Hirano and S. Baba, *Tetrahedron*, 2020, **76**, 131064. See also ref. 1.

[3] E. Tayama, R. Nishio and Y. Kobayashi, *Org. Biomol. Chem.*, 2018, **16**, 5833.

1499, 1461, 1425, 1397, 1372, 1357, 1327, 1254, 1223, 1141, 1078, 1029, 958, 930, 877, 837, 802, 768, 754, 736, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.36 (5H, m, Ph), 4.98 (1H, ddd, J = 10.4, 10.0, 9.7 Hz, 4-H), 4.83 (1H, d, J = 12.6 Hz, CH_2Ph), 4.08 (1H, d, J = 12.6 Hz, CH_2Ph), 3.51 (1H, ddd, J = 9.9, 9.7, 2.4 Hz, 4-H), 3.16 (1H, ddd, J = 11.2, 10.4, 9.9 Hz, 3-H), 3.02-2.82 (1H, m, 3-H), 2.95 (3H, s, NCH_3), 2.45-2.28 (2H, m, C$H_2$$CH_3$), 1.53 (9H, s, *t*Bu), 0.97 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.7, 131.8, 130.5, 129.4, 126.4, 120.6 (q, J = 322 Hz), 86.2, 85.4, 61.3, 58.9, 46.3, 27.6, 25.5, 22.7, 7.5; HRMS (ESI): calcd. for $C_{18}H_{28}NO_2$ $[M - OTf]^+$ 290.2115, found 290.2108.

3. Copies of ^{1}H, ^{13}C, and ^{19}F NMR (representative) spectra of substrates and products

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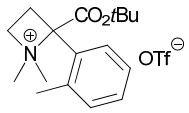

2a

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^{13}C (101 MHz, $CDCl_3$)

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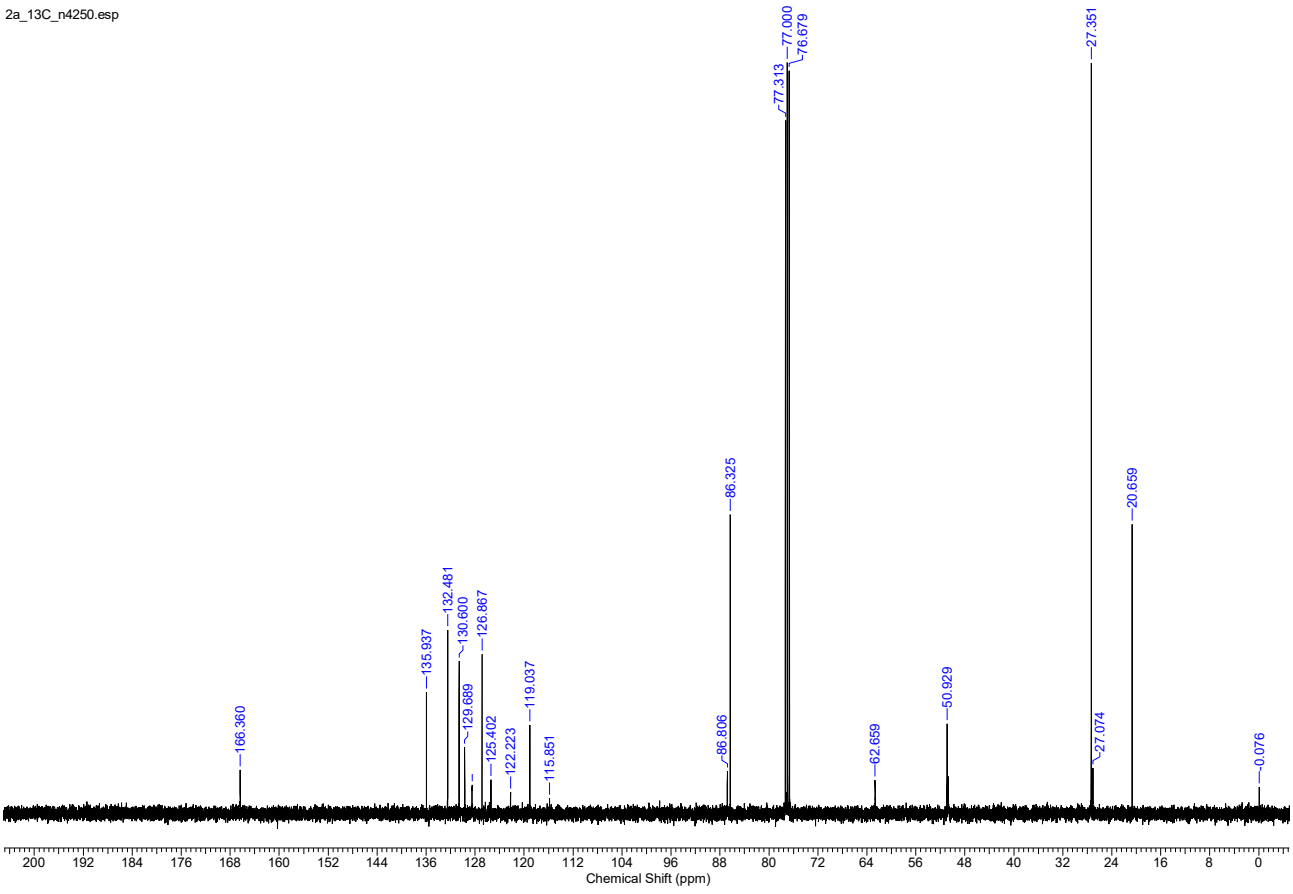

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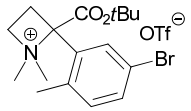

2b

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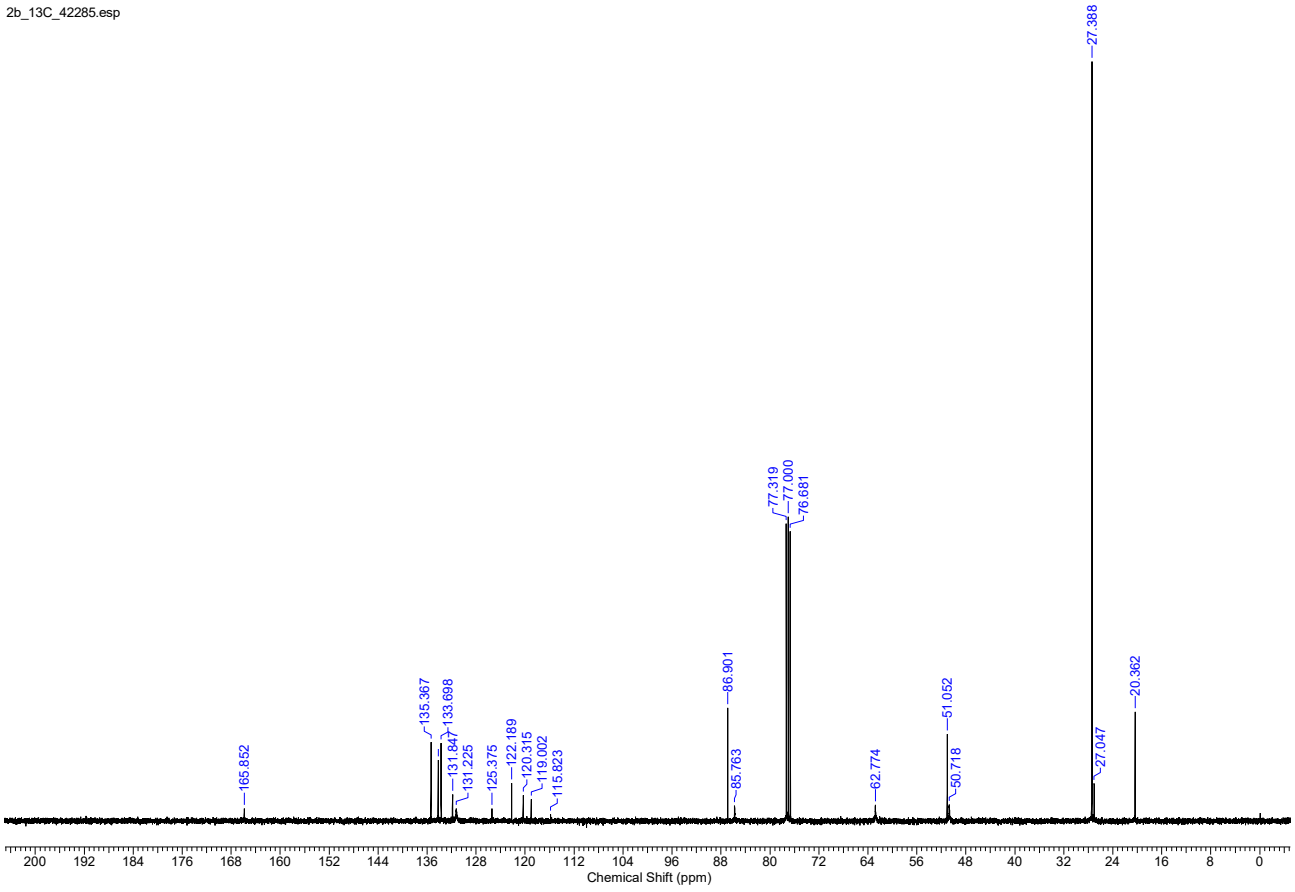

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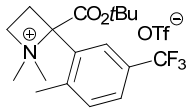

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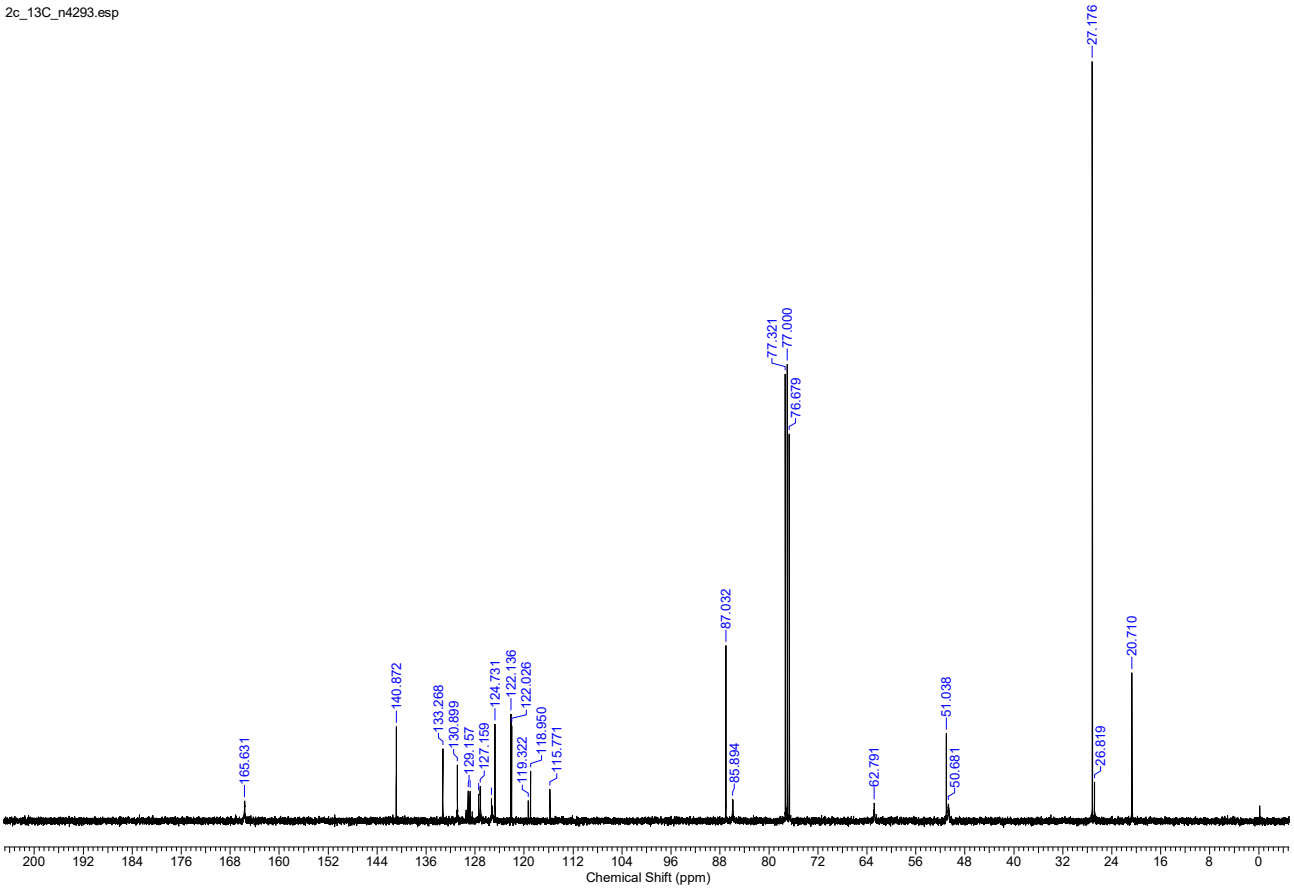

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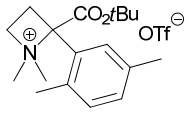

2d

^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

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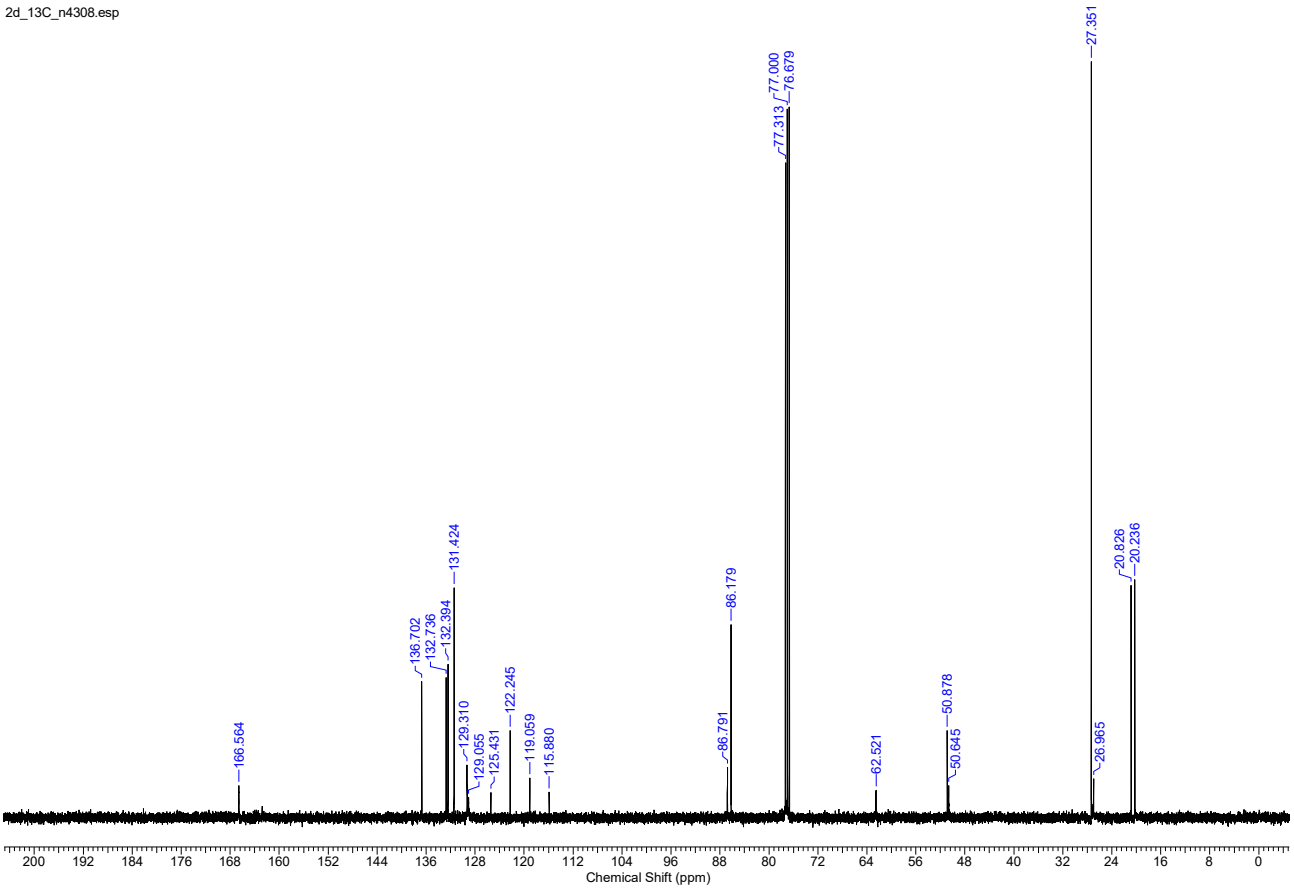

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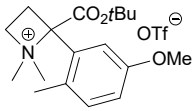

2e

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^{13}C (101 MHz, $CDCl_3$)

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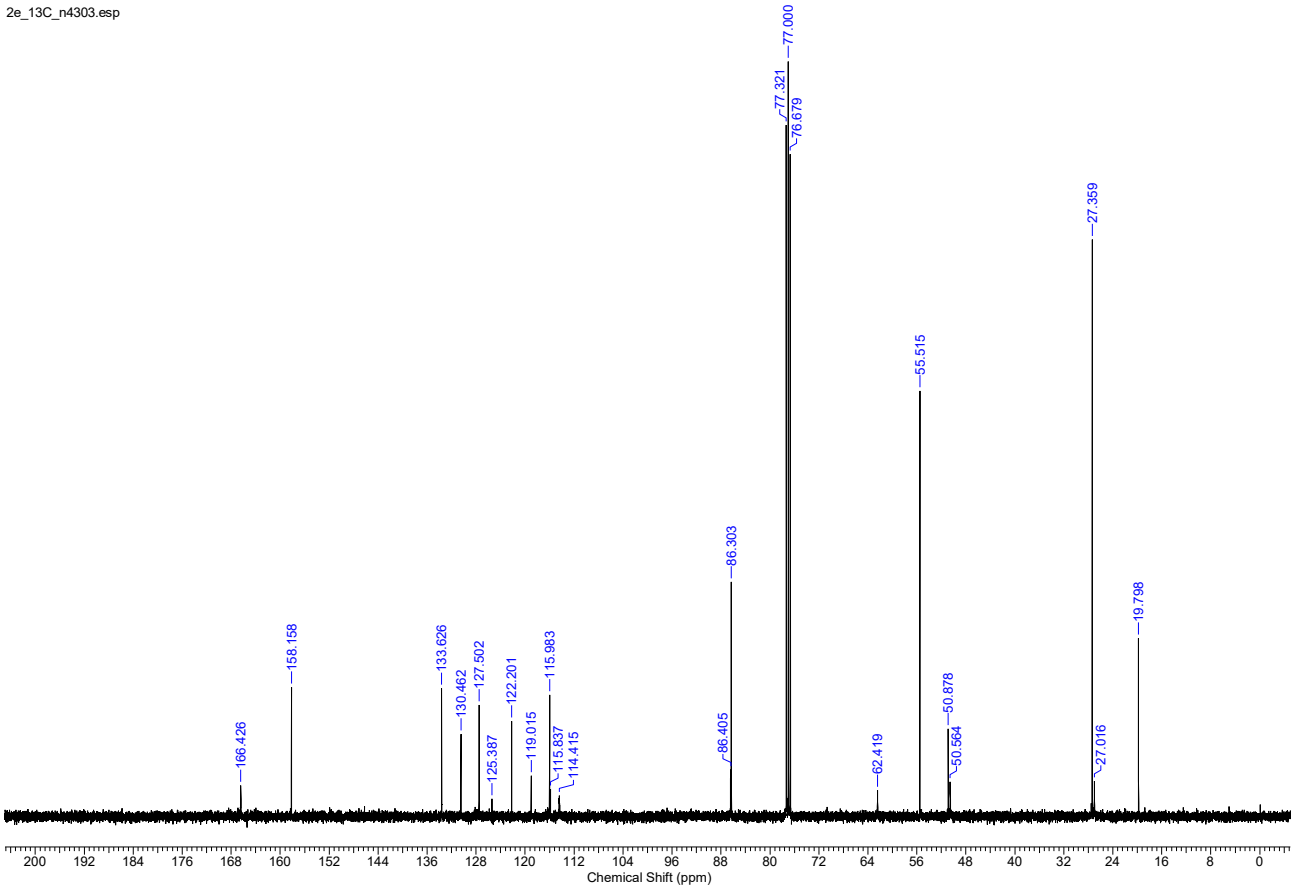

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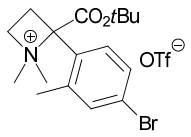

2f

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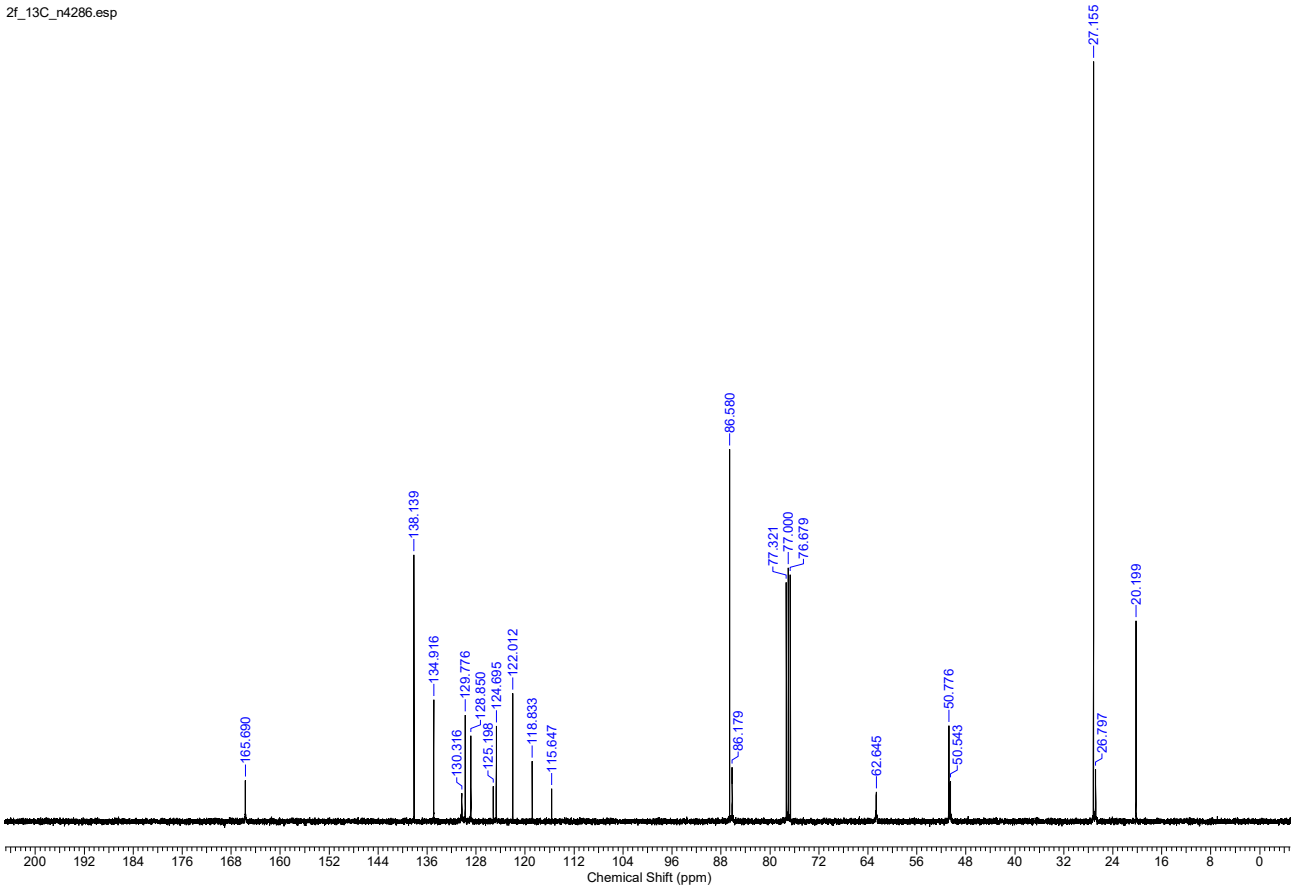

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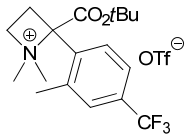

2g

^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

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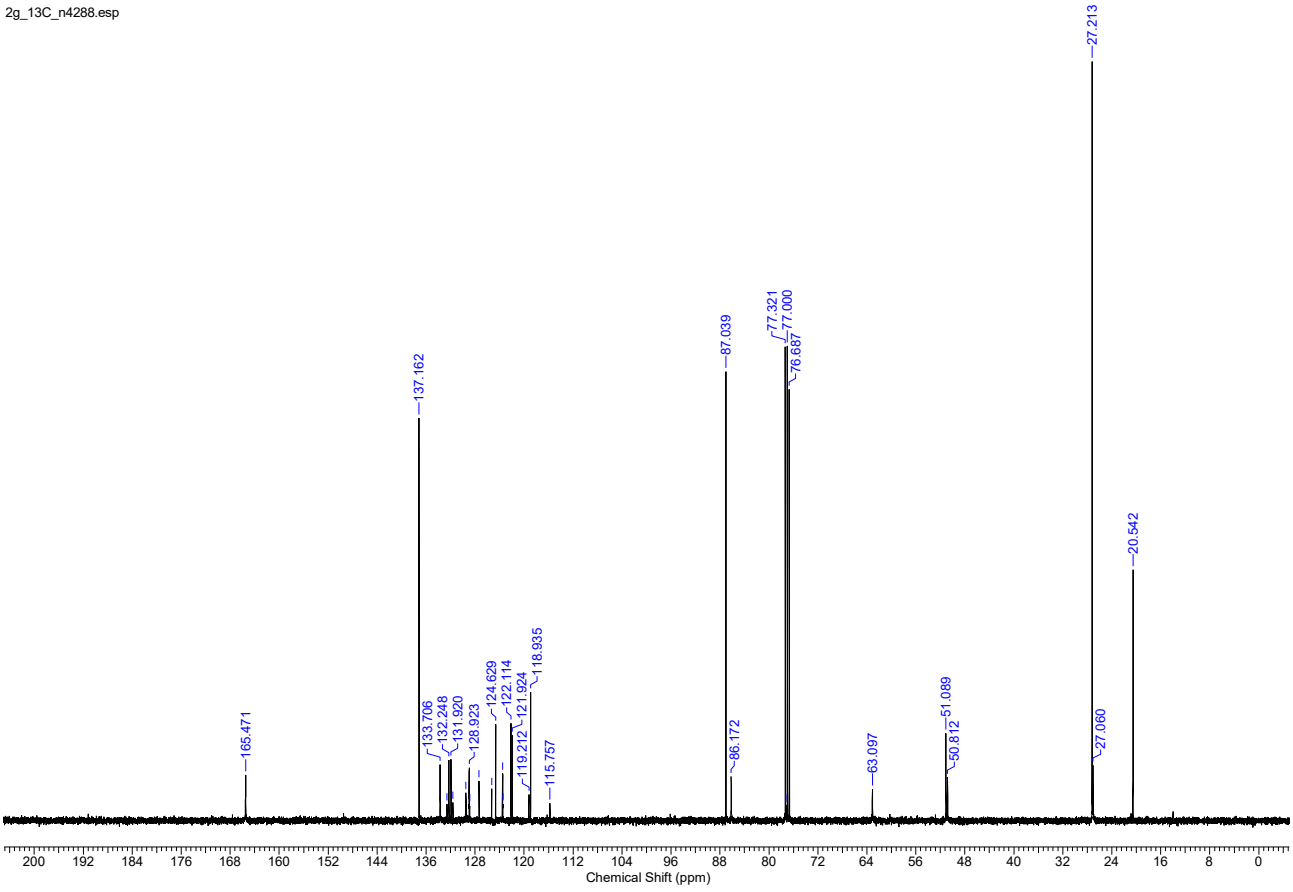

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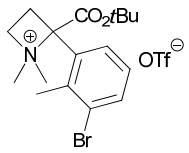
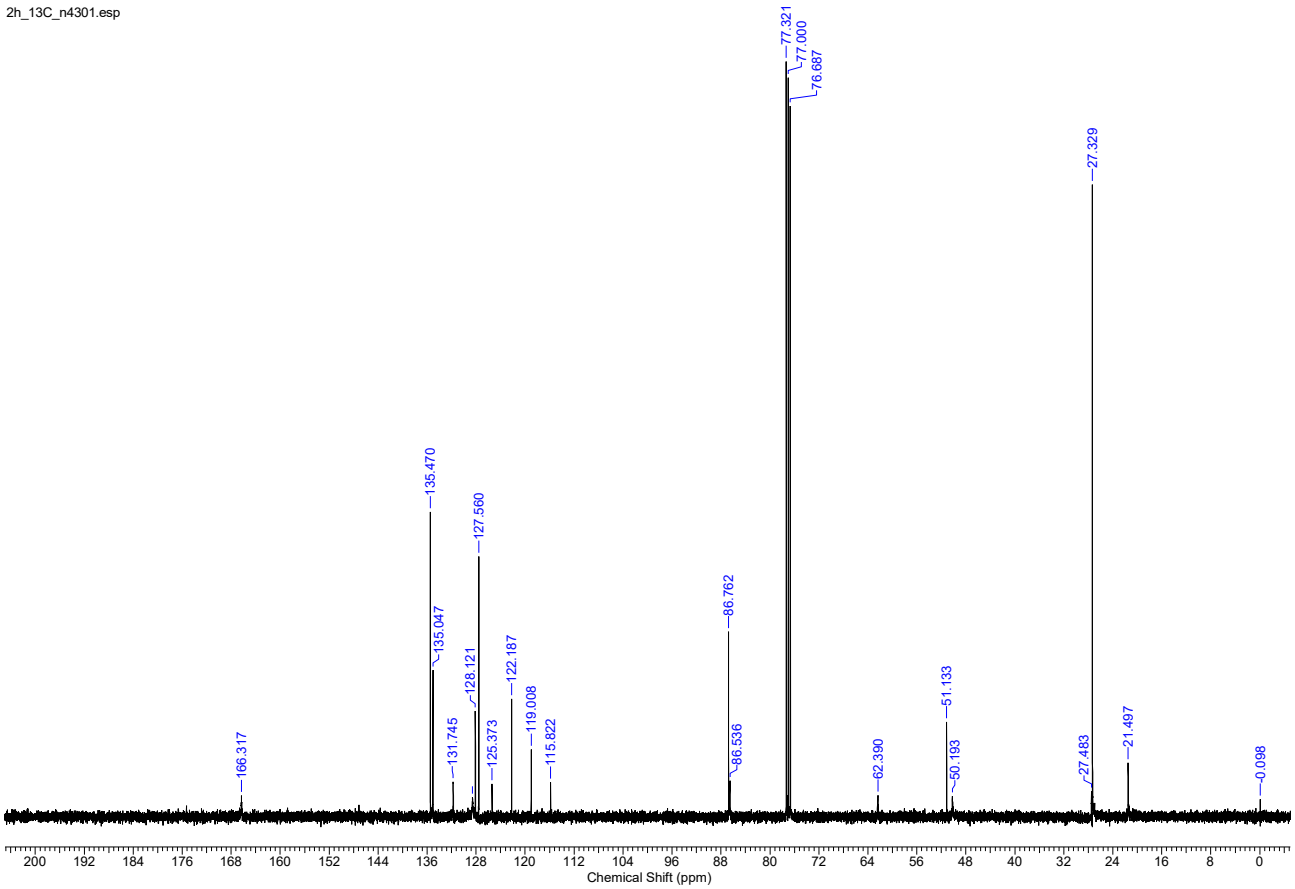


2h

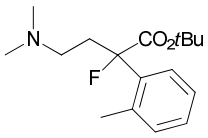
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

2h_13C_n4301.esp



3aa_1H_n4258.esp

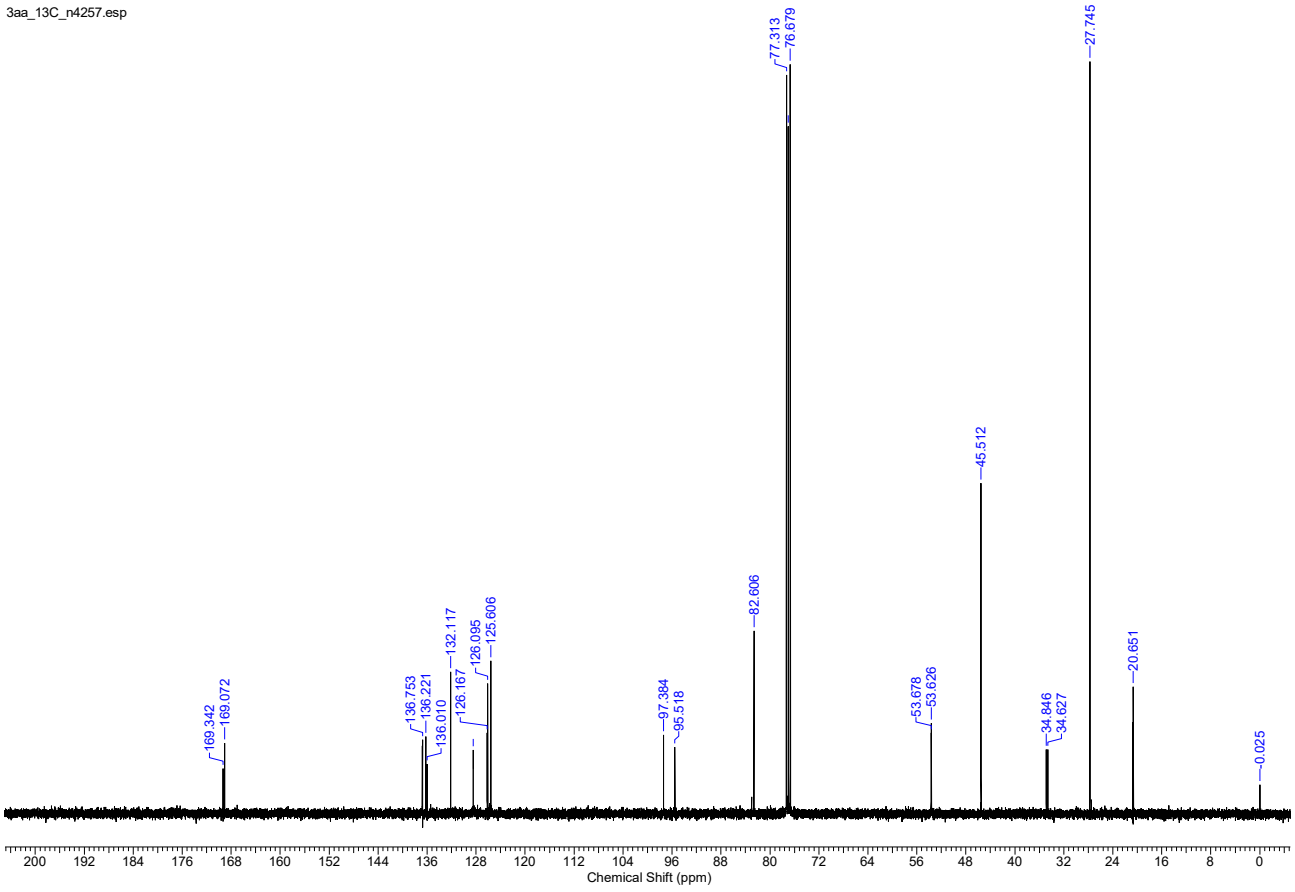


3aa

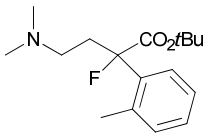
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3aa_13C_n4257.esp



3aa_19F_4549.esp

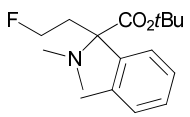


3aa

^{19}F (376 MHz, $CDCl_3$)

C_6F_6: δ –162.9 ppm

4aa_1H_43995.esp

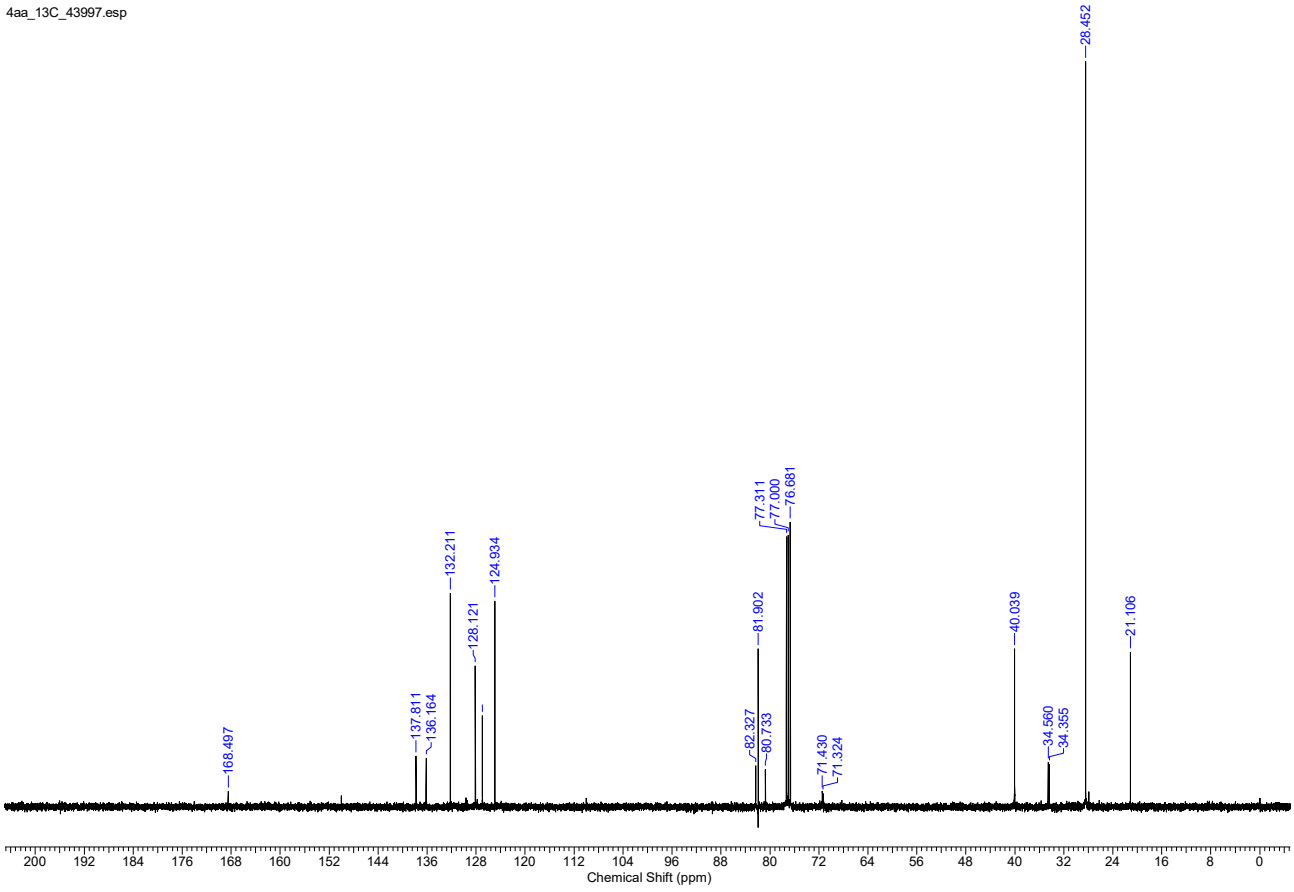


4aa

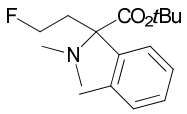
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4aa_13C_43997.esp



4aa_19F_44002.esp

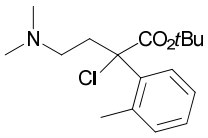


4aa

^{19}F (376 MHz, $CDCl_3$)

C_6F_6: δ –162.9 ppm

3ab_1H_n4223.esp

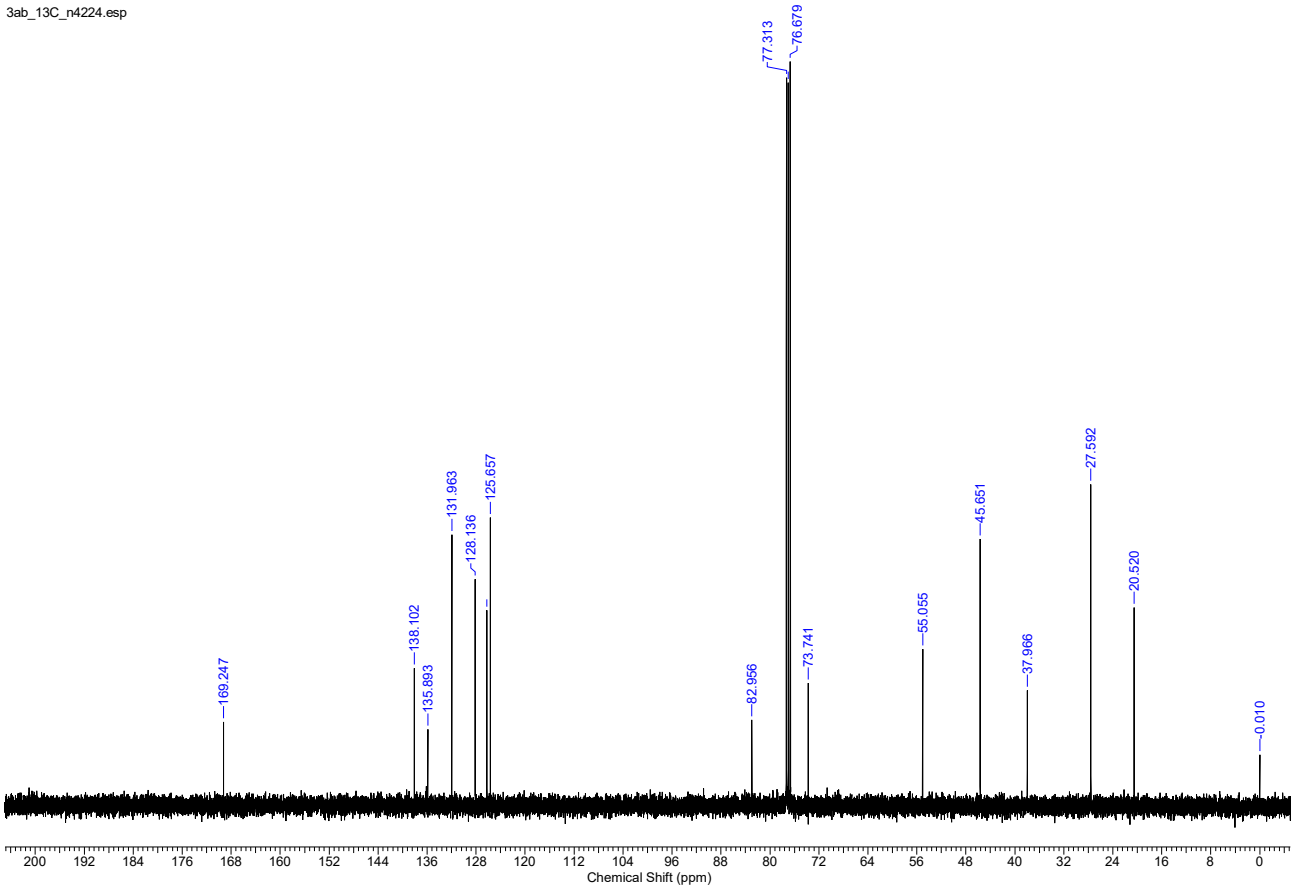


3ab

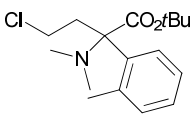
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ab_13C_n4224.esp



4ab_1H_n4235.esp

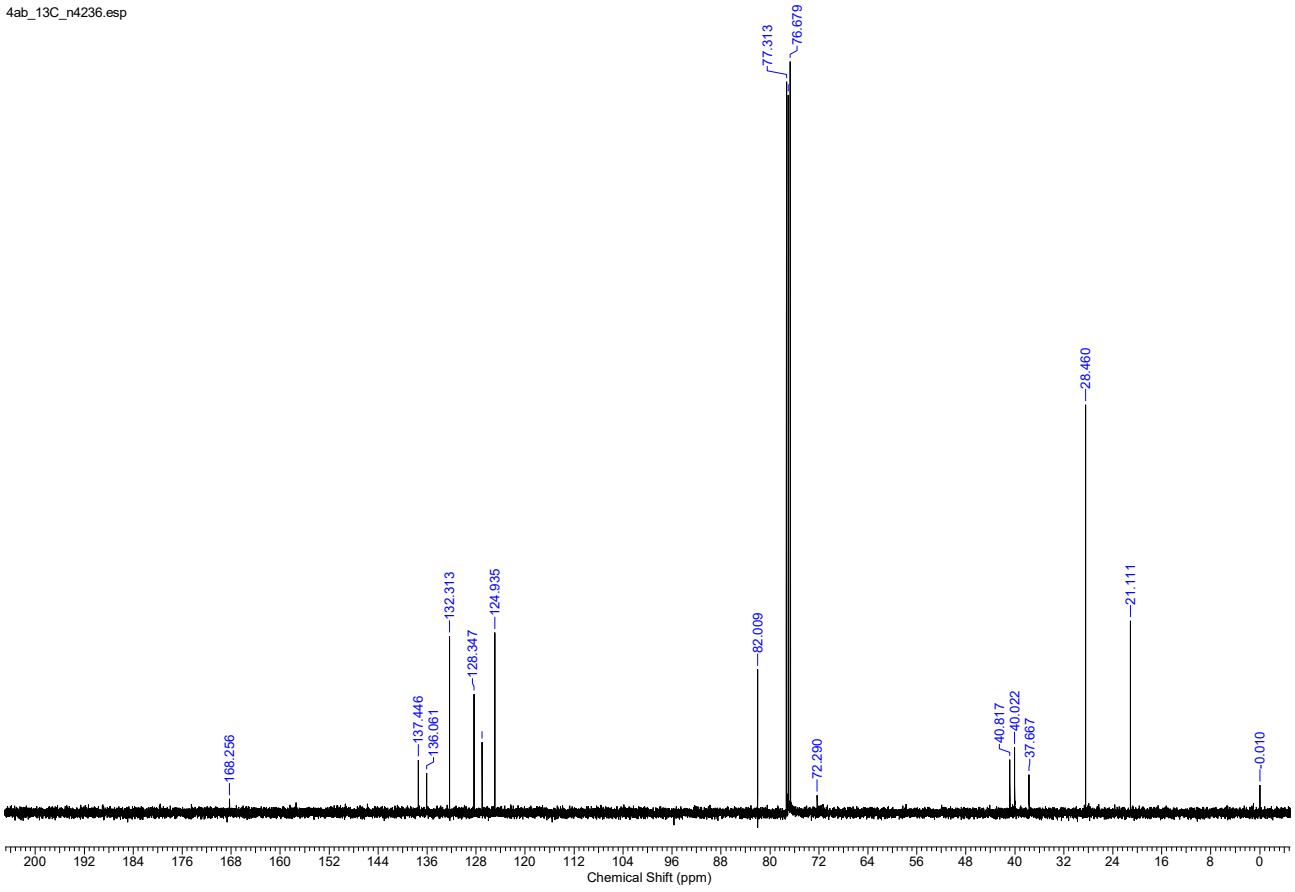


4ab

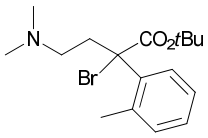
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4ab_13C_n4236.esp



3ac_1H_n4247.esp

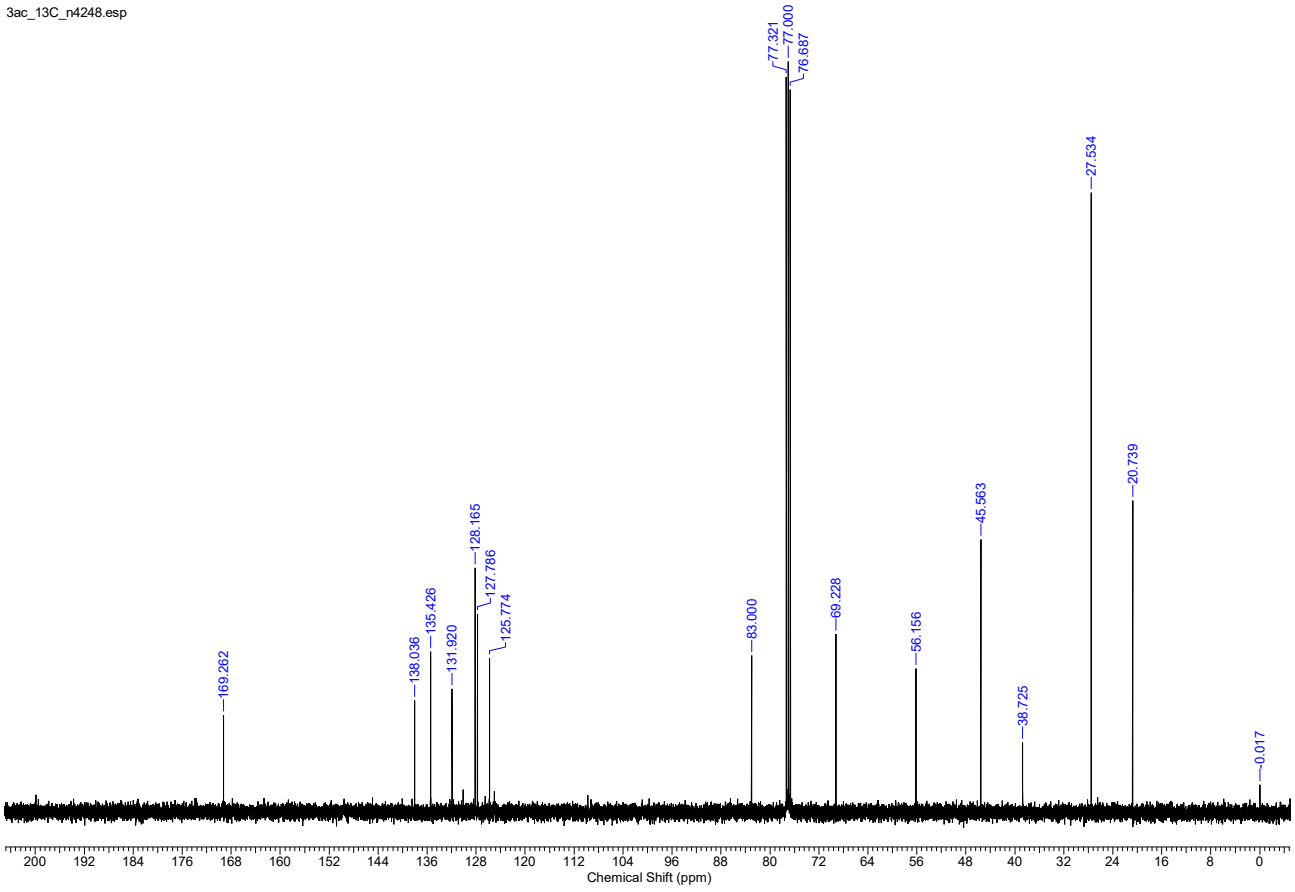


3ac

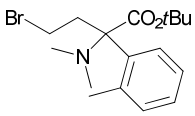
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ac_13C_n4248.esp



4ac_1H_n4245.esp

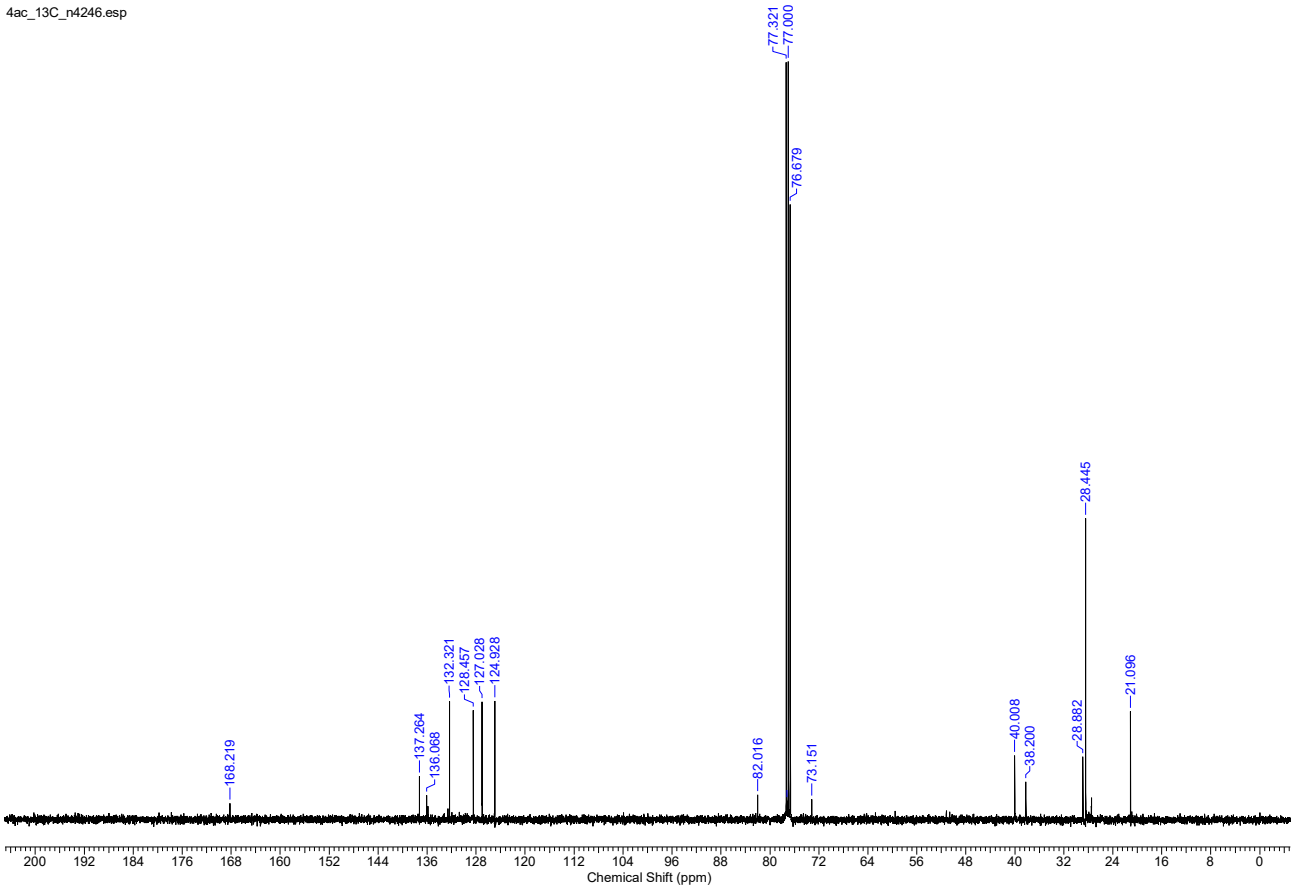


4ac

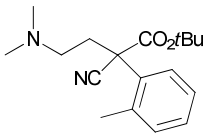
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4ac_13C_n4246.esp



3ae_1H_4280.esp

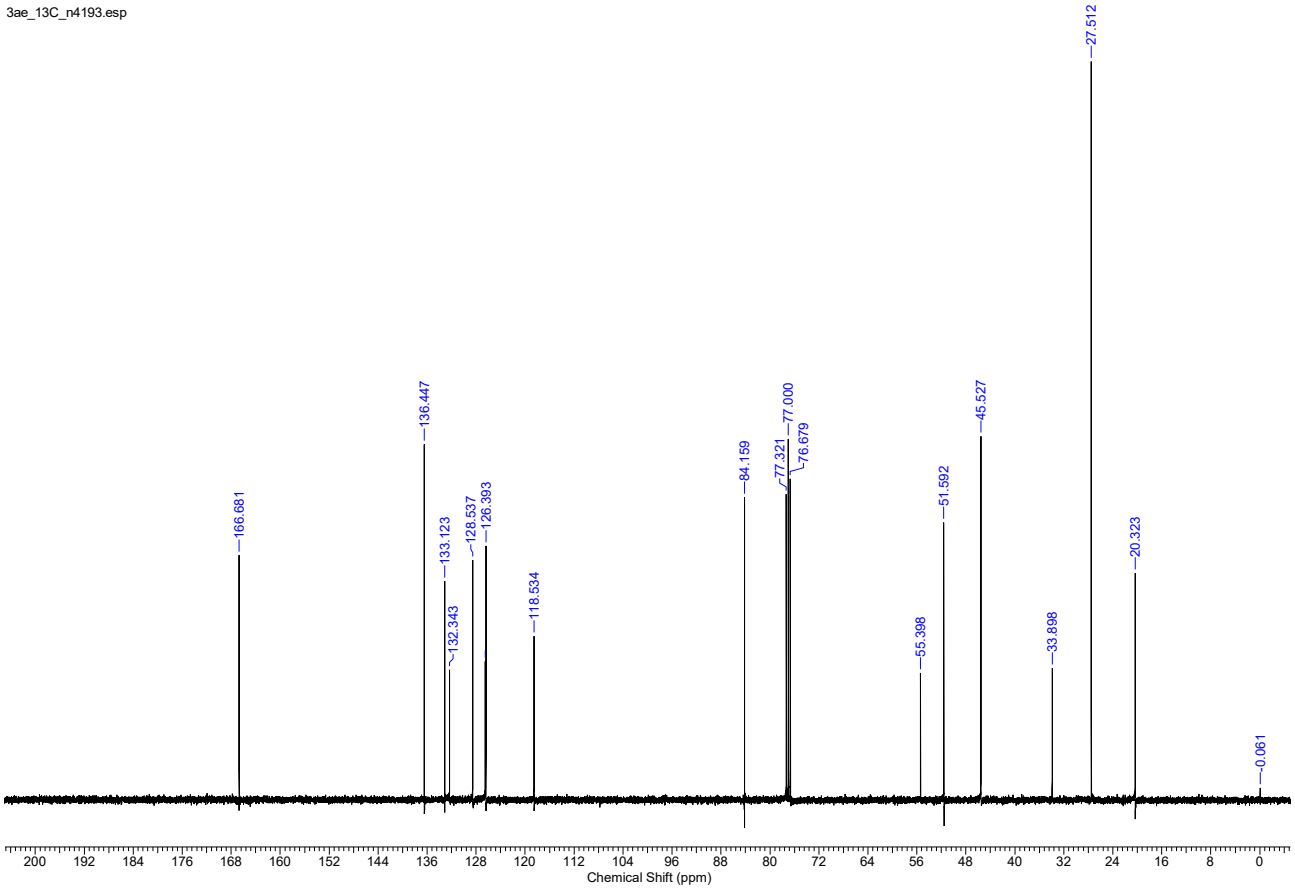


3ae

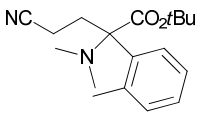
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ae_13C_n4193.esp



4ae_1H_4532.esp

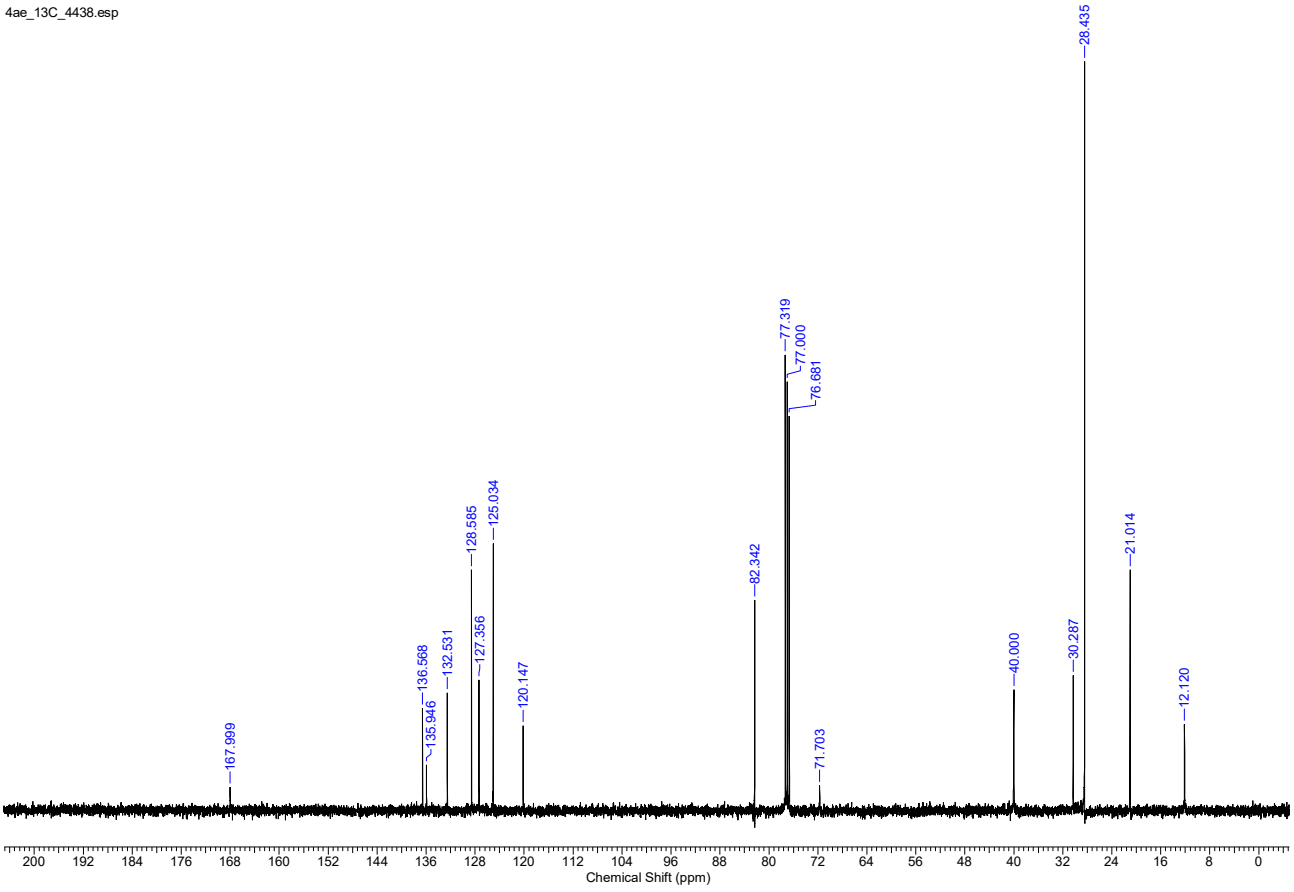


4ae

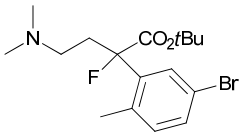
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4ae_13C_4438.esp



3ba_1H_n4232.esp

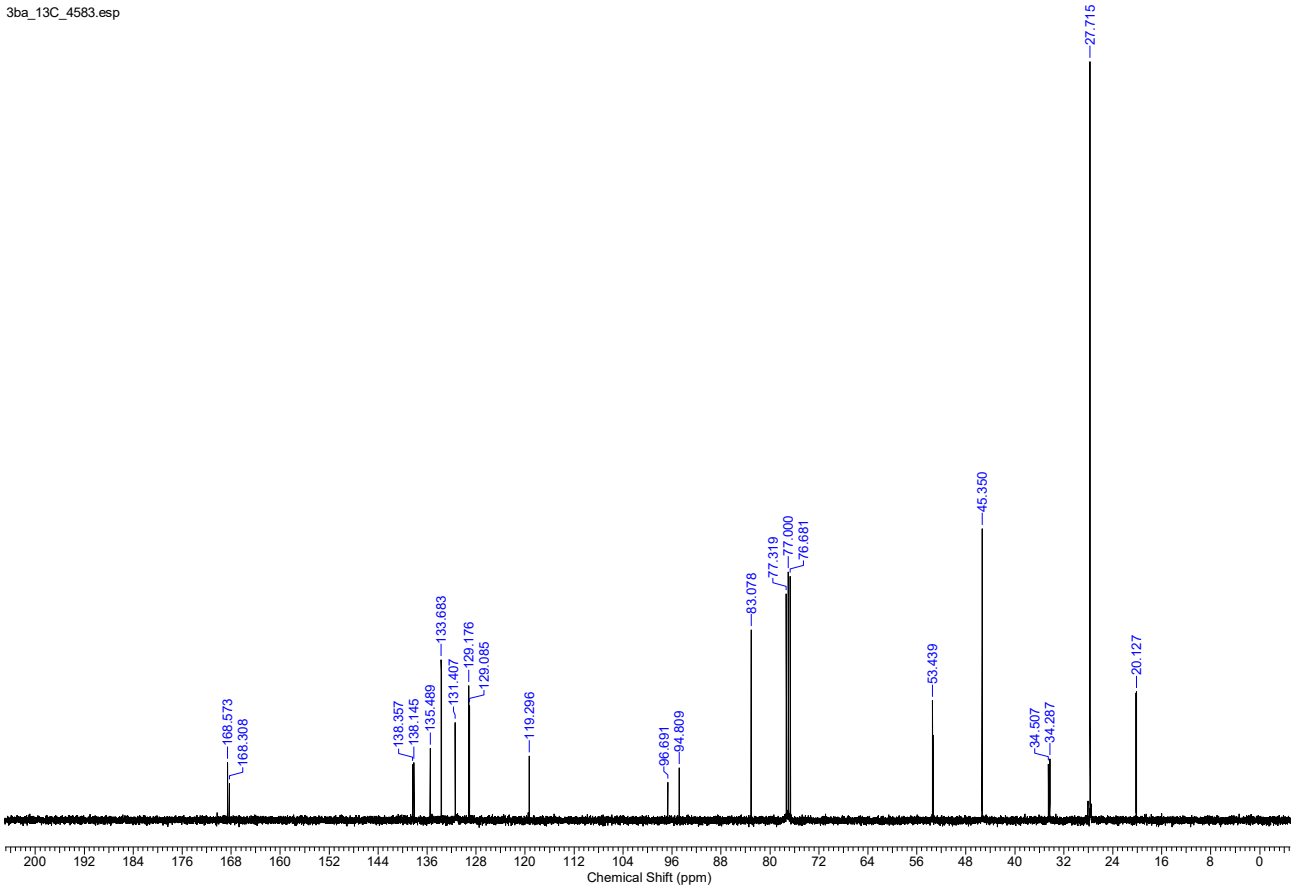


3ba

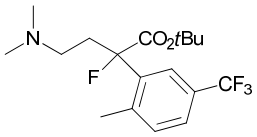
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ba_13C_4583.esp



3ca_1H_4526.esp

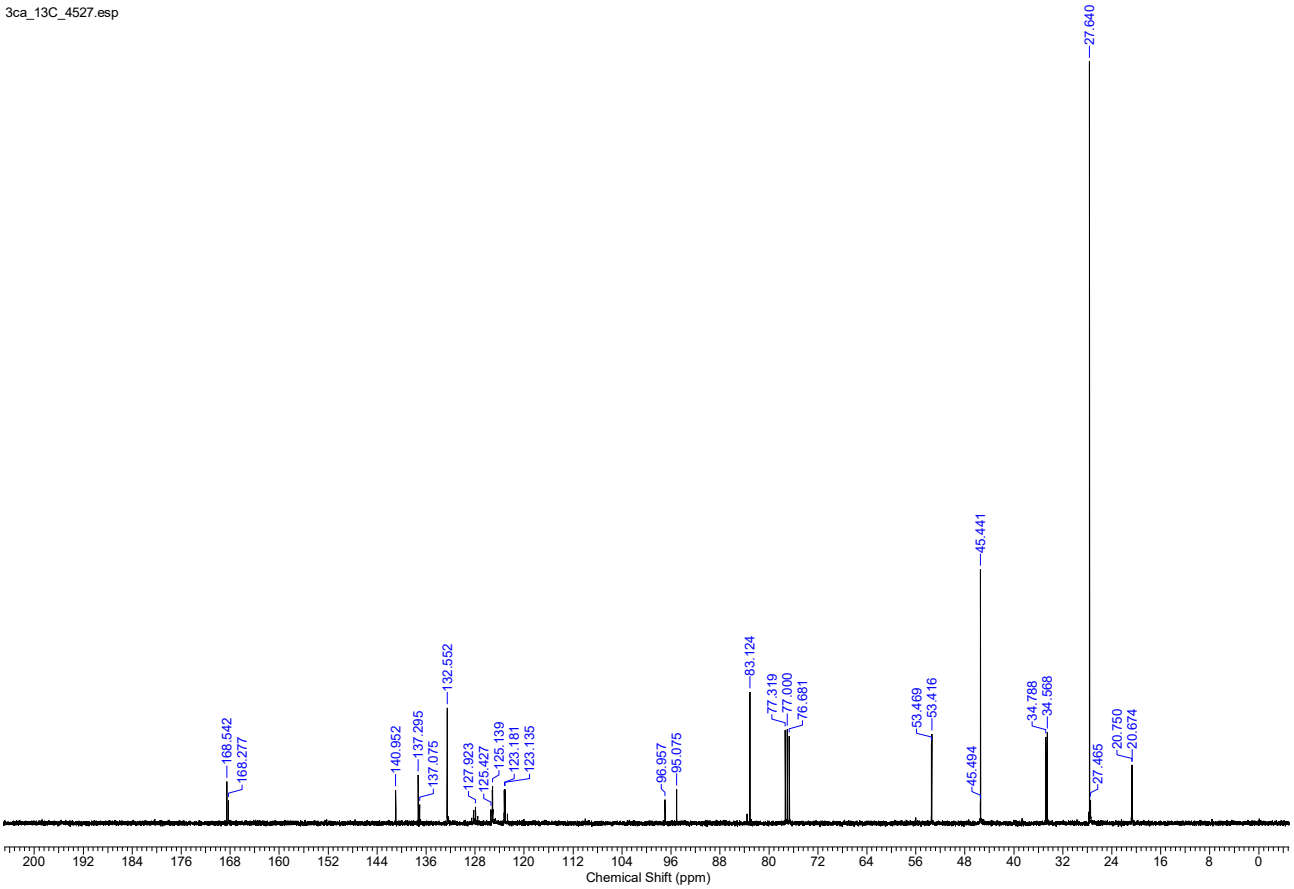


3ca

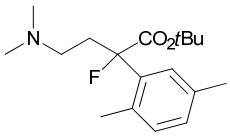
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ca_13C_4527.esp



3da_1H_4504.esp

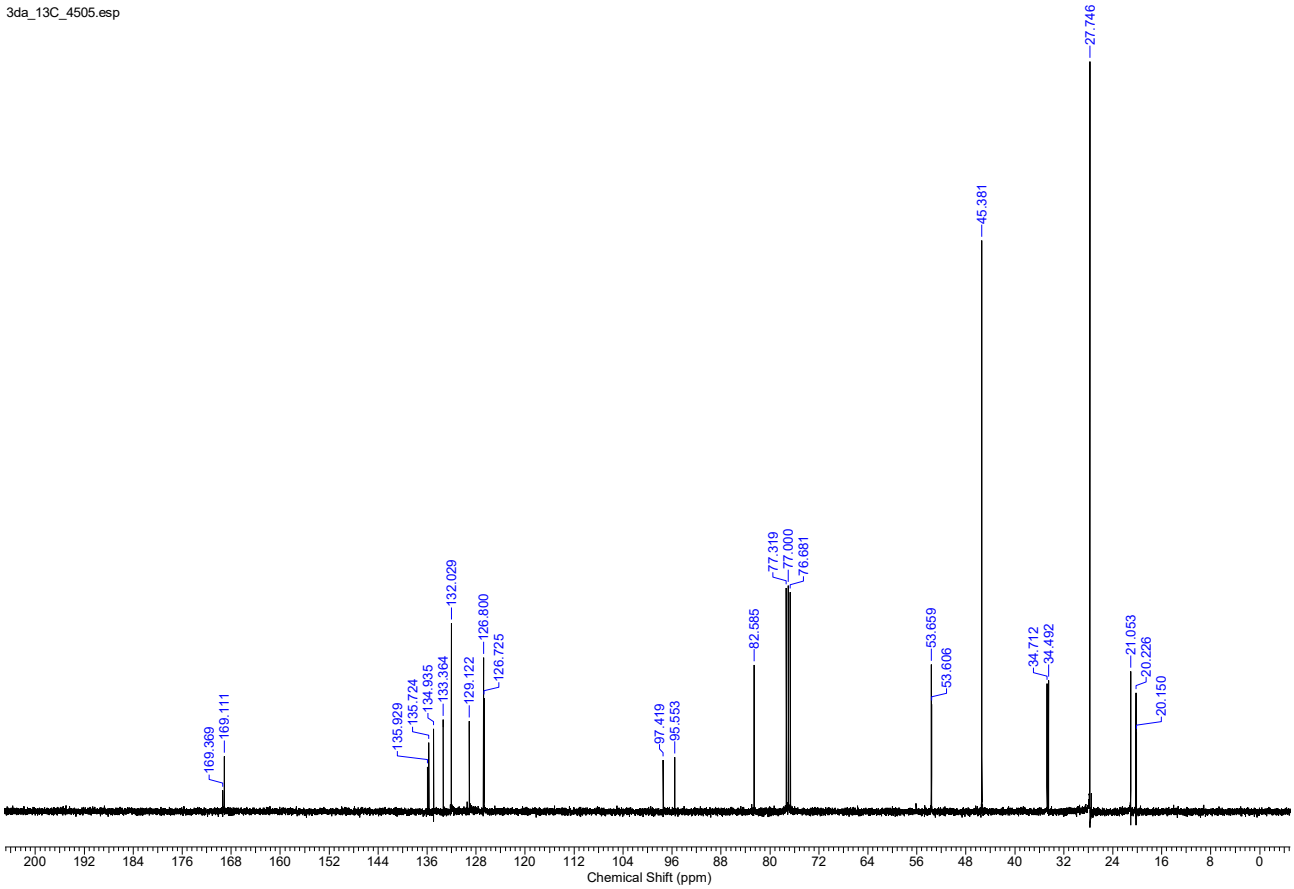


3da

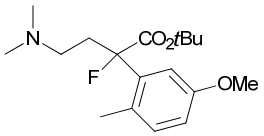
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3da_13C_4505.esp



3ea_1H_4517.esp

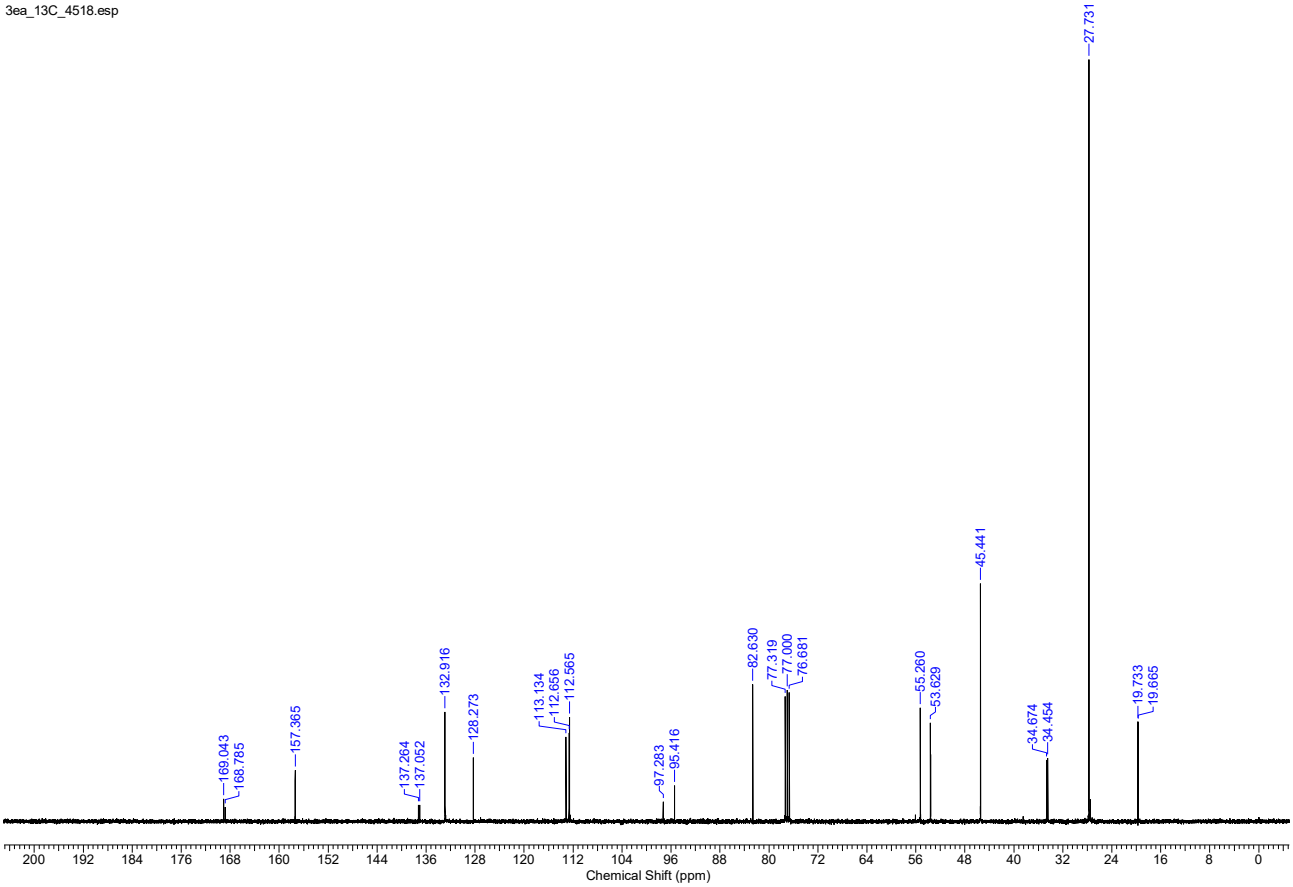


3ea

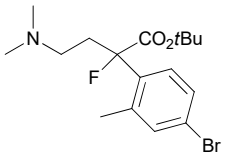
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ea_13C_4518.esp



3fa_1H_4492.esp

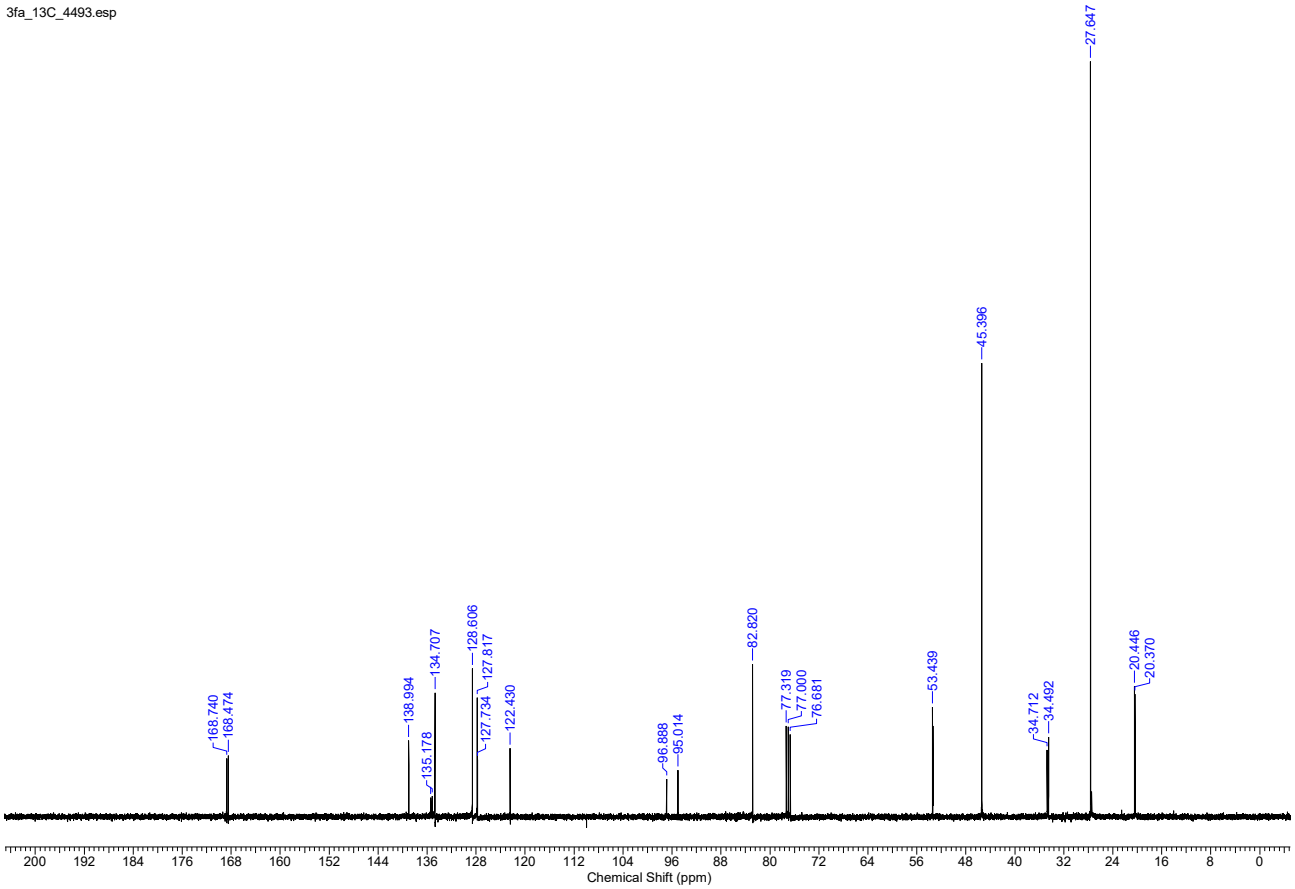


3fa

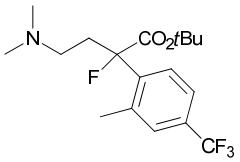
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3fa_13C_4493.esp



3ga_1H_n4280.esp

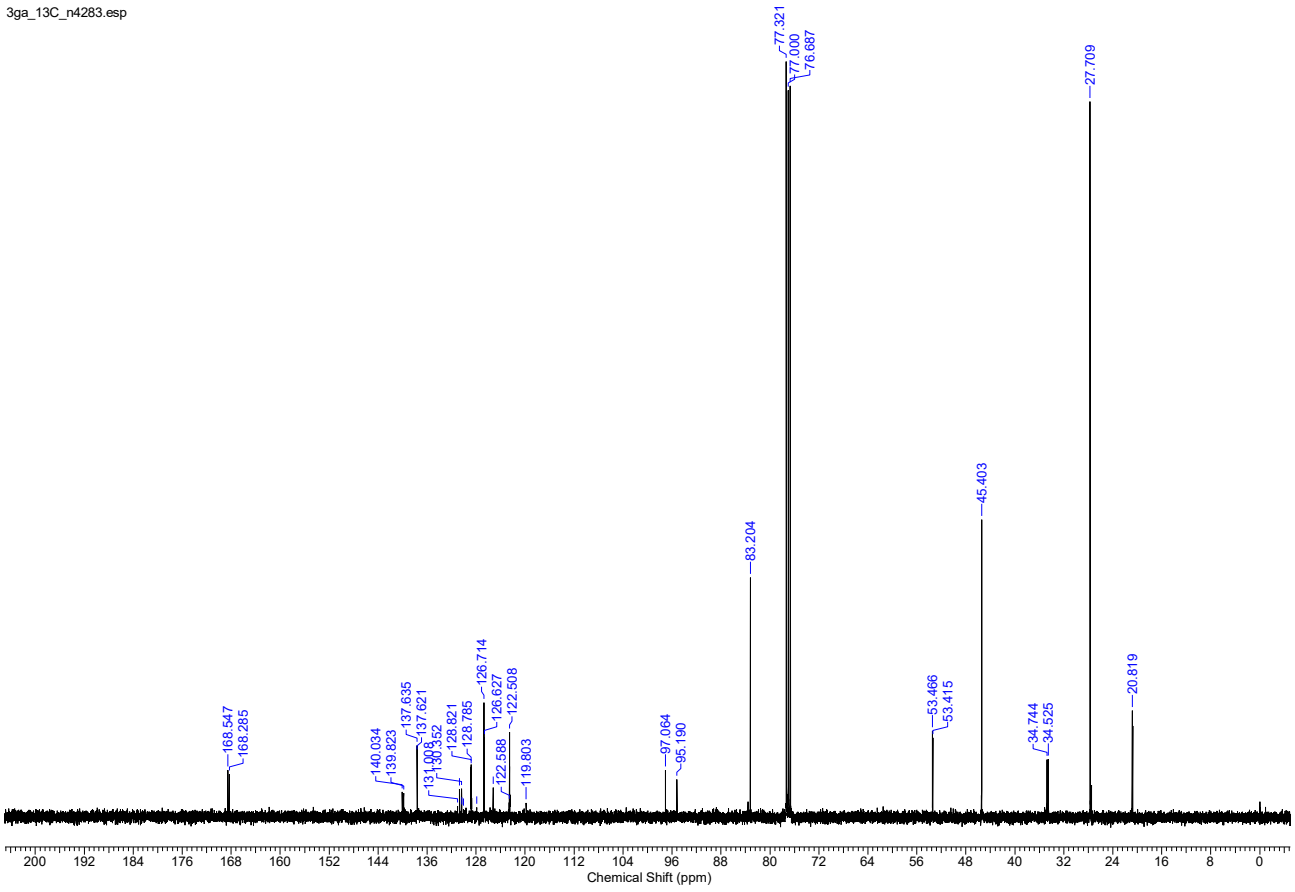


3ga

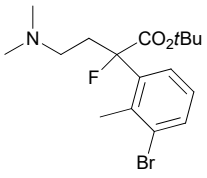
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ga_13C_n4283.esp



3ha_1H_4560.esp

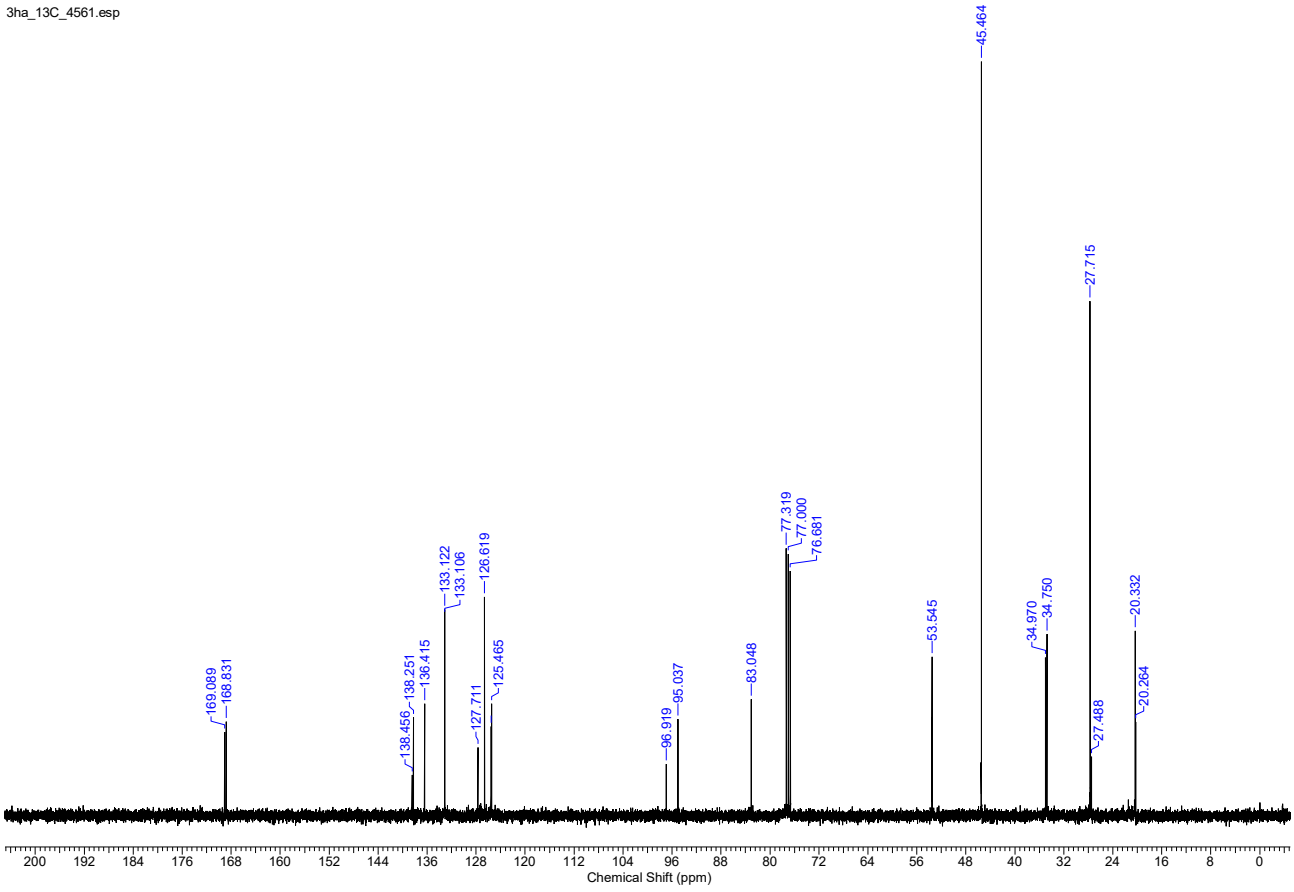


3ha

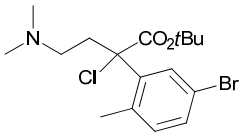
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3ha_13C_4561.esp



3bb_1H_43862.esp

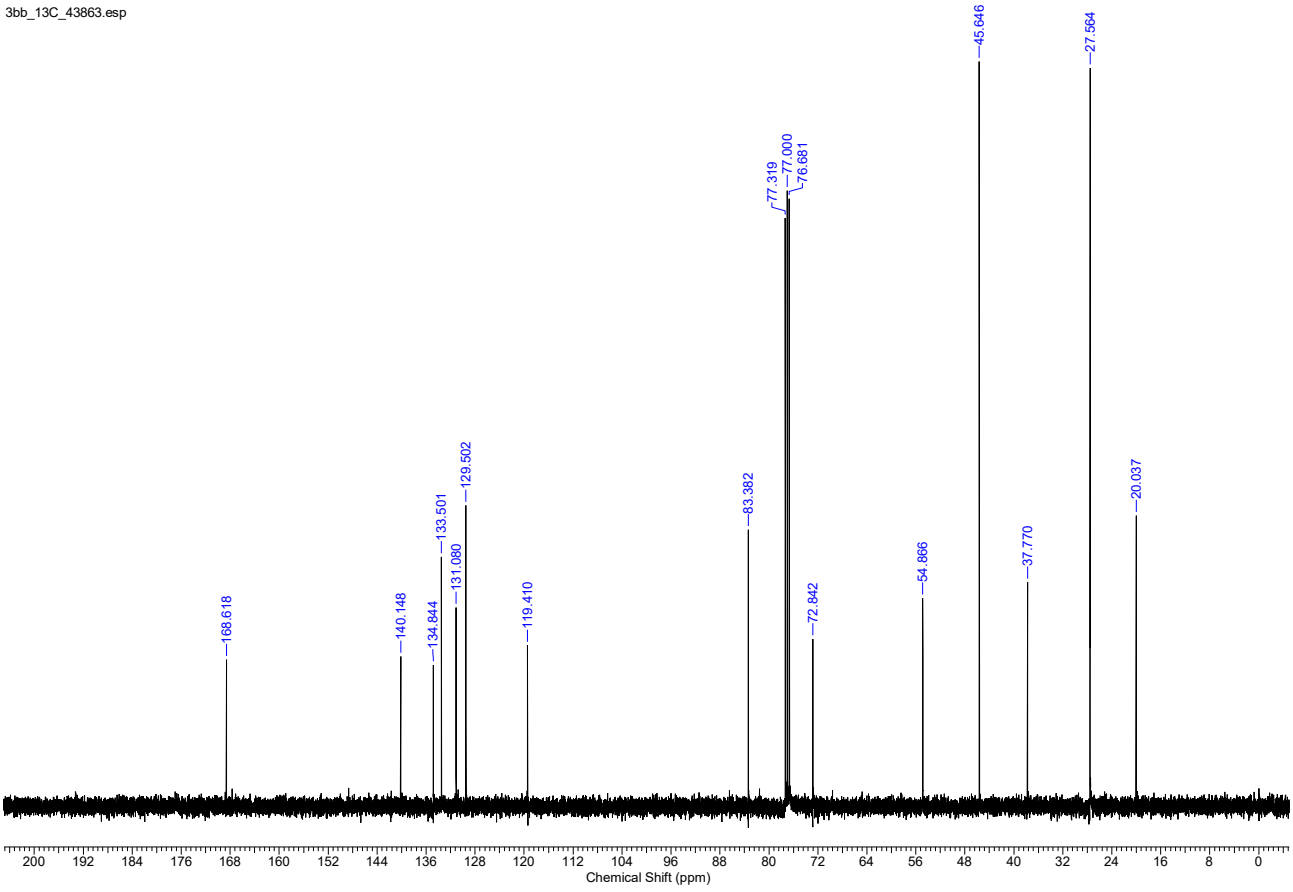


3bb

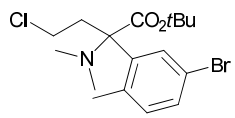
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3bb_13C_43863.esp



4bb_1H_43864.esp

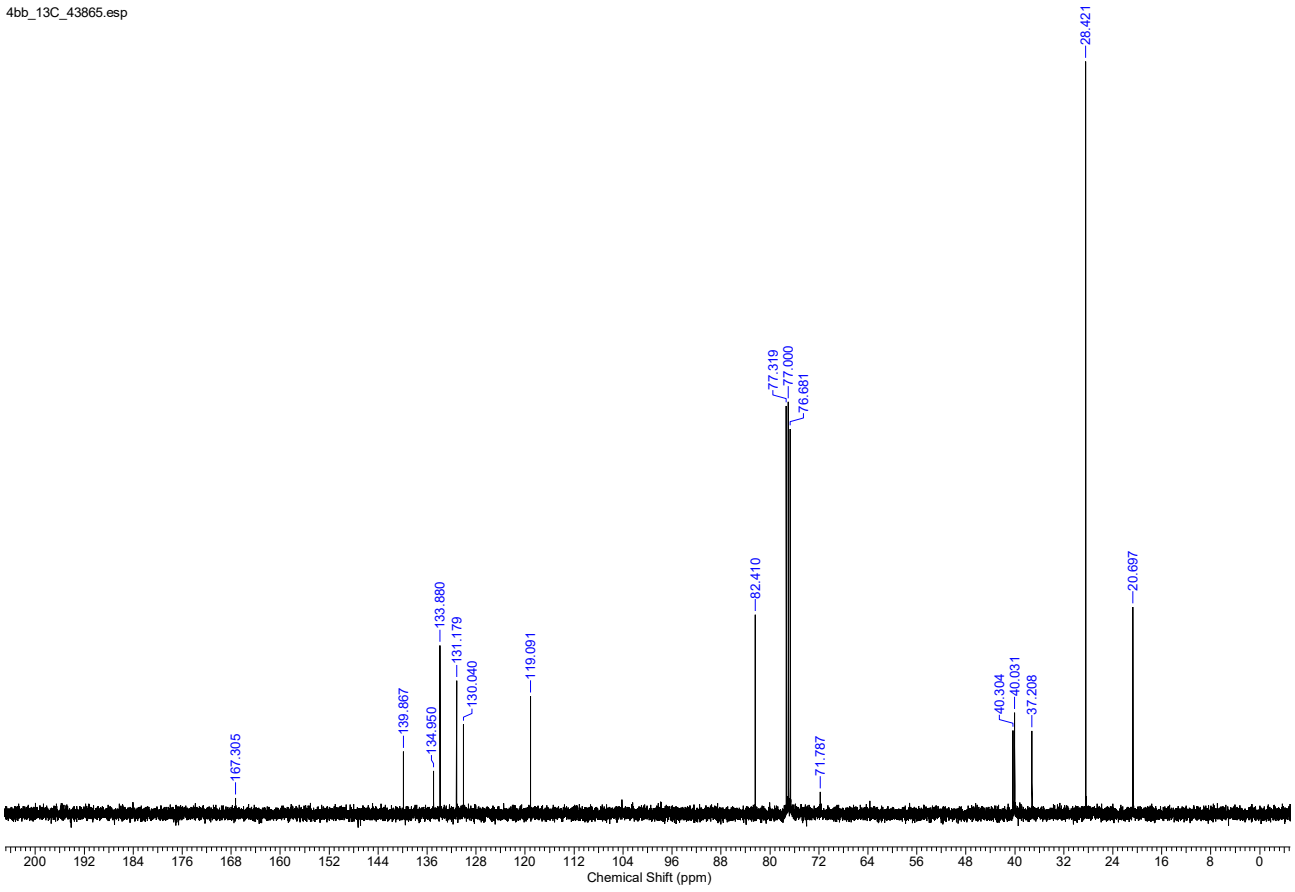


4bb

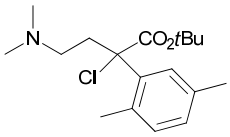
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4bb_13C_43865.esp



3db_1H_4524.esp

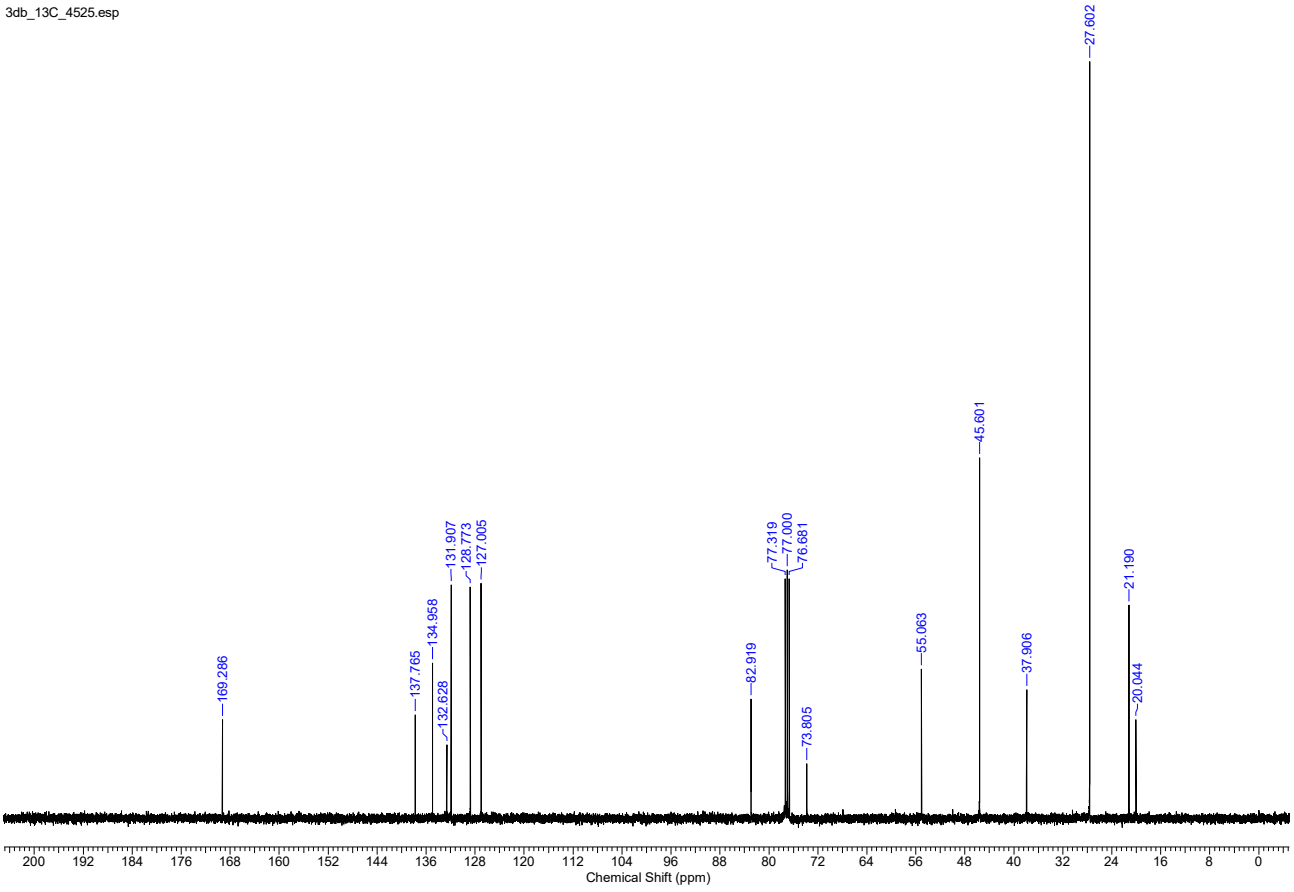


3db

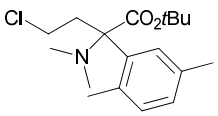
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3db_13C_4525.esp



4db_1H_4530.esp

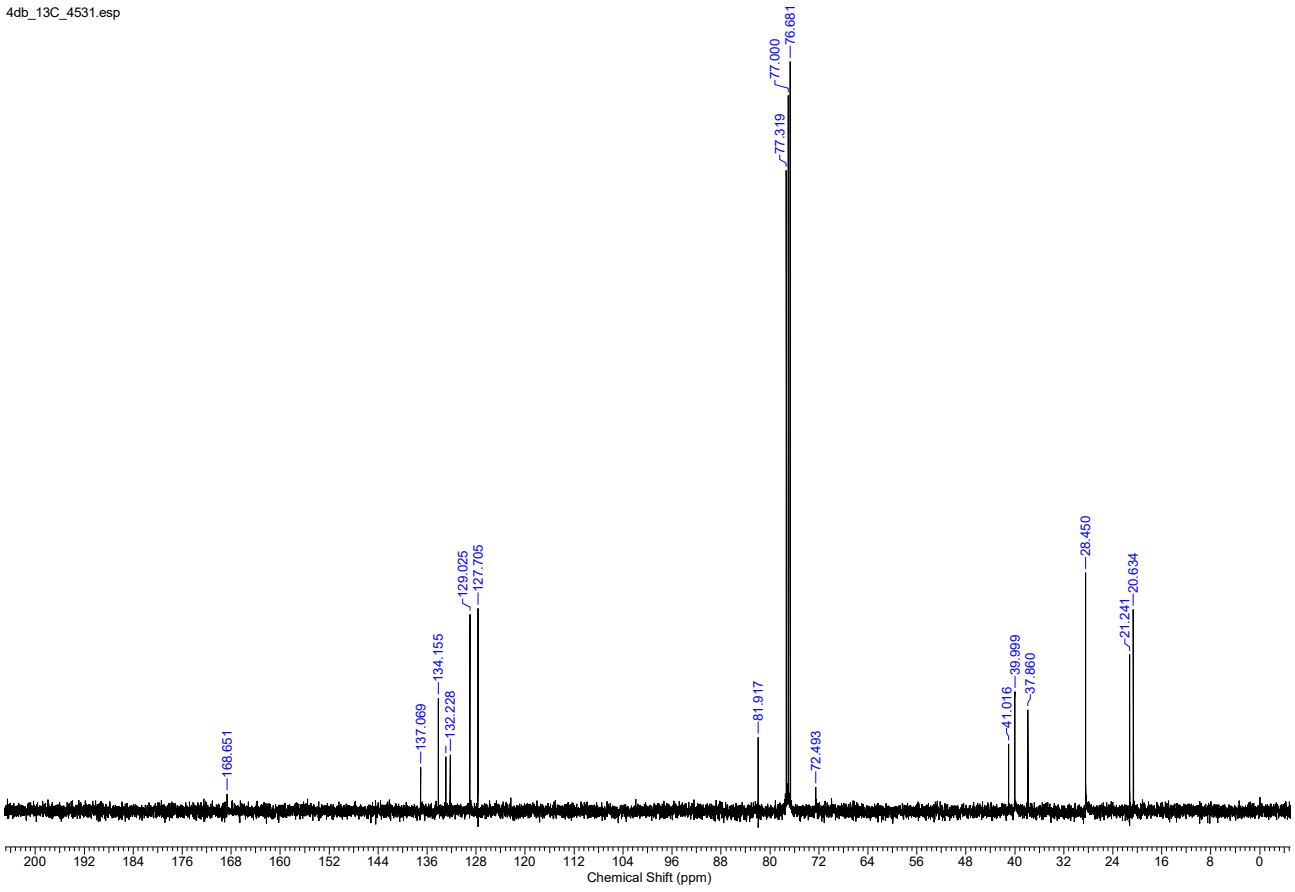


4db

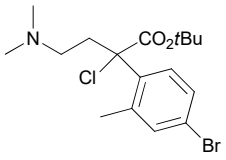
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4db_13C_4531.esp



3fb_1H_n4261.esp

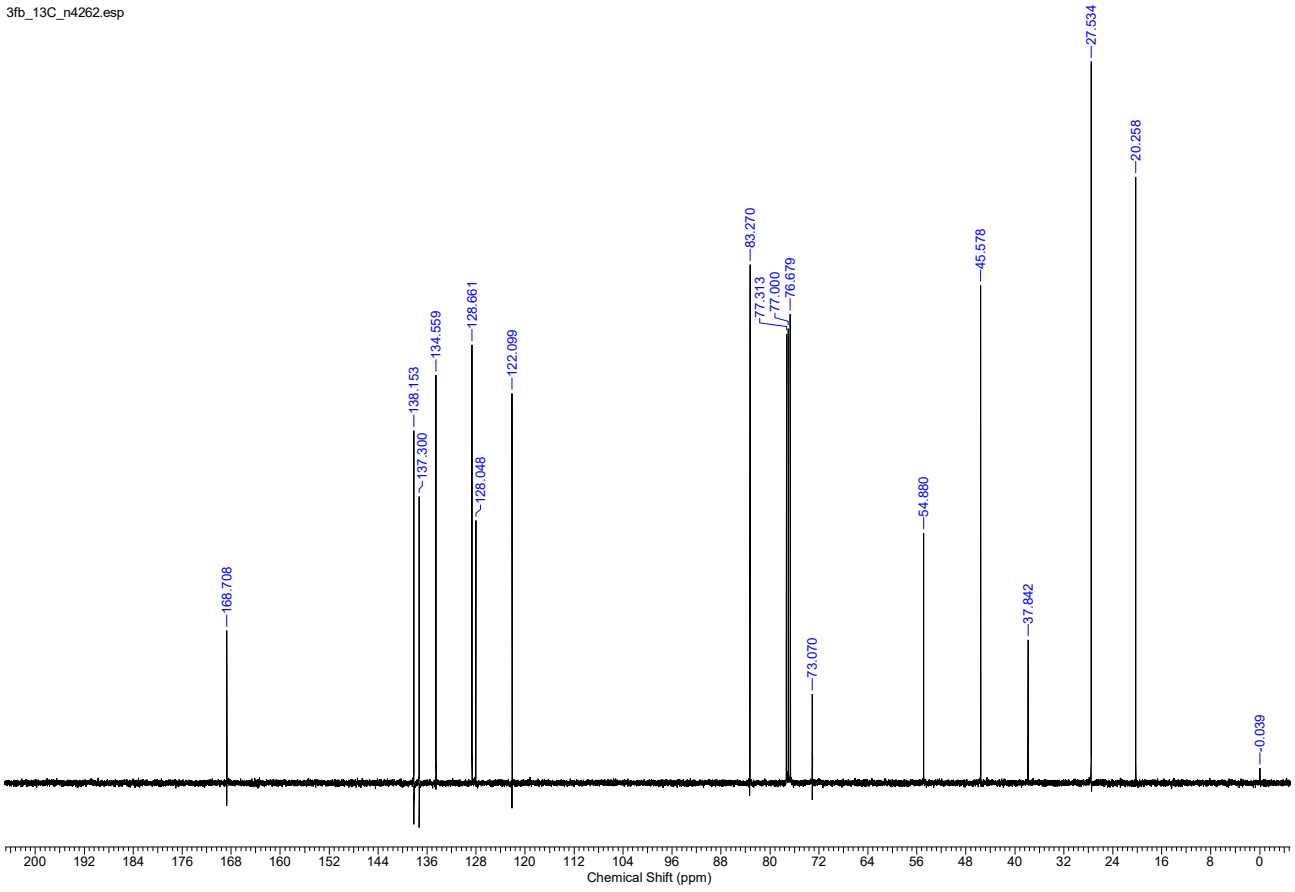


3fb

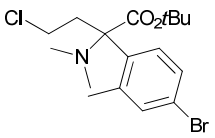
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3fb_13C_n4262.esp



4fb_1H_n4263.esp

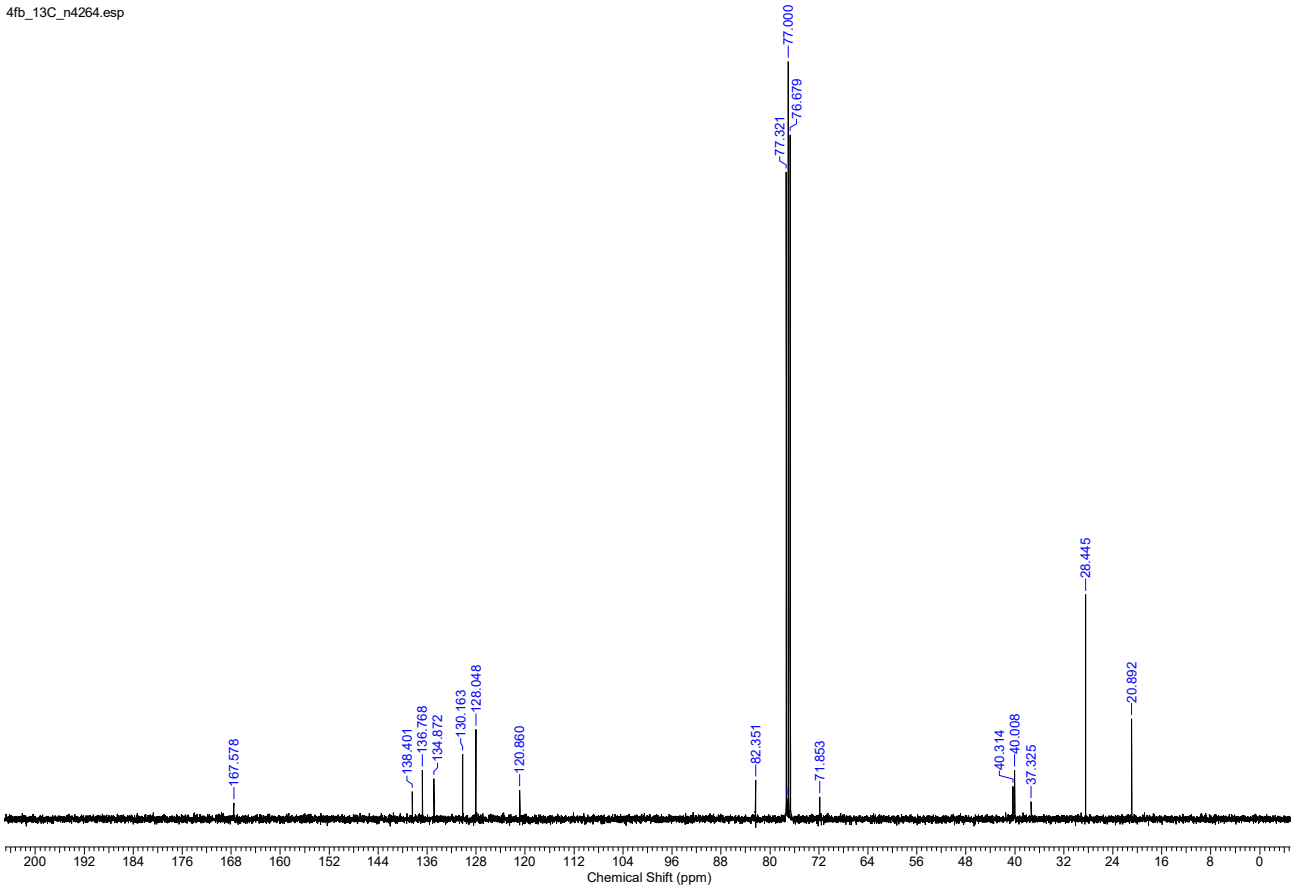


4fb

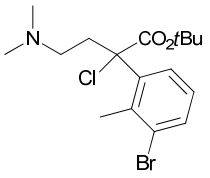
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4fb_13C_n4264.esp



3hb_1H_4567.esp

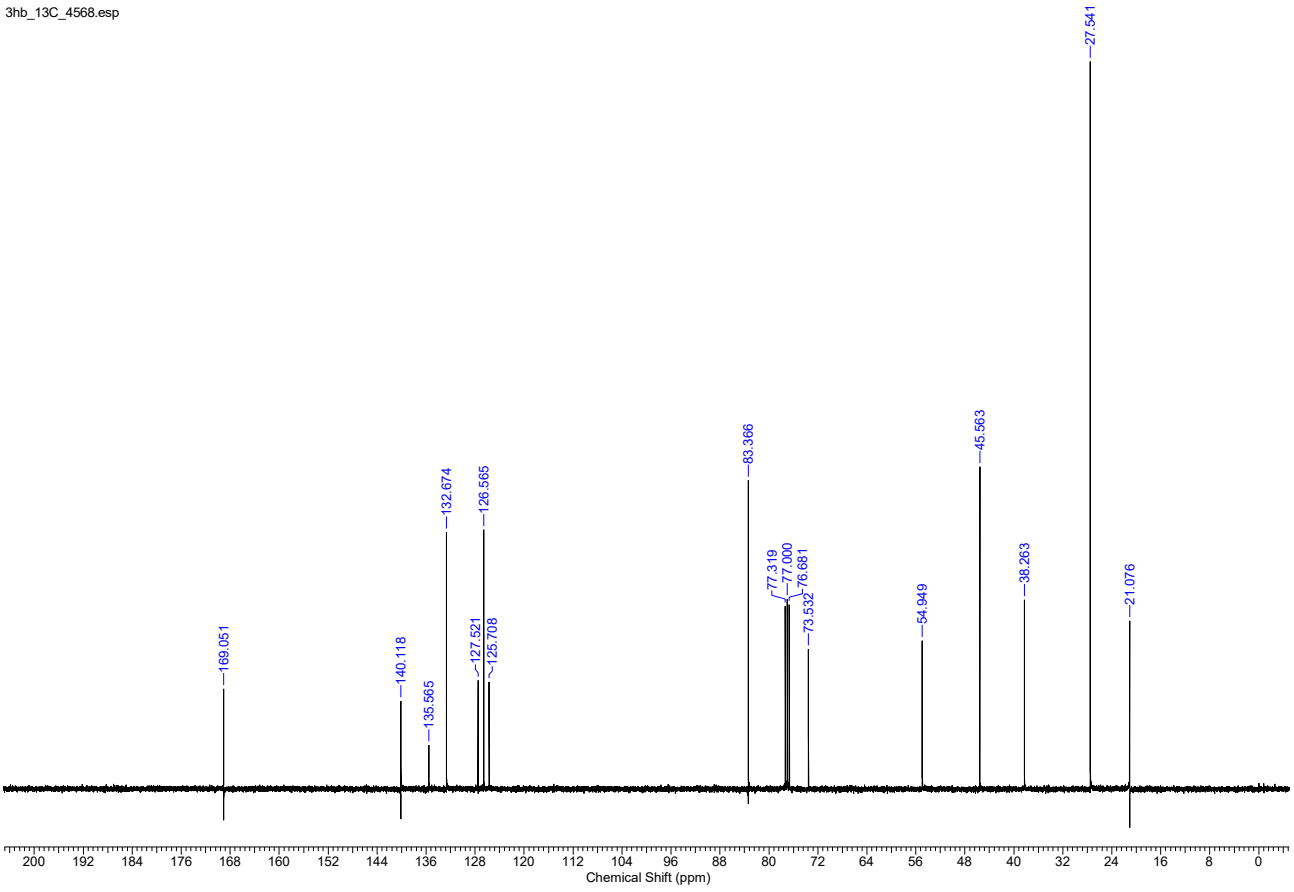


3hb

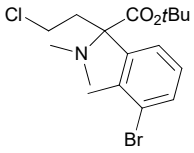
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

3hb_13C_4568.esp



4hb_1H_4563.esp

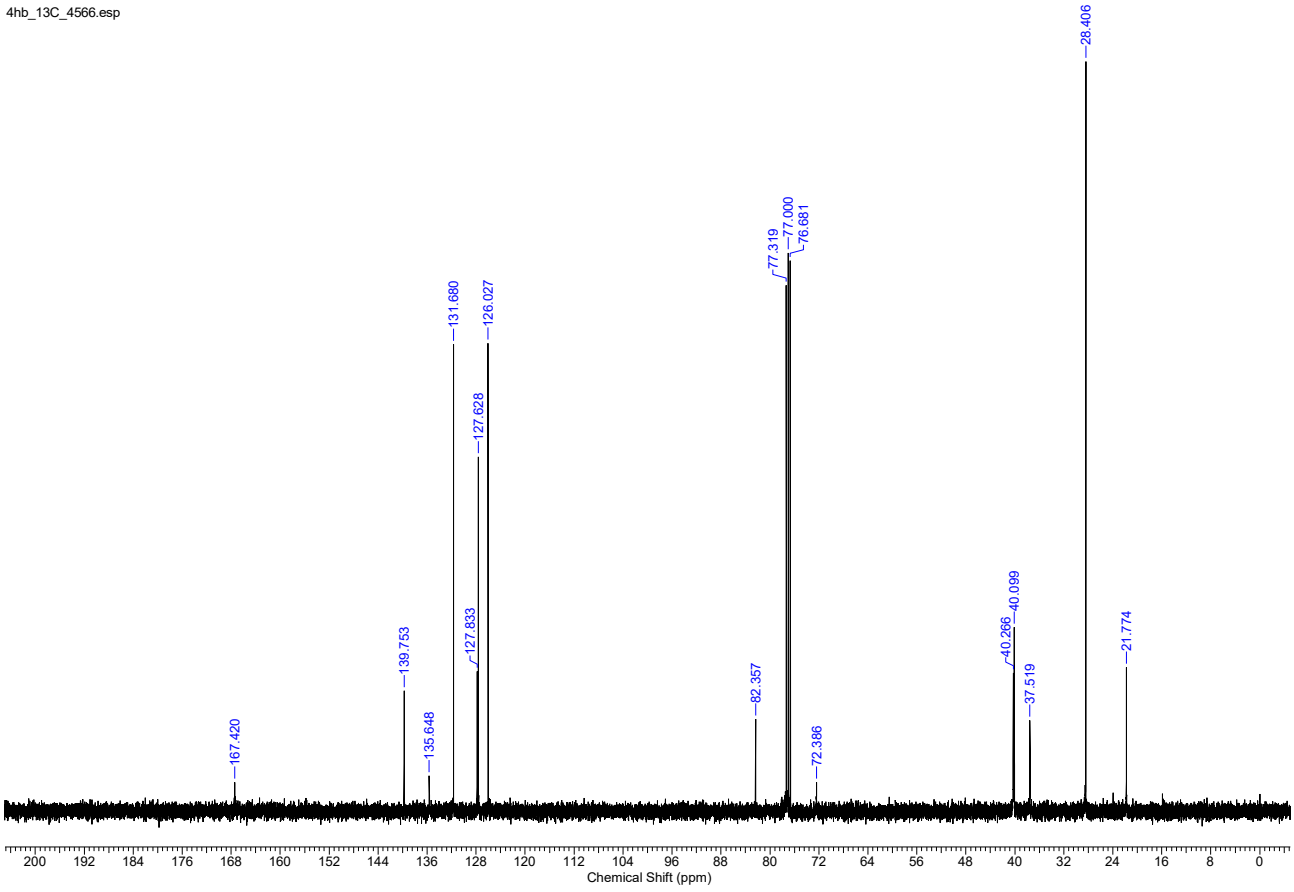


4hb

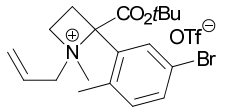
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

4hb_13C_4566.esp



5_1H_ace_4614.esp



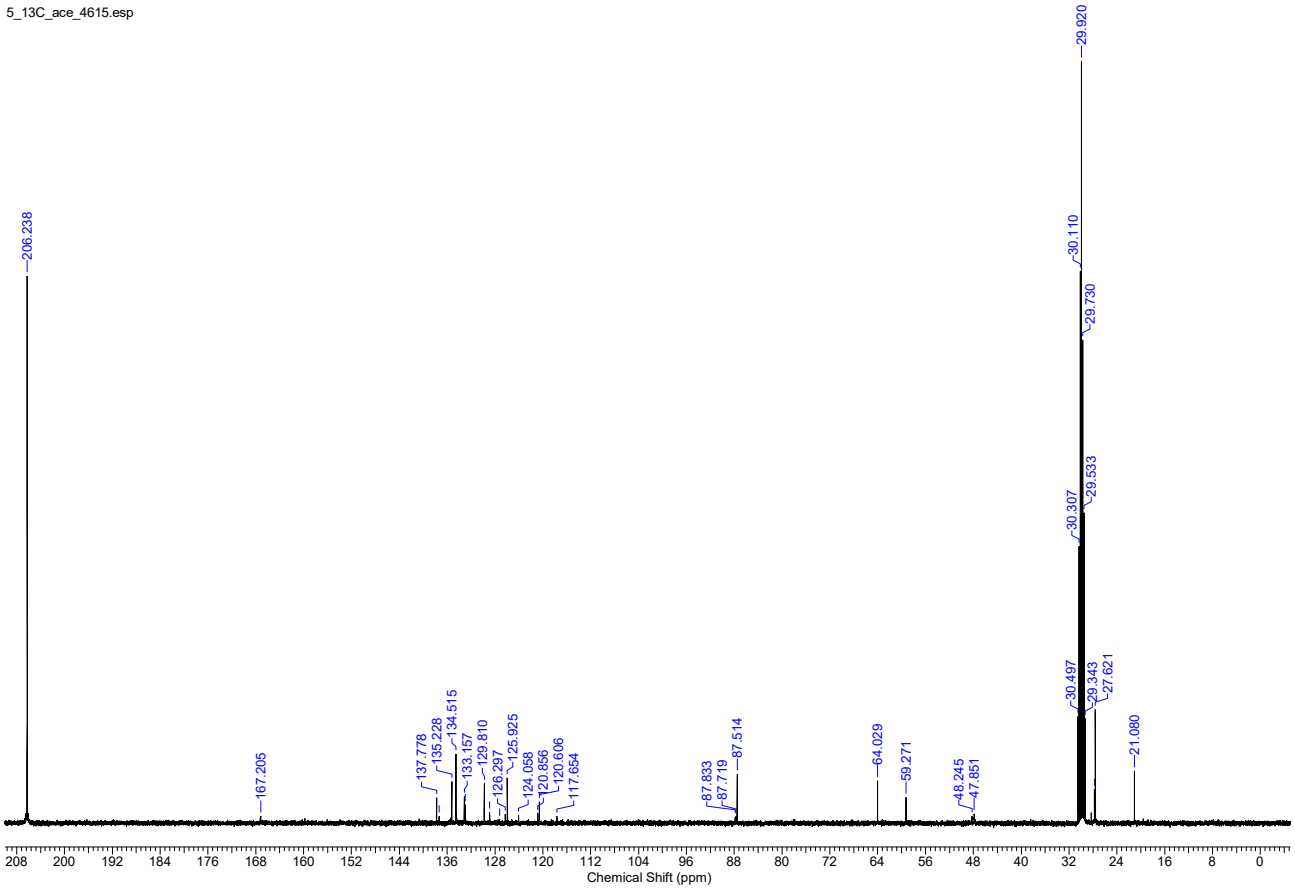
5

8/2 dr

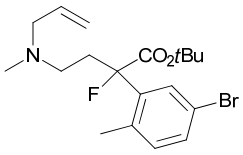
^{1}H (400 MHz, acetone-d_6)

^{13}C (101 MHz, acetone-d_6)

5_13C_ace_4615.esp



6_1H_4481.esp

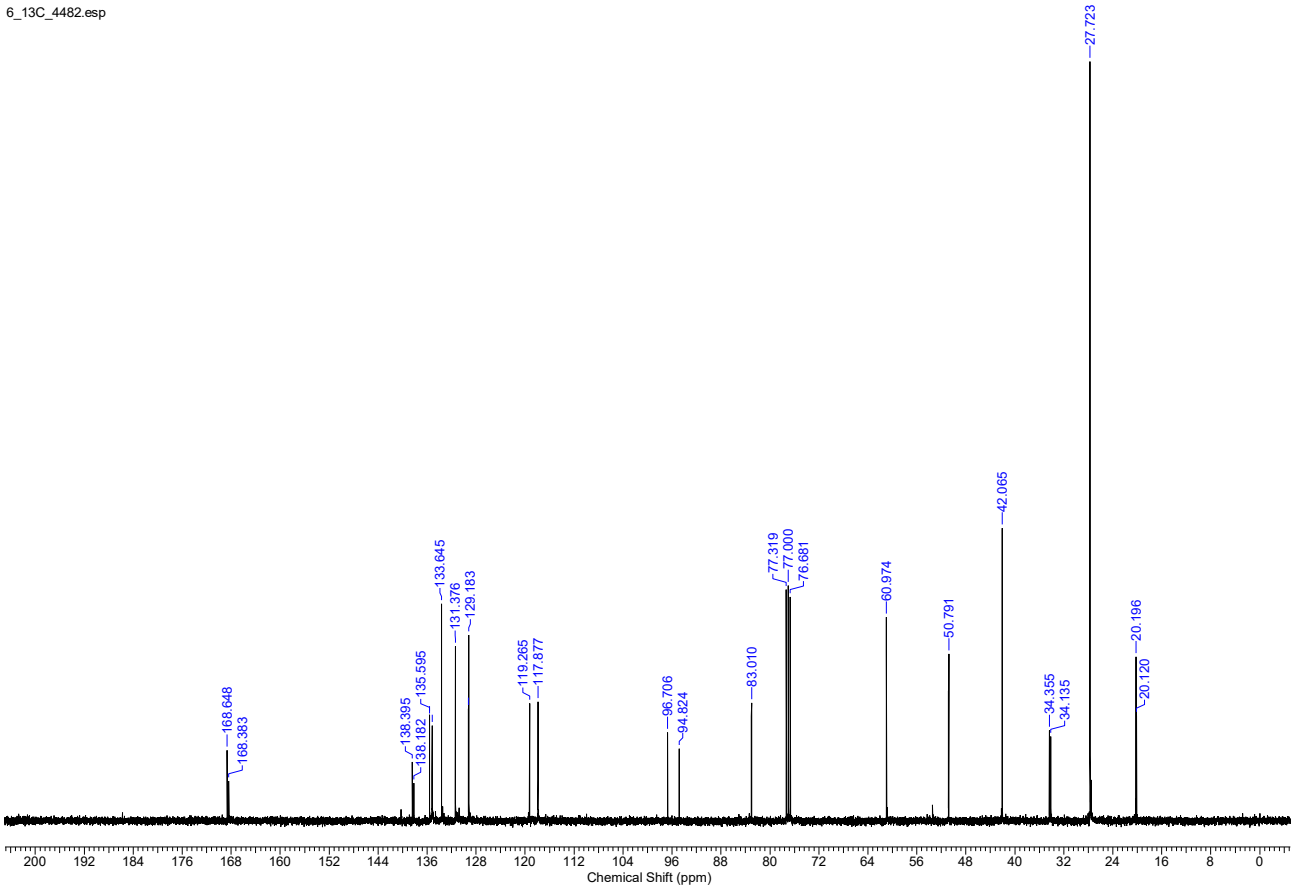


6

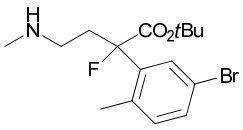
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

6_13C_4482.esp



7_1H_44074.esp

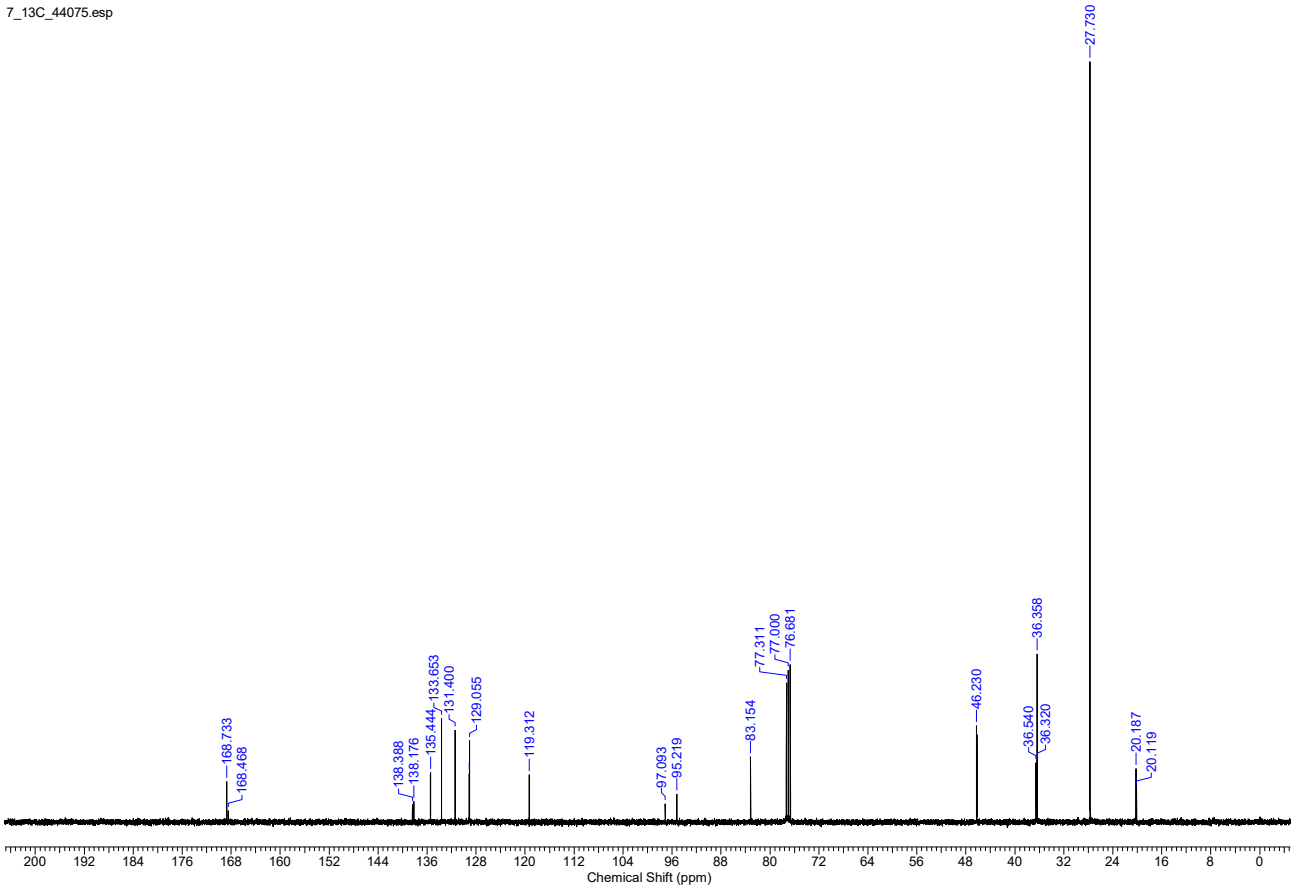


7

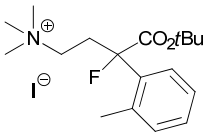
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

7_13C_44075.esp



8-I_1H_4537.esp

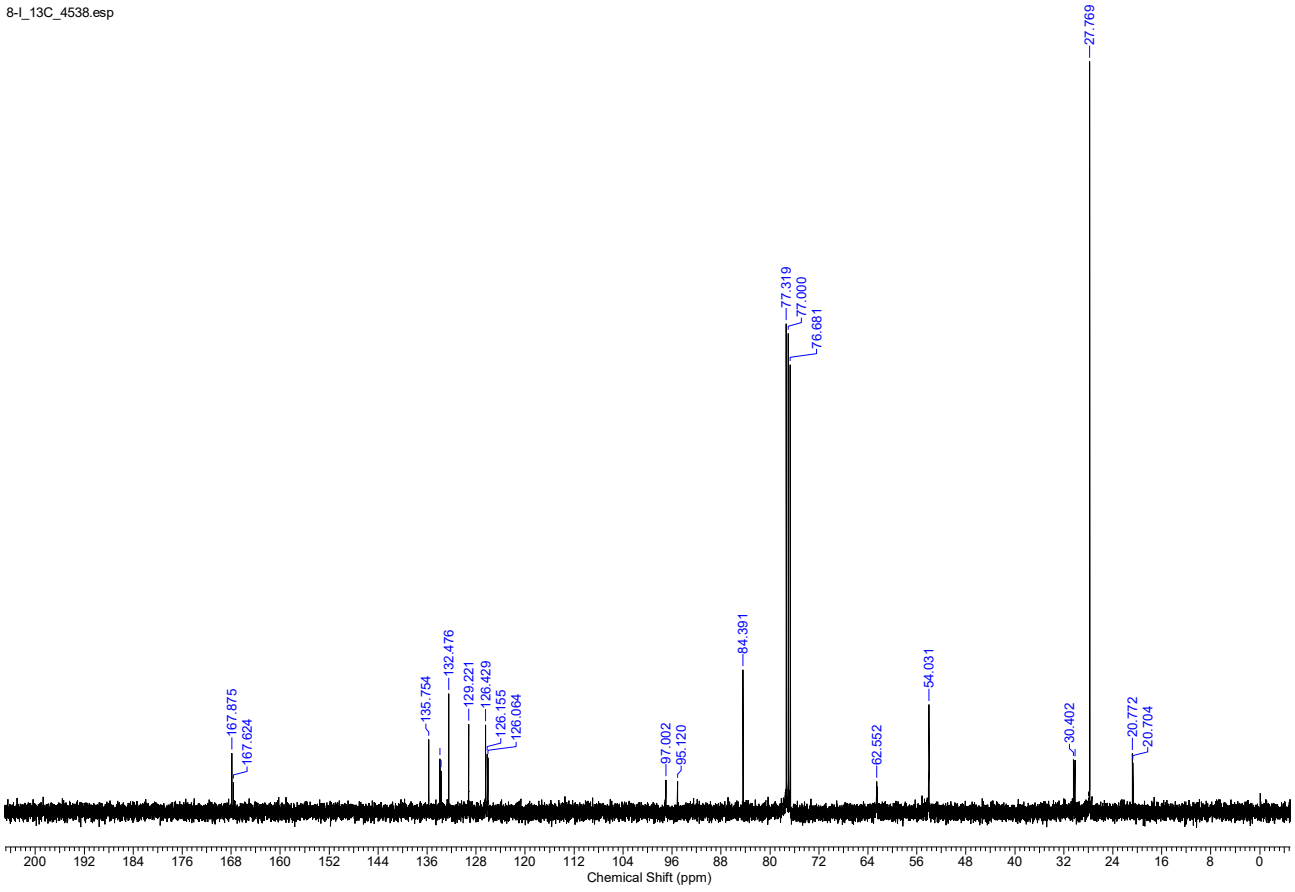


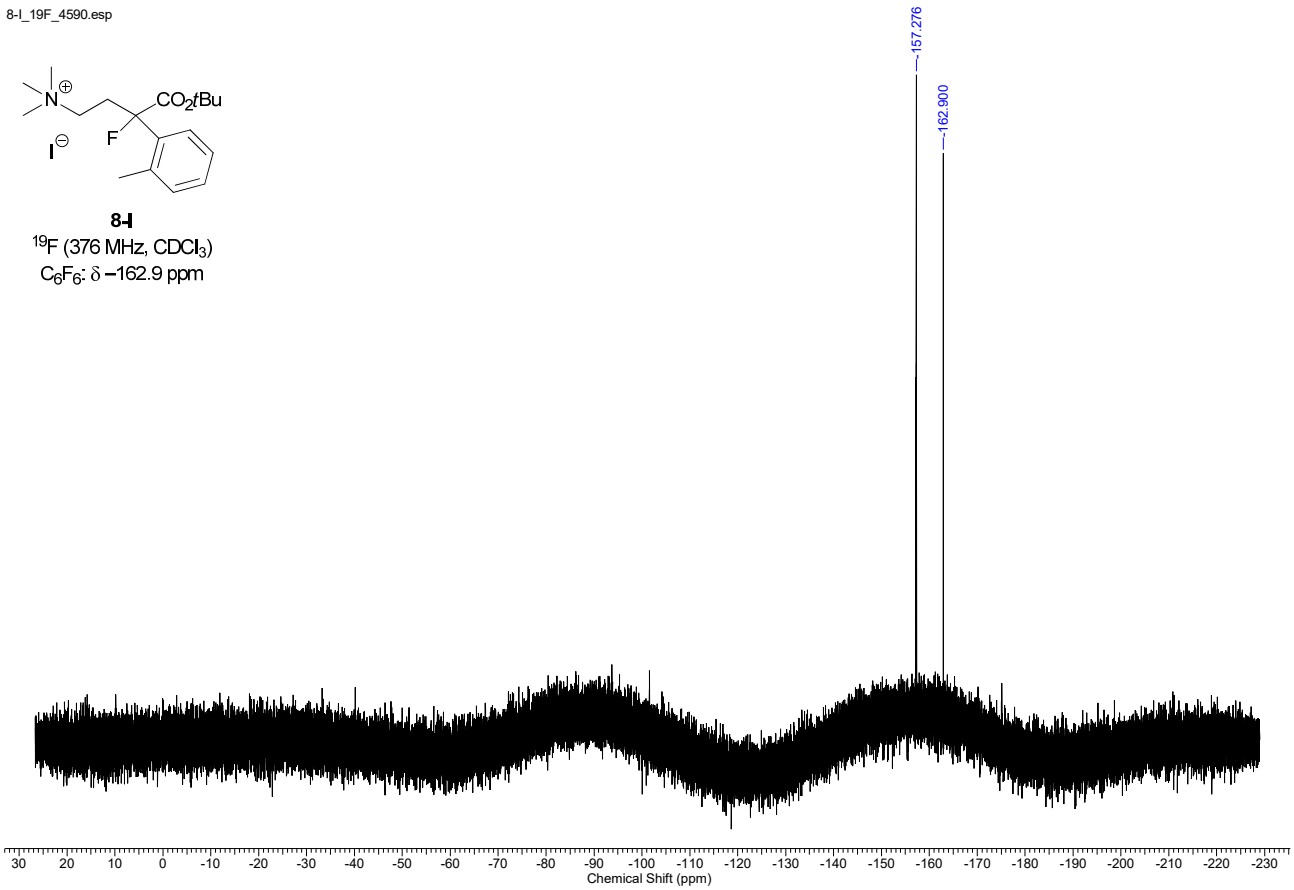
8-I

^{1}H (400 MHz, $CDCl_3$)

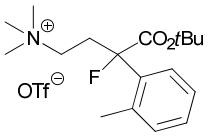
^{13}C (101 MHz, $CDCl_3$)

8-I_13C_4538.esp




8-I_19F_4590.esp
157.276
162.900
CO2tBu
F
I
8-I
19F (376 MHz, CDCl3)
C6F6: δ −162.9 ppm
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
Chemical Shift (ppm)

8-OTf_1H_4571.esp

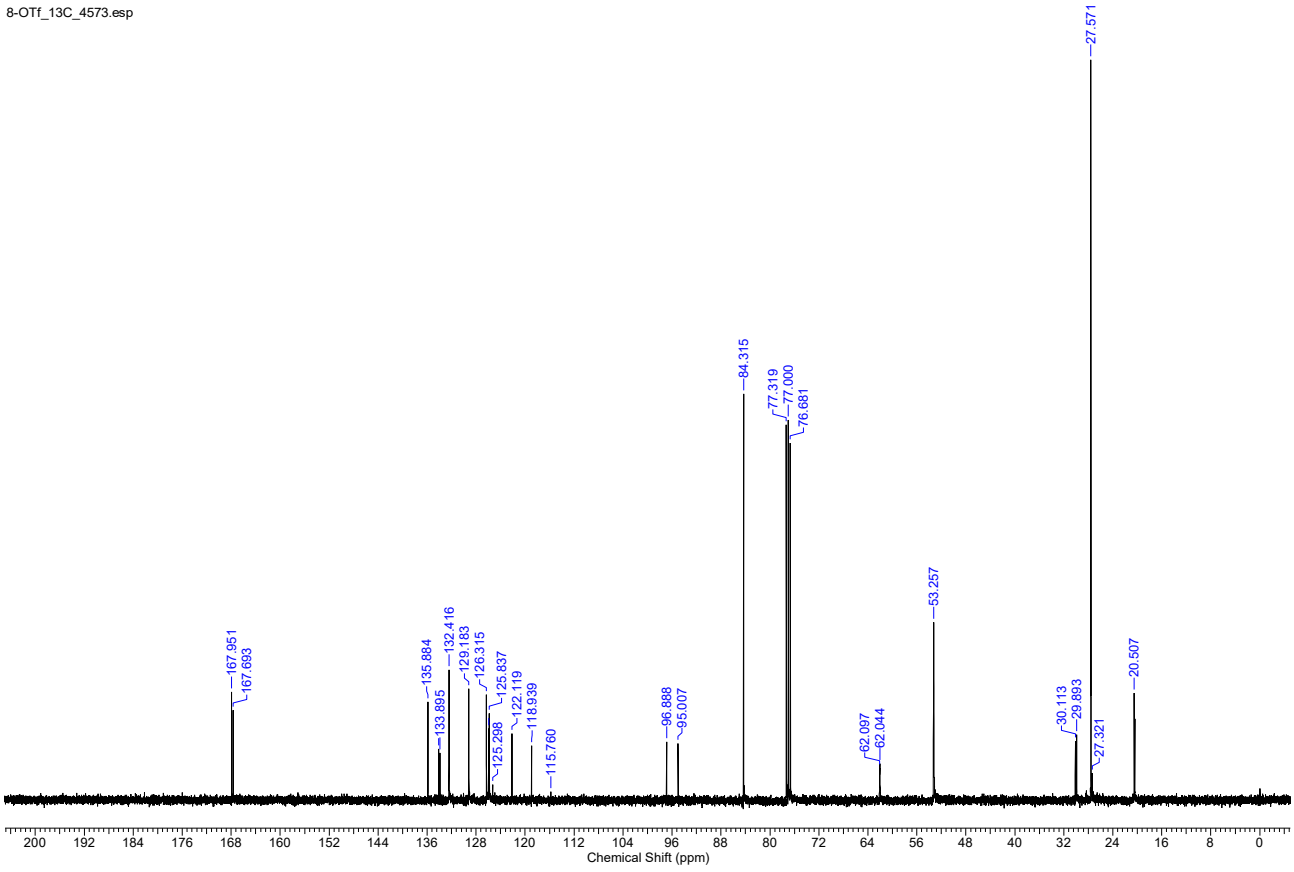


8-OTf

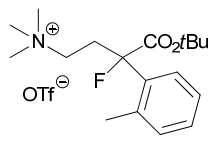
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

8-OTf_13C_4573.esp



8-OTf_19F_4594.esp

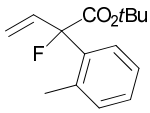


8-OTf

^{19}F (376 MHz, $CDCl_3$)

C_6F_6: δ –162.9 ppm

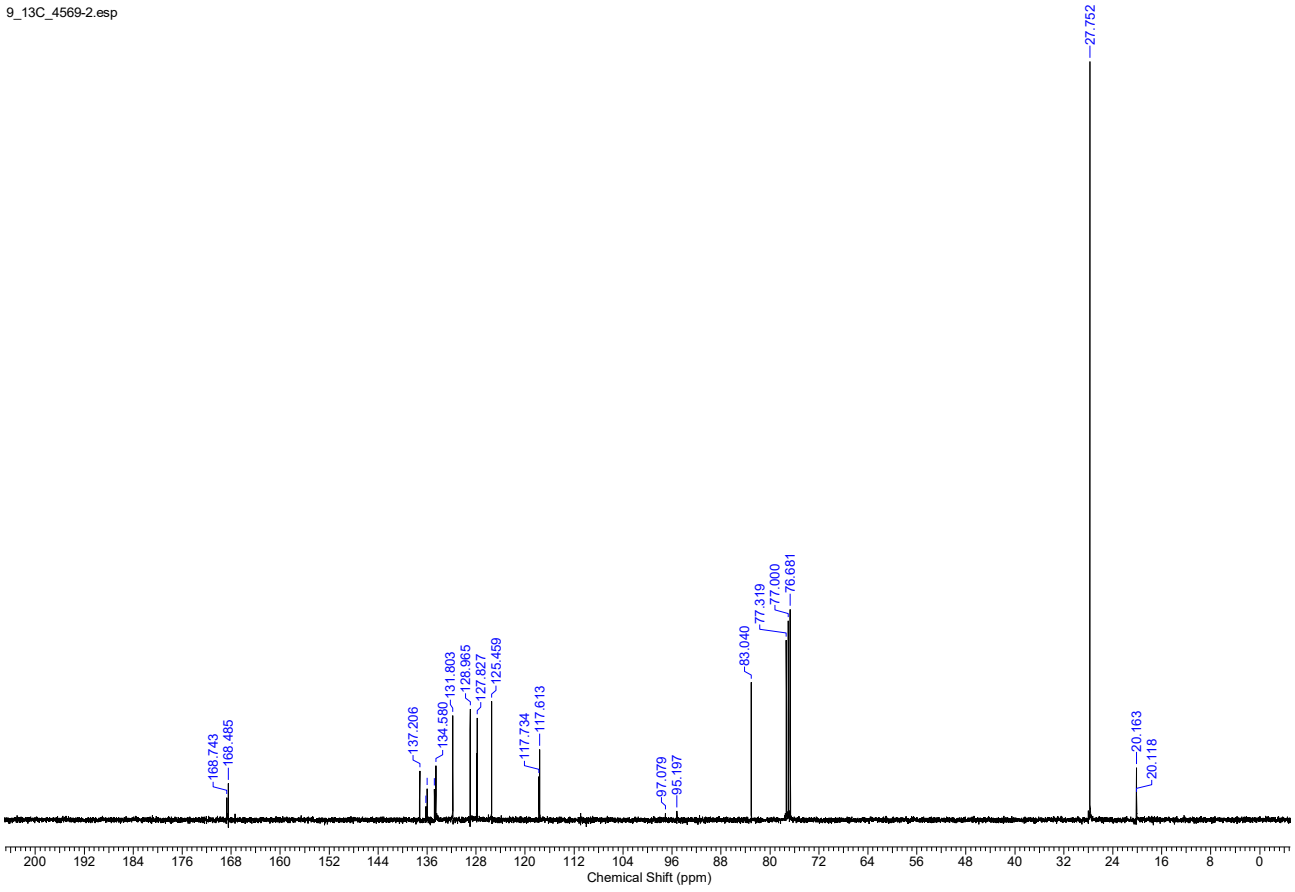
9_1H_4562.esp



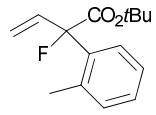
9

^{1}H (400 MHz, $CDCl_3$)
^{13}C (101 MHz, $CDCl_3$)

9_13C_4569-2.esp



9_19F_4596.esp

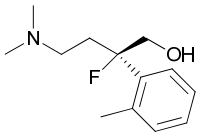


9

^{19}F (376 MHz, $CDCl_3$)

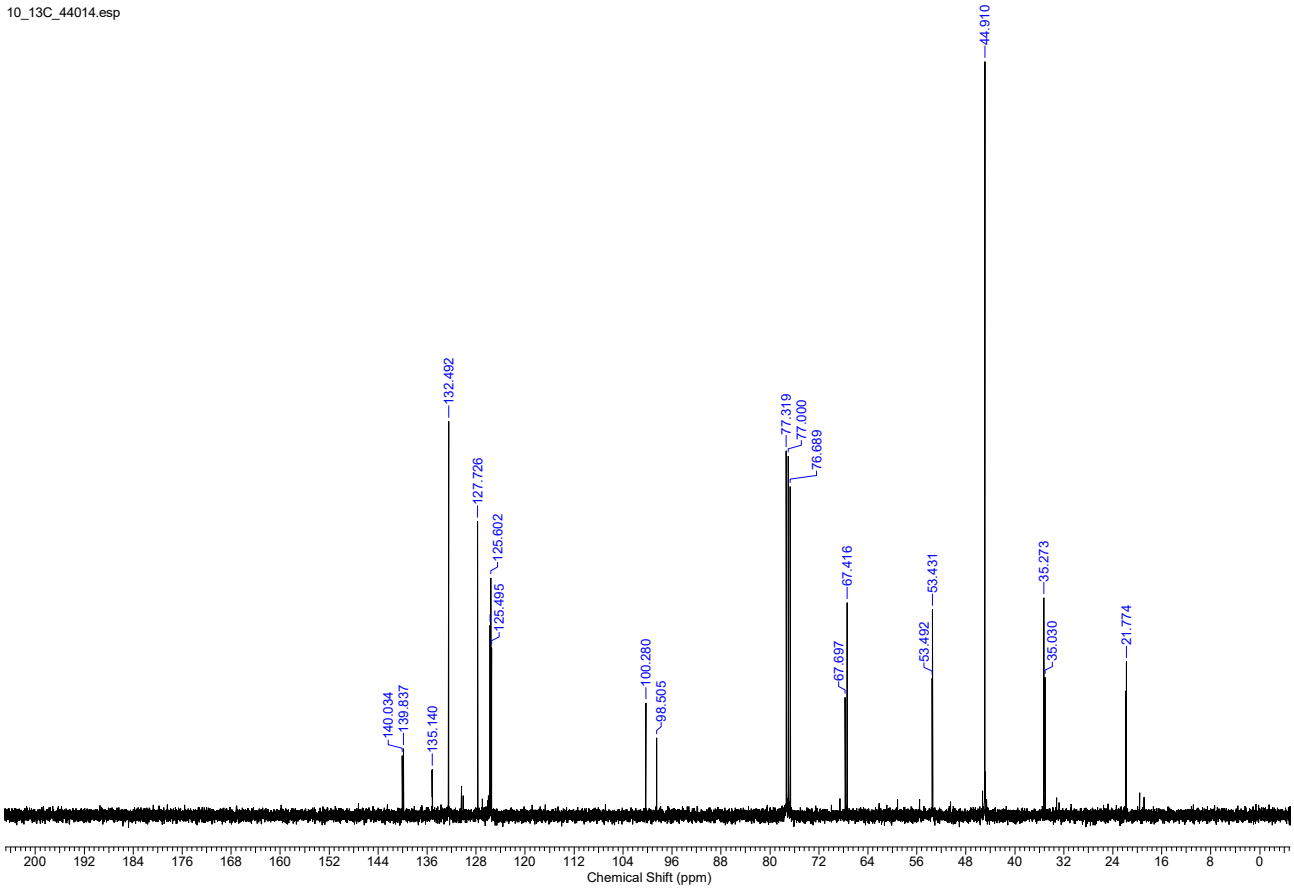
C_6F_6: δ −162.9 ppm

10_1H_44010.esp

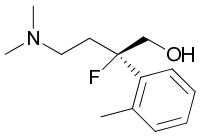


(*R*)-**10**
^{1}H (400 MHz, $CDCl_3$)
^{13}C (101 MHz, $CDCl_3$)

10_13C_44014.esp

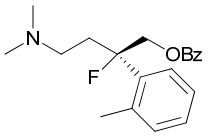


10_19F_44011.esp



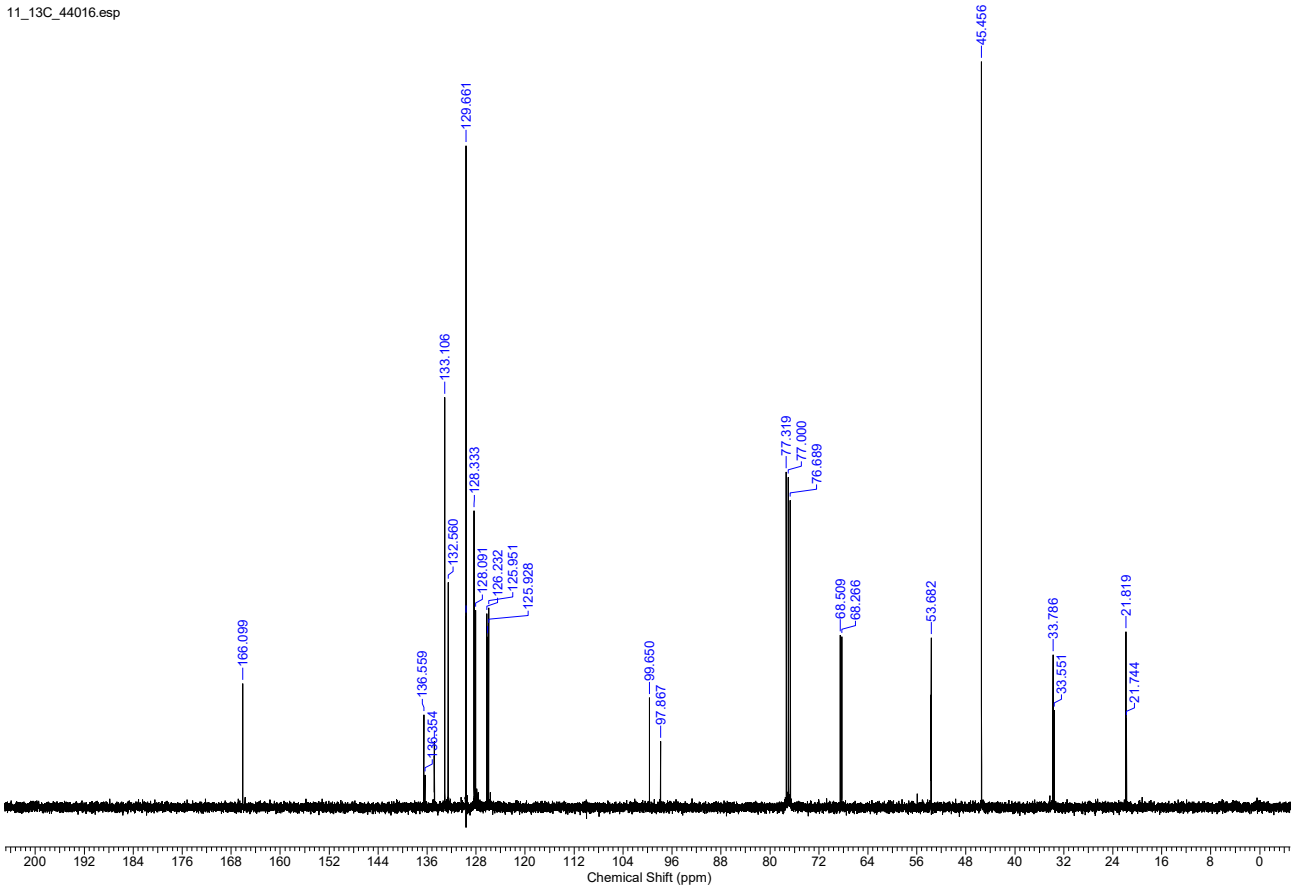
(*R*)-**10**
^{19}F (376 MHz, $CDCl_3$)
C_6F_6: δ −162.9 ppm

11_1H_44015.esp

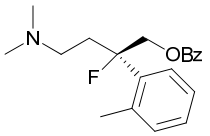


(*R*)-**11**
^{1}H (400 MHz, $CDCl_3$)
^{13}C (101 MHz, $CDCl_3$)

11_13C_44016.esp

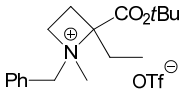


11_19F_44017.esp



(*R*)-**11**
^{19}F (376 MHz, $CDCl_3$)
C_6F_6: δ −162.9 ppm

12_1H_n4317.esp

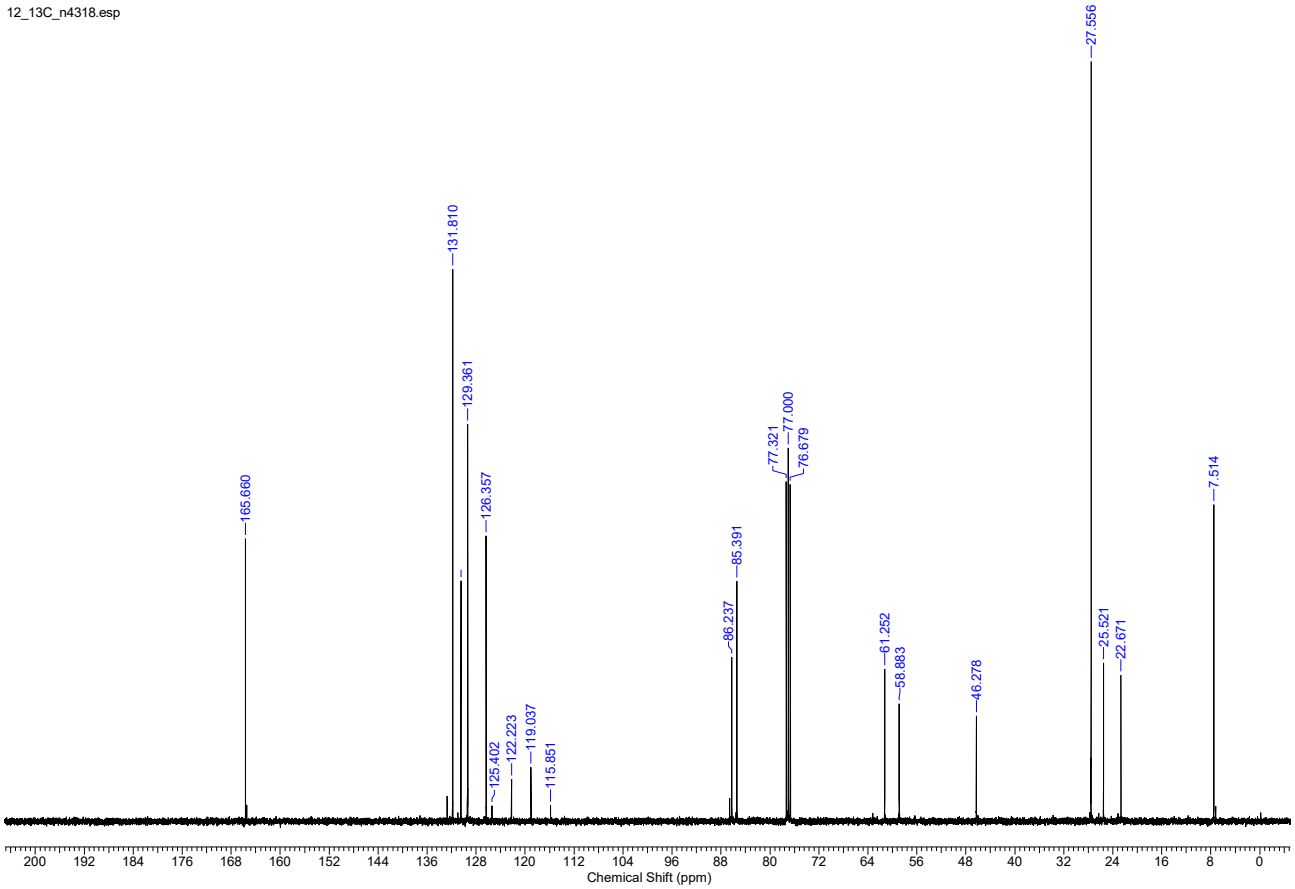


12

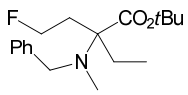
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

12_13C_n4318.esp



14_1H_4655.esp

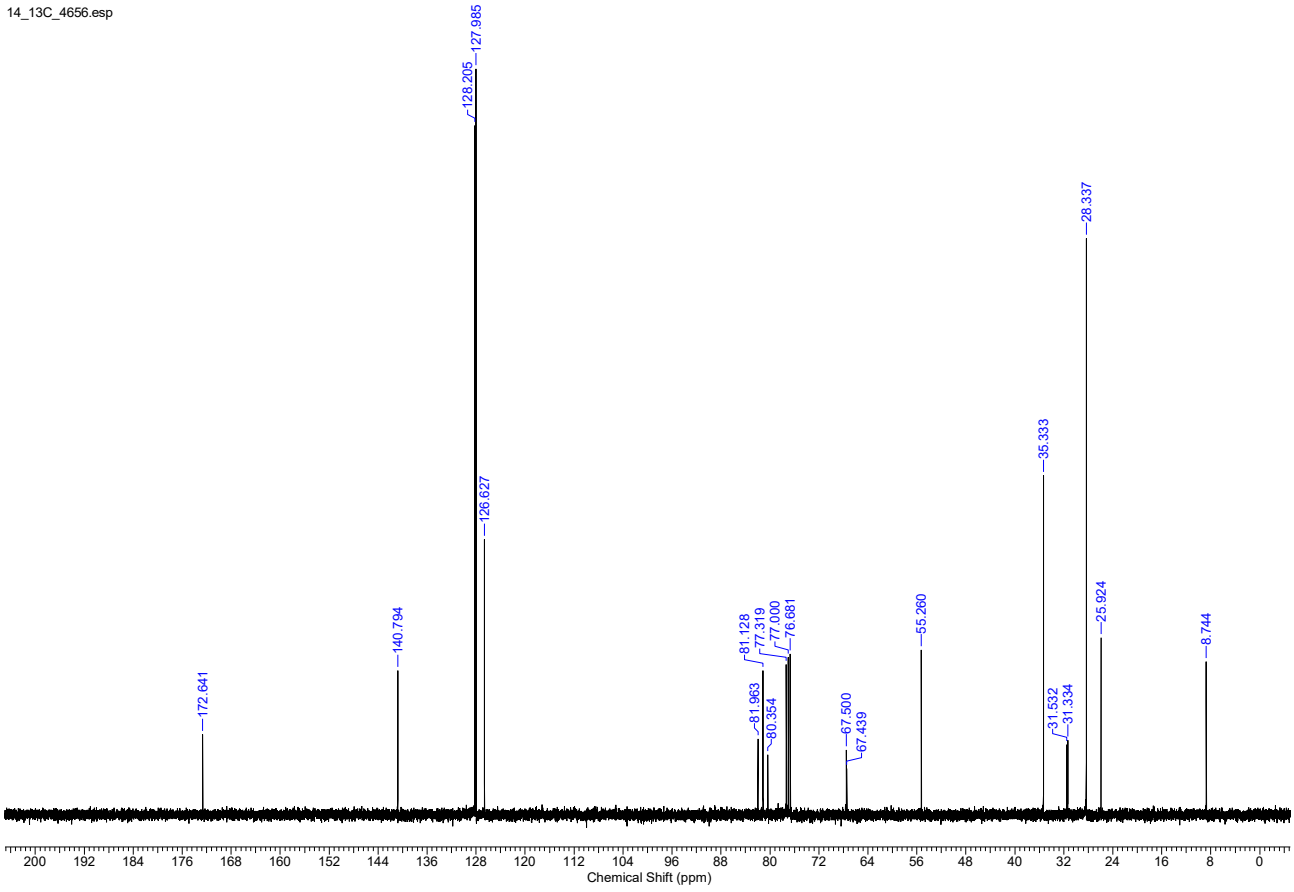


14

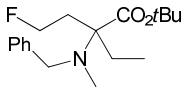
^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

14_13C_4656.esp



14_19F_4658.esp

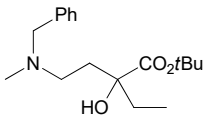


14

^{19}F (376 MHz, $CDCl_3$)

C_6F_6: δ −162.9 ppm

15_1H_4659.esp



15

^{1}H (400 MHz, $CDCl_3$)

^{13}C (101 MHz, $CDCl_3$)

15_13C_44081.esp