Stereochemical Diversity in Chiral Ligand Design: Discovery and Optimization of Catalysts for the Enantioselective Addition of Allylic Halides to Aldehydes

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Table of Contents

General Methods:

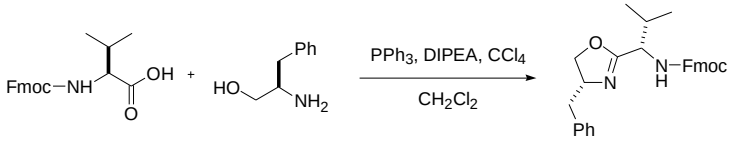
Unless otherwise noted all reactions were performed under a nitrogen atmosphere with stirring. THF was distilled from benzophenone and sodium ketyl, NEt_3 was distilled from CaH_2 before use. $CrCl_2$, $CrCl_3$ and Mn(0) (325 mesh) were purchased from commercial sources and used without further purification. Fmoc and Boc protected amino acids were obtained from commercial sources and rigorously dried by azeotroping from toluene or benzene before use. Amino alcohols were prepared by methods reported in literature.[1] DIPEA was distilled from CaH_2 before use. Flash chromatography was performed using Silica 60 (230-400 mesh.). Analytical thin layer chromatography was performed with Silica gel 60Å plates. All melting points are uncorrected and were recorded on an Electrothermal Melting Point apparatus. Optical rotations were recorded on Perkin Elmer Model 343 Polarimeter. IR spectra were recorded using a Mattson Satellite FTIR instrument. ^{1}H-NMR spectra were obtained at 300 MHz and referenced to the $CHCl_3$ singlet at 7.27 ppm, ^{13}C-NMR spectra were obtained at 75 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.0 ppm. HRMS were recorded using a Finnigan MAT 95 spectrometer. GC analysis was performed using a GC equipped with a HP-Chiral permethylated β-cyclodextrin column. HPLC analysis was performed using a HPLC equipped with a chiral column (as indicated).

Purification of PPh_3:

PPh_3 was purified by recrystallization from hexane after a hot filtration. The crystals are washed with hexane and repeatedly azeotroped with dry toluene followed by drying under high vacuum.

Purification of CCl_4:

CCl_4 is stirred overnight with one fifth its volume of satd. KOH. After washing with water (3 x 20 mL), nitrogen is bubbled through for two hours. It is then percolated through a 2,4-dinitrophenylhydrazine column, distilled from CaH_2 and stored under Nitrogen.



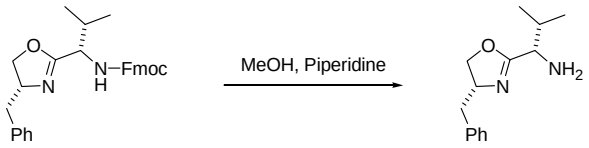
Procedure for Synthesis of Fmoc Protected Oxazoline:

Amino alcohol (377 mg, 2.49 mmol, 1 equiv.), Fmoc protected amino acid (845 mg, 2.49 mmol, 1 equiv.) and PPh_3 (1.96 g, 7.47 mmol, 3 equiv.) is added to a single neck round bottom flask fitted with a stir-bar. Reagents were dissolved in 60 mL CH_2Cl_2 followed by the addition of DIPEA (1.23 mL, 7.47 mmol, 3 equiv.) and cooled to 0 ^{o}C. CCl_4 (1.2

[1]Myers, A. I.; McKenon, M. J. *J. Org. Chem.* **1993,** *58,* 3568.

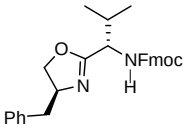
mL, 12.45 mmol, 5 equiv.) is added dropwise over three hours via syringe pump. During this time the flask is kept at 0 °C. When the addition is complete the reaction is allowed to warm to room temperature while stirring for 24 hours.

Toluene (60 mL) is added to the reaction flask and the content is reduced to ca. 80 mL in vacuo. Hexanes (80 mL) is then added and the flask is allowed to stand for 30 minutes. The precipitates are filtered by eluting through a pad of celite and washed with Toluene:Hexanes (3:4). The filtrate is concentrated to ca. 15 mL and loaded onto a column consisting of 125 mL of silica. 200 mL of 10% EtOAc:Hexanes was used to elute the column, followed by 33% EtOAc:Hexanes for the duration of the process. The fractions containing the desired product were collected and the solvent removed in vacuo to yield the product as a white solid (2.57 g, 70%).

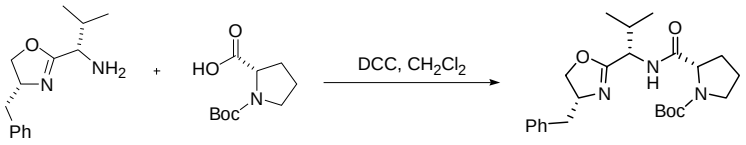


Procedure for Deprotection of the F-moc Protected Oxazoline:

In a single neck round bottom flask, the protected oxazoline (2.57 g, 5.64 mmol, 1 equiv.) was dissolved in MeOH (38 mL) and cooled to 0 °C with an ice bath. Pyridine (39 mL) was added dropwise over ca. 10 minutes and the reaction was allowed to warm to room temperature. The reaction progress was monitored by TLC. After completion, the solvent is removed in vacuo and the residue was purified by column chromatography (200 mL). The column was eluted with 33% EtOAc:Hexanes for the first 100 mL, followed by 4% MeOH:CH_2Cl_2 for the remainder. The fractions containing the desired product were collected and the solvent removed in vacuo to yield a white powder (1.1 g, 83%).



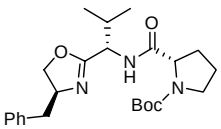
(Fmoc-Oxazoline): Yield: 70%; white powder; mp: 114.6-116.2 °C; $[\alpha]_D^{20}$ = -43.6° (c = 0.25, $CHCl_3$); IR (KBr) 3180.1, 3066.1, 3025.7, 2988.8, 2900.4, 1684.5, 1671.7, 1539.8, 1450.5, 1286.3, 1245.4, 1036.1, 989.0, 737.8 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.32 Hz, 2H), 7.63 (dd, *J* = 6.84, 3.42 Hz, 2H), 7.39 (t, *J* = 7.32 Hz, 2H), 7.34-7.18 (m, 7H), 5.29 (bs, 1H), 4.50-4.20 (m, 6H), 4.02 (t, *J* = 7.32 Hz, 1H), 3.07 (dd, *J* = 14.16, 5.86 Hz, 1H), 2.69 (dd, *J* = 13.67, 7.81 Hz, 1H), 2.15-2.04 (m, 1H), 0.95 (dd, *J* = 9.77, 6.84 Hz, 6H); ^{13}CNMR {^{1}H} (75 MHz, $CDCl_3$) δ 166.7, 156.1, 143.8, 141.3, 137.6, 129.2, 128.5, 127.6, 127.0, 126.6, 125.1, 119.9, 77.2, 72.2, 66.9, 54.5, 47.2, 41.7, 31.5, 18.8, 17.6; HRMS (E.I) m/z $(M)^+$ calcd. 454.2256, obsd. 454.2251.



Ligand Synthesis:

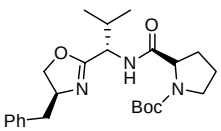
DCC was placed in a single neck round bottom flask, dissolved in 10 mL of CH_2Cl_2, and cooled to 0 ^oC in an ice bath. To this was added a solution of Boc-(S)-proline (980 mg in 10 mL CH_2Cl_2, 4.56 mmol, 1 equiv.). The resulting mixture was allowed to stir at 0 ^oC for 30 minutes. The oxazoline amine (1.06 g, 4.56 mmol, 1 equiv.) was dissolved in 10 mL of CH_2Cl_2 and added to the reaction flask at 0 ^oC. The reaction mixture is allowed to stir overnight while warming to room temperature. The solvent is removed in vacuo, EtOAc (40 ml) is added, and the solution was set aside for 20 minutes. The white precipitate is filtered off by passing the solution through a pad of celite and washing twice with EtOAc (20 mL). The filtrate is washed with 5% $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), followed by drying with Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography, eluting with 1.5:1 EtOAc:Hexanes. The fractions containing the desired product where collected and the solvent removed in vacuo to yield a tan colored solid. The solid was dissolved in ca. 8 mL of 1:1 Et_2O:Hexanes and the Et_2O was removed in vacuo until solid began to precipitate. Et_2O was then added dropwise to redissolve the solid. The flask was then placed in a ca. 10 ^oC refrigerator to recrystallize the product. The mother liquor was removed by pipette and the crystals were washed with 5 mL of cold hexanes and dried in vacuo to yield white crystals (1.61 g, 82%).

Analytical Data



1a

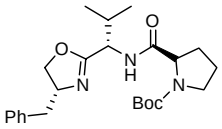
(1a): Yield: 77%; white powder; mp: 90.0-94.1 ^oC; $[\alpha]_D^{20}$ -35.6^o (c 0.25, MeOH); IR (KBr) 3273.8, 3061.6, 2962.4, 2872.6, 1702.3, 1661.0, 1550.0, 1453.4, 1398.5, 1226.6, 1162.5, 982.8, 700.7 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) at 70 ^oC δ 7.29-7.16 (m, 5H), 6.80 (bs, 1H), 4.58 (dd, *J* = 9.28, 4.88 Hz, 1H), 4.41-4.29 (m, 2H), 4.20 (t, *J* = 8.79 Hz, 1H), 3.97 (t, *J* = 7.32 Hz, 1H), 3.48-3.41 (m, 2H), 2.99 (dd, *J* = 14.16, 5.86 Hz, 1H), 2.65 (dd, *J* = 14.16, 7.81 Hz, 1H), 2.26-1.99 (m, 3H), 1.96-1.76 (m, 2H), 1.47 (s, 9H), 0.94 (dd, *J* = 14.65, 6.84 Hz, 6H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) at 70 ^oC δ 171.9, 166.5, 155.1, 138.0, 129.2, 128.5, 126.5, 80.3, 72.3, 67.1, 61.0, 52.5, 47.1, 41.8, 31.6, 28.5, 24.0, 18.9, 17.7; HRMS (E.I) m/z $(M)^+$ calcd. 429.2628, obsd. 429.2604.



1b

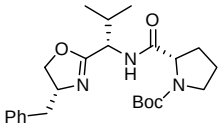
(1b): Yield: 79%; white crystals; mp: 89.8-93.8 ^oC; $[\alpha]_D^{20}$ -90.0^o (c 0.16, MeOH); IR (KBr) 3273.8, 3061.6, 2962.4, 2872.6, 1702.3, 1661.0, 1550.0, 1453.4, 1398.5, 1226.6, 1162.5, 982.8, 700.7 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) at 70 ^oC δ 7.31-7.17 (m, 5H), 4.60 (dd, *J* = 8.30, 5.37 Hz, 1H), 4.43-4.30 (m, 2H), 4.18 (t, *J* = 8.30 Hz, 1H), 3.98 (t, *J* = 7.32 Hz, 1H), 3.50-3.37 (m, 2H), 3.08 (dd, *J* = 13.67, 5.37 Hz, 1H), 2.63 (dd, *J* = 13.67, 8.30 Hz, 1H), 2.37-2.21

(m, 2H), 2.19-2.04 (m, 1H), 2.02-1.82 (m, 2H), 1.48 (s, 9H), 0.92 (dd, J = 6.84, 2.93 Hz, 6H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) at 70 ^{o}C δ 171.7, 166.2, 155.2, 137.9, 129.2, 128.5, 126.5, 80.3, 72.0, 67.2, 60.6, 52.6, 47.0, 41.7, 31.7, 28.4, 24.2, 18.8, 17.8; HRMS (E.I) m/z $(M)^+$ calcd. 429.2628, obsd. 429.2609.



1c

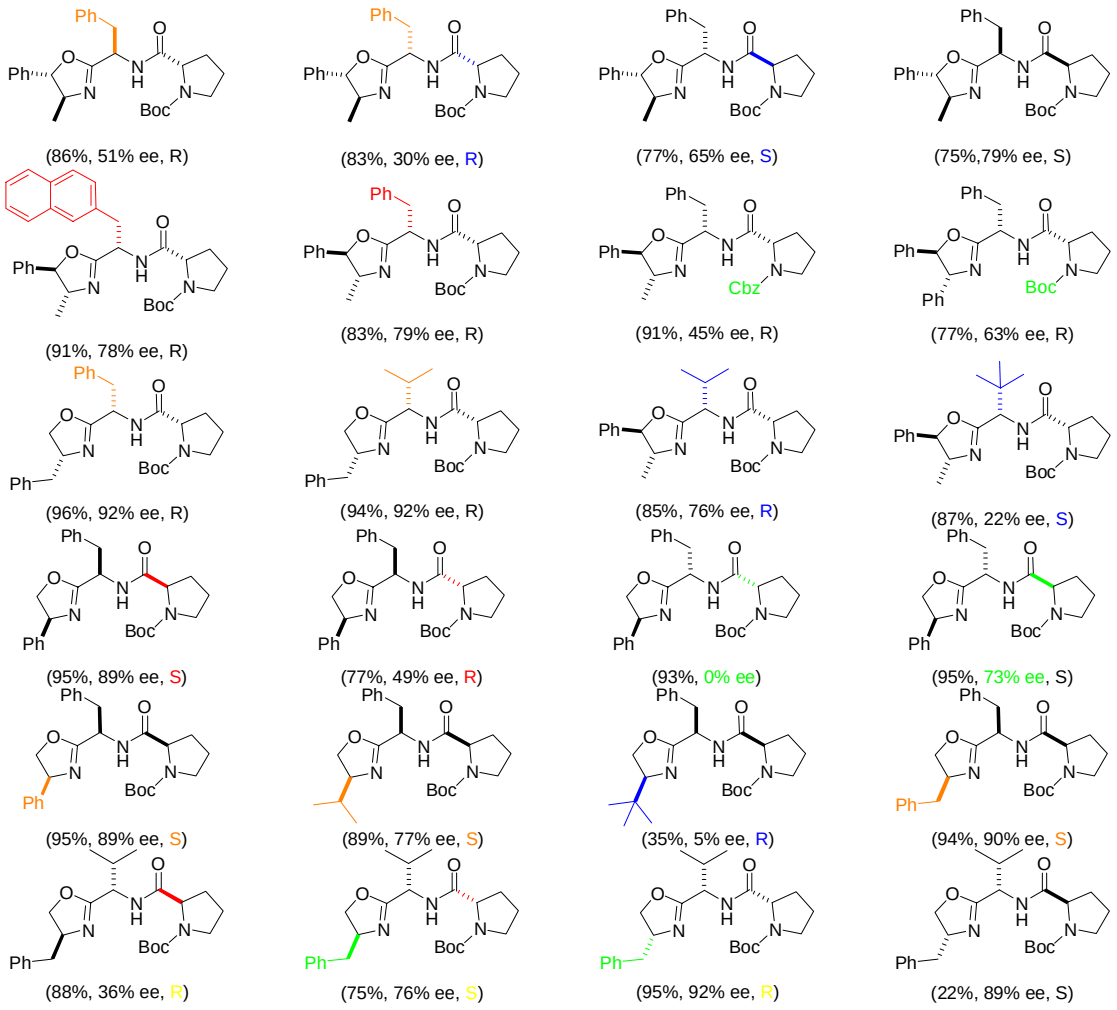
(1c): Yield: 66%; white powder; mp: 118.0-126.0 ^{o}C; $[\alpha]_D^{20}$ +14.8^{o} (c 0.25, MeOH); IR (KBr) 3273.8, 3061.6, 2962.4, 2872.6, 1702.3, 1661.0, 1550.0, 1453.4, 1398.5, 1226.6, 1162.5, 982.8, 700.7 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) at 70 ^{o}C δ 7.31-7.18 (m, 5H), 6.79 (bs, 1H), 4.59 (ddd, J = 8.79, 4.88, 1.0 Hz, 1H), 4.40-4.28 (m, 2H), 4.23 (t, J = 8.30 Hz, 1H), 3.94 (t, J = 7.81 Hz, 1H), 3.47-3.43 (m, 2H), 3.03 (dd, J = 14.16, 5.86 Hz, 1H), 2.66 (dd, J = 14.16, 7.81 Hz, 1H), 2.27-1.98 (m, 3H), 1.95-1.77 (m, 2H), 1.48 (s, 9H), 0.94 (dd, J = 12.21, 6.84 Hz, 6H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) at 70 ^{o}C δ 171.9, 166.5, 155.1, 138.0, 129.3, 128.5, 126.5, 80.3, 72.4, 67.2, 61.0, 52.5, 47.1, 41.9, 31.5, 28.5, 25.0, 24.0, 18.9, 17.7; HRMS (E.I) m/z $(M)^+$ calcd. 429.2628, obsd. 429.2612.



1d

(1d): Yield: 82%; white powder; mp: 83.3-85.8 ^{o}C; $[\alpha]_D^{20}$ -70^{o} (c 0.25, MeOH); IR (KBr) 3273.8, 3061.6, 2962.4, 2872.6, 1702.3, 1661.0, 1550.0, 1453.4, 1398.5, 1226.6, 1162.5, 982.8, 700.7 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) at 70 ^{o}C δ 7.31-6.97 (m, 5H), 4.58 (dd, J = 8.30, 5.37 Hz, 1H) 4.42-4.27 (m, 2H), 4.22 (t, J = 8.79 Hz, 1H), 3.96 (t, J = 7.81 Hz, 1H), 3.49-3.42 (m, 2H), 3.09 (dd, J = 14.16, 5.37, 1H), 2.65 (dd, J = 13.67, 8.30 Hz, 1H), 2.36-2.21 (m, 2H), 2.12 (sext, J = 13.62, 6.92, 1H), 2.04-1.82 (m, 2H), 1.47 (s, 9H), 0.92 (dd, J = 6.84, 1.47 Hz, 6H); ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) at 70 ^{o}C δ 171.8, 166.4, 155.1, 138.0, 129.3, 128.5, 126.5, 80.3, 72.2, 67.2, 60.6, 52.5, 47.0, 41.8, 31.8, 28.4, 24.2, 24.0, 18.8, 17.7; HRMS (E.I) m/z $(M)^+$ calcd. 429.2628, obsd. 429.2611.

Ligand Optimization via Method A:



Procedure for the synthesis of homoallylic alcohols:

All homoallylic alcohols in the scope were synthesized by the following methods unless otherwise noted.

$CrCl_2$ Method (A):

In an inert atmosphere glove box, a 1.5 dram vial was charged with $CrCl_2$ (3 mg, 0.024 mmol, 0.05 equiv.), Mn^o 325 mesh (54 mg, 0.98 mmol, 2 equiv.), ligand (**1d**) (21 mg, 0.048 mmol, 0.1 equiv.), THF (2.4 ml) and a magnetic stir-bar. The vial is capped with a permeable Teflon lid and rapped with a strip of Teflon tape to insure an oxygen free atmosphere. The vial is then removed from the glove box and NEt_3 (7 µl, 0.05 mmol, 0.1 equiv.) is added to the mixture via syringe. The green solution is allowed to stir for 20 min followed by the addition of allyl bromide (85 µl, 0.98 mmol, 2 equiv.), resulting in a black-colored solution. After 30 min, benzaldehyde (50 µl, 0.49 mmol, 1 equiv.) and

TMSCl (125 μl, 0.98 mmol, 2 equiv.) are sequentially added via syringe. The reaction mixture is allowed to stir at room temperature for 20 h.

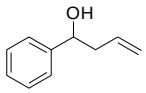
Workup: The cap is removed and the deep blue/green reaction mixture is quenched with sat. $NaHCO_3$ (1.5 ml). Take caution to add the solution slowly as a large amount of gas evolves. The mixture is then passed through a celite plug, using Et_2O to elute, followed by addition of TBAF (1.5 mL, 1M in THF) to deprotect the TMS protected alcohol. After 10 minutes the contents of the flask are placed in a sepratory funnel and extracted with Et_2O (5 ml x 3), dried with Na_2SO_4, and filtered. After removal of the solvent in vacuo, the light oil is loaded onto a short silica column (100 ml) and eluted with (1:9) EtOAc : Hexanes (Rf = 0.65, 1:2 EtOAc:Hexanes). The product is isolated and the solvent is removed in vacuo to yield the resulting product as clear oil.

$CrCl_3$ Method (B):

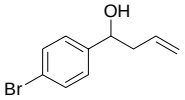
In a 1.5 dram vial was placed $CrCl_3$ (7.9 mg, 0.05 mmol, 0.1 equiv.), Mn(0) 325 mesh (55 mg, 1.0 mmol, 2 equiv.), ligand (**1d**) (21 mg, 0.05 mmol, 0.1 equiv.) and a magnetic stir-bar. The vial is fitted with a permeable Teflon cap and placed under vacuum and refilled with house N_2. A small strip of Teflon was used to wrap the cap to insure no air penetrates the seal. The vial is then charged with THF (2.4 ml) and allowed to stir vigorously for 2 min. at which time NEt_3 (10 μl, 0.075 mmol, 0.15 equiv) and TMSCl (125 μl, 1.0 mmol, 2 equiv.) were added. The reaction mixture was stirred for an additional 20 min. During this time the clear solution turned a deep purple color. Allyl bromide (85 μl, 1.0 mmol, 2 equiv.) was added in one portion and the reaction stirred for 45 minutes. During this time, the deep purple solution turned black. After 45 minutes, benzaldehyde (51 μl, 0.5 mmol, 1 equiv.) was added in one part to the vial. A strip of Teflon tape was used to seal the top of the cap to insure that it remained air free and the mixture was allowed to stir for 20 h. Over the course of the reaction, the solution turned to a deep blue-green color with a white precipitate. Workup is the same as in method A.

All alcohols in the scope were derived in this method unless noted in the experimental.

Analytical Data

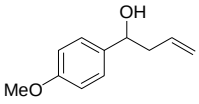


(R)-(1-Phenyl-but-3-en-1-ol); $[\alpha]_D^{20}$ +49.4° (c 1.9, benzene), lit: $[\alpha]_D^{22}$ +56.5° (c 1.0, benzene)[2]; The enantioselectivity was determined to be 94% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{major} = 15.9 min (R), t_{minor} = 18.4 min (S).

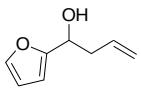


(R)-(1-(4-Bromo-phenyl)-but-3-en-1-ol); $[\alpha]_D^{20}$ +22.7° (c 4.1, benzene), lit: $[\alpha]_D^{24}$ +23.2° (c 1.0, benzene)[2]; The enantioselectivity was determined by ^{19}F NMR of the corresponding (R)-mosher ester and was calculated to be 91% ee..

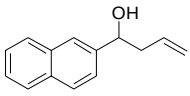
[2] Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593-5601.



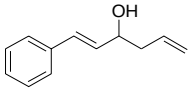
(R)-(1-(4-Methoxy-phenyl)-but-3-en-1-ol); $[\alpha]_D^{20}$ +30.0° (c 6.4, benzene), lit: $[\alpha]_D^{23}$ +30.5° (c 1.0, benzene)[2]; The enantioselectivity was determined to be 89% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{major} = 20.6 min (R), t_{minor} = 26.1 (S).



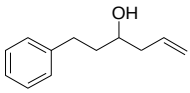
(R)-(1-Furan-2-yl-but-3-en-1-ol); $[\alpha]_D^{20}$ +29.4 (c 2.2, Et_2O), lit: $[\alpha]_D^{26}$ +29.9° (c 1.0, Et_2O)[2]; The enantioselectivity was determined to be 92% ee by HPLC analysis (Chiralcel OJ, hexane/*i*-PrOH = 98.5/1.5, flow rate = 1.0 mL/min): t_{minor} = 16.7 min (S), t_{major} = 18.4 min (R).



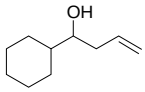
(R)-(1-Naphthalen-2-yl-but-3-en-1-ol); Addition of the aldehyde required a small portion of THF be used to dissolve the solid in order for it to be injected into the reaction mixture. $[\alpha]_D^{20}$ +25.2° (c 0.25, MeOH), lit: $[\alpha]_D^{24}$ +37.5° (c 0.99, benzene)[3]; The enantioselectivity was determined to be 94% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{minor} =35.9 min (S), t_{major} = 38.4 min (R).



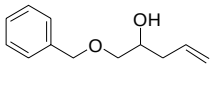
(R)-((E)-1-Phenyl-hexa-1,5-dien-3-ol); $[\alpha]_D^{20}$ -17.0 (c 2.0, Et_2O), lit: $[\alpha]_D^{26}$ -12.3° (c 1.0, Et_2O)[2]; The enantioselectivity was determined to be 88% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98.5/1.5, flow rate = 1.5 mL/min): t_{major} = 24.4 min (R), t_{minor} = 52.4 min (S).



(S)-(1-Phenyl-hex-5-en-3-ol); $[\alpha]_D^{20}$ -9.6° (c 4.2, $CHCl_3$), lit: $[\alpha]_D^{24}$ -26.4° (c 1.0, benzene)[2]; The enantioselectivity was determined to be 48% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{major} = 19.3 min (S), t_{minor} = 34.5 min (R).



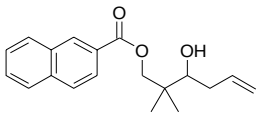
(R)-(1-Cyclohexyl-but-3-en-1-ol); $[\alpha]_D^{20}$ +9.5 (c 1.6, ethanol), lit: $[\alpha]_D^{25}$ +13.7° (c 1.0, ethanol)[2]; The enantioselectivity was determined to be 88% ee by HPLC analysis of the 3,5-dinitrobenzoate derivative of the product (Chiralcel OD-H, hexane/*i*-PrOH = 95/5, flow rate = 1.0 mL/min): t_{major} = 42.6 min (R), t_{minor} = 46.1 min (S).



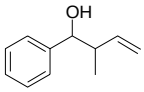
(S)-(1-Benzyloxy-pent-4-en-2-ol); $[\alpha]_D^{20}$ +0.9 (c 2.5, $CHCl_3$), lit: $[\alpha]_D^{20}$ +1.4° (c 1.00, $CHCl_3$)[4]; The enantioselectivity was determined by ^{19}F NMR of the corresponding (R)-mosher ester and was calculated to be 53% ee.

[3] Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199-6200.

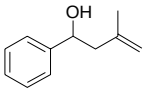
[4] Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920-7921.



(S)-Naphthalene-2-carboxylic acid 3-hydroxy-2,2-dimethyl-hex-5-enyl ester; $[\alpha]_D^{20}$ +10.0 (c 0.25, $CHCl_3$), lit: $[\alpha]_D^{25}$ +11.9° (c 0.95, $CHCl_3$)[5]; The enantioselectivity was determined to be 91% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{minor} = 21.5 min (R); t_{major} = 28.4 min (S).

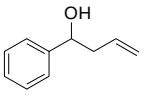


(2-Methyl-1-phenyl-but-3-en-1-ol); $[\alpha]_D^{20}$ +9.5 (c 1.6, ethanol), lit: $[\alpha]_D^{25}$ +13.7° (c 1.0, ethanol)[6]; The stereochemistry was determined via chiral GC analysis of the corresponding methyl ether (HP chiral 20% Permethylated β-cyclodextrin, method: 65 °C isotherm), T_r: 56.9 (*S*,*R*), 58.1 (*R*,*S*), 66.4 (*S*,*S*), 69.2 (*R*,*R*) min) thus providing a diastereomeric ratio *anti*:*syn* of 71:29 and the enantiomeric ratio of ($syn_{1S,2R}$) : ($syn_{1R,2S}$) = 97.3 : 2.7 (95% ee), ($anti_{1S,2S}$) : ($anti_{1R,2R}$) = 95.5 : 4.5 (91% ee).

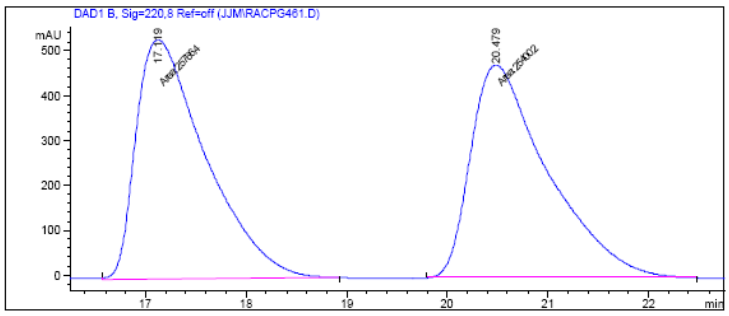


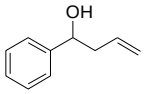
(R)-(3-Methyl-1-phenyl-but-3-en-1-ol); $[\alpha]_D^{20}$ +51.3 (c 5.2, benzene), lit: $[\alpha]_D^{23}$ +55.3° (c 1.3, benzene)[7]; The enantioselectivity was determined to be 91% ee by HPLC analysis (Chiralcel OD, hexane/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{minor} = 13.4 min (S); t_{major} = 15.9 min (R).

[5] Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410-6224.
[6] Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2327-2330.
[7] Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723-4724.



HPLC Conditions: Chiralcel OD, 2% IPA/Hexanes, 1 ml/min





Racemic Product

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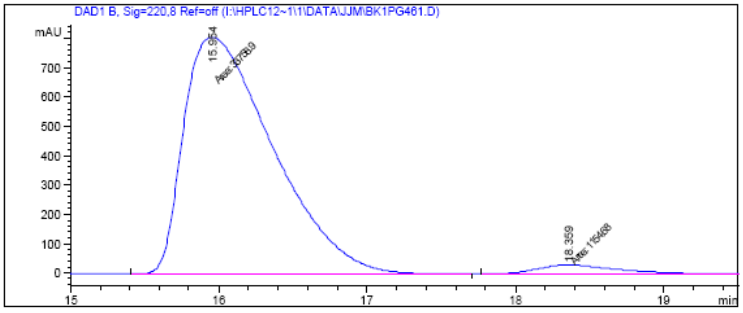
================================================================================
                          Area Percent Report
================================================================================

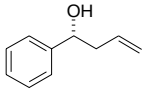
Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area       Height      Area
  #   [min]             [mAU*s]     [mAU]        %
----|-------|---|----|----------|----------|--------|
   1  17.119  1  MM   2.57664e4   534.02887  50.3579
   2  20.479  1  MM   2.54002e4   474.95355  49.6421

Totals :               5.11665e4  1008.98242
================================================================================
```





Reaction Product

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================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area       Height      Area
  #   [min]             [mAU*s]     [mAU]        %
----|-------|---|----|----------|----------|--------|
   1  15.954  1  MM   3.37589e4   808.57599  96.6928
   2  18.359  1  MM   1154.68042   30.86376   3.3072

Totals :               3.49136e4   839.43975
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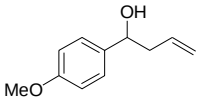
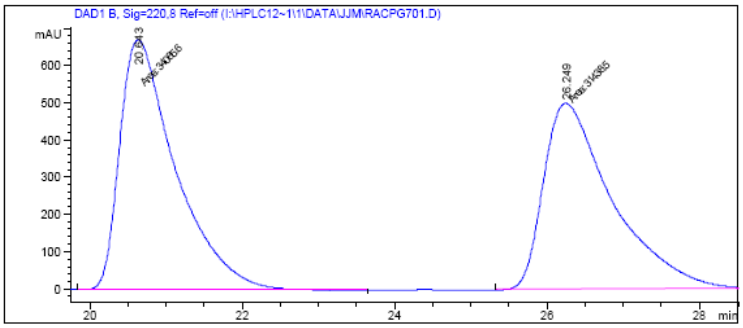
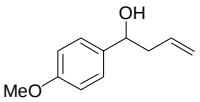


HPLC Conditions: Chiralcel OD, 2% IPA/Hexanes, 1 ml/min





Racemic Product

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================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area       Height     Area
  #   [min]              [mAU*s]    [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  20.643  1  MM   3.40856e4   671.44659  52.0199
   2  26.249  1  MM   3.14385e4   499.82336  47.9801

Totals :               6.55241e4  1171.26996
================================================================================
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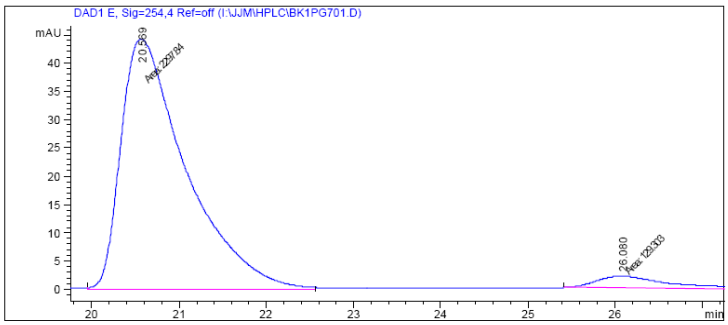

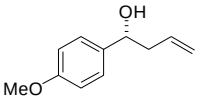

Reaction Product

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================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=254,4 Ref=off

Peak RetTime Sig Type    Area       Height     Area
  #   [min]              [mAU*s]    [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  20.569  1  MM   2297.84351   44.30569  94.6726
   2  26.080  1  MM    129.30327    2.17143   5.3274

Totals :               2427.14677   46.47712
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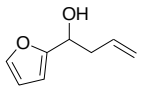
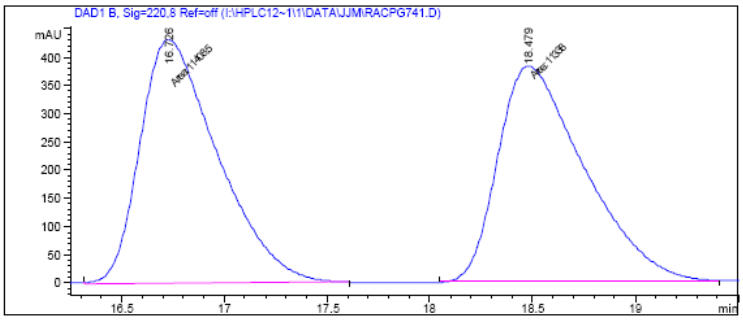
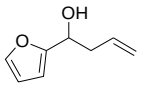


HPLC Conditions: Chiralcel OJ-H, 1.5% IPA/Hexanes, 1 ml/min





Racemic Product

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================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area       Height     Area
  #    [min]            [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  16.726  1  MM   1.14085e4   432.62442  50.1550
   2  18.479  1  MM   1.13380e4   383.58707  49.8450

Totals :               2.27464e4   816.21149
================================================================================
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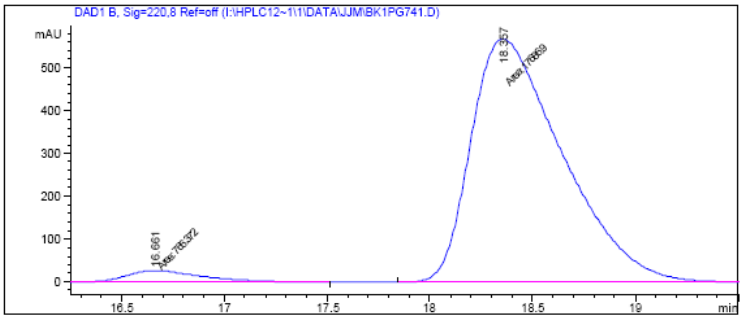

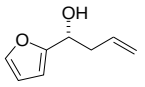

Reaction Product

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================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area       Height     Area
  #    [min]            [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  16.661  1  MM    766.37231   28.42892   4.1530
   2  18.357  1  MM   1.76869e4   570.56561  95.8470

Totals :              1.84533e4   598.99453
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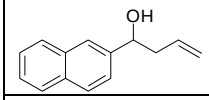
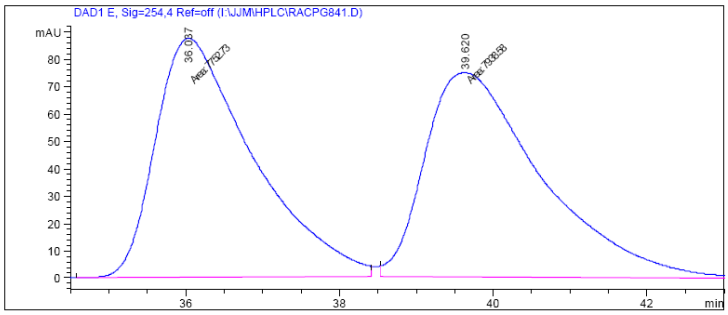
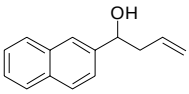


HPLC Conditions: Chiralcel OD, 2% IPA/Hexanes, 1 ml/min





Racemic Product

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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=254,4 Ref=off

Peak RetTime Sig Type    Area       Height      Area
  #   [min]             [mAU*s]     [mAU]        %
----|-------|---|----|----------|----------|--------|
   1  36.037  1  MM   7752.73193   87.78820  49.4078
   2  39.620  1  MM   7938.58154   74.94825  50.5922

Totals :               1.56913e4   162.73645
==========================================================================
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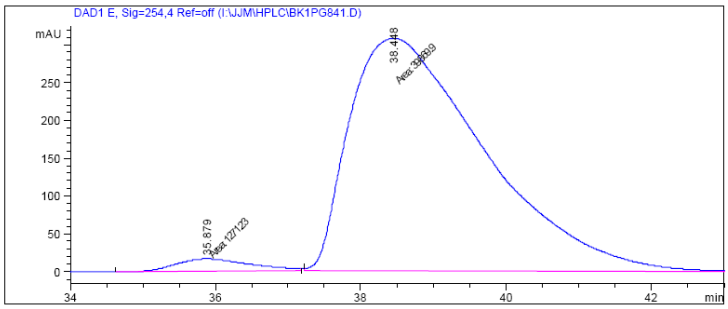

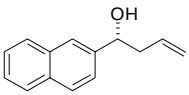

Reaction Product

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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=254,4 Ref=off

Peak RetTime Sig Type    Area       Height      Area
  #   [min]             [mAU*s]     [mAU]        %
----|-------|---|----|----------|----------|--------|
   1  35.879  1  MM   1271.23071   17.00602   3.0899
   2  38.448  1  MM   3.98699e4   308.36526  96.9101

Totals :               4.11411e4   325.37128
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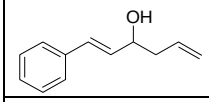
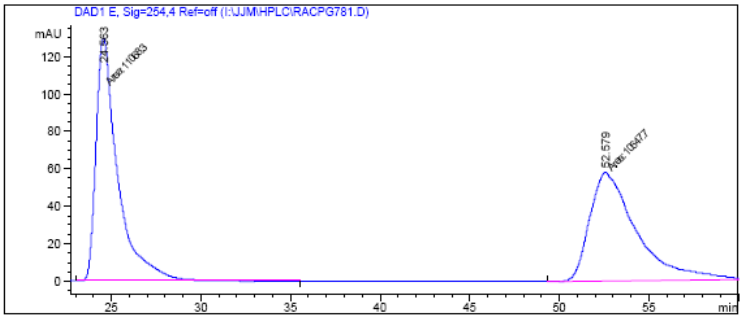
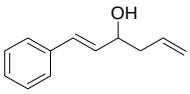


HPLC Conditions: Chiralcel OD, 1.5% IPA/Hexanes, 1.5 ml/min





Racemic Product

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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=254,4 Ref=off

Peak RetTime Sig Type    Area      Height     Area
  #   [min]             [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  24.563  1  MM   1.10683e4   129.54230  50.9686
   2  52.579  1  MM   1.06477e4    58.19971  49.0314

Totals :              2.17160e4   187.74200
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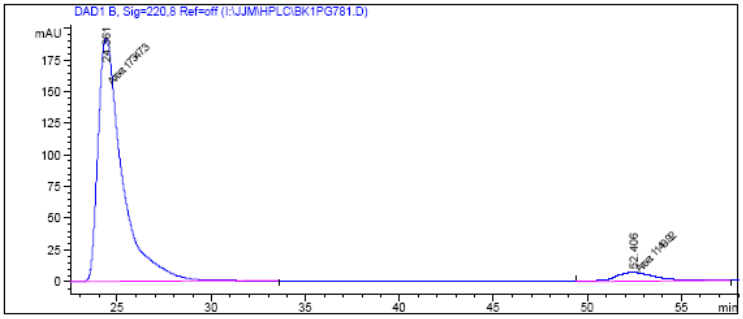

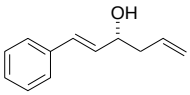

Reaction Product

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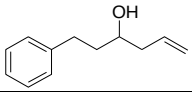
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

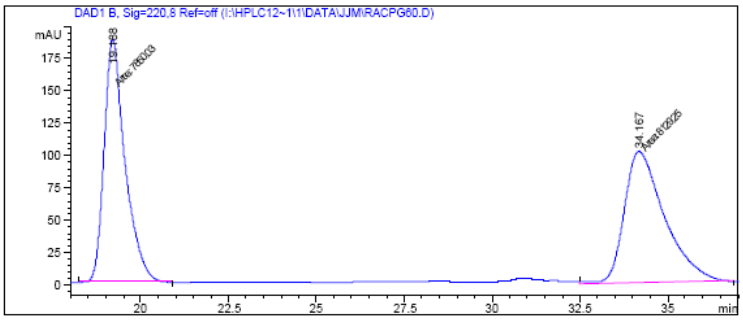
Signal 1: DAD1 B, Sig=220,8 Ref=off

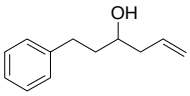
Peak RetTime Sig Type    Area      Height     Area
  #   [min]             [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  24.361  1  MM   1.73473e4   192.40419  93.7833
   2  52.406  1  MM   1149.92456    6.83473   6.2167

Totals :              1.84972e4   199.23892
```



HPLC Conditions: Chiralcel OD, 2% IPA/Hexanes, 1 ml/min





Racemic Product

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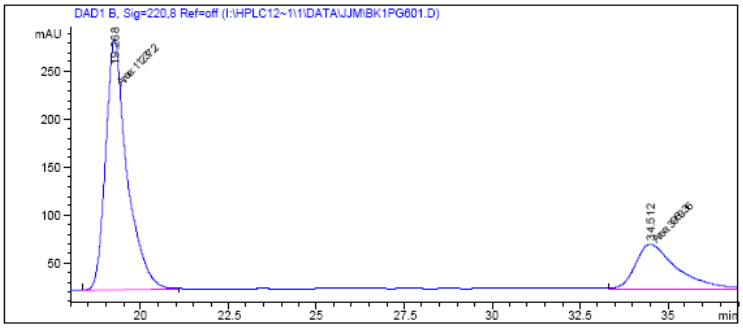
==========================================================================
                        Area Percent Report
==========================================================================

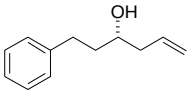
Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area       Height     Area
  #    [min]            [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  19.188  1  MM   7850.03467  188.35583  49.1263
   2  34.167  1  MM   8129.25146  101.82943  50.8737

Totals :               1.59793e4   290.18526
```





Reaction Product

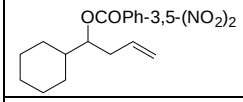
```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

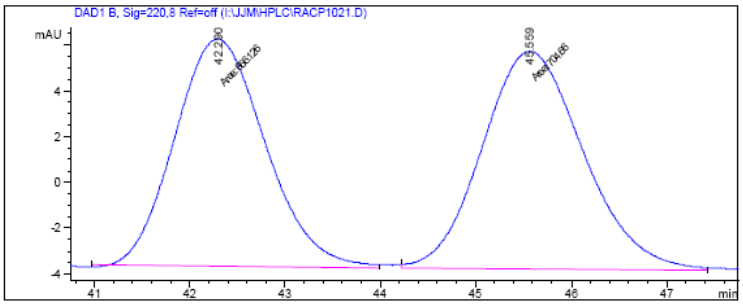
Signal 1: DAD1 B, Sig=220,8 Ref=off

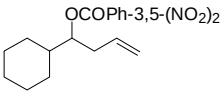
Peak RetTime Sig Type    Area       Height     Area
  #    [min]            [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  19.268  1  MM   1.12372e4   262.42023  73.8971
   2  34.512  1  MM   3969.36084   47.29820  26.1029

Totals :               1.52066e4   309.71843
```



HPLC Conditions: Chiralcel OD-H, 5% IPA/Hexanes, 1 ml/min





Racemic Product

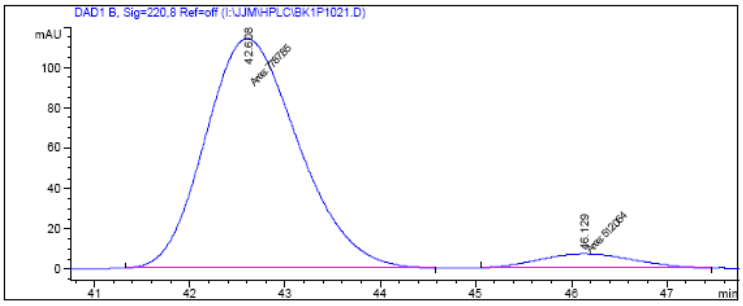
```
                          Area Percent Report

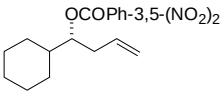
Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area      Height     Area
  #   [min]             [mAU*s]    [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  42.290  1  MM    656.12592    9.94324  48.2167
   2  45.559  1  MM    704.65997    9.51931  51.7833

Totals :              1360.78589   19.46255
```





Reaction Product

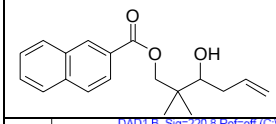
```
                          Area Percent Report

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

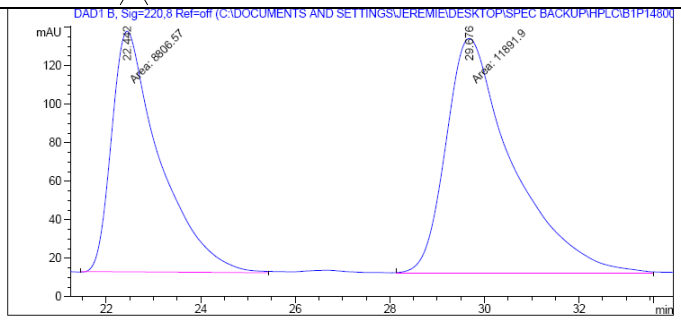
Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area      Height     Area
  #   [min]             [mAU*s]    [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  42.608  1  MM   7787.85449  114.24649  93.8305
   2  46.129  1  MM    512.06421    7.20011   6.1695

Totals :              8299.91870  121.44660
```



HPLC Conditions: Chiral OD, 2% IPA/Hexanes, 1 ml/min



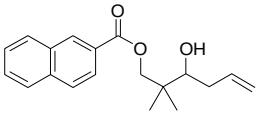

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

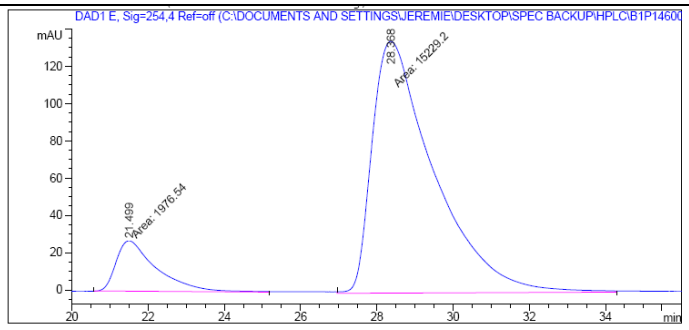

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  22.442 MM    1.1752 8806.57227  124.89345  42.5471
   2  29.676 MM    1.6294 1.18919e4   121.63763  57.4529

Totals :                  2.06984e4   246.53108
```



Racemic Product



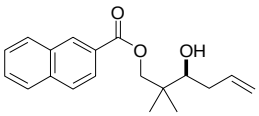

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

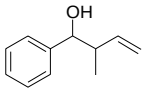

Signal 1: DAD1 E, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.499 MM    1.2193 1976.53967   27.01683  11.4877
   2  28.368 MM    1.8798 1.52292e4   135.02512  88.5123

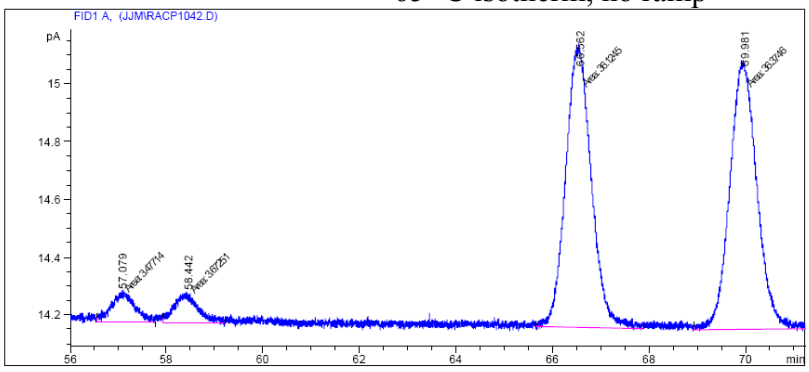
Totals :                  1.72058e4   162.04194
```

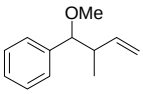


Reaction Product



GC Conditions: HP Chiral (20% Permethlated β-cyclodextrin, 65 °C isotherm, no ramp





Racemic Product

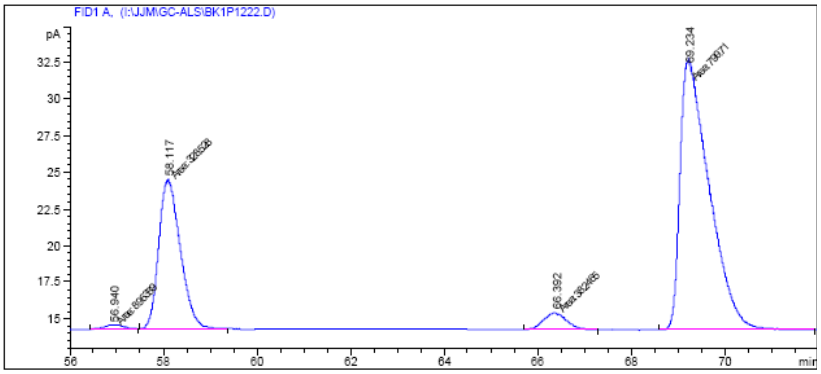
```
=====================================================================
                        Area Percent Report
=====================================================================

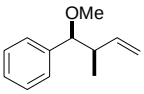
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: FID1 A,

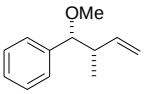
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1  57.079 MM    0.5655    3.47714 1.02479e-1  4.36560
   2  58.442 MM    0.5944    3.67251 1.02972e-1  4.61089
   3  66.562 MM    0.6150   36.12446 9.79038e-1 45.35476
   4  69.981 MM    0.6544   36.37455 9.26397e-1 45.66875

Totals :                    79.64867    2.11089
```





Reaction Product 56.94 min.



Reaction Product 58.12 min.

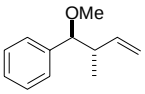
```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

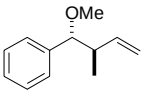
Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1  56.940 MM    0.4763    8.96389 3.13672e-1  0.76259
   2  58.117 MM    0.5336  328.52835   10.26058 27.94918
   3  66.392 MM    0.5665   38.24651    1.12522  3.25378
   4  69.234 MM    0.7161  799.71027   18.61213 68.03445

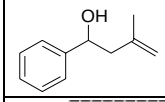
Totals :                  1175.44902   30.31160
```



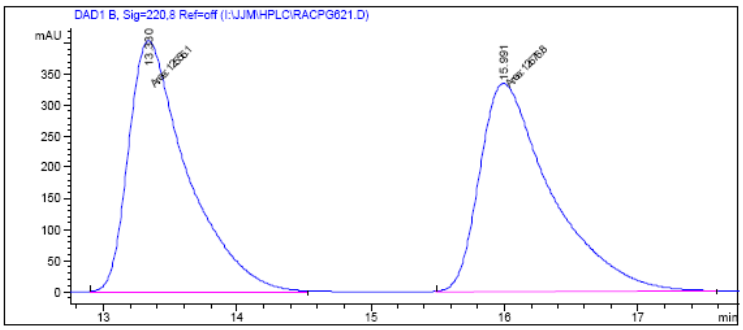
Reaction Product 66.39 min.

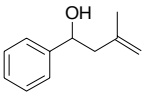


Reaction Product 69.23 min.



HPLC Conditions: Chiralcel OD, 2% IPA/Hexanes, 1 ml/min





Racemic Product

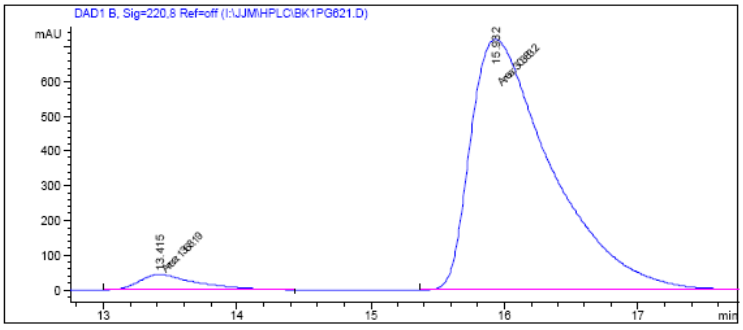
```
Area Percent Report

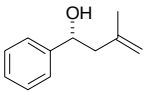
Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area      Height     Area
  #   [min]            [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  13.330  1  MM   1.25551e4   406.04471  49.7587
   2  15.991  1  MM   1.26768e4   336.86868  50.2413

Totals :              2.52319e4   742.91339
```





Reaction Product

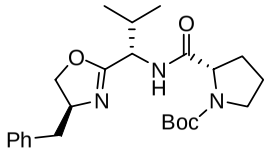
```
Area Percent Report

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,8 Ref=off

Peak RetTime Sig Type    Area      Height     Area
  #   [min]            [mAU*s]     [mAU]       %
----|-------|---|----|----------|----------|--------|
   1  13.415  1  MM   1368.18848   44.87090   4.3091
   2  15.932  1  MM   3.03832e4   722.06104  95.6909

Totals :              3.17514e4   766.93193
```



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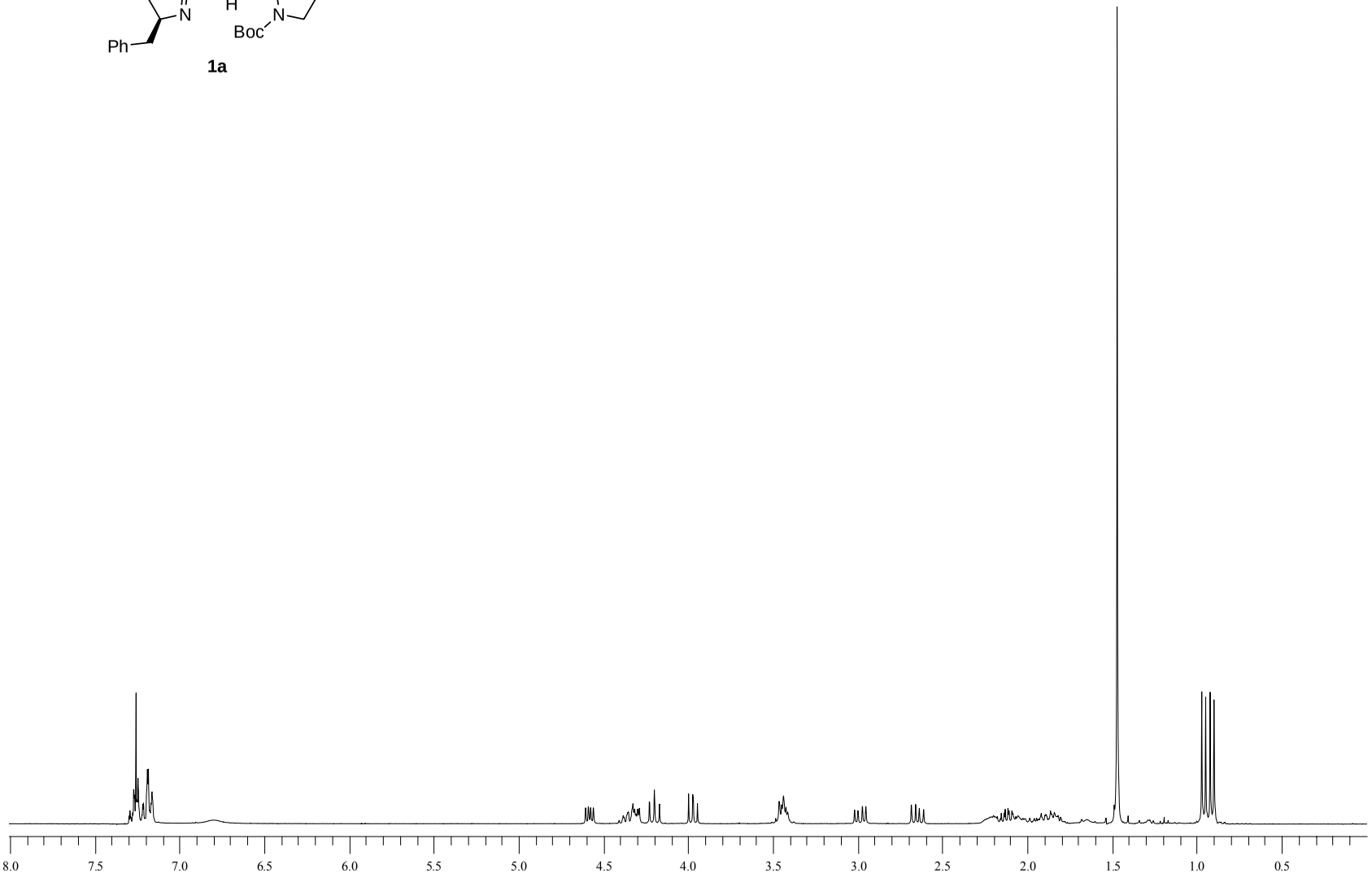
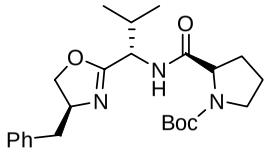
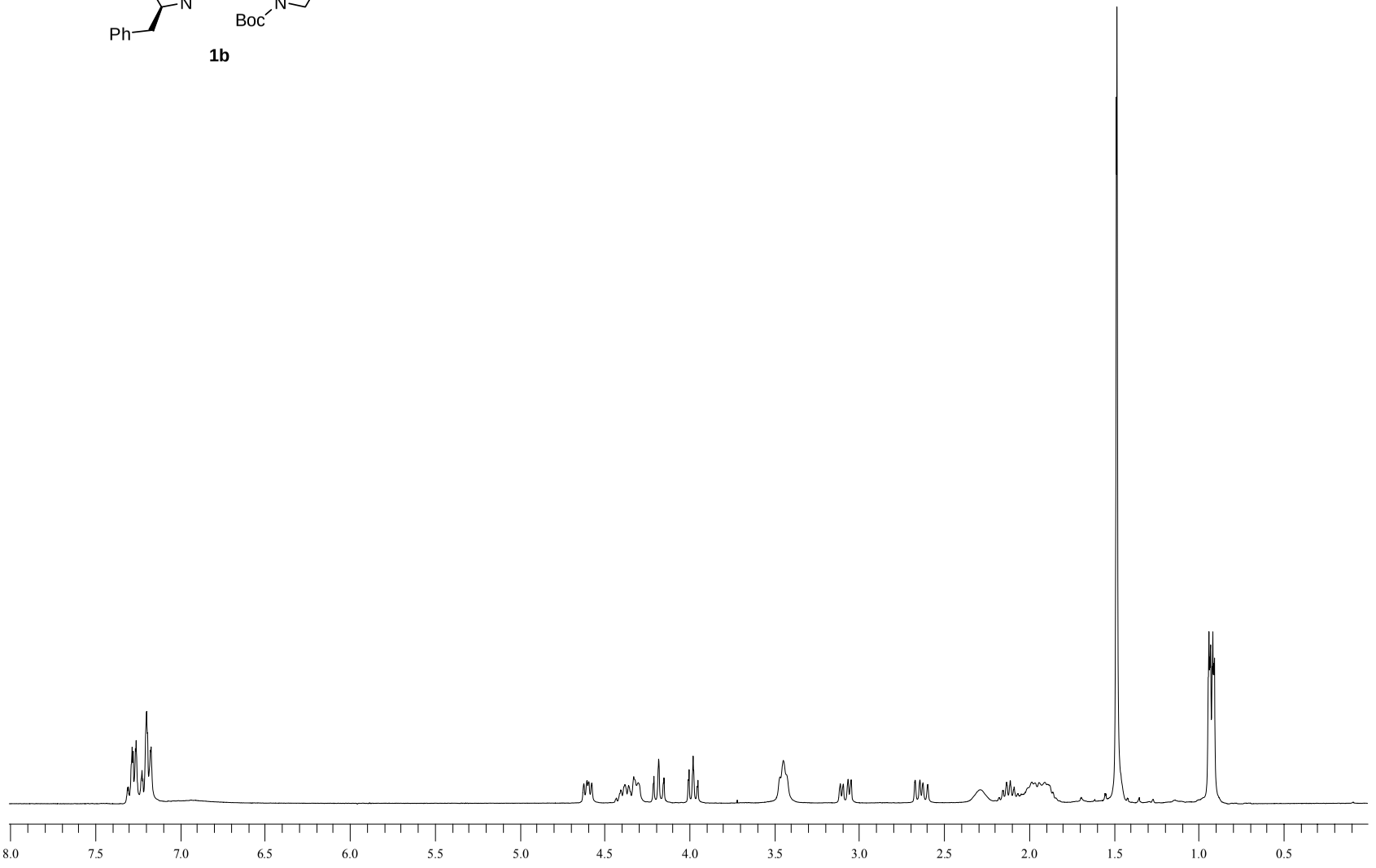
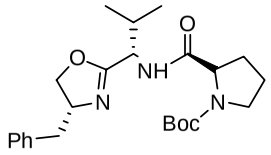


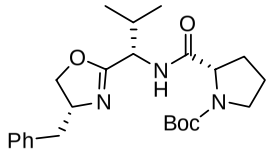


1b

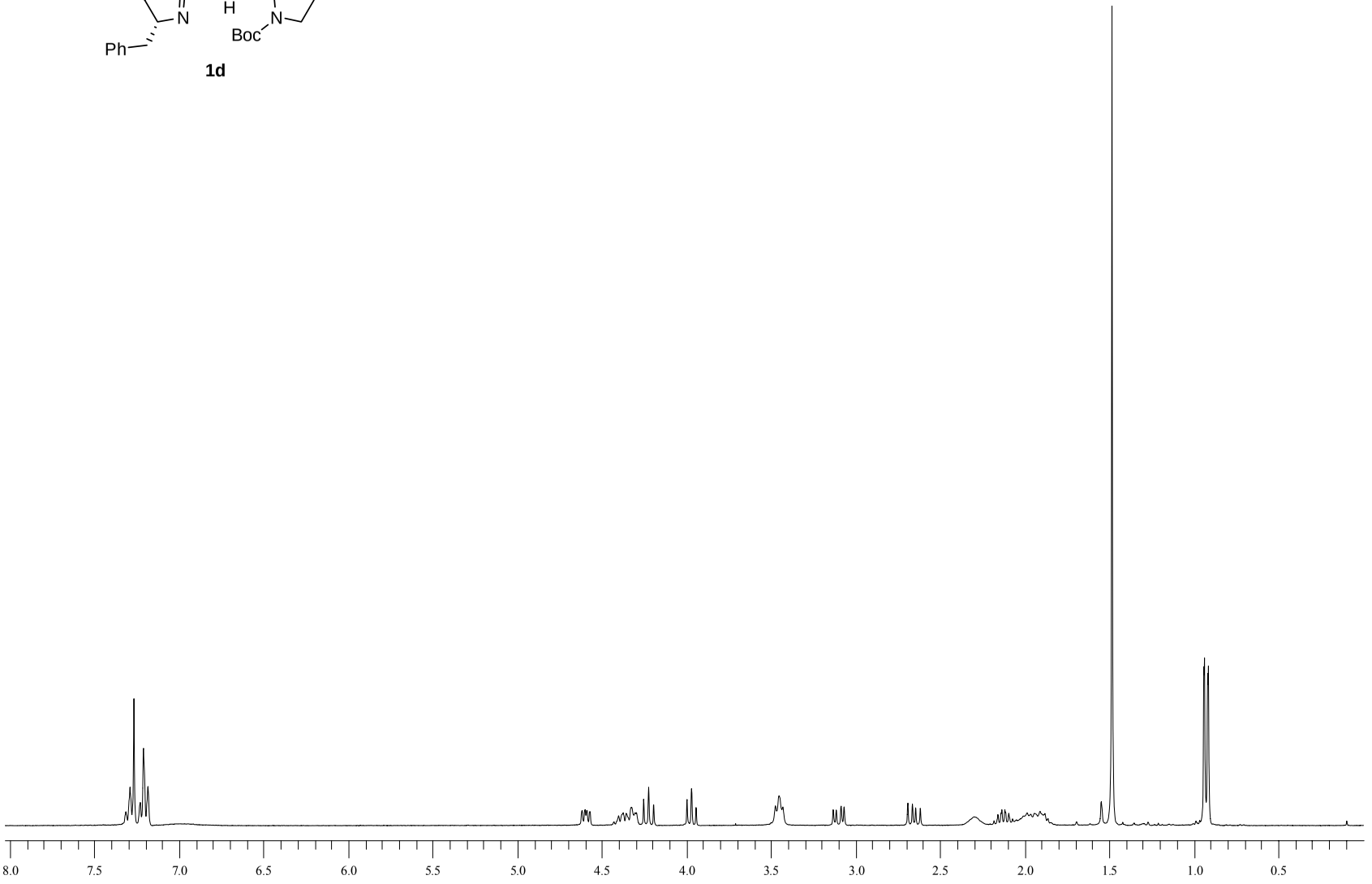


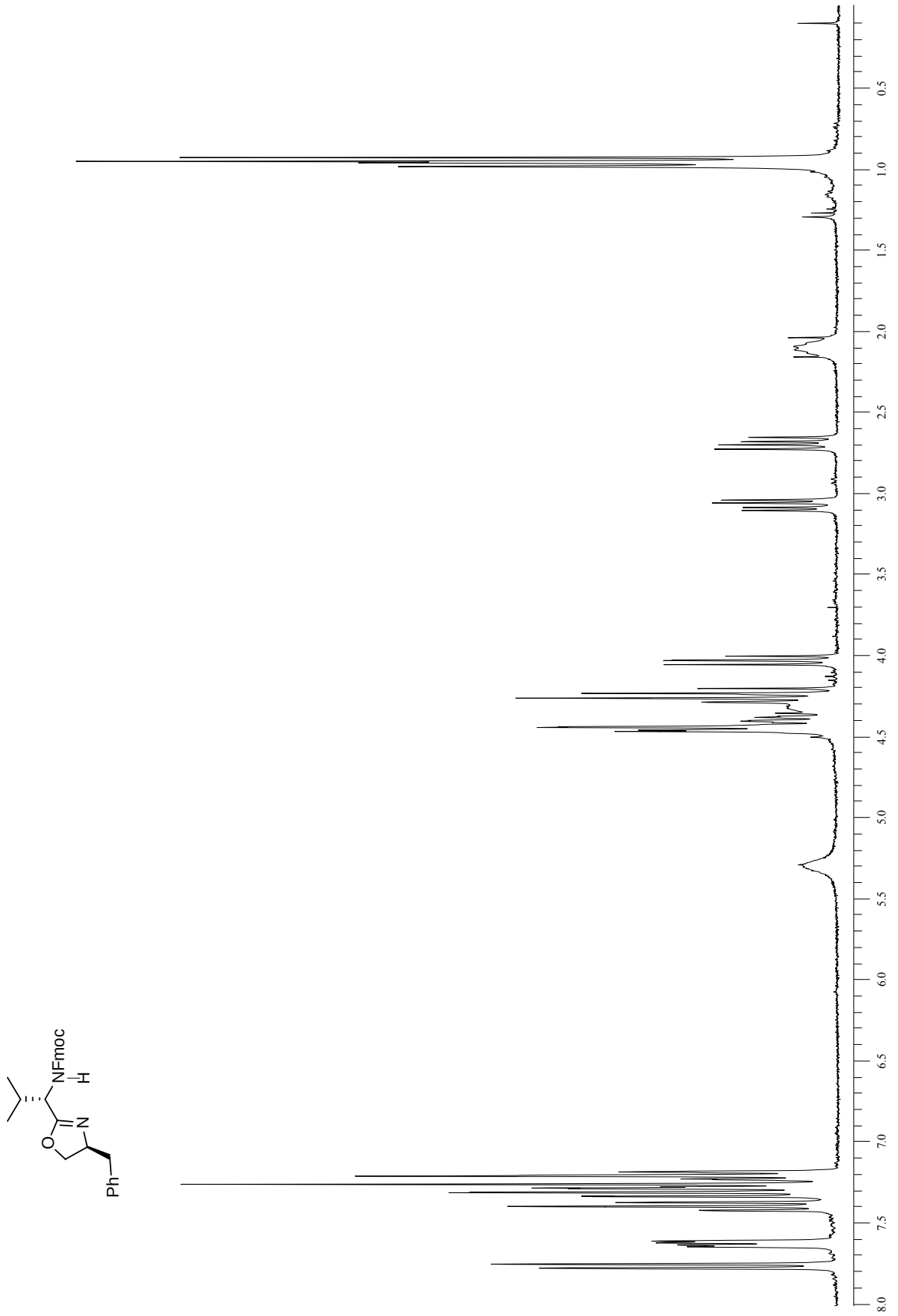


1c



1d




NFmoc
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Ph
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7.0
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6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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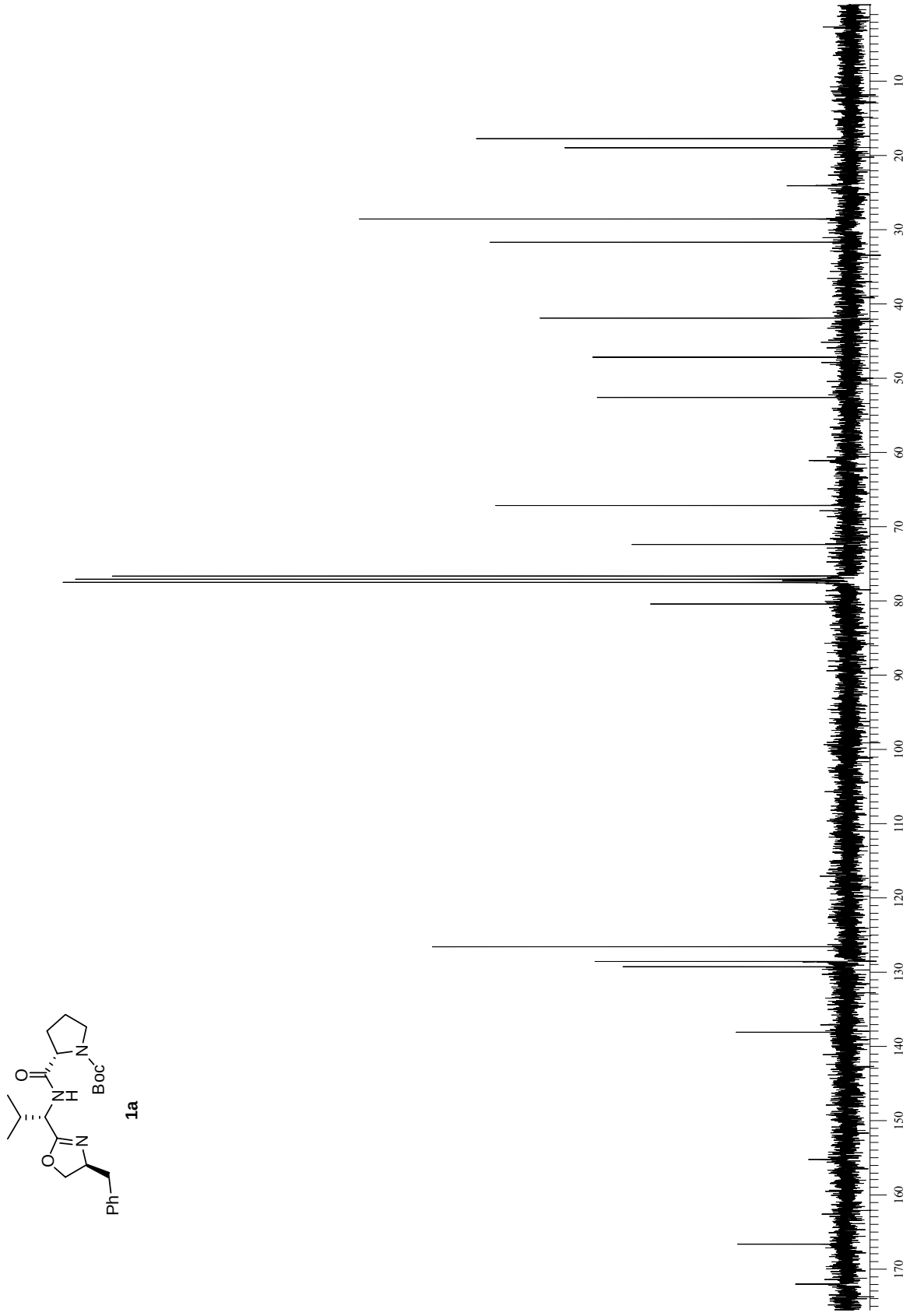
0.5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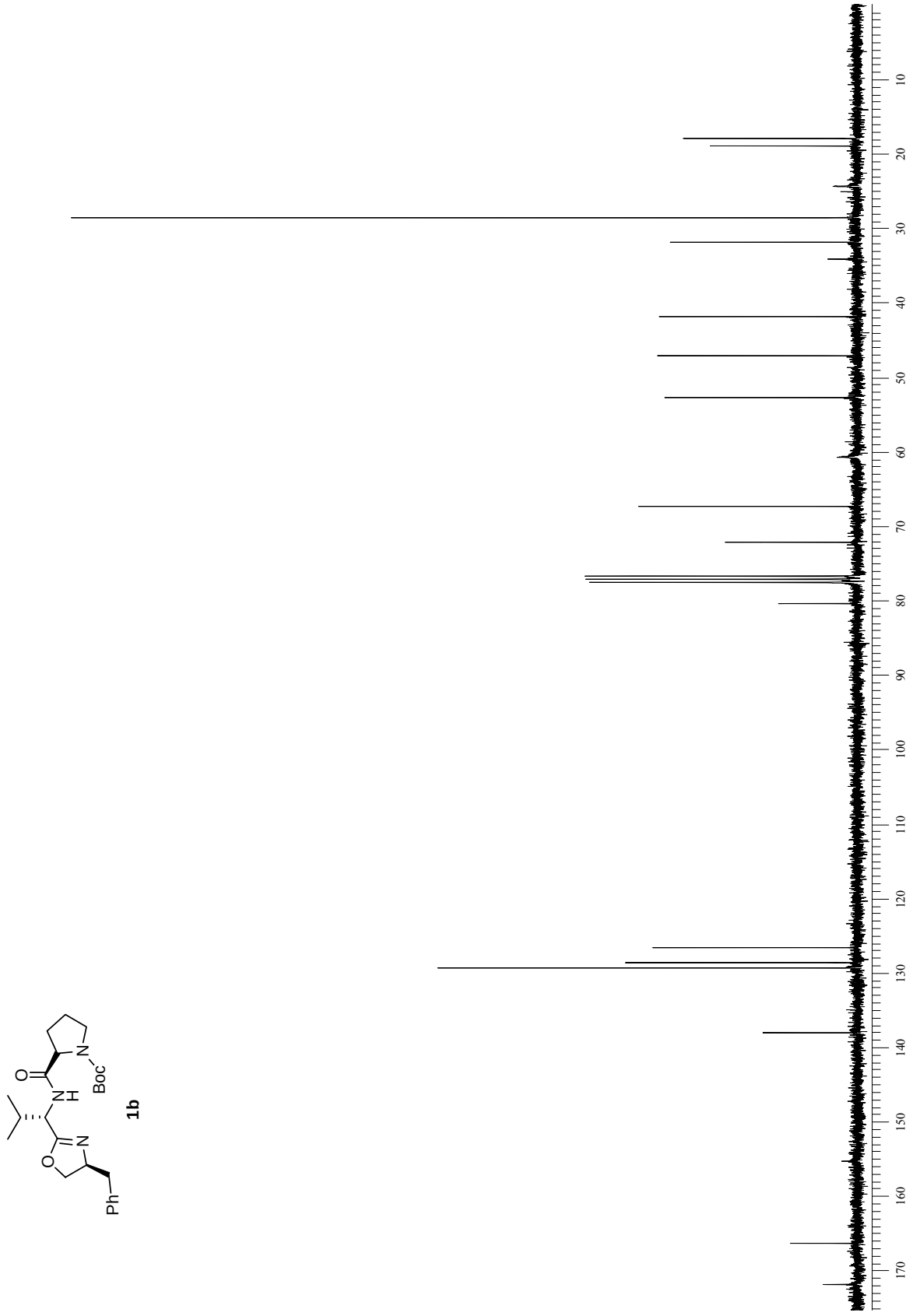
170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Boc
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Ph
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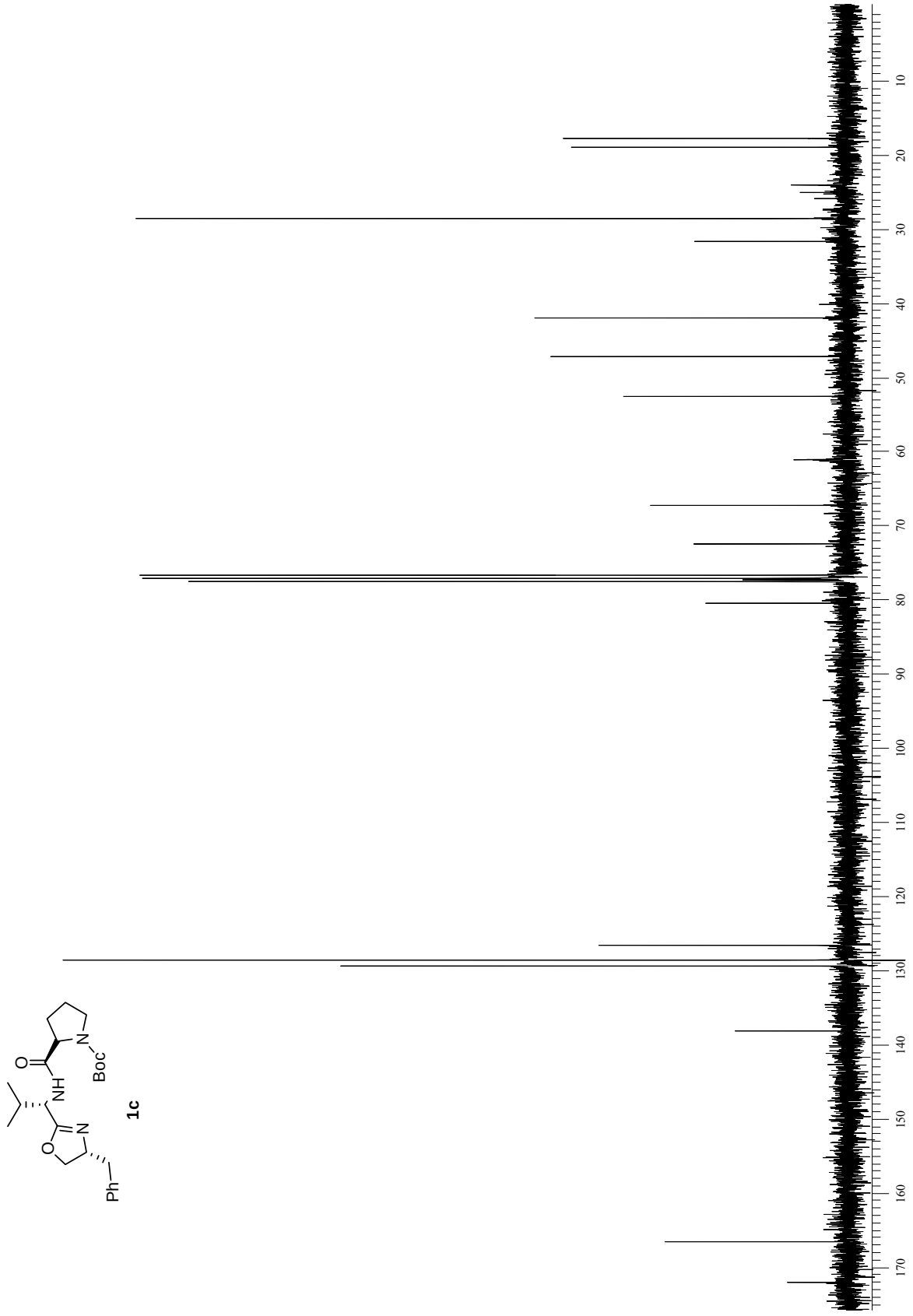
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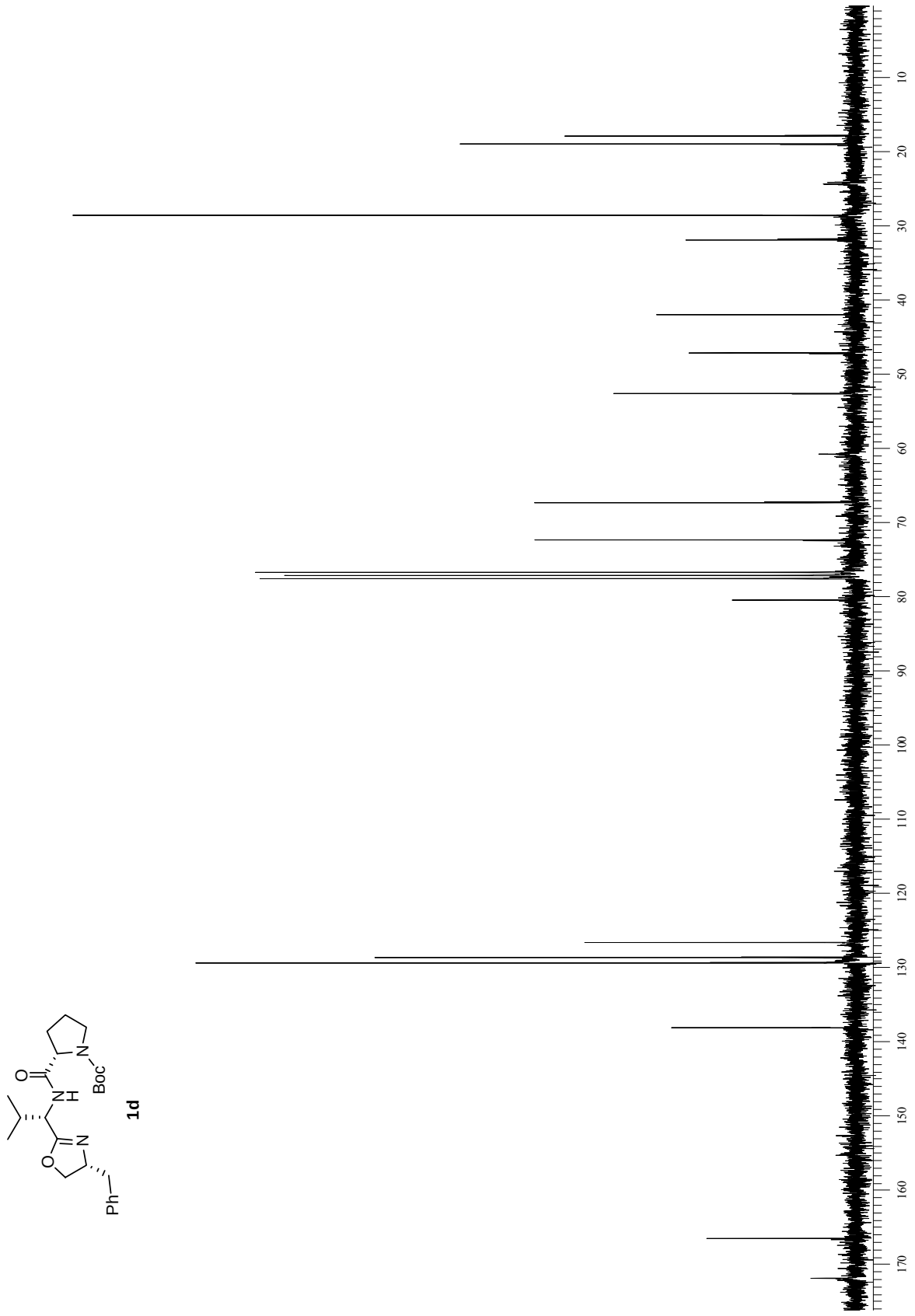
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Boc
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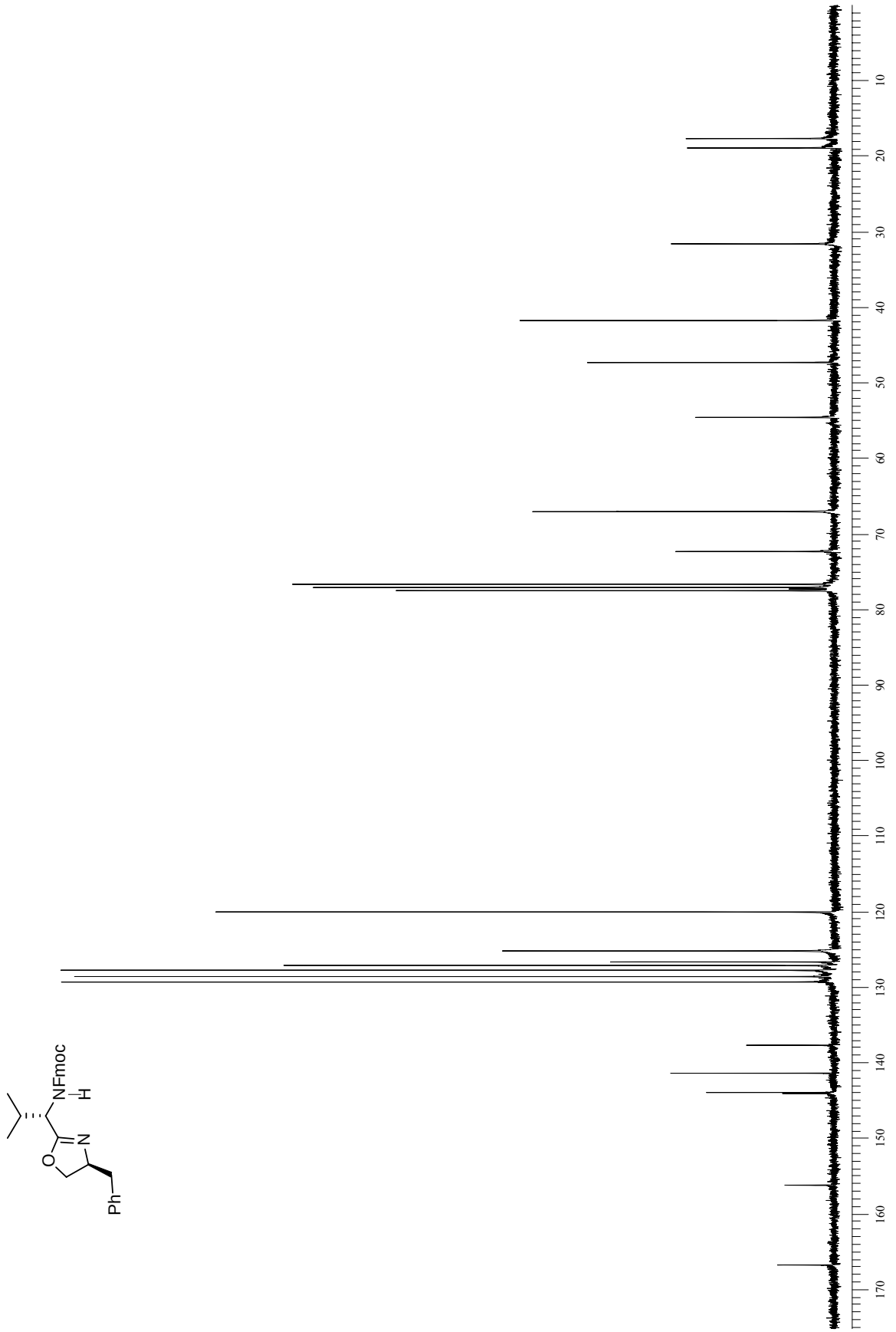
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Ph
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