The Synthesis and Application of Phosphinoferrocenylaminophosphine Ligands for Asymmetric Catalysis

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Supporting Information

Contents:

General: Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate was obtained from Alfa Aesar. *S*,*S*-Methyl DuPHOS, *R*,*S*-Josiphos, and (*R*,*R*)-(-)-1,2-Bis[(o-methoxyphenyl)(phenyl)phosphino]ethane(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate [(*R*,*R*-DIPAMP)(COD)rhodium tetrafluoroborate] were obtained from Strem Chemical. *S*,*S*-CHIRAPHOS was obtained from Aldrich Chemical Company. Dimethyl *E*-phenylitaconate[1] and *E*-phenylitaconic acid[2] were prepared using literature methodology. Melting points are uncorrected. Absolute configurations of hydrogenation products are indicated where known (references given). All others are determined by analogy using chromatographic elution order.

General Procedure A for Low Pressure Asymmetric Hydrogenation Screening. Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (5 µmol; 0.01 equiv) was placed into a reaction vessel and purged with argon for 15 minutes. A solution of the ligand **1** (6 µmol; 0.012 equiv) in the desired solvent (2.0 mL) was degassed with argon for 15 minutes, then added via cannula to the bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate. This solution was stirred at 25°C under argon for 15 minutes. A solution of dehydroamino acid **5** (0.5 mmol) in the desired solvent (2.0 mL) was degassed with argon for 20 minutes, then added to the catalyst solution via cannula. The solution was then flushed with hydrogen and pressurized to 10 psig hydrogen. Samples were taken and analyzed for conversion and enantiomeric excess using standard analytical techniques (see below).

General Procedure B for High Pressure Asymmetric Hydrogenation Screening. Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (5 µmol; 0.01 equiv) and ligand **1** (6 µmol; 0.012 equiv) were placed in a high pressure reaction vessel which was sealed and purged with argon. The desired solvent was degassed with argon for 15 minutes, then 2.0 mL was added to the reaction vessel via syringe. This solution was stirred at 25°C under argon for 15 minutes. A solution of the desired substrate (0.5 mmol) in the desired degassed solvent (2 mL) was then added to the catalyst solution via syringe. The substrate was washed in with 1 mL of the degassed solvent. The solution was then purged five times with argon and pressurized with hydrogen to the desired pressure (100-300 psig). The reactions were run for 6 hours at the desired pressure, then depressurized and purged with argon. Samples were taken and analyzed for enantiomeric excess using standard analytical techniques (see below).

***N*-Acetyl phenylalanine (6b)**.[3] A sample was treated with diazomethane to make the methyl ester (**6a**) for enantiomeric purity and configurational analysis.
^{1}H NMR (CD_3OD) δ 7.20-7.08 (m, 6H); 4.58-4.54 (dd, 1H, *J* = 5.2, 9.1 Hz); 3.14-3.07 (dd, 1H, *J* = 4.9, 13.9 Hz); 2.88-2.80 (dd, 1H, *J* = 9.1, 14.0 Hz); 1.8 (s, 3H).

***N*-t-Butyloxycarbonyl phenylalanine methyl ester (6c)**. The analytical properties of **13c** were identical to an authentic sample (Aldrich Chemical Company).
Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 140°C isothermal, 15 psig He): t_R(*R*-**6c**) 19.14 min, t_R(*S*-**6c**) 19.66 min, t_R(**5c**) 40.14 min. The absolute configuration was determined by comparison to an authentic sample (Aldrich Chemical Company).

***N*-Benzamido phenylalanine methyl ester (6d)**.[4] ^{1}H NMR (CD_3OD) δ 7.72-7.70 (d, 2H, J = 7.3 Hz); 7.50-7.47 (m, 1H); 7.40-7.23 (m, 2H); 7.20-7.17 (m, 5H); 4.85-4.83 (m, 1H); 3.69 (s, 3H); 3.65 (s, 1H); 3.29-3.26 (m, 1H); 3.13-3.08 (m, 1H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 150°C isothermal, 15 psig He): t_R(*R*-**6d**) 11.69 min, t_R(*S*-**6d**) 12.68 min, t_R(**5d**) 18.5 min.

***N*-Acetyl 4-cyanophenylalanine methyl ester (6e)**.[5] ^{1}H NMR (DMSO-d_6) δ 8.388 (d, 1H, *J* = 7.97 Hz); 7.763 (d, 2H, *J* = 7.69 Hz); 7.429 (d, 1H, *J* = 7.97 Hz); 4.55-4.47 (m, 1H); 3.608 (s, 3H); 3.120 (dd, 1H, *J* = 5.49, 13.46 Hz); 2.952 (dd, 1H, *J* = 9.61, 13.74 Hz); 1.770 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 190°C isothermal, 20 psig He): t_R(*R*-**6e**) 8.73 min, t_R(*S*-**6e**) 9.17 min.

***N*-Acetyl 4-nitrophenylalanine methyl ester (6f)**.[6] ^{1}H NMR (CD_3OD) δ 8.15-8.13 (d, 2H, *J* = 8.9 Hz); 7.45-7.43 (d, 2H, *J* = 8.6 Hz); 4.75-4.71 (dd, 1H, *J* = 5.5, 9.2 Hz);

3.69 (s, 3H); 3.67 (s, 1H); 3.30-3.25 (m, 1H); 3.08-3.02 (m, 1H); 1.88 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 185°C isothermal, 20 psig He): t_R(*R*-**6f**) 15.73 min, t_R(*S*-**6f**) 16.79 min.

***N*-Acetyl 4-chlorophenylalanine methyl ester (6g)**.[6] ^{1}H NMR (CD_3OD) δ 7.27-7.25 (d, 2H, *J* = 8.7 Hz); 7.18-7.16 (d, 2H, *J* = 8.7 Hz); 4.64-4.62 (dd, 1H, *J* = 5.5, 9.2 Hz); 3.70 (s, 1H); 3.67 (s, 3H); 3.13-3.09 (dd, 1H, *J* = 5.5, 13.7 Hz); 2.93-2.89 (dd, 1H, *J* = 9.2, 13.9 Hz); 1.88 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 175°C isothermal, 20 psig He): t_R(*R*-**6g**) 7.29 min, t_R(*S*-**6g**) 7.76 min, t_R(**5g**) 15.72 min.

***N*-Acetyl 4-fluorophenylalanine methyl ester (6h)**.[7] ^{1}H NMR ($CDCl_3$) δ 7.054 (m, 2H); 6.979 (t, 2H, *J* = 8.79 Hz); 5.960 (br d, 1H, *J* = 6.32 Hz), 4.828 (q, *J* = 5.53 Hz, 1H), 3.732 (s, 3H); 3.140 (dd, 1H, *J* = 6.04, 14.01 Hz), 3.062 (dd, 1H, *J* = 5.77, 14.01 Hz), 1.998 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 160°C, 9 min; 160-185°C, 70°C/min; 185°C, 8 min; 15 psig He): t_R(*R*-**6h**) 7.01 min, t_R(*S*-**6h**) 7.47 min, t_R(**5h**) 12.03 min.

***N*-Acetyl 4-methoxyphenylalanine methyl ester (6i)**.[4] ^{1}H NMR (CD_3OD) δ 7.09-7.07 (d, 2H, *J* = 8.9 Hz); 6.82-6.80 (d, 2H, *J* = 8.9 Hz); 4.59-4.56 (dd, 1H, *J* = 5.8, 8.9 Hz); 3.73 (s, 3H); 3.70 (s, 1H); 3.65 (s, 3H); 3.06-3.01 (dd, 1H, *J* = 5.8, 13.7 Hz); 2.88-2.82 (dd, 1H, *J* = 8.9, 13.9 Hz); 1.88 (s, 3H). Chiral GC conditions: Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 185°C isothermal, 20 psig He, t_R(*R*-**6i**) 6.04 min, t_R(*S*-**6i**) 6.32 min, t_R(**5i**) 15.13 min.

***N*-Acetyl 3-methoxyphenylalanine methyl ester (6j)**.[3] ^{1}H NMR (CD_3OD) δ 7.19-7.15 (t, 1H, *J* = 7.9 Hz); 6.78-6.74 (m, 3H); 4.66-4.62 (dd, 1H, *J* = 5.5, 9.0 Hz); 3.75 (s, 3H); 3.72-3.69 (m, 1H); 3.67 (s, 3H); 3.12-3.07 (dd, 1H, *J* = 5.8, 13.9 Hz); 2.92-2.88 (dd, 1H, *J* = 8.9, 13.7 Hz); 1.89 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 185°C isothermal, 20 psig He): t_R(*R*-**6j**) 7.73 min, t_R(*S*-**6j**) 8.18 min.

***N*-Acetyl 2-methoxyphenylalanine methyl ester (6k)**.[8] ^{1}H NMR (CD_3OD) δ 7.21-7.19 (t, 1H, *J* = 7.3 Hz); 7.06-7.05 (d, 1H, *J* = 7.3 Hz); 6.92-6.90 (d, 1H, J = 7.8 Hz); 6.84-6.82 (t, 1H, *J* = 7.8 Hz); 4.67-4.66 (m, 1H); 3.82 (s, 3H); 3.70 (s, 1H); 3.63 (s, 3H); 3.16-3.13 (dd, 1H, *J* = 6.0, 13.5 Hz); 2.90-2.86 (dd, 1H, *J* = 8.7, 13.3 Hz); 1.86 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 185°C isothermal, 20 psig He): t_R(*R*-**6k**) 4.87 min, t_R(*S*-**6k**) 5.07 min, t_R(**5k**) 8.96 min.

***N*-Benzamido 3-furanylalanine methyl ester (6m)**.[9] ^{1}H NMR (CD_3OD) δ 7.77-7.75 (m, 2H); 7.53-7.36 (m, 6H); 4.79-4.75 (dd, 1H, *J* = 5.2, 9.3 Hz); 3.72 (s, 3H); 3.69 (s, 1H); 3.11-3.06 (dd, 1H, *J* = 5.2, 14.6 Hz); 2.99-2.93 (dd, 1H, *J* = 9.5, 14.6 Hz). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 175°C isothermal, 20 psig He): t_R(*R*-**6m**) 12.57 min, t_R(*S*-**6m**) 13.29 min, t_R(**5m**) 9.39 min.

***N*-*t*-Butyloxycarbonyl 3-furanylalanine methyl ester (6n)**.[9] ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H); 7.25 (s, 1H); 6.21 (s, 1H); 5.12-5.09 (m, 1H); 4.53-4.51 (m, 1H); 3.73 (s, 3H); 2.93-2.92 (m, 2H); 1.44 (s, 9H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 140°C isothermal, 20 psig He): t_R(*R*-**6n**) 7.61 min, t_R(*S*-**6n**) 7.89 min, t_R(**5n**) 17.97 min.

***N*-Acetyl 1-Naphthylalanine methyl ester (6o)**.[7] ^{1}H NMR ($CDCl_3$) δ 8.083 (d, 1H, *J* = 8.24 Hz); 7.855 (d, 1H, *J* = 7.69 Hz); 7.769 (d, 1H, *J* = 7.97 Hz); 7.510 (m(5), 2H, *J* = 7.97 Hz); 7.385 (t, 1H, *J* = 7.14 Hz); 7.230 (d, 1H, *J* = 6.87 Hz); 5.98 (br s, 1H); 5.017 (q, 1H, *J* = 6.59 Hz); 3.626 (s, 3H); 3.57 (m, 2H); 1.926 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 185°C, 22 min; 185-195°C, 10°C/min; 195°C, 17 min; 15 psig He): t_R(*R*-**6o**) 18.83 min, t_R(*S*-**6o**) 19.76 min.

***N*-*t*-Butyloxycarbonyl 1-Naphthylalanine methyl ester (6p)**.[10] ^{1}H NMR ($CDCl_3$) δ 8.075 (d, 1H, *J* = 7.96 Hz); 7.858 (d, 1H, *J* = 7.69 Hz); 7.767 (d, 1H, *J* = 8.24 Hz); 7.512 (m(5), 2H, *J* = 7.97 Hz); 7.391 (t, 1H, *J* = 7.14 Hz); 7.27 (m, 1H); 5.057 (br d, 1H, *J* = 7.69

Hz); 4.719 (q, 1H, *J* = 7.69 Hz); 3.744 (s, 3H); 3.7-3.4 (m, 2H); 1.395 (s, 9H). Chiral HPLC (Chiralcel OD-H [Chiral Technologies], 250 x 4.6 mm, 95:5 hexane:isopropanol, 1 mL/min, λ = 254 nm): t_R(*R*-**6p**) 14.05 min, t_R(*S*-**6p**) 17.64 min.

***N*-Acetyl 2-Naphthylalanine methyl ester (6q)**.[7] ^{1}H NMR ($CDCl_3$) δ 7.85-7.75 (m, 3H); 7.553 (s, 1H); 7.47 (m, 2H); 7.218 (d, 1H, *J* = 8.52 Hz); 6.01 (br s, 1H); 4.966 (q, 1H, *J* = 6.04 Hz); 3.727 (s, 3H); 3.314 (dd, 1H, *J* = 5.77, 13.74 Hz); 3.244 (dd, 1H, *J* = 6.04, 14.01 Hz); 1.973 (s, 3H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 185°C isothermal, 15 psig He): t_R(*R*-**6q**) 22.02 min, t_R(*S*-**6q**) 23.26 min.

***N*-*t*-Butyloxycarbonyl 2-Naphthylalanine methyl ester (6r)**.[11] ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 3H); 7.586 (s, 1H); 7.45 (m, 2H); 7.26 (m, 1H); 5.000 (br d, 1H, *J* = 7.14 Hz); 4.677 (q, 1H, *J* = 6.87 Hz); 3.713 (s, 3H); 3.35-3.15 (m, 2H); 1.399 (s, 9H). Chiral HPLC conditions: Chiralcel OD-H (Chiral Technologies), 250 x 4.6 mm, 95:5 hexane:isopropanol, 1 mL/min, λ = 254 nm, t_R(*R*-**6r**) 12.86 min, t_R(*S*-**6r**) 14.41 min.

***N*-Acetyl alanine methyl ester (6s)**.[7] ^{1}H NMR (CD_3OD) δ 4.42-4.38 (dd, 1H, *J* = 7.3, 14.7 Hz); 3.72 (s, 3H); 1.98 (s, 3H); 1.38-1.37 (d, 3H, *J* = 7.3 Hz). Chiral GC (Cyclosil-B [J&W Scientific] 30 m x 0.25 mm ID, 0.25 μm film thickness, 40-100°C 70°C/min; 100°C 15 min; 100-170°C, 15°C/min; 170°C 7 min; 6 psig He 6 min; 6-20 psig He, 80 psig/min; 20 psig, 22 min): t_R(*R*-**6s**) 19.36 min, t_R(*S*-**6s**) 19.12 min, t_R(**5s**) 17.91 min. $[\alpha]_D^{23}$ –82.3° (c 2.0, H_2O) indicates that the *S* enantiomer was obtained from hydrogenation using ligand *R,S*-**1b**.[7,12]

***N*-Acetyl alanine (6t)**.[3] A sample was treated with diazomethane to make the methyl ester for enantiomeric purity and configurational analysis.

***N*-Benzyloxycarbonyl alanine methyl ester (6u)**.[13] ^{1}H NMR ($CDCl_3$) δ 7.33-7.26 (m, 5H); 5.07 (s, 2H); 4.23-4.19 (m, 1H); 3.69 (s, 3H); 1.36-1.34 (d, 3H, *J* = 7.3 Hz).

Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12μm, 150°C isothermal, 15 psig He): t_R(*R*-**6u**) 11.37 min, t_R(*S*-**6u**) 11.70 min, t_R(**5u**) 10.10 min.

***N*-Benzyloxycarbonyl homophenylalanine ethyl ester (6v)**.[14] ^{1}H NMR ($CDCl_3$) δ 7.37-7.15 (m, 10H), 5.38-5.36 (d, 1H, *J* =7.9 Hz); 5.12 (s, 2H), 4.44-4.39 (dd, 1H, *J* = 7.6, 13.0 Hz), 4.20-4.15 (dd, 2H, *J*=7.0, 14.3 Hz), 2.73-2.60 (m, 2H); 2.27-2.14 (m, 1H), 2.02-1.93 (m, 1H), 1.28-1.25 (t, 3H, *J* = 7.0 Hz). Chiral HPLC (Cyclobond I 2000 SN column [Advanced Separation Technologies, Inc.], 97:3 heptane:isopropanol, 210 nm): t_R(*R*-**6v**) 28.93 min, t_R(*S*-**6v**) 30.99 min, t_R(**5v**) 33.39 min.

***N*-*t*-Butyloxycarbonyl cyclopropylalanine benzyl ester (6w)**.[15] ^{1}H NMR ($CDCl_3$) δ 7.41-4.30 (m, 5H); 5.13-5.12 (m, 1H); 5.02 (s, 2H); 1.70-1.60 (m, 2H); 1.45 (s, 9H); 0.69-0.61 (m, 1H); 0.42-0.39 (m, 2H); 0.02-0.01 (m, 2H). Chiral GC (Chirasil L-Valine [Varian] 25 m x 0.25 mm ID, film thickness 0.12 μm, 175°C isothermal, 15 psig He): t_R(*R*-**6w**) 15.03 min, t_R(*S*-**6w**) 15.48 min, t_R(**6w**) 25.98 min.

Dimethyl *R*-2-Methylsuccinate (8a). The analytical properties of **8a** were identical to an authentic sample (Aldrich Chemical Company). Chiral GC (Cyclosil-B, J&W Scientific, 30 m x 0.25 mm ID, film thickness 0.25 μm, 90°C isothermal, 15 psig He): t_R(*R*-**8a**) 17.36 min, t_R(*S*-**8a**) 17.82 min, t_R(**7a**) 23.16 min. The absolute configuration was determined by comparison to an authentic sample (Aldrich Chemical Company).

***R*-2-Methylsuccinic Acid (8b)**. The analytical properties of **8b** were identical to an authentic sample (Aldrich Chemical Company). A sample was treated with trimethylsilyldiazomethane to make the methyl ester (**6a**) for enantiomeric purity and configurational analysis.

2-Benzylsuccinic Acid (8c).[16] ^{1}H NMR (methanol-d_4) δ 7.31-7.19 (m, 5H), 3.08-2.99 (m, 2H); 2.85-2.77 (m, 1H); 2.61-2.53 (m, 1H); 2.355 (dd, 1H, *J* = 4.67, 17.03 Hz). Chiral HPLC (250 x 4.6 mm Chiralcel OD-H [Chiral Technologies], 95:5 hexane:isopropanol [containing 1.3% trifluoroacetic acid], 1 mL/min, λ = 254 nm): t_R(*R*-

8c) 14.3 min, t_R(*S*-**8c**) 16.6 min. $[\alpha]_D^{23}$ +25.6° (c 1.57, ethyl acetate) indicates that the *R* enantiomer was obtained from hydrogenation using ligand ***R*,*S*-1b**.[16]

Dimethyl 2-Benzylsuccinate (8d).[17] ^{1}H NMR ($CDCl_3$) δ 7.35-7.10 (m, 5H), 3.668 (s, 3H); 3.635 (s, 3H); 3.131 (m, 1H); 3.1-3.0 (m, 1H); 2.8-2.6 (m, 2H); 2.402 (dd, 1H, *J* = 4.94, 16.76 Hz). Chiral HPLC (250 x 4.6 mm Chiralcel OD-H [Chiral Technologies], 70:30 hexane:isopropanol, 1 mL/min, λ = 254 nm): t_R(*R*-**8d**) 12.6 min, t_R(*S*-**8d**) 18.2 min. The absolute configuration was determined by correlation with compound **8c** above.

Methyl *R*-Lactate (10a). The analytical properties of **10a** were identical to an authentic sample (Aldrich Chemical Company). Chiral GC (Cyclosil-B, J&W Scientific, 30 m x 0.25 mm ID, film thickness 0.25 μm, 75°C isothermal, 15 psig He): t_R(*R*-**10a**) 7.75 min, t_R(*S*-**10a**) 9.16 min, t_R(**9a**) 5.16 min. The absolute configuration was determined by comparison to an authentic sample (Aldrich Chemical Company).

Ethyl Lactate (10b). The analytical properties of **10b** were identical to an authentic sample (Aldrich Chemical Company). Chiral GC (Cyclosil-B, J&W Scientific, 30 m x 0.25 mm ID, film thickness 0.25 μm, 75°C isothermal, 14 psig He): t_R(*R*-**10b**) 11.40 min, t_R(*S*-**10b**) 13.24 min, t_R(**9b**) 7.73 min. The absolute configuration was determined by comparison to an authentic sample (Aldrich Chemical Company).

Methyl 2-Hydroxy-3-phenylpropionate (10c).[18] ^{1}H NMR (DMSO-d_6) δ 7.3-7.1 (m, 5H); 5.547 (d, 1H, *J* = 6.04 Hz); 4.22 (m, 1H); 3.584 (s, 3H); 2.923 (dd, 1H, *J* = 5.22, 13.74 Hz); 2.289 (dd, 1H, *J* = 8.24, 13.74 Hz). Chiral GC (Cyclosil-B, J&W Scientific, 30 m x 0.25 mm ID, film thickness 0.25 μm, 140°C isothermal, 18 psig He): t_R(*R*-**10d**) 19.62 min, t_R(*S*-**10d**) 21.54 min, t_R(**9d**) 18.54 min.

Ethyl 2-Hydroxy-4-phenylbutyrate (10d). The analytical properties of **10d** were identical to an authentic sample (Aldrich Chemical Company). ^{1}H NMR ($CDCl_3$) δ 7.4-7.1 (m, 5H); 4.213 (q, 1H, *J* = 7.14 Hz); 4.15 (m, 1H); 2.77 (m, 2H); 2.12 (m, 1H); 1.96 (m, 1H); 1.286 (t, 3H, *J* = 7.14 Hz). Chiral GC (Cyclosil-B, J&W Scientific, 30 m x 0.25 mm

ID, film thickness 0.25 μm, 150°C isothermal, 18 psig He): t_R(*R*-**10d**) 26.49 min, t_R(*S*-**10d**) 27.09 min, t_R(**9d**) 23.98 min. The absolute configuration was determined by comparison to an authentic sample (Aldrich Chemical Company).

2-Hydroxy-3,3-dimethyl-γ-butyrolactone (10e). The analytical properties of **10e** were identical to an authentic sample (Aldrich Chemical Company). ^{1}H NMR ($CDCl_3$) δ 4.114 (s, 1H); 4.023 (d, 1H, *J* = 8.52 Hz); 3.936 (d, 1H, *J* = 8.52 Hz); 1.223 (s, 3H); 1.071 (s, 3H). Chiral GC (Cyclosil-B, J&W Scientific, 30 m x 0.25 mm ID, film thickness 0.25 μm, 140°C isothermal, 14 psig He): t_R(*R*-**10e**) 11.18 min, t_R(*S*-**10e**) 11.66 min, t_R(**9e**) 7.99 min. The absolute configuration was determined by comparison to an authentic sample (Aldrich Chemical Company).

General Procedure C for Kinetics of Hydrogenation at High Substrate to Catalyst Ratios. The substrate (10 mmol) was added to a Fisher-Porter bottle. Argon-degassed solvent (12.3 mL) was added to afford a homogeneous solution which was purged with argon for 5 minutes. The bottle was fitted with a pressure head and evacuated and filled with helium ten times. Bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 0.005 mmol) and the desired ligand (0.006 mmol; 1.2 equiv based on rhodium) were added to a 25-mL Schlenk tube and purged with argon for 5 min. Solvent (5.0 mL) was added and the mixture was stirred for 15 min to afford a homogeneous solution. 1.0 mL of this solution (0.001 mmol; 0.0001 equiv; S:C 10,000:1) was added via a gas-tight syringe to the Fisher-Porter bottle containing the substrate solution. The bottle was evacuated and filled with helium ten times, and then evacuated and filled with hydrogen 5 times. The bottle was pressurized with 40 psig hydrogen, sealed, and stirred vigorously at ambient temperature and the pressure drop was followed with a pressure sensor. After completion the reaction mixture was evacuated and filled with helium five times and then depressurized. The reaction mixture was sampled and analyzed for conversion and enantioselectivity. The pressure decrease within the bottle was correlated with the extent of conversion to afford conversion vs time.

Kinetics Experiments Using Methyl 2-acetamidocinnamate (5a). Methyl 2-acetamidocinnamate (**5a**; 2.19 g; 10.0 mmol) was hydrogenated to afford **6a** according to General Procedure C in methanol using the following catalyst stoichiometries:

S,*S*-CHIRAPHOS: 1.0 mL of a 20 mM solution (0.02 mmol; 0.002 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (18.8 mg; 0.040 mmol) and *S*,*S*-CHIRAPHOS (18.8 mg; 0.044 mmol; 1.2 equiv based on rhodium) in 2.0 mL of THF, S:C 500:1.

R,*R*-DIPAMP: 1.0 mL of a 10 mM solution (0.01 mmol; 0.001 equiv) of (1,5-cyclooctadiene)(*R*,*R*-DIPAMP)rhodium tetrafluoroborate (15.1 mg; 0.02 mmol) in 2.0 mL of methanol, S:C 1000:1.

S,*S*-Methyl DuPHOS: 1.0 mL of a 1 mM solution (0.001 mmol; 0.0001 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 μmol) and *S*,*S*-Methyl DuPHOS (1.8 mg; 6 μmol; 1.2 equiv based on rhodium) in 5.0 mL of methanol, S:C 10,000:1.

R,*S*-JOSIPHOS: 1.0 mL of a 2 mM solution (0.002 mmol; 0.0002 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 μmol) and *R*,*S*-JOSIPHOS (3.6 mg; 6 μmol; 1.2 equiv based on rhodium) in 2.5 mL of methanol, S:C 5000:1.

Reactions using other substrates using the rhodium complex of *R,S*-**1b** were run under identical conditions using the following stoichiometries:

2-Acetamidocinnamic Acid (**5b**): 2.05 g (10 mmol) in 12.3 mL of methanol was treated with 1.0 mL of a 1 mM solution (0.001 mmol; 0.0001 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (2.3 mg; 5 μmol) and ligand (*R*,*S*)-**1b** (3.7 mg; 6 μmol; 1.2 equiv based on rhodium) in 5.0 mL of methanol, S:C 10,000:1.

Methyl 2-acetamido-3-(4-chlorophenyl)propenoate (**5g**): 1.27 g (5 mmol) in 10.0 mL of toluene was treated with 1.0 mL of a 2 mM solution (0.002 mmol; 0.0004 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (4.7 mg; 10 μmol) and ligand (*R*,*S*)-**1b** (7.6 mg; 12 μmol; 1.2 equiv based on rhodium) in 5.0 mL of methanol, S:C 2500:1.

Methyl 2-acetamido-3-(4-fluorophenyl)propenoate (**5h**): 2.37 g (10 mmol) in 9.0 mL of methanol was treated with 1.0 mL of a 4 mM solution (0.004 mmol; 0.0004 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (5.6 mg; 12 μmol) and ligand (*R*,*S*)-**1b** (9.2 mg; 15 μmol; 1.2 equiv based on rhodium) in 3.0 mL of methanol, S:C 2500:1.

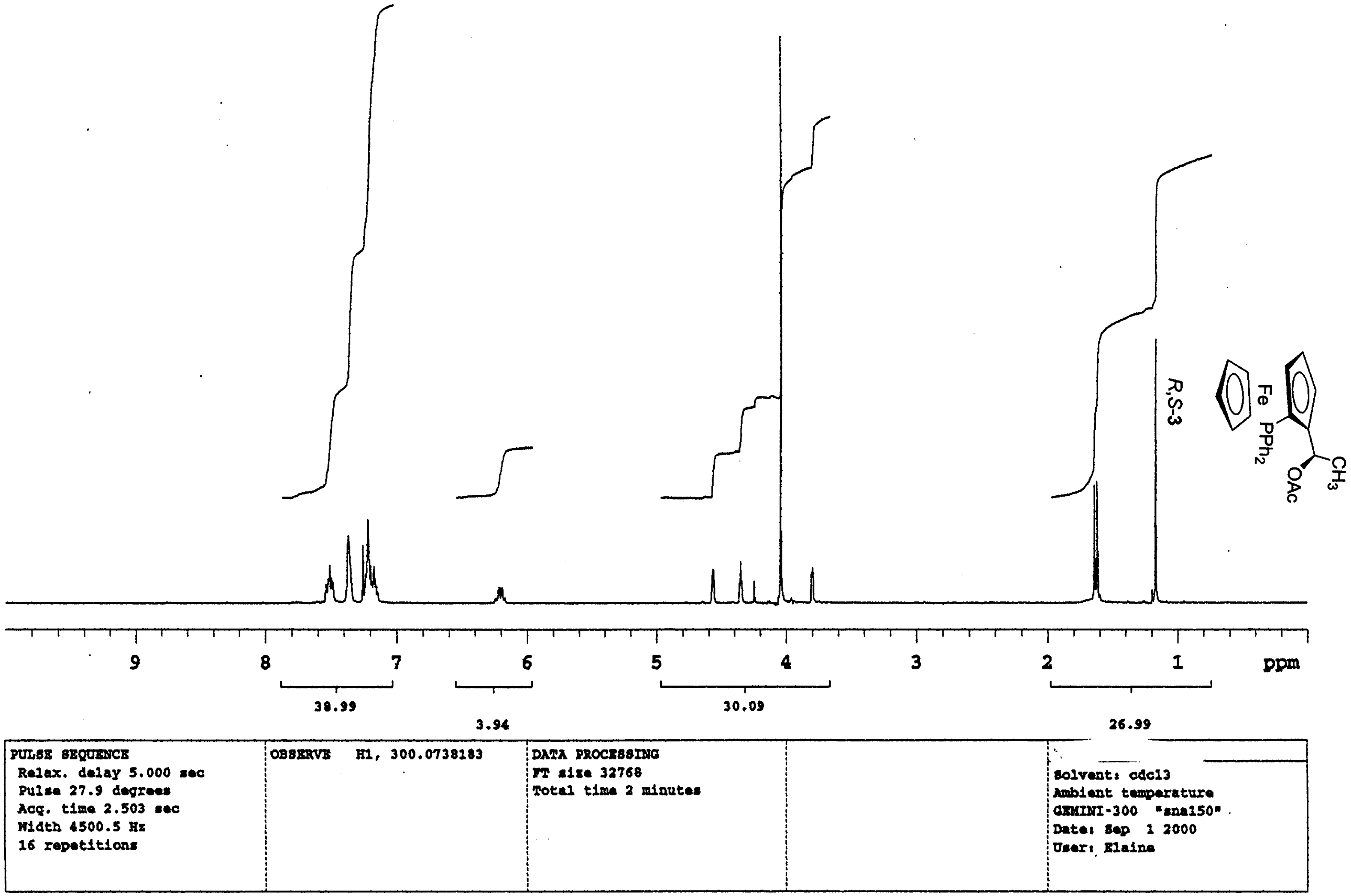
Methyl 2-acetamido-3-(2-naphthyl)propenoate (**5r**): 5.38 g (20 mmol) in 15.0 mL of toluene was treated with 1.0 mL of a 8 mM solution (0.008 mmol; 0.0004 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (11.2 mg; 24 μmol) and ligand (*S*,*R*)-**1b** (18.3 mg; 30 μmol; 1.2 equiv based on rhodium) in 3.0 mL of methanol, S:C 2500:1.

Benzyl 2-tert-butyloxycarbonylamino-3-cyclopropylpropenoate (**5w**): 3.17 g (10 mmol) in 9.0 mL of methanol was treated with 1.0 mL of a 10 mM solution (0.01 mmol; 0.001 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (14.1 mg; 30 μmol) and ligand (*R*,*S*)-**1b** (22.0 mg; 36 μmol; 1.2 equiv based on rhodium) in 3.0 mL of methanol, S:C 2500:1.

Kinetics Example: *R*-2-Methylsuccinic Acid (*R*-8b) using Ligand *R,S*-1b. Itaconic acid (**7b**, 1.30 g; 10.0 mmol) was hydrogenated according to General Procedure C in methanol using 1.0 mL of a 4 mM solution of the rhodium complex of (*R*,*S*)-**1b** (0.004 mmol; 0.0004 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (5.6 mg; 12 μmol) and ligand (*R*,*S*)-**1b** (9.2 mg; 15 μmol; 1.2 equiv based on rhodium) in 3.0 mL of methanol for 1 hour to afford 100% conversion to *R*-2-methylsuccinic acid (*R*-**8b**) which was identical to an authentic sample (Aldrich Chemical Company). Conversion to the dimethyl ester (trimethylsilyldiazaomethane) and analysis by chiral GC as above for **8a** indicated 96 % ee. Graphical analysis of the initial 50% of the reaction and adjusting for the 2500:1 substrate to catalyst ratio indicated a catalyst turnover frequency of 53,200 turnovers per hour.

Kinetics Example: *R*-2-Benzylsuccinic Acid (*R*-8e) using Ligand *R,S*-1a with Triethylamine. Phenylitaconic acid (**7e**, 2.06 g; 10.0 mmol) was hydrogenated according to General Procedure C in 9 mL of methanol containing triethylamine (139 μL; 1.0 mmol; 0.10 equiv) using 1.0 mL of a 10 mM solution of the rhodium complex of (*R*,*S*)-**1a** (0.01 mmol; 0.001 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (14.1 mg; 30 μmol) and ligand (*R*,*S*)-**1a** (22.4 mg; 37.5 μmol; 1.25 equiv based on rhodium) in 3.0 mL of methanol for 3 hours to afford 93.6% conversion (^{1}H NMR analysis) to *R*-2-benzylsuccinic acid (*R*-**8e**) with 98.0 % ee as determined by chiral HPLC analysis. Graphical analysis of the initial 40% of the reaction and adjusting for the 1000:1 substrate to catalyst ratio indicated a catalyst turnover frequency of 11,000 turnovers per hour.

Kinetics Example: *R*-2-Hydroxy-3,3-dimethyl-γ-butyrolactone (*R*-10e) using Ligand *R,S*-1e. Dihydro-4,4-dimethylfuran-2,3-dione (**9e**, 1.28 g; 10.0 mmol) was hydrogenated according to General Procedure C in ethyl acetate (9 mL) using 1.0 mL of a 10 mM solution of the rhodium complex of (*R*,*S*)-**1e** (0.01 mmol; 0.001 equiv) prepared from bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (14.1 mg; 30 μmol) and ligand (*R*,*S*)-**1e** (22.4 mg; 36 μmol; 1.2 equiv based on rhodium) in 3.0 mL of THF for 1.25 hour to afford 99.7% conversion to *R*-2-hydroxy-3,3-dimethyl-γ-butyrolactone (*R*-**10e**) with 95.8 % ee as determined by chiral GC analysis. The solvent was removed at reduced pressure to afford 1.30 g (99%) of *R*-**10e**. Graphical analysis of the initial 20% of the reaction and adjusting for the 1000:1 substrate to catalyst ratio indicated a catalyst turnover frequency of 7770 turnovers per hour. All other α-ketoeseter substrates were run in an identical fashion.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OAc
Fe
PPh2
R,S-3
9
8
7
6
5
4
3
2
1
ppm
38.99
3.94
30.09
26.99
PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 27.9 degrees
Acq. time 2.503 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0738183
DATA PROCESSING
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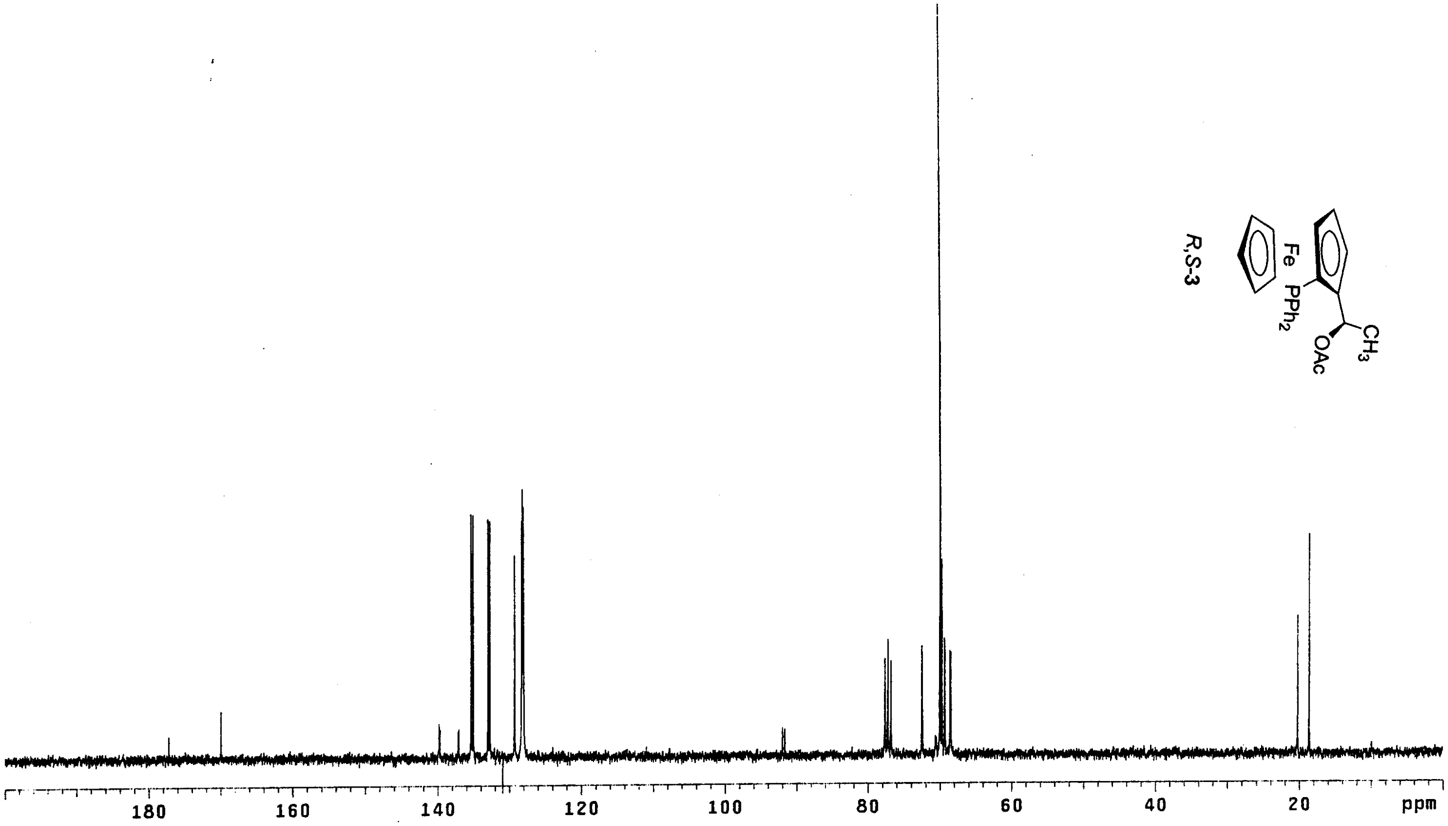
Total time 2 minutes
Solvent: cdcl3
Ambient temperature
GEMINI-300 "sna150"
Date: Sep 1 2000
User: Elaine



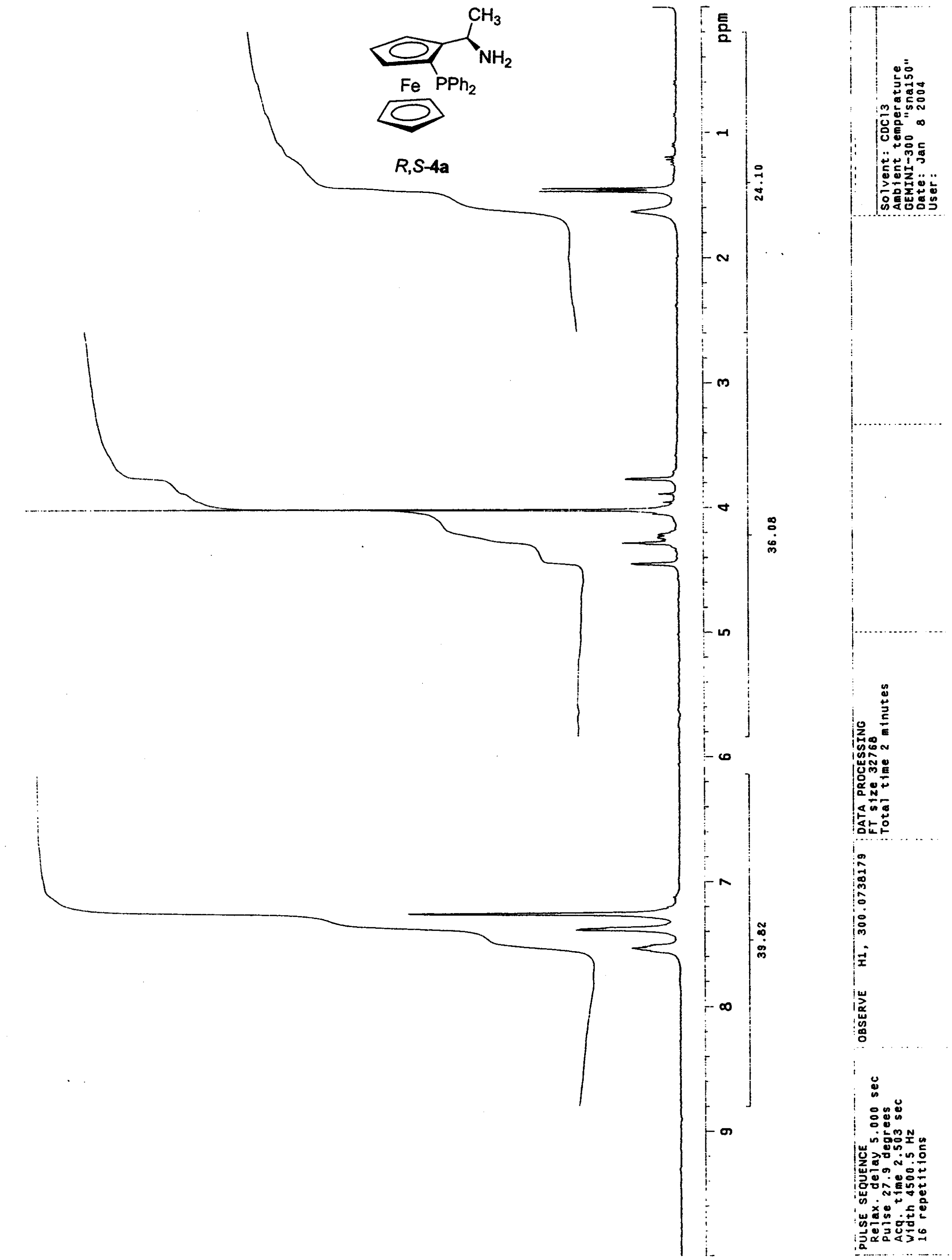
R,*S*-**3**

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 92.1 degrees
Acq. time 1.000 sec
Width 18761.7 Hz
256 repetitions

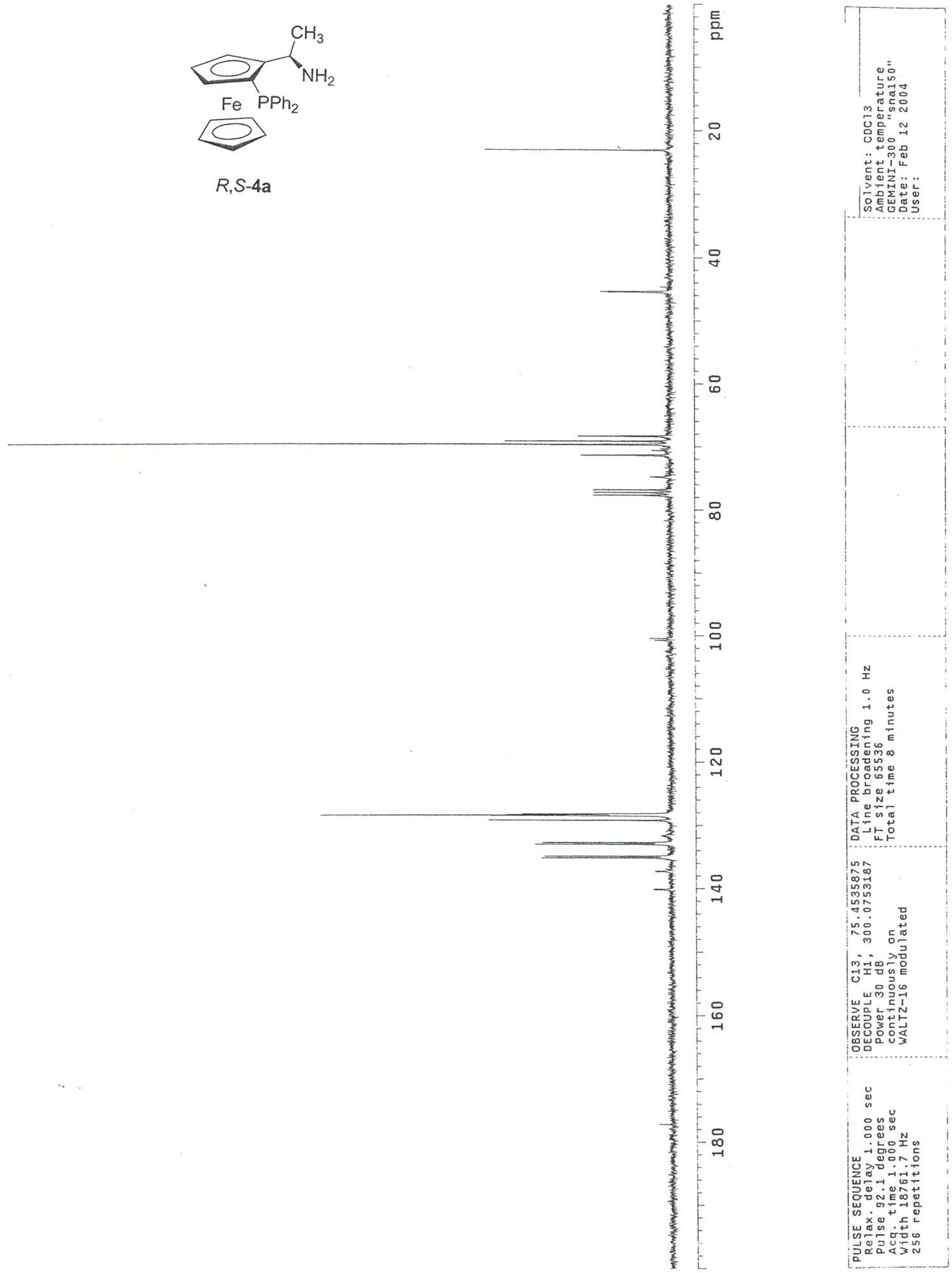
OBSERVE C13, 75.4535847
DECOUPLE H1, 300.0753187
Power 30 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 8 minutes

Solvent: CDCl3
Ambient temperature
GEMINI-300 "snai50"
Date: Feb 12 2004
User:


R,*S*-**4a**

CH3
NH2
Fe
PPh2
ppm
1
2
3
4
5
6
7
8
9
24.10
36.08
39.82
Solvent: CDCl3
Ambient temperature
GEMINI-300 "sna150"
Date: Jan 8 2004
User:
DATA PROCESSING
FT size 32768
Total time 2 minutes
OBSERVE H1, 300.0738179
PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 27.9 degrees
Acq. time 2.503 sec
Width 4500.5 Hz
16 repetitions



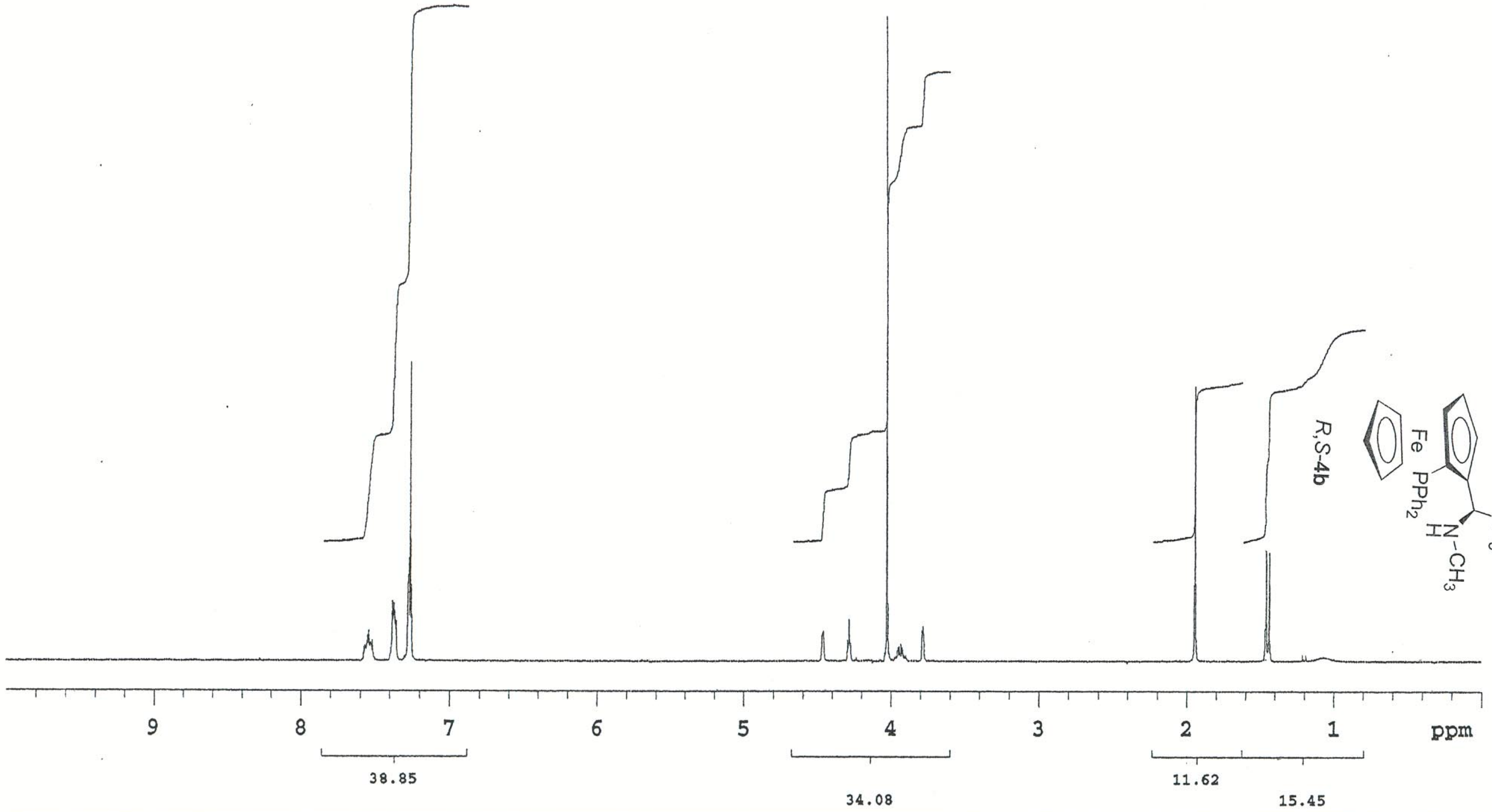
R,*S*-**4a**

Solvent: CDCl3
Ambient temperature
GEMINI-300 "sna150"
Date: Feb 12 2004
User:

DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 8 minutes

OBSERVE C13, 75.4535875
DECOUPLE H1, 300.0753187
Power 30 dB
continuously on
WALTZ-16 modulated

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 92.1 degrees
Acq. time 1.000 sec
Width 18761.7 Hz
256 repetitions



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Pulse 27.9 degrees
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16 repetitions

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DATA PROCESSING
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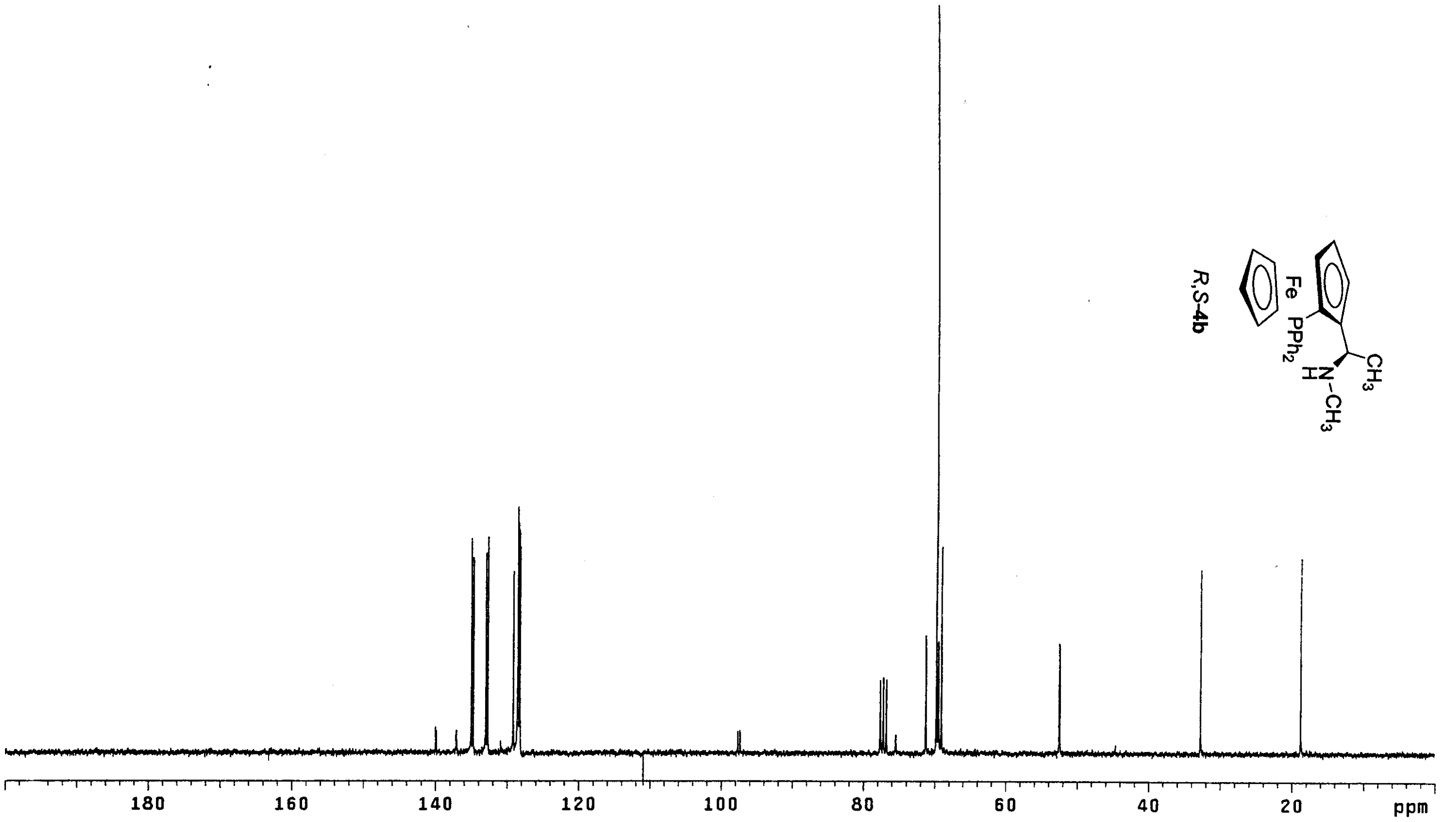
Total time 2 minutes

Solvent: CDCl3
Ambient temperature
GEMINI-300 "sna150"
Date: Oct 30 2000
User: Elaine



R,S-**4b**

```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 92.1 degrees
 Acq. time 1.000 sec
 Width 18761.7 Hz
 512 repetitions
```

```
OBSERVE  C13,  75.4535847
DECOUPLE  H1, 300.0753187
 Power 30 dB
 continuously on
 WALTZ-16 modulated
```

```
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 17 minutes
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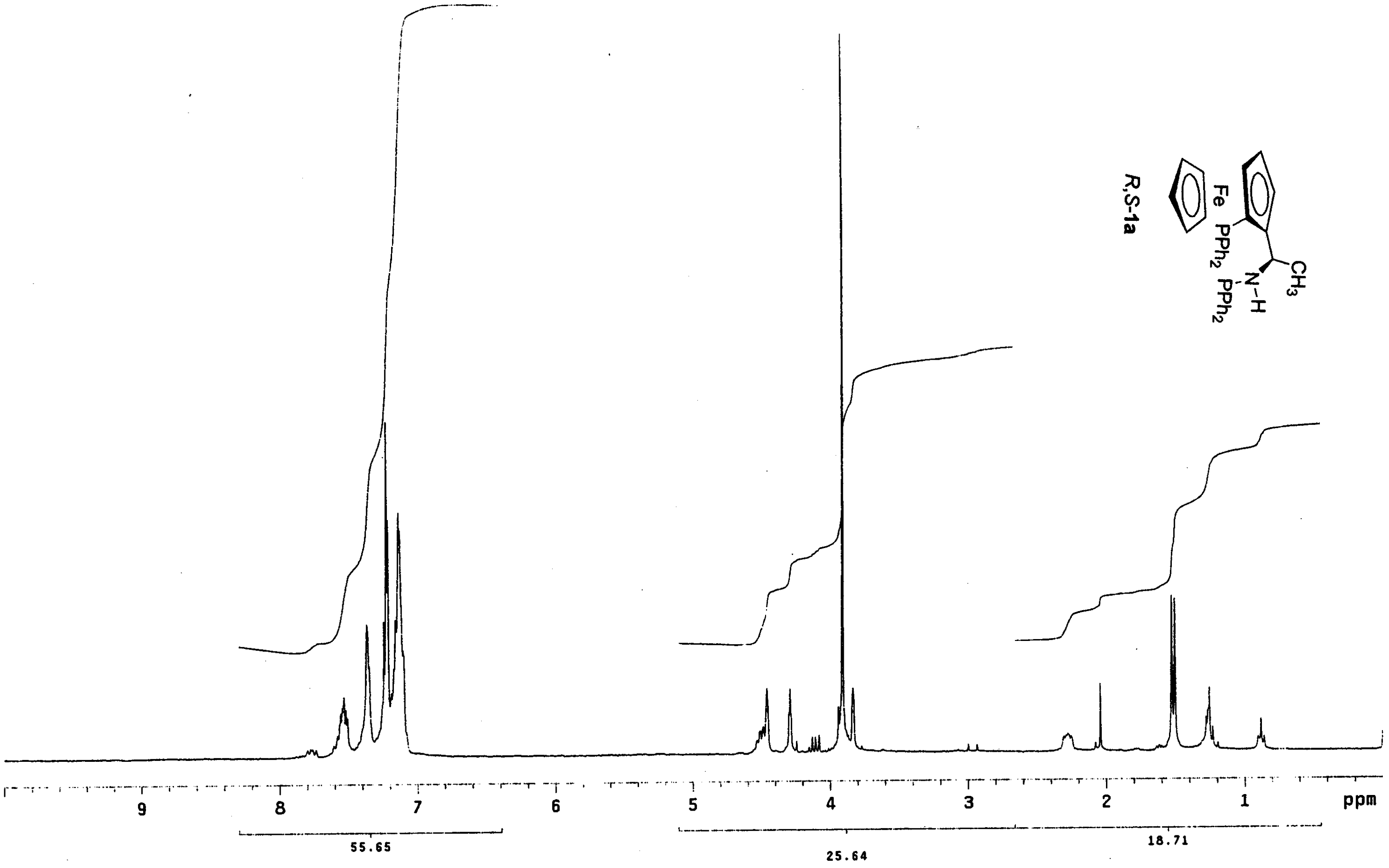
```
Solvent: CDCl3
Ambient temperature
GEMINI-300  "sna150"
Date: May  4 2002
User:
```

R,*S*-**1a**



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PULSE SEQUENCE                 OBSERVE    H1, 300.0738225   DATA PROCESSING                                            Solvent: CDCl3
 Relax. delay 5.000 sec                                     FT size 32768                                              Ambient temperature
 Pulse 27.9 degrees                                         Total time 2 minutes                                       GEMINI-300  "sna150"
 Acq. time 2.503 sec                                                                                                   Date: Jan  6 2004
 Width 4500.5 Hz                                                                                                       User:
 16 repetitions
```
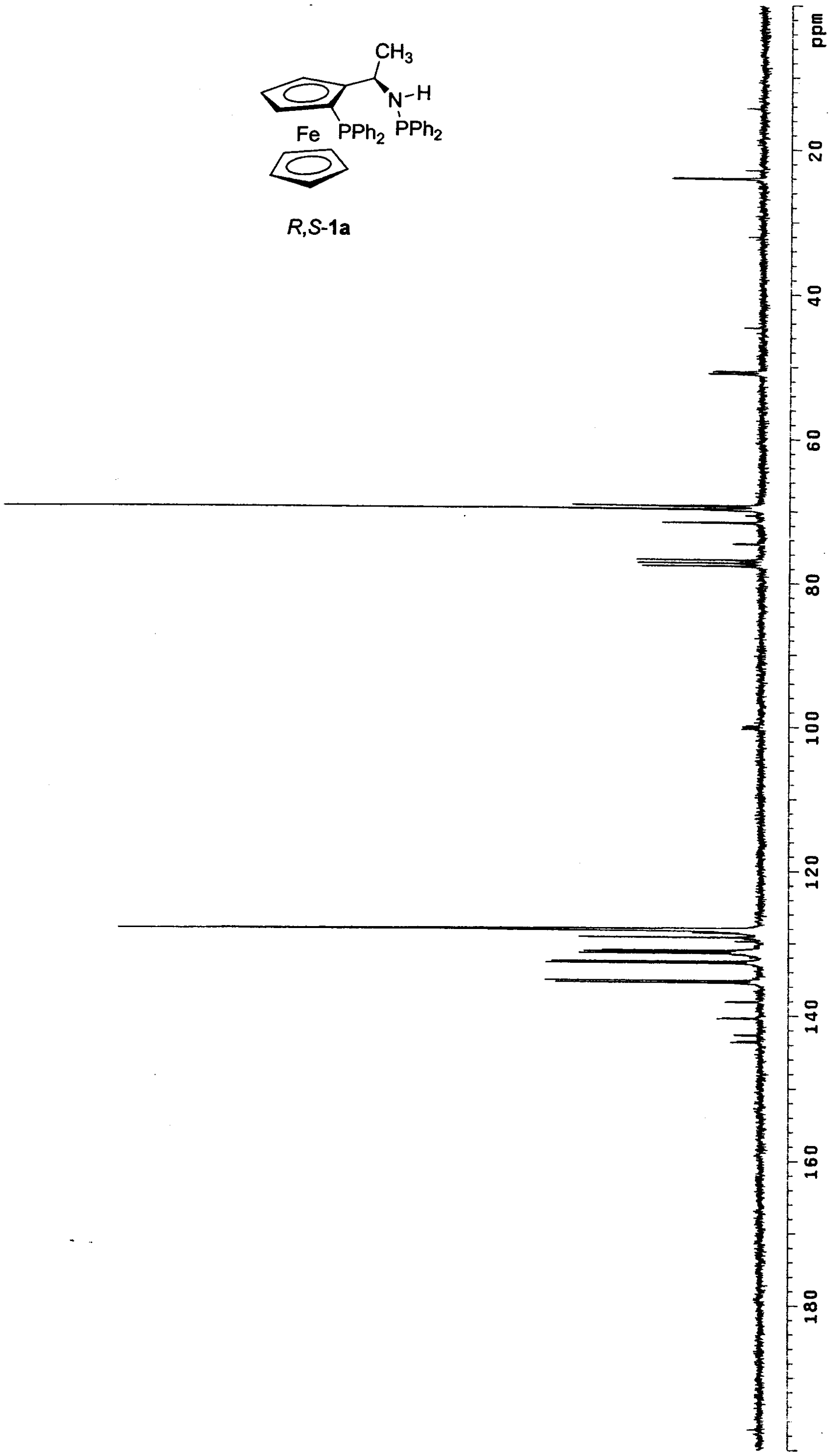

R,*S*-**1a**



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PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 92.1 degrees
 Acq. time 1.000 sec
 Width 18761.7 Hz
 512 repetitions
OBSERVE   C13,  75.4535864
DECOUPLE   H1, 300.0753187
 Power 30 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 17 minutes
Solvent: CDCl3
Ambient temperature
GEMINI-300  "sna150"
Date: Mar  3 2004
User: u614665
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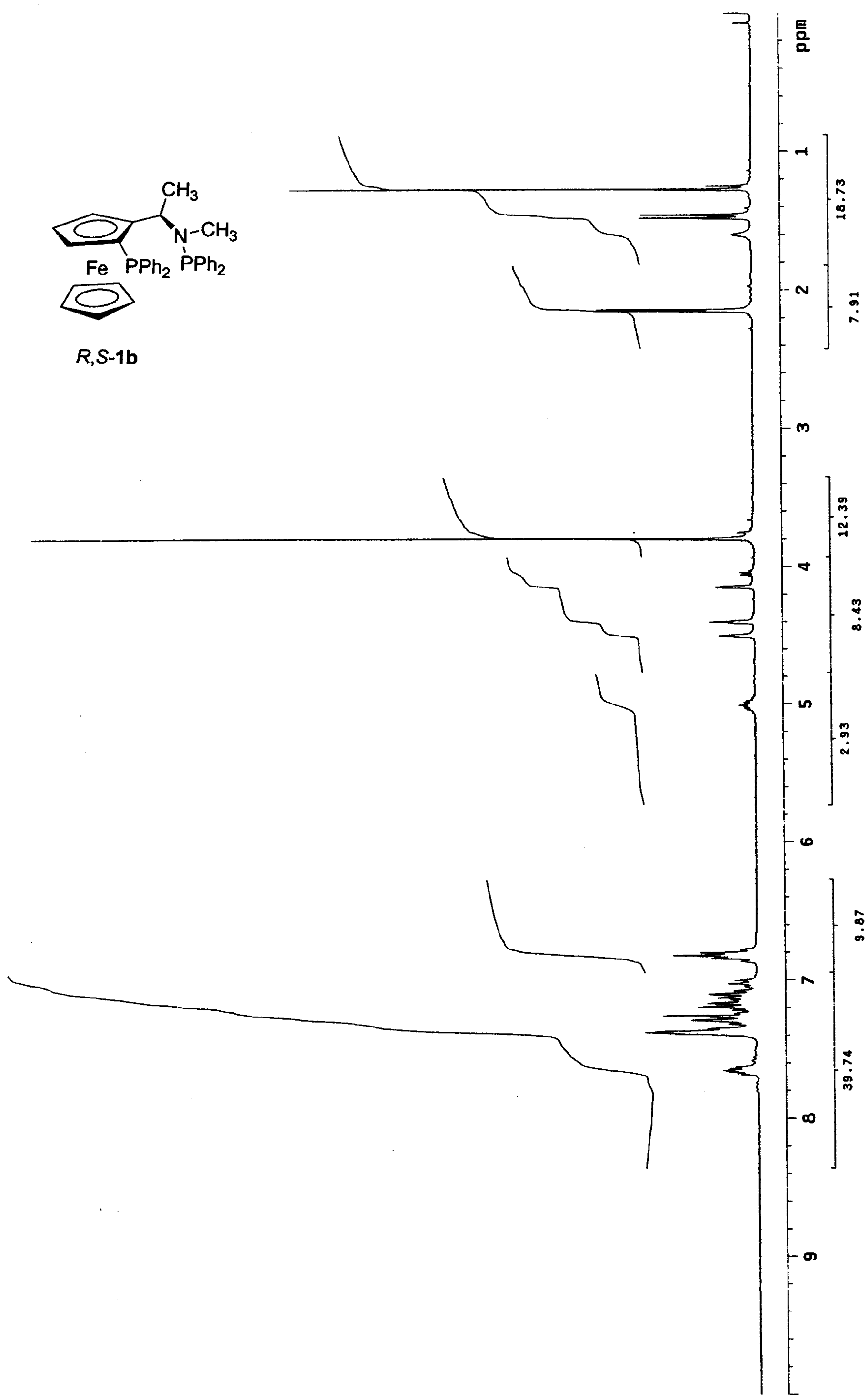
R,*S*-**1b**



PULSE SEQUENCE
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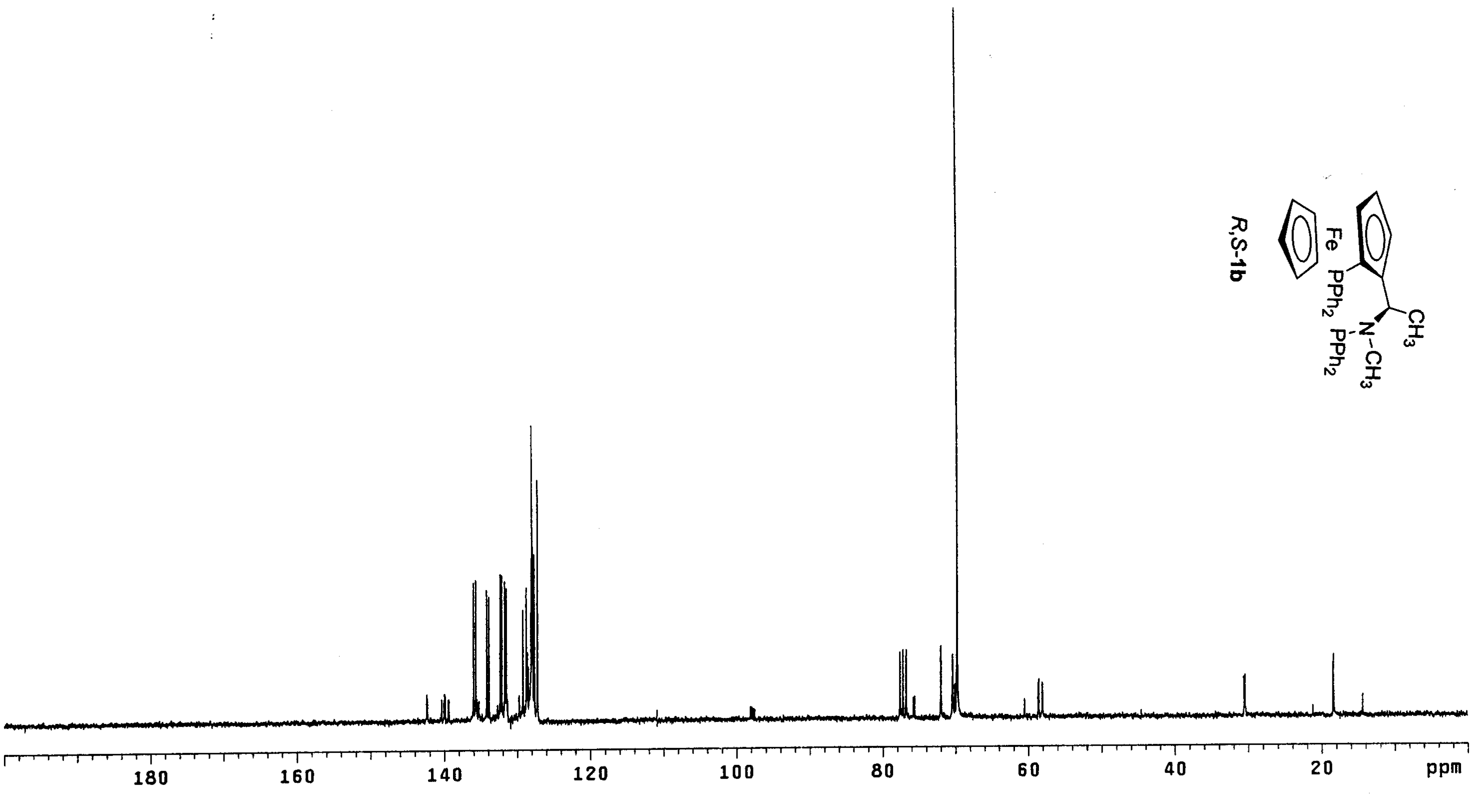
Pulse 27.9 degrees
Acq. time 2.503 sec
Width 4500.5 Hz
16 repetitions

OBSERVE H1, 300.0738190

DATA PROCESSING
FT size 32768
Total time 2 minutes

Solvent: CDCl3
Ambient temperature
GEMINI-300 "sna150"
Date: Nov 7 2003
User:



R,S-**1b**

```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 92.1 degrees
 Acq. time 1.000 sec
 Width 18761.7 Hz
 512 repetitions
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```
OBSERVE  C13,  75.4535870
DECOUPLE  H1, 300.0753187
 Power 30 dB
 continuously on
 WALTZ-16 modulated
```

```
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 17 minutes
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```
Methyl BoPhoz
Solvent: CDCl3
Ambient temperature
GEMINI-300  "sna150"
Date: May  6 2002
User:
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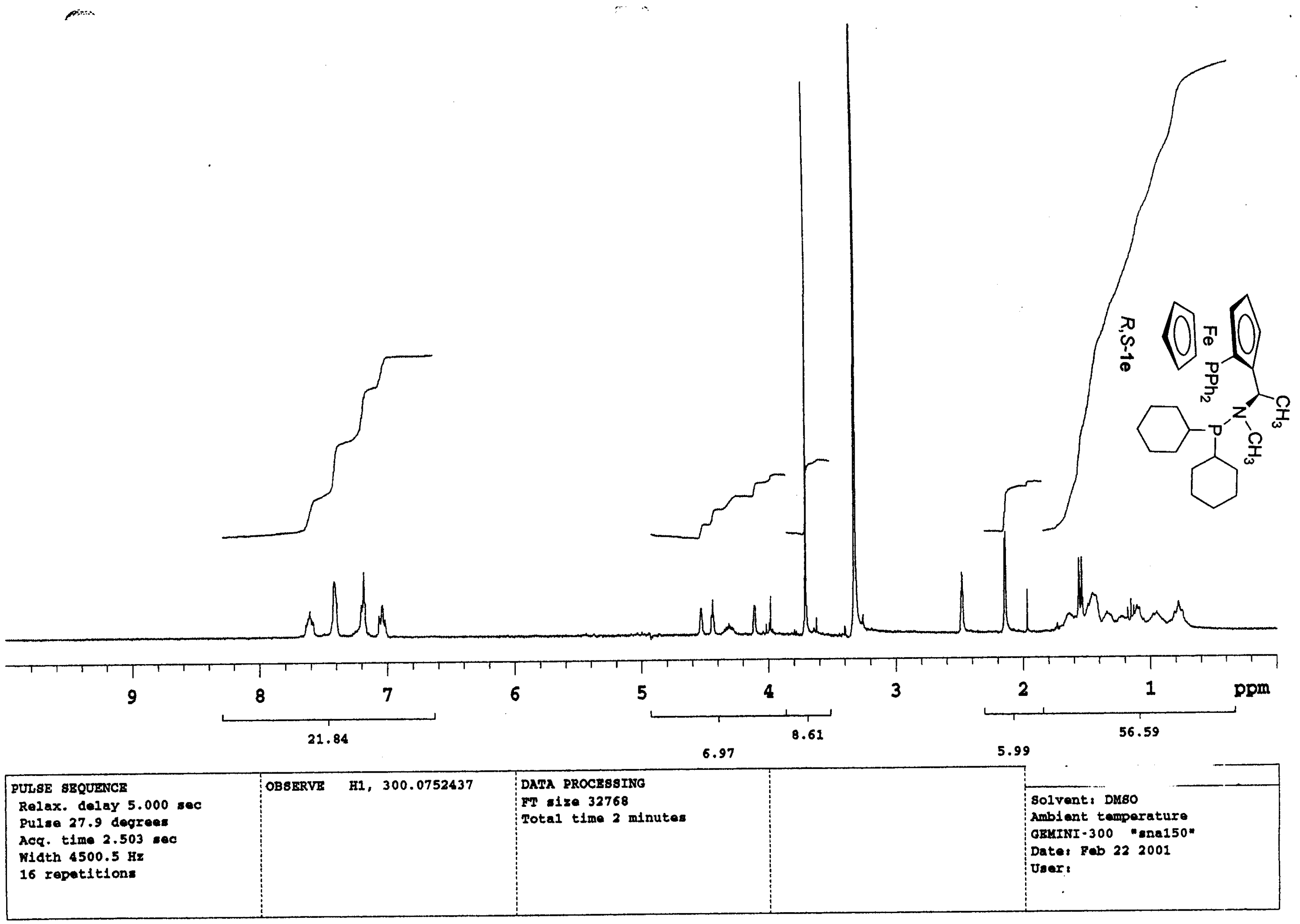


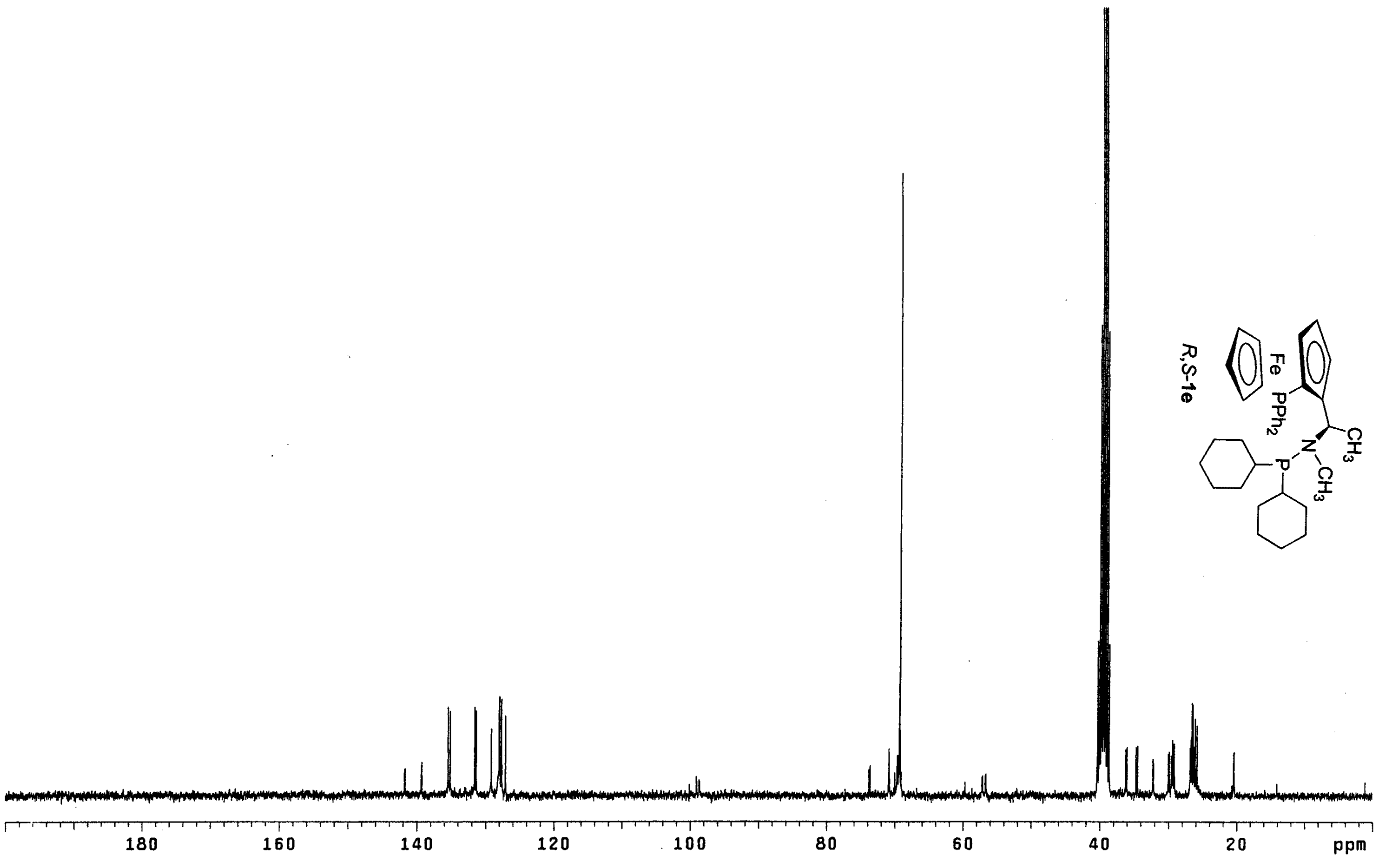
R,*S*-**1e**

PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 27.9 degrees
Acq. time 2.503 sec
Width 4500.5 Hz
16 repetitions

OBSERVE H1, 300.0752437

DATA PROCESSING
FT size 32768
Total time 2 minutes

Solvent: DMSO
Ambient temperature
GEMINI-300 "sna150"
Date: Feb 22 2001
User:



R,*S*-**1e**

```
PULSE SEQUENCE
 Relax. delay 1.000 sec
 Pulse 92.1 degrees
 Acq. time 1.000 sec
 Width 18761.7 Hz
 4096 repetitions

OBSERVE  C13,  75.4539684
DECOUPLE  H1, 300.0767441
 Power 30 dB
 continuously on
 WALTZ-16 modulated

DATA PROCESSING
 Line broadening 1.0 Hz
FT size 65536
Total time 2.3 hours

Solvent: DMSO
Ambient temperature
GEMINI-300  "sna150"
Date: May  2 2004
User:
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References

(1) Schmidt, Michelle A.; Talley, John J. *Chemical Industries (Dekker)* **1995**, *62*, 105-114.

(2) Ulrich, L.; Jendralla, J. H.; Seuring, B.; Rainer, H. Eur. Pat. Appl. **EP 512415 A2**, 1992.

(3) Rajanbabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012.

(4) Evans, D. E.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534-3543.

(5) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Hendrerickx, H. J. W.; de Vries, J. G. *Adv. Synth. Cat*. **2003**, *345*, 308-323.

(6) Zhu, S.-F.; Fu, Y.; Xie, J.-H.; Liu, B.; Xing, L.; Zhou, Q.-L. *Tetrahedron:Asymmetry* **2003**, *14*, 3219-3224.

(7) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(8) Carlström, A.-S.; Frejd, T. *Synthesis* **1989**, 414-418.

(9) Boaz, N. W.; Debenham, S. D. PCT Intl. Appl **WO 2002026750**, 2002.

(10) Jackson, R. F.; Moore, R. J.; Dexter, C. S.; Elliot, J.; Mowbray, C. E. *J. Org. Chem. 1998*, **63**, 7875-7884.

(11) Krause, H. W.; Kruezfeld, H.-J.; Schmidt, U.; Döbler, Ch.; Michalik, M.; Taudien, S.; Fischer, Ch. *Chirality* **1996**, *8*, 173-188.

(12) Wolf, J. P., III; Neimann, C. *Biochemistry* **1963**, *2*, 493.

(13) Miyazawa, T.; Tanaka, K.; Ensatsu, E.; Yanagihara, R.; Yamada, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 87-93.

(14) Chang, C.-Y.; Kang, T.-K. *Tetrahedron:Asymmetry* **2003**, *14*, 2081-2085.

(15) Boaz, N. W.; Debenham, S. D.; Large, S. E.; Moore, M. K. *Tetrahedron:Asymmetry* **2003**, *14*, 3575-3580.

(16) (a) Edwards, O. E.; Blackwell, B. A.; Driega, A. B.; Bensimmon, C.; ApSimon, J. W. *Tetrahedron Lett.* **1999**, *40*, 4515. (b) Jendralla, H. *Tetrahedron Lett.* **1991**, *32*, 3671.

(17) Takeuchi, S.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955-958.

(18) Chênevert, R.; Létourneau, M. *Can. J. Chem.* **1990**, *68*, 314-316.