Enantioselective Aldol Reaction of Cyclic Ketones with Aryl Aldehydes Catalyzed by Cyclohexanediamine Derived Salt in the Presence of Water

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General information: ^{1}H NMR spectra were recorded with a Bruker AM-300 (300 M Hz), or Varian VXR (300 MHz) spectrometer. ^{19}F NMR spectra were recorded with a Bruker AM-300 (282 MHz) with $CFCl_3$ as an external standard (negative for up field). ^{13}C NMR spectra were recorded with a Bruker AM-400 (100 MHz) spectrometer. MS was recorded with a Hewlett–Packard HP-5989A spectrometer. Elemental analyses were obtained with a Perkin–Elmer 2400 Series II Elemental Analyzer. Infrared spectra were measured with a Perkin–Elmer 983 spectrometer. Optical rotations were measured on a JASCO P-1030 Polarimeter at λ=589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on Waters 515 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column. N,N-disubstituted diamines were prepared according to literature procedure.[1, 2] Unless otherwise noted, reagents were commercially available and used as received.

Typical procedure for the synthesis of catalyst 1a-1c and 1f:
Aqueous hydrochloric acid (0.9 mmol) was added to the solution of diamine (1 mmol) in water (2 mL) and the mixture was stirred overnight. Then the solution was washed by ethyl ether (3×10 mL). Water was removed under reduced pressure to give the diamine salt. The salt in methanol (3 mL) was added slowly to the methanol (3 mL) solution of sodium 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (420 mg, 1 mmol). The reaction mixture was stirred for 12 hours. The solvent was concentrated in vacuum and the residue was added to dichloromethane (5 mL). After filtration, the solvent was removed under reduced pressure and the pure product was obtained.

(*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidinium
1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (**1a**)
Viscous oil; 82% yield; $[\alpha]_D^{25}$ =14.1 (c = 0.60, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.70 (1H, tt, J = 51.1, 5.3 Hz), 3.78~3.66 (1H, m), 3.28~3.19 (2H, m), 2.87 (1H, t, J = 12.5 Hz), 2.81~2.67 (2H, m), 2.66~2.52 (3H, m), 2.24~2.10 (1H, m), 2.09~1.95 (2H, m), 1.89~1.75 (4H, m), 1.71~1.57 (m, 1H); ^{19}F NMR (CD_3OD, 282 MHz) δ -83.94~-84.10 (m, 2F), -85.43~-85.67 (m, 2F), -120.08 (s, 2F), -129.40~-129.55 (m, 2F), -132.34~-132.55 (m, 2F), -140.33~-140.67 (m, 2F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 58.07, 56.41, 53.88, 45.46, 28.16, 23.59, 23.33; IR (film) (cm^{-1}): 3080, 2975, 2810, 1618, 1465, 1349, 1285, 1193, 1146, 1054, 974, 913, 811, 640; MS (ESI): 155.2 [cation]$^+$, 397.0 [anion]$^-$; Anal. Calcd for $C_{15}H_{20}F_{12}N_2O_4S$: C, 32.62; H, 3.65; N, 5.07; Found: C, 32.70; H, 3.71; N, 4.89.

(*S*)-1-(pyrrolidin-2-ylmethyl)piperidinium
1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (**1b**)
Viscous oil; 84% yield; $[\alpha]_D^{23}$ = 16.9 (c = 0.86, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.70 (1H, tt, J = 51.2, 5.6 Hz), 3.89~3.75 (1H, m), 3.29~3.17 (2H, m), 2.76~2.52 (4H, m), 2.45 (2H, br), 2.23~1.93 (3H, m), 1.73~1.55 (5H, m), 1.55~1.36 (2H, m); ^{19}F NMR (CD_3OD, 282 MHz) δ -83.91~-84.09 (m, 2F), -85.43~-85.65 (m, 2F), -120.07 (s, 2F), -129.33~-129.55 (m, 2F), -132.32~-132.60 (m, 2F), -140.34~-140.68 (m, 2F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 58.99, 56.57, 54.31, 45.40, 27.99, 25.12, 23.56, 23.38; IR (film) (cm^{-1}): 3085, 2946, 2862, 1618, 1459, 1350, 1285, 1245, 1197, 1147, 1055, 975, 811, 640; MS (ESI): 169.2 [cation]$^+$, 396.8 [anion]$^-$; Anal. Calcd for $C_{16}H_{22}F_{12}N_2O_4S \cdot H_2O$: C, 32.88; H, 4.14; N, 4.79; Found: C, 33.24; H, 4.04; N, 4.58.

(*S*)-4-(pyrrolidin-2-ylmethyl)morpholin-4-ium 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (**1c**)
Viscous oil; 84% yield; $[\alpha]_D^{24}$ = 21.3 (*c* = 0.66, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.71 (1H, tt, *J* = 51.0, 5.8 Hz), 3.88~3.78 (1H, m), 3.74~3.64 (4H, m), 3.29~3.19 (2H, m), 2.70~2.51 (4H, m), 2.49~2.33 (2H, m), 2.22~1.95 (3H, m), 1.71~1.57 (1H, m); ^{19}F NMR (CD_3OD, 282 MHz) δ -83.95~-84.10 (m, 2F), -85.45~-85.65 (m, 2F), -120.10 (s, 2F), -129.39~-129.55 (m, 2F), -132.39~-132.56 (m, 2F), -140.33~-140.69 (m, 2F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 66.53, 58.92, 56.79, 53.13, 45.44, 27.72, 23.51; IR (film) (cm^{-1}): 3090, 2968, 2866, 2825, 1620, 1460, 1350, 1285, 1249, 1195, 1147, 1118, 1055, 975, 811, 640; MS (ESI): 171.2 [cation]$^+$, 396.8 [anion]$^-$; Anal. Calcd for $C_{15}H_{20}F_{12}N_2O_5S$: C, 31.70; H, 3.55; N, 4.93; Found: C, 31.47; H, 3.94; N, 4.80.

(*1R,2R*)-2-(dipropylamino)cyclohexanaminium 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (**1f**)
Viscous oil; 84% yield; $[\alpha]_D^{26}$ = -47.4 (*c* = 1.69, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.69 (1H, tt, *J* = 50.8, 5.7 Hz), 2.99~2.87 (1H, m), 2.56~2.32 (5H, m), 2.15~2.05(1H, m), 1.98~1.70 (3H, m), 1.61~1.22 (8H, m), 0.90 (6H, t, *J* = 7.4 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -83.86~-84.00 (m, 2F), -85.38~-85.60 (m, 2F), -119.97 (s, 2F), -129.34~-129.46 (m, 2F), -132.30~-132.47 (m, 2F), -140.27~-140.60(m, 2F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 63.51, 51.57, 30.43, 24.64, 24.08, 23.48, 21.17 (br), 11.29; IR (film) (cm^{-1}): 2964, 2879, 1461, 1349, 1285, 1255, 1201, 1147, 1054, 971, 809, 639; MS (ESI): 199.6 [cation]$^+$, 397.0 [anion]$^-$; Anal. Calcd for $C_{18}H_{28}F_{12}N_2O_4S$: C, 36.25; H, 4.73; N, 4.70; Found: C, 36.39; H, 4.79; N, 4.64.

Typical procedure for the synthesis of catalyst 1d and 1e:
To the solution of diamine (0.55 mmol) in water (2 mL) was added the water (3 mL) solution of 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonic acid (199 mg, 0.5 mmol) and the mixture was stirred overnight. An oil product was obtained and crowded at the bottom. The crude product was first separated by decantion and washed by water (3×4 mL). And then it was dissolved in dichloromethane (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the pure product was obtained.

(*S*)-*N,N*-dipropyl-*N*-(pyrrolidin-2-ylmethyl) aminium 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (**1d**)
Viscous oil; 93% yield; $[\alpha]_D^{23}$ = 18.5 (*c* = 0.31, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.71 (1H, tt, *J* = 51.2, 5.6 Hz), 3.78~3.67 (1H, m), 3.28~3.20 (2H, m), 2.75~2.40 (6H, m), 2.21~1.94 (3H, m), 1.72~1.60 (1H, m), 1.60~1.36 (4H, m), 0.90 (6H, t, *J* = 7.3 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -83.96~-84.11 (m, 2F), -85.46~-85.73 (m, 2F), -120.11 (s, 2F), -129.41~-129.56 (m, 2F), -132.33~-132.66 (m, 2F), -140.37~-140.72(m, 2F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 57.20, 55.32, 54.90, 45.04, 27.76, 23.26, 19.30, 11.31; IR (film) (cm^{-1}): 3084, 2969, 2880, 2821, 1614, 1463, 1350, 1055, 975, 811, 640; MS (ESI): 185.5 [cation]$^+$, 397.0 [anion]$^-$; Anal. Calcd for $C_{17}H_{26}F_{12}N_2O_4S$: C, 35.06; H, 4.50; N, 4.81; Found: C, 35.53; H, 4.61; N, 4.56.

(*S*)-*N,N*-dibutyl-*N*-(pyrrolidin-2-ylmethyl) aminium 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)ethanesulfonate (**1e**)
Viscous oil; 91% yield; $[\alpha]_D^{24}$ = 16.4 (*c* = 0.88, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.71 (1H,

tt, J = 51.2, 5.6 Hz), 3.78~3.66 (1H, m), 3.28~3.20 (2H, m), 2.75~2.42 (6H, m), 2.32~1.91 (3H, m), 1.73~1.58 (1H, m); 1.56~1.19 (8H, m), 0.94 (6H, t, J = 7.2 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -83.92~-84.10 (m, 2F), -85.42~-85.68 (m, 2F), -120.06 (s, 2F), -129.36~-129.56 (m, 2F), -132.35~-132.61 (m, 2F), -140.31~-140.69(m, 2F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 57.09, 54.75, 53.13, 44.99, 28.14, 27.78, 23.32, 20.26, 13.71; IR (film) (cm^{-1}): 3084, 2965, 2940, 2877, 1466, 1350, 1286, 1249, 1195, 1145, 1054, 974, 809, 639; MS (ESI): 213.5 [cation]$^+$, 397.0 [anion]$^-$; Anal. Calcd for $C_{19}H_{30}F_{12}N_2O_4S$: C, 37.38; H, 4.95; N, 4.59; Found: C, 37.62; H, 5.02; N, 4.46.

Typical procedure for the synthesis of catalyst 1g-1h and 1k-1m:

To the dichloromethane (2 mL) solution of CF_3SO_3H (1 mmol) was added the solution of (1*R*,2*R*)-2-(dipropylamino)cyclohexanamine (1 mmol) in dichloromethane (2 mL) and the mixture was stirred overnight. The solvent was removed under reduced pressure. The resulting residue was then purified by flash chromatography to give (1*R*,2*R*)-2-(dipropylamino)cyclohexanaminium trifluoromethanesulfonate (**1g**). Viscous oil; 90% yield; $[\alpha]_D^{25}$ = -72.8 (c = 1.07, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.06~2.93 (1H, m), 2.55~2.25 (5H, m), 2.17~2.06(1H, m), 1.99~1.71 (3H, m), 1.64~1.18 (8H, m), 0.91 (6H, t, J = 7.4 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -80.56 (s, 3F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 120.14 (q, J = 318.7 Hz), 63.28, 51.51, 30.28, 24.67, 24.14, 23.45, 21.11, 11.39; IR (film) (cm^{-1}): 2943, 2875, 1616, 1477, 1287, 1243, 1167, 1031, 639; MS (ESI): 199.6 [cation]$^+$, 149.1 [anion]$^-$; Anal. Calcd for $C_{13}H_{27}F_3N_2O_3S$: C, 44.81; H, 7.81; N, 8.04; Found: C, 45.20; H, 7.48; N, 7.98.

(1*R*,2*R*)-2-(dipropylamino)cyclohexanaminium 2,2,2-trifluoroacetate (**1h**)

White solid; 96% yield; $[\alpha]_D^{24}$ = -74.8 (c = 0.48, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.06~2.94 (1H, m), 2.55~2.29 (5H, m), 2.16~2.06(1H, m), 2.00~1.70 (3H, m), 1.62~1.22 (8H, m), 0.91 (6H, t, J = 7.3 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -77.39 (s, 3F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 161.94, 62.28, 51.35, 29.29, 24.83, 24.14, 23.40, 21.78 (br), 11.63; IR (film) (cm^{-1}): 2967, 2938, 2878, 1677, 1586, 1420, 1200, 1174, 1137, 832, 797, 720; MS (ESI): 199.6 [cation]$^+$, 113.2 [anion]$^-$; Anal. Calcd for $C_{14}H_{27}F_3N_2O_2 \cdot H_2O$: C, 50.89; H, 8.85; N, 8.48; Found: C, 50.86; H, 8.68; N, 8.08.

(1*R*,2*R*)-2-(diethylamino)cyclohexanaminium trifluoromethanesulfonate (**1k**)

Viscous oil; 95% yield; $[\alpha]_D^{23}$ = -57.9 (c = 0.55, $CHCl_3$); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.07~2.92 (1H, m), 2.76~2.59 (2H, m), 2.56~2.37(3H, m), 2.17~2.05 (1H, m), 1.98~1.69 (3H, m), 1.44~1.23 (m, 4H), 1.08 (6H, t, J = 7.2 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -80.55 (s, 3F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 120.13 (q, J = 327.3 Hz), 62.94, 51.57, 43.62 (br), 30.60, 24.65, 24.09, 23.81, 13.29; IR (film) (cm^{-1}): 3512, 3114, 2942, 2868, 1624, 1477, 1458, 1388, 1285, 1246, 1167, 1031, 759, 639; MS (ESI): 171.4 [cation]$^+$, 149.0 [anion]$^-$; Anal. Calcd for $C_{11}H_{23}F_3N_2O_3S$: C, 41.24; H, 7.24; N, 8.74; Found: C, 41.35; H, 7.32; N, 8.66.

(1*R*,2*R*)-2-(dimethylamino)cyclohexanaminium trifluoromethanesulfonate (**1l**)

White solid; 92% yield; $[\alpha]_D^{25}$ = -27.3 (c = 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.09 (3H, br), 2.93~2.81 (1H, m), 2.66~2.53 (1H, m), 2.45 (6H, s), 2.24~2.12 (1H, m), 1.98~1.74 (3H, m), 1.56~1.18 (4H, m); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.67 (s, 3F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 120.12 (q, J = 321.4 Hz), 66.22, 51.06, 39.39 (br), 31.56, 24.32, 24.22, 21.69; IR (film) (cm^{-1}):

3500, 3103, 2945, 2870, 1653, 1475, 1255, 1228, 1170, 1032, 640; MS (ESI): 143.4 [cation]$^+$, 149.0 [anion]$^-$; Anal. Calcd for $C_9H_{19}F_3N_2O_3S \cdot 0.5H_2O$: C, 35.87; H, 6.69; N, 9.30; Found: C, 35.43; H, 6.43; N, 9.01.

(1*R*,2*R*)-2-(dibutylamino)cyclohexanaminium trifluoromethanesulfonate (**1m**)
White solid; 95% yield; $[\alpha]_D^{25}$ = -68.9 (*c*=1.03, $CHCl_3$) ^{1}H NMR (CD_3OD, 300 MHz) δ 3.06~2.88 (1H, m), 2.65~2.31 (5H, m), 2.17~2.05 (1H, m), 1.99~1.67 (3H, m), 1.53~1.22 (12H, m), 0.95 (6H, t, *J* = 7.3 Hz); ^{19}F NMR (CD_3OD, 282 MHz) δ -80.59 (s, 3F); ^{13}C NMR ($CDCl_3$, 100MHz) δ 120.17 (q, *J* = 325.7 Hz), 63.34, 51.65, 30.24, 24.68, 24.09, 23.51, 20.39, 13.67; IR (film) (cm^{-1}): 3219, 3161, 2956, 2872, 2839, 1619, 1465, 1443, 1287, 1239, 1221, 1166, 1030, 989, 637; MS (ESI): 227.4 [cation]$^+$, 149.0 [anion]$^-$; Anal. Calcd for $C_{15}H_{31}F_3N_2O_3S$: C, 47.85; H, 8.30; N, 7.44; Found: C, 48.12; H, 8.37; N, 7.58.

Typical procedure for the aldol reaction:
To a suspension of catalyst **1m** (18.8 mg, 0.05 mmol) in water (2 mL) was added cyclic ketone (1 mmol). After stirring for one minute, aryl aldehyde (0.5 mmol) was introduced. Then the reaction was kept at room temperature for the time indicated in Table 2. After completion of the reaction, the product precipitated as solid. The crude product was collected by filtration. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude product. Further column chromatography gave the pure product.

2-(Hydroxy(p-nitrophenyl)methyl)cyclohexanone (**4a**)
95% Yield; $[\alpha]_D^{27}$ = -12.1 (*c*=0.75, $CHCl_3$), 95% ee; ^{1}H NMR (300MHz, $CDCl_3$): *δ* 8.21 (2H, d, *J* = 8.7 Hz), 7.51 (2H, d, *J* = 8.7 Hz), 4.90 (1H, dd, *J* = 8.4, 3.0 Hz), 4.09 (1H, d, *J* = 3.0 Hz), 2.65~2.45 (2H, m), 2. 43~2.30 (1H, m), 2.18~2.08 (1H, m), 1.87~1.78 (1H, m), 1.72~1.34 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 17.8 min, minor enantiomer tr = 22.8 min.

2-(Hydroxy(m-nitrophenyl)methyl)cyclohexanone (**4b**)
94% Yield; $[\alpha]_D^{22}$= -33.3 (*c*=1.09, $CHCl_3$), 96% ee; ^{1}H NMR (300MHz, $CDCl_3$): *δ* 8.21 (1H, s), 8.16 (1H, d, *J*= 7.8 Hz), 7.67 (1H, d, *J* = 7.5 Hz), 7.53 (1H, t, *J* = 7.8 Hz), 4.89 (1H, dd, *J* = 8.7, 3.0 Hz), 4.12(1H, d, *J* = 3.0 Hz), 2.67~2.56 (1H, m), 2.55~2.45 (1H, m), 2.44~2.30 (1H, m), 2.17~2.07 (1H, m), 1.87~1.78 (1H, m), 1.75~1.23 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 214 nm, 0.7mL/min; major enantiomer tr = 19.12 min, minor enantiomer tr = 15.64 min.

2-(Hydroxy(p-(trifluoromethyl)phenyl)methyl)cyclohexanone (**4c**)
94% Yield; $[\alpha]_D^{22}$ = -23.8 (*c* = 1.05, $CHCl_3$), 96% ee; ^{1}H NMR (300MHz, $CDCl_3$): *δ* 7.61 (2H, d, *J*= 7.8 Hz), 7.45 (2H, d, *J* = 7.8 Hz), 4.85 (1H, dd, *J* = 8.8, 2.7 Hz), 4.03 (1H, d, *J* = 2.7 Hz), 2.66~2.55 (1H, m), 2.54~2.45(1H, m), 2.43~2.30 (1H, m), 2.17~2.06 (1H, m), 1.87~1.76 (1H, m), 1.76~1.23 (4H, m); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.5 (s, 3F); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 12.08 min, minor enantiomer tr = 14.09 min.

2-(Hydroxy-(*p*-cyanophenyl)methyl)cyclohexanone (**4d**)
82% Yield; $[\alpha]_D^{23}$ = -19.6 (c = 0.77, $CHCl_3$), 86% ee. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.65 (2H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.1 Hz), 4.84 (1H, dd, J = 8.6, 3.0 Hz), 4.04 (1H, d, J = 3.0 Hz), 2.63~2.45 (2H, m), 2.43~2.30 (1H, m), 2.17~2.06 (1H, m), 1.88~1.78 (1H, m), 1.76~1.24 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 16.08 min, minor enantiomer tr = 19.63min.

2-(Hydroxy(p-bromophenyl)methyl)cyclohexanone (**4e**)
>99% Yield; $[\alpha]_D^{27}$ =-22.7 (c = 0.79, $CHCl_3$), 98% ee. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.47 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 8.1Hz), 4.75 (1H, dd, J = 8.9, 2.7 Hz), 3.98 (1H, d, J = 2.7 Hz), 2.62~2.43 (2H, m), 2.42~2.28 (1H, m), 2.16~2.03 (1H, m), 1.86~1.75 (1H, m), 1.75~1.19 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 13.32 min, minor enantiomer tr = 15.02 min.

2-((4-chlorophenyl)(hydroxy)methyl)cyclohexanone (**4f**)
96% Yield; $[\alpha]_D^{24}$ = -26.0 (c = 1.09, $CHCl_3$), 93% ee. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.29 (4H, dd, J = 20.0, 8.5 Hz), 4.76 (1H, dd, J = 8.6, 2.7 Hz), 3.98 (1H, d, J = 2.7 Hz), 2.64~2.43 (2H, m), 2,41~2.28 (1H, m), 2.18~2.00 (1H, m), 1.86~1.73 (1H, m), 1.70~1.16 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 12.55 min, minor enantiomer tr = 13.98 min.

2-((2,4-dichlorophenyl)(hydroxy)methyl)cyclohexanone (**4g**)
84% Yield; $[\alpha]_D^{23}$ = -21.3 (c = 1.06, $CHCl_3$), 97% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (1H, d, J = 8.4 Hz), 7.35 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 8.4, 2.0 Hz), 5.29 (1H, d, J = 8.0 Hz), 4.05 (1H, br), 2.68~2.57 (1H, m), 2.52~2.42 (1H, m), 2.41~2.27 (1H, m), 2.16~2.04 (1H, m), 1.88~1.78 (1H, m), 1.77~1.50 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (9:1hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 14.22 min, minor enantiomer tr = 16.89 min.

2-((3,4-dichlorophenyl)(hydroxy)methyl)cyclohexanone (**4h**)
94% Yield; $[\alpha]_D^{23}$ = -19.8 (c = 0.82, $CHCl_3$), 96% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (1H, d, J = 2.1 Hz), 7.41 (1H, d, J = 8.2 Hz), 7.15 (1H, dd, J = 8.2, 2.1 Hz), 4.74 (1H, dd, J = 8.7, 3.0 Hz), 4.01 (1H, d, J = 3.0 Hz), 2.60~2.44 (2H, m), 2.41~2.28 (1H, m), 2.16~2.05 (1H, m), 1.87~1.76(1H, m), 1.75~1.48 (3H, m), 1,40~1.23 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.30, 141.50, 132.76, 131.99, 130.49, 129.21, 126.66, 73.98, 57.42, 42.89, 30.94, 27.89, 24.90; IR (film, cm^{-1}): 3505, 2944, 2917, 1704, 1560, 1465, 1127, 1029, 888; MS (EI): 274, 272, 256, 254, 219, 175, 145; Anal. Calcd for $C_{13}H_{14}Cl_2O_2$: C, 57.16; H, 5.17; Found: C, 57.16; H, 5.10; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 20.02 min, minor enantiomer tr = 18.29 min.

2-(biphenyl-4-yl(hydroxy)methyl)cyclohexanone (**4i**)
56% Yield; $[\alpha]_D^{23}$ = -21.1 (c = 0.59, $CHCl_3$), 93% ee. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.61~7.54

(4H, m), 7.48~7.31 (5H, m), 4.84 (1H, dd, *J* = 8.8, 2.7 Hz), 3.99 (1H, d, *J* = 2.7 Hz), 2.74~2.60 (1H, m), 2.57~2.31 (2H, m), 2.17~2.03 (1H, m), 1.86~1.74 (1H, m), 1.72~1.22 (4H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 28.25 min, minor enantiomer tr = 31.62 min.

2-(hydroxy(p-nitrophenyl)methyl)cyclopentanone (**4j**)
34% Yield; $[\alpha]_D^{22}$ = 3.22 (*c* = 0.73, $CHCl_3$), 84% ee. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.23 (2H, d, *J* = 8.6 Hz), 7.54 (2H, d, *J* = 8.6 Hz), 5.43 (1H, br) (*syn*), 4.85 (1H, d, *J* = 9.2 Hz) (*anti*), 4.75 (1H, s), 2.56~1.63 (7H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (19:1 hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 40.85 min, minor enantiomer tr = 44.78 min.

3-(hydroxy(4-nitrophenyl)methyl)dihydro-2H-pyran-4(3H)-one (**4k**)
57% Yield; $[\alpha]_D^{23}$ = 3.6 (*c* = 0.90, $CHCl_3$), 98% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (2H, d, *J* = 8.6 Hz), 7.52 (2H, d, *J* = 8.6 Hz), 4.99 (1H, dd, *J* = 8.6, 3.4 Hz), 4.27~4.16 (1H, m), 3.84~3.67 (3H, m), 3.46 (1H, dd, *J* = 12.2, 9.9 Hz), 2.96~2.85 (1H, m), 2.75~2.63 (1H, m); 2.58~2.47 (1H, m); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1 hexane:2-propanol), 254 nm, 0.7 mL/min; major enantiomer tr = 30.05 min, minor enantiomer tr = 35.55 min.

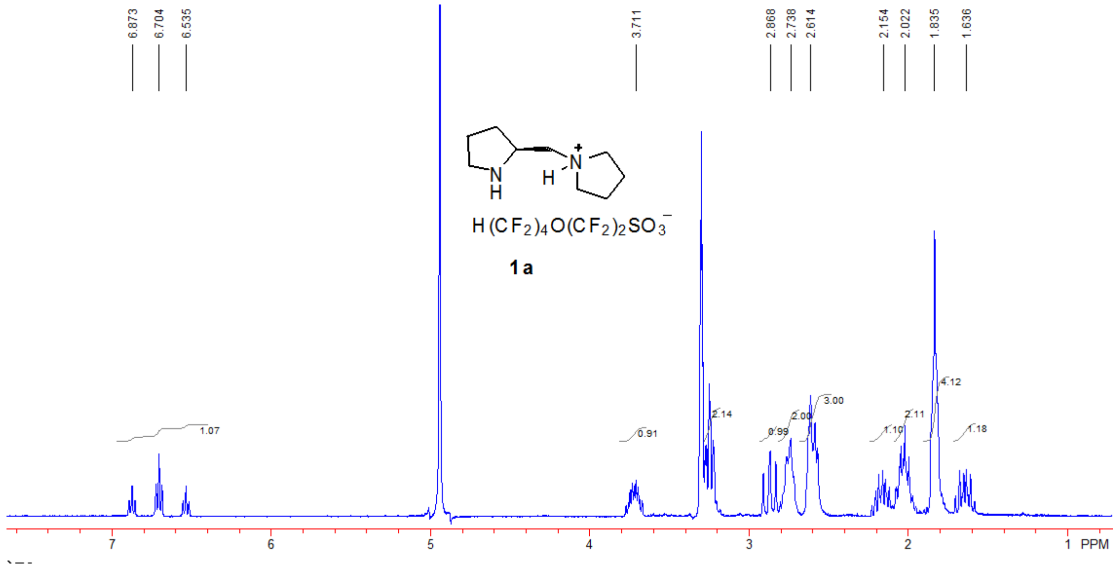
3-(hydroxy(4-(trifluoromethyl)phenyl)methyl)dihydro-2H-pyran-4(3H)-one (**4l**)
75% Yield; $[\alpha]_D^{27}$ = -9.5 (*c* = 0.76, $CHCl_3$), 95% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (2H, d, *J* = 7.6 Hz), 7.46 (2H, d, *J* = 7.6 Hz), 4.94 (1H, d, *J* = 8.5 Hz), 4.25~4,14 (1H, m), 3.81~3.65 (3H, m), 3.41 (1H, t, *J* = 11.0 Hz), 2.94~2.83 (1H, m), 2.75~2.61 (1H, m); 2.58~2.48 (1H, m); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.5 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.40, 144.20, 130.45 (q, *J* = 30.6 Hz), 126.95, 125.57 (q, *J* = 3.6 Hz), 123.94 (q, *J* = 272 Hz), 71.48, 69.73, 68.32, 57.82, 42.65; IR (film, cm^{-1}): 3446, 2979, 2868, 1701, 1621, 1478, 1335, 1096, 843; MS (EI): 274, 256, 175,173, 145; Anal. Calcd for $C_{13}H_{13}F_3O_3$: C, 56.94; H, 4.78; Found: C, 56.92; H, 4.72; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (4:1hexane:2-propanol), 214 nm, 0.7 mL/min; major enantiomer tr = 12.79 min, minor enantiomer tr = 15.29 min.

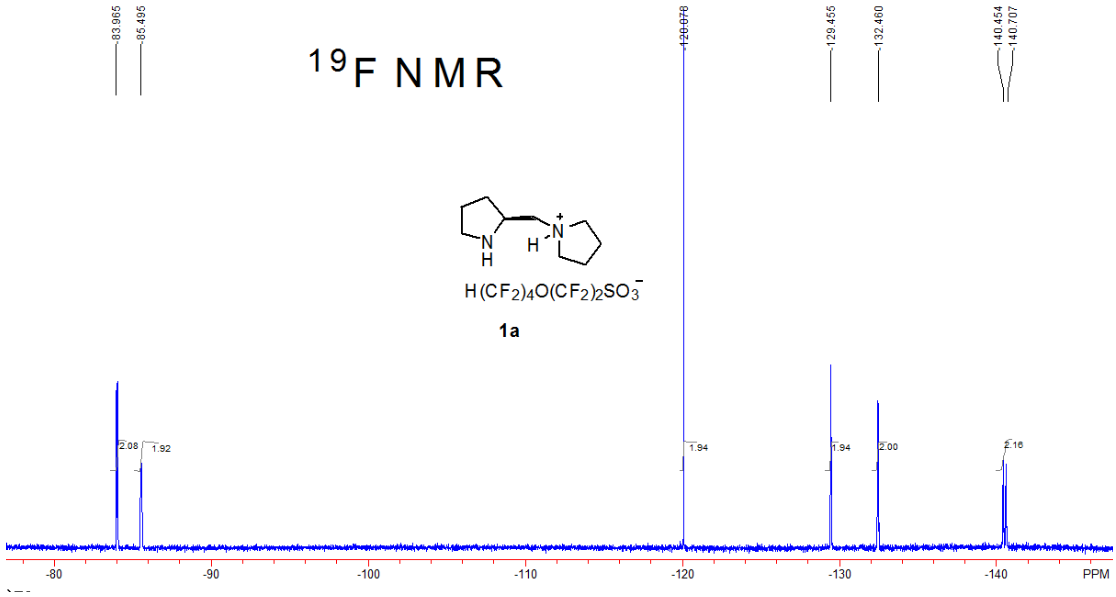
Crystal data for **1m (**CCDC 737246**)**: $C_{15}H_{31}F_3N_2O_3S$, *M* = 376.48, Orthorhombic, space group P2 (1)2(1)2(1), *a* = 7.6593 (7) Å, *b* = 12.5747 (11) Å, *c* =20.4376(18) Å, alpha = beta = gamma = 90 deg. *V* = 1968.4(3) Å^3, *T* = 293(2) K, *Z* = 4, μ(Mo-Kα) = 0.206 mm^{-1}, *R*1 = 0.0451, *wR*2 = 0.1018 (I > 2σ (I)); *R*1 = 0.0521, *wR*2 = 0.1048 (all data). Reflections collected / unique: 11642 / 4266 [R(int) = 0.0617].

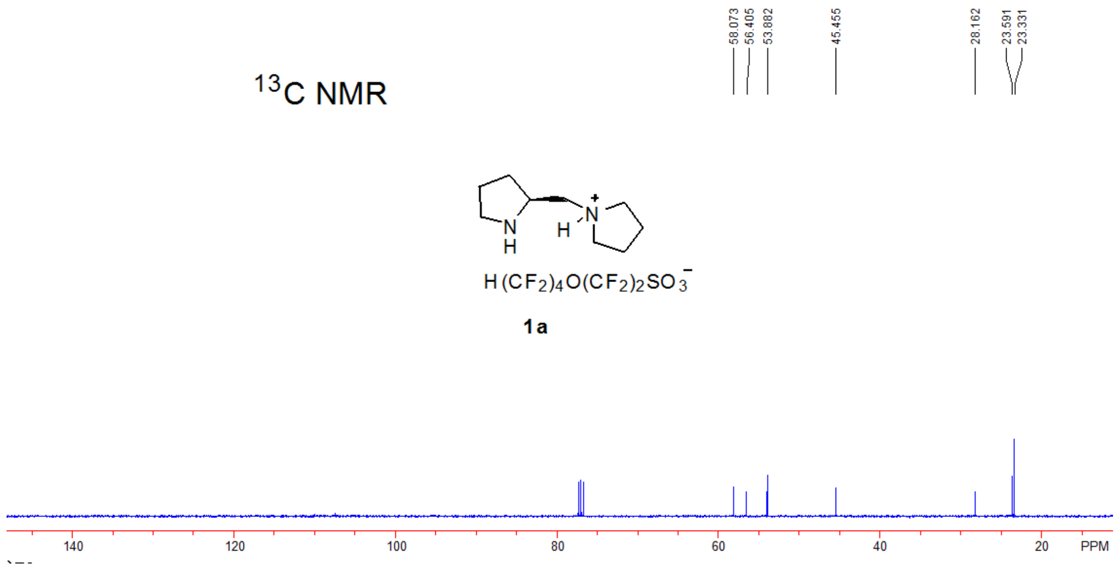
References:

1. M. Asami, *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 721-727.
2. S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074-3075.

Copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR of Compounds:



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53.882
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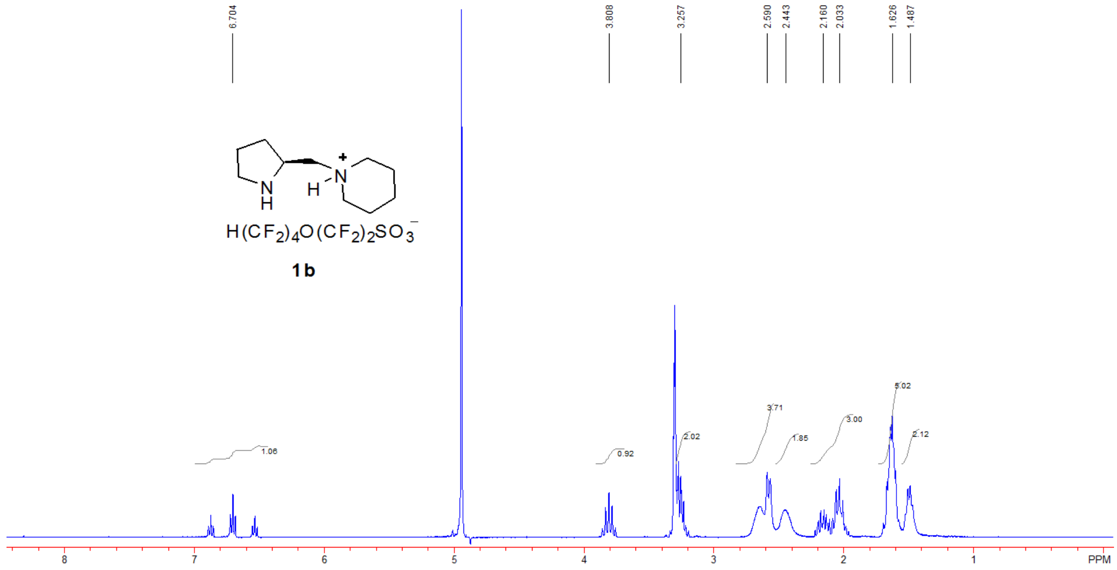
23.331
H(CF2)4O(CF2)2SO3
1a
140
120
100
80
60
40
20
PPM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3.808
3.257
2.590
2.443
2.160
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1.626
1.487
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1b
1.06
0.92
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1.85
3.00
5.02
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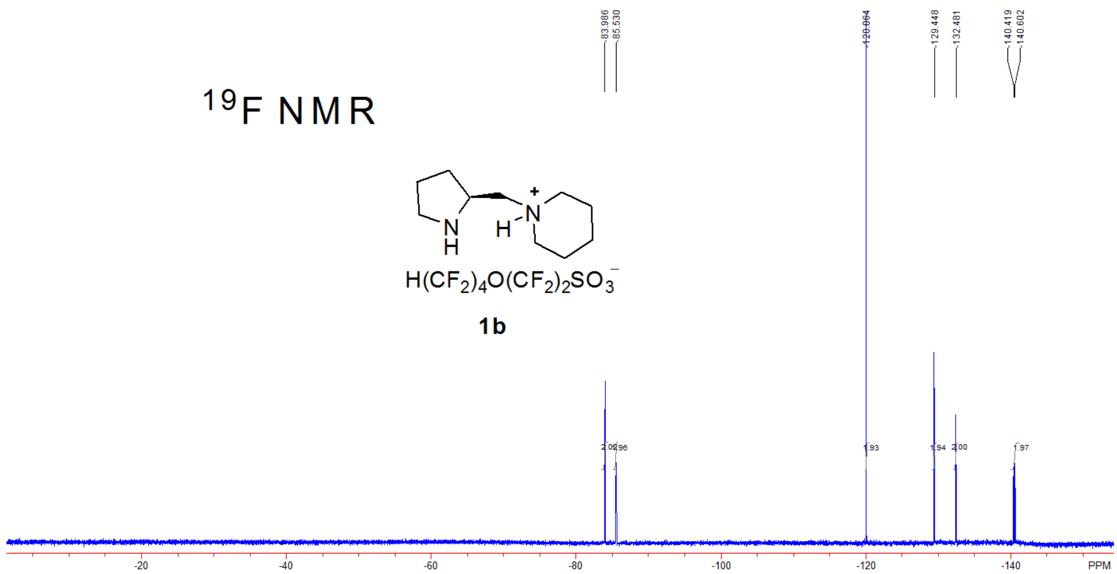
7
6
5
4
3
2
1
PPM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129.448
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19F NMR
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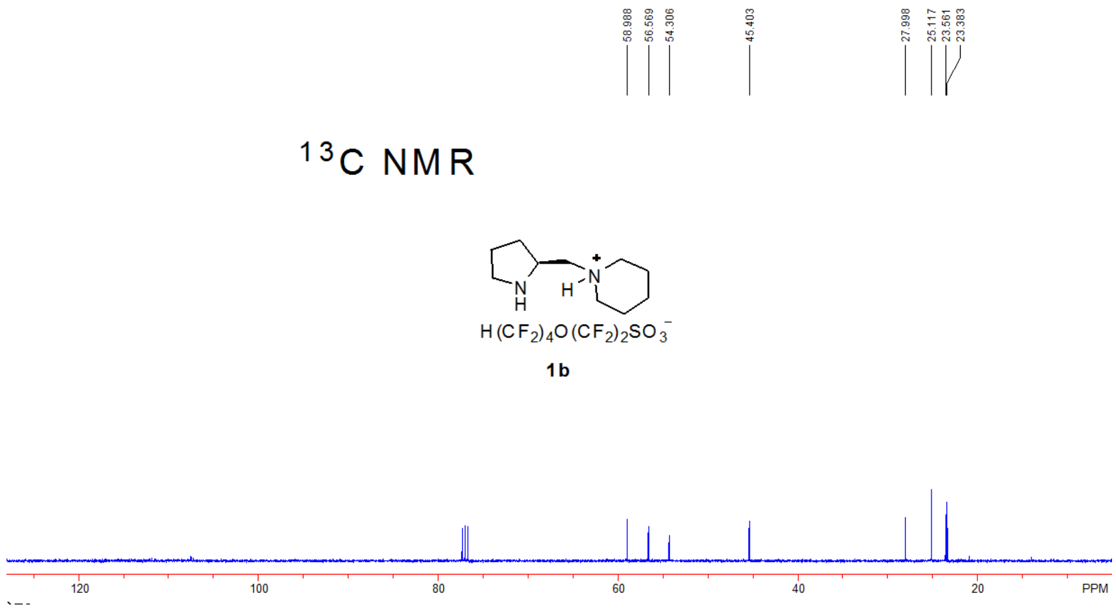
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13C NMR
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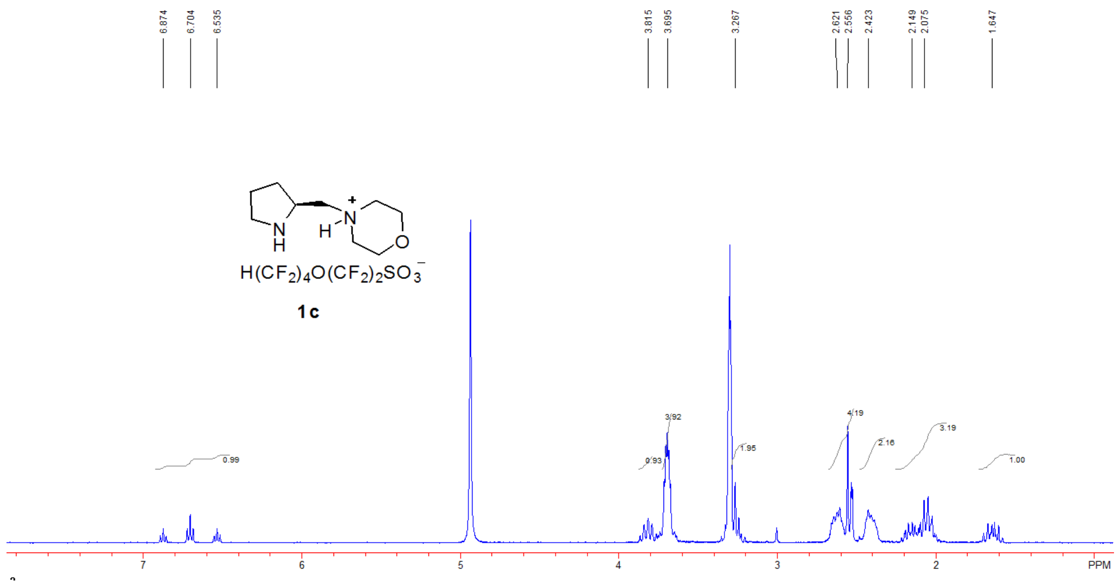
1b
120
100
80
60
40
20
PPM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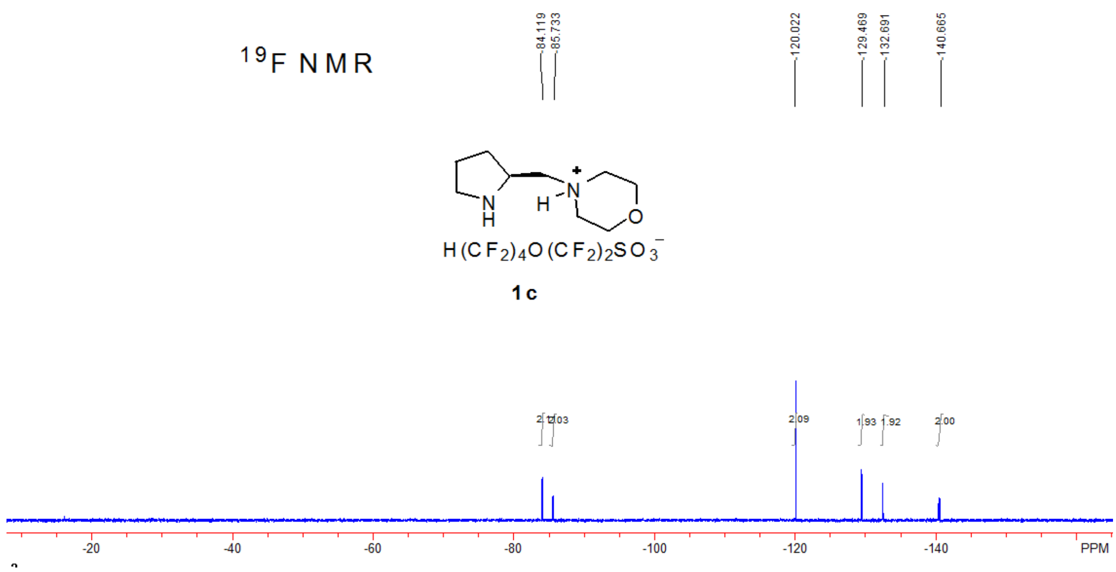
3.695
3.267
2.621
2.556
2.423
2.149
2.075
1.647
H(CF2)4O(CF2)2SO3
1c
0.99
0.93
3.92
1.95
4.19
2.16
3.19
1.00
7
6
5
4
3
2
PPM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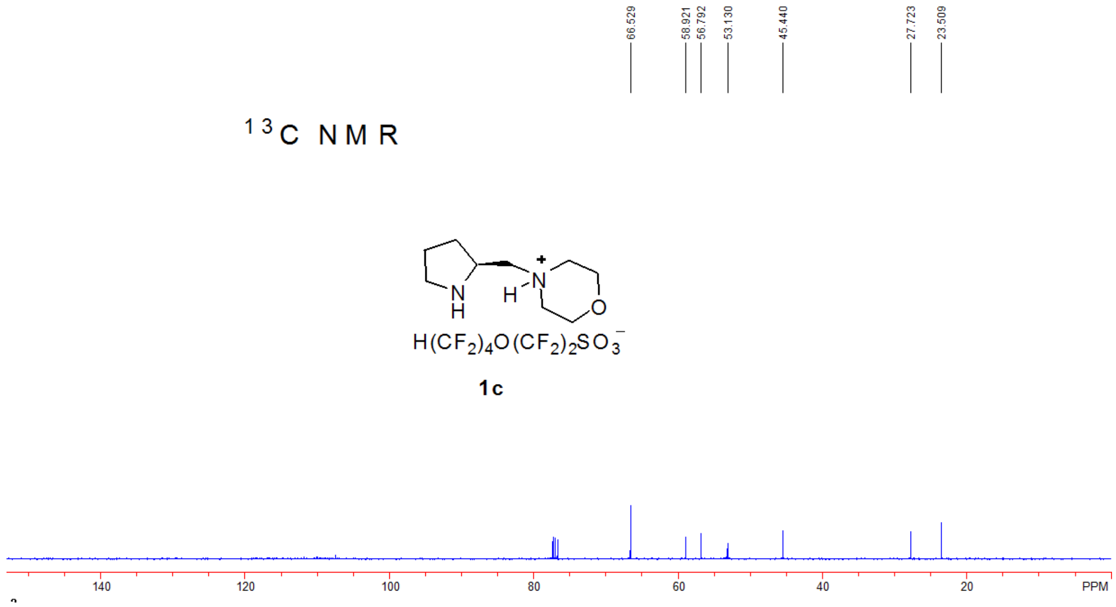
PPM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27.723
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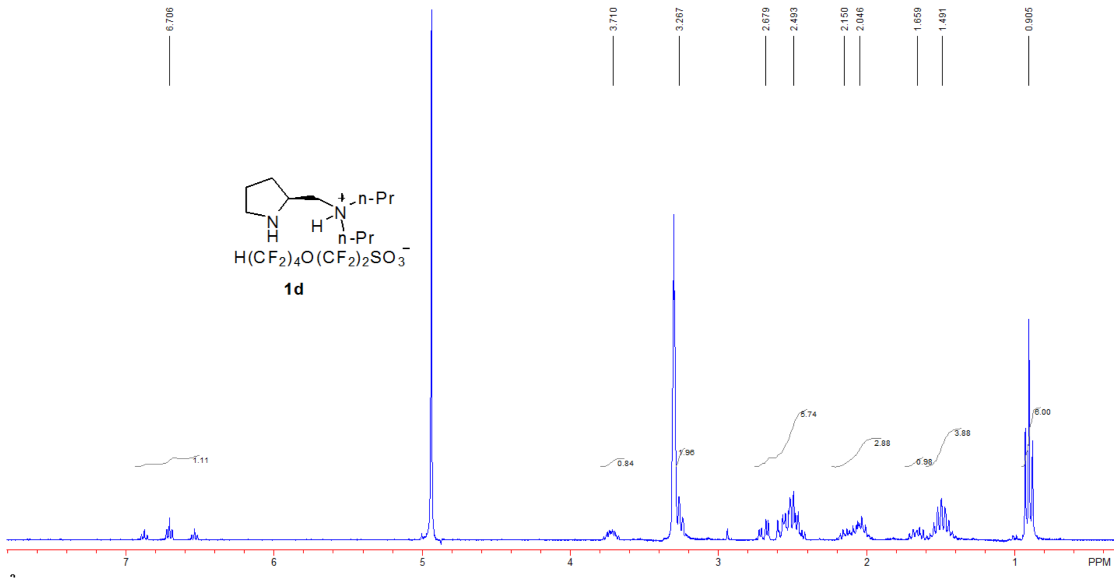
13C NMR
H
N
H
N
O
H(CF2)4O(CF2)2SO3
1c
140
120
100
80
60
40
20
PPM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H
n-Pr
H(CF2)4O(CF2)2SO3
1d
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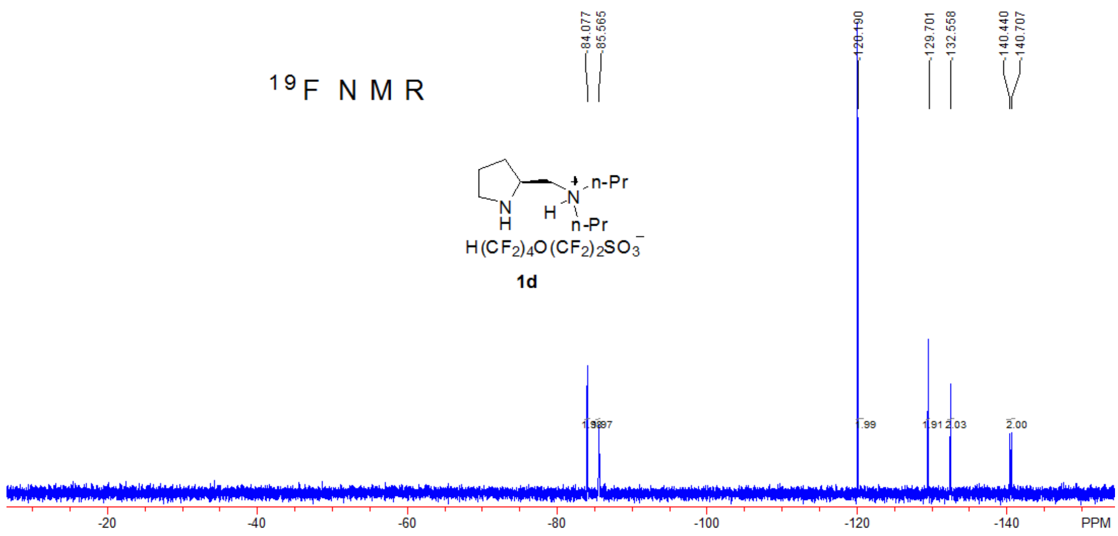
4
3
2
1
PPM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-120
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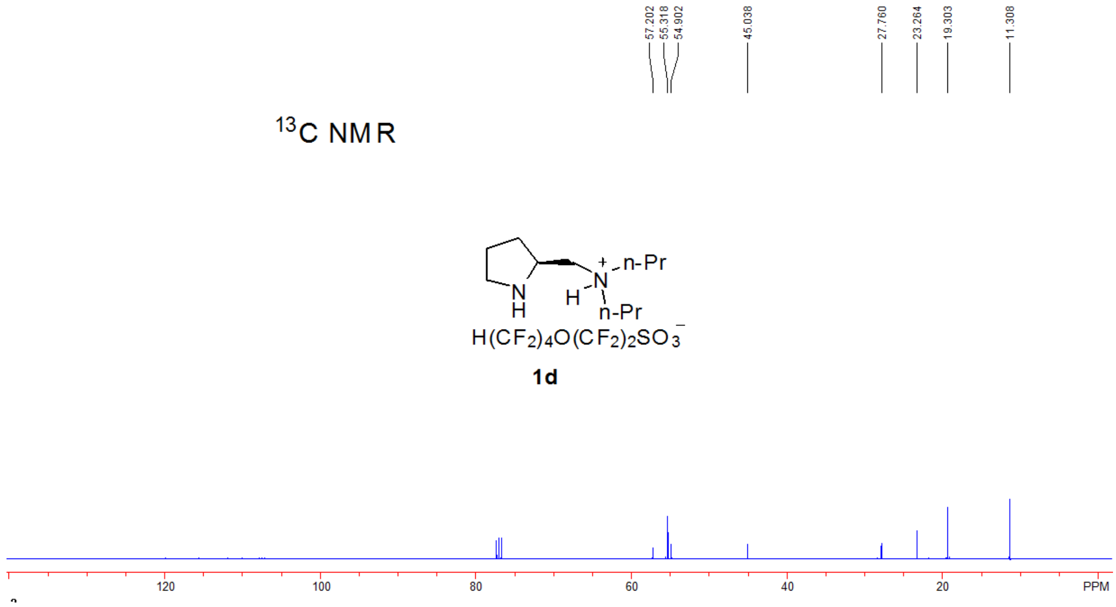
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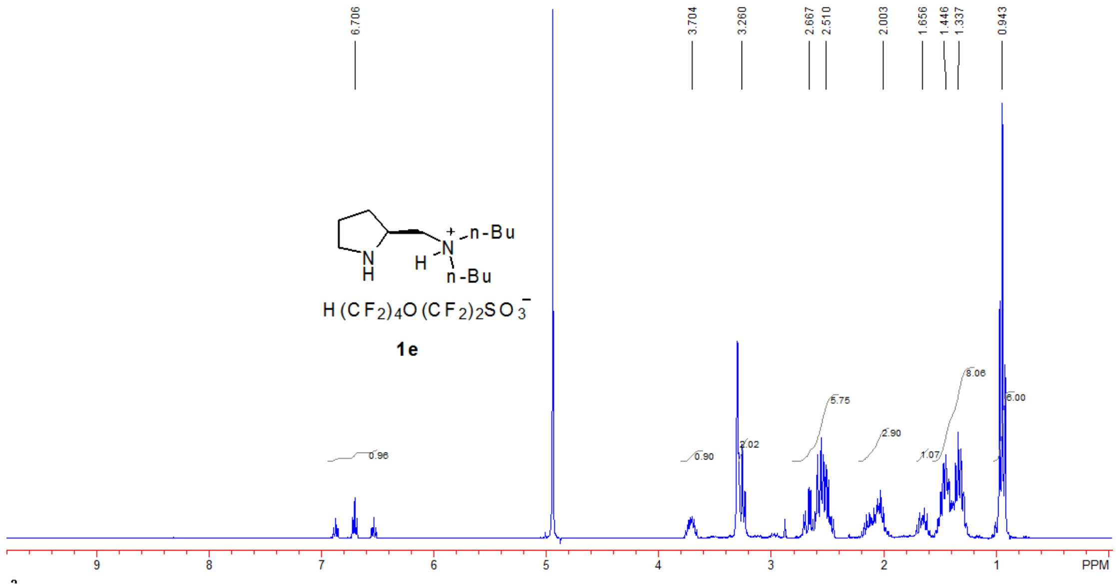
H
N
H
n-Pr
H(CF2)4O(CF2)2SO3
1d
120
100
80
60
40
20
PPM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H
n-Bu
H(CF2)4O(CF2)2SO3
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0.96
0.90
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3
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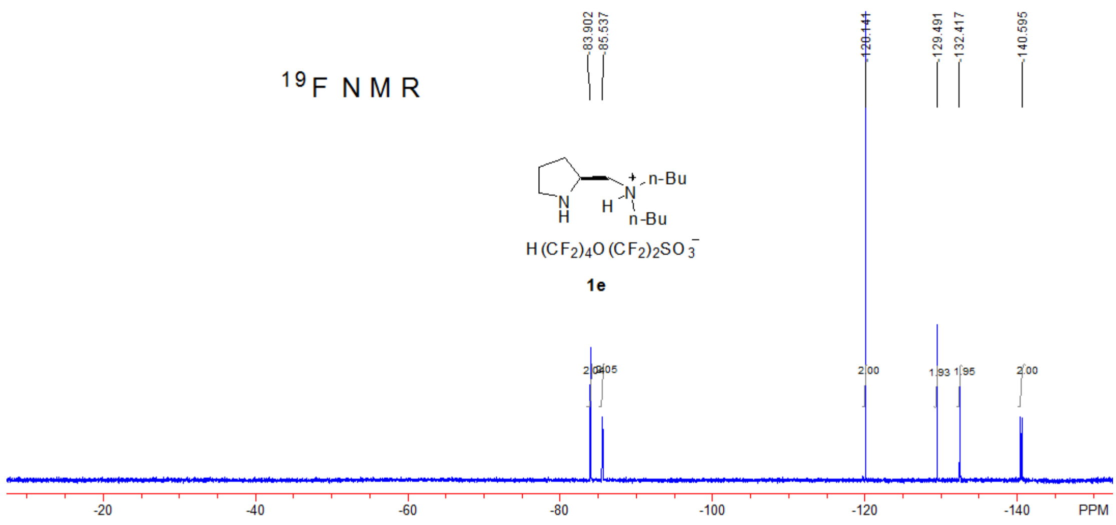
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N
H
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1e
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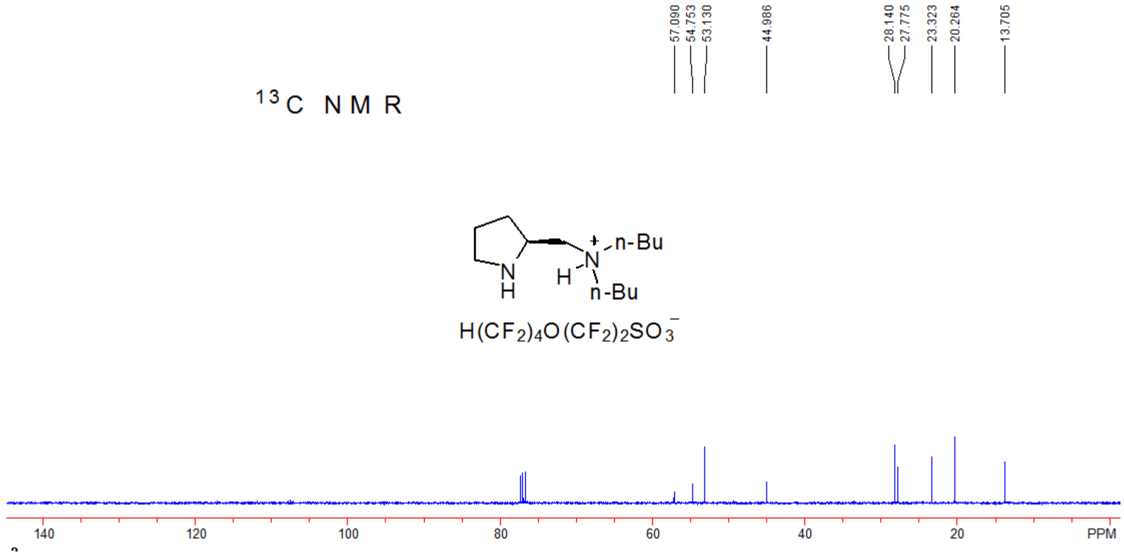
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120
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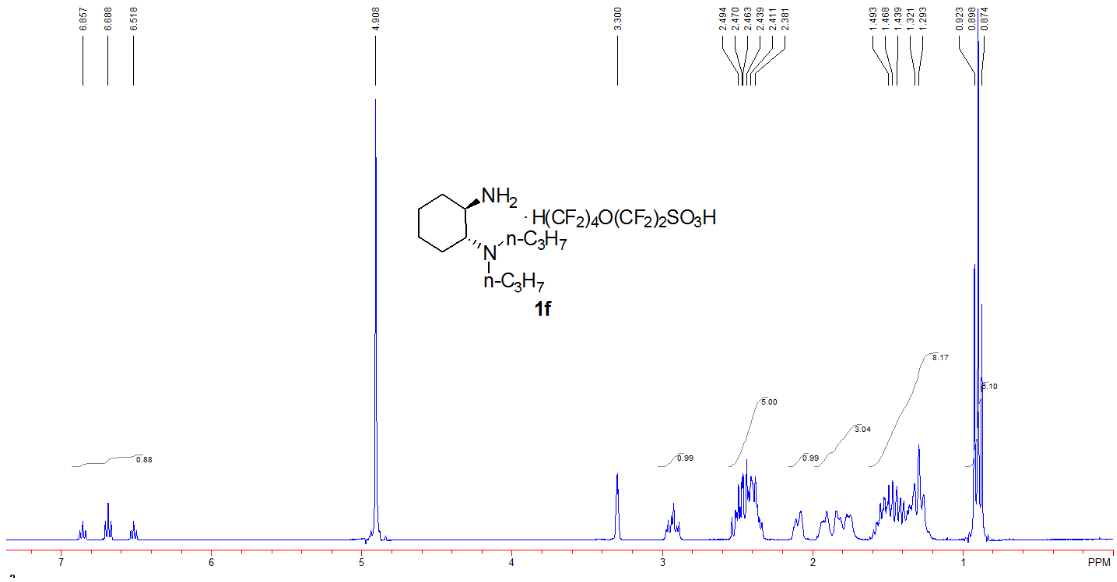
80
60
40
20
PPM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1.439
1.321
1.293
0.923
0.898
0.874
NH2
· H(CF2)4O(CF2)2SO3H
n-C3H7
N
n-C3H7
1f
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6
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4
3
2
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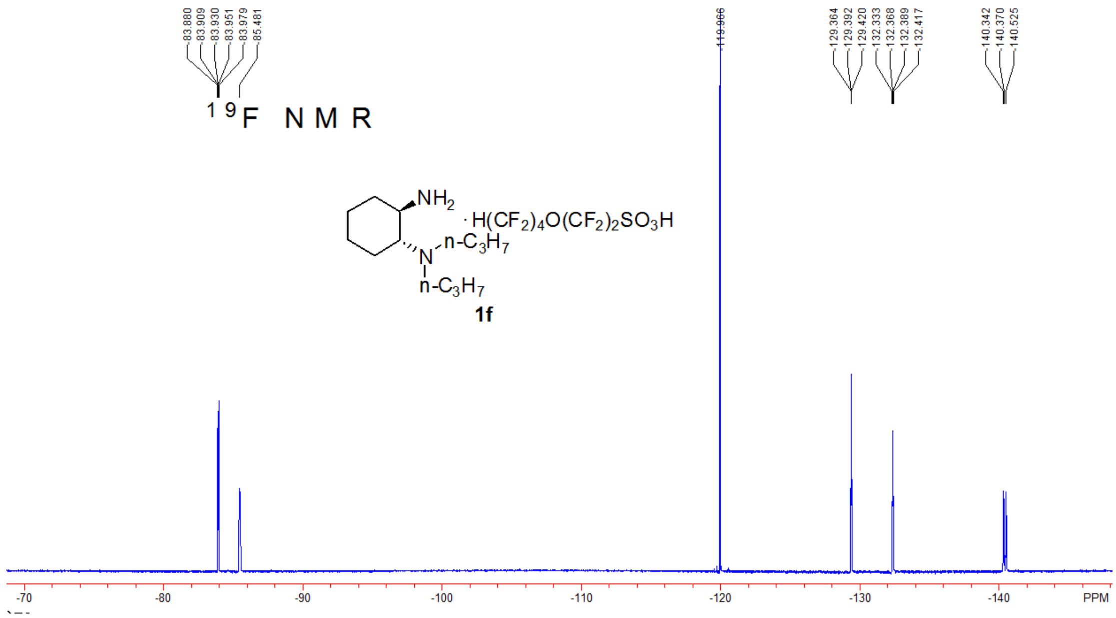
PPM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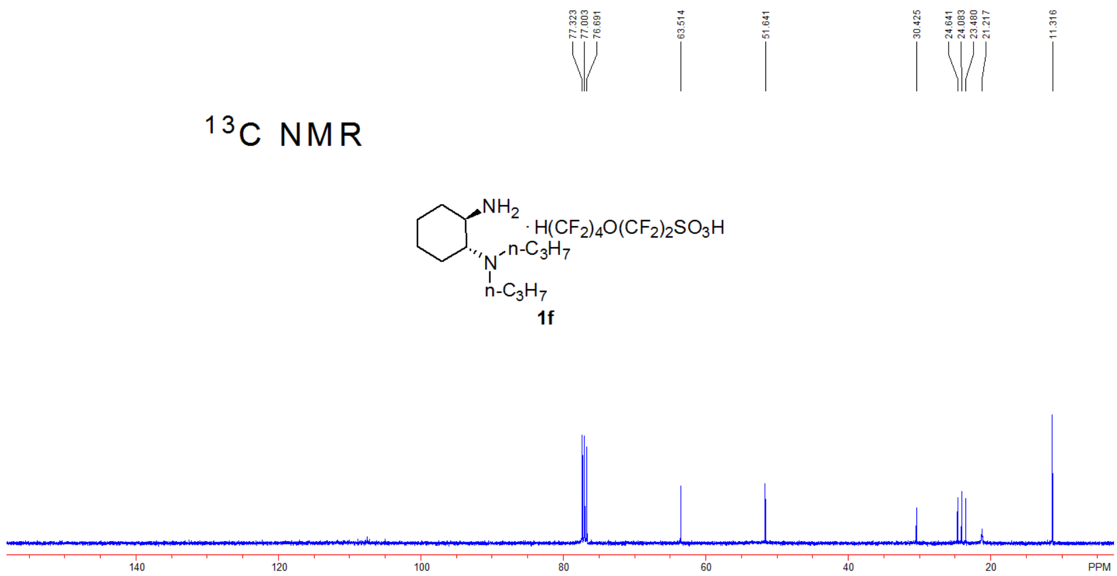
1f
PPM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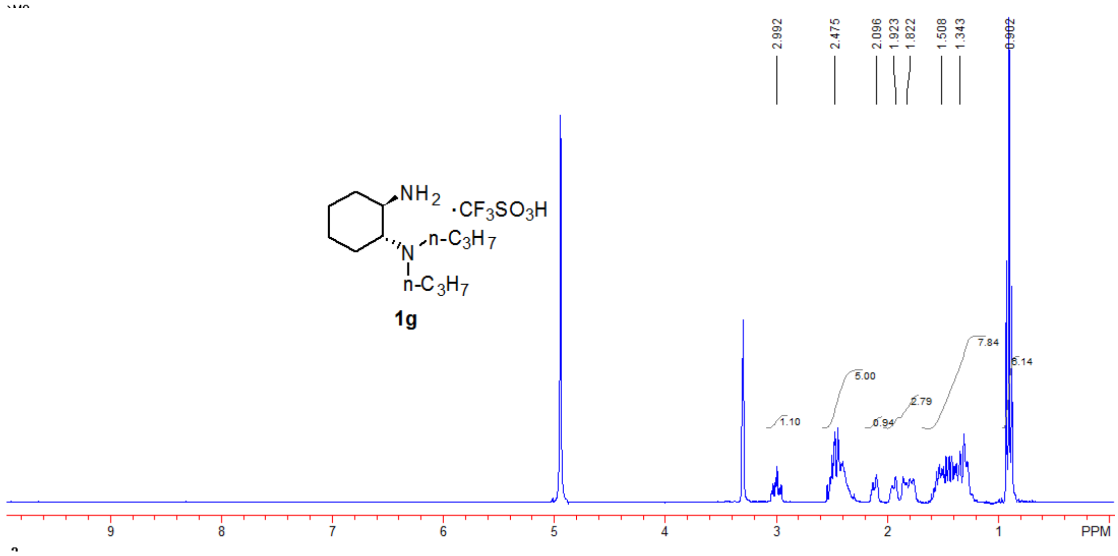
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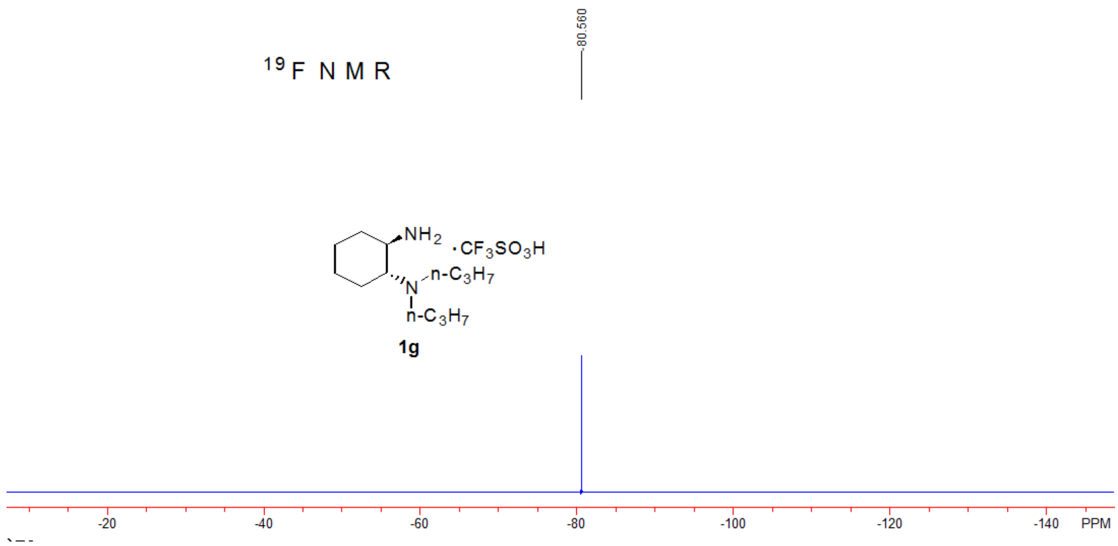
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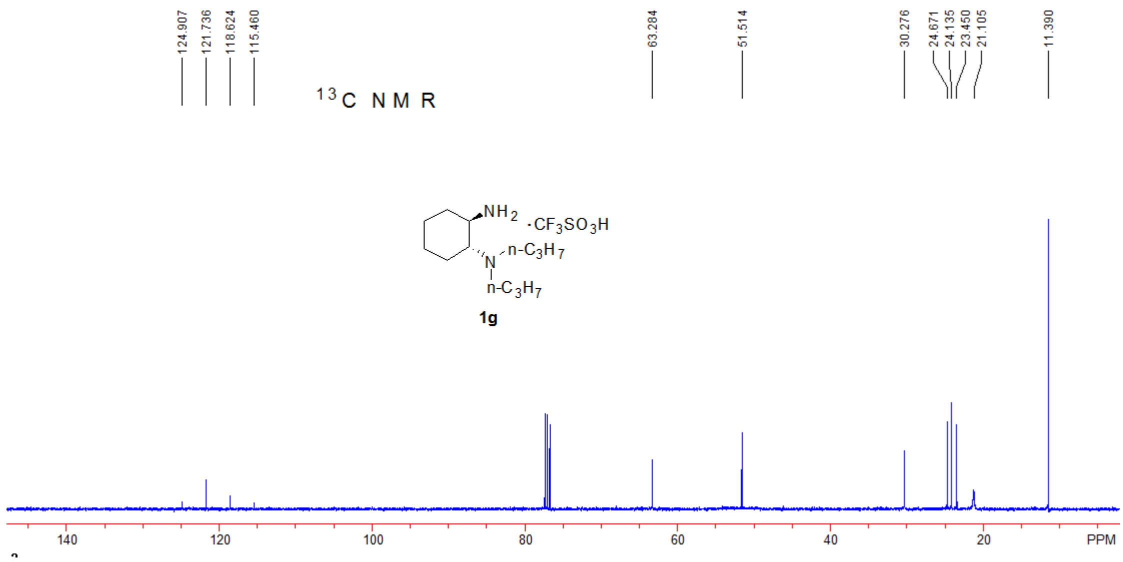
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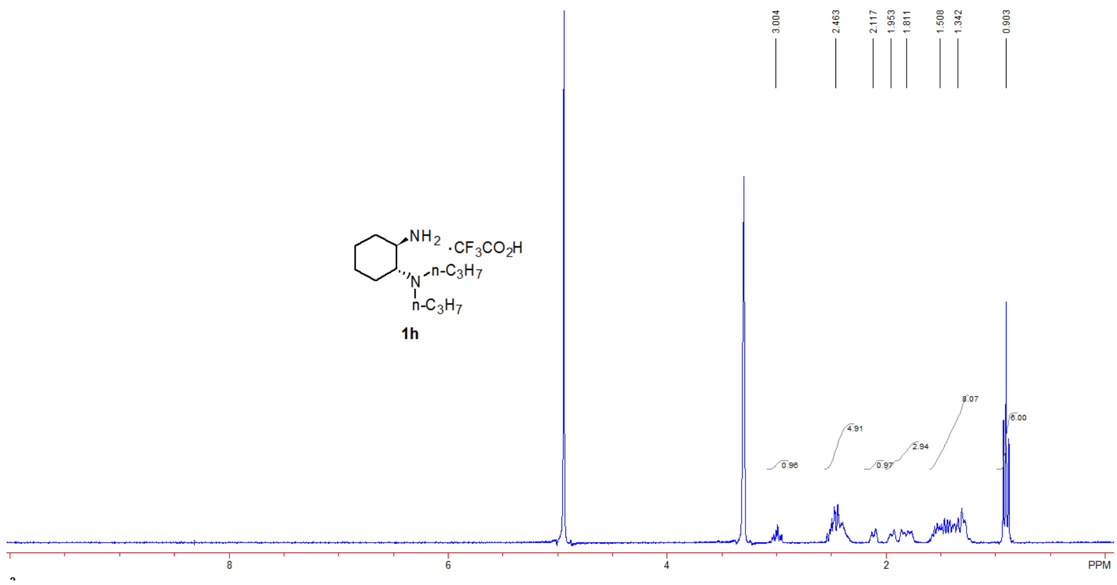
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2
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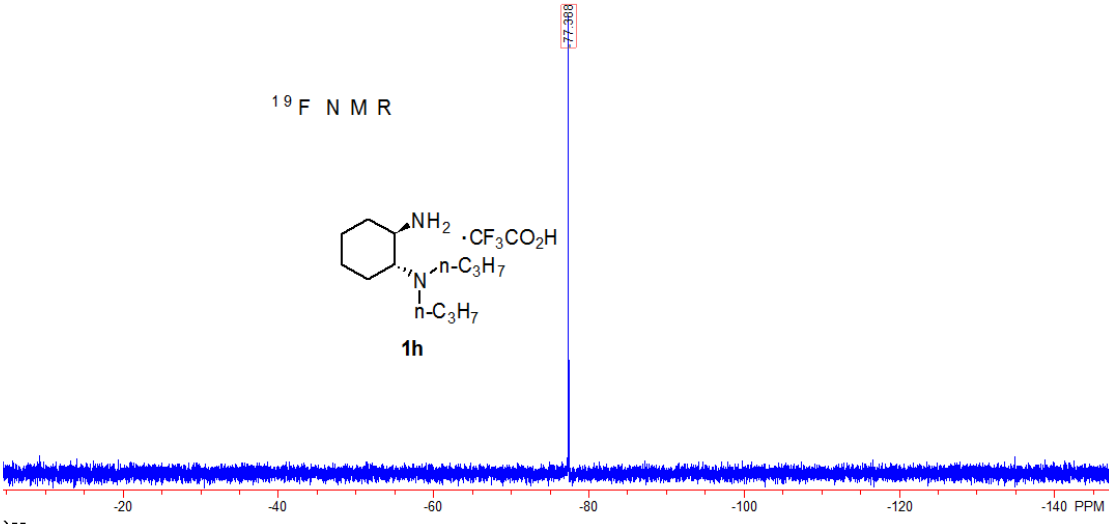

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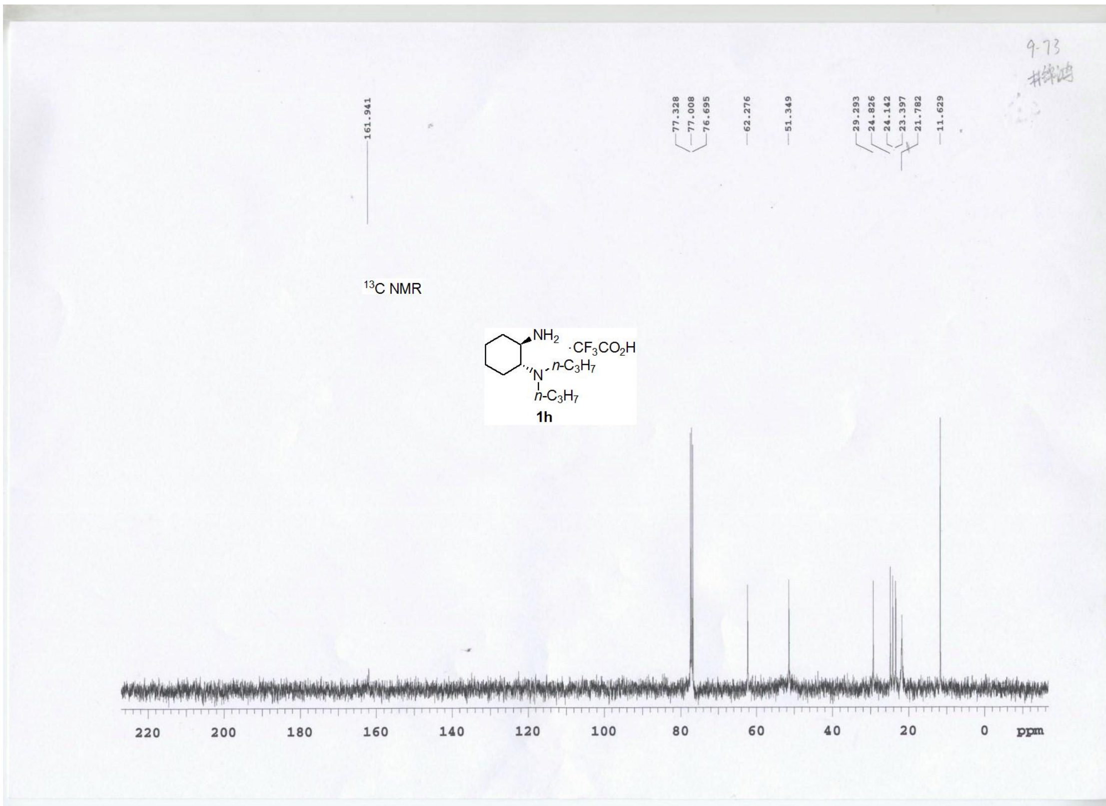

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13C NMR
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·CF3CO2H
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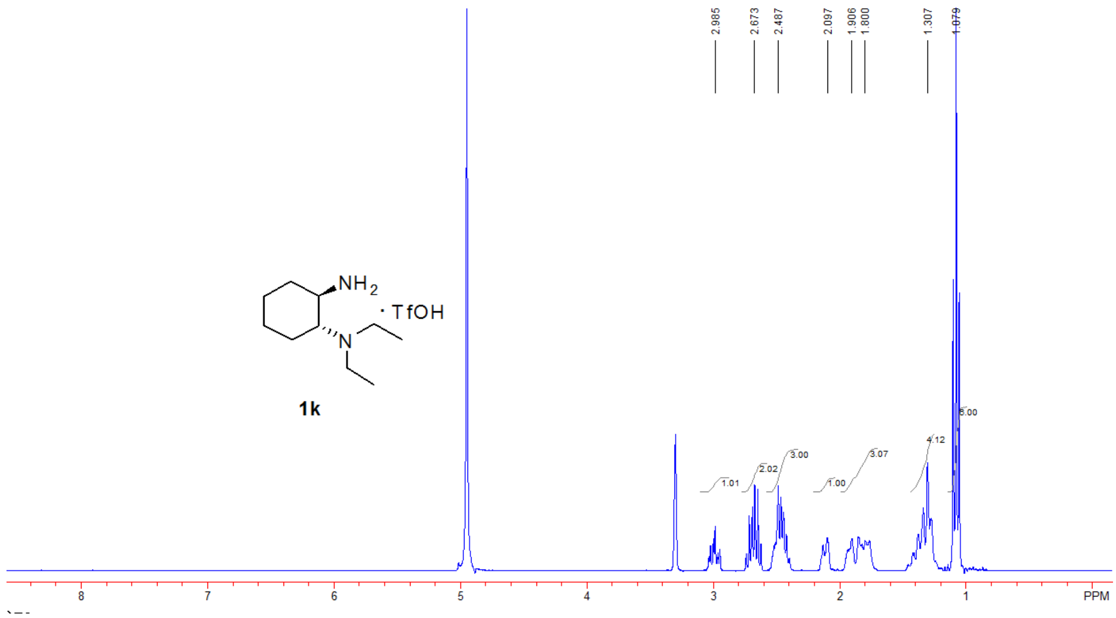
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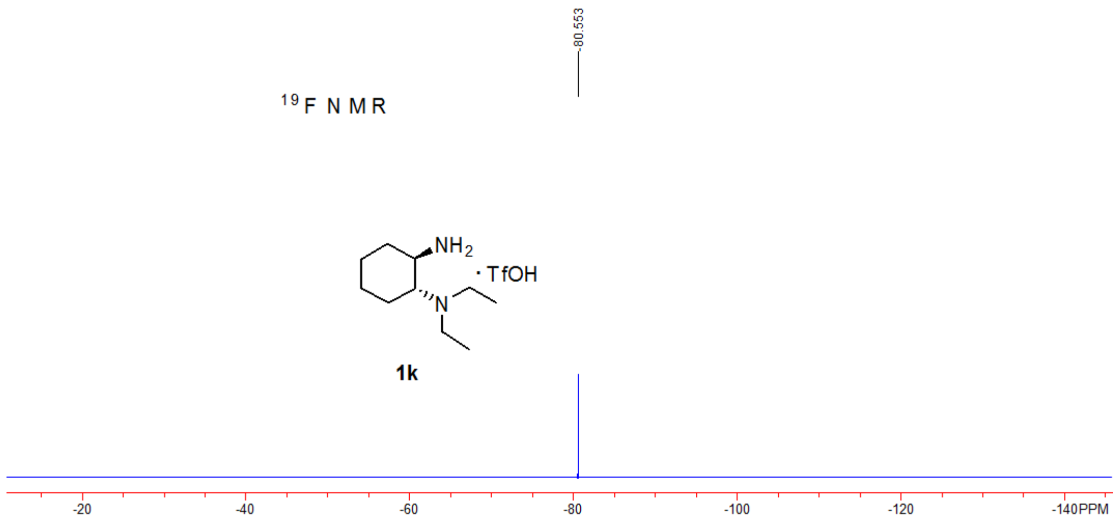
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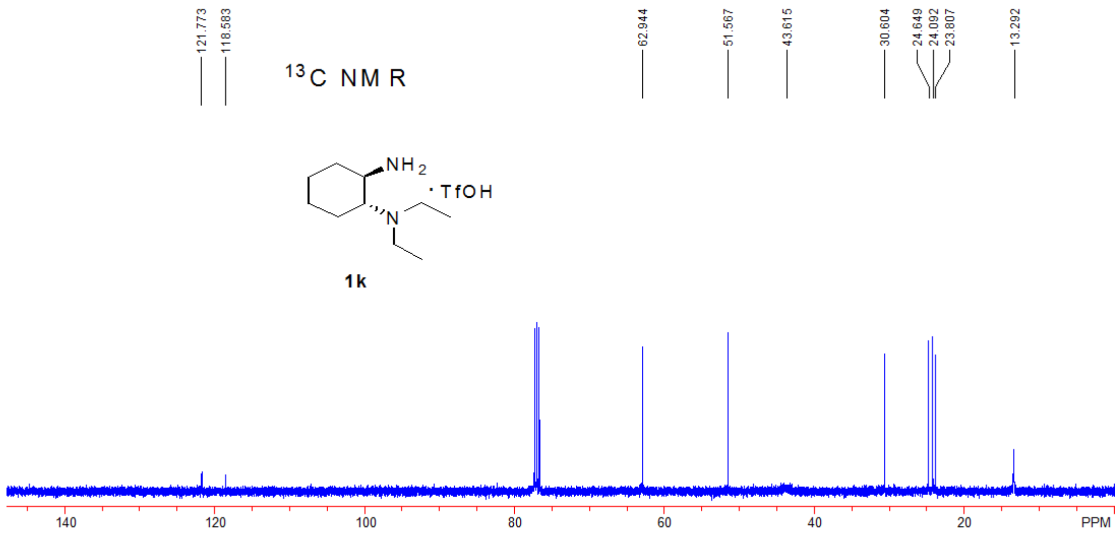
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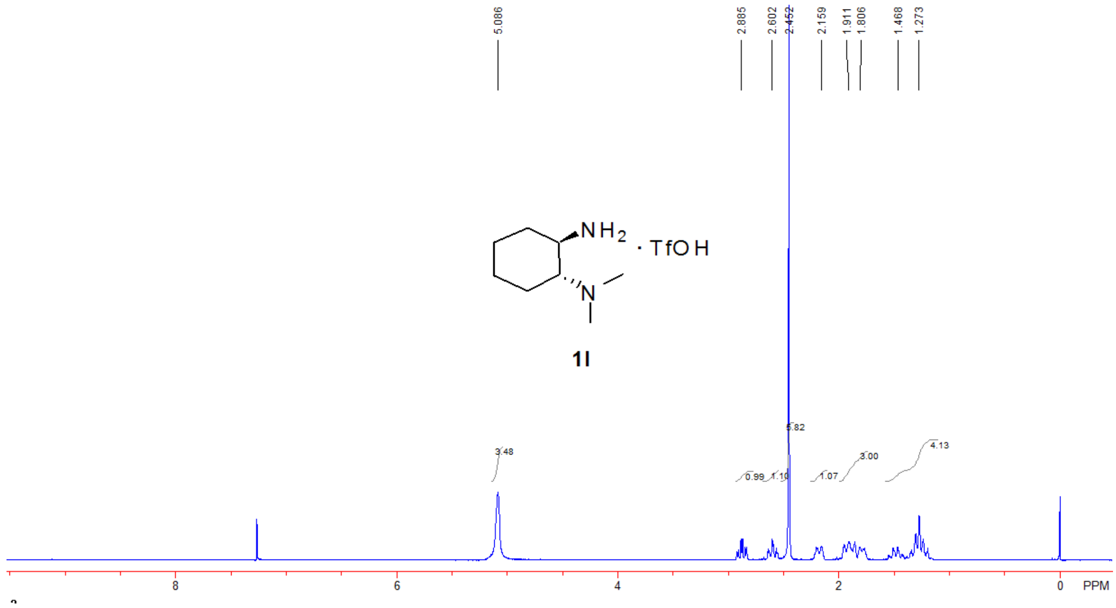
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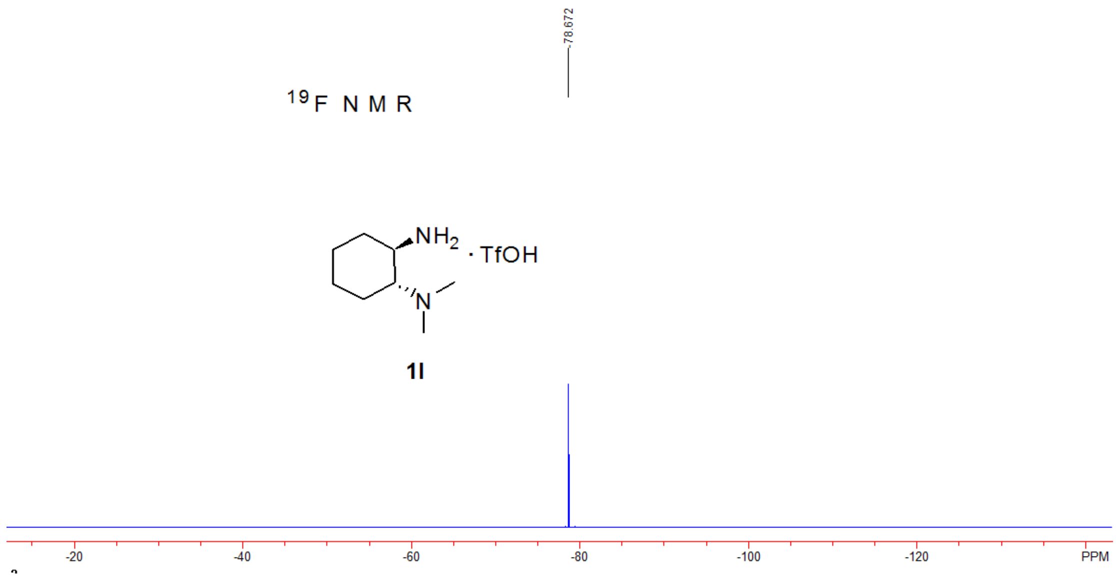
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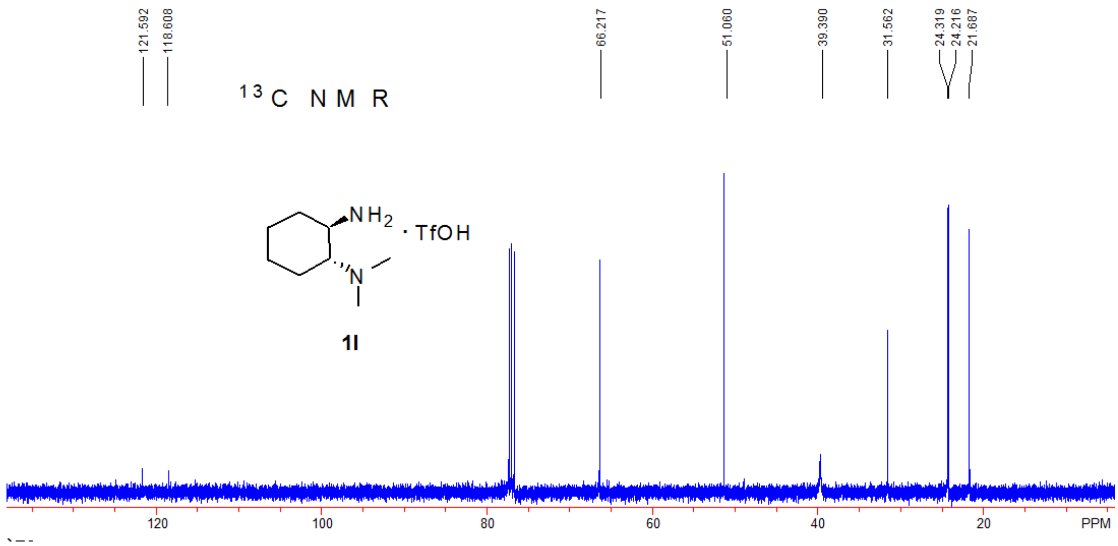
NH2
· TfOH
N
1l
-20
-40
-60
-80
-100
-120
PPM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· TfOH
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1l
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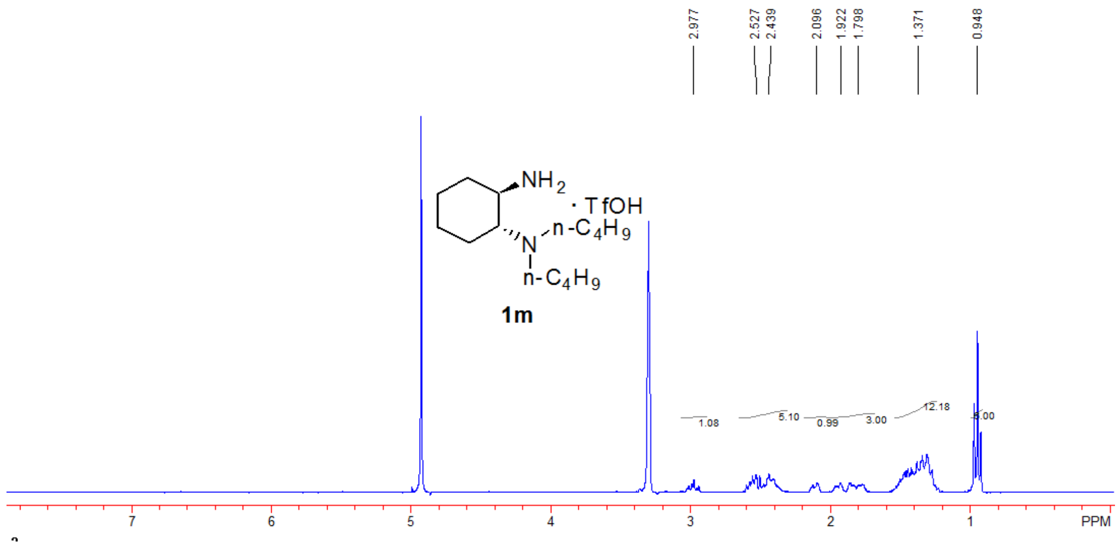
20
PPM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2.439
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1.922
1.798
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0.948
NH2
· TfOH
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N
n-C4H9
1m
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5.10
0.99
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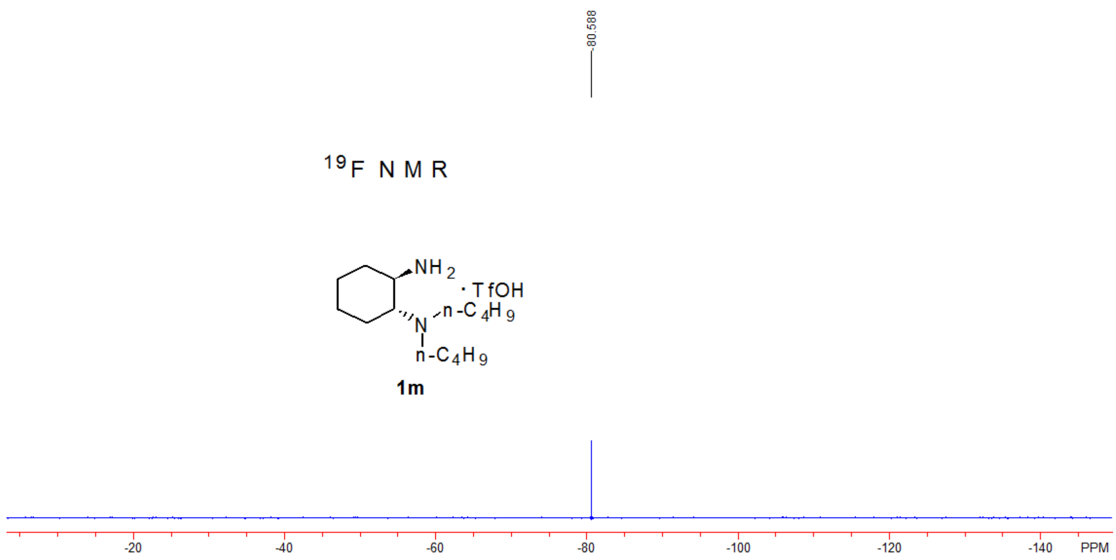
12.18
6.00
7
6
5
4
3
2
1
PPM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NH2
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N
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1m
-20
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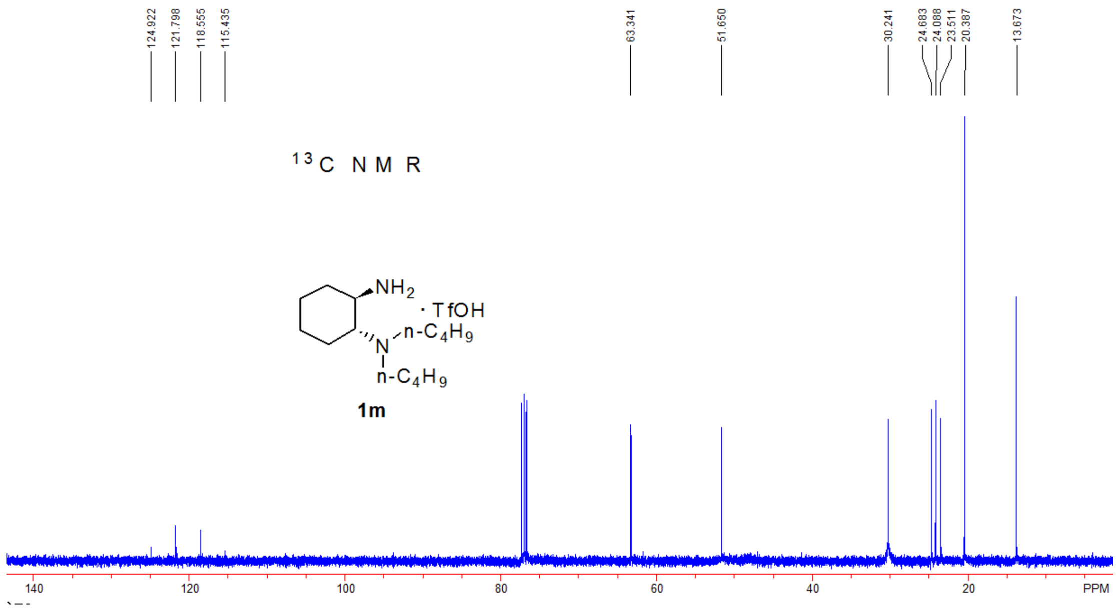
-120
-140
PPM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118.555
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63.341
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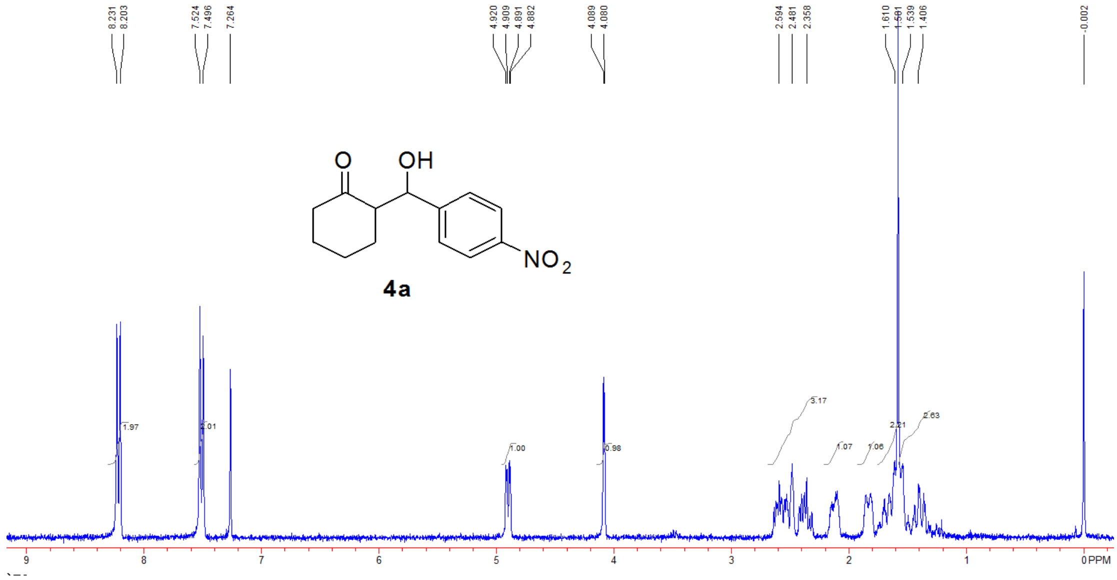
30.241
24.683
24.088
23.511
20.387
13.673
13C NMR
NH2
· TfOH
n-C4H9
N
n-C4H9
1m
140
120
100
80
60
40
20
PPM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4.089
4.080
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2.481
2.358
1.610
1.581
1.539
1.406
-0.002
O
OH
NO2
4a
1.97
2.01
1.00
0.98
3.17
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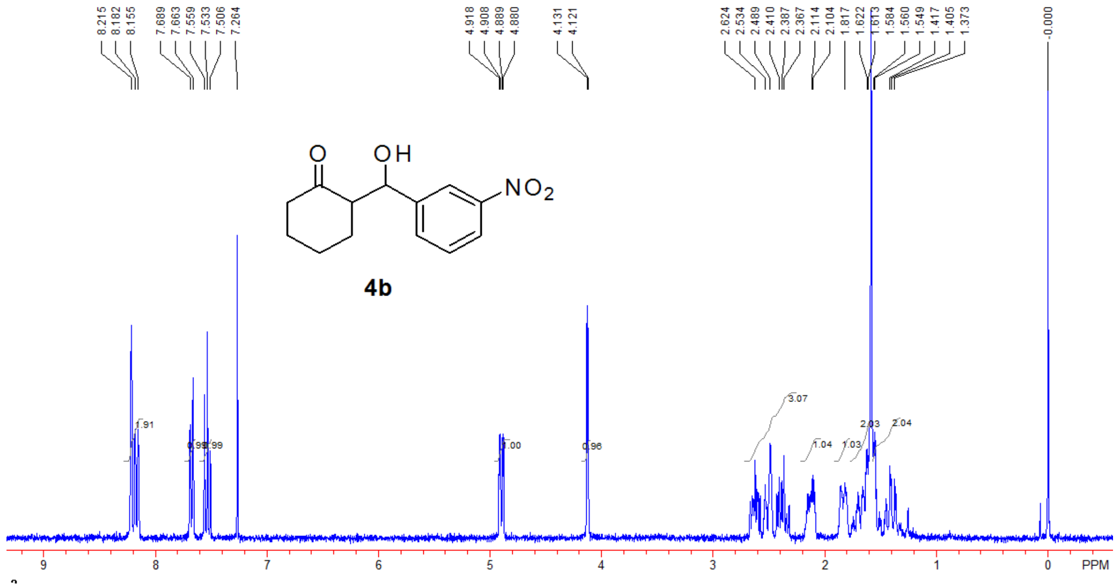
1.06
2.21
2.63
9
8
7
6
5
4
3
2
1
0 PPM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OH
NO2
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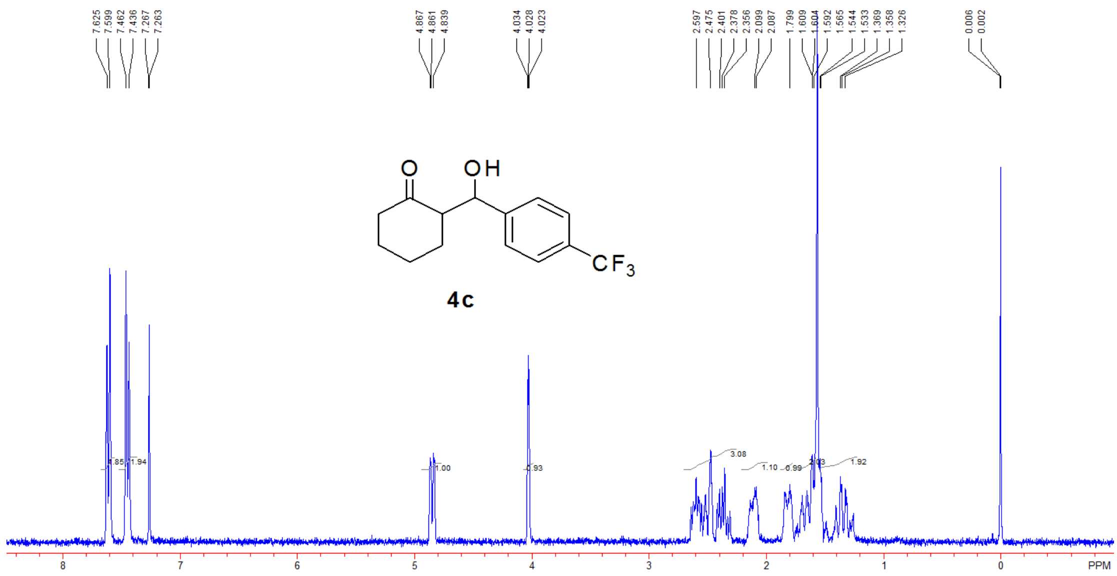
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CF3
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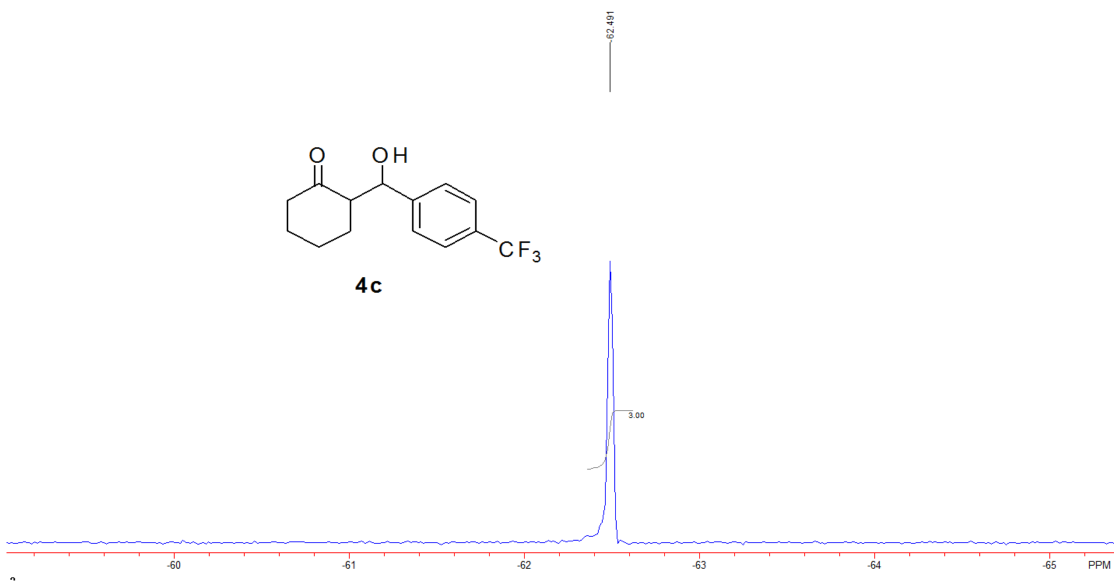
PPM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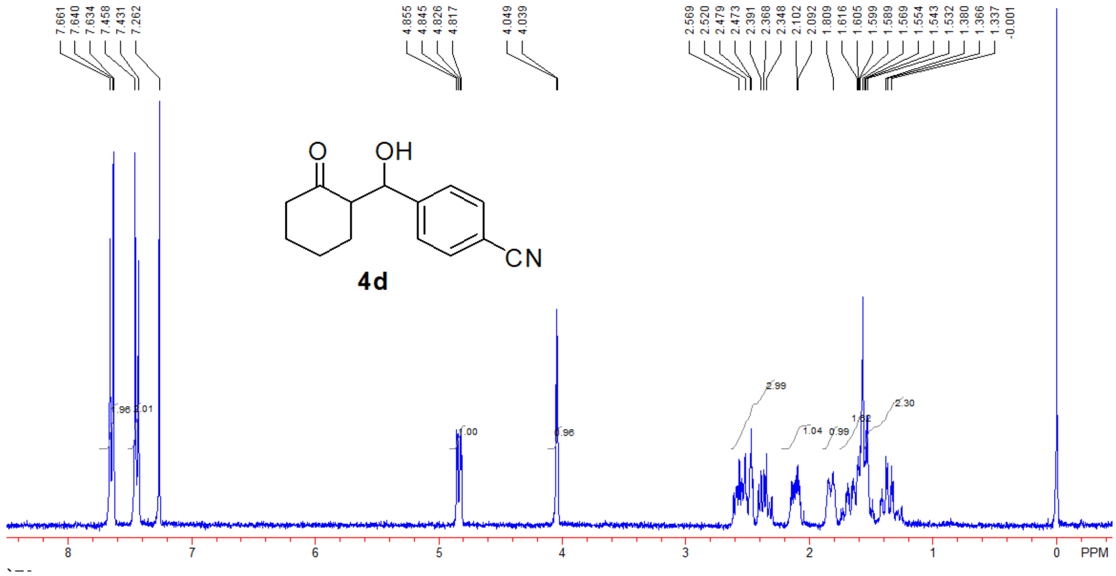

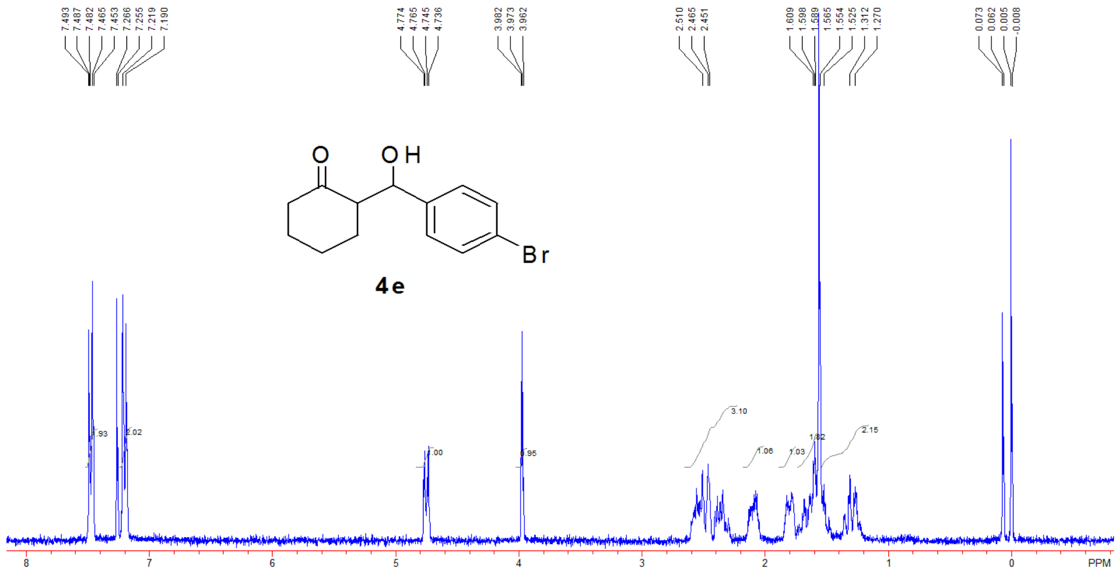

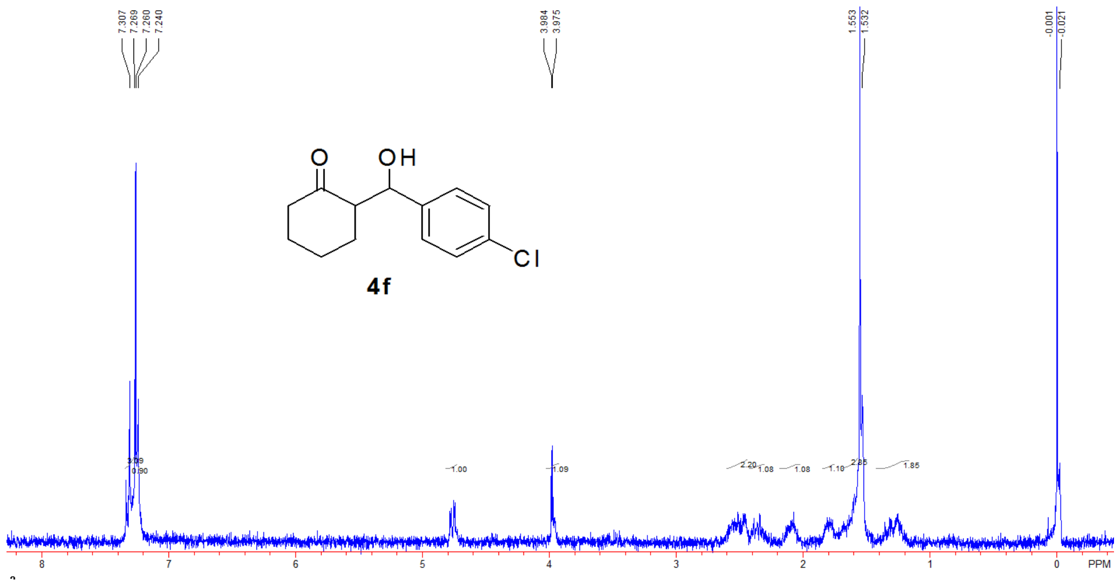

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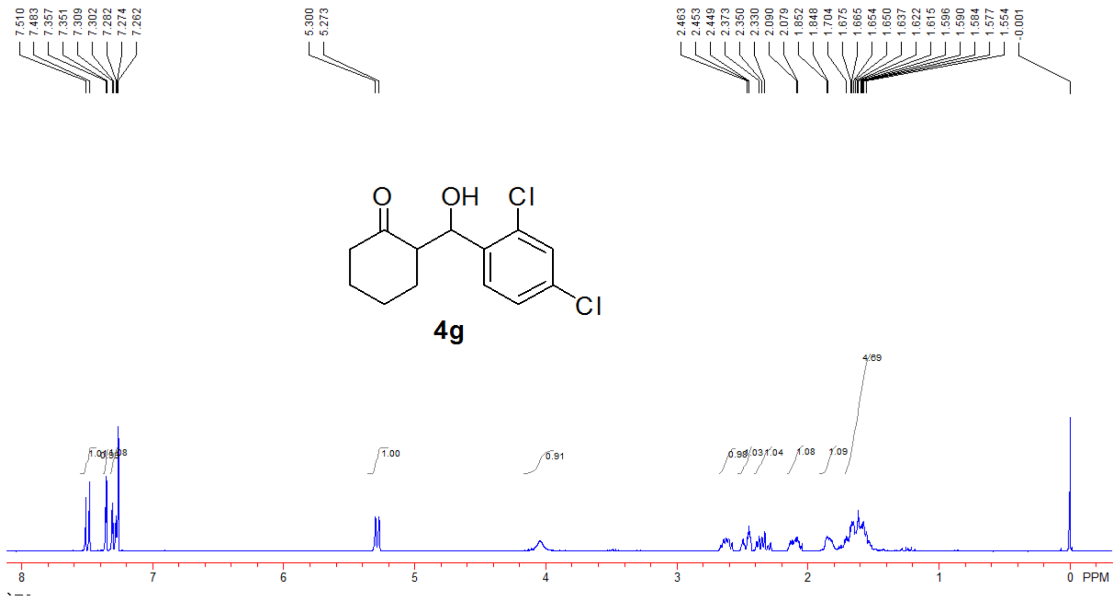

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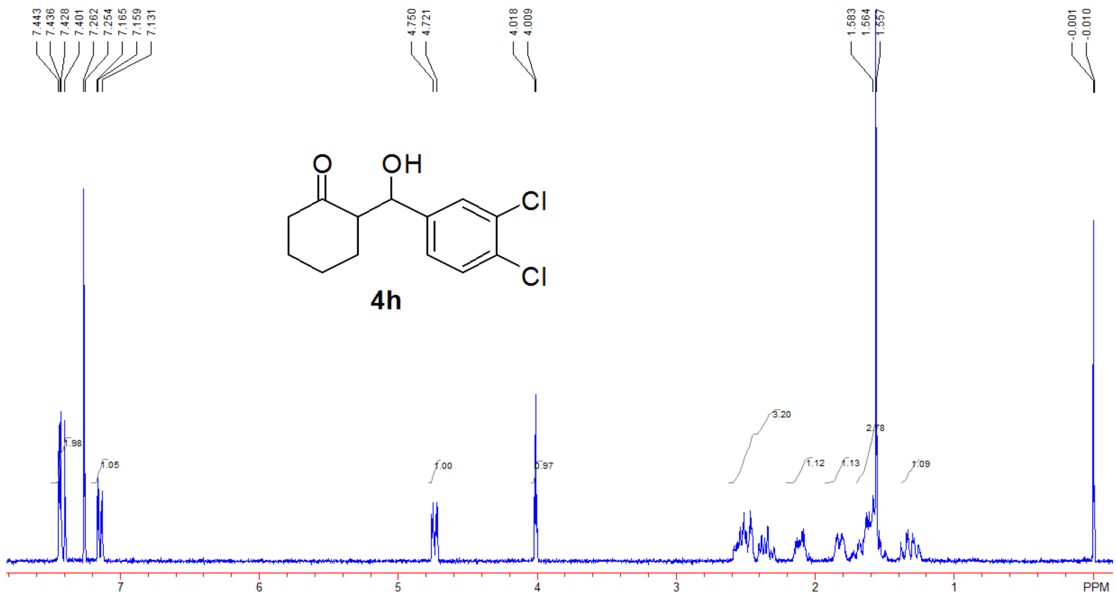
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7.159
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4.018
4.009
1.583
1.564
1.557
-0.001
-0.010
OH
O
Cl
Cl
4h
1.98
1.05
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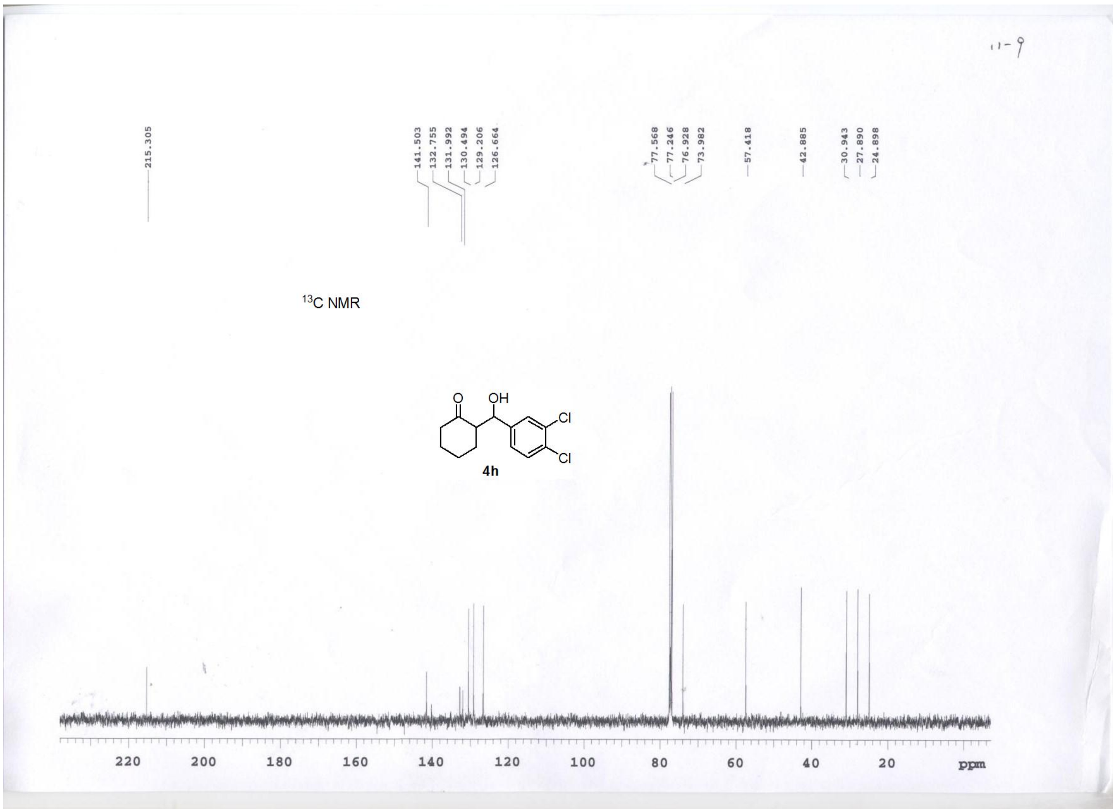
1.12
1.13
2.78
1.09
7
6
5
4
3
2
1
PPM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57.418
42.885
30.943
27.890
24.898
13C NMR
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OH
Cl
Cl
4h
220
200
180
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140
120
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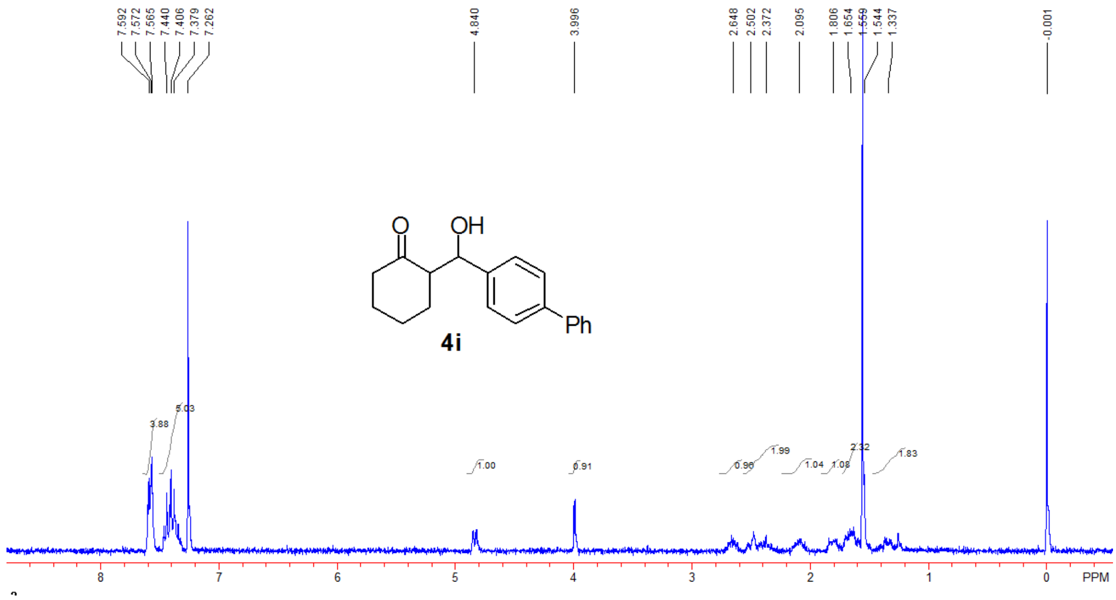
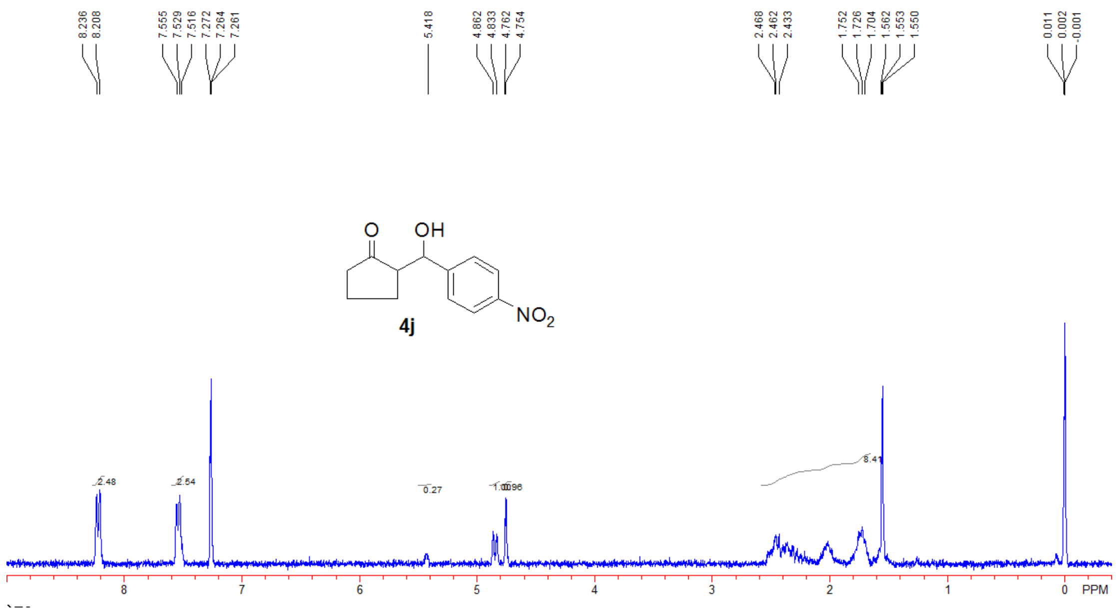
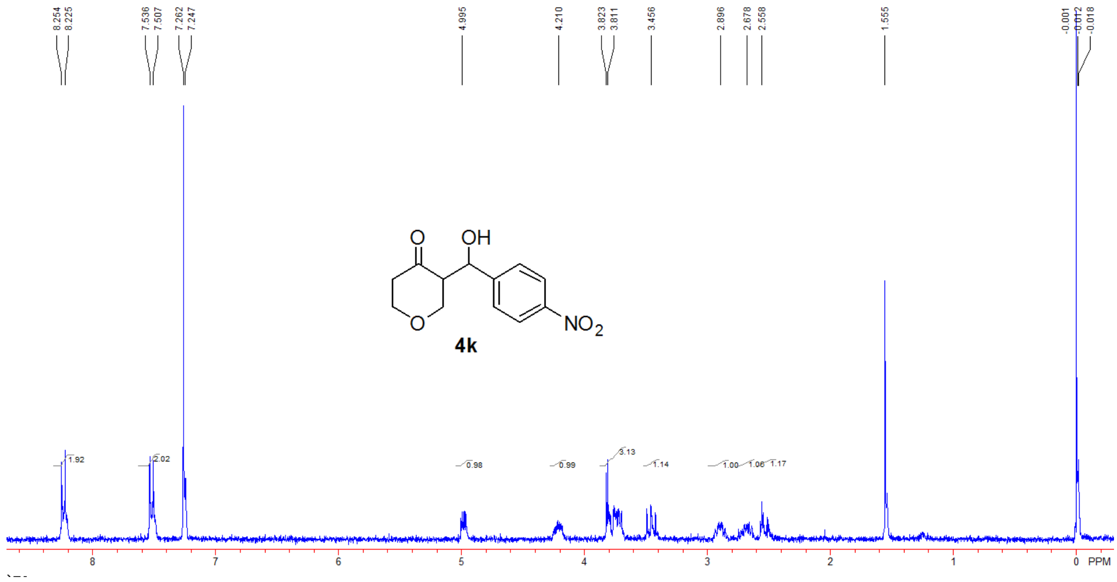
80
60
40
20
ppm



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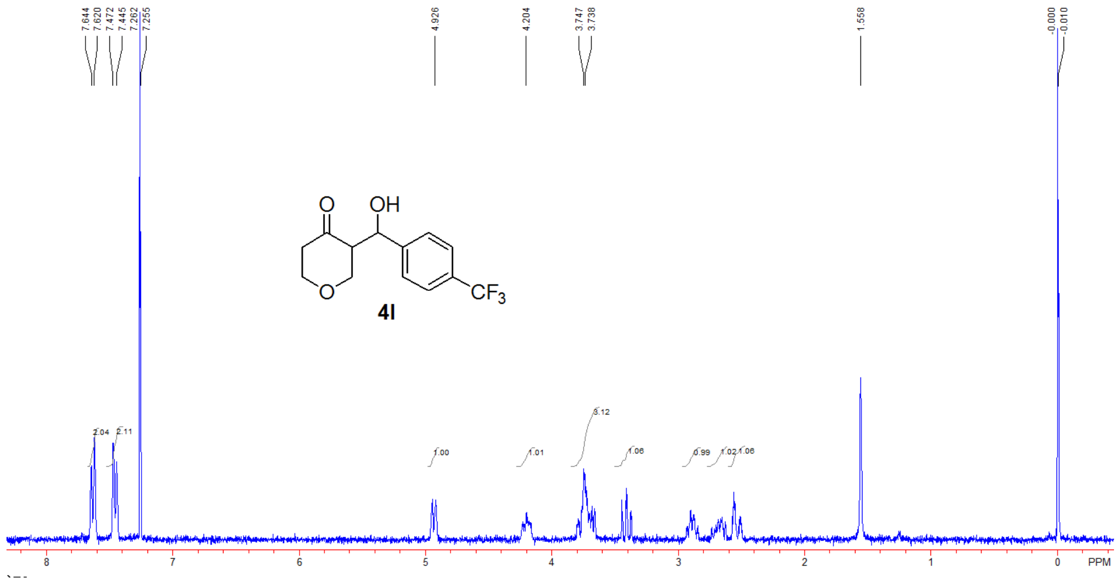
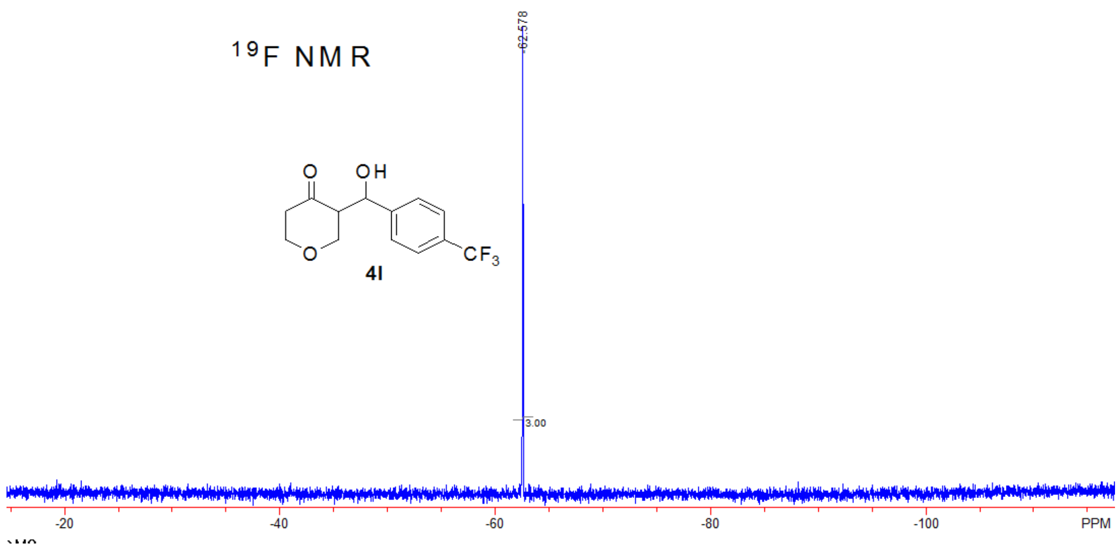
OH
O
NO2
4k
PPM


O
OH
O
CF3
4l
PPM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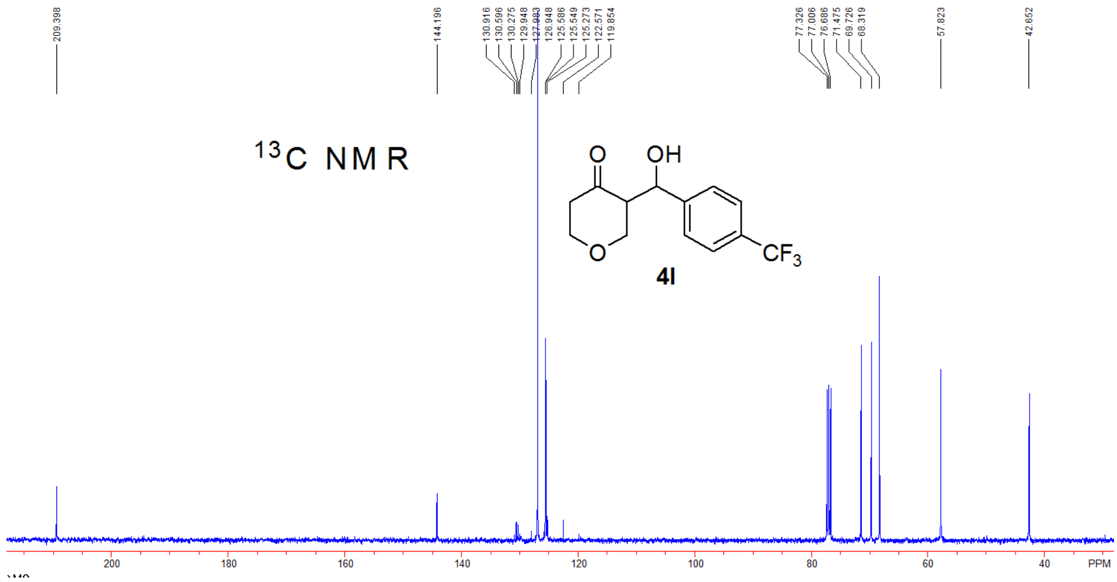
O
OH
O
CF3
4l
3.00
PPM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119.854
77.326
77.006
76.686
71.475
69.726
68.319
57.823
42.652
^{13}C NMR
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4l
200
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80
60
40
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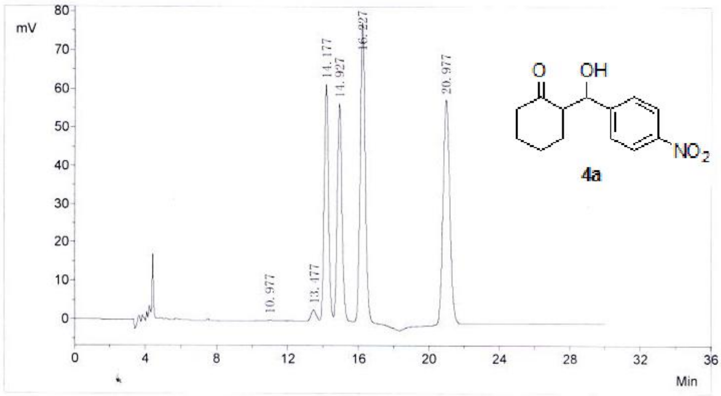
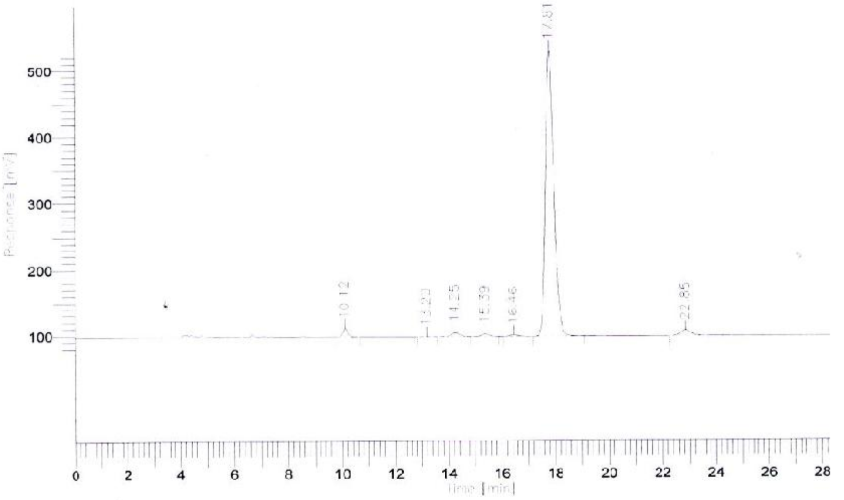
Copies of HPLC Spectra of Michael Reaction Products:

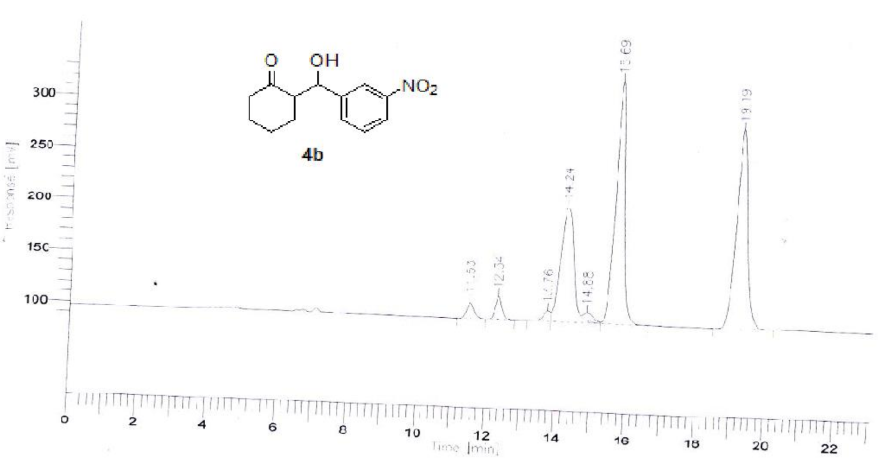


序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		10.977	139.7	6525.0	0.1189
2	2		13.477	2915.8	62073.5	1.1313
3	3		14.177	61695.3	1058146.4	19.2845
4	4		14.927	56936.2	1062249.8	19.3593
5	5		16.227	78232.6	1642681.3	29.9376
6	6		20.977	58915.0	1655342.8	30.1683
合计:				258834.7	5487021.8	100.0000



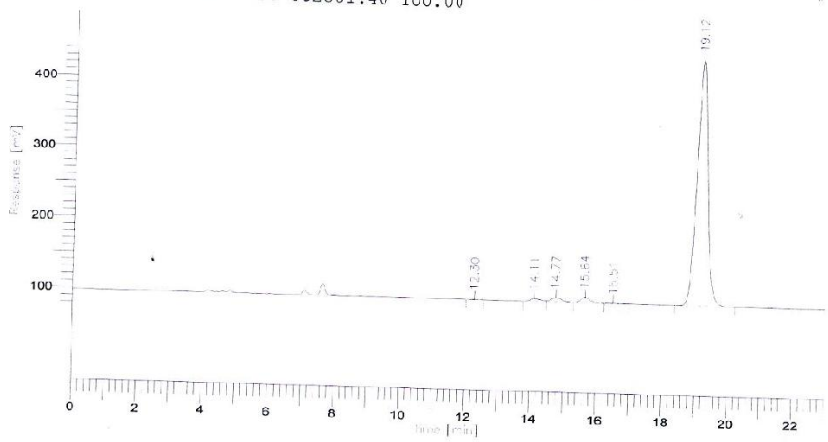
DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]	Height [uv]	Area [%]	BL
1	10.124	157211.00	12025.79	1.60	BB
2	13.198	3131.21	167.27	0.03	BV
3	14.249	113601.93	5373.75	1.16	VV
4	15.390	69374.87	3883.48	0.71	VB
5	16.457	43251.20	2256.58	0.44	BV
6	17.807	9202852.80	430655.10	93.88	VB
7	22.852	213017.00	7905.99	2.17	BB
		9802440.00	462267.97	100.00	



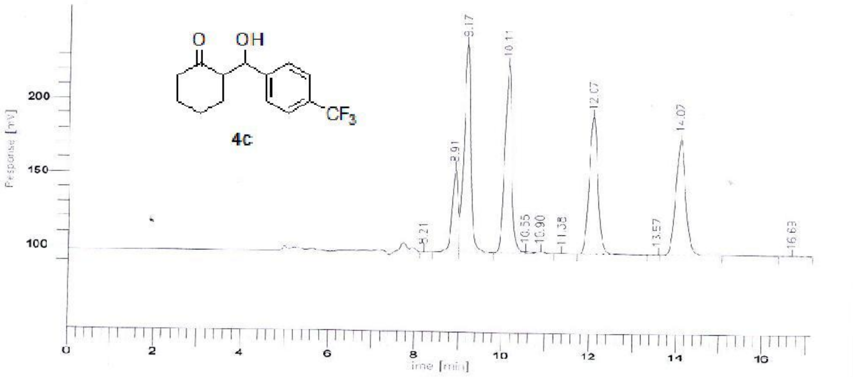
DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]	Height [uv]	Area [%]	BL
1	11.527	251884.99	16024.58	1.99	BV
2	12.341	208045.02	21856.22	2.28	VB
3	13.764	144551.38	9997.78	1.14	BV
4	14.237	2977682.15	109794.13	23.57	VE
5	14.880	153980.00	7663.51	1.22	EV
6	15.689	4387013.46	234550.00	34.73	VB
7	19.193	4427926.00	192495.18	35.06	BB
		12631083.00	592381.40	100.00	



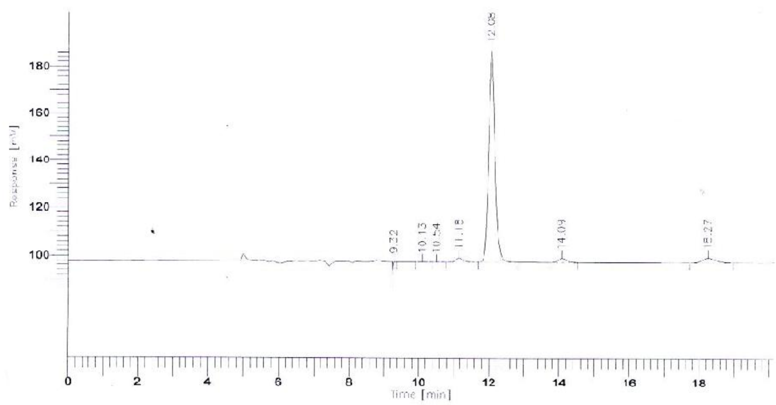
DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]	Height [uv]	Area [%]	BL
1	12.301	2382.50	198.49	0.03	BB
2	14.114	78352.26	3419.43	0.95	BV
3	14.772	131638.02	5721.39	1.59	VV
4	15.644	147125.72	7509.10	1.78	VB
5	16.508	2511.00	99.99	0.03	BB
6	19.117	7920029.00	346424.45	95.63	BB
		8282038.50	363372.85	100.00	



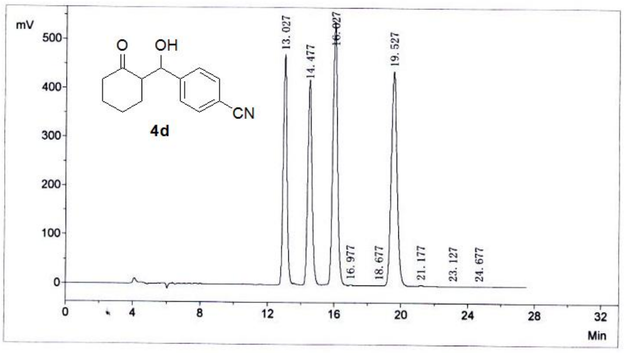
DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]	Height [uv]	Area [%]	BL
1	8.211	1298.39	114.41	0.02	*BV
2	8.909	545125.14	56357.04	8.96	VV
3	9.168	1508818.47	141585.49	24.80	VB
4	10.110	1460100.39	128149.32	24.00	BE
5	10.548	12827.00	1003.91	0.21	EV
6	10.895	14494.84	1144.37	0.24	VV
7	11.379	5903.77	362.62	0.10	VB
8	12.065	1267168.34	92878.87	20.83	BV
9	13.565	1489.83	122.03	0.02	VV
10	14.070	1263763.83	78413.92	20.77	VB
11	16.692	2319.00	115.76	0.04	BB
		6083309.00	500247.74	100.00	



DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]	Height [uv]	Area [%]	BL
1	9.323	21933.00	3351.55	1.63	BB
2	10.131	1221.30	86.28	0.09	BV
3	10.537	819.06	61.61	0.06	VV
4	11.179	24344.64	1721.59	1.81	VB
5	12.077	1220675.00	89894.59	90.53	BB
6	14.092	27712.50	1744.86	2.06	BB
7	18.271	51715.00	2003.14	3.84	BB
		1348420.50	98863.62	100.00	



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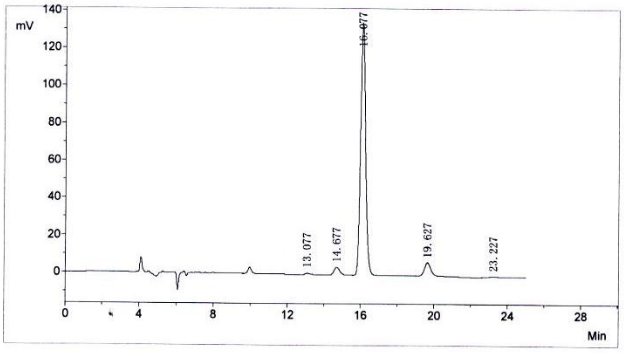
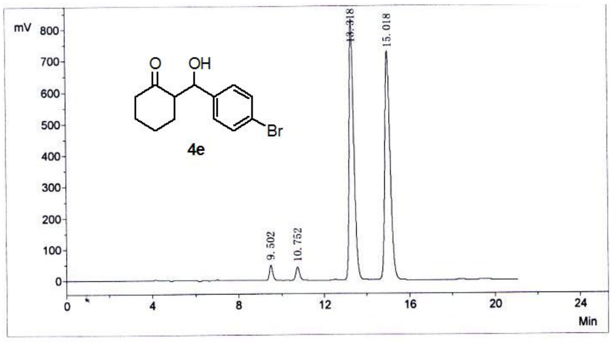
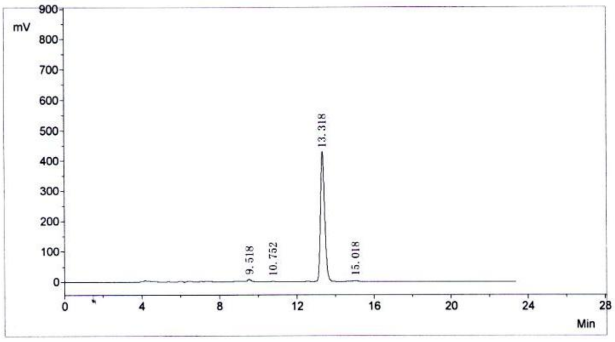
1	1		13.027	469578.1	7299058.9	20.4150
2	2		14.477	410648.2	7371516.0	20.6176
3	3		16.027	531675.1	10468165.9	29.2788
4	4		16.977	138.2	2315.6	0.0065
5	5		18.677	329.3	16740.4	0.0468
6	6		19.527	436577.8	10556281.3	29.5252
7	7		21.177	1148.9	30885.9	0.0864
8	8		23.127	69.8	1521.7	0.0043
9	9		24.677	180.5	6953.2	0.0194
合计:				1850345.9	35753438.8	100.0000



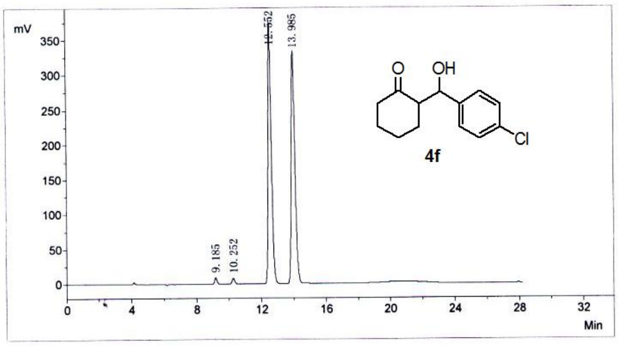
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		13.077	685.4	13092.6	0.4549
2	2		14.677	4043.3	92709.7	3.2213
3	3		16.077	133895.4	2573941.6	89.4349
4	4		19.627	7198.5	186912.3	6.4945
5	5		23.227	355.4	11348.6	0.3943
合计:				146178.0	2878004.7	100.0000



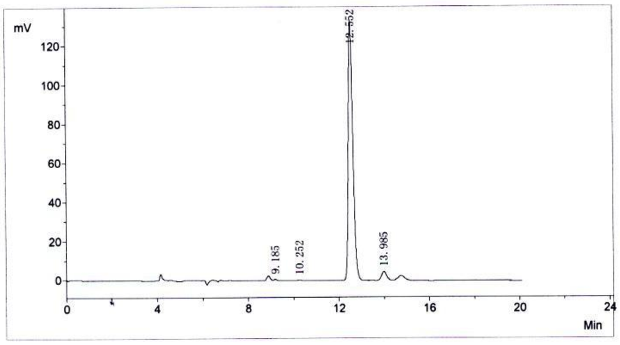
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		9.502	48495.0	507954.0	1.9283
2	2		10.752	42517.4	503668.6	1.9120
3	3		13.318	827797.2	12608842.9	47.8654
4	4		15.018	721377.2	12721827.2	48.2943
合计:				1640186.8	26342292.6	100.0000



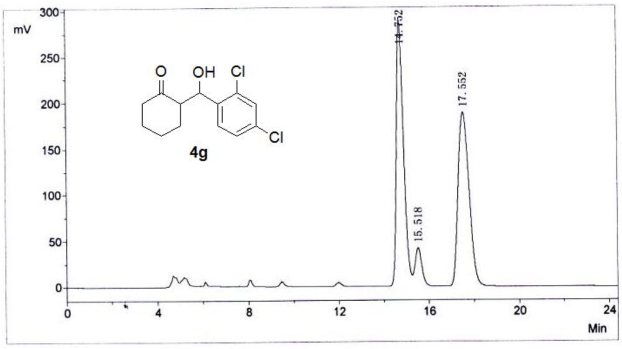
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		9.518	7434.7	80583.4	1.2111
2	2		10.752	812.6	9822.5	0.1476
3	3		13.318	424278.7	6485537.2	97.4706
4	4		15.018	3445.6	77895.9	1.1707
合计:				435971.6	6653839.0	100.0000



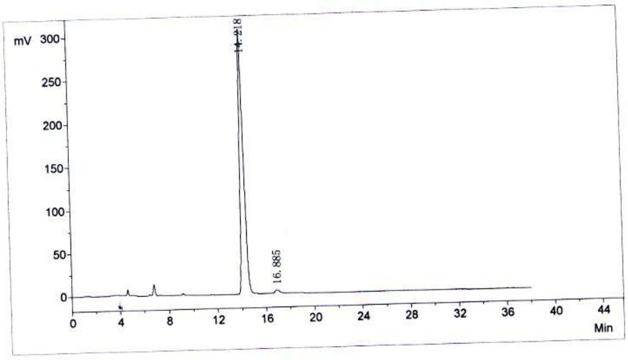
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		9.185	8716.3	91072.5	0.8374
2	2		10.252	8042.4	92169.7	0.8475
3	3		12.552	375286.4	5354472.2	49.2350
4	4		13.985	329677.0	5337631.4	49.0801
合计:				721722.1	10875345.8	100.0000



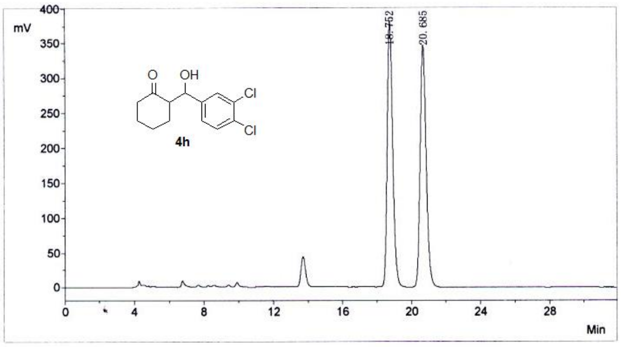
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		9.185	506.0	3154.4	0.1618
2	2		10.252	357.6	4085.1	0.2096
3	3		12.552	133200.9	1872351.9	96.0495
4	4		13.985	4555.6	69769.1	3.5791
合计:				138620.1	1949360.5	100.0000



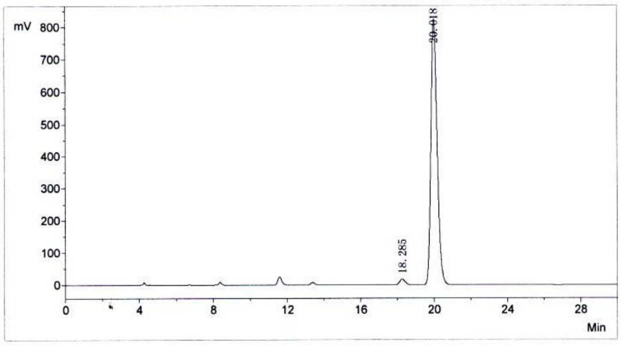
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		14.752	287196.0	6353454.1	46.4474
2	2		15.518	41901.0	894733.4	6.5410
3	3		17.552	188673.5	6430620.5	47.0116
合计:				517770.5	13678808.0	100.0000



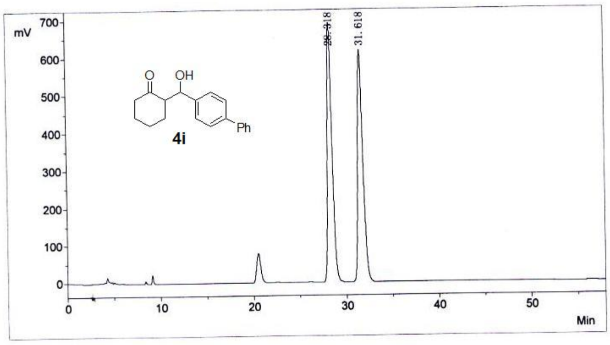
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		14.218	304728.1	6594047.2	98.3724
2	2		16.885	3958.4	109097.6	1.6276
合计:				308686.5	6703144.8	100.0000



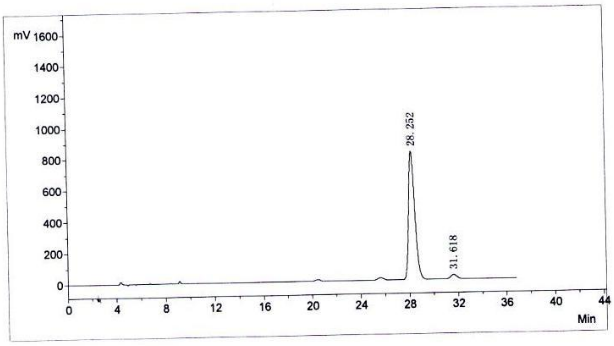
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		18.752	380143.6	8391453.6	49.9635
2	2		20.685	347193.4	8403710.9	50.0365
合计:				727337.0	16795164.5	100.0000



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		18.285	17773.4	375779.9	1.9056
2	2		20.018	822621.2	19343987.6	98.0944
合计:				840394.6	19719767.5	100.0000

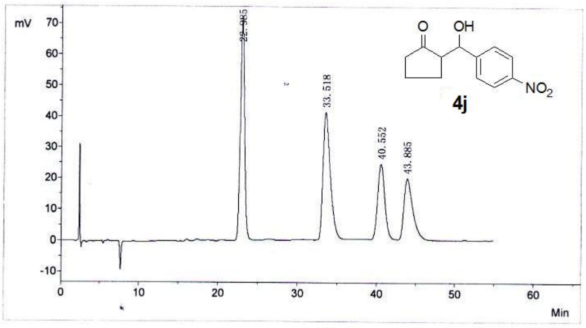


序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		28.318	692614.7	24383848.6	49.9438
2	2		31.618	617143.2	24438684.8	50.0562
合计:				1309757.9	48822533.4	100.0000

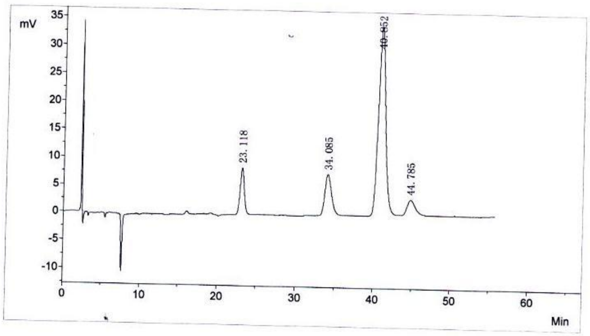


序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		28.252	821396.1	29192313.0	96.3696
2	2		31.618	28816.8	1099710.4	3.6304
合计:				850212.8	30292023.4	100.0000

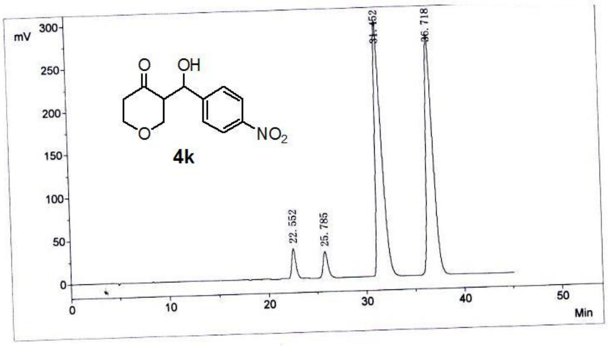
Supplementary Material (ESI) for Green Chemistry



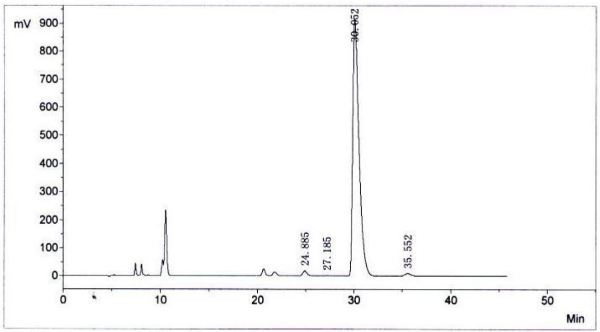
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		22.985	71260.8	2628714.8	31.7495
2	2		33.518	41052.2	2614324.0	31.5757
3	3		40.552	24175.3	1518336.0	18.3384
4	4		43.885	19439.0	1518173.4	18.3364
合计:				155927.4	8279548.2	100.0000



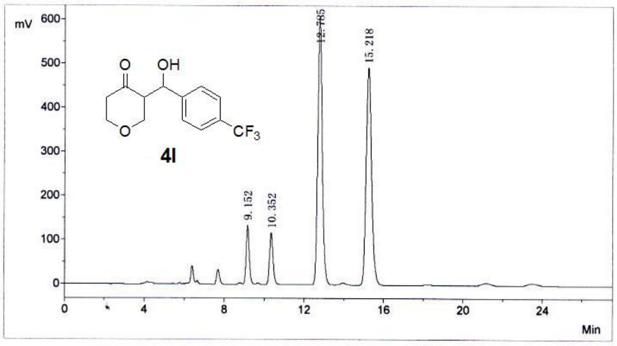
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		23.118	8462.2	310538.5	9.8926
2	2		34.085	7458.1	440752.7	14.0407
3	3		40.852	33843.4	2183295.8	69.5516
4	4		44.785	2754.8	204513.3	6.5150
合计:				52518.5	3139100.3	100.0000



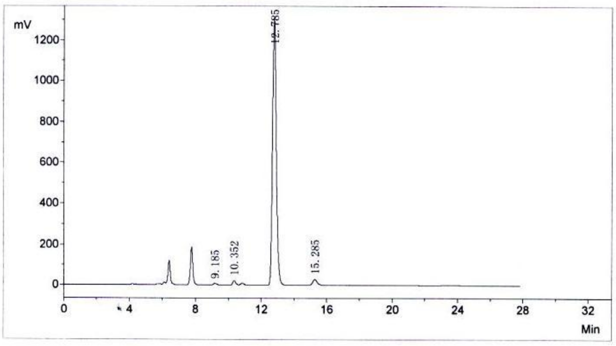
序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		22.552	34974.4	1021975.0	3.5029
2	2		25.785	30401.6	1025950.3	3.5166
3	3		31.452	297497.7	13562338.1	46.4863
4	4		36.718	278958.7	13564623.8	46.4942
合计:				641832.3	29174887.2	100.0000



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		24.885	17939.2	575346.6	1.3630
2	2		27.185	1481.8	49513.9	0.1173
3	3		30.052	915812.2	41161240.3	97.5086
4	4		35.552	9320.3	426840.3	1.0112
合计:				944553.5	42212941.1	100.0000



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		9.152	132890.8	1404086.3	6.4570
2	2		10.352	115820.2	1443891.9	6.6401
3	3		12.785	595606.5	9450490.0	43.4603
4	4		15.218	491004.6	9446626.1	43.4426
合计:				1335322.0	21745094.4	100.0000



序号	峰号	组份名	保留时间	峰高	峰面积	面积百分比(%)
1	1		9.185	6625.5	86733.1	0.3949
2	2		10.352	21342.8	249048.1	1.1339
3	3		12.785	1291917.3	21108551.8	96.1063
4	4		15.285	27578.0	519427.4	2.3649
合计:				1347463.5	21963760.5	100.0000