Readily Available Phosphine-Phosphoramidite Ligands for Highly Efficient Rh-Catalyzed Enantioselective Hydrogenations

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General Information

All reactions were conducted under a nitrogen or argon atmosphere unless otherwise noted. Anhydrous procedures were conducted using oven dried or flame dried glassware and standard syringe and cannula transfer techniques. To eliminate the influence of environmental factors such as air and humidity in the catalytic reaction, hydrogenation reaction was carried out in glove-box by use of a stainless steel autoclave. Solvents were of reagent grade, dried and distilled before use following standard procedures. BINOL-based chlorophosphite **5** was synthesized according to the literature method¹. α -Dehydroamino acid esters **6a-e**², and enamides **8a-g**³ were known compounds, which were synthesized according to the literature procedure. All other chemicals were obtained commercially. Optical rotations were recorded on a polarimeter at ambient temperature (c = g/100 mL). ¹H, ¹³C and ³¹P NMR spectra were recorded on a 400 MHz instrument using CDCl₃ as the solvent. Enantiomeric excesses were determined by capillary GC analysis with a chiral column.

Synthesis of (S)-1-[2-(diphenylphosphino)phenyl]ethylamine [(S)-DPPNH₂] 3

To a solution of (S)- α -phenylethylamine 2 (1.21 g, 10.0 mmol) in 10 mL of ether at -35 °C was dropwise added 4.0 mL (10.0 mmol) of a 2.5M solution of *n*-BuLi in hexanes. The resulting solution was stirred at -35 °C for 15 minutes, and then 1.39 mL (11.0 mmol, 1.1equiv) of Me₃SiCl was added slowly at the same temperature. The reaction mixture was stirred for 1 hour and then 12.0 mL (30.0 mmol, 3 equiv) of a 2.5M solution of *n*-BuLi was added dropwise. After the addition was completed, the reaction mixture was stirred at -35 °C for 3 h. The reaction mixture was slowly warm to room temperature and stirred overnight. The reaction mixture was cooled to -35 °C again, and a solution of 1.80 mL (10.0 mmol) of chlorodiphenylphosphine in 10 mL of ether was added dropwise during 1 hour. The reaction mixture was stirred for another 3 hours at the same temperature, and then warmed to room temperature. After stirring for another 4 hours, a solution of 1M aqueous HCl was added slowly until the reaction mixture became clear in both phases. The aqueous phase was extracted with ether (3×10 mL). Combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes / acetate, 8 / 1) to give 1.22 g (40% yield) of the targeted (S)-DPPNH₂ **3** as a white solid; mp 80~82 ; $[\alpha]_D^{13} = -56.7$ (c 0.53, CHCl₃); ¹H NMR $(CDCl_3)$: § 1.23 (d, J = 6.8 Hz, 3H), 1.38 (s, 2H), 4.90 (m, 1H), 6.83-7.59 (m, 14H); ³¹P NMR (CDCl_3): . δ -16.3; ¹³C NMR δ 24.3, 47.5, 124.8, 126.5, 128.1, 128.3, 129.0, 132.8, 133.2, 133.4, 136.1, 136.2, 136.5, 136.6, 151.3, 151.5; HRMS (m/z) calcd for $C_{20}H_{20}NP + H$: 306.1412, found: 306.1406.

Synthesis of (S)-N-methyl-1-[2-(diphenylphosphino)phenyl]ethylamine[(S)-DPPNHMe] 4

A mixture of (S)-DPPNH₂ **3** (1.22 g, 4 mmol) and ethyl formate (1.45 mL) was stirred at 45~50 $^{\circ}$ C overnight, and then volatile component was removed under reduced pressure to give the crude product, which did not need purification and used directly for next step.

In a 100 ml freshly oven-dried three-necked flask placed 0.27 g of LiAlH₄ and 10 mL of THF was slowly added a solution of above-mentioned crude product in 10 mL of THF under nitrogen atmosphere. The reaction mixture was refluxed for 5 hours, and then cooled to 0 °C by ice-bath. 10% KOH aqueous solution (5 mL) was added slowly. The reaction mixture was filtered and the solid was thoroughly washed with THF. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexanes / acetate, 10 / 1) to give 0.66 g (52% yield) of the targeted (*S*)-DPPNHMe **4** as a white solid; mp 81~83 °C; $[\alpha]_D^{23} = -57.1$ (c 0.48, CHCl₃); ¹H NMR (CDCl₃): δ 1.19-1.22 (d, *J* = 12 Hz, 3H), 2.14(s, 3H), 4.46-4.51 (m, 1H), 6.84-7.53 (m, 14H); ³¹P NMR (CDCl₃): δ - 16.5; ¹³C NMR δ 23.2, 34.2, 56.6, 125.8, 125.9, 126.9, 128.5, 128.6, 128.7, 129.4, 133.4, 133.8, 134.0, 134.2, 135.2, 136.7, 136.8, 137.0, 137.1, 149.8, 150.0; HRMS (m/z) calcd for C₂₁H₂₂NP: 319.1490, found: 319.1492.

General Procedure for the Synthesis of phosphine-phosphoramidite derivatives PEAPhos 1

(*R*)-Chlorophosphite **5** (350.5 mg, 1.0 mmol) was dissolved in 4.0 mL of dried toluene, which was cooled to 0 °C. A solution of (*S*)-DPPNH₂ **3** or (*S*)-DPPNHMe **4** (1.0 mmol) and Et₃N (303 mg, 3.0 mmol) in 4.0 mL of toluene was added to above solution during 30 min. The resulting mixture was left standing at room temperature overnight. The precipitate was filtered, and the solid was washed with toluene (5 mL x 1). The filtrate was collected, and concentrated under reduced pressure. The residue was purified by column chromatography to give the crude product, which can be further purified by crystallizing from hexane/dichloromethane.

N-{(*S*)-1-[2-(diphenylphosphino)phenyl]ethyl}-(*R*)-1,10-bi-2-naphthylphosphoramidite (*S_c*,*R_a*)-**PEAPhos 1a**: white solids; mp 107~109 °C; $[\alpha]_D^{24} = -87.0$ (c 1.02, CHCl₃); ¹H NMR (CDCl₃): § 1.33-1.35 (d, *J* = 6.8 Hz, 3H), 3.68-3.75 (m, 1H), 5.37-5.45(m, 1H), 6.71-7.92 (m, 26H); ³¹P NMR (CDCl₃); § -18.0, 152.7; ¹³C NMR § 25.6, 48.4, 122.5, 124.7, 125.9, 126.0, 126.9, 127.0, 128.2, 128.3, 128.5, 128.6, 128.7, 129.6, 133.6, 133.8, 133.9, 134.0, 134.1, 136.8, 147.4, 149.4, 150.8; HRMS (m/z) calcd for C₄₀H₃₁NO₂P₂: 619.1830, found: 619.1835.

N-methyl-*N*-{(*S*)-1-[2-(diphenylphosphino)phenyl]ethyl}-(*R*)-1,10-bi-2-naphthylphosphoramidite

(*S_c*,*R_a*)-**PEAPhos 1b**: white solids; mp 174~176 °C; $[\alpha]_D^{24} = -122.9$ (c 1.01, CHCl₃); ¹H NMR (CDCl₃): δ 1.60-1.62 (d, *J* = 9.88 Hz, 3H), 1.99 (s, 3H), 5.40-5.44 (m, 1H), 7.03-7.94 (m, 26H); ³¹P NMR (CDCl₃); δ -18.4, 148.4; ¹³C NMR δ 21.6, 30.5, 56.6, 122.1, 124.4, 125.96, 125.99, 126.9, 127.0, 128.1, 128.3, 128.5, 128.6, 128.7, 129.3, 129.9, 130.1, 133.7, 133.9, 134.0, 136.9, 147.8, 149.8, 150.5; HRMS (m/z) calcd for C₄₁H₃₃NO₂P₂: 633.1987, found: 633.1981.

N-{(*S*)-1-[2-(diphenylphosphino)phenyl]ethyl}-(*S*)-1,10-bi-2-naphthylphosphoramidite (*S_c*,*S_a*)-**PEAPhos 1c**: white solids; mp 108~110 °C; $[\alpha]_D^{24} = 56.5$ (c 0.44, CHCl₃); ¹H NMR (CDCl₃): δ 1.22-1.26 (d, *J* = 14 Hz, 3H), 3.46-3.49 (m, 1H), 5.44 (m, 1H), 6.92-7.92 (m, 26 H); ³¹P NMR (CDCl₃): δ -16.9, 153.9; ¹³C NMR δ 26.0, 48.5, 122.6, 124.7, 126.0, 126.9, 127.0, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.6, 133.7, 133.92, 134.0, 134.1, 147.2, 149.4, 150.3; HRMS (m/z) calcd for C₄₀H₃₁NO₂P₂: 619.1830, found: 619.1825.

N-methyl-*N*-{(*S*)-1-[2-(diphenylphosphino)phenyl]ethyl}-(*S*)-1,10-bi-2-naphthylphosphoramidite

(*S_c*,*S_a*)-**PEAPhos 1d**: white solids; mp 206~208 °C; $[\alpha]_D^{24} = 195.7$ (c 0.58, CHCl₃); ¹H NMR (CDCl₃): δ 1.66-1.69 (d, *J* = 9.8 Hz, 3H), 1.87 (s, 3H), 5.42 (m, 1H), 6.99-7.91 (m, 26H); ³¹P NMR (CDCl₃); δ -17.8, 147.6; ¹³C NMR δ 21.6, 30.1, 56.7, 124.4, 125.9, 127.00, 127.06, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 130.1, 133.7, 133.9, 134.0, 147.4, 149.7, 150.7; HRMS (m/z) calcd for C₄₁H₃₃NO₂P₂: 633.1987, found: 633.1992.

General procedure for asymmetric hydrogenation

In a nitrogen-filled glovebox, a stainless steel autoclave was charged with $Rh(COD)_2BF_4$ (2.0 mg, 0.5 x 10^{-2} mmol) and PEAPhos **1** (0.55 x 10^{-2} mmol) in 1.5 mL of a degassed CH_2Cl_2 . After stirring for 10 min at room temperature. A substrate (0.5 mmol) in 1.5 mL of the same solvents was added to the reaction mixture, and then the hydrogenation was performed at room temperature under an H₂ pressure of 10 bar for 12 hours. The reaction mixture was passed through a short silica gel column to remove the catalyst. After evaporating the solvent, the crude reaction mixture was subjected to GC to determine the enantiomeric excesses and yields of hydrogenation products.

Determination of Enantiomeric Excesses for α -amino acid esters 7a-e:

Chiral Capillary GC Column. CP-Chiralsil-L-Val column ($25m \ge 0.25mm \ge 0.12 \ \mu m$). Carrier gas: N₂. The racemic products were obtained by hydrogenation of substrates with an achiral catalyst prepared from PPh₃ and Rh(COD)₂BF₄. The following are the retention times for the racemic products.

Methyl 2-Acetamido-3-phenylpropanoate (7a): (capillary GC, CP-Chiralsil-L–Val column, 160 °C, 20 psi) t(R) = 8.59, t(S) = 9.45.

Methyl 2-Acetamido-3-(2-chlorophenyl)propanoate (7b): (capillary GC, CP-Chiralsil-L–Val column, $160 \,^{\circ}$ C, 20 psi) t(R) = 16.45, t(S) = 18.32.

Methyl 2-Acetamido-3-(4-chlorophenyl)propanoate (7c): (capillary GC, CP-Chiralsil-L–Val column, $160 \,^{\circ}$ C, 20 psi) t(R) = 22.67, t(S) = 25.95.

Methyl 2-Acetamido-3-(2-methoxyphenyl)propanoate (7d): (capillary GC, CP-Chiralsil-L–Val column, 160 °C, 20 psi) t(R) = 16.79, t(S) = 18.54.

Methyl 2-Acetamido-3-(4-methoxyphenyl)propanoate (7e): (capillary GC, CP-Chiralsil-L–Valcolumn, 160 $^{\circ}$ C, 20 psi) t(R) = 23.19, t(S) = 25.81.

Determination of Enantiomeric Excesses for N-Acetyl-1-Arylethylamine 9a-g:

Chiral Capillary GC Column. Chiral Select-1000 column (dimensions 30 m x 0.25 mm(i.d.)). Carrier gas: N_2 . The racemic products were obtained by hydrogenation of substrates with an achiral catalyst prepared from PPh₃ and Rh(COD)₂BF₄. The following are the retention times for the racemic products.

N-Acetyl-1-phenylethylamine (9a): (capillary GC, Chiral Select-1000 column, 130 °C, 10psi) t(S) = 21.44, t(R) = 23.38.

N-Acetyl-1-(4-methylphenyl)ethylamine (9b): (capillary GC, Chiral Select-1000 column, 130 °C, 15 psi) t(S) = 25.12, t(R) = 26.97.

N-Acetyl-1-(4-trifluoromethyl)ethylamine (9c): (capillary GC, Chiral Select-1000 column, 130 °C, 15 psi) t(S) = 22.70, t(R) = 25.06.

N-Acetyl-1-(4-bromophenyl)ethylamine (9d): (capillary GC, Chiral Select-1000 column, 140 °C, 15 psi) t(S) = 62.43, t(R) = 66.18.

N-Acetyl-1-(4-chlorophenyl)ethylamine (9e): (capillary GC, Chiral Select-1000 column, 140 °C, 10 psi) t(S) = 51.15, t(R) = 54.35.

N-Acetyl-1-(4-methoxyphenyl)ethylamine (9f): (capillary GC, Chiral Select-1000 column, 140 °C, 10 psi) t(S) = 58.02, t(R) = 60.98.

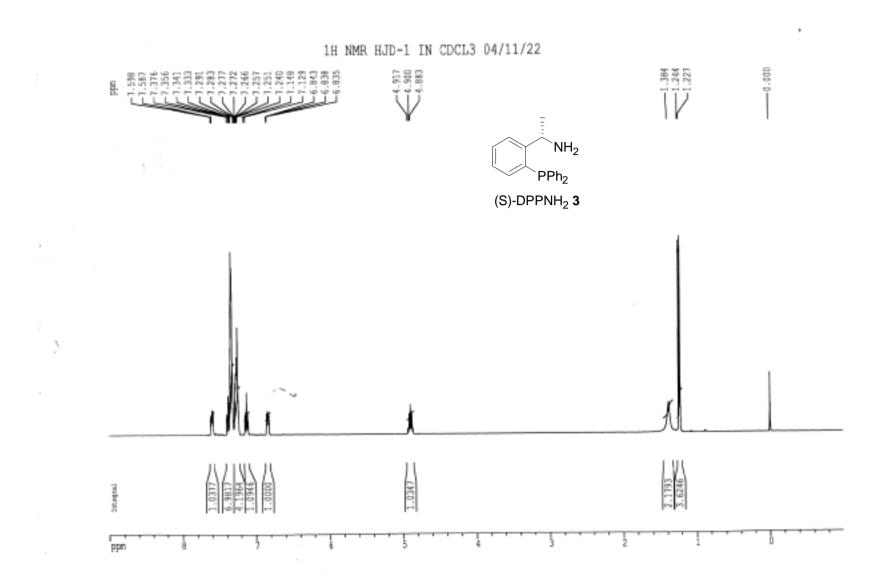
N-Acetyl-1-(3-methoxyphenyl)ethylamine (9g): (capillary GC, Chiral Select-1000 column, 130 °C, 10psi) t(*S*) = 78.30, t(*R*) = 83.16.

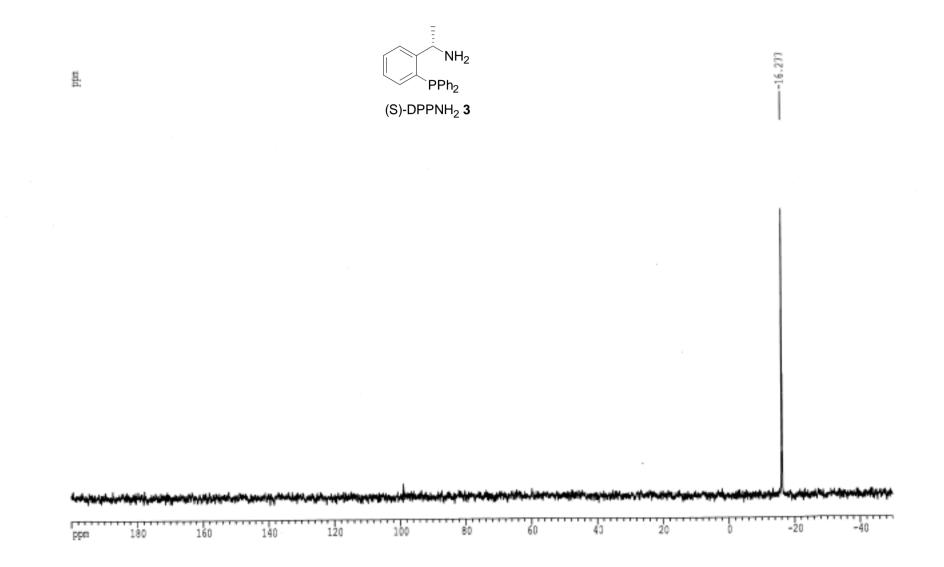
References and Notes

1. Franciò, G.; Arena, C. G.; Faraone, F.; Graiff, C.; Lanfranchi, M.; Tiripicchio, A. *Eur.J. Inorg. Chem.* **1999**, 1219.

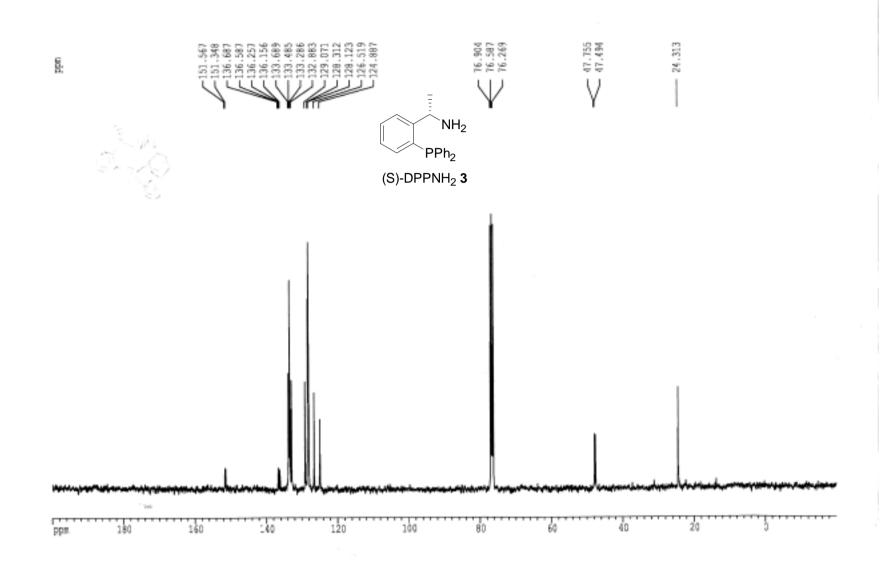
2. Blott, A. H. Org. Syn., Coll. Vol. 1950, p1

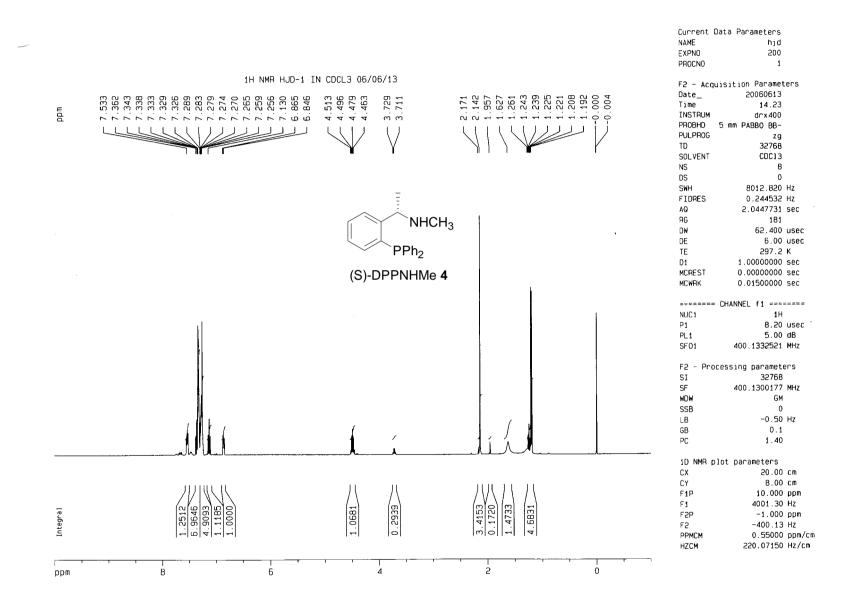
3. (a) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, J. G.; Feringa, B. L. J. *Am. Chem. Soc.* **2000**, *122*, 11539. (b) Burk, M. J.; Casy, G.; Johnson, N. B. J. Org. Chem. **1998**, *63*, 6084.



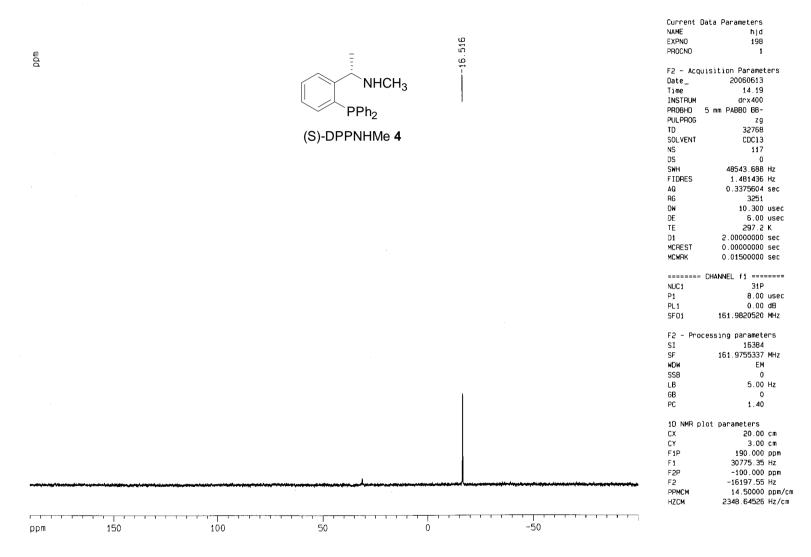


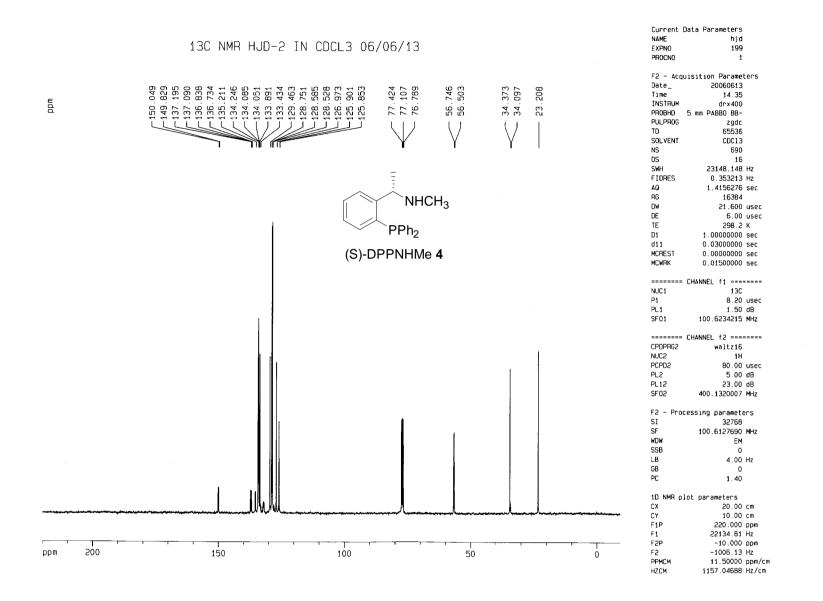
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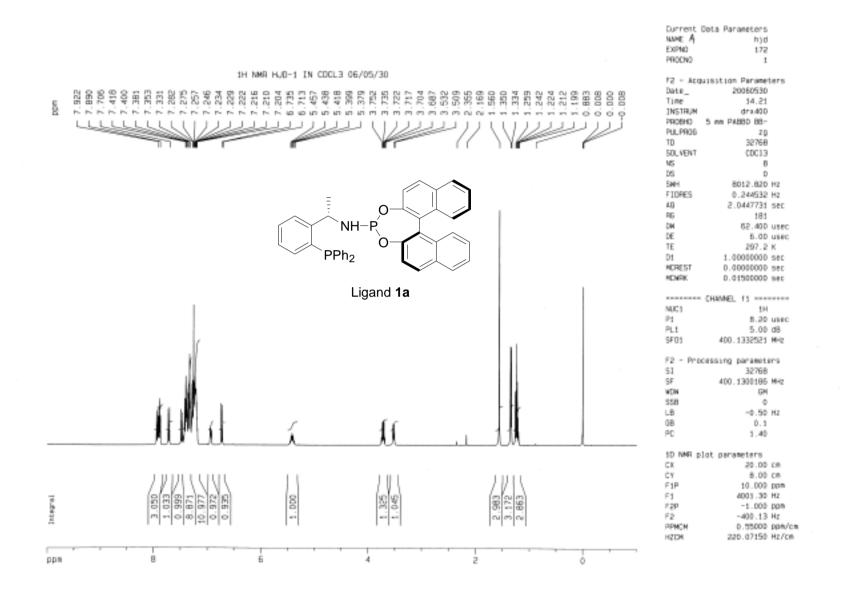


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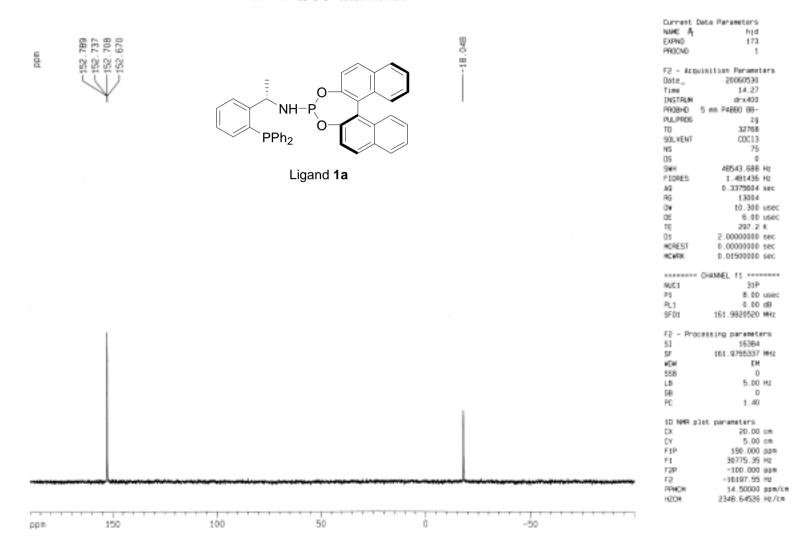


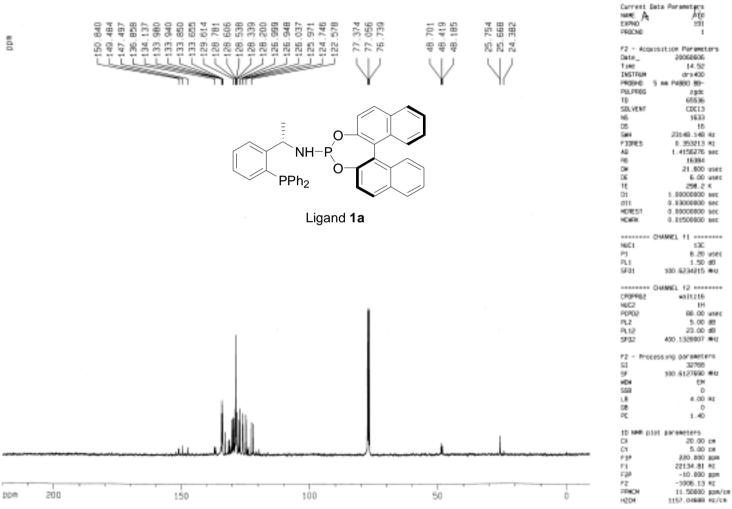


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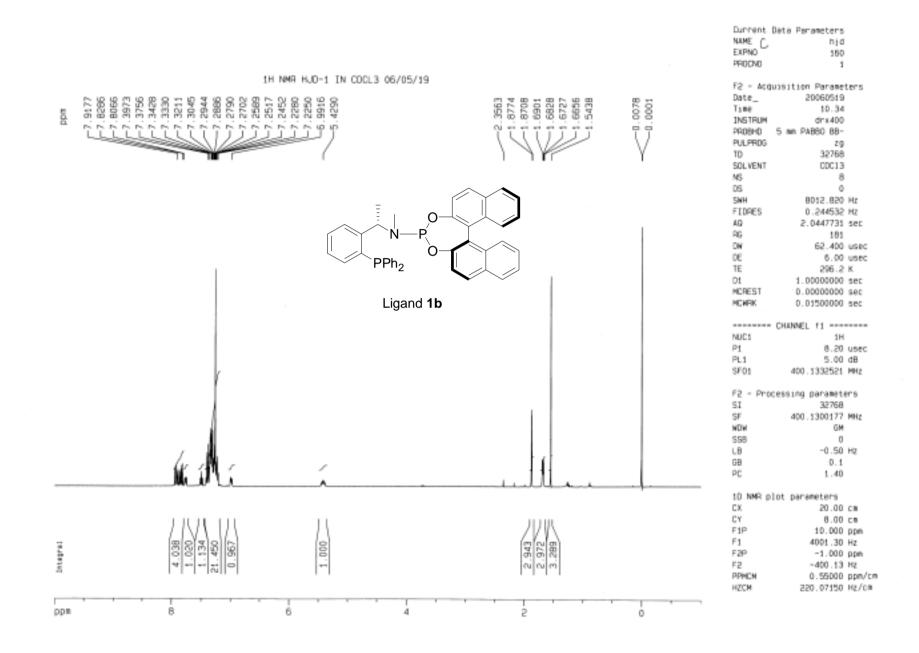




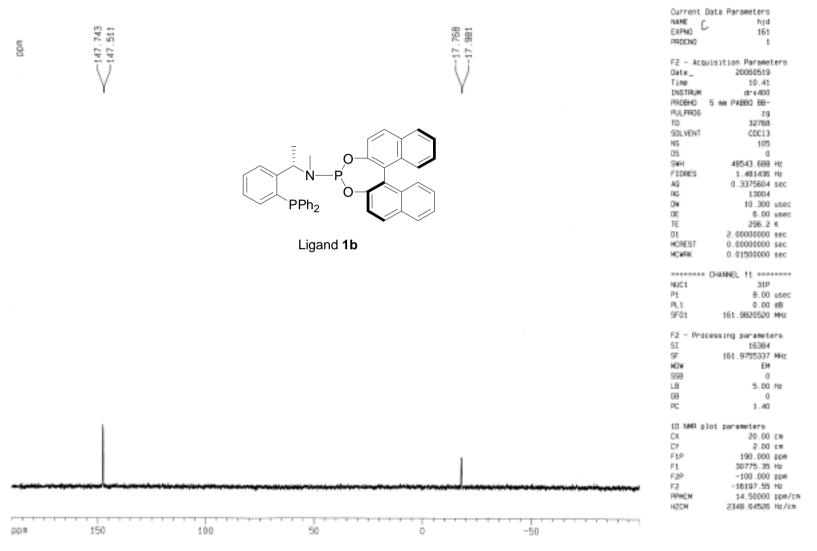


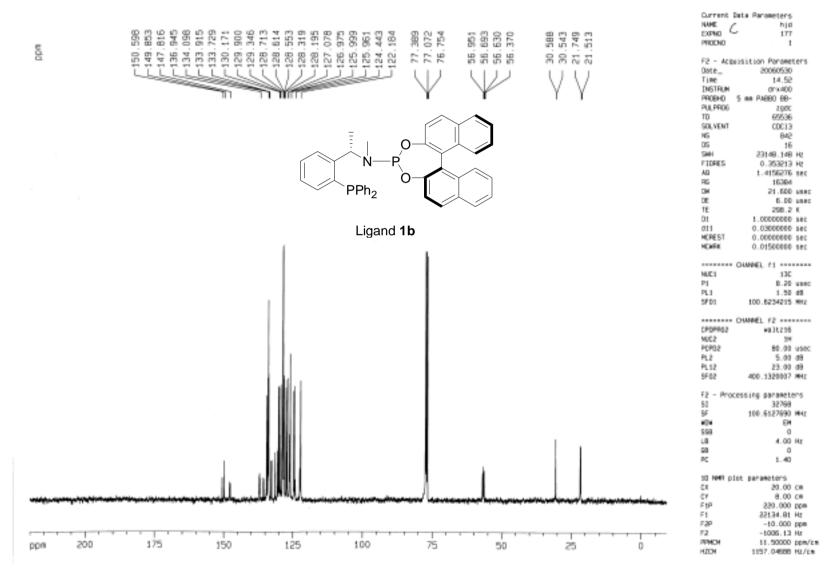


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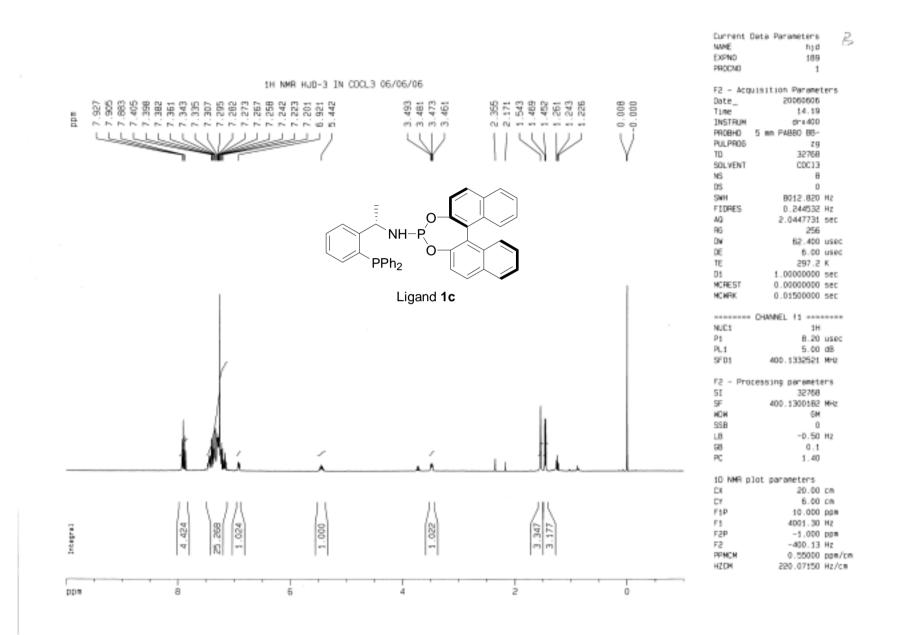






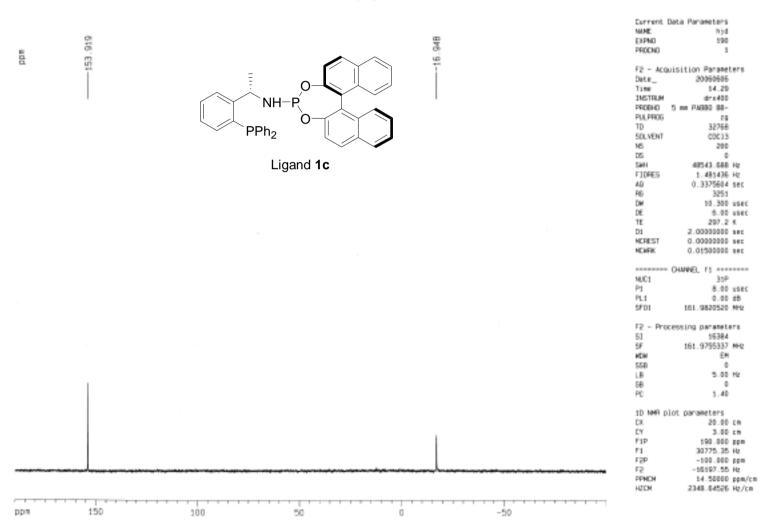


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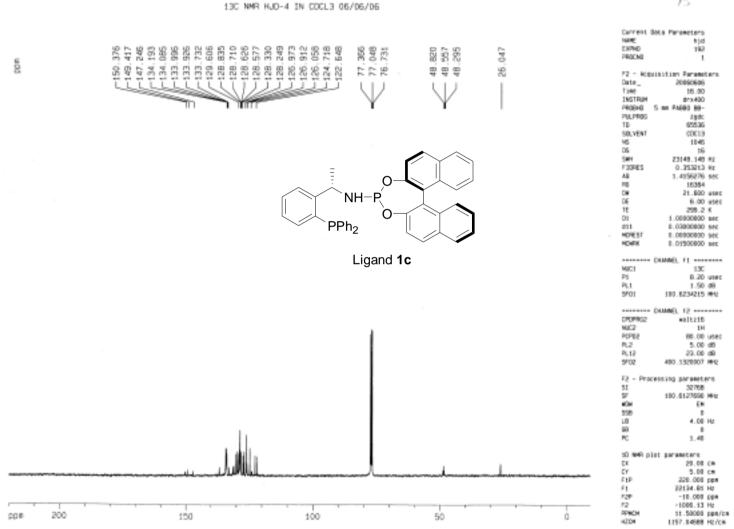


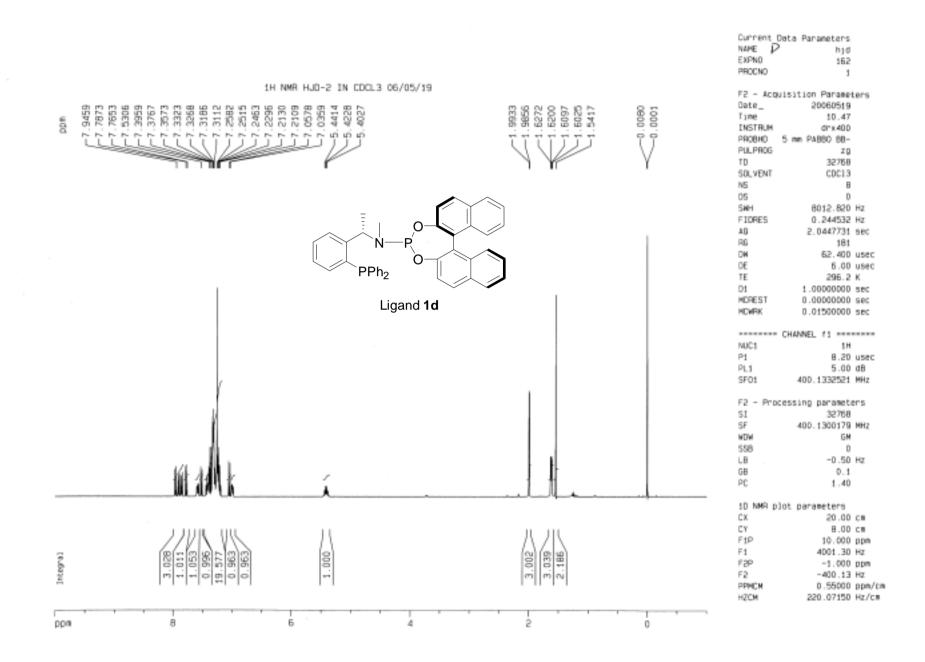
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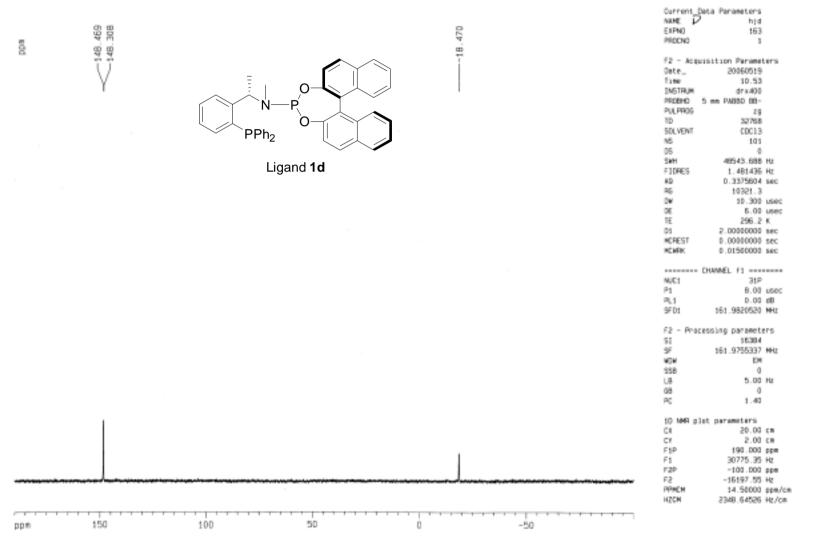
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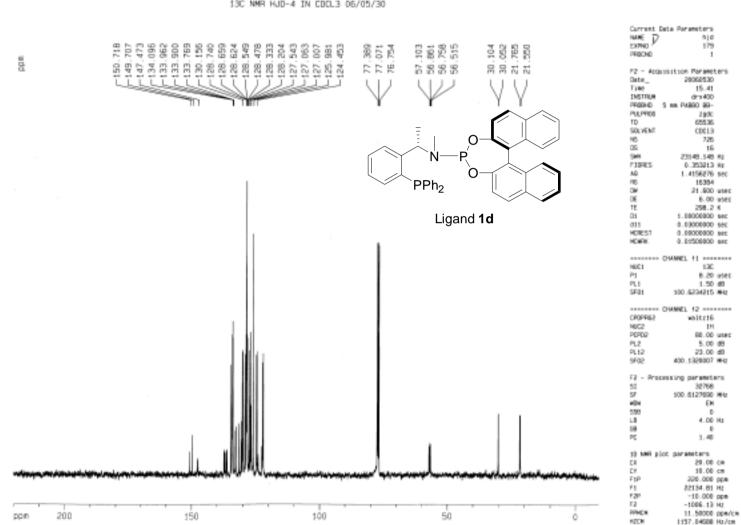
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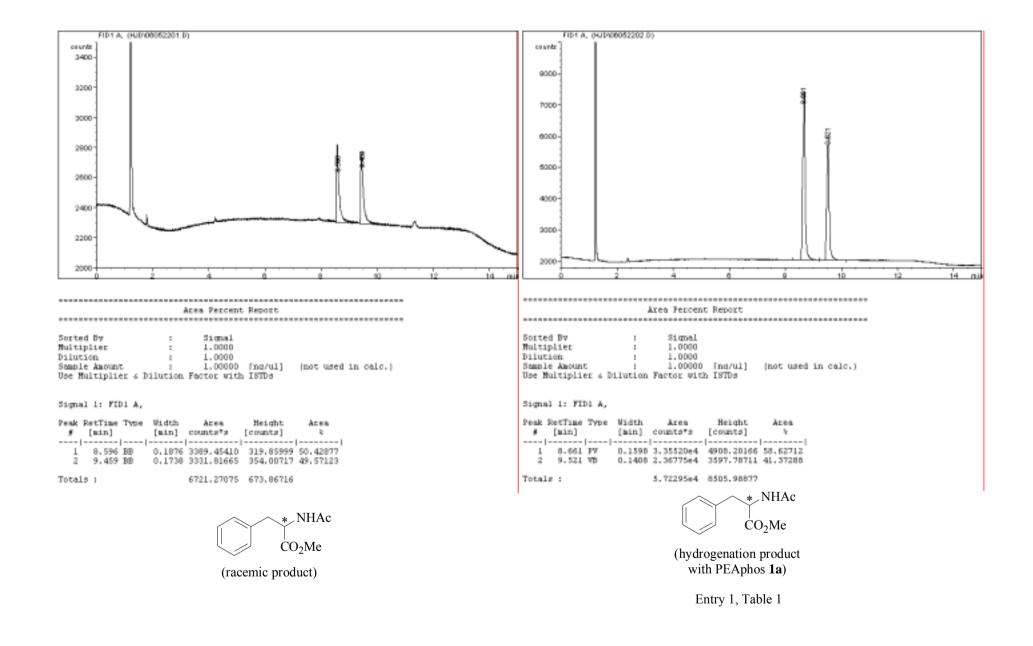


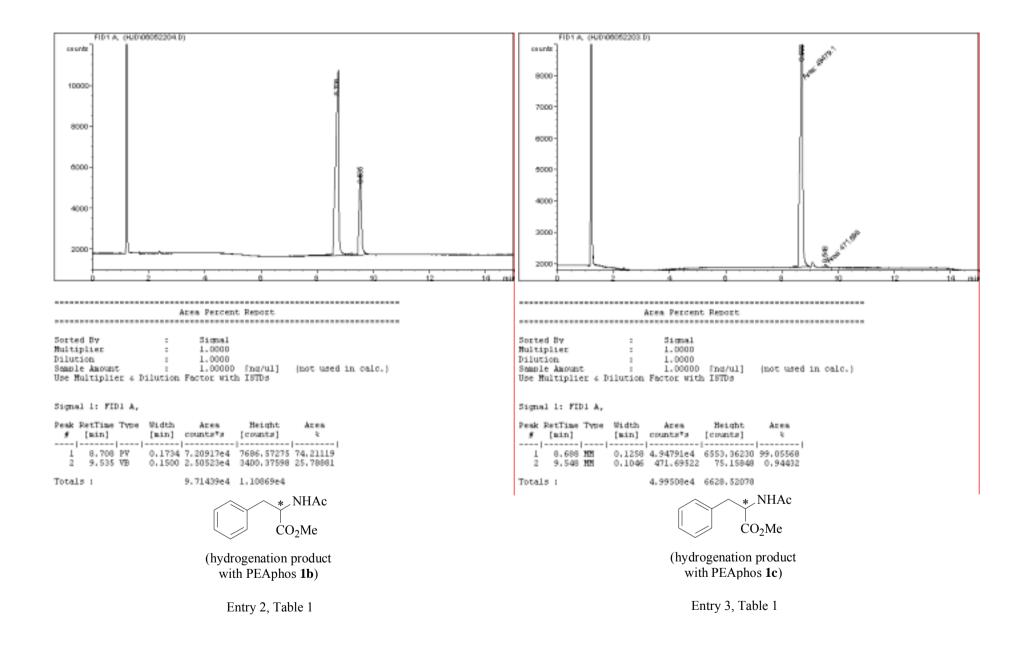
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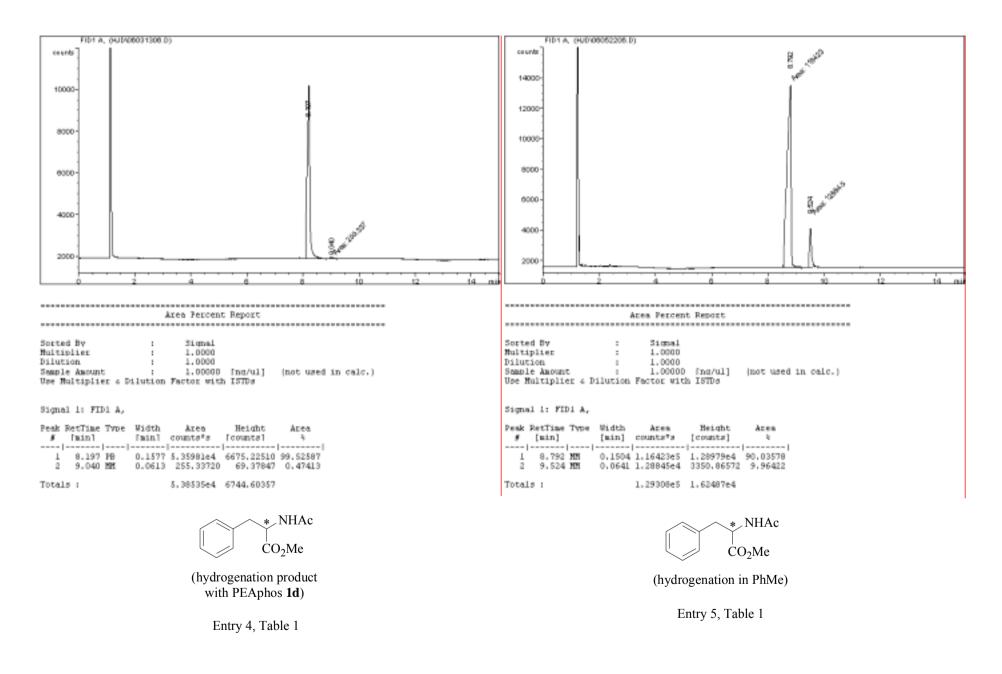


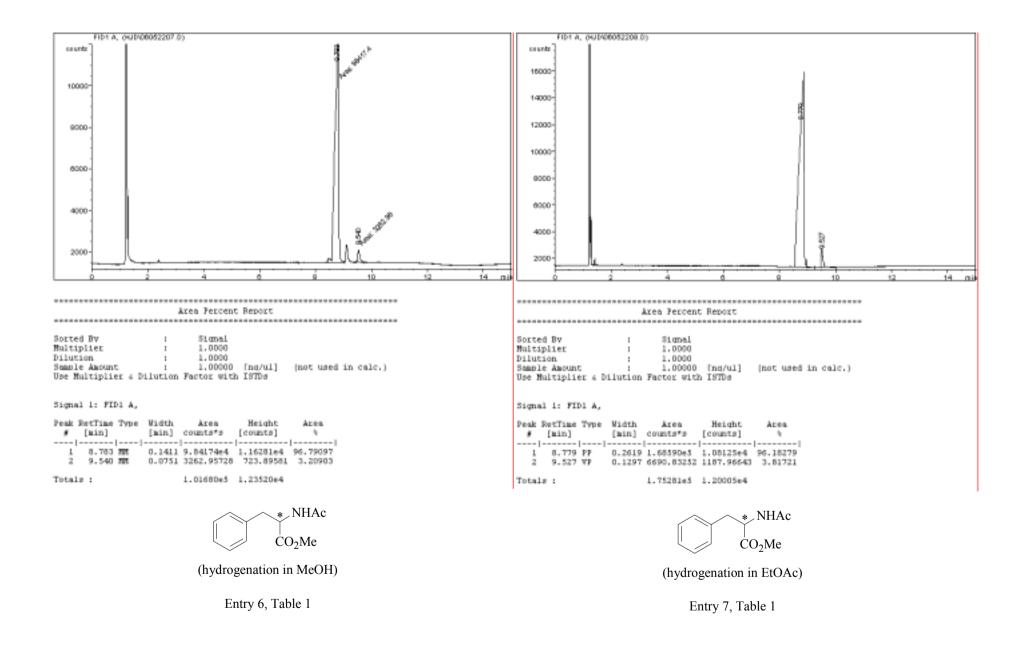


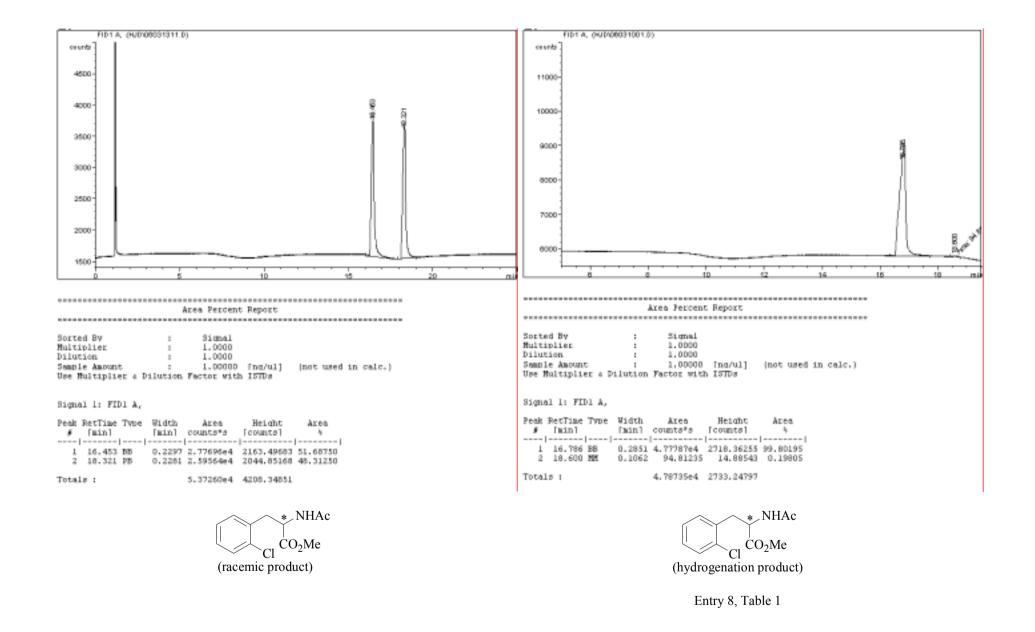
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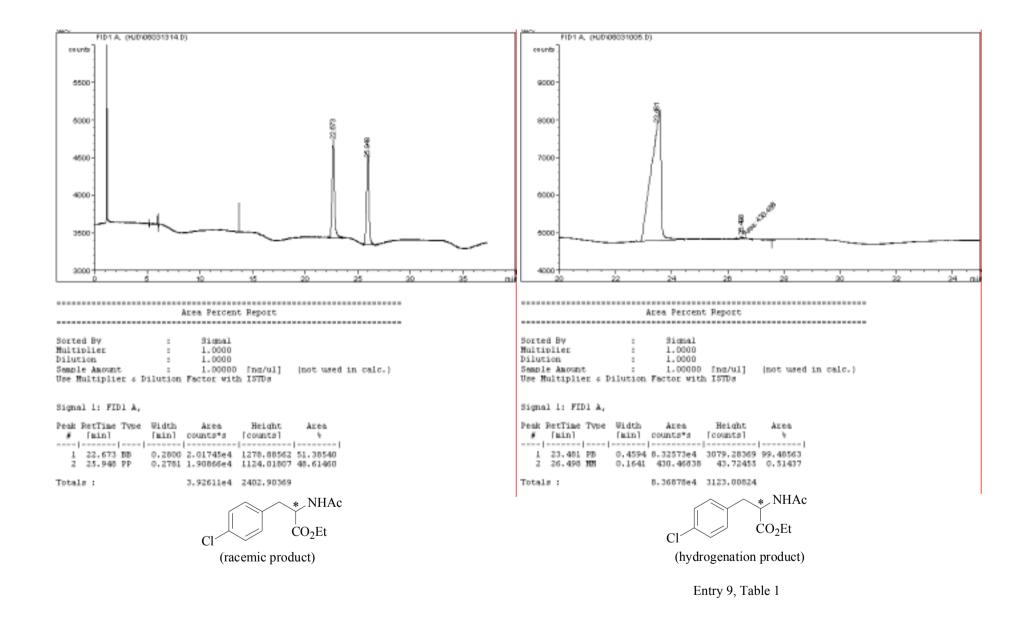


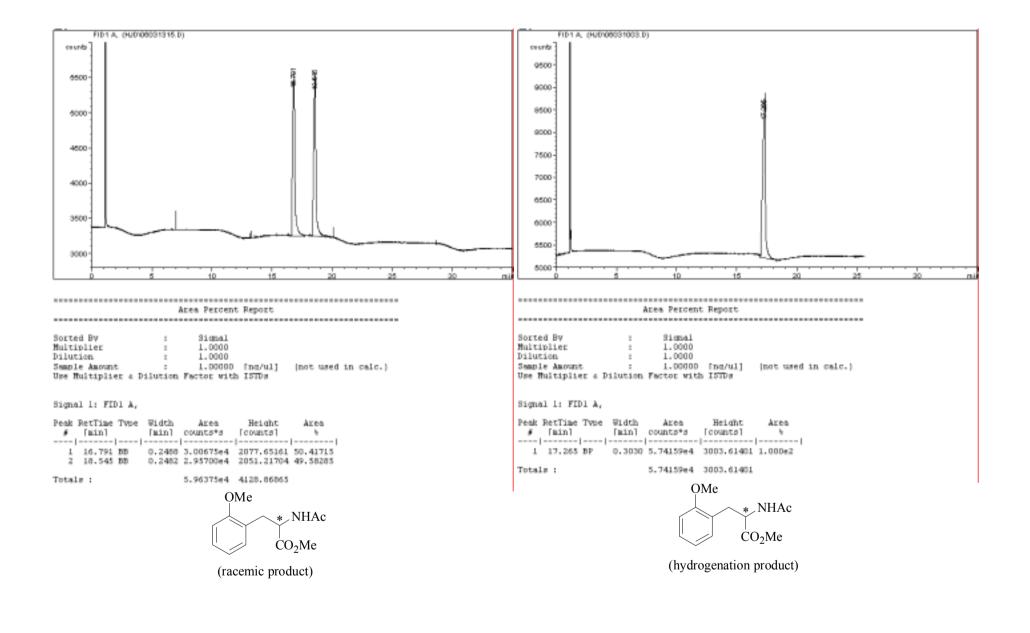


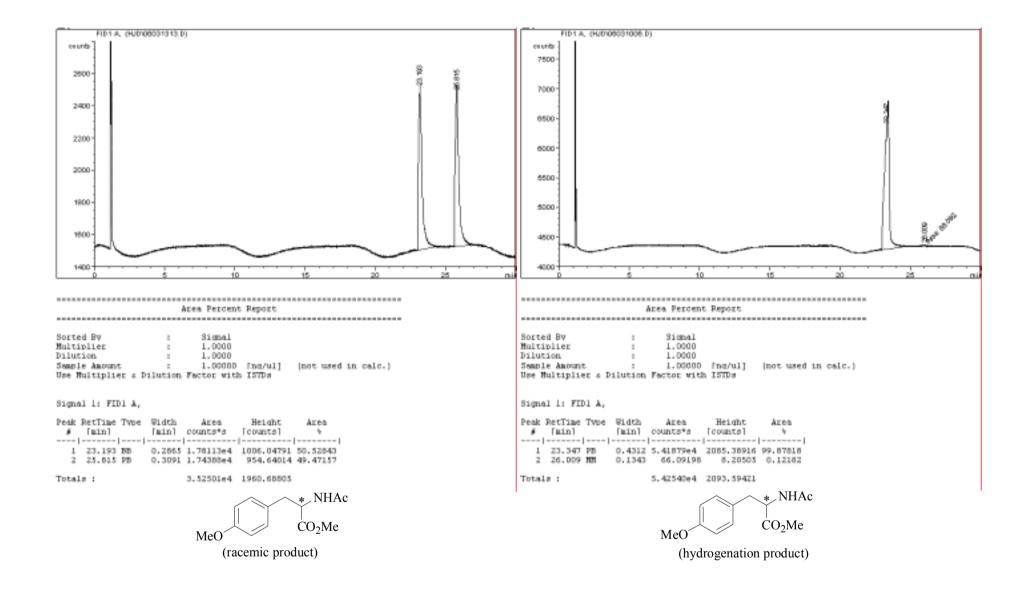


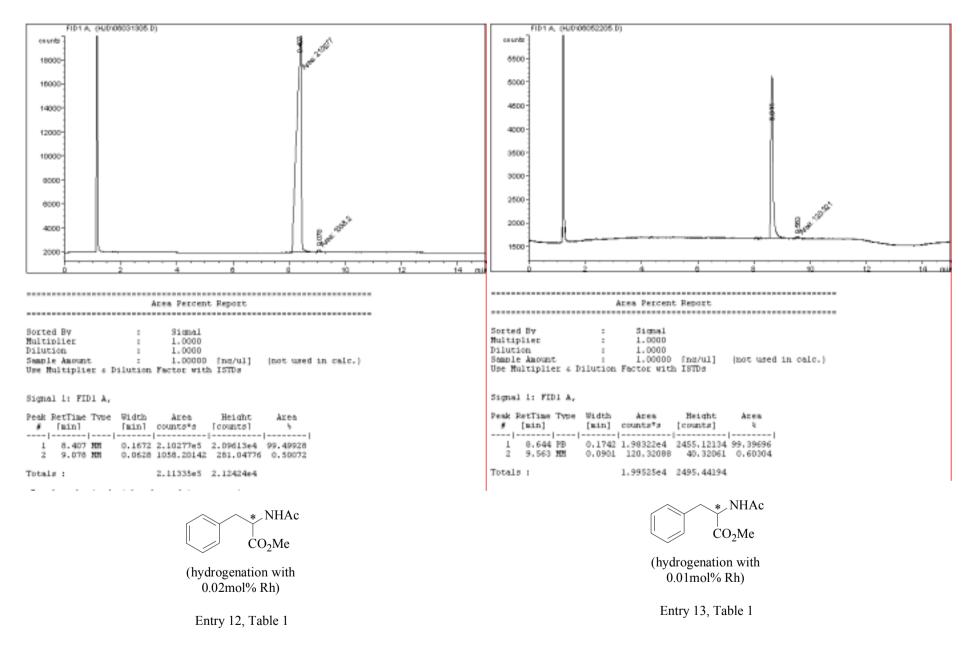


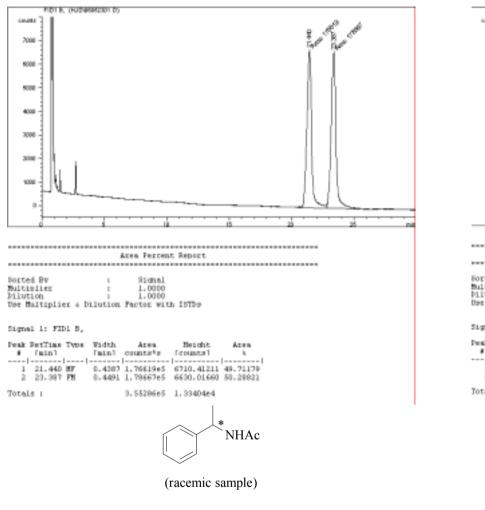


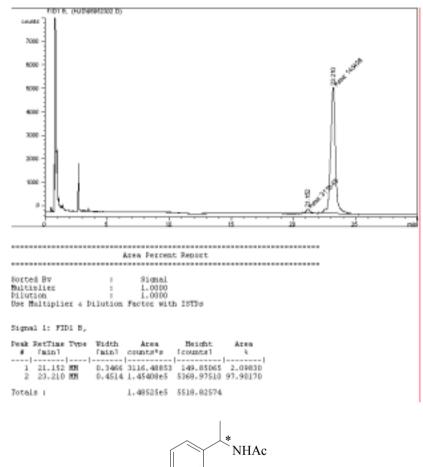




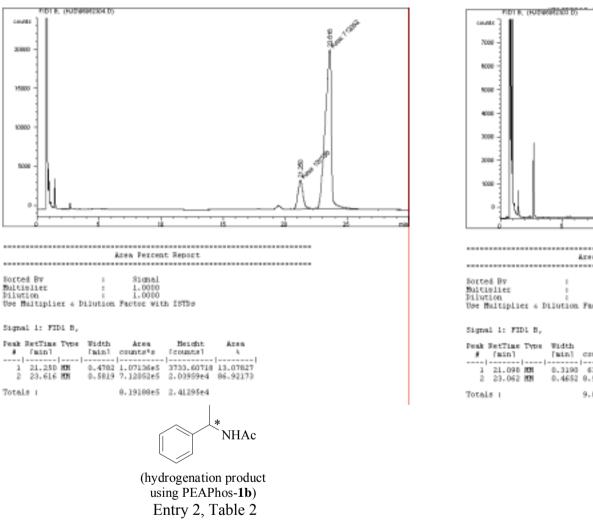


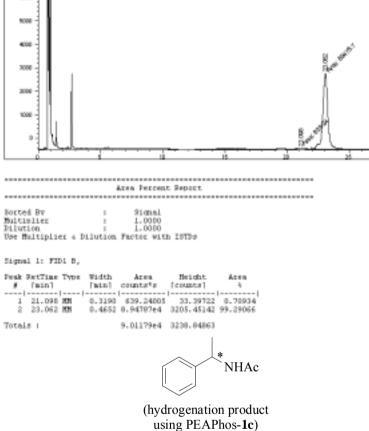




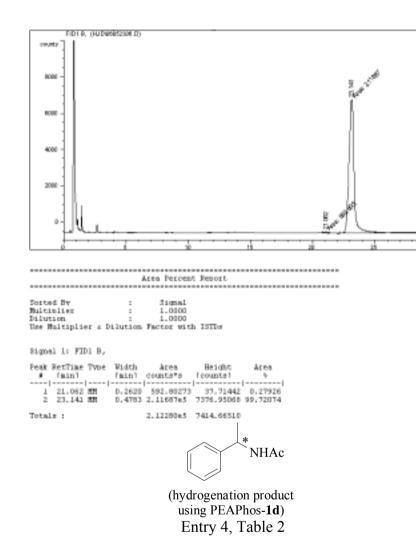


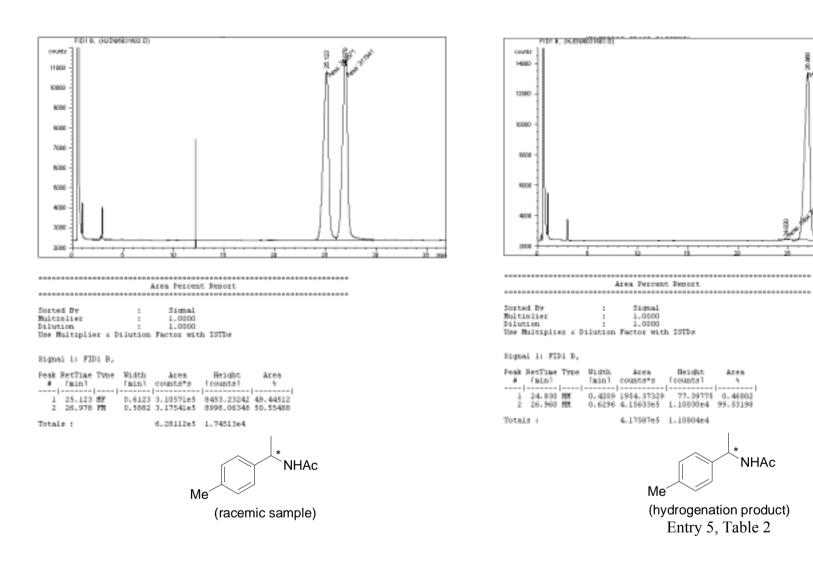
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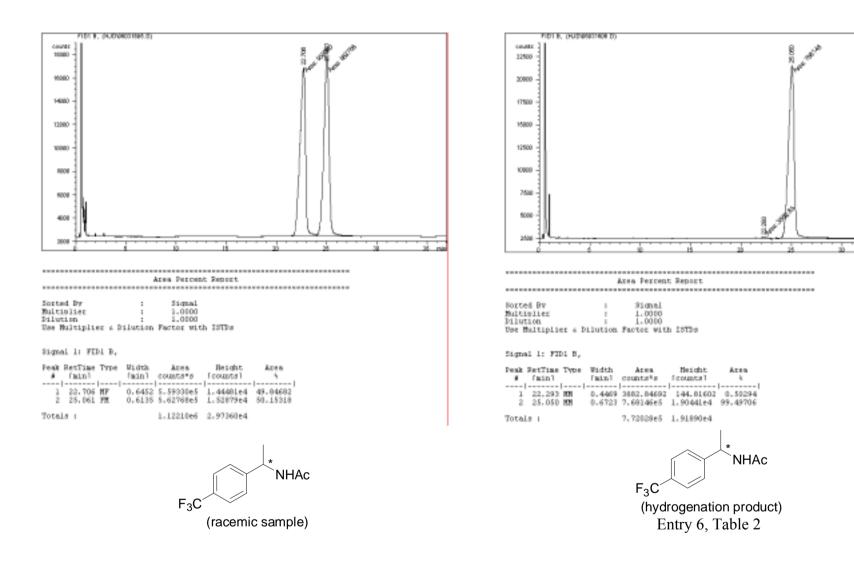


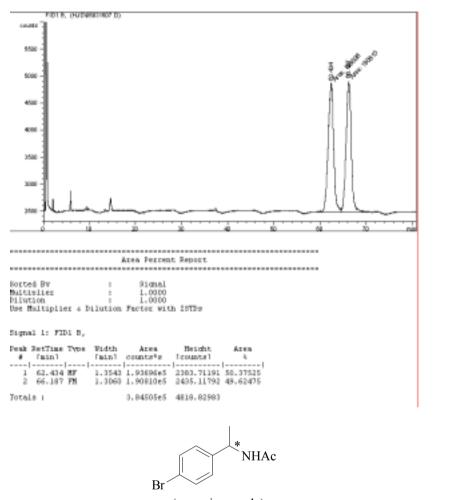
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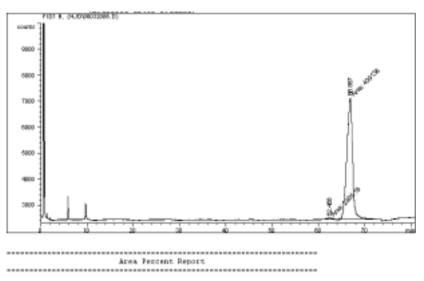


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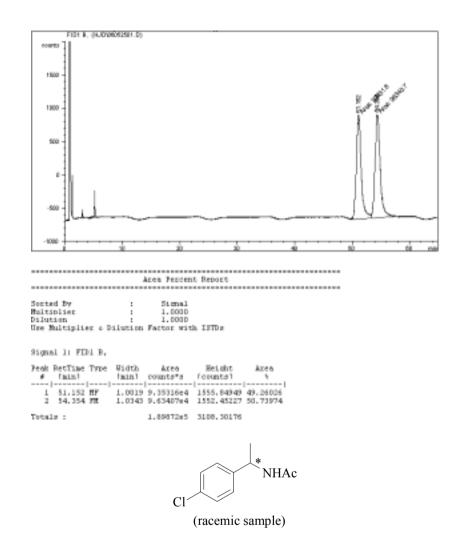
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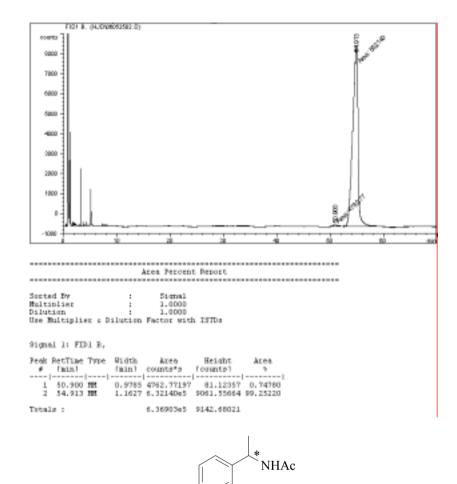


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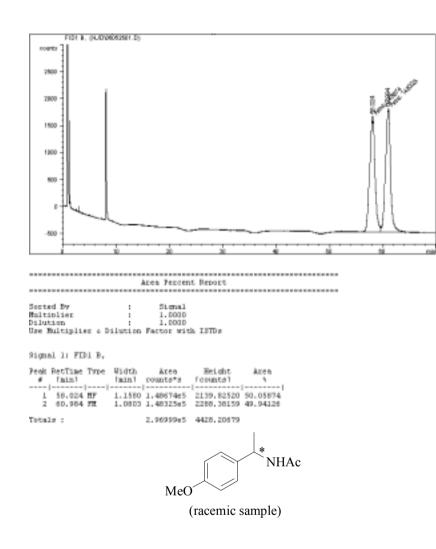
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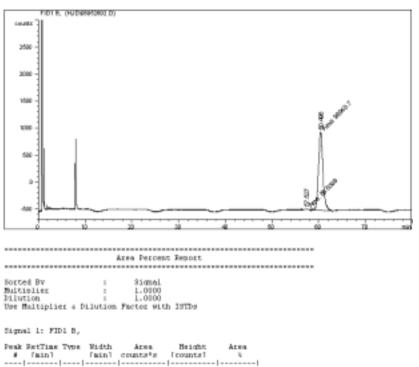
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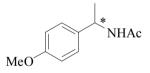


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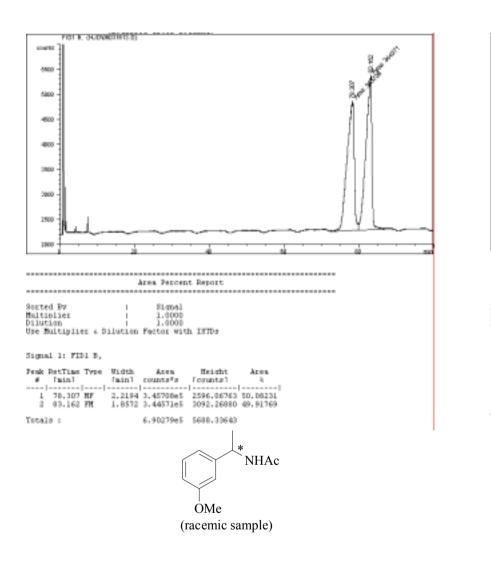


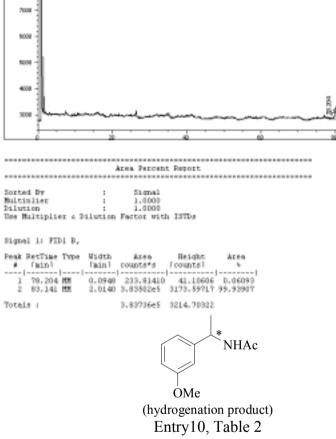


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(hydrogenation product) Entry 9, Table 2





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