Supporting Information

Enantio- and Diastereoselective Double Mannich Reaction of Malononitrile with *N*-Boc Imines Using Bifunctional Organoiodine Catalyst

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Contents

1. General

Dry solvents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with 0.25 mm 230-400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). Silica gel column chromatography was performed on Kanto silica gel 60 (spherical, 63-210 μm). IR spectra were recorded on JASCO FT/IR-4100 using ATR. High-resolution mass spectra were recorded on a Thermo Fisher Scientific Exactive Orbitrap mass spectrometer (ESI), and a JEOL JMS-T100GCv "AccuTOF GCv" (FD).^{1}H-NMR spectra were recorded on JEOL ECS-400 (400 MHz), ECA-500 (500 MHz), ECX-400 (400 MHz) spectrometers. Chemical shifts of ^{1}H-NMR spectra were reported relative to tetramethyl silane (δ 0). ^{13}C-NMR spectra were recorded on JEOL ECS-400 (100 MHz), ECA-500 (125 MHz), ECX-400 (100 MHz) spectrometers. Chemical shifts of ^{13}C-NMR spectra were reported relative to $CDCl_3$ (δ 77.0). Splitting patterns were reported as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

N-Boc aldimines were synthesized according to known procedure.[1]

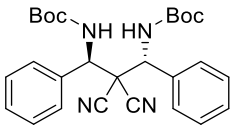
[1] Wenzel, A.-G.; Jacobsen, E.-N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

2. General procedure for asymmetric Mannich reaction of malononitrile with *N*-Boc aldimines

Catalyst **3b** (1.9 mg, 0.003 mmol, 0.03 eq) and malononitrile **2** (6.6 mg, 0.1 mmol, 1 eq) were added to a glass tube containing a stir bar under Ar. $CHCl_3$ (0.5 ml) was added to the flask, and the mixture was cooled to -50 °C. To the resulting suspension, imine **3** (0.22 mmol, 2.2 eq) was added. After being stirred for 48 h, solvent was removed under reduced pressure. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The mixture was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) to afford product **4**. The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using Daicel OD-H, OD-3, AD-H, IA, and AZ-3 column.

3. Analytical data of double Mannich products

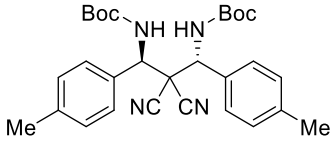
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-diphenylpropane-1,3-diyl)dicarbamate (4a)



Reaction time: 48 h; colorless oil (47.4 mg, >99% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 (s, 10H), 5.47 (br, 2H), 5.33 (br, 2H), 1.45 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.1, 134.87, 129.7, 129.1, 127.7, 113.1, 81.3, 56.5, 51.6, 28.1; **IR** (neat) 3316, 3010, 2979, 1703, 1497, 1366, 1166, 754 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{32}N_4NaO_4$ $[M + Na]^+$: 499.2316, found: 499.2309; $[\alpha]_D^{21}$ = −41.9 (*c* = 1.0, $CHCl_3$, >99.5% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer t_R = 16.6 min, major enantiomer t_R = 18.2 min, >99.5% ee.

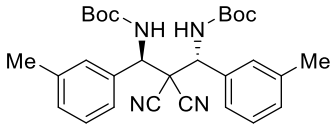
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-di-p-tolylpropane-1,3-diyl)dicarbamate (4b)



Reaction time: 48 h; colorless oil (49.7 mg, 99% yield, *dl*:*meso* = 16:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.2 Hz, 4H), 7.21 (d, *J* = 8.2 Hz, 4H), 5.42 (d, *J* = 9.3 Hz, 2H), 5.24 (d, *J* = 10.2 Hz, 2H), 2.37 (s, 6H), 1.44 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.1, 139.7, 131.9, 129.7, 127.6, 113.3, 81.2, 56.2, 51.8, 28.1, 21.1; **IR** (neat) 3346, 2979, 1700, 1509, 1366, 1162, 733 cm^{-1}; **HRMS** (ESI+) calcd for $C_{29}H_{36}N_4NaO_4$ $[M + Na]^+$: 527.2629, found: 527.2626; **$[\alpha]_D^{20}$** = −36.2 (*c* = 1.0, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer t_R = 10.4 min, major enantiomer t_R = 24.3 min, 99% ee.

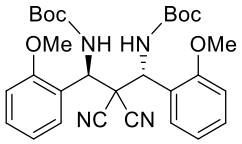
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-di-m-tolylpropane-1,3-diyl)dicarbamate (4c)



Reaction time: 48 h; colorless oil (50.0 mg, >99% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.11-7.33 (m, 8H), 5.44 (s, 2H), 5.23 (s, 2H), 2.36 (s, 6H), 1.38 (d, *J* = 48.2 Hz, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.0, 138.7, 134.7, 130.4, 128.9, 128.8, 124.4, 113.2, 81.2, 56.5, 51.6, 28.1, 21.3; **IR** (neat) 3344, 2979, 1699, 1366, 1159, 730 cm^{-1}; **HRMS** (ESI+) calcd for $C_{29}H_{36}N_4NaO_4$ $[M + Na]^+$: 527.2629, found: 527.2620; **$[\alpha]_D^{18}$** = −43.0 (*c* = 1.0, $CHCl_3$, >99.5% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm); minor enantiomer t_R = 16.9 min, major enantiomer t_R = 26.0 min, >99.5% ee.

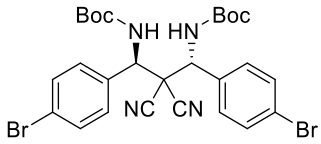
di-tert-butyl ((1S,3S)-2,2-dicyano-1,3-bis(2-methoxyphenyl)propane-1,3-diyl)dicarbamate (4d)



Reaction time: 48 h; colorless oil (53.4 mg, >99% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.40 (m, 2H), 7.26 (s, 2H), 6.89-6.98 (m, 4H), 6.29 (s, 2H), 5.97 (s, 2H), 3.87 (s, 6H), 1.47 (s, 19H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.0, 155.0, 130.6, 129.2, 124.3, 120.8, 113.5, 111.2, 80.8, 55.1, 54.49, 51.0, 28.3; **IR** (neat) 3345, 2978, 1716, 1491, 1248, 1163, 754 cm^{-1}; **HRMS** (ESI+) calcd for $C_{29}H_{36}N_4NaO_6$ $[M + Na]^+$: 559.2527, found: 559.2524; **$[\alpha]_D^{19}$** = −27.5 (*c* = 1.0, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm); minor enantiomer t_R = 19.0 min, major enantiomer t_R = 27.1 min, 99% ee.

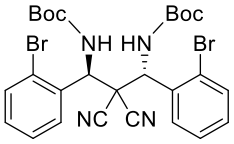
di-tert-butyl ((1R,3R)-1,3-bis(4-bromophenyl)-2,2-dicyanopropane-1,3-diyl)dicarbamate (4e)



Reaction time: 48 h; colorless oil (62.0 mg, 96% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (dt, *J* = 8.9, 2.3 Hz, 4H), 7.30-7.34 (m, 4H), 5.41 (d, *J* = 10.4 Hz, 2H), 5.31 (d, *J* = 9.7 Hz, 2H), 1.44 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.9, 133.8, 132.4, 129.3, 124.1, 112.6, 81.7, 56.0, 51.1, 28.1; **IR** (neat) 2979, 1701, 1365, 728 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_4NaO_4Br_2$ $[M + Na]^+$: 655.0526, found: 655.0524; **$[\alpha]_D^{21}$** = −27.3 (*c* = 1.0, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 0.2 mL/min, 254 nm); minor enantiomer t_R = 46.8 min, major enantiomer t_R = 42.6 min, 99% ee.

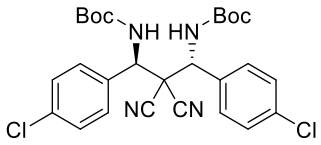
di-tert-butyl ((1S,3S)-1,3-bis(2-bromophenyl)-2,2-dicyanopropane-1,3-diyl)dicarbamate (4f)



Reaction time: 48 h; white solids (62.0 mg, 98% yield, *dl*:*meso* = 19:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63-7.68 (m, 4H), 7.42-7.46 (m, 2H), 7.26-7.31 (m, 2H), 6.18 (s, 2H), 5.53 (d, *J* = 7.0 Hz, 2H), 1.46 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.8, 135.3, 133.5, 130.9, 128.4, 127.6, 124.8, 111.7, 81.5, 54.7, 50.9, 28.1; **IR** (neat) 2979, 1702, 1365, 1158, 728 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_4NaO_4Br_2$ $[M + Na]^+$: 655.0526, found: 655.0521; **$[\alpha]_D^{20}$** = −92.3 (*c* = 1.0, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer t_R = 9.8 min, major enantiomer t_R = 30.9 min, 99% ee.

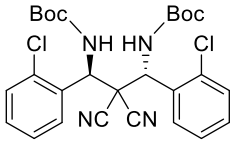
di-tert-butyl ((1R,3R)-1,3-bis(4-chlorophenyl)-2,2-dicyanopropane-1,3-diyl)dicarbamate (4g)



Reaction time: 48 h; colorless oil (54.1 mg, >99% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 9.0 Hz, 4H), 7.38 (d, *J* = 8.8 Hz, 4H), 5.42 (d, *J* = 10.3 Hz, 2H), 5.33 (d, *J* = 9.4 Hz, 2H), 1.44 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.9, 135.9, 133.4, 129.4, 129.0, 112.6, 81.7, 55.9, 51.3, 28.1; **IR** (neat) 3313, 2980, 1698, 1491, 1160, 730 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_4NaO_4Cl_2$ $[M + Na]^+$: 567.1536, found: 567.1534; **$[\alpha]_D^{21}$** = −32.7 (*c* = 1.0, $CHCl_3$, >99.5% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 98:2, 1.0 mL/min, 254 nm); minor enantiomer t_R = 31.8 min, major enantiomer t_R = 44.9 min, >99.5% ee.

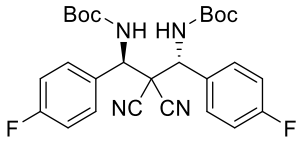
di-tert-butyl ((1S,3S)-1,3-bis(2-chlorophenyl)-2,2-dicyanopropane-1,3-diyl)dicarbamate (4h)



Reaction time: 48 h; colorless oil (53.6 mg, 98% yield, *dl*:*meso* = 19:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64-7.66 (m, 2H), 7.34-7.49 (m, 6H), 6.20 (s, 2H), 5.56 (s, 2H), 1.45 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.9, 134.2, 133.6, 130.6, 130.2, 127.8, 127.5, 111.8, 81.5, 52.2, 50.8, 28.1; **IR** (neat) 3333, 2979, 1702, 1367, 1156, 729 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_4NaO_4Cl_2$ $[M + Na]^+$: 567.1536, found: 567.1535; **$[\alpha]_D^{20}$** = −78.0 (*c* = 1.0, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer t_R = 11.8 min, major enantiomer t_R = 17.4 min, 99% ee.

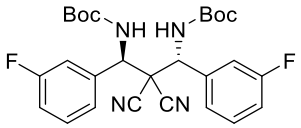
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-bis(4-fluorophenyl)propane-1,3-diyl)dicarbamate (4i)



Reaction time: 48 h; colorless oil (50.2 mg, 98% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.45 (m, 4H), 7.10-7.15 (m, 4H), 5.45 (d, *J* = 10.3 Hz, 2H), 5.32-5.35 (m, 2H), 1.45 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.3 (d, $^1J_{CF}$ = 250.1 Hz), 154.0, 129.6 (d, $^3J_{CF}$ = 8.4 Hz), 116.2 (d, $^2J_{CF}$ = 22.8 Hz), 112.8, 81.6, 55.9, 51.7, 28.1; **IR** (neat) 3316, 2980, 1699, 1509, 1160, 730 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_4NaO_4F_2$ $[M + Na]^+$: 535.2127, found: 535.2117; **$[\alpha]_D^{19}$** = −42.4 (*c* = 1.0, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm); minor enantiomer t_R = 13.1 min, major enantiomer t_R = 15.4 min, 99% ee.

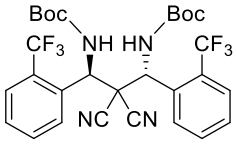
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-bis(3-fluorophenyl)propane-1,3-diyl)dicarbamate (4j)



Reaction time: 48 h; colorless oil (50.2 mg, 98% yield, *dl*:*meso* = 16:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.45 (m, 2H), 7.25-7.28 (m, 2H), 7.12-7.17 (m, 4H), 5.47 (d, *J* = 10.3 Hz, 2H), 5.38 (s, 2H), 1.45 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.7 (d, $^1J_{CF}$ = 248.9 Hz), 154.0, 137.2 (d, $^3J_{CF}$ = 7.5 Hz), 130.9 (d, $^3J_{CF}$ = 8.5 Hz), 123.4, 116.9 (d, $^2J_{CF}$ = 20.7 Hz), 115.0 (d, $^2J_{CF}$ = 22.6 Hz), 112.5, 81.8, 56.1, 51.1, 28.1; **IR** (neat) 3304, 2979, 1698, 1489, 1367, 1157, 730 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_4NaO_4F_2$ $[M + Na]^+$: 535.2127, found: 535.2120; **$[\alpha]_D^{27}$** = −8.0 (*c* = 0.5, $CHCl_3$, 98% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm); minor enantiomer t_R = 16.8 min, major enantiomer t_R = 25.5 min, 98% ee.

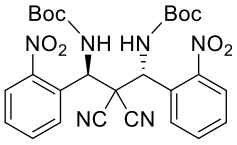
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-bis(2-(trifluoromethyl)phenyl)propane-1,3-diyl)dicarbamate (4k)



Reaction time: 48 h; colorless oil (60.0 mg, 98% yield, *dl*:*meso* = >20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 5.95 (d, *J* = 9.6 Hz, 2H), 5.42 (d, *J* = 9.0 Hz, 2H), 1.47 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.5, 135.0, 132.9, 128.6 (d, $^2J_{CF}$ = 30.0 Hz), 127.5, 126.7 (d, $^3J_{CF}$ = 5.6 Hz), 123.6 (d, $^1J_{CF}$ = 274.3 Hz), 112.3, 81.7, 52.2, 51.7, 28.1, 27.9; **IR** (neat) 3157, 2981, 1703, 1490, 1310, 1155, 730 cm^{-1}; **HRMS** (ESI+) calcd for $C_{29}H_{30}N_4NaO_4F_6$ $[M + Na]^+$: 635.2063, found: 635.2053; **$[\alpha]_D^{19}$** = −89.5 (*c* = 1.0, $CHCl_3$, >99.5% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm); minor enantiomer t_R = 41.9 min, major enantiomer t_R = 55.3 min, >99.5% ee.

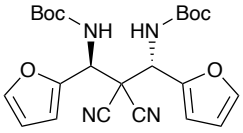
di-tert-butyl ((1R,3R)-2,2-dicyano-1,3-bis(2-nitrophenyl)propane-1,3-diyl)dicarbamate (4l)



Reaction time: 48 h; 3.3 equiv of *N*-Boc imine were used; pale yellow oil (56.0 mg, 98% yield, *dl*:*meso* = 16:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.23 (br, 2H), 7.88 (br, 2H), 7.79 (t, *J* = 7.7 Hz, 2H), 7.63 (t, *J* = 7.9 Hz, 2H), 6.86 (s, 2H), 6.00 (s, 2H), 1.46-1.47 (m, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.8, 147.8, 134.5, 131.7, 130.5, 128.6, 125.9, 111.6, 81.9, 50.7, 50.5, 28.2, 28.1; **IR** (neat) 3360, 2980, 1703, 1529, 1346, 729 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{30}N_6NaO_8$ $[M + Na]^+$: 589.2017, found: 589.2011; **$[\alpha]_D^{21}$** = +51.3 (*c* = 1.0, $CHCl_3$, 94% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 70:30, 1.0 mL/min, 254 nm); minor enantiomer t_R = 28.0 min, major enantiomer t_R = 11.7 min, 94% ee.

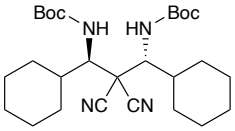
di-*tert*-butyl ((1*S*,3*S*)-2,2-dicyano-1,3-di(furan-2-yl)propane-1,3-diyl)dicarbamate (4m)



Reaction time: 48 h; 3.3 equiv of *N*-Boc imine were used; colorless oil (43.2 mg, 95% yield, *dl*:*meso* = 2.3:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 1.1 Hz, 2H), 6.51 (d, *J* = 2.9 Hz, 2H), 6.43-6.44 (m, 2H), 5.47 (s, 2H), 5.41 (s, 2H), 1.45 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.0, 146.9, 144.0, 112.4, 110.8, 110.5, 81.6, 51.2, 28.1, 21.0; **IR** (neat) 3355, 2930, 1706, 1498, 1366, 1159 cm^{-1}; **HRMS** (ESI+) calcd for $C_{23}H_{29}N_4O_6$ $[M + H]^+$: 457.2087, found: 457.2083; **$[\alpha]_D^{27}$** = -11.7 (*c* = 0.5, $CHCl_3$, 91% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer t_R = 16.3 min, major enantiomer t_R = 22.0 min, 91% ee.

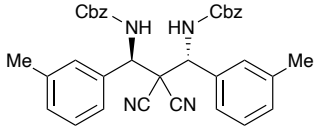
di-*tert*-butyl ((1*R*,3*R*)-2,2-dicyano-1,3-dicyclohexylpropane-1,3-diyl)dicarbamate (4n)



Reaction time and temperature: 48 h at -50 °C and 48 h at 0 °C; 3.3 equiv of *N*-Boc imine were used; 10 mol% of **1b** were used; colorless oil (46.0 mg, 94% yield, *dl*:*meso* = 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.87 (d, *J* = 10.6 Hz, 2H), 4.21 (s, 2H), 1.68-2.05 (m, 12H), 1.47 (s, 18H), 1.13-1.38 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.0, 114.1, 80.7, 56.8, 46.0, 41.0, 31.3, 28.2, 26.9, 26.0, 25.7; **IR** (neat) 3344, 2979, 1709, 1152, 750 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{45}N_4O_4$ $[M + H]^+$: 489.3435, found: 489.3436; **$[\alpha]_D^{27}$** = +35.8 (*c* = 0.5, $CHCl_3$, 83% ee).

Enantiomeric excess was determined by HPLC with a Chiralcel OD-3 column (hexane:2-propanol = 95:5, 0.5 mL/min, 220 nm); minor enantiomer t_R = 15.1 min, major enantiomer t_R = 19.2 min, 83% ee.

dibenzyl ((1R,3R)-2,2-dicyano-1,3-di-m-tolylpropane-1,3-diyl)dicarbamate (4o)



Reaction time: 48 h; colorless oil (50.4 mg, 88% yield, *dl*:*meso* = 4:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35-7.22 (m, 16H), 7.16 (s, 2H), 5.65 (d, *J* = 9.7 Hz, 2H), 5.37 (d, *J* = 9.5 Hz, 2H), 5.11-5.08 (m, 4H), 2.36 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.1, 139.1, 135.4, 134.3, 130.7, 129.1, 128.6, 128.5, 128.4, 124.5, 112.9, 68.0, 57.2, 51.5, 21.4; **IR** (neat) 3449, 2980, 1700, 1508, 1370 cm^{-1}; **HRMS** (ESI+) calcd for $C_{35}H_{32}N_4NaO_4$ $[M + Na]^+$: 595.2321, found: 595.2316; **$[\alpha]_D^{25}$** = −24.0 (*c* = 0.5, $CHCl_3$, 94% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak AZ-3 column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm); minor enantiomer t_R = 25.5 min, major enantiomer t_R = 19.2 min, 94% ee.

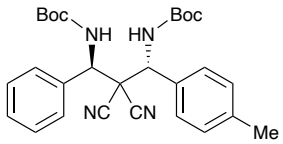
4. 3 mmol scale synthesis

Catalyst **3b** (54.3 mg, 0.09 mmol, 0.03 eq) and malononitrile **2** (199 mg, 3 mmol, 1 eq) were added to a glass tube containing a stir bar under Ar. $CHCl_3$ (15 ml) was added to the flask, and the mixture was cooled to –50 °C. To the resulting suspension, *N*-Boc imine **3a** (1.35 g, 6.6 mmol, 2.2 eq) was added. After being stirred for 72 h, solvent was removed under reduced pressure. Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture (dr = 98:2). The mixture was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) to afford product **4a** (1.43 g, >99% yield). The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using Chiralpak IA column (99% ee).

5. Synthesis of unsymmetrical 1,3-diamine

Catalyst **3b** (1.9 mg, 0.003 mmol, 0.03 eq) and malononitrile **2** (6.6 mg, 0.1 mmol, 1 eq) were added to a glass tube containing a stir bar under Ar. $CHCl_3$ (0.5 ml) was added to the flask, and the mixture was cooled to –50 °C. To the resulting suspension, imine **3a** (0.22 mmol, 2.2 eq) was added. After being stirred for 15 h, imine **3b** (0.22 mmol, 2.2 eq) was added. After being stirred for 48 h, solvent was removed under reduced pressure. The mixture was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) to afford product **4ab** (35.1 mg, 72% yield).

di-tert-butyl ((1R,3R)-2,2-dicyano-1-phenyl-3-(p-tolyl)propane-1,3-diyl)dicarbamate (4ab)

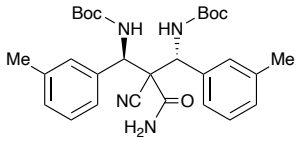


Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 (s, 5H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.49-5.43 (m, 2H), 5.28 (br, 2H), 2.37 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.1, 139.8, 134.9, 131.9, 129.8, 129.7, 129.1, 127.8, 127.6, 113.3, 81.4, 56.6, 51.8, 28.2, 21.2; **IR** (neat) 3649, 3021, 2927, 1727, 1511, 1216, 758 cm^{-1}; **HRMS** (ESI+) calcd for $C_{28}H_{34}N_4NaO_4$ $[M + Na]^+$: 513.2478, found: 513.2473; $[\alpha]_D^{25}$ = −41.6 (*c* = 0.5, $CHCl_3$, 80% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm); minor enantiomer t_R = 17.2 min, major enantiomer t_R = 16.3 min, 80% ee.

6. Transformation of chiral 1,3-diamine derivative 4.

di-tert-butyl ((1R,3R)-2-carbamoyl-2-cyano-1,3-di-m-tolylpropane-1,3-diyl)dicarbamate (5c)

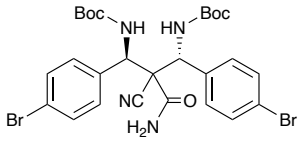


A glass tube equipped was charged with a stir bar, **4c** (50.0 mg, 0.100 mmol, 1.0 eq), acetamide (29.5 mg, 0.500 mmol, 5.0 eq), MeCN (0.3 mL), and H_2O (0.05 mL). To the mixture was added $Pd(NO_3)_2$•$2H_2O$ (2.3 mg, 0.01 mmol, 10 mol%) and the mixture was stirred at room temperature. After being stirred for 16 h, the H_2O was added. Separated aqueous layer was extracted with EtOAc three times. Combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1) to afford **5c** (white solids, 32.9 mg, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.11 (m, 8H), 6.88 (d, J = 9.7 Hz, 1H), 5.62 (d, J = 10.3 Hz, 1H), 5.45 (s, 1H), 5.38 (d, J = 10.6 Hz, 1H), 5.28 (d, J = 9.5 Hz, 1H), 5.11 (s, 1H), 2.340 (s, 3H), 2.344 (s, 3H), 1.42 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.0, 154.3, 154.1, 138.2, 138.0, 137.1, 136.7, 129.4, 129.3, 128.9, 128.7, 128.5, 128.3, 124.8, 124.6, 118.3, 80.6, 79.8, 77.2, 77.0, 76.7, 60.3, 56.3, 55.2, 28.4, 28.3, 21.5; **IR** (neat) 3455, 3366, 3299, 2977, 1723, 1677, 1366, 1168 cm^{-1}; **HRMS** (ESI+) calcd for $C_{29}H_{38}N_4NaO_5$ $[M + Na]^+$: 545.2734, found: 545.2728; **$[\alpha]_D^{20}$** = +12.4 (c = 0.26, $CHCl_3$, >99.5% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm); minor enantiomer t_R = 19.6 min, major enantiomer t_R = 8.3 min, >99.5% ee.

di-tert-butyl ((1R,3R)-1,3-bis(4-bromophenyl)-2-carbamoyl-2-cyanopropane-1,3-diyl)dicarbamate (5e)

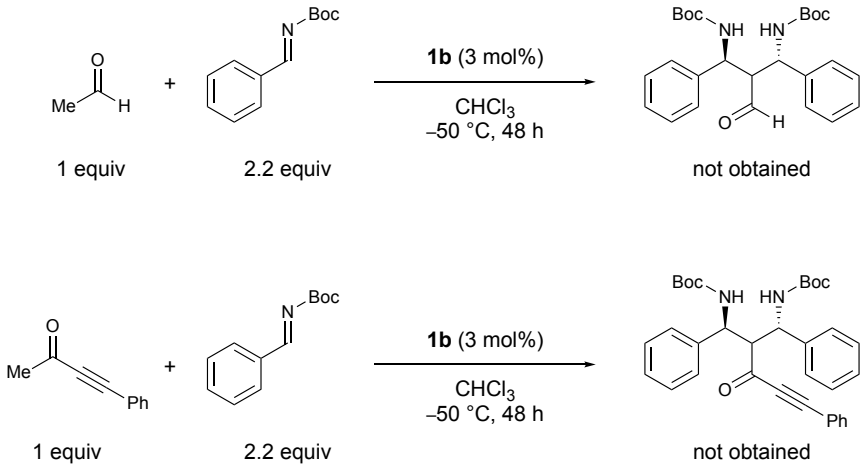


A glass tube equipped was charged with a stir bar, **4e** (60.0 mg, 0.0946 mmol, 1.0 eq), acetamide (27.9 mg, 0.473 mmol, 5.0 eq), MeCN (0.3 mL), and H_2O (0.05 mL). To the mixture was added $Pd(NO_3)_2$•$2H_2O$ (2.2 mg, 0.00946 mmol, 10 mol%) and the mixture was stirred at room temperature. After being stirred for 24 h, the H_2O was added. Separated aqueous layer was extracted with EtOAc three times. Combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1) to afford **5e** (white solids, 46.8 mg, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, J = 8.3, 2.9 Hz, 4H), 7.33-7.26 (m, 4H), 6.84 (d, J = 9.7 Hz, 1H), 5.63-5.19 (m, 5H), 1.41 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.5, 154.3, 154.0, 136.1, 135.7, 131.9, 131.7, 129.6, 129.5, 123.1, 122.9, 117.9, 81.1, 80.3, 77.3, 77.0, 76.8, 59.9, 55.8, 54.8, 28.3, 28.2; **IR** (neat) 3172, 2956, 2866, 1718, 1699, 1487, 1116 cm^{-1}; **HRMS** (ESI+) calcd for $C_{27}H_{32}Br_2N_4NaO_5$ $[M + Na]^+$: 675.0611, found: 675.0604; **$[\alpha]_D^{20}$** = +0.84 (c = 0.23, $CHCl_3$, 99% ee).

Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm); minor enantiomer t_R = 10.1 min, major enantiomer t_R = 7.5 min, 99% ee.

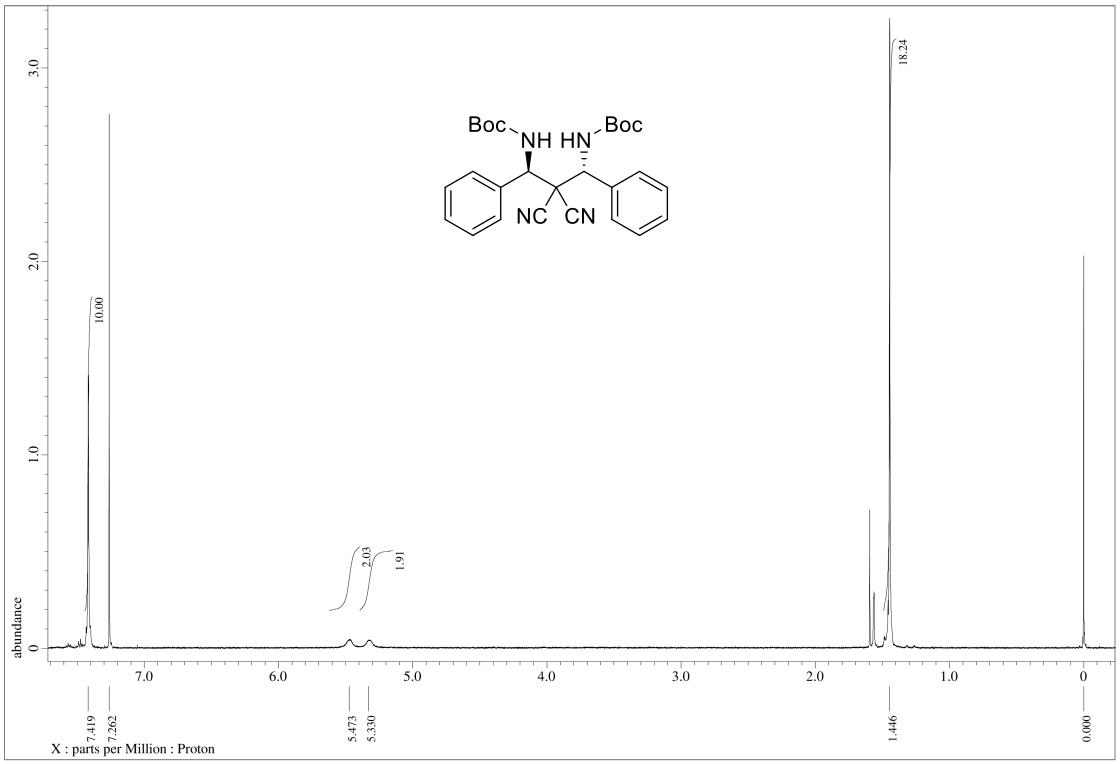
7. Reactions using acetaldehyde and ynone as nucleophiles



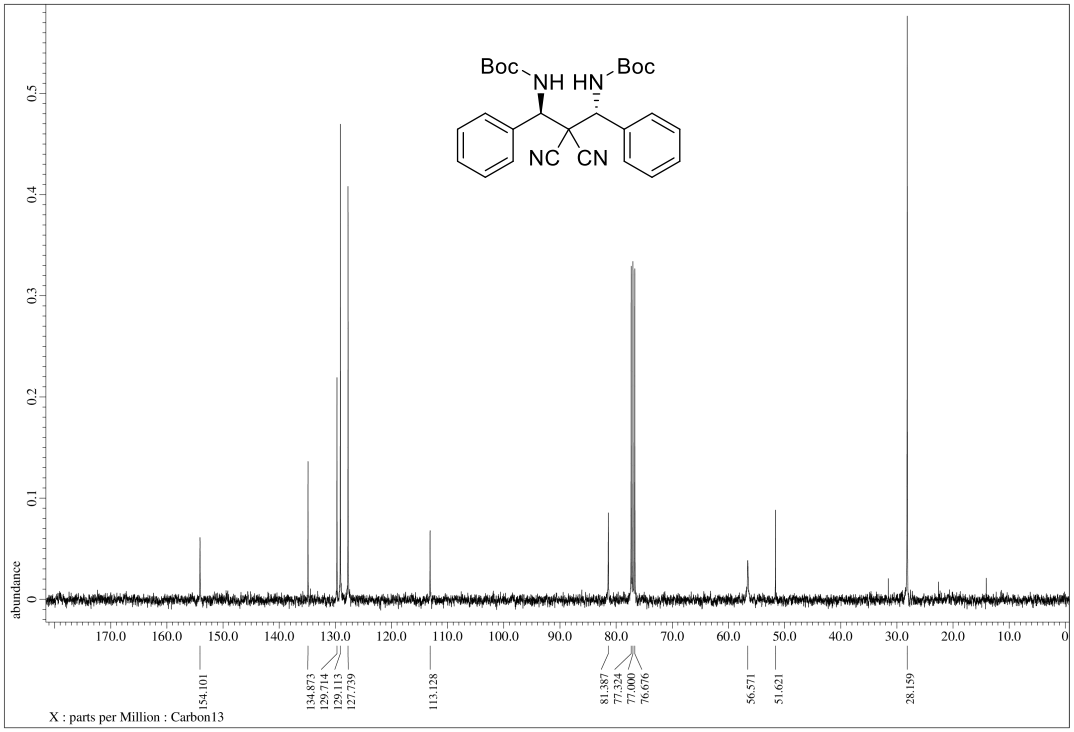
Acetaldehyde and ynone were applied to the double Mannich reaction as nucleophiles. No reactions were observed based on TLC monitoring and crude ^{1}H NMR analysis.

8. ^{1}H NMR and ^{13}C NMR spectra

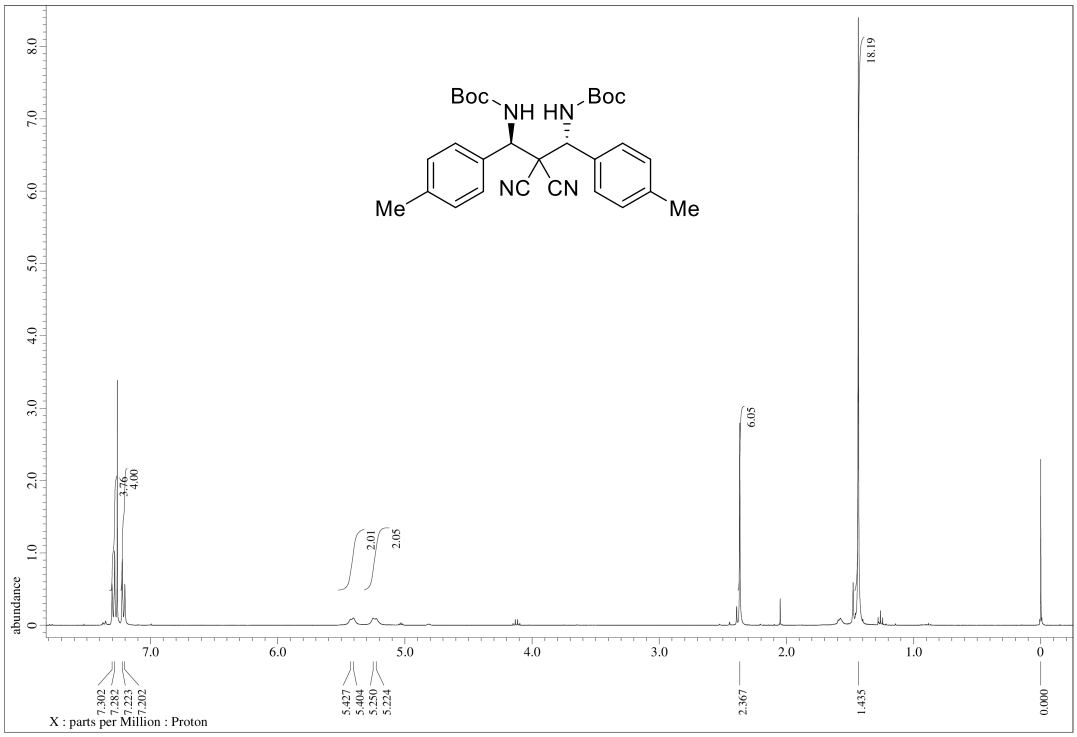
^{1}H NMR (500 MHz, $CDCl_3$) (**4a)**



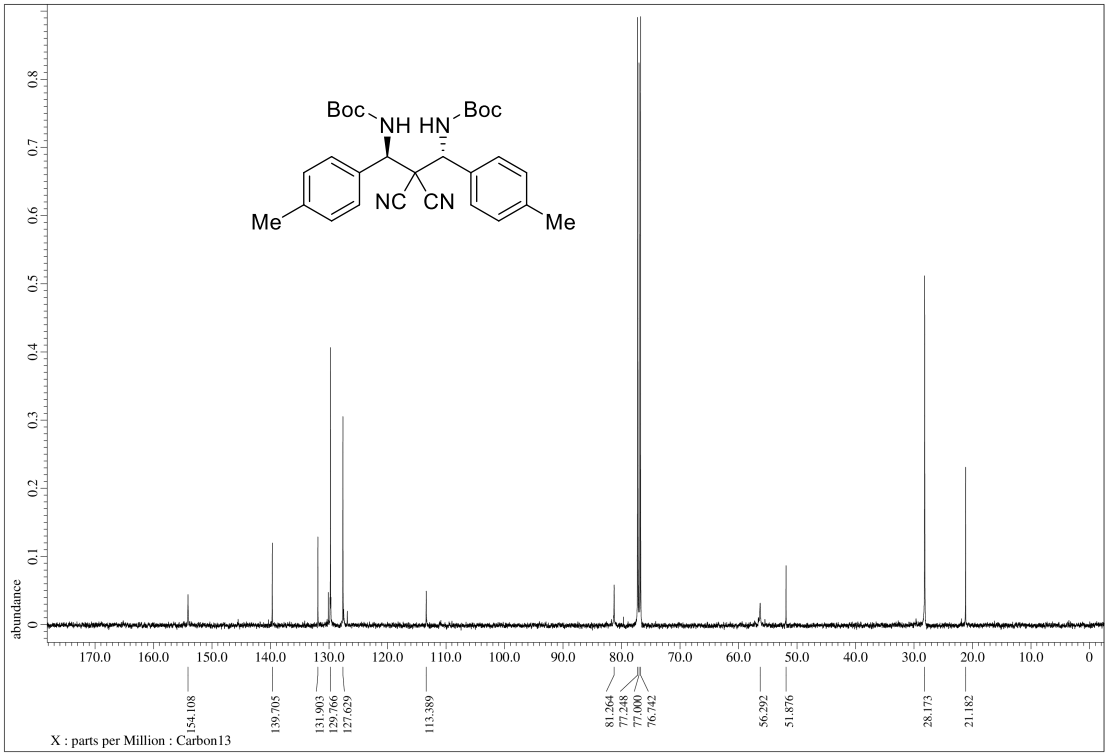
^{13}C NMR (100 MHz, $CDCl_3$) (**4a)**



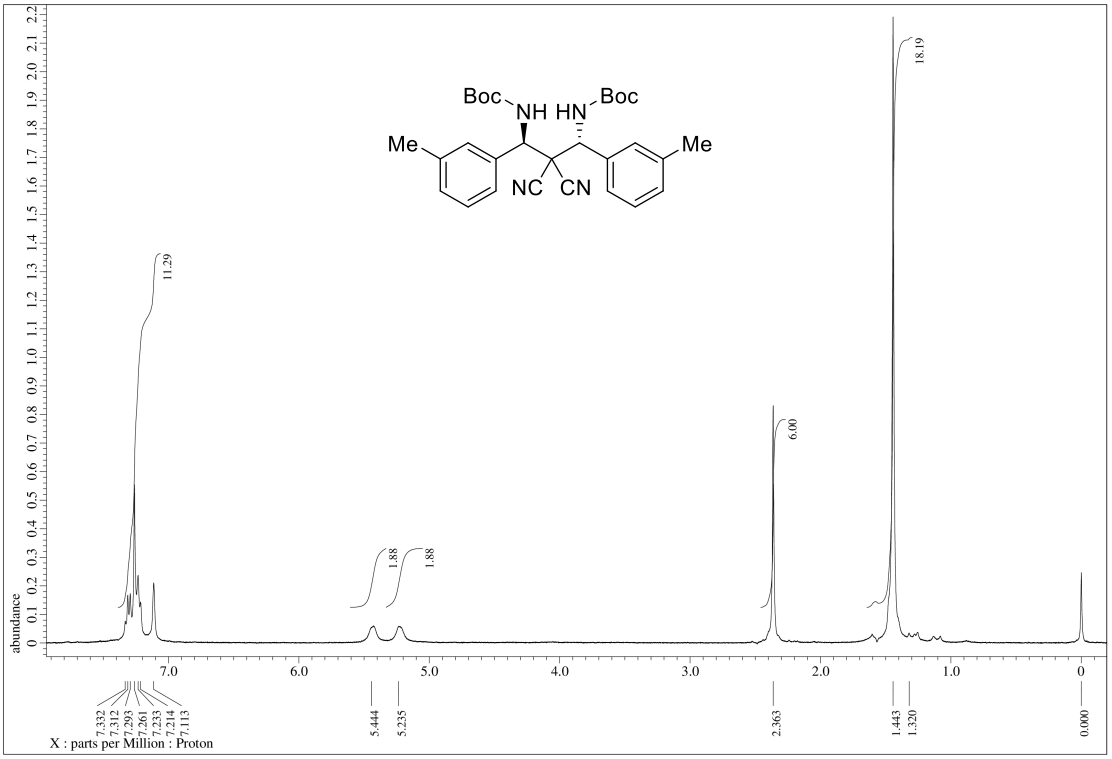
^{1}H NMR (400 MHz, $CDCl_3$) (**4b)**



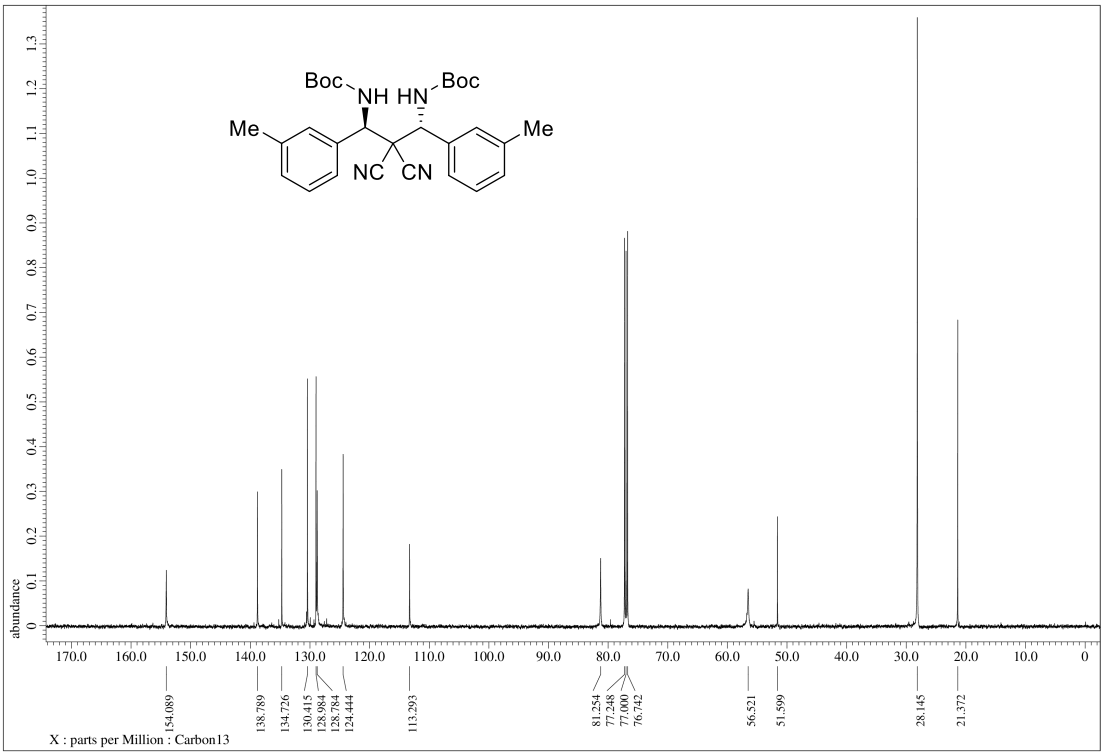
^{13}C NMR (125 MHz, $CDCl_3$) (**4b)**



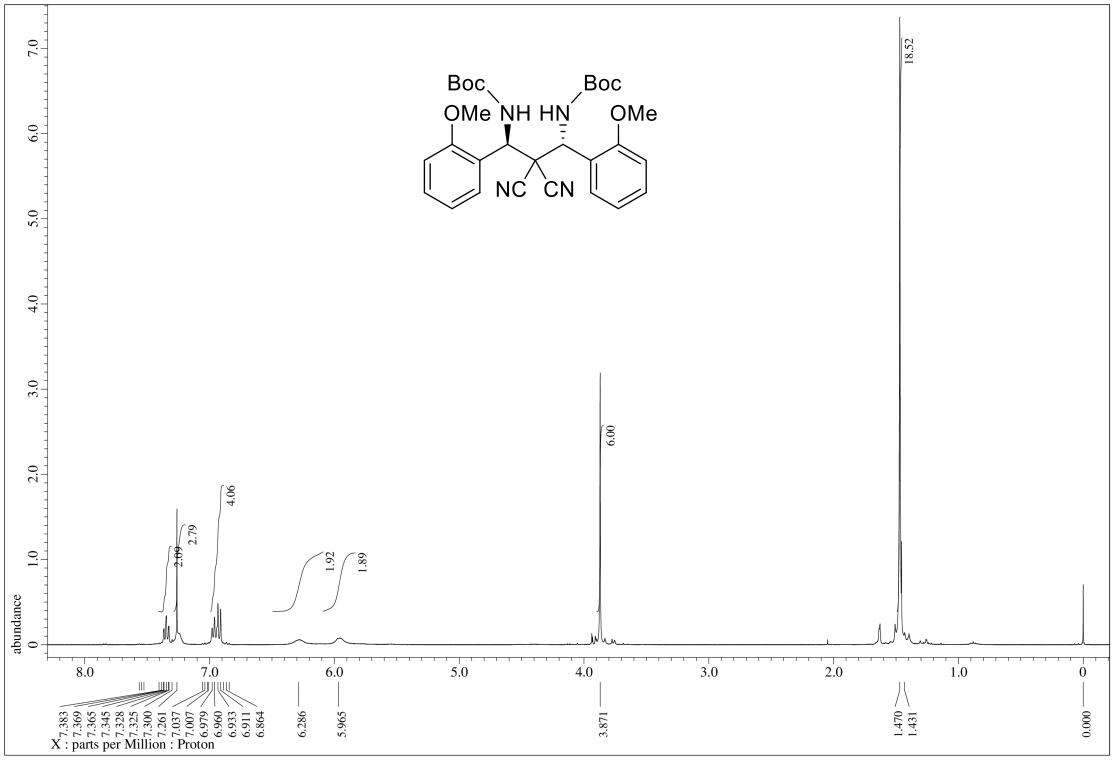
^{1}H NMR (400 MHz, $CDCl_3$) (**4c)**



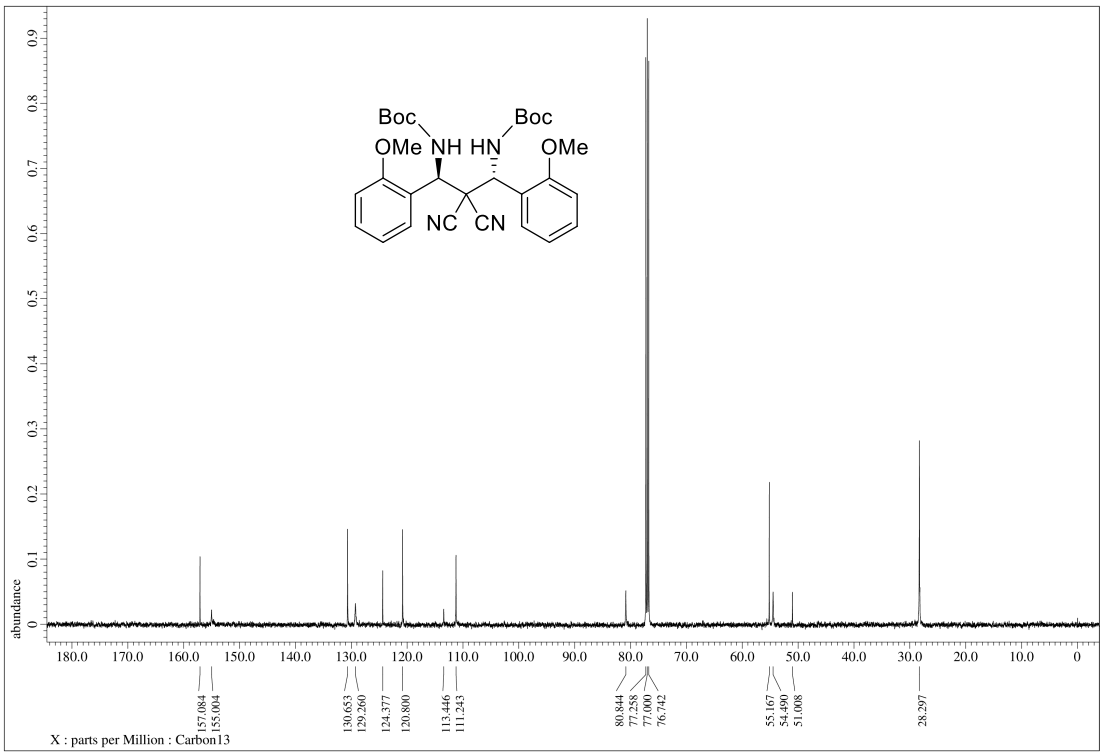
^{13}C NMR (125 MHz, $CDCl_3$) (**4c)**



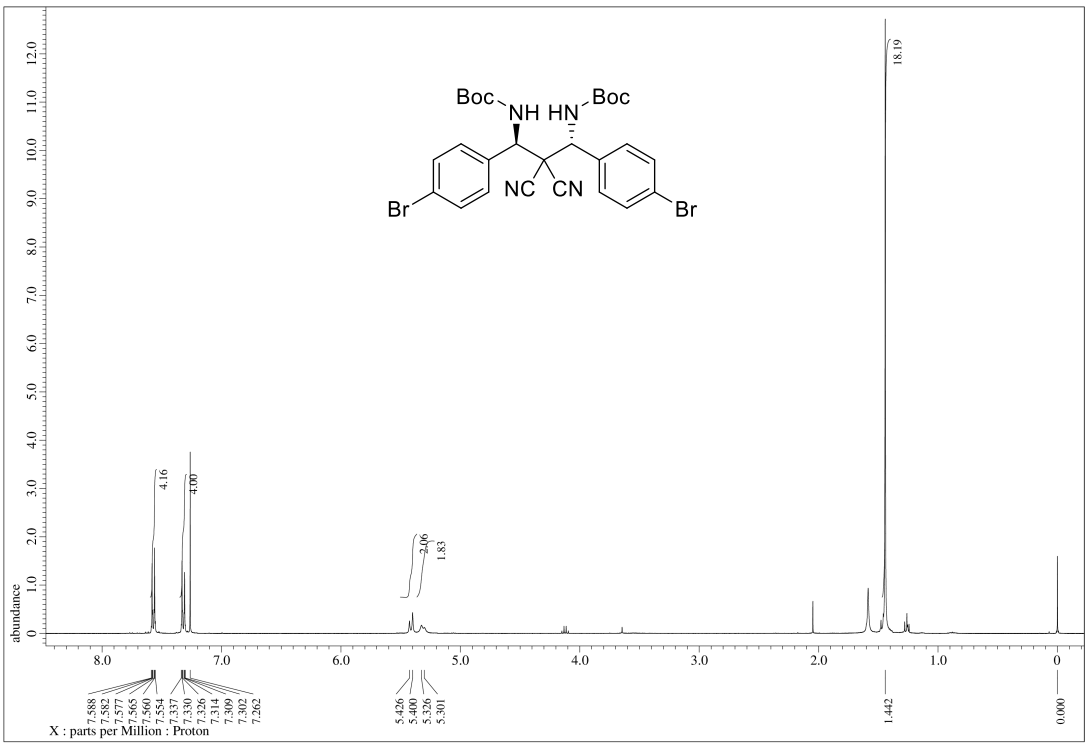
^{1}H NMR (400 MHz, $CDCl_3$) (**4d)**



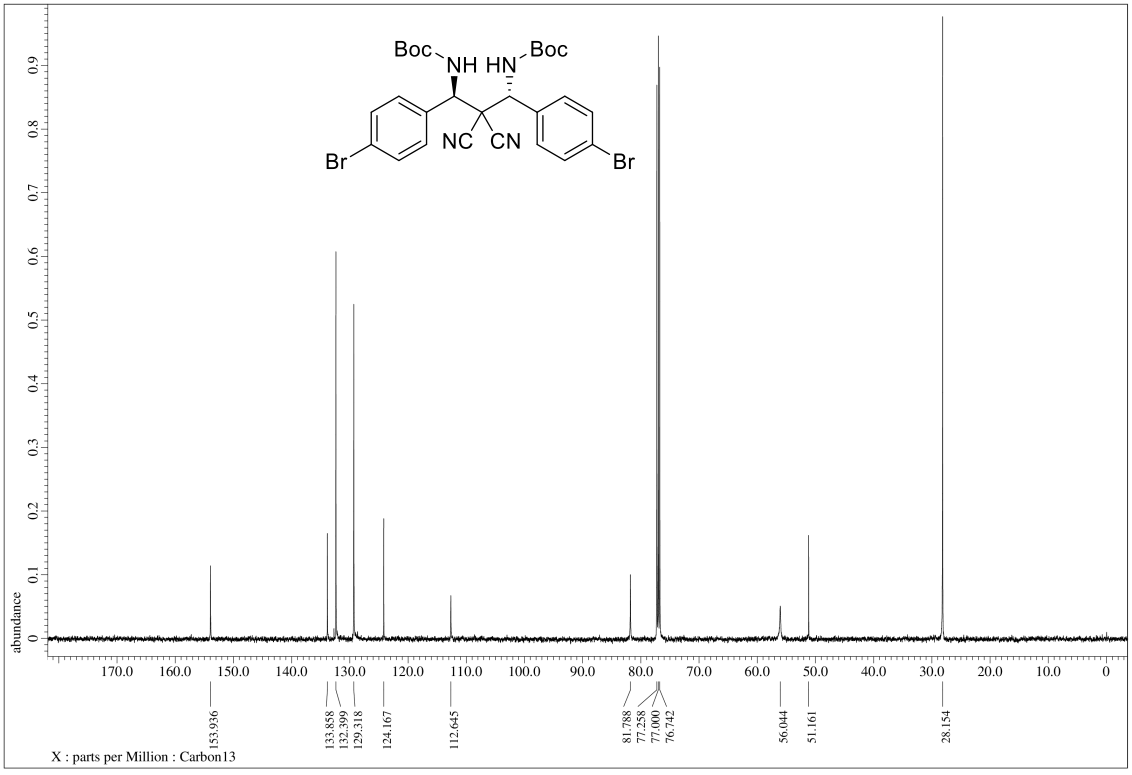
^{13}C NMR (125 MHz, $CDCl_3$) (**4d)**



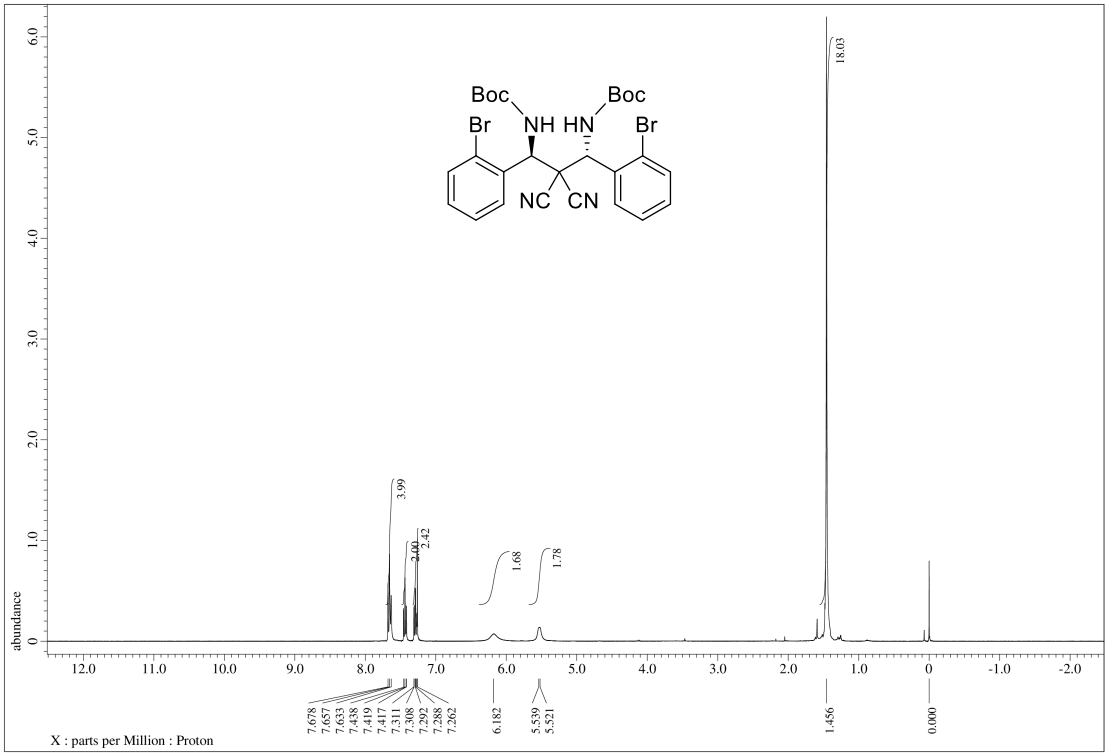
^{1}H NMR (400 MHz, $CDCl_3$) (**4e)**



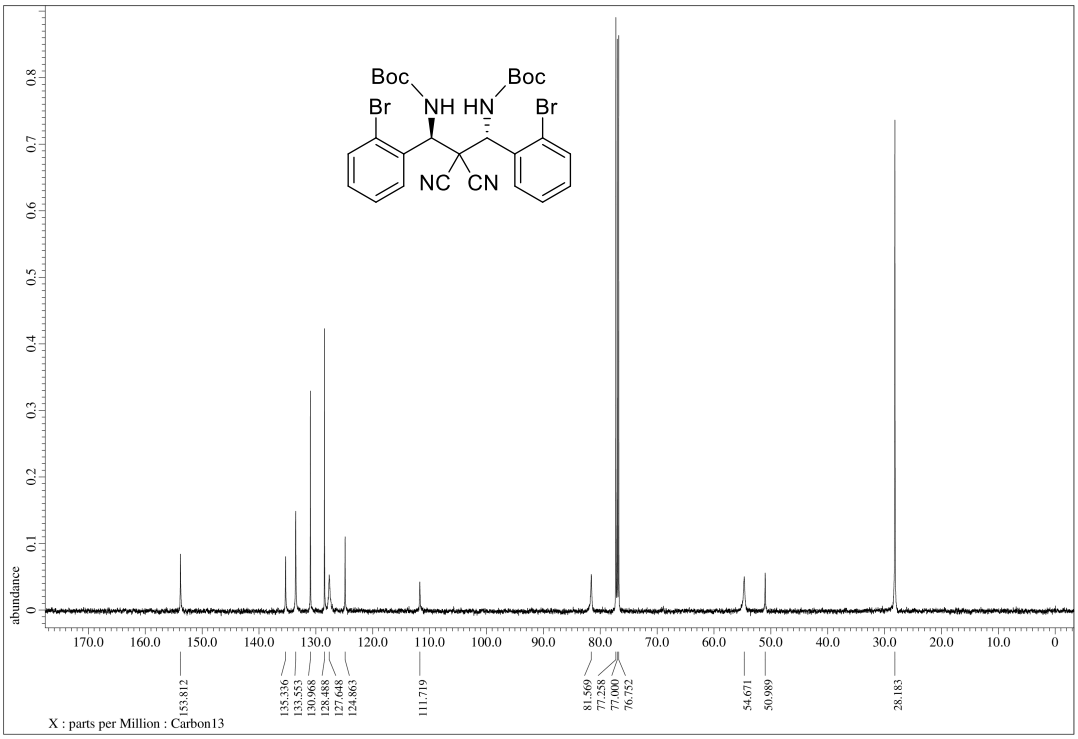
^{13}C NMR (125 MHz, $CDCl_3$) (**4e)**



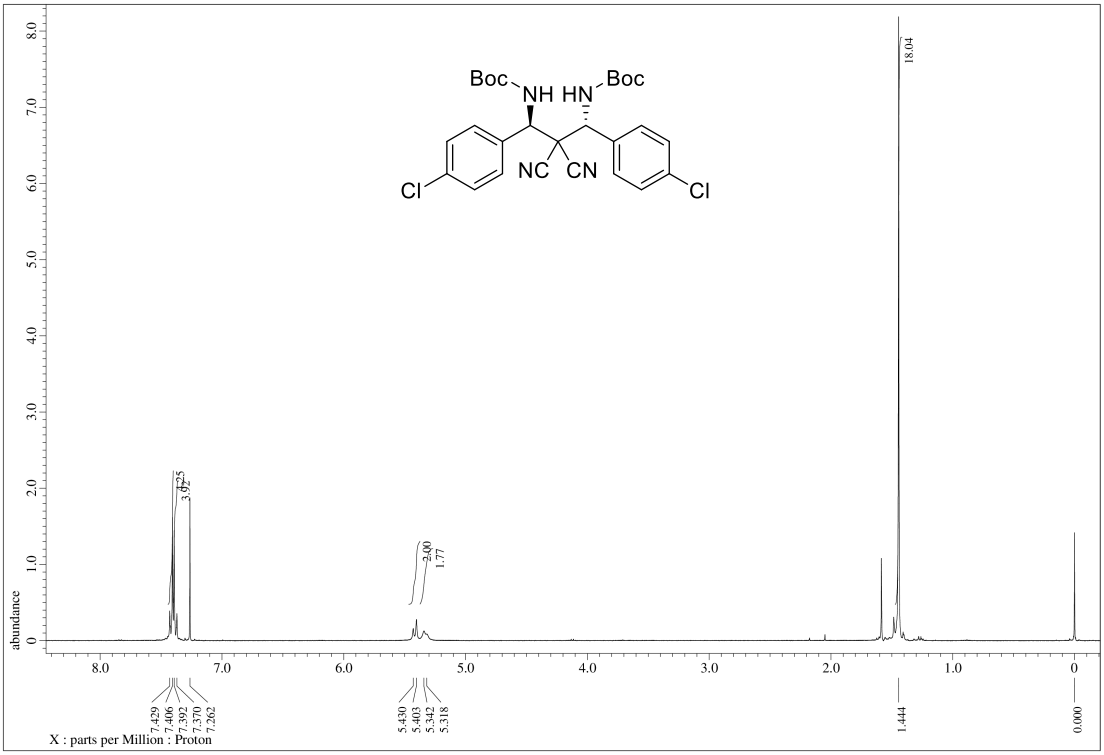
^{1}H NMR (400 MHz, $CDCl_3$) (**4f**)



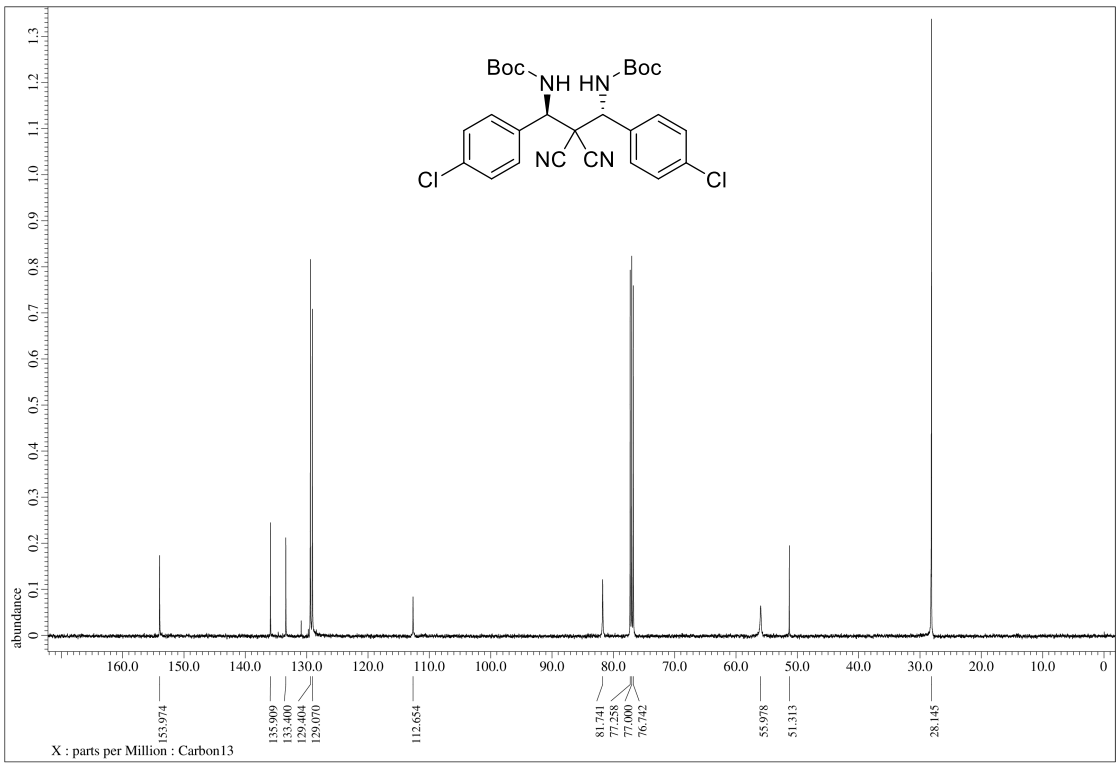
^{13}C NMR (125 MHz, $CDCl_3$) (**4f**)



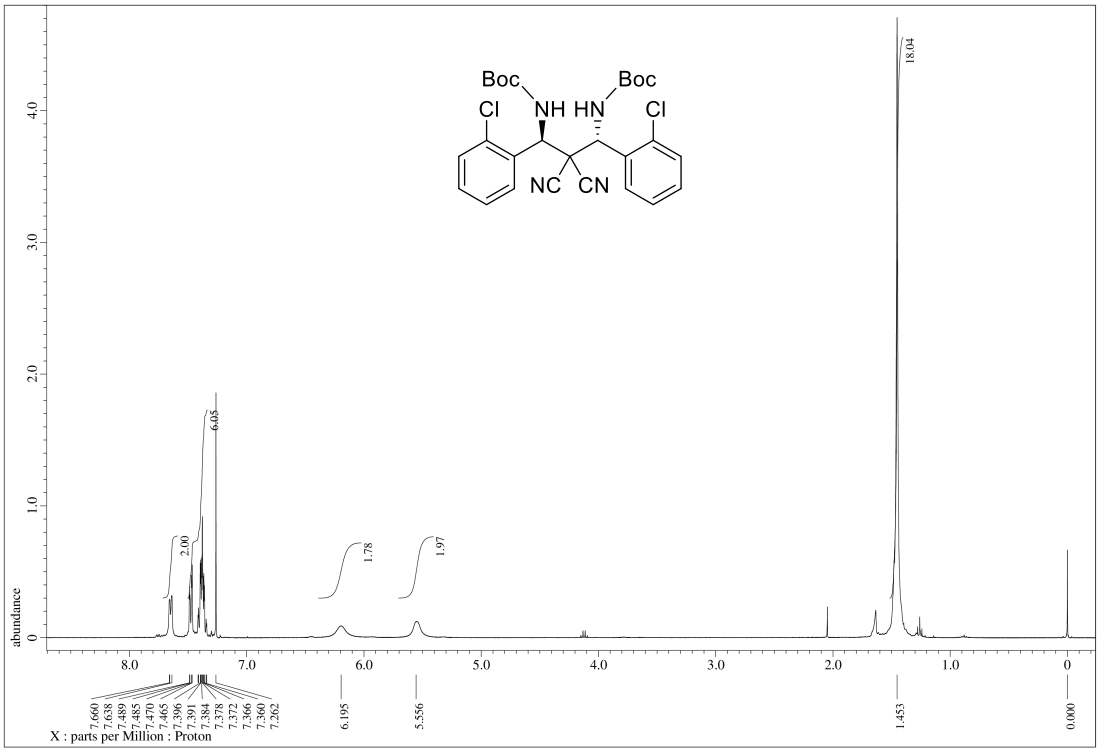
^{1}H NMR (400 MHz, $CDCl_3$) (**4g)**



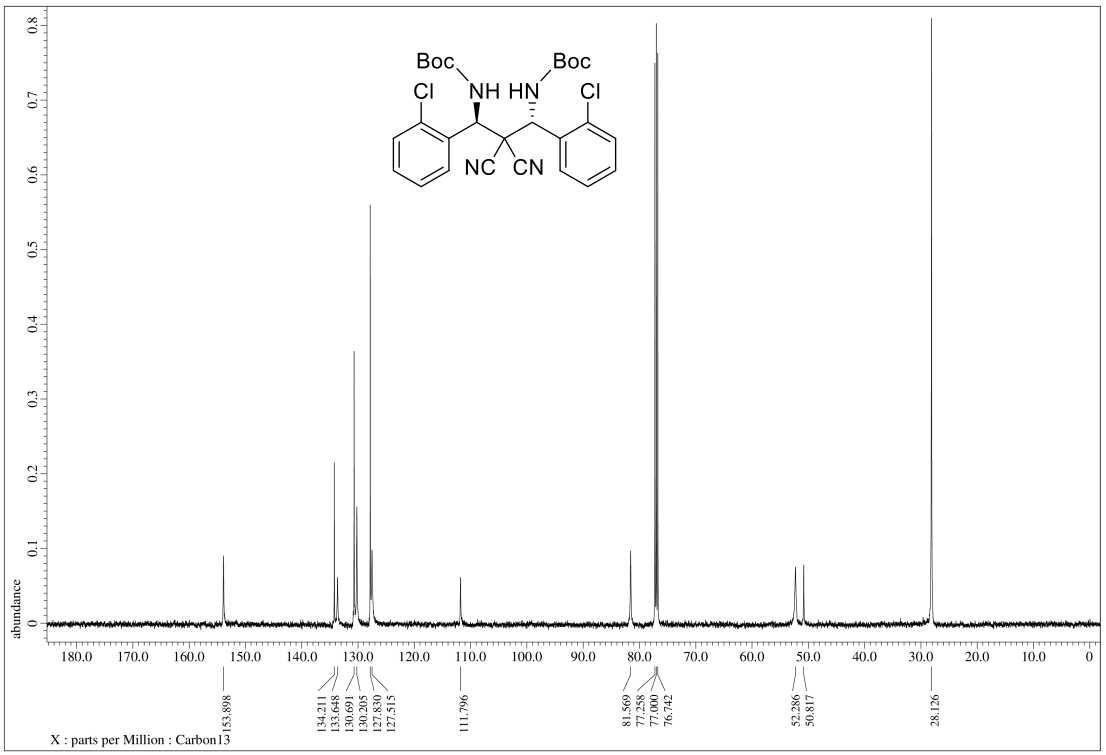
^{13}C NMR (125 MHz, $CDCl_3$) (**4g)**



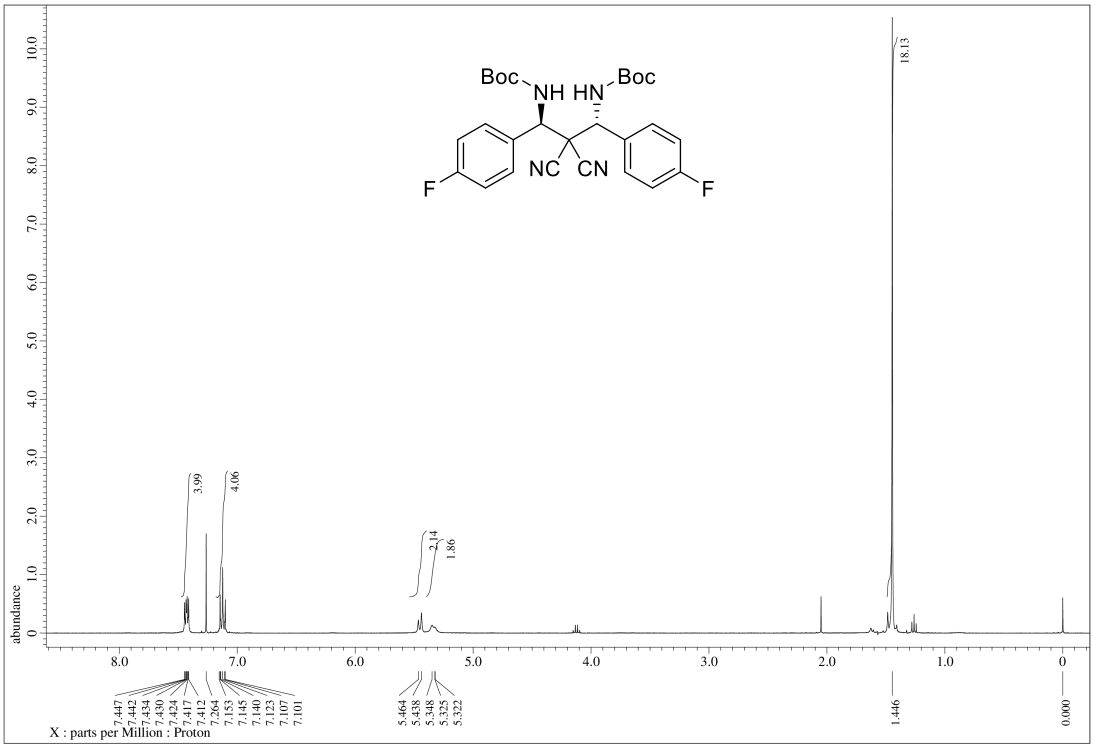
^{1}H NMR (400 MHz, $CDCl_3$) (**4h)**



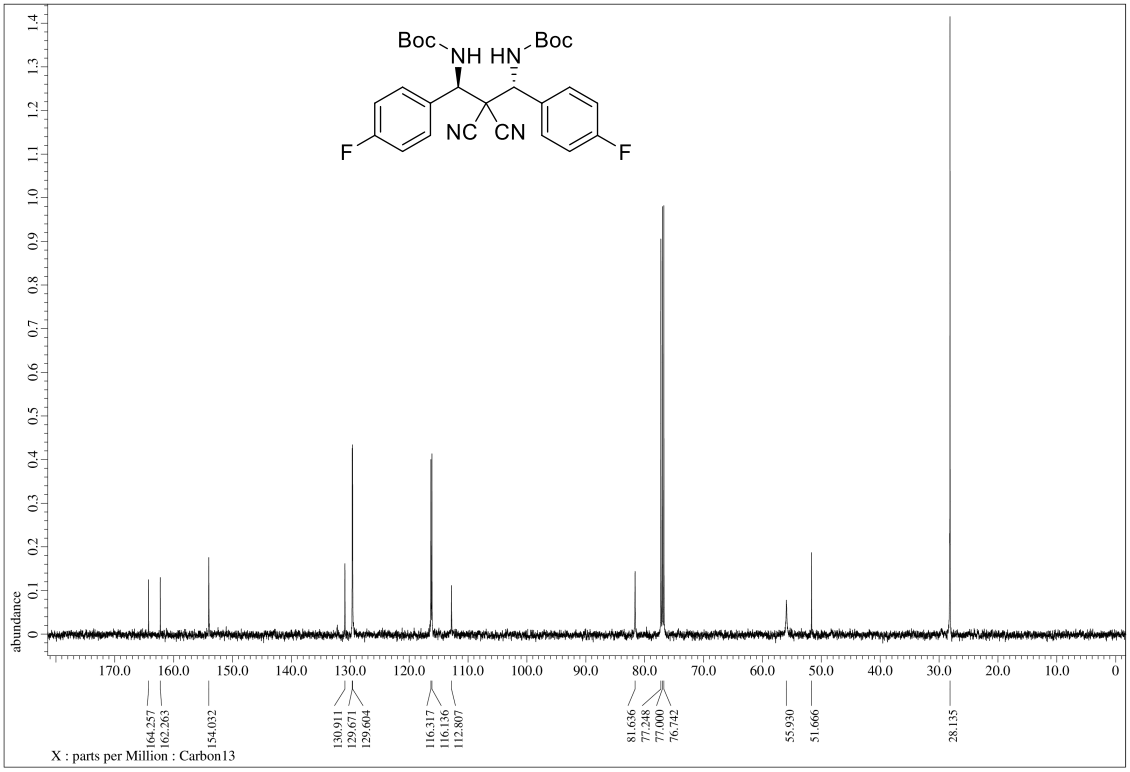
^{13}C NMR (125 MHz, $CDCl_3$) (**4h)**



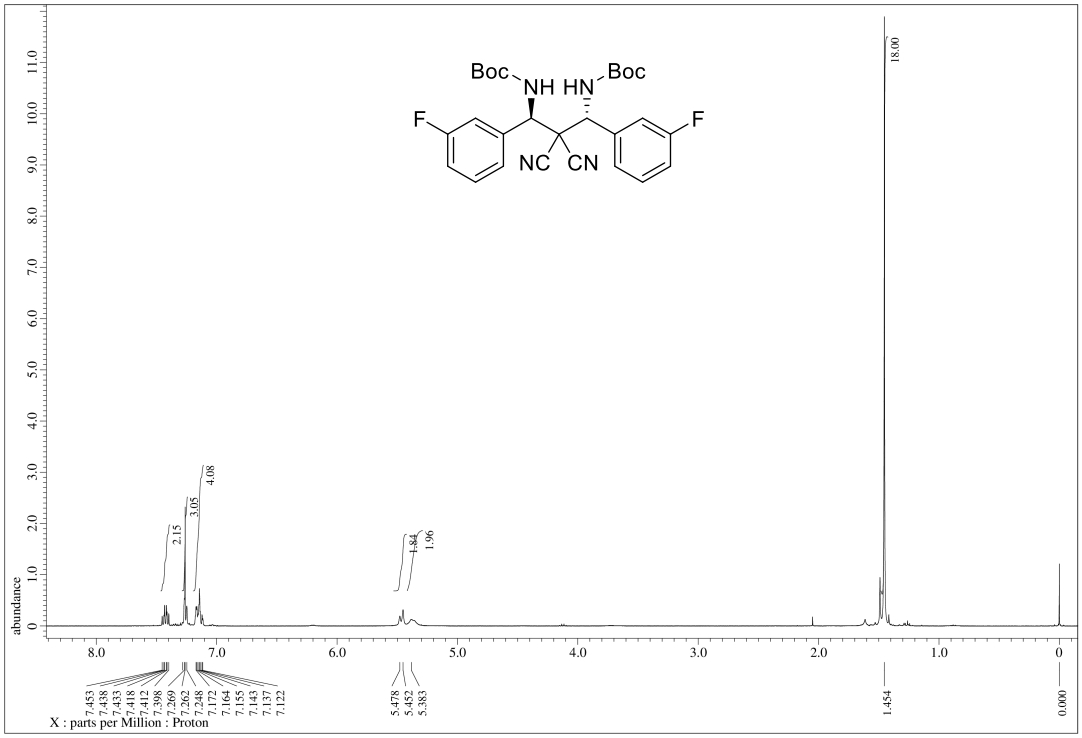
^{1}H NMR (400 MHz, $CDCl_3$) (**4i)**



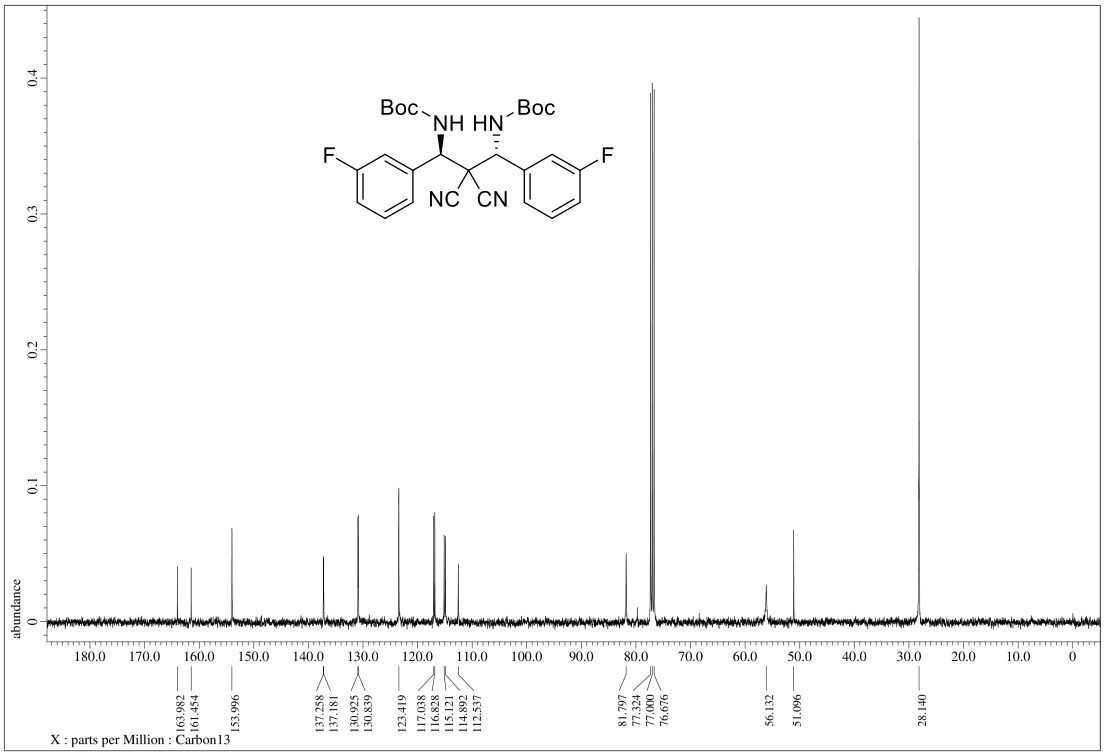
^{13}C NMR (125 MHz, $CDCl_3$) (**4i)**



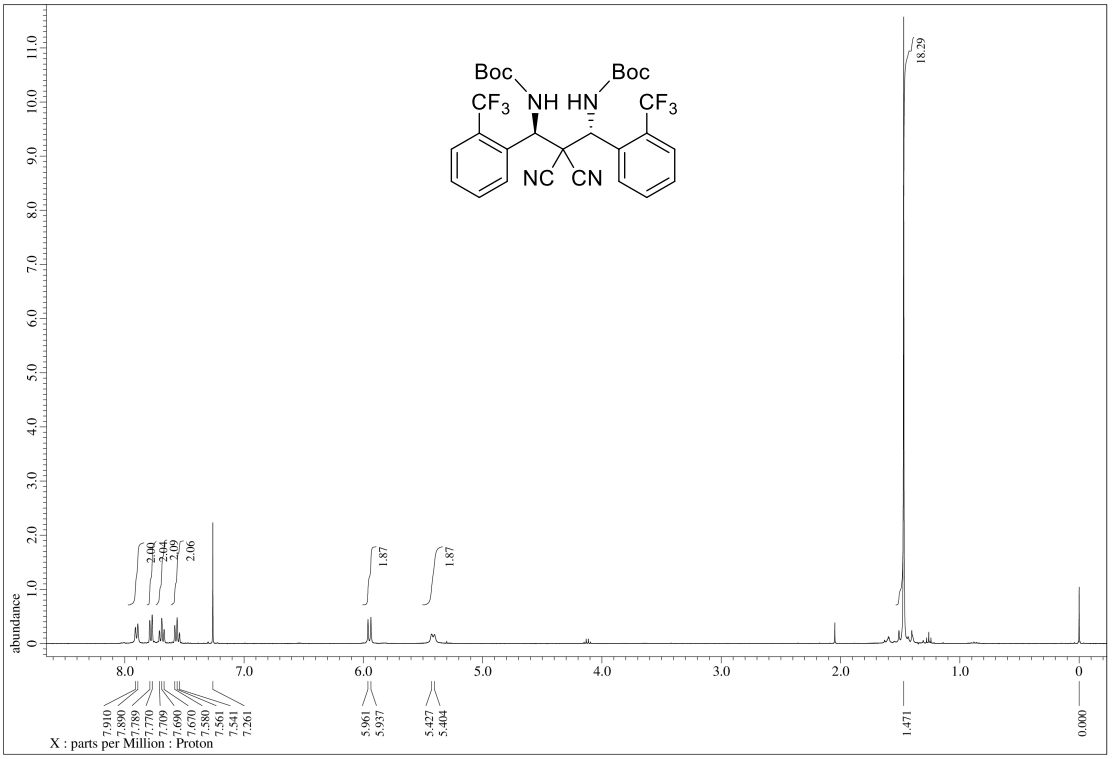
^{1}H NMR (400 MHz, $CDCl_3$) (**4j)**



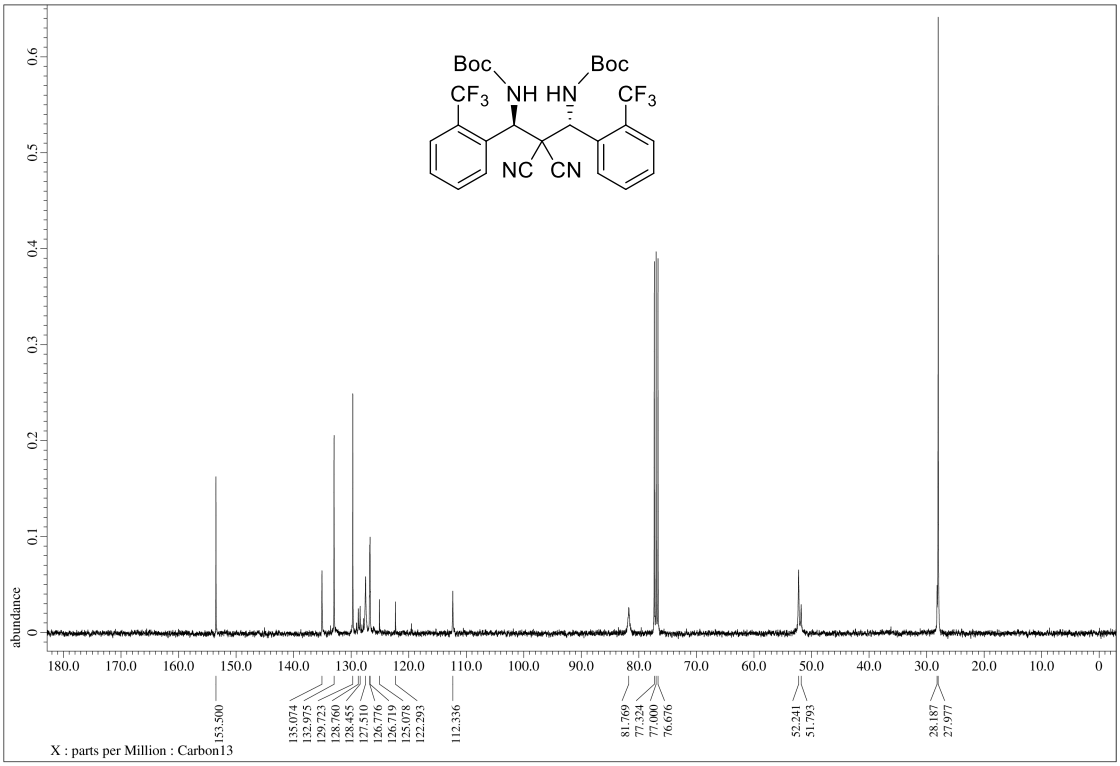
^{13}C NMR (100 MHz, $CDCl_3$) (**4j)**



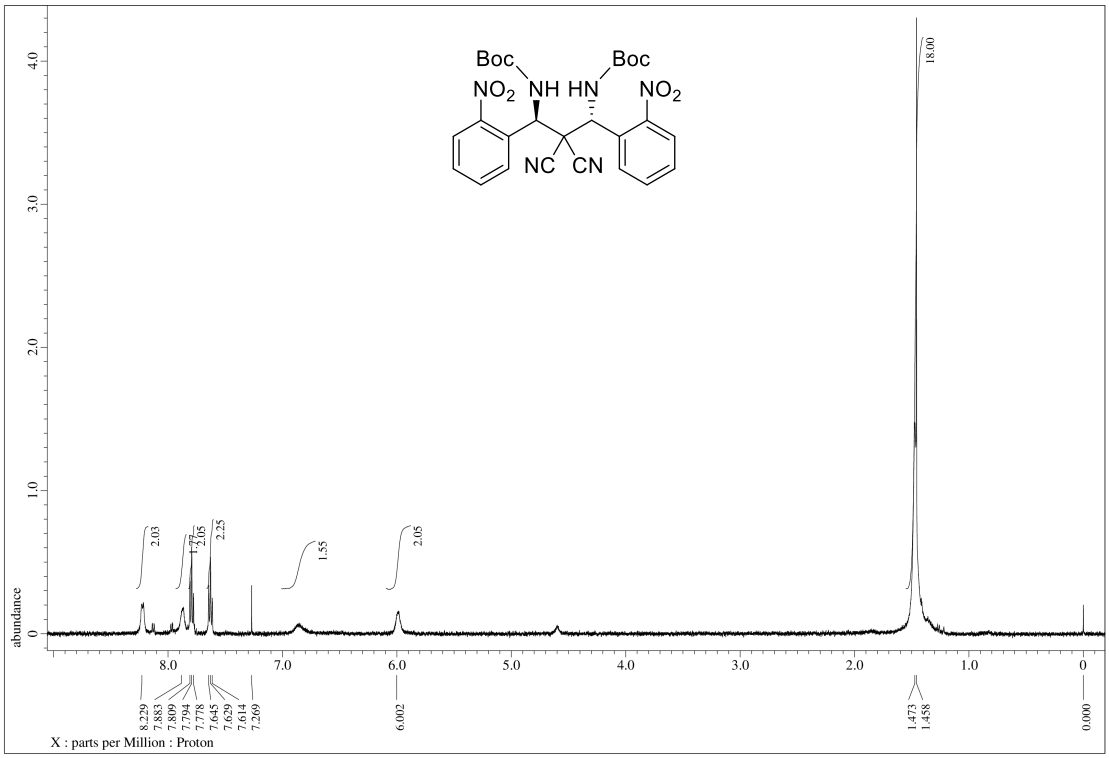
^{1}H NMR (400 MHz, $CDCl_3$) (**4k**)



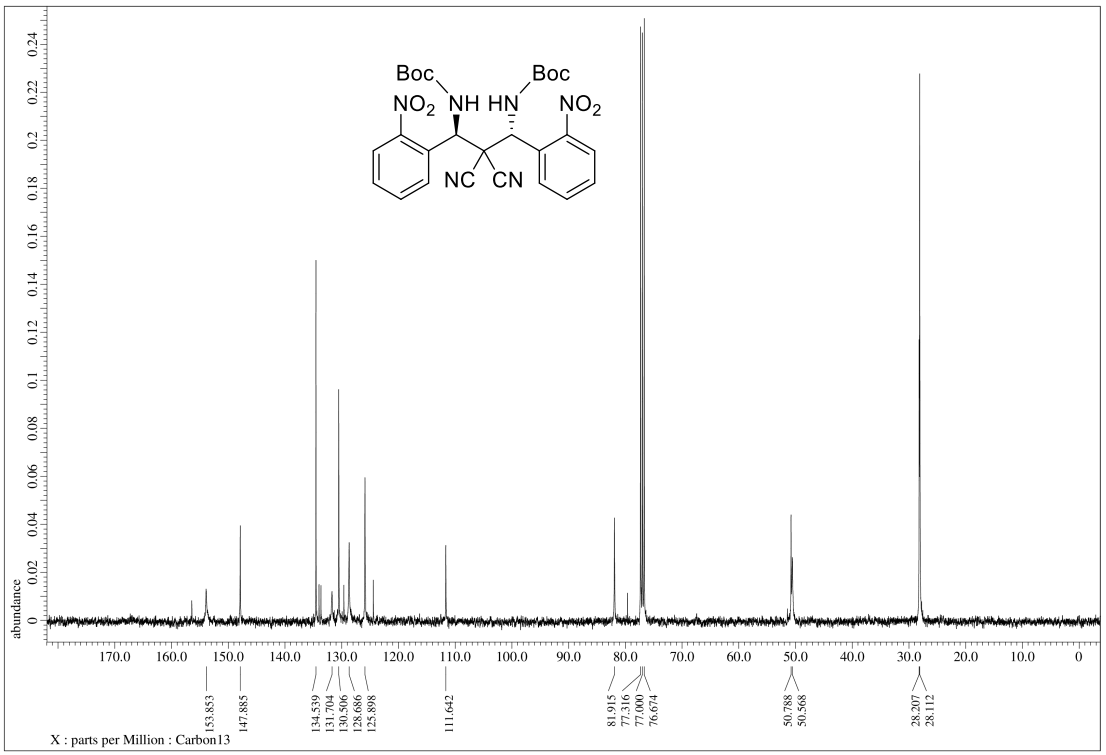
^{13}C NMR (100 MHz, $CDCl_3$) (**4k**)



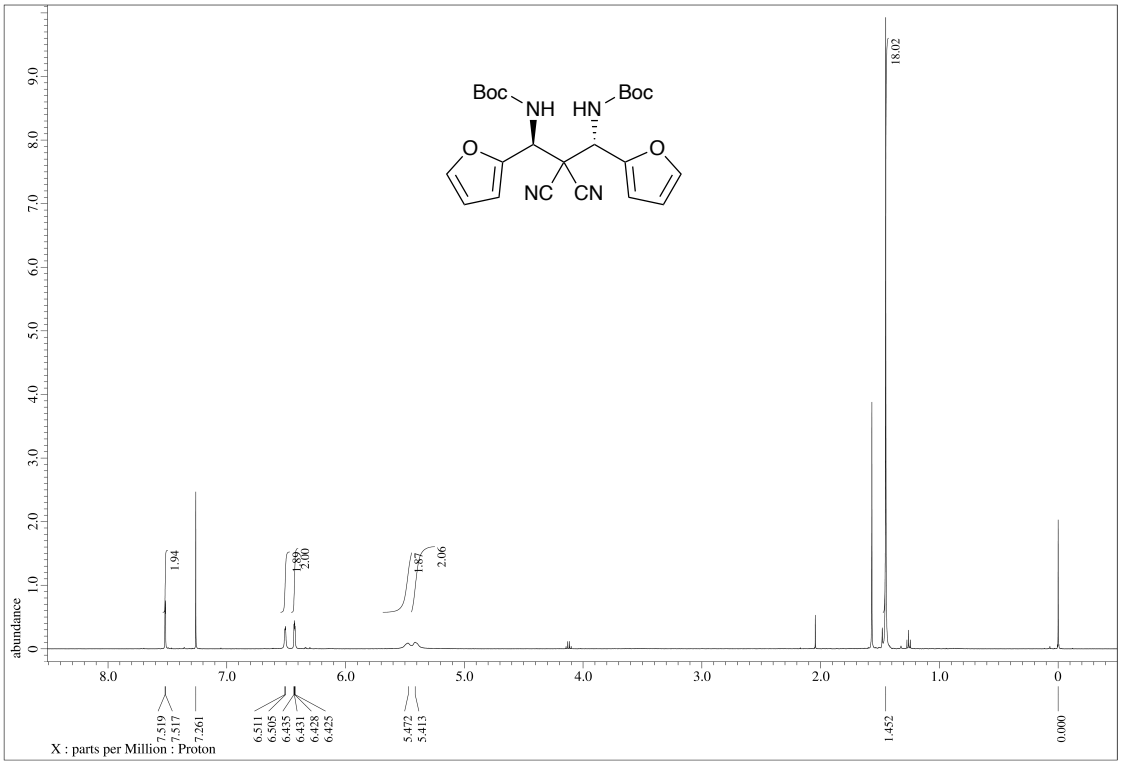
^{1}H NMR (500 MHz, $CDCl_3$) (**4l**)



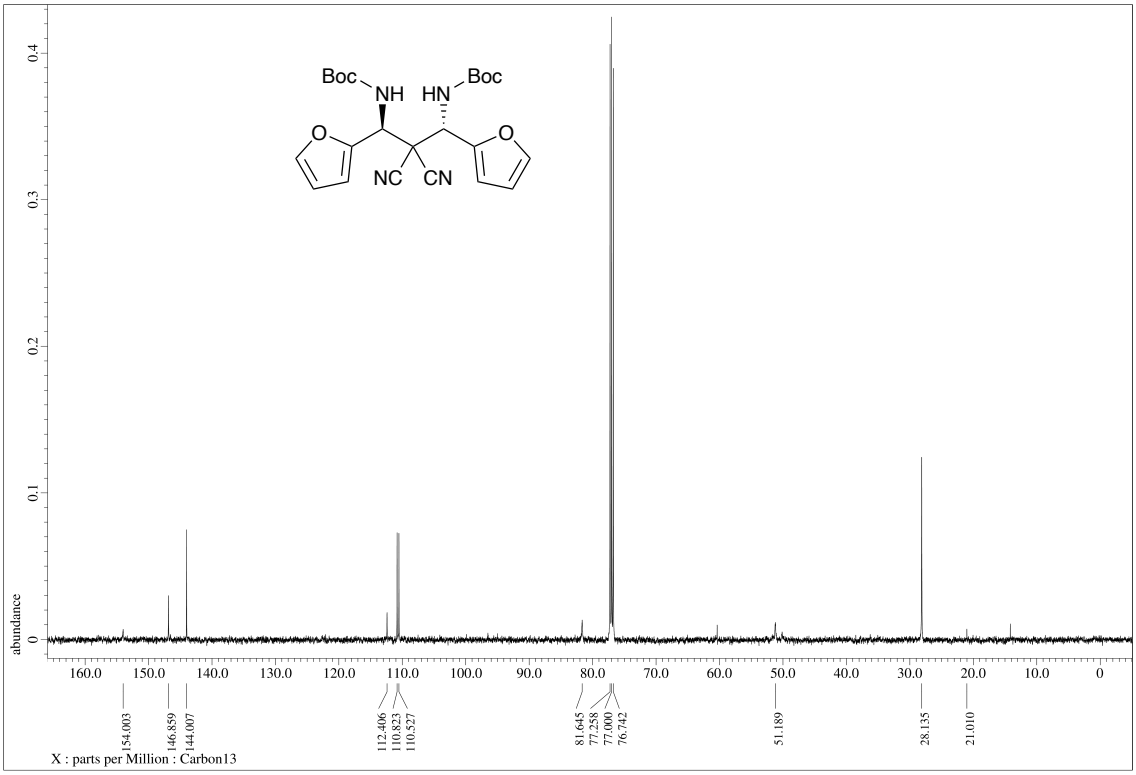
^{13}C NMR (100 MHz, $CDCl_3$) (**4l**)



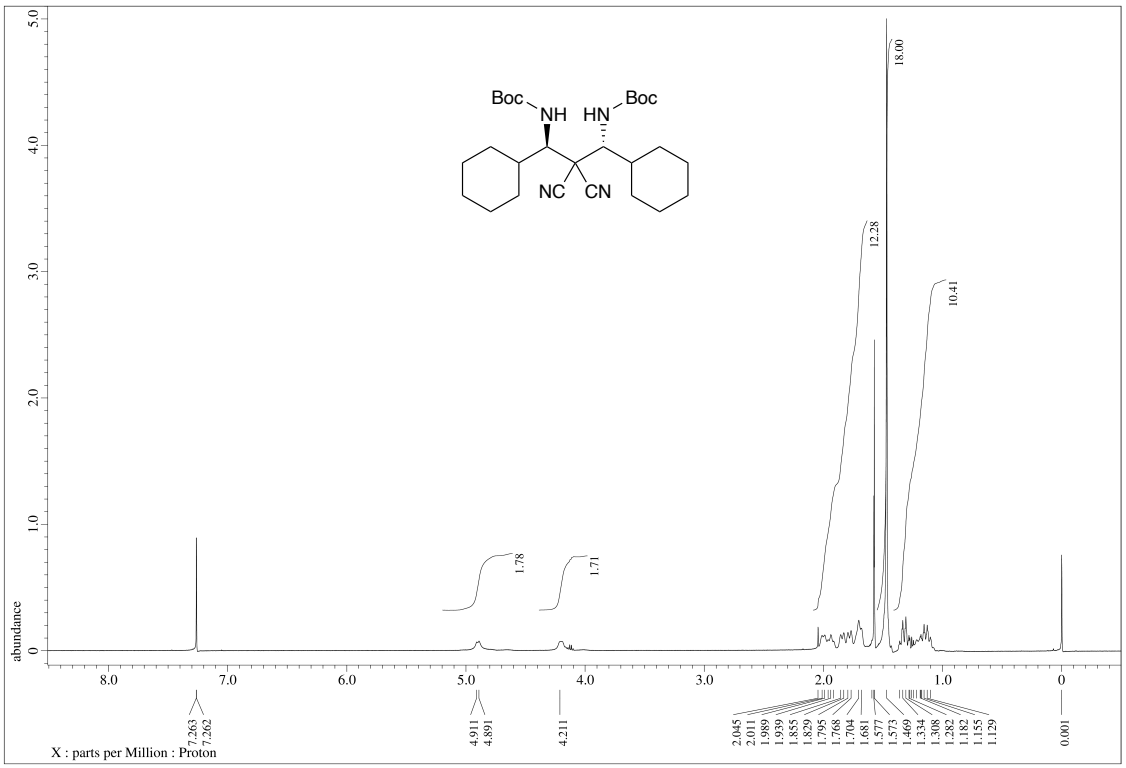
^{1}H NMR (500 MHz, $CDCl_3$) (**4m)**



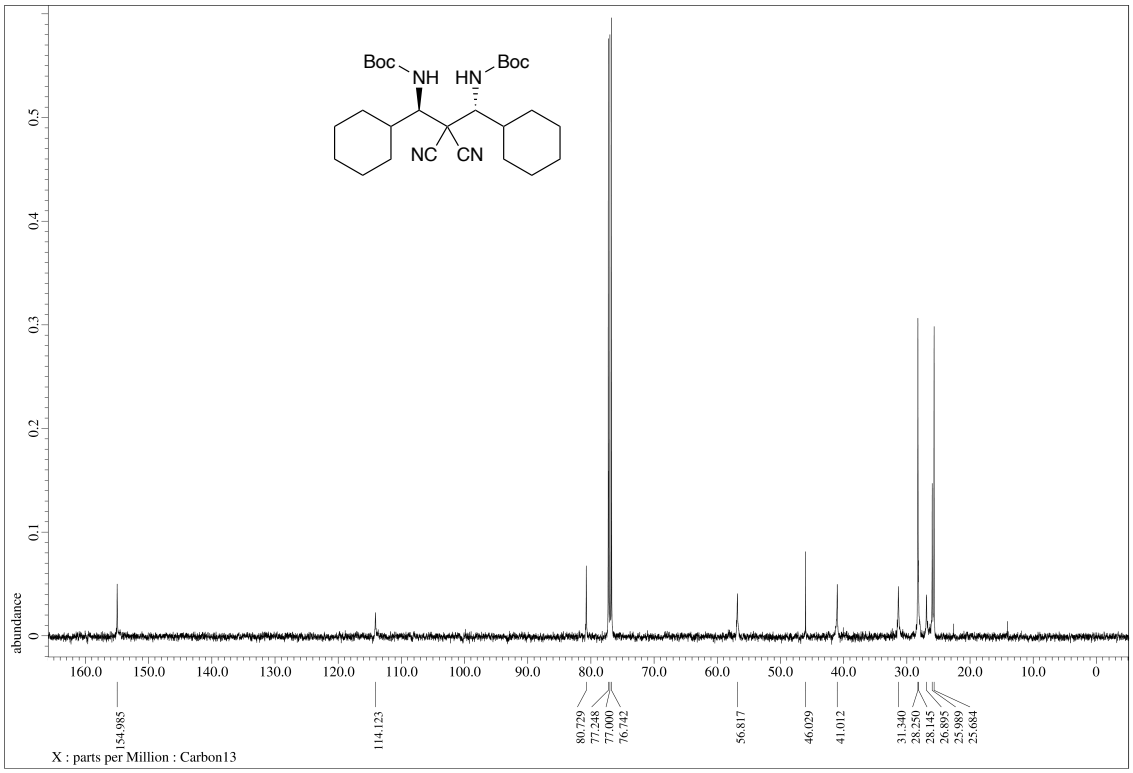
^{13}C NMR (125 MHz, $CDCl_3$) (**4m)**



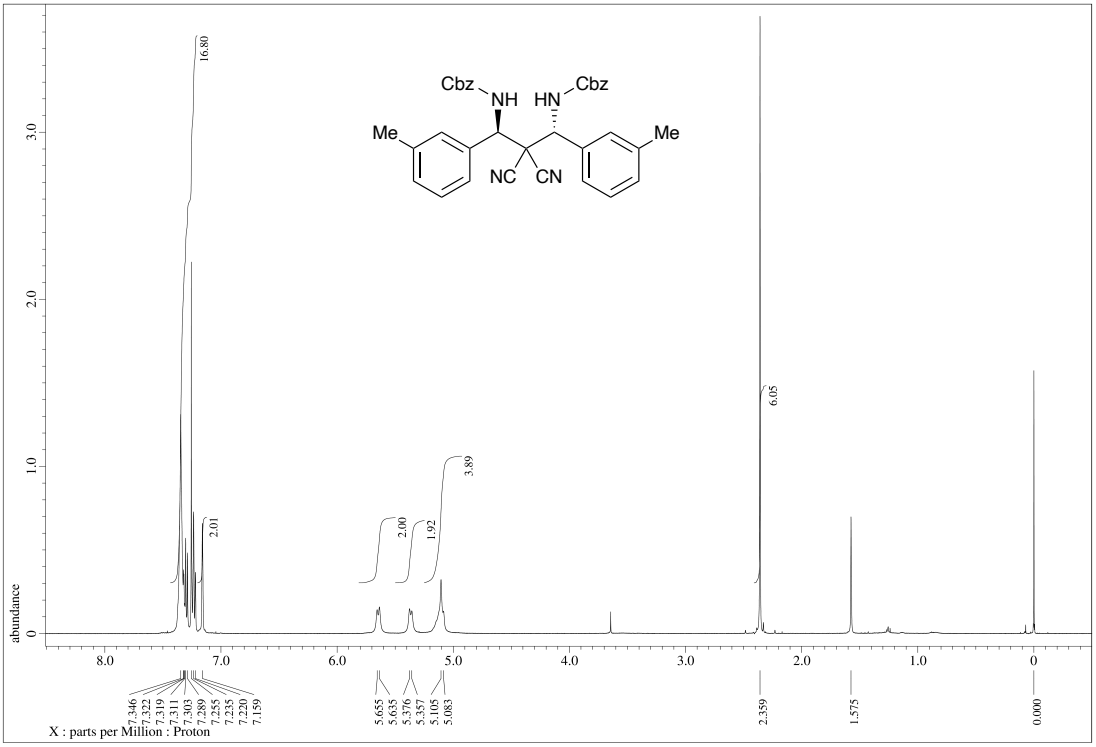
^{1}H NMR (500 MHz, $CDCl_3$) (**4n)**



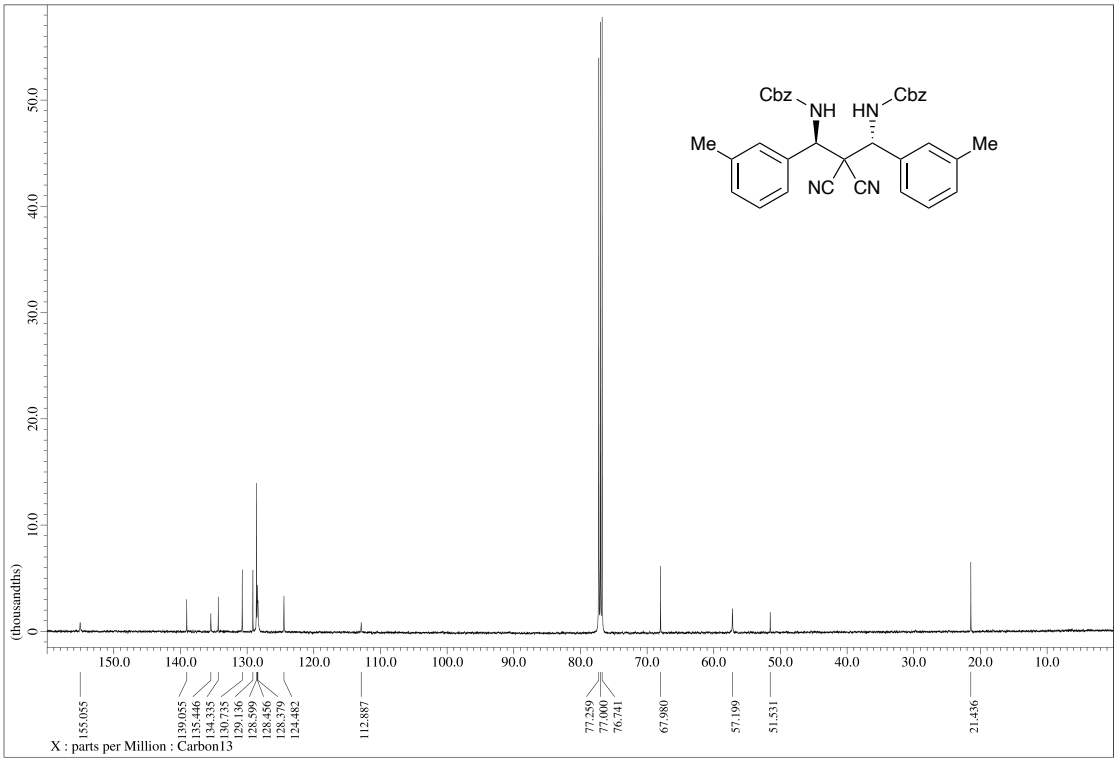
^{13}C NMR (125 MHz, $CDCl_3$) (**4n)**



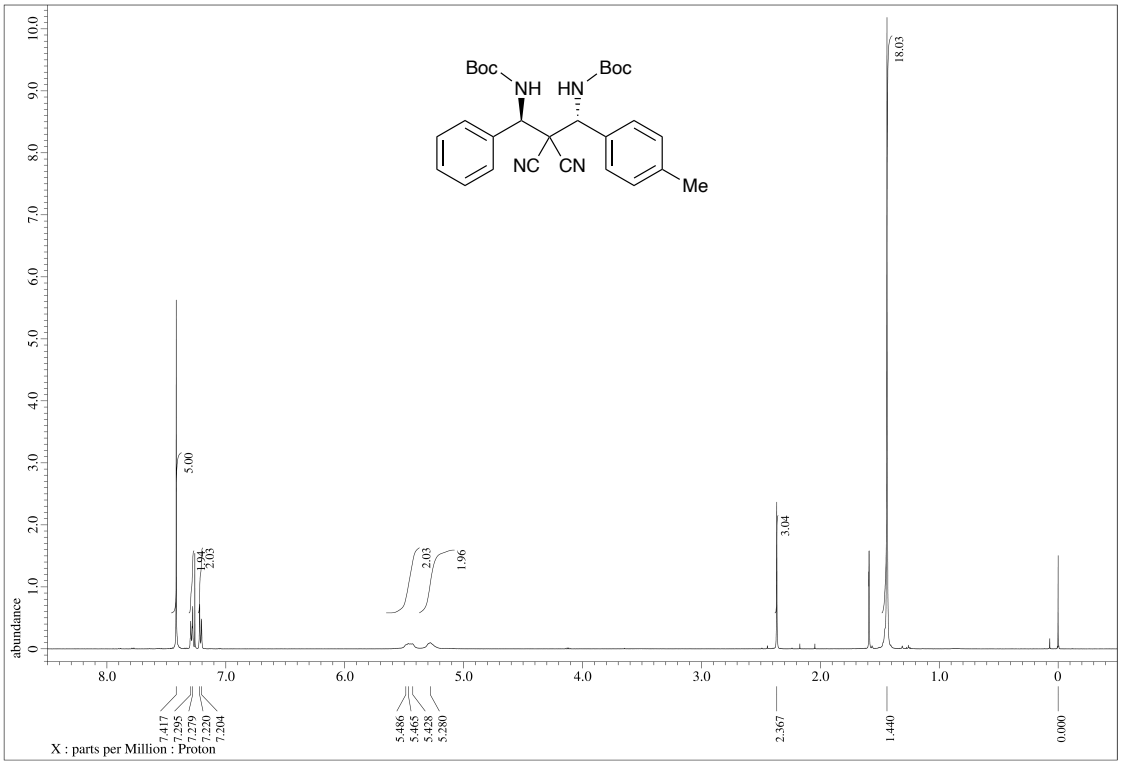
^{1}H NMR (500 MHz, $CDCl_3$) (**4o**)



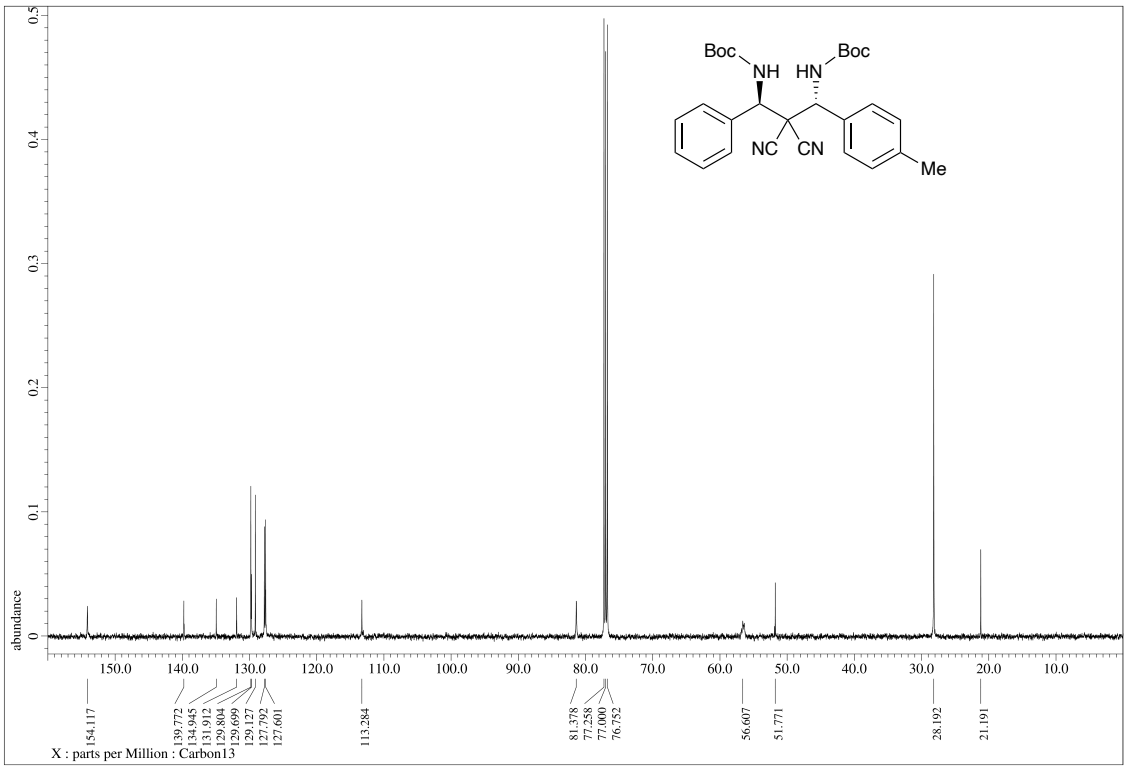
^{13}C NMR (125 MHz, $CDCl_3$) (**4o**)



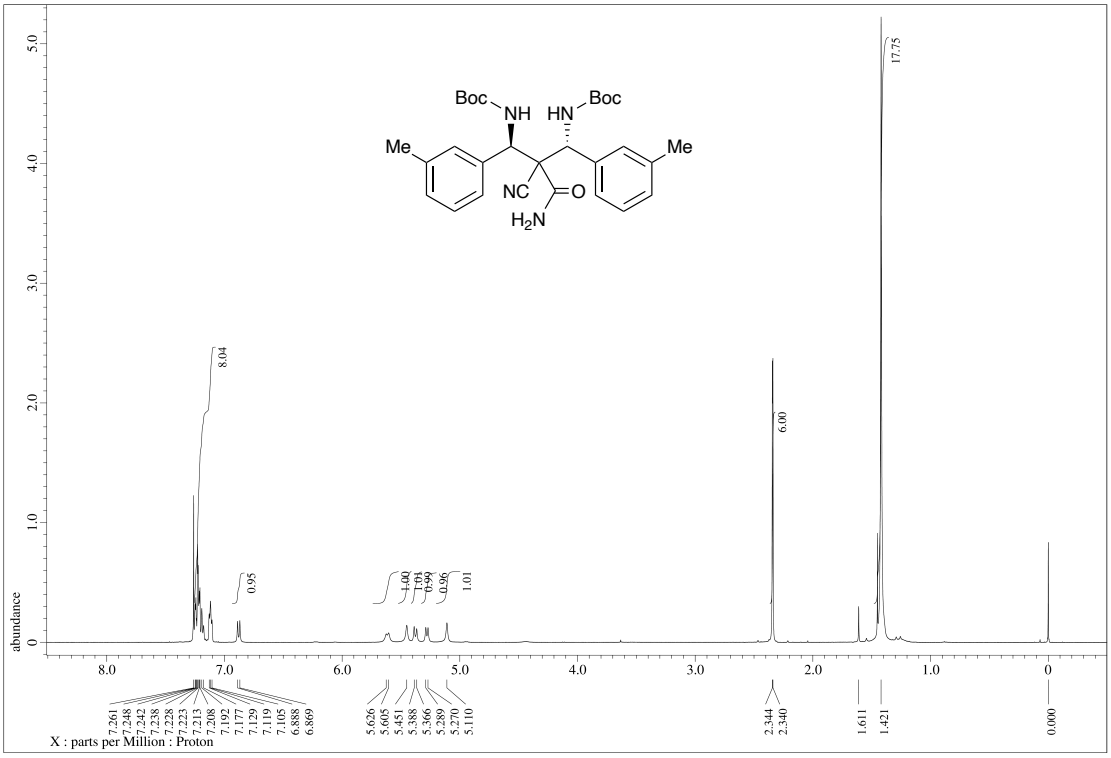
^{1}H NMR (500 MHz, $CDCl_3$) (**4ab)**



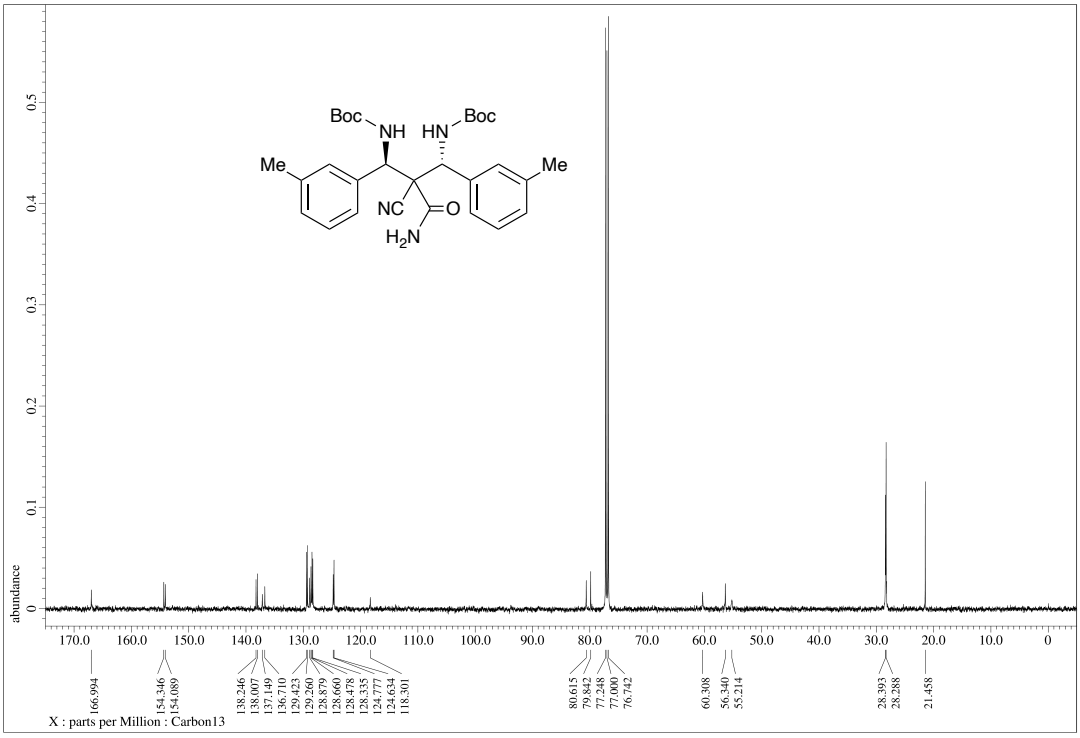
^{13}C NMR (125 MHz, $CDCl_3$) (**4ab)**



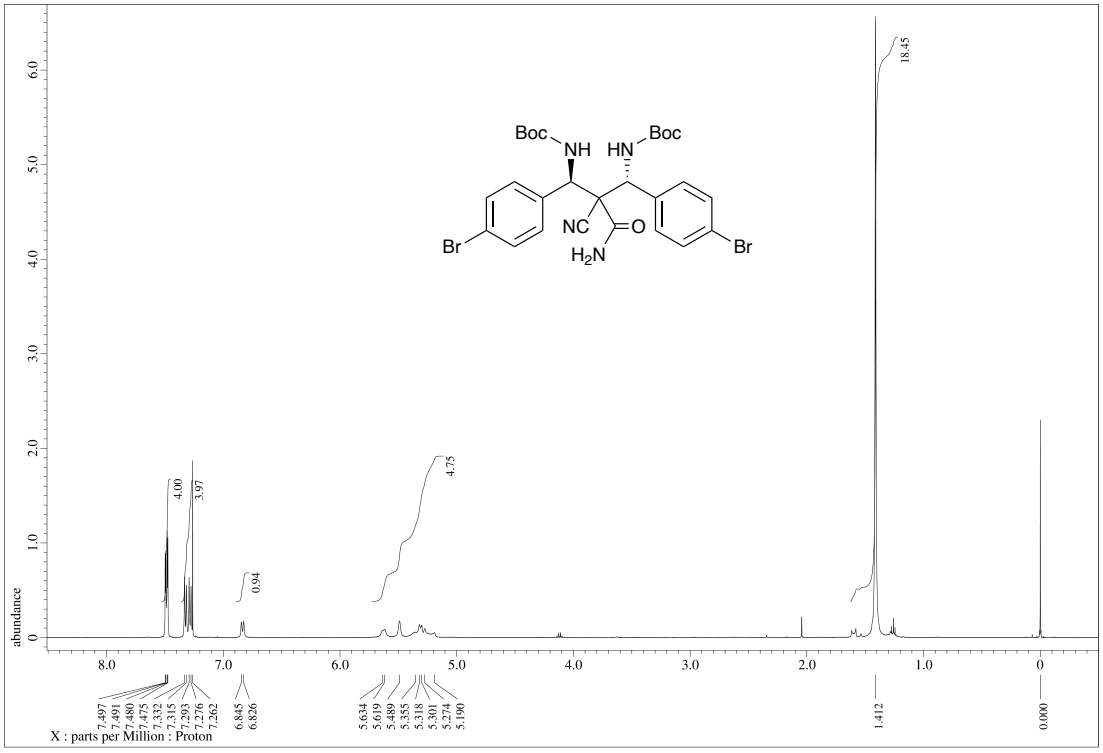
^{1}H NMR (500 MHz, $CDCl_3$) **(5c)**



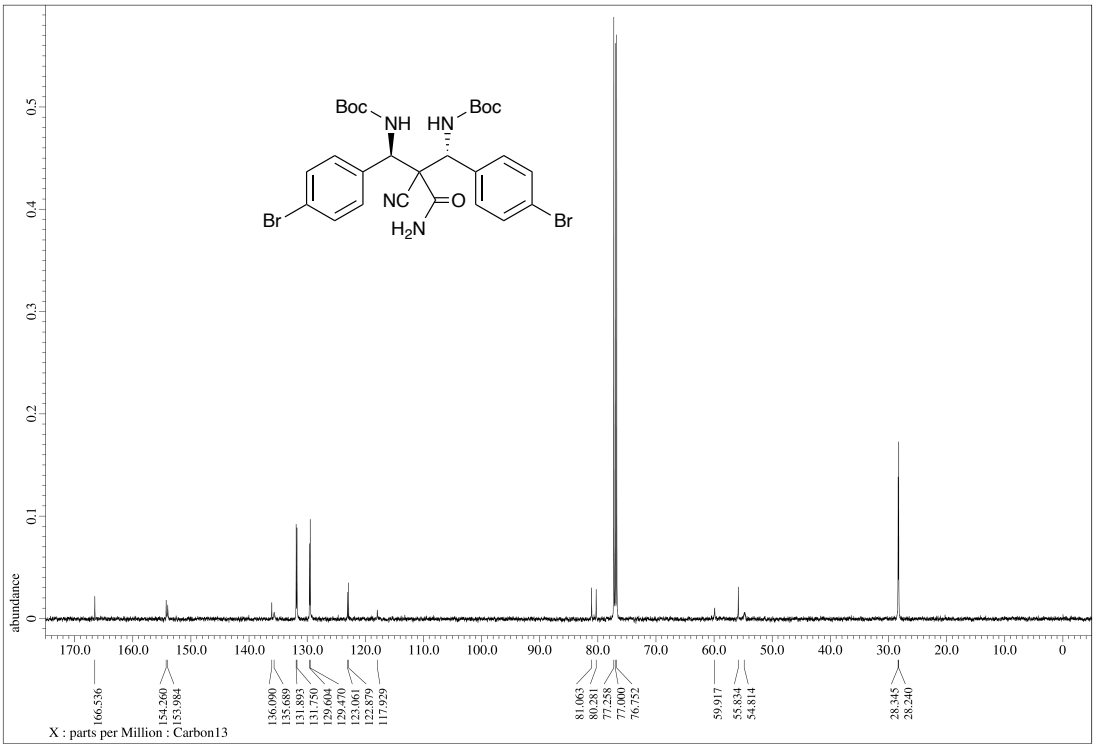
^{13}C NMR (125 MHz, $CDCl_3$) **(5c)**



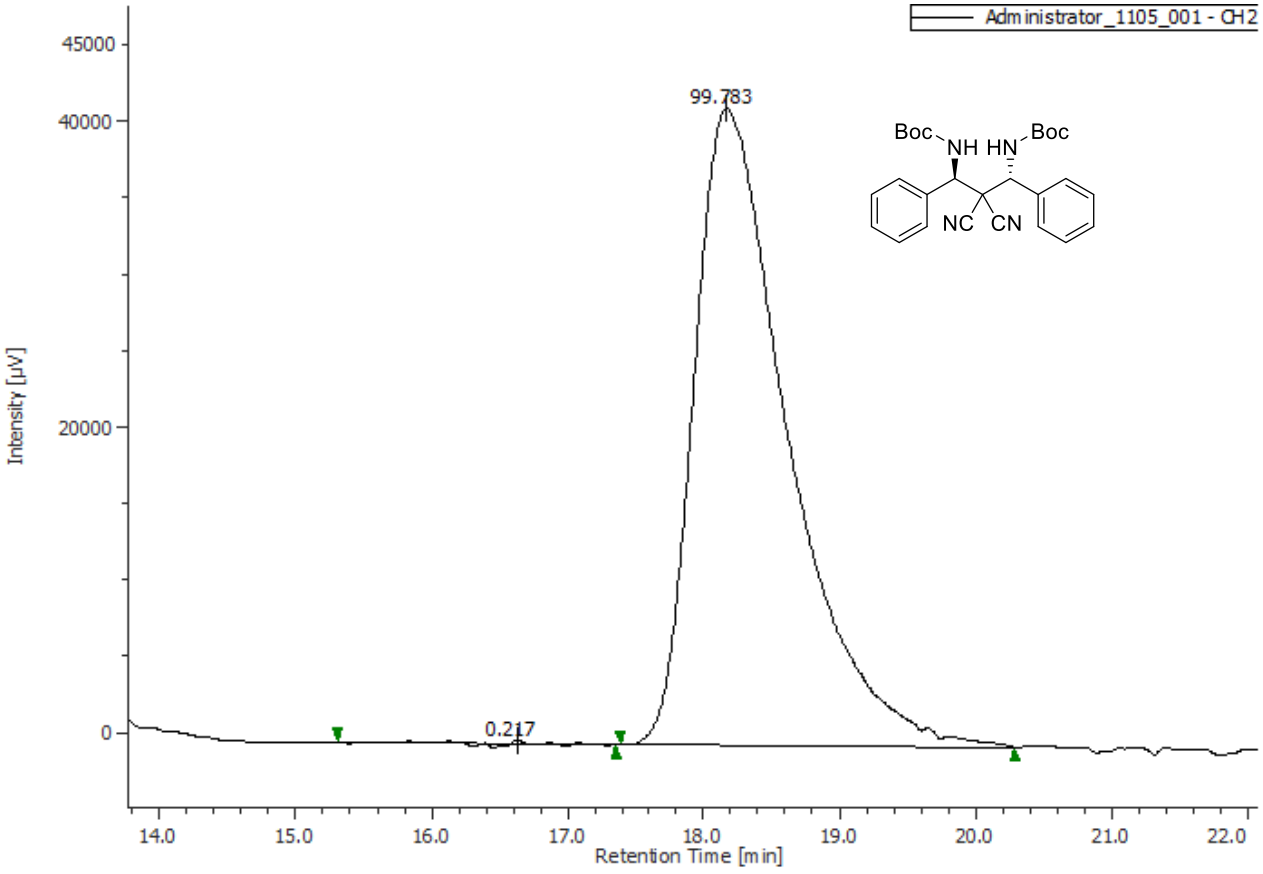
^{1}H NMR (500 MHz, $CDCl_3$) (**5e)**

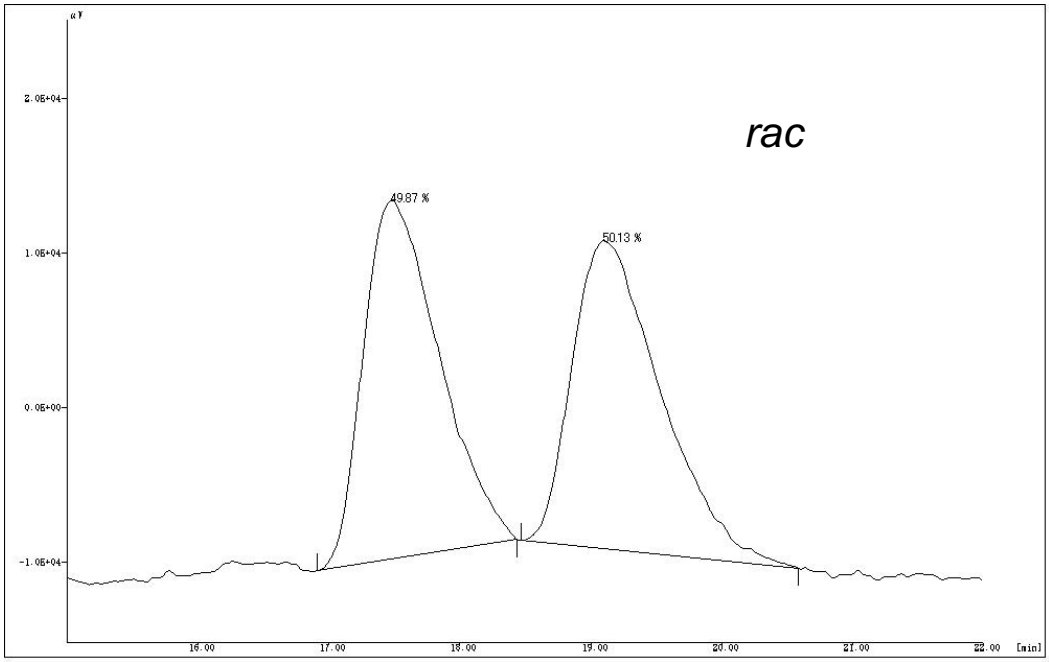


^{13}C NMR (125 MHz, $CDCl_3$) (**5e)**

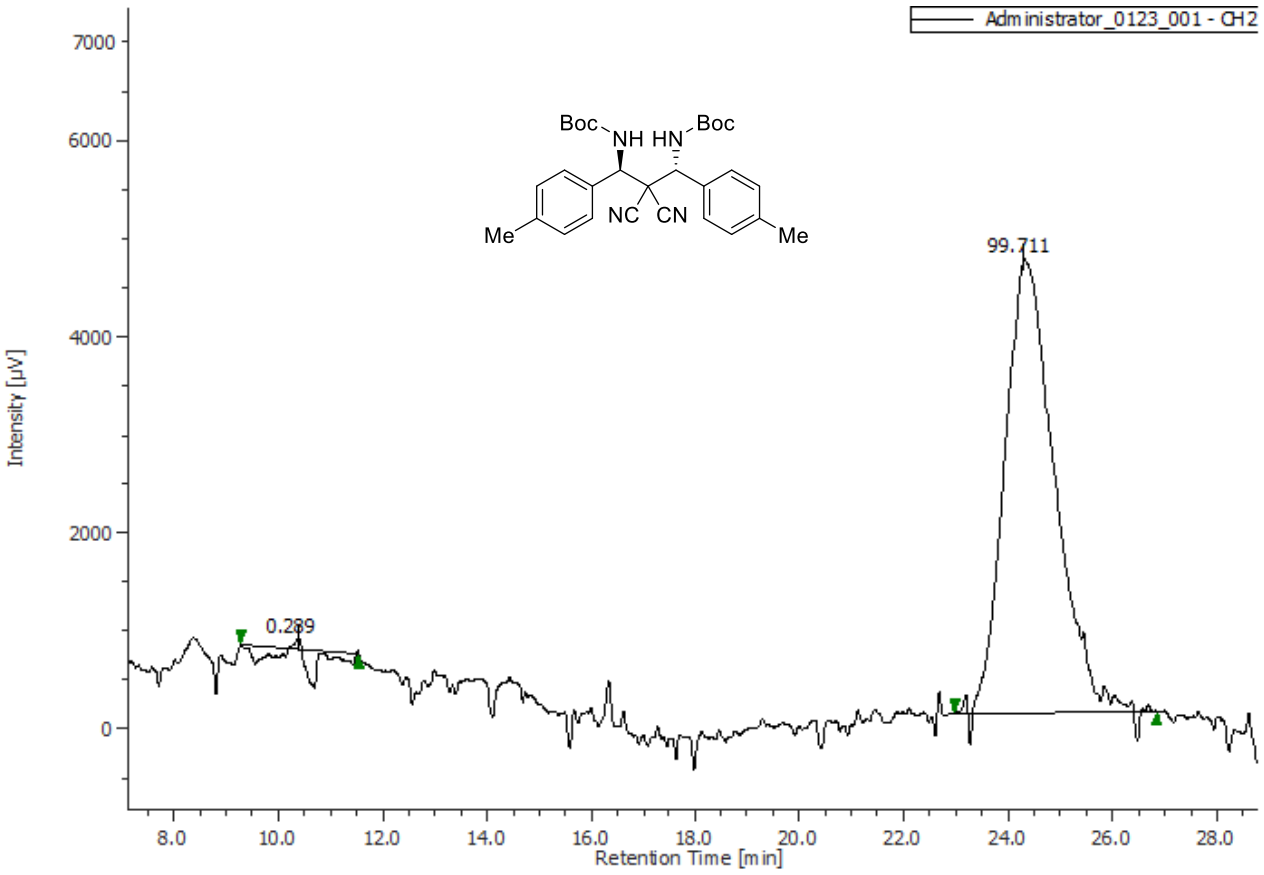


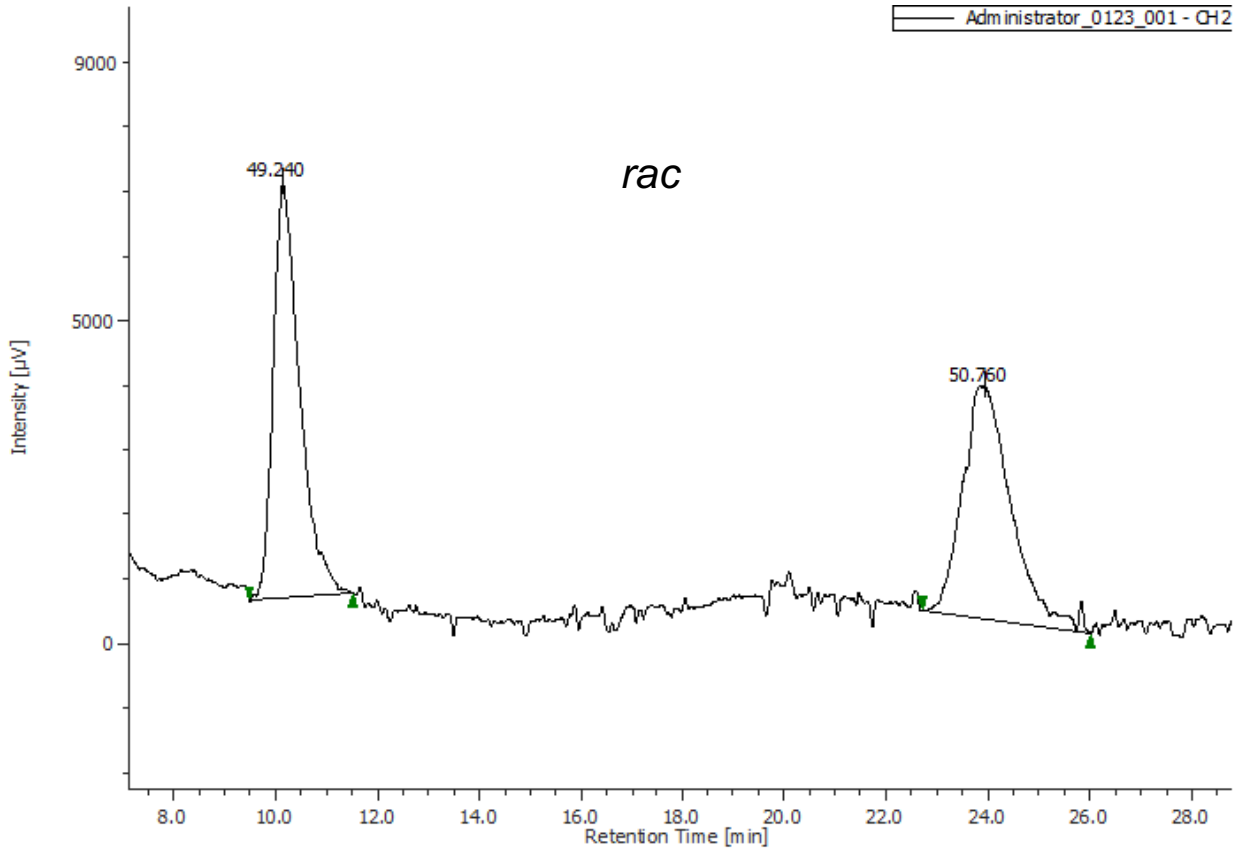
9. HPLC spectra



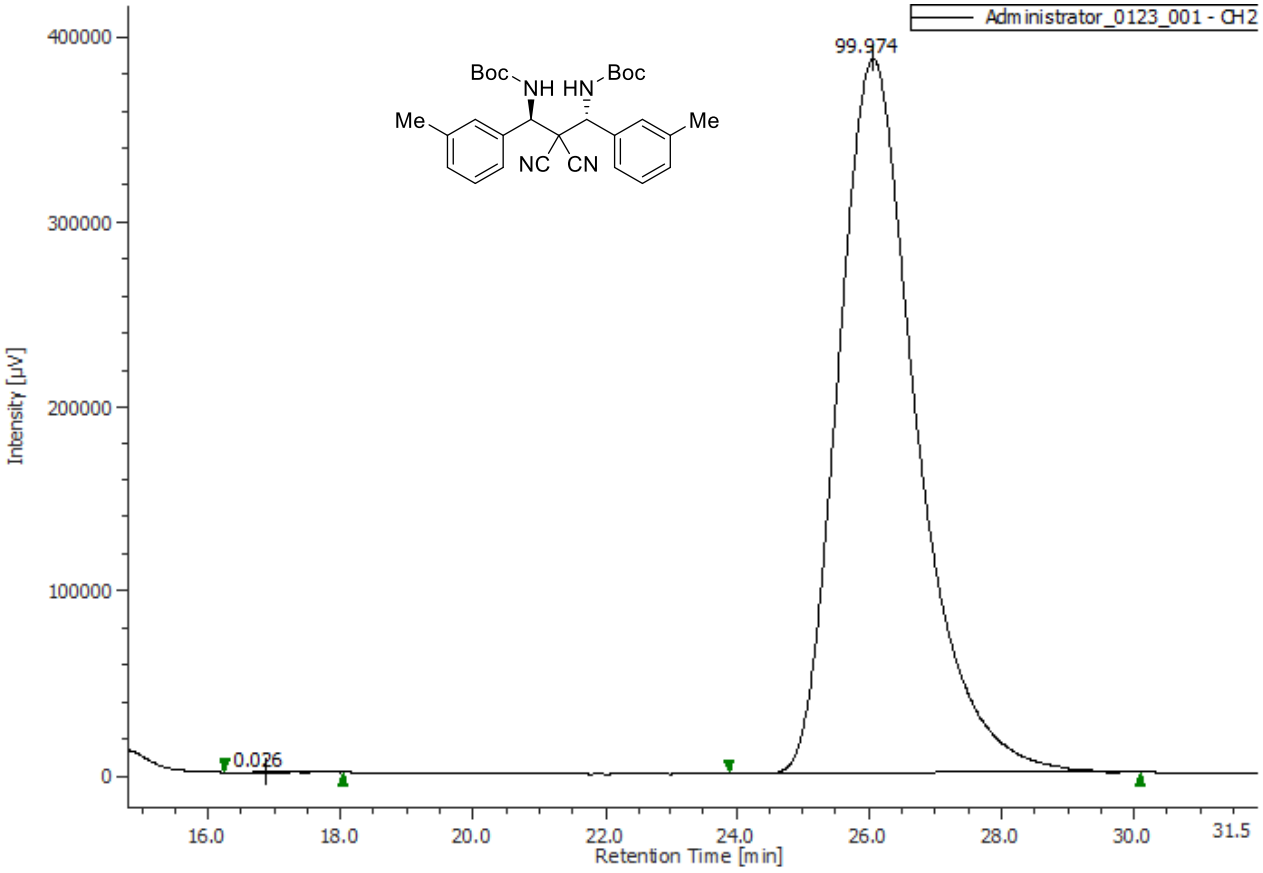


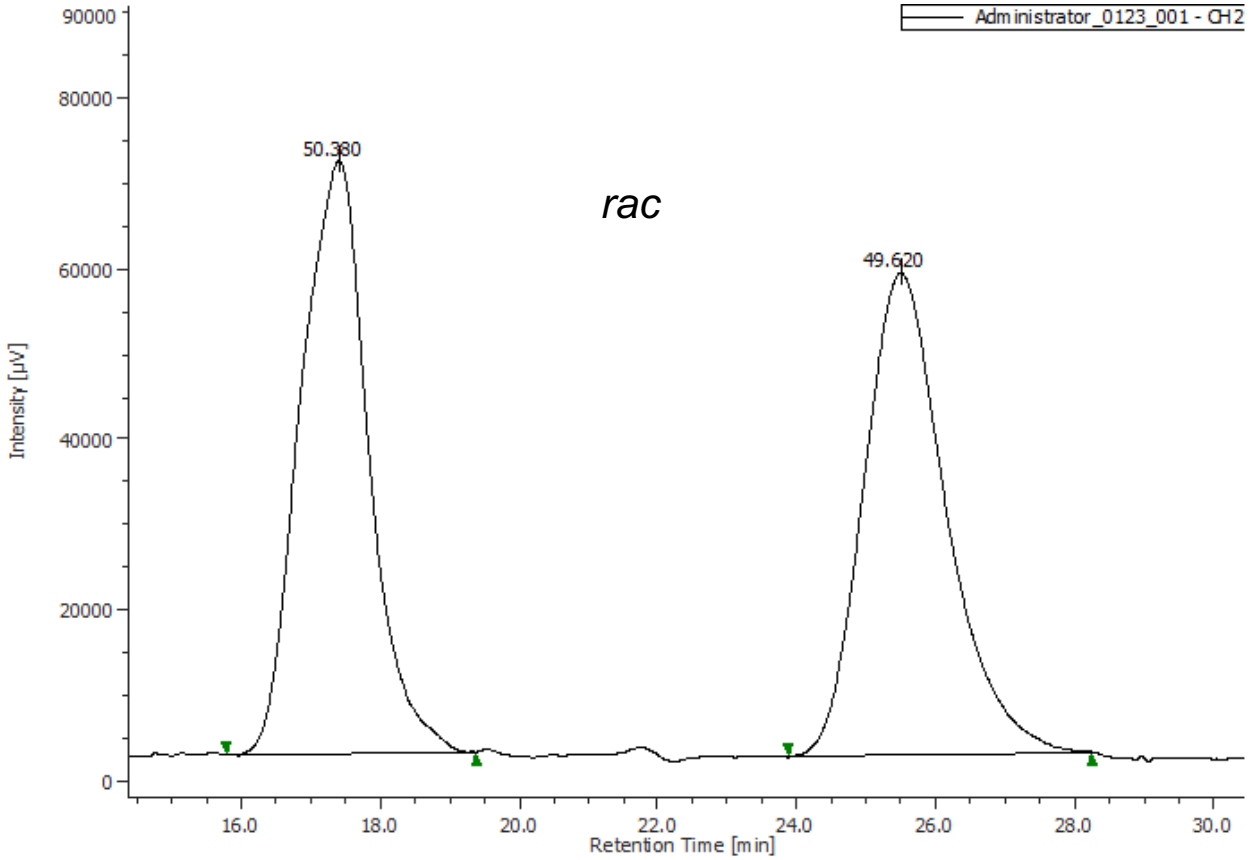
Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm)



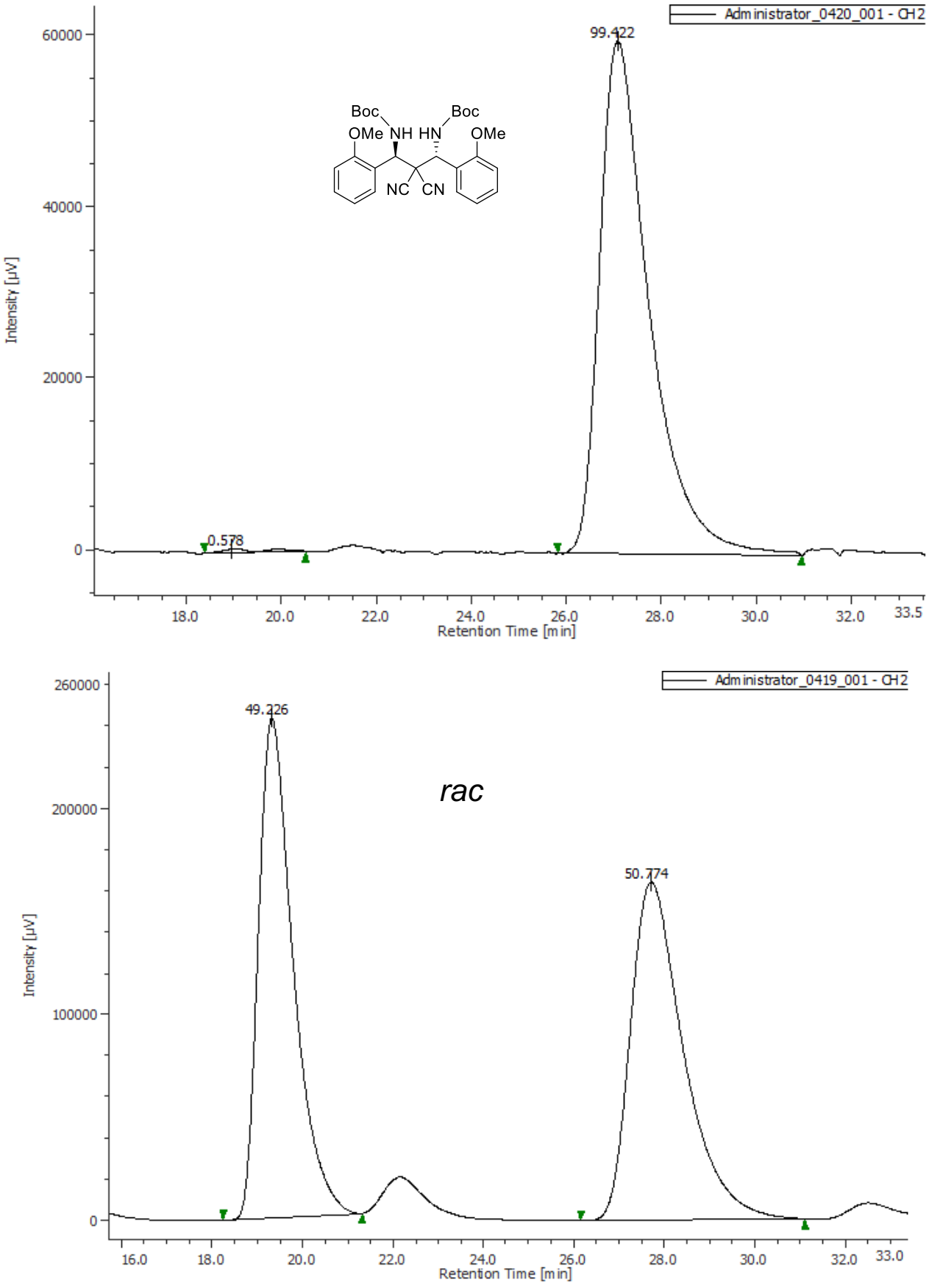


Chiralcel OD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)

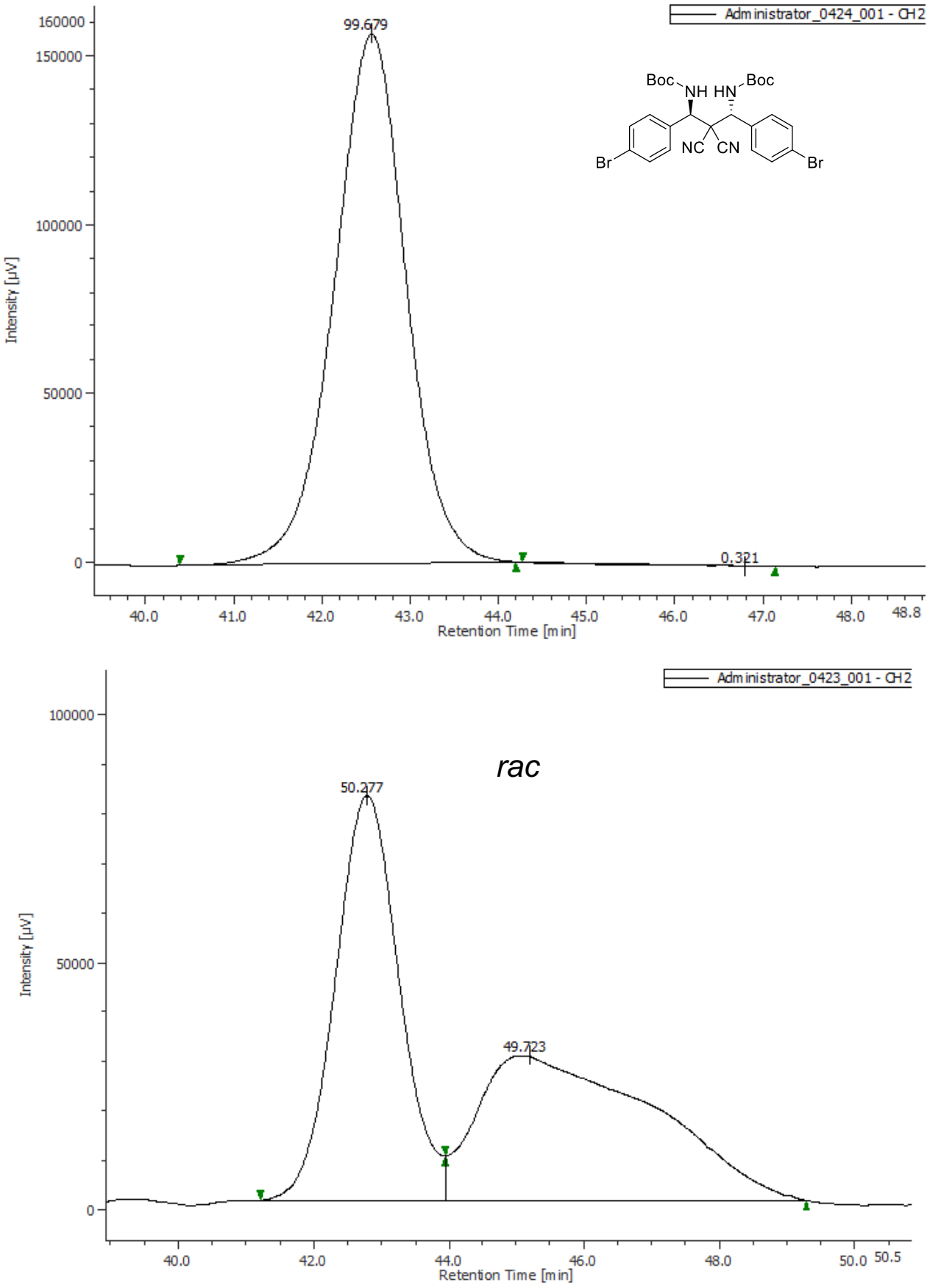




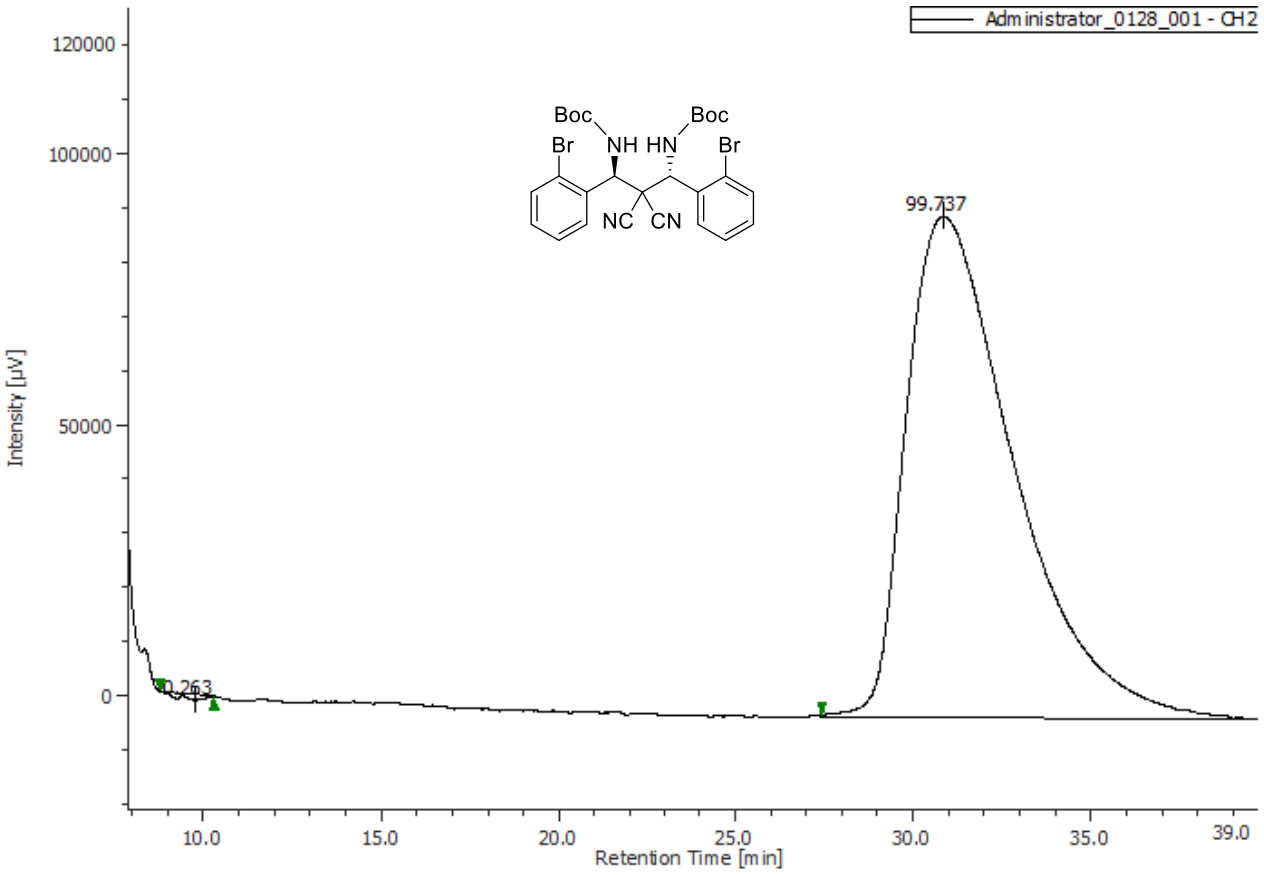
Chiralpak IA column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm)

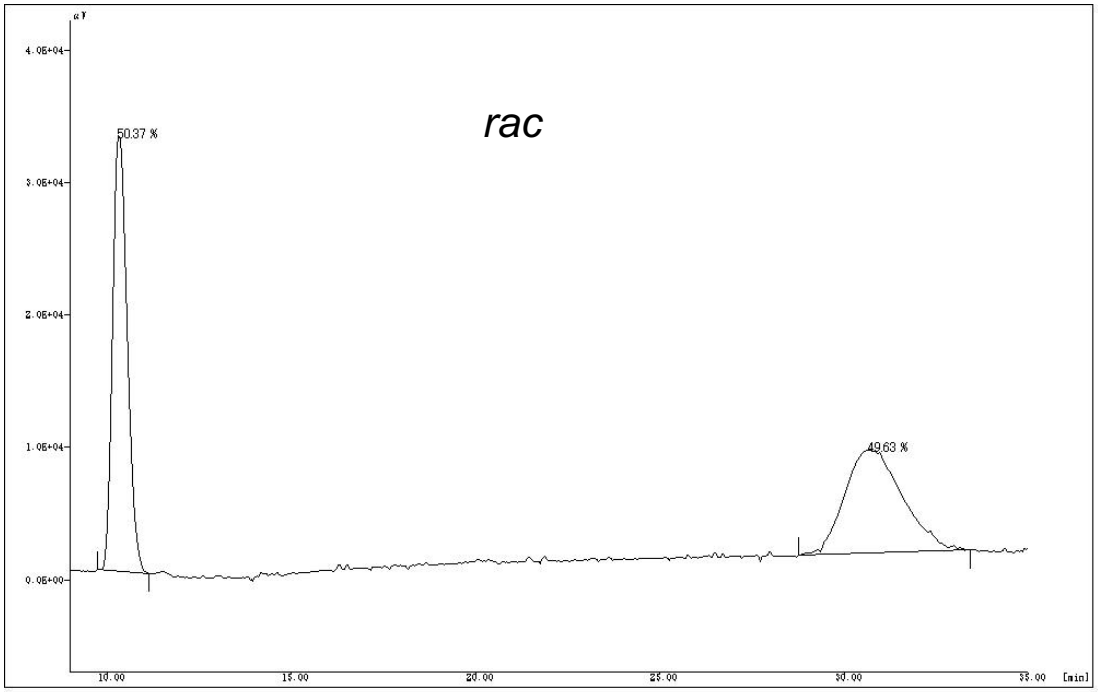


Chiralpak IA column (hexane:2-propanol = 90:10, 0.5 mL/min, 254 nm)

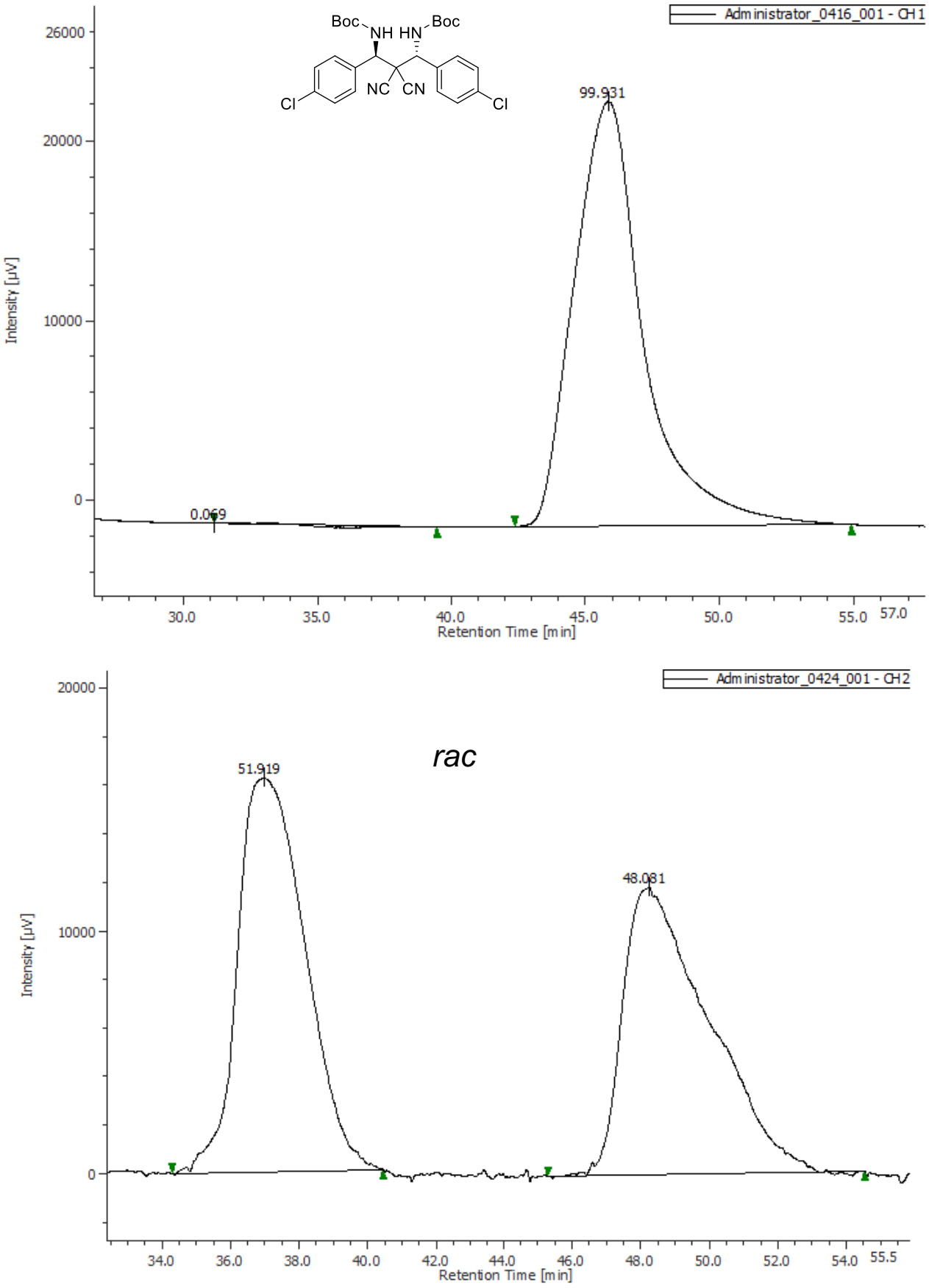


Chiralpak IA column (hexane:2-propanol = 90:10, 0.2 mL/min, 254 nm)

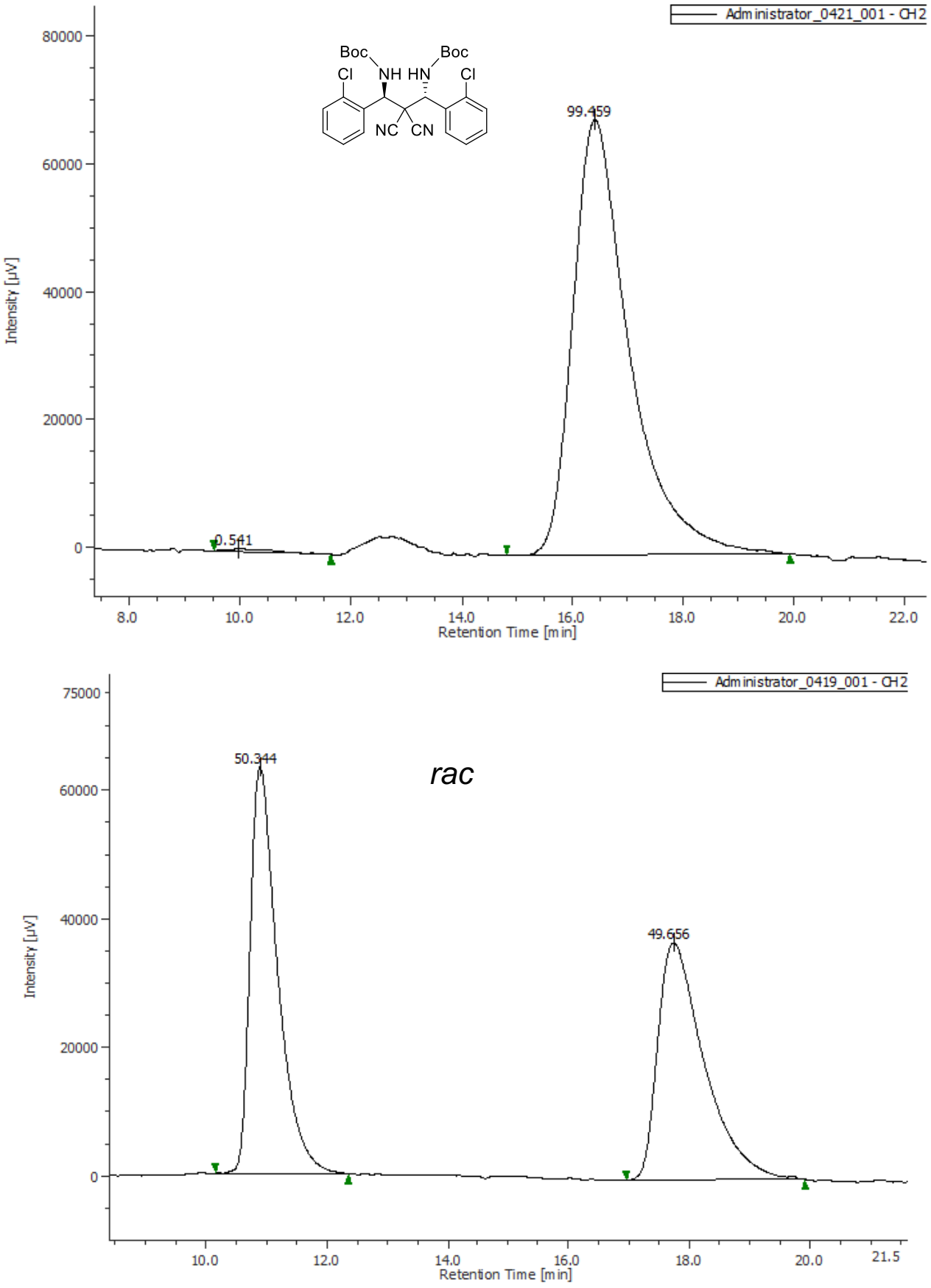




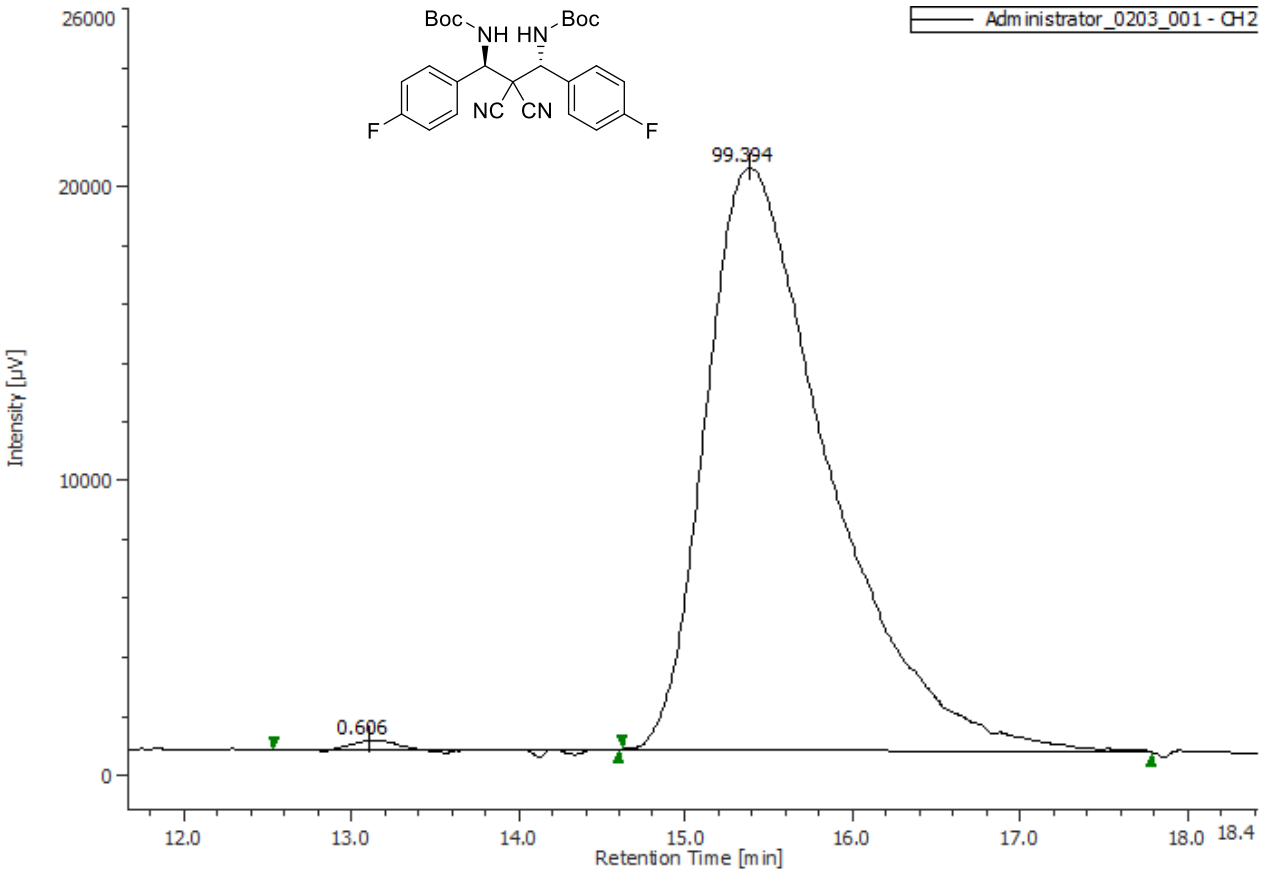
Chiralpak AD-H column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)

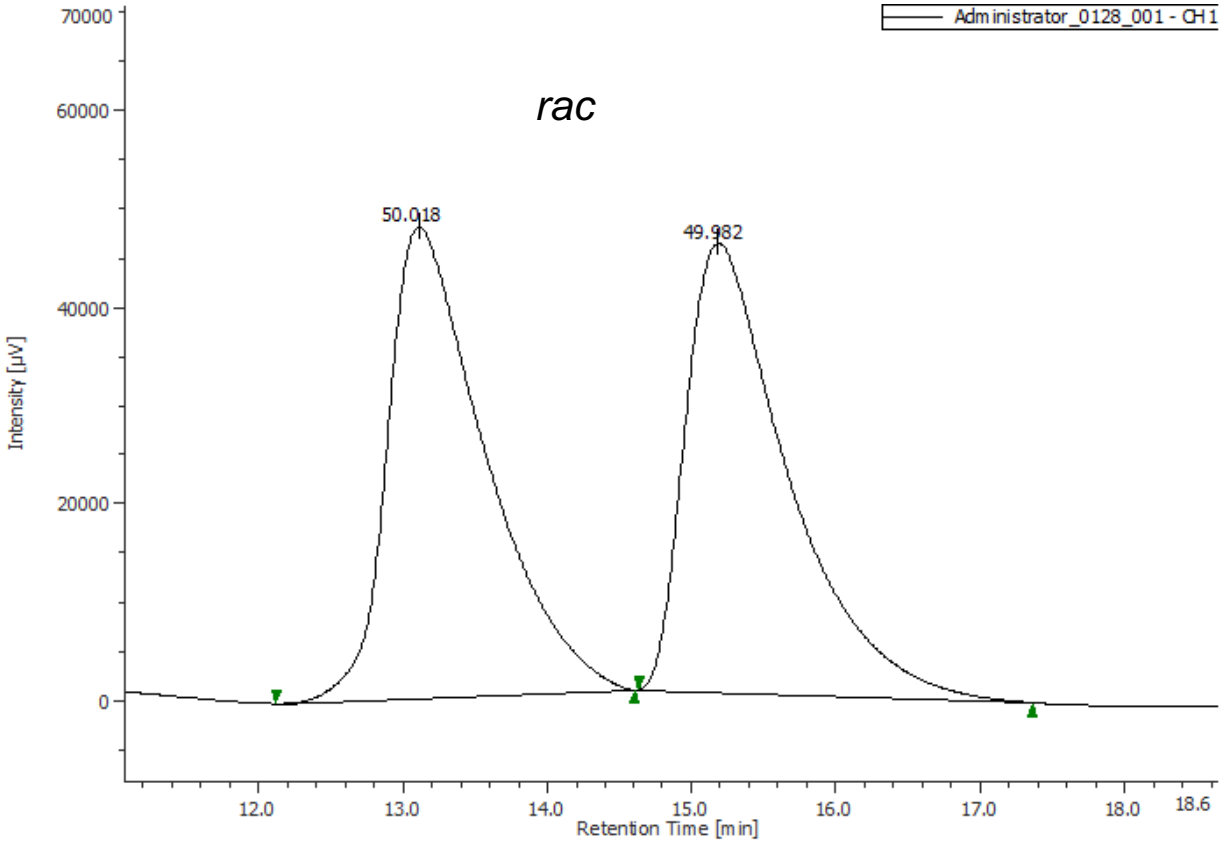


Chiralpak IA column (hexane:2-propanol = 98:2, 1.0 mL/min, 254 nm)

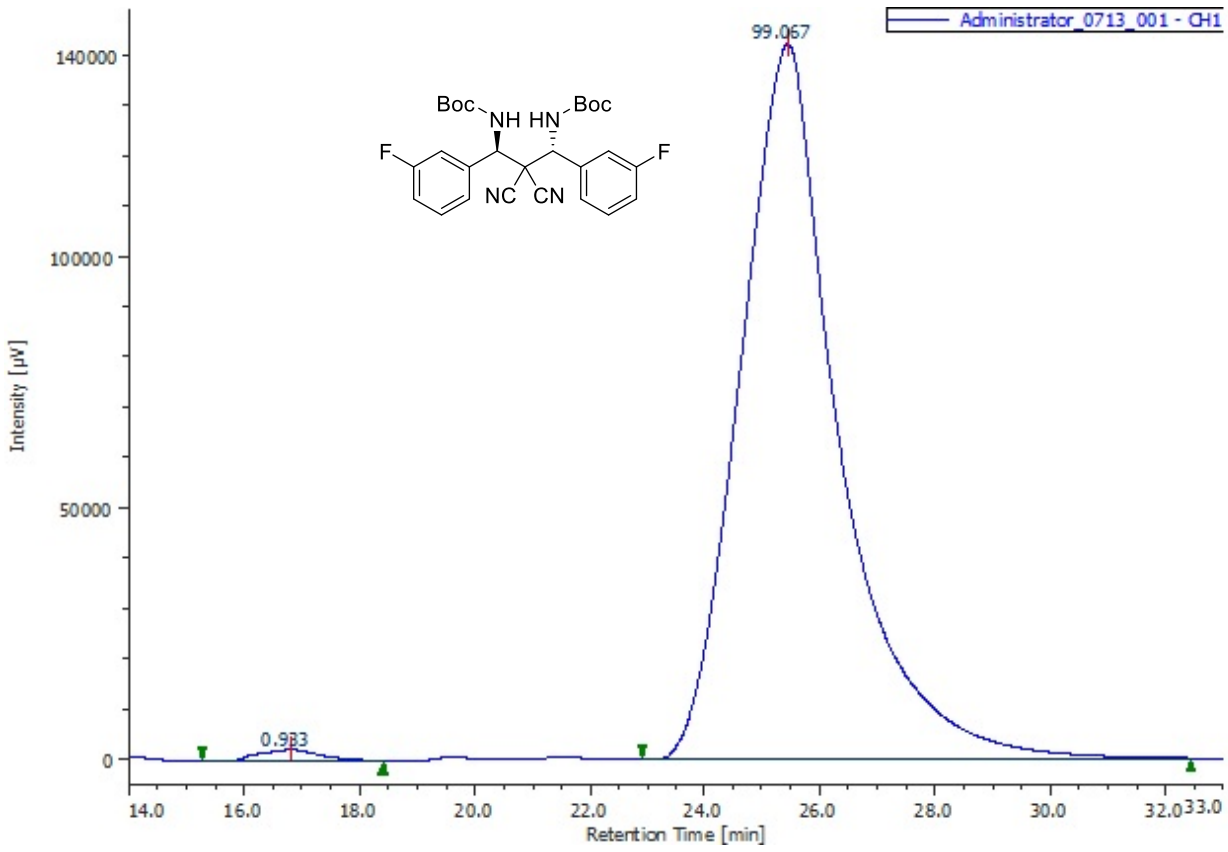


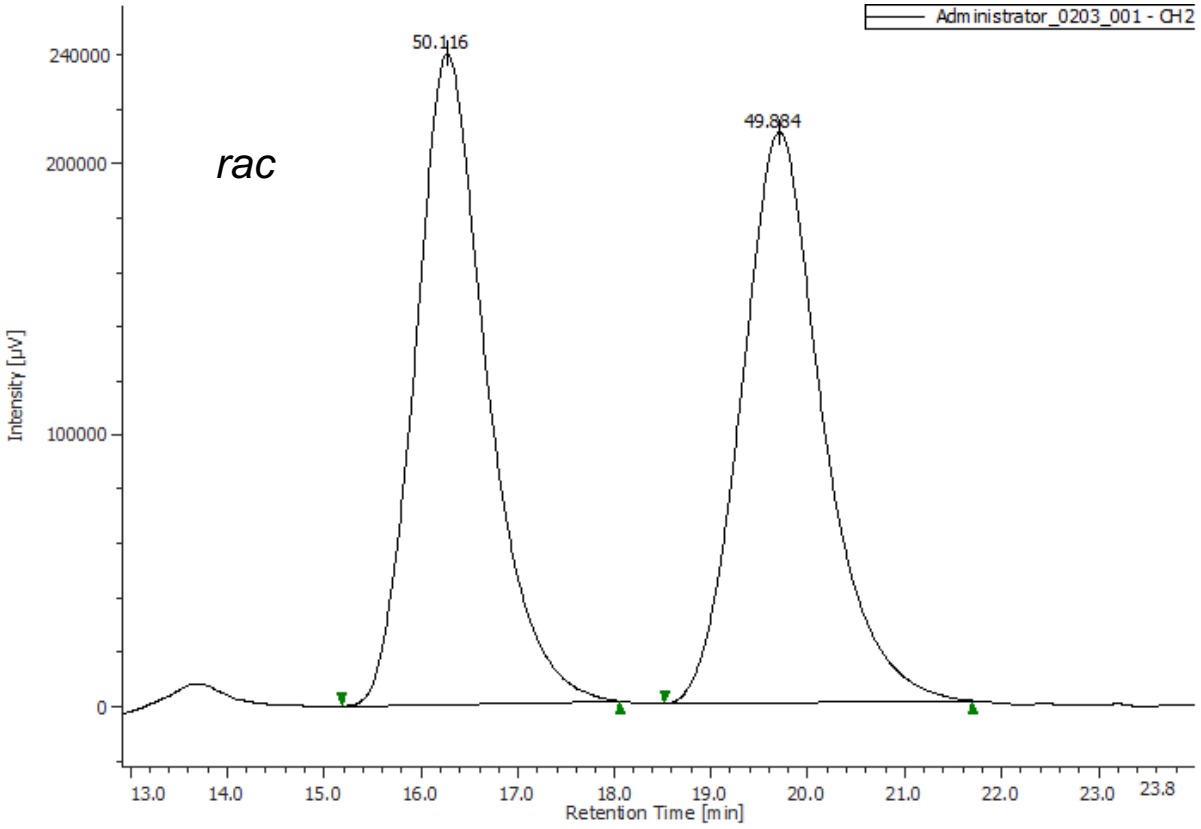
Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)



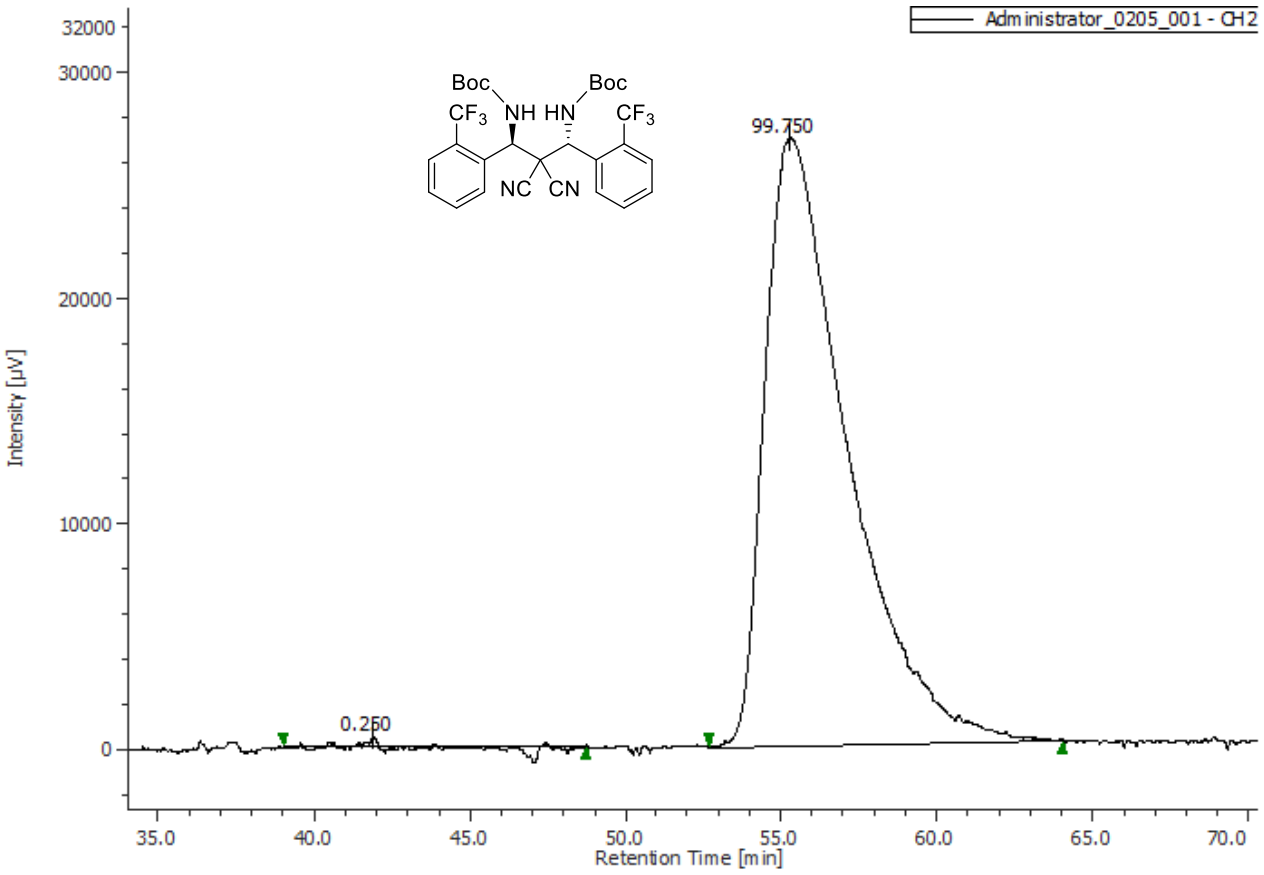


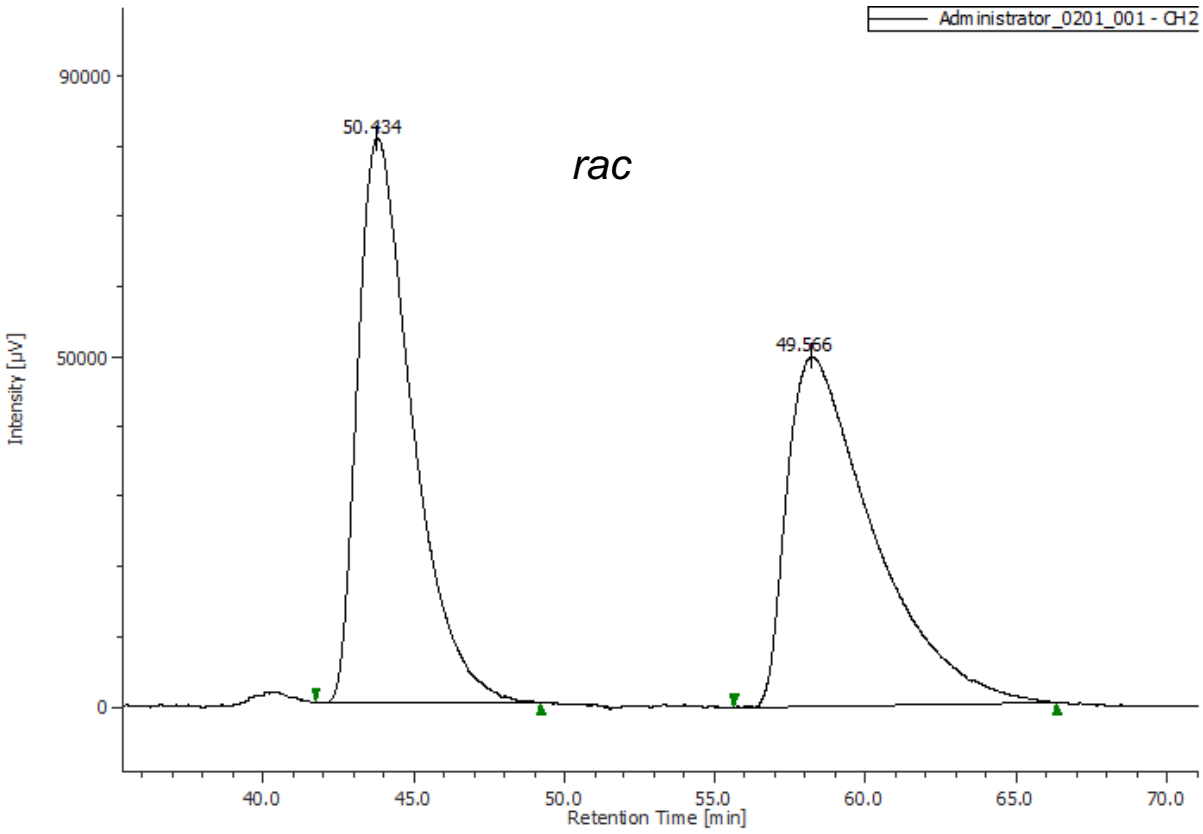
Chiralpak IA column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm)



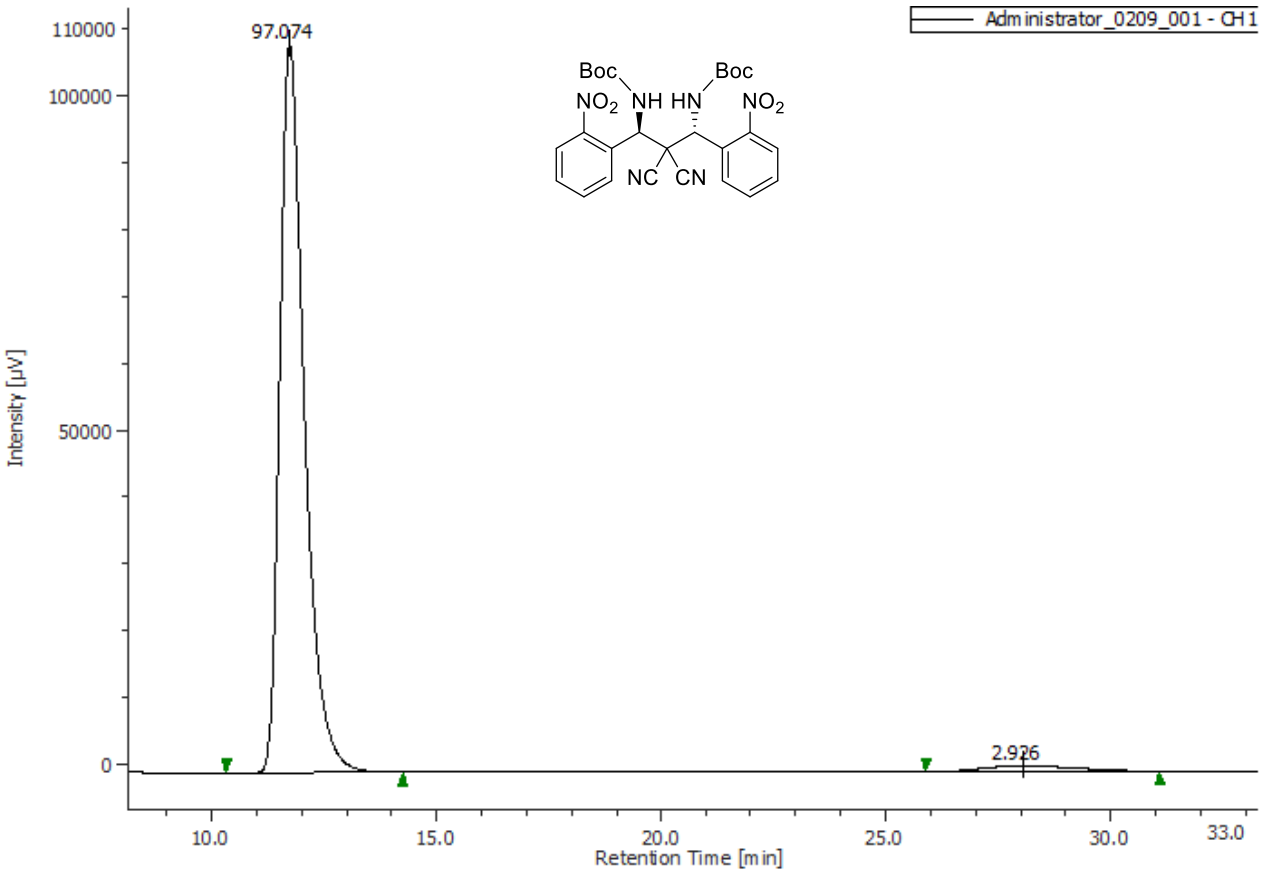


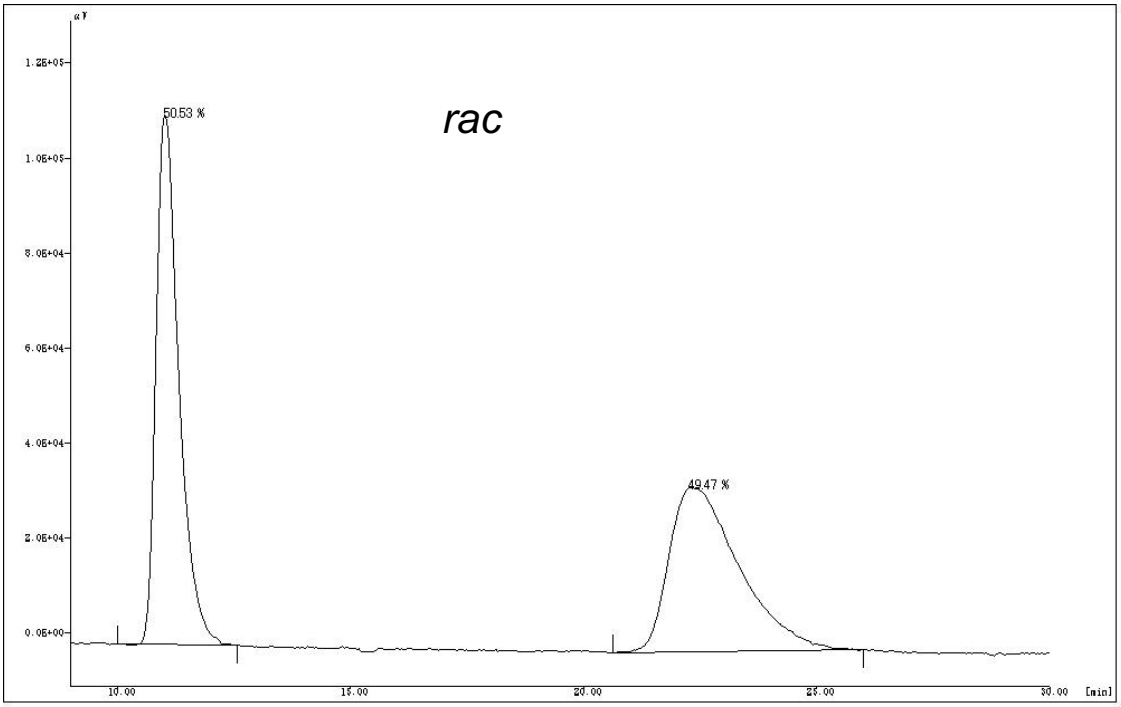
Chiralpak IA column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm)



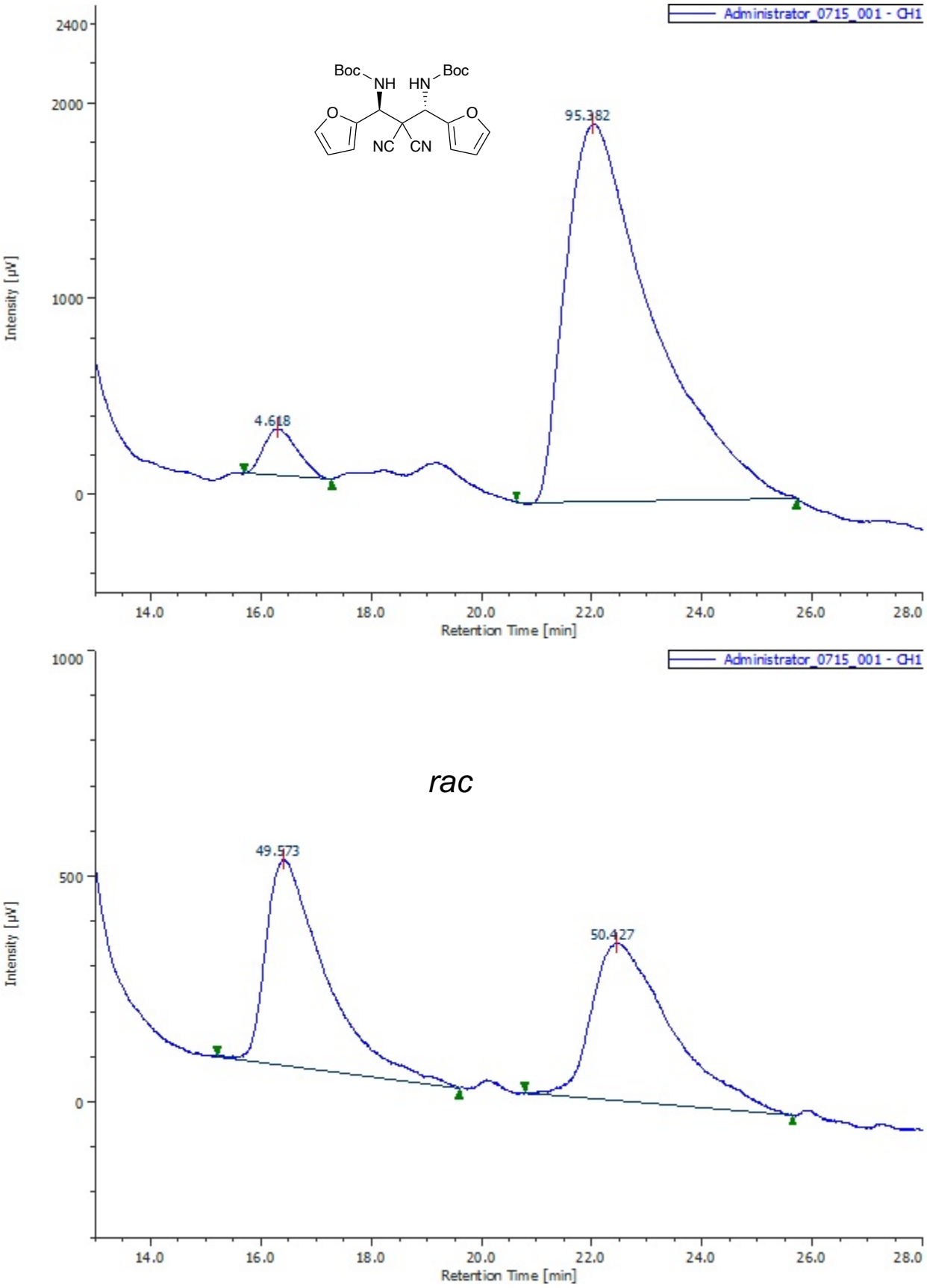


Chiralpak IA column (hexane:2-propanol = 95:5, 0.5 mL/min, 254 nm)

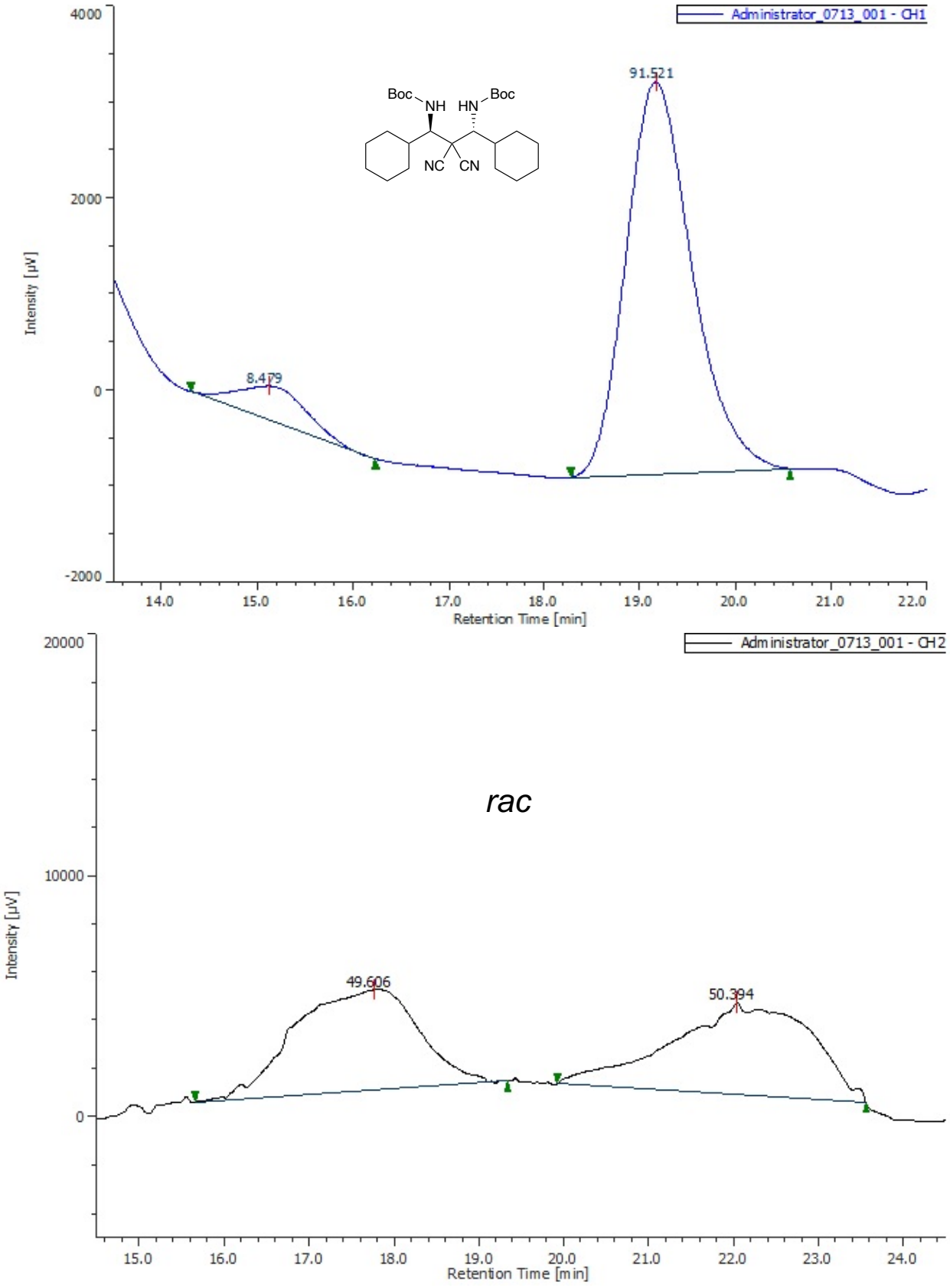




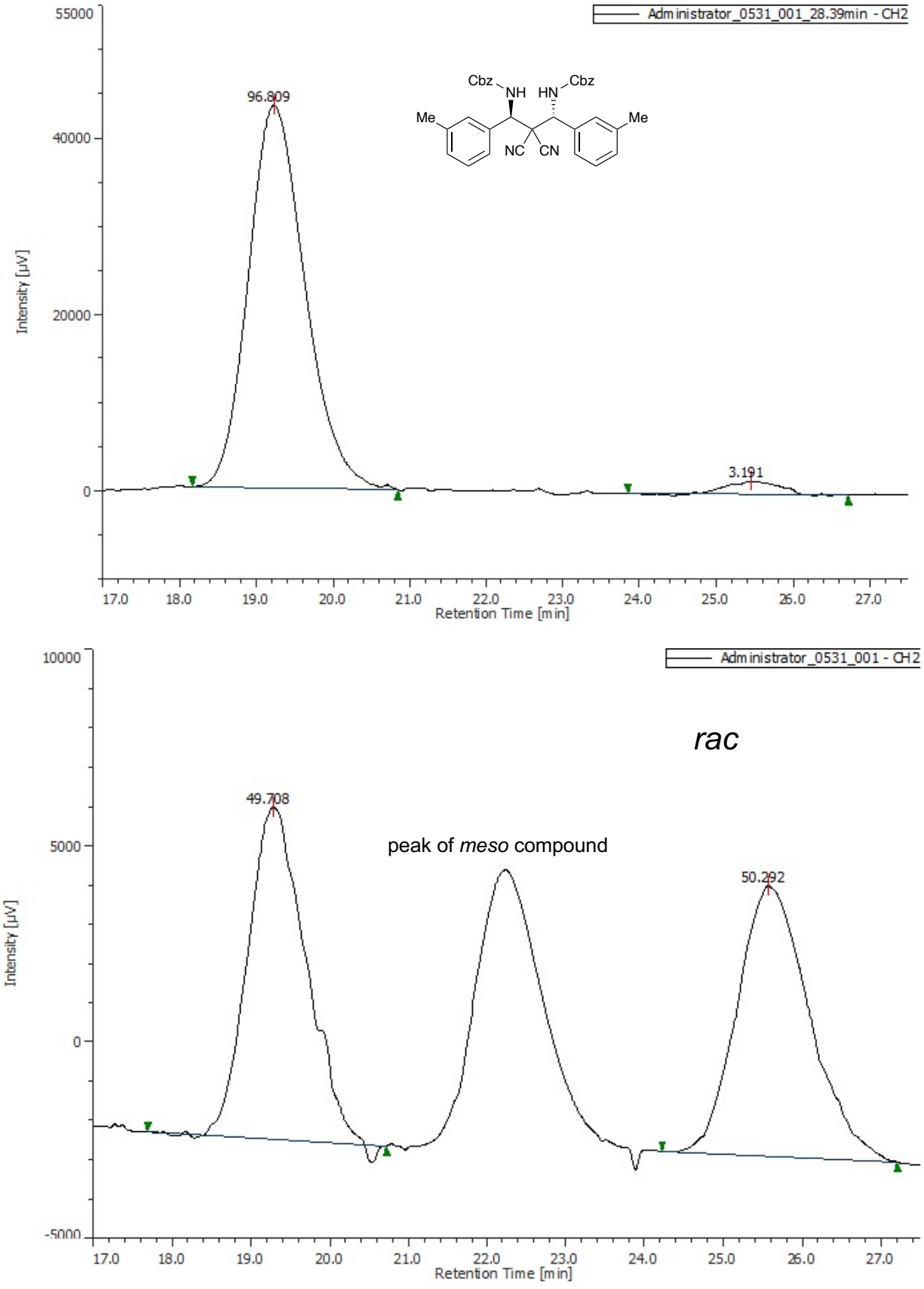
Chiralpak IA column (hexane:2-propanol = 70:30, 1.0 mL/min, 254 nm)



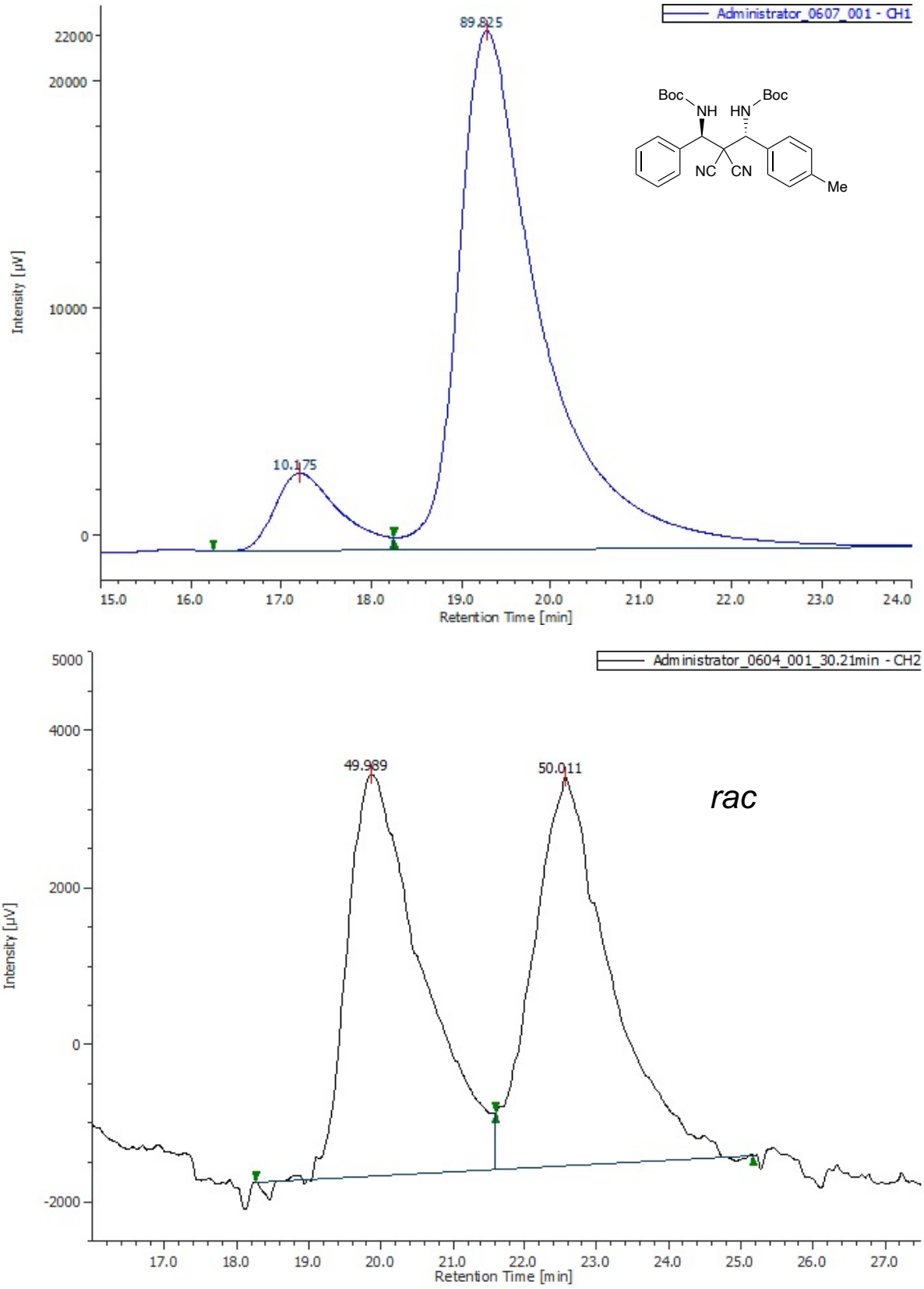
Chiralpak IA column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)



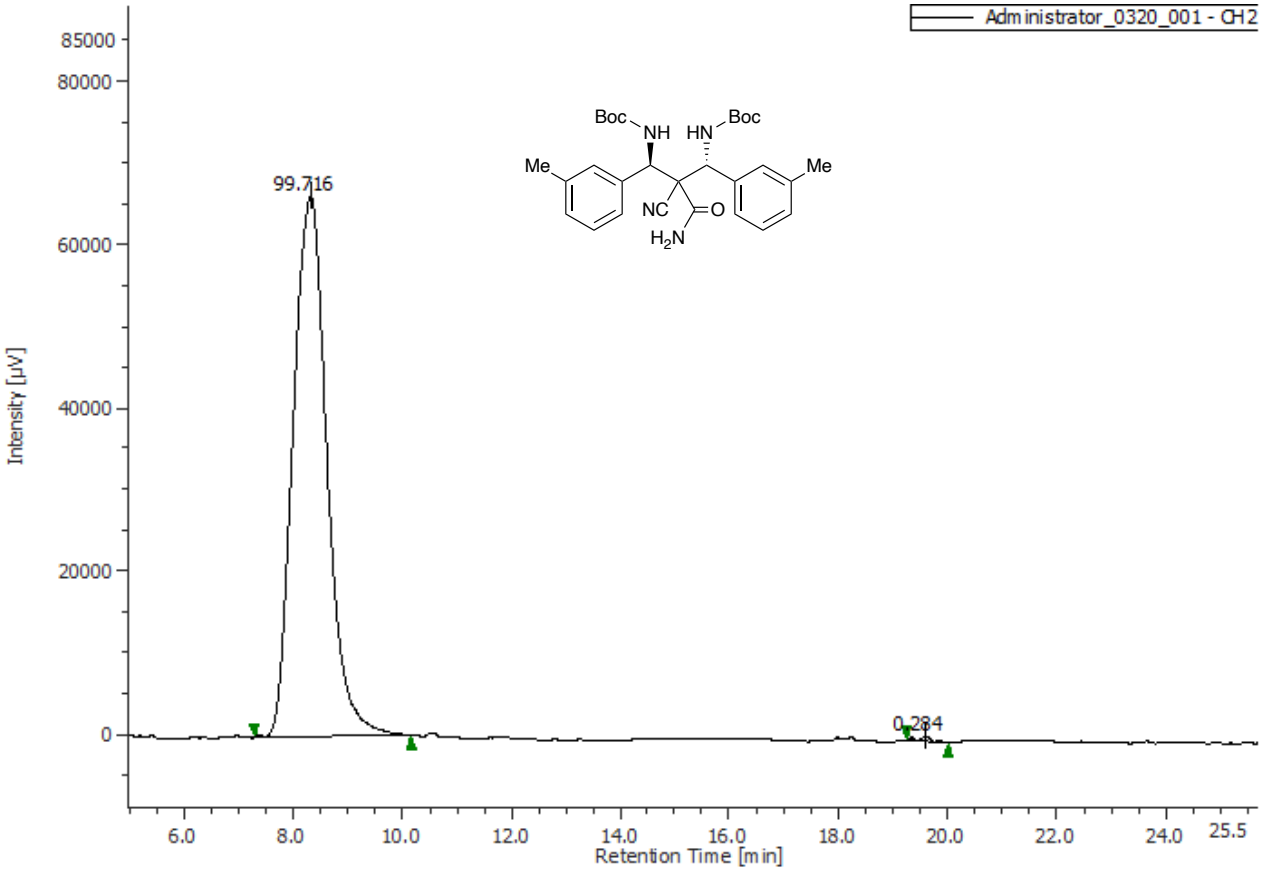
Chiralcel OD-3 column (hexane:2-propanol = 95:5, 0.5 mL/min, 220 nm)

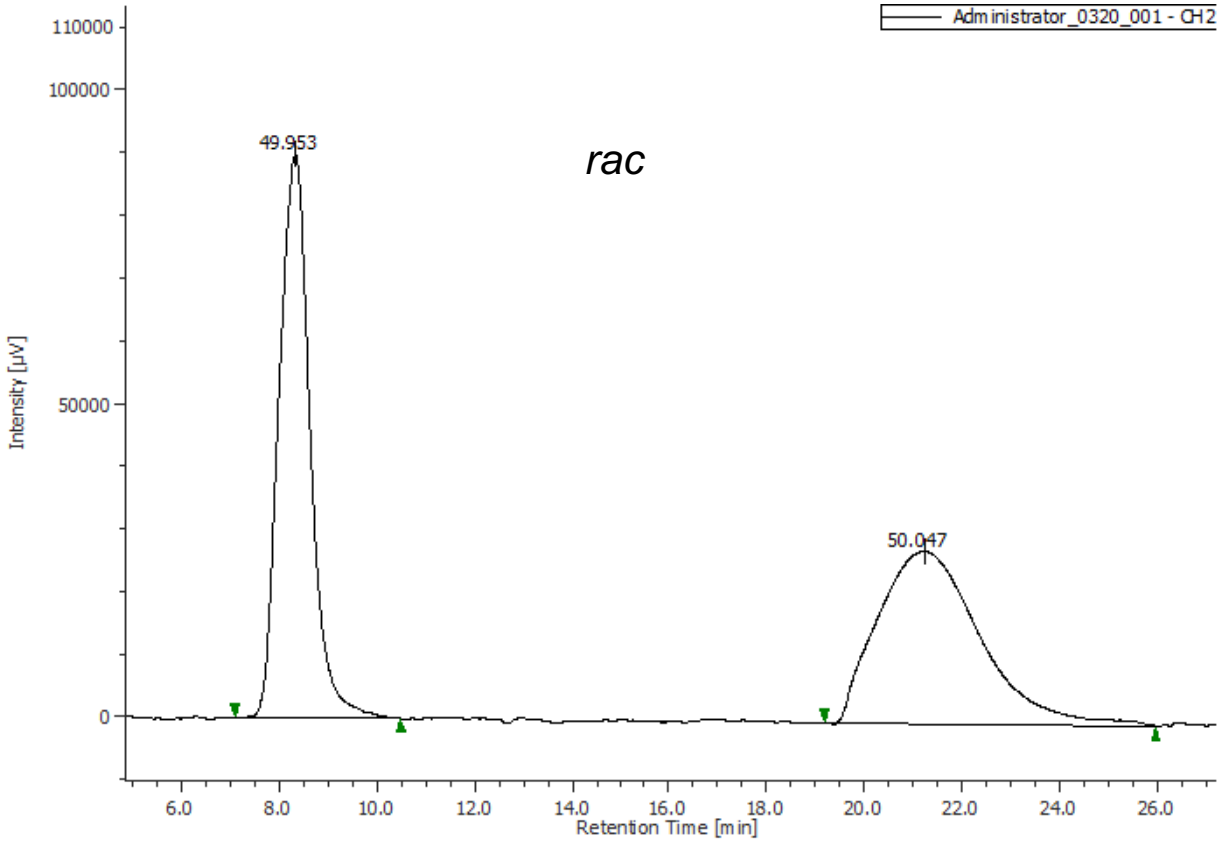


Chiralpak AZ-3 column (hexane:2-propanol = 90:10, 1.0 mL/min, 254 nm)

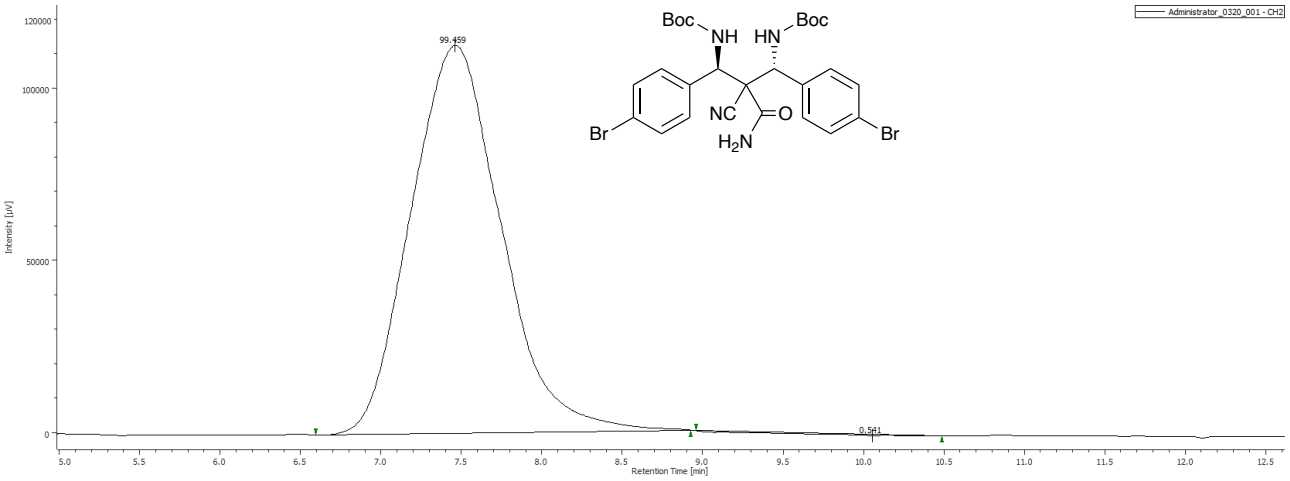


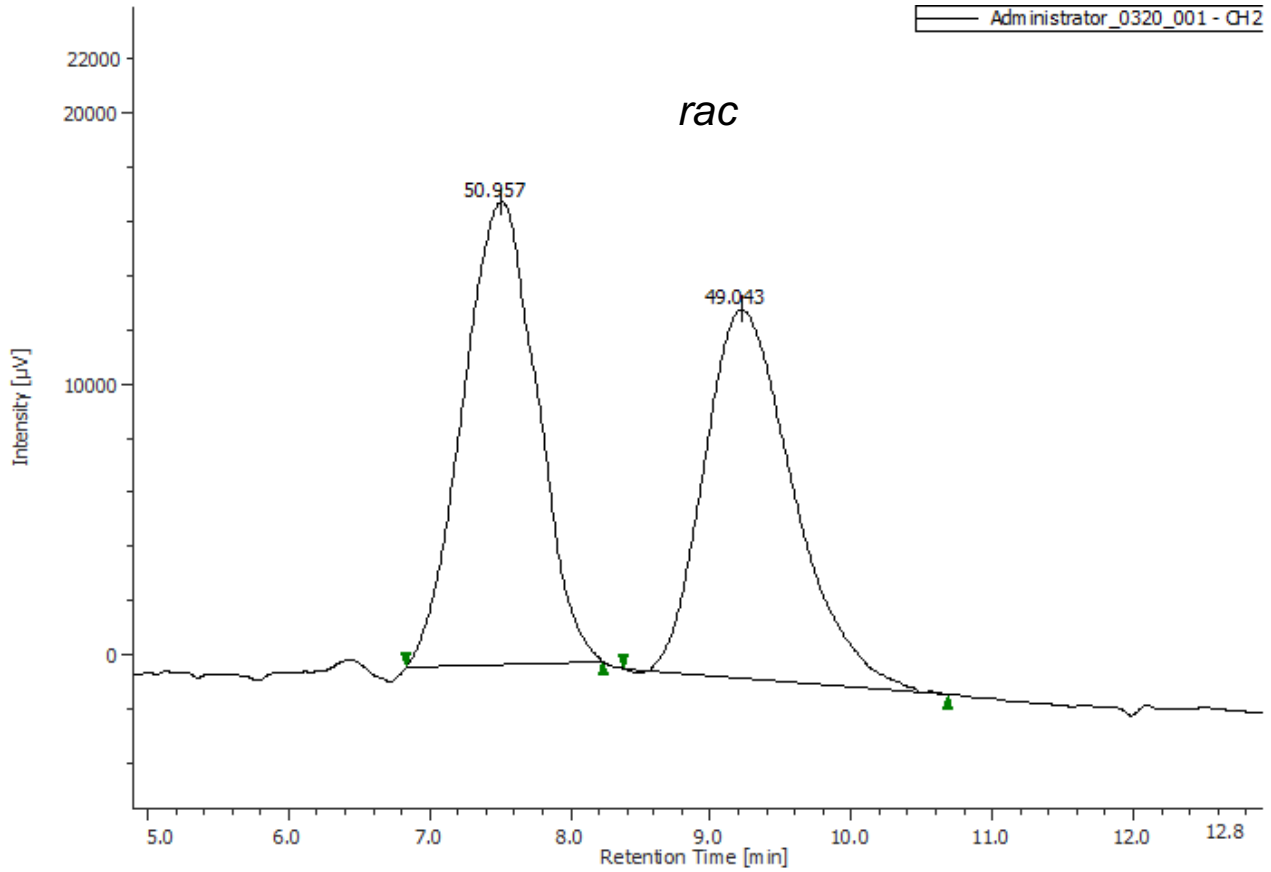
Chiralpak IA column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm)





Chiralpak IC-3 column column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm)





Chiralpak IC-3 column column (hexane:2-propanol = 95:5, 1.0 mL/min, 254 nm)