Supplementary Material (ESI) for Chemical Communications

Bicyclic Guanidine-Catalyzed Enantioselective Phospha-Michael Reactions: Synthesis of Chiral β-Aminophosphine Oxides and β-Aminophosphines

Xiao Fu, Zhiyong Jiang, Choon-Hong Tan*

Department of Chemistry, 3 Science Drive 3, National University of Singapore, Singapore 117543
E-mail: chmtanch@nus.edu.sg

Supplementary Information

1	General procedures and methods	S2
2	Experimental protocols	S2
3	Characterization of the Michael adducts	S3
4	Preparation and characterization of starting materials	S18
5	Reduction of adducts	S20
6	Determination of relative configuration of **6a**	S22
7	Copies of NMR spectrum	S22

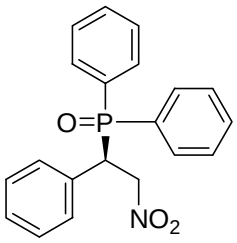
1. General procedures and methods.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker ACF300 (300MHz), DPX300 (300MHz) or AMX500 (500MHz) spectrometer. Chemical shifts are reported in parts per million (ppm). The residual solvent peak was used as an internal reference. Low resolution mass spectra were obtained on a VG Micromass 7035 spectrometer in EI mode, a Finnigan/MAT LCQ spectrometer in ESI mode. High resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer and Shimadzu-IT-TOF spectrometer. Infrared spectra were recorded on a BIO-RAD FTS 165 FTIR spectrometer. Enantiomeric excesses were determined by chiral HPLC analysis on Jasco HPLC units, including a Jasco DG-980-50 Degasser, a LG-980-02 Ternary Gradient Unit, a PU-980 Intelligient HPLC Pump, UV-975 Intelligient UV/VIS Detectors, and an AS-950 Intelligient Sampler. Optical rotations were recorded on a Jasco DIP-1000 polarimeter. Melting points were determined on a BÜCHI B-540 melting point apparatus. Analytical thin layer chromatography (TLC) was performed with Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on Merck 60 (0.040 - 0.063mm) mesh silica gel. Diethyl ether and THF were freshly distilled from sodium/benzophenone before use. CH_2Cl_2 were freshly distilled from calcium hydride. All distilled solvents were stored under N_2. All other reagents and solvents are of commercial grade and were used as supplied without further purification, unless otherwise stated.

2. Experimental protocols: Standard bicyclic guanidine catalyzed reactions between diaryl phosphine oxide and nitroalkenes.

To a 50 ml RBF containing catalyst **1** (1.8 mg, 0.008 mmol, 10 mol %) and a stirring bar, di(1-naphthyl) phosphine oxide **2f** (24.2 mg, 0.08 mmol), anhydrous diethyl ether (25ml), were added in this sequence and stirred under -40 ^{o}C for one hour. 4-Chloro-β-nitrostyrene (73.4 mg, 0.4 mmol, 5eq.) was added to the reaction mixture and stirred at -40 ^{o}C for 12 hours. Solvent was removed from the reaction mixture and loaded onto a short silica gel column. This was followed by flash chromatography (gradient elution with hexane/EA mixtures; 10/1 to 2/1). Adduct **4a** (36.5mg) was obtained as a white solid in 94% yield and 96% ee.

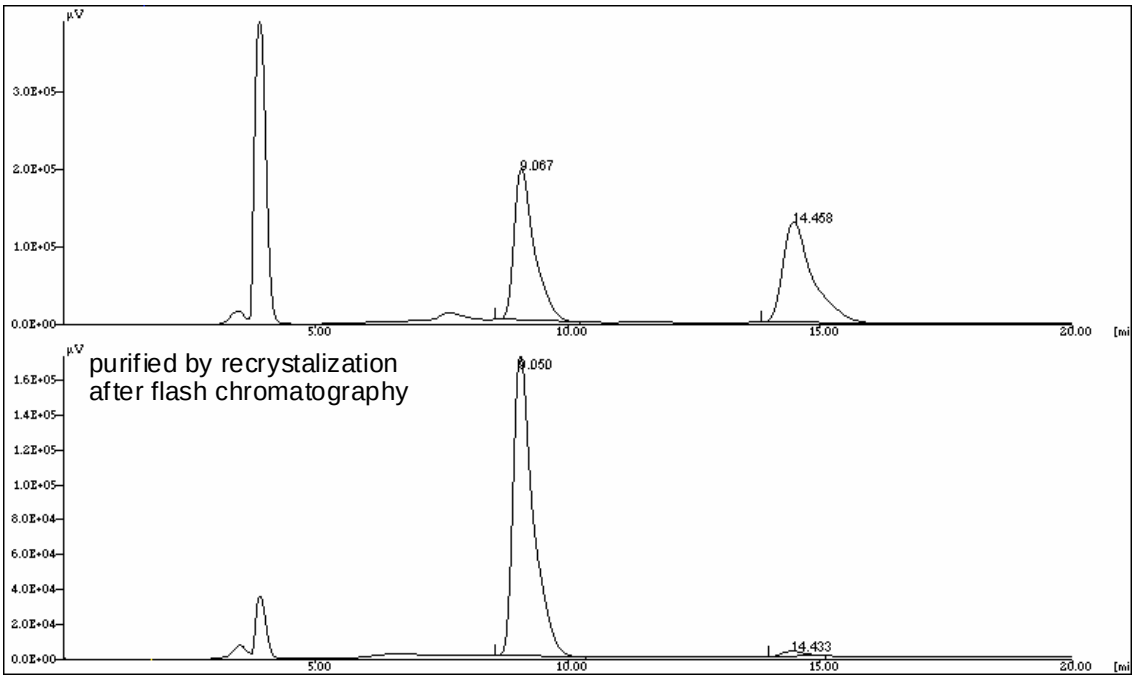
3. Characterization of the Michael adducts

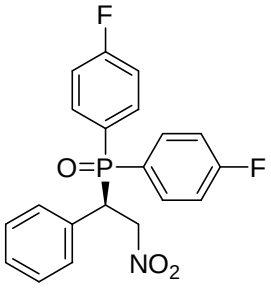


(3a) (2-Nitro-1-phenylethyl)diphenyl phosphine oxide

White solid. mp 204.3-205.1 ^{o}C. 64% yield, 60% ee; after recrystallization from MeOH, 96% ee. $[\alpha]_D^{27}$ -58.7 (*c* 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.37-4.45 (m, 1H), 4.72-4.78 (m, 1H), 5.05-5.15 (m, 1H), 7.19-8.01(m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.4, 46.3, 75.7, 75.8, 128.2, 128.4, 128.8, 129.2, 129.4 (two peaks), 129.5, 130.7, 130.9, 131.0, 131.1, 131.2, 131.6, 131.7, 132.0, 132.1, 132.7 (two peaks). ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 30.5. IR (KBr) 708, 1185, 1551, 3060 cm^{-1}. LRMS (ESI) m/z 374.0 ($M+Na^+$), HRMS (ESI) m/z 374.0932 ($M+Na^+$), calc. for $C_{20}H_{18}NO_3PNa$ 374.0917.

The ee was determined by chiral HPLC; CHIRALCEL IA (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 9.1 min and 14.4 min.

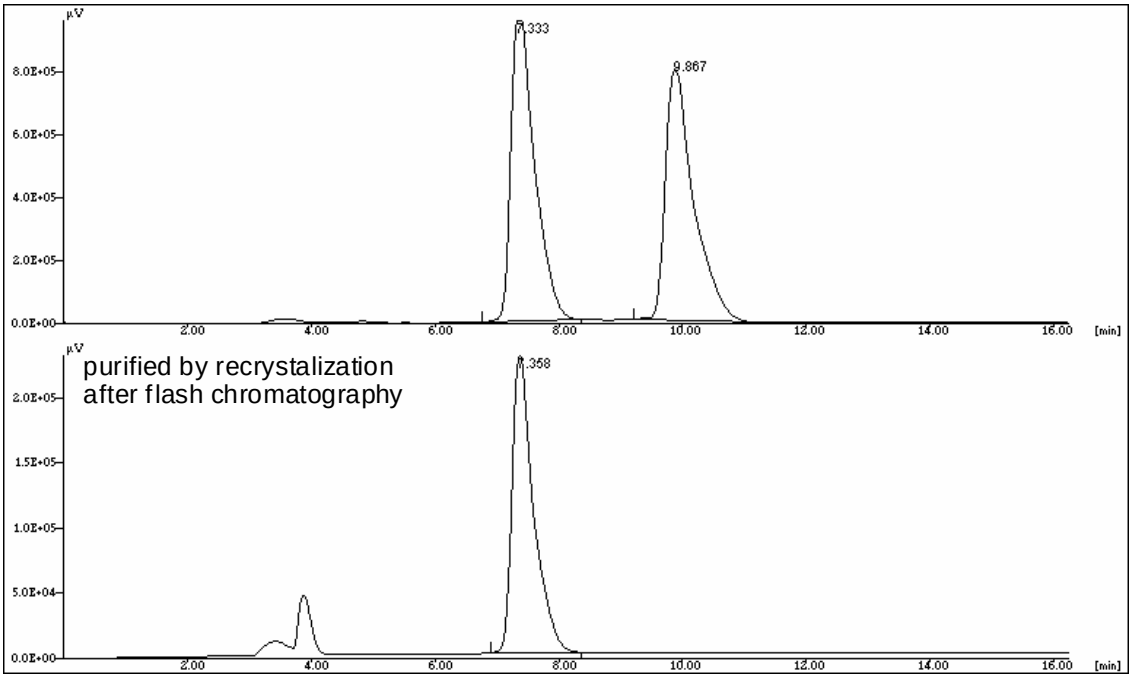


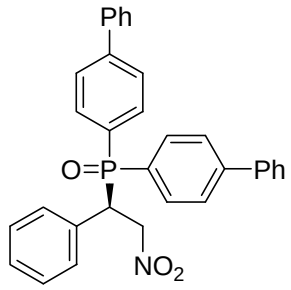


(3b) (2-Nitro-1-phenylethyl)di-4-fluorophenyl phosphine oxide

White solid. mp 186.4-187.7 ^{o}C. 92% yield, 60% ee; after recrystallization from ^{t}BuOMe/CH_2Cl_2 mixture, >99% ee. $[\alpha]_D^{27}$ -142.4 (*c* 0.71, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.31-4.40 (m, 1H), 4.71-4.79 (m, 1H), 5.03-5.13 (m, 1H), 6.94-8.02 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.6, 46.5, 75.5, 75.6, 115.7, 115.8, 115.9, 116.1, 116.7, 116.9, 117.0, 117.2, 128.5, 128.9, 129.3, 129.4, 131.4, 133.4, 133.5, 133.6 (two peaks), 133.7, 133.9, 163.4, 163.9, 166.7, 167.3. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 29.6. IR (KBr) 758, 1162, 1594, 3077 cm^{-1}. HRMS (ESI) m/z 410.0731 ($M+Na^+$), calc. for $C_{20}H_{16}F_2NO_3PNa$ 410.0734.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 7.4 min and 9.9 min.

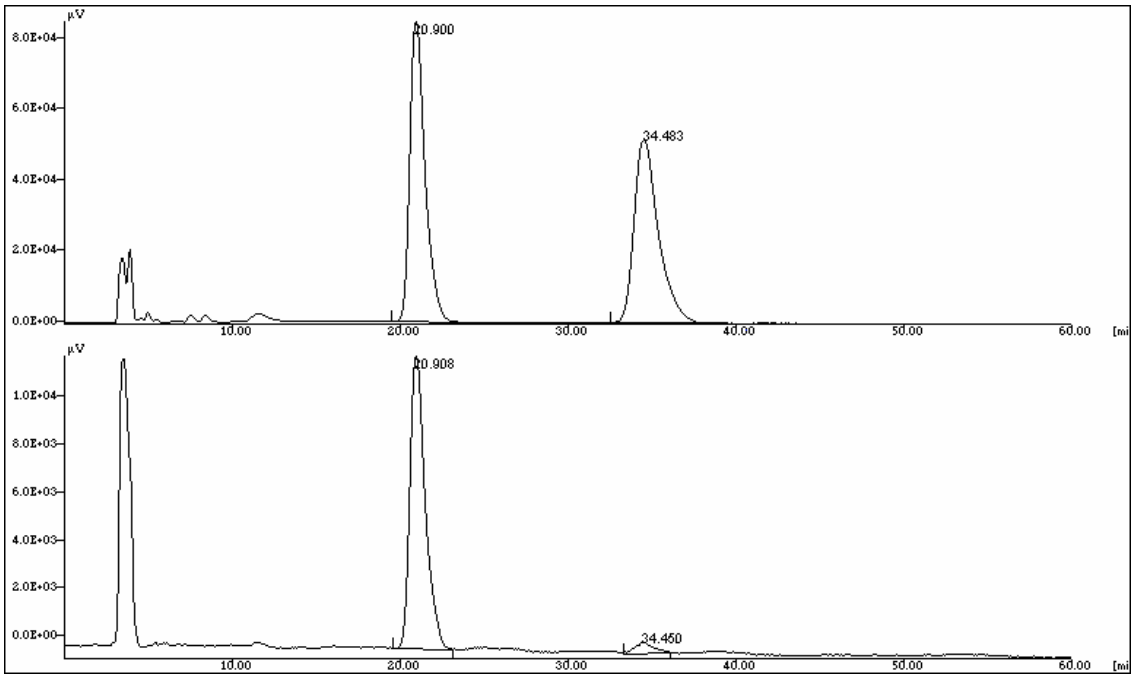


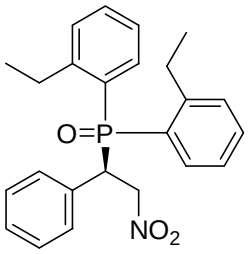


(3c) (2-Nitro-1-phenylethyl)di-4-phenylphenyl phosphine oxide

White solid. mp 236.9-238.5 ^{o}C. 85% yield, 50% ee; after recrystallization from MeOH, 91% ee. $[\alpha]_D^{27}$ -64.5 (*c* 0.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.43-4.52 (m, 1H), 4.80-4.88 (m, 1H), 5.11-5.21 (m, 1H), 7.23-8.10 (m, 23H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.6, 46.5, 75.8, 75.9, 126.9, 127.0, 127.2, 127.3, 127.9, 128.0, 128.3, 128.4, 128.5, 128.9 (two peaks), 129.1, 129.2, 129.3, 129.5, 129.6, 131.5, 131.6, 131.7, 131.8, 139.5, 144.8, 145.7. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 30.6. IR (KBr) 761, 1176, 1552, 3030 cm^{-1}. HRMS (ESI) m/z 504.1722 ($M+H^+$), calc. for $C_{32}H_{27}NO_3P$ 504.1729.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 20.9 min and 34.5 min.

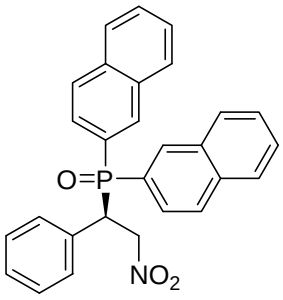




(3d) (2-Nitro-1-phenylethyl)di-2-ethylphenyl phosphine oxide

Colorless oil. 77% yield, 75% ee. $[\alpha]_D^{27}$ -36.1 (*c* 0.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 0.76 (t, *J*=7.4Hz, 3H), 0.92 (t, *J*=7.4Hz, 3H), 2.34-2.47 (m, 1H), 2.68-2.78 (m, 1H), 2.80-2.91 (m, 2H), 4.62-4.69 (m, 1H), 5.05-5.12 (m, 1H), 5.20-5.30 (m, 1H), 7.00-7.95 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 15.0, 15.3, 26.5, 26.6, 27.1, 27.2, 44.5, 45.0, 76.5, 76.6, 125.2, 125.3, 126.0, 126.1, 128.1 (two peaks), 128.5, 128.6, 129.3, 129.4 (two peaks), 129.7, 129.8, 130.2 (two peaks), 130.6, 131.3, 131.4, 132.0 (three peaks), 132.1, 132.2 (two peaks), 132.6 (two peaks), 148.4, 148\5, 149.7, 149.8. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 35.0. IR (film) 771, 1217, 1524, 3021 cm^{-1}. LRMS (ESI) m/z 408.0 ($M+H^+$), HRMS (ESI) m/z 408.1745 ($M+H^+$), calc. for $C_{24}H_{27}NO_3P$ 408.1729.

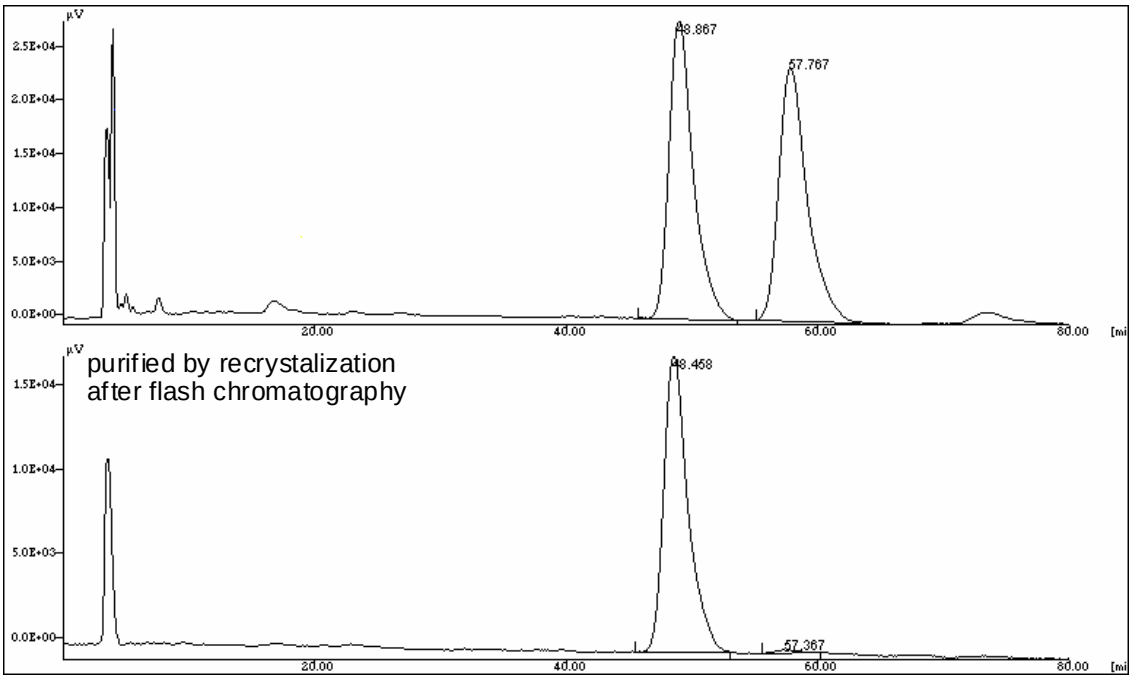
The ee was determined by chiral HPLC; CHIRALCEL IA (4.6 mm i.d. x 250 mm); hexane/2-propanol 90/10; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 11.2min and 12.6min.

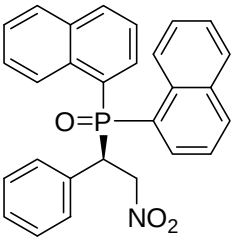


(3e) (2-Nitro-1-phenylethyl)di-2-naphthyl phosphine oxide

White solid. mp 229.1-230.4 °C. 92% yield, 65% ee; after recrystallization from MeOH, 99% ee. $[\alpha]_D^{27}$ -73.5 (*c* 0.34, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 4.61-4.69 (m, 1H), 4.79-4.87 (m, 1H), 5.13-5.23 (m, 1H), 7.17-8.68 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.4, 46.2, 75.9, 76.0, 125.1, 125.2, 125.3, 125.4, 126.5, 126.9, 127.5, 127.7, 127.8, 127.9 (two peaks), 128.1, 128.2, 128.3 (two peaks), 128.4, 128.8 (two peaks), 129.0, 129.2, 129.4, 129.5 (two peaks), 131.7, 131.8, 132.1, 132.3, 132.6, 132.8, 133.6, 133.7, 133.9, 134.0, 134.5, 134.6, 134.9, 135.0. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 30.8. IR 745, 1175, 1550, 3055 cm^{-1}. LRMS (ESI) m/z 452.1 ($M+H^+$), HRMS (ESI) m/z 452.1410 ($M+H^+$), calc. for $C_{28}H_{23}NO_3P$ 452.1410.

The ee was determined by chiral HPLC; CHIRALCEL ADH (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 48.9 min and 57.8 min.

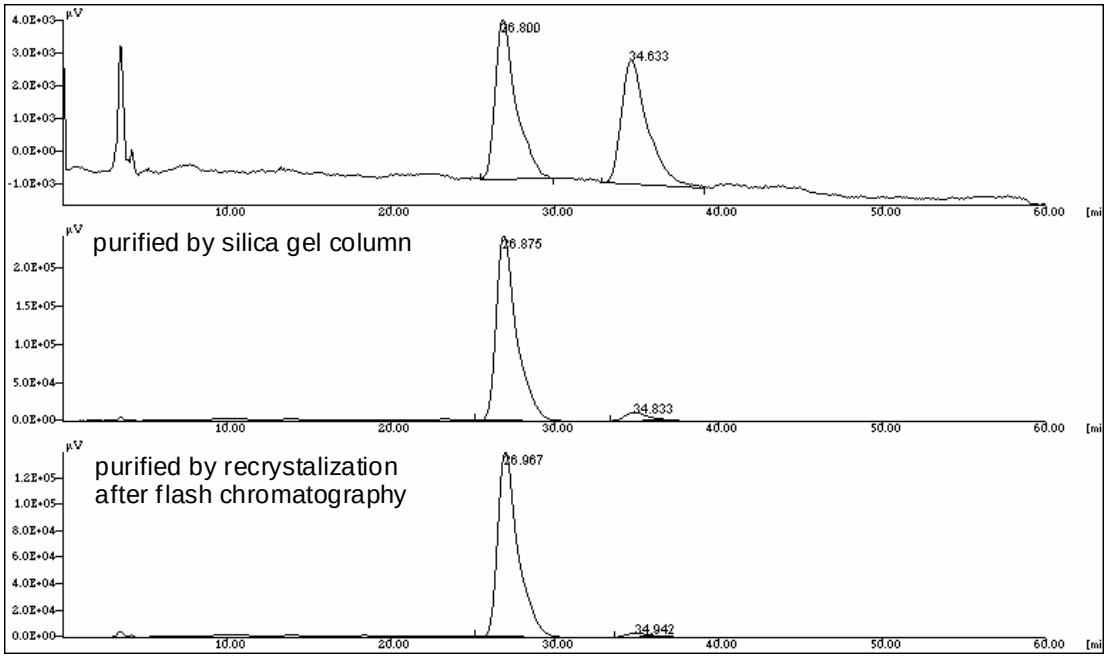


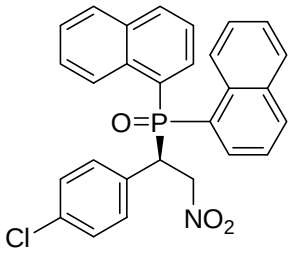


(3f) (2-Nitro-1-phenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 203.8-205.7 ^{o}C. 94% yield, 91% ee; after recrystallization 95% ee. $[\alpha]_D^{26}$ -86.7 (*c* 0.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.86-4.94 (m, 1H), 5.14-5.22 (m, 1H), 5.32-5.40 (m, 1H), 7.00-8.77 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.2, 46.1, 76.5, 76.6, 123.9, 124.1, 124.4, 124.6, 125.7, 125.8, 126.2, 126.4, 126.5, 126.6, 126.8, 127.2, 127.5, 127.8, 128.0, 128.1, 128.5 (two peaks), 128.6, 128.7, 129.1, 129.3, 129.4, 130.6, 130.8, 131.9 (two peaks), 132.3, 132.4, 133.2, 133.3, 133.4, 133.5, 133.6, 133.7, 133.8, 133.9, 134.0, 134.2, 134.3. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.7. (KBr) 773, 1161, 1550, 3044 cm^{-1}. LRMS (ESI) m/z 452.2 ($M+H^+$), HRMS (ESI) m/z 452.1435 ($M+H^+$), calc. for calc. for $C_{28}H_{23}NO_3P$ 452.1416.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 26.9 min and 34.8 min.

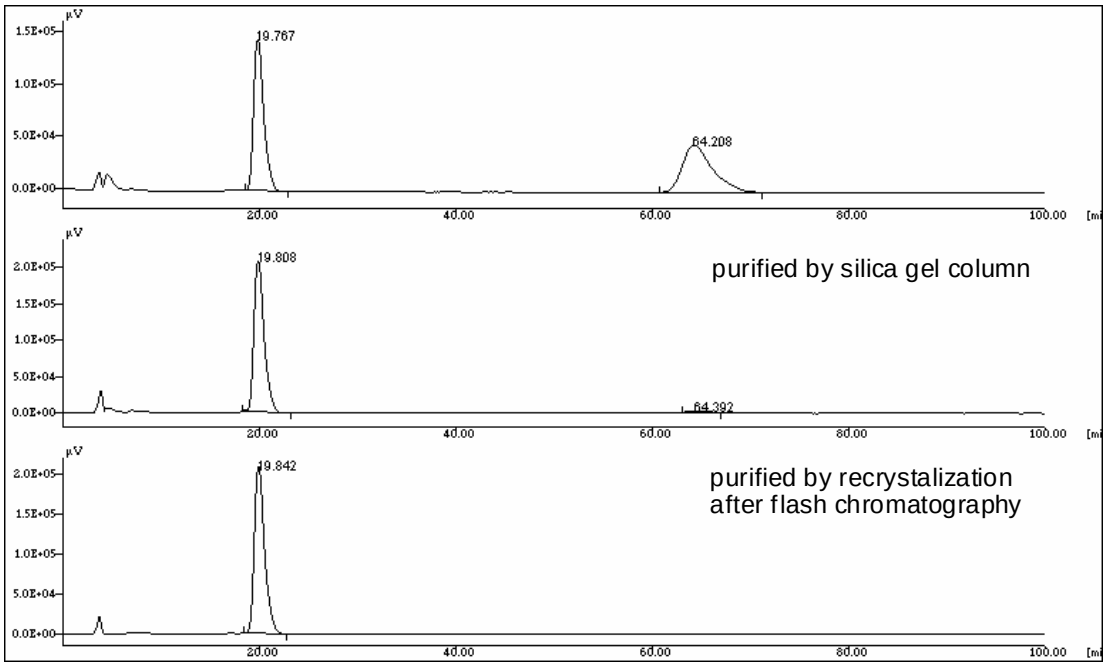


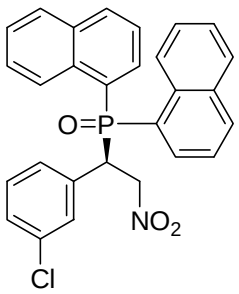


(4a) (2-Nitro-1-(4-chlorophenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 237.2-238.8 ^{o}C. 94% yield, 96% ee; after recrystallization >99% ee. $[\alpha]_D^{24}$ -88.2 (*c* 3.59, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.82-4.90 (m, 1H), 5.12-5.19 (m,1H), 5.26-5.35 (m, 1H), 6.97-8.76 (m, 18H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm): δ 44.7, 45.5, 76.3, 76.4, 124.0, 124.2, 124.4, 125.6 (two peaks), 126.2, 126.3, 126.5 (two peaks), 127.0, 127.3, 127.5, 127.9, 128.3, 128.7, 129.2, 130.5, 130.6, 130.7 (two peaks), 132.3, 132.4, 133.3, 133.4, 133.6 (two peaks), 133.8, 134.1, 134.2 (two peaks), 134.4. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.6. IR (KBr): 768, 1158, 1550, 3051 cm^{-1}. LRMS (ESI) m/z 486.2 ($M+H^+$), HRMS (ESI) m/z 486.1050 ($M+H^+$), calc. for $C_{28}H_{22}ClO_3P$ 486.1026.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 60/40; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 19.8 min and 64.4 min.

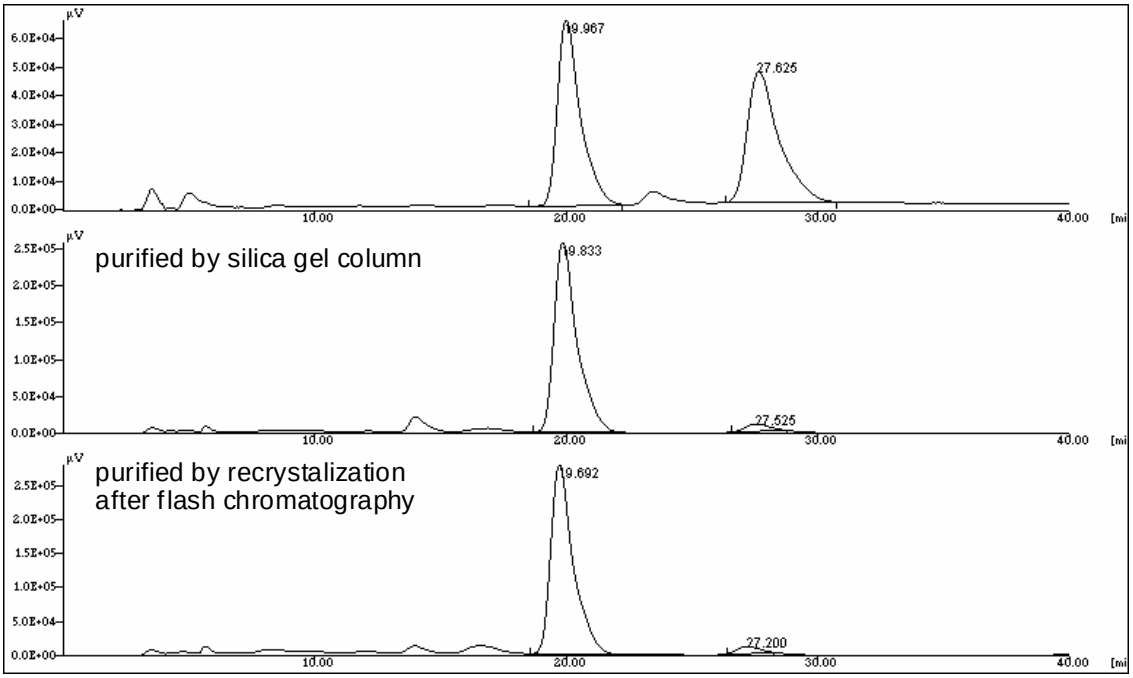


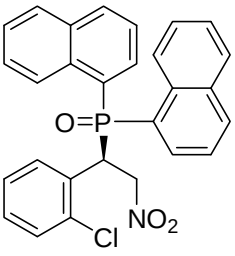


(4b) (2-Nitro-1-(2-nitrophenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 176.2-177.7 ^{o}C. 96% yield, 92% ee; after recrystallization 95% ee. $[\alpha]_D^{26}$ -80.8 (*c* 1.38, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.79-4.87 (m, 1H), 5.15-5.22 (m, 1H), 5.28-5.38 (m, 1H), 6.87-8.74 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 44.9, 45.8, 76.0, 76.1, 124.0, 124.2, 124.4, 124.6, 125.6, 125.7, 126.4, 126.6 (two peaks), 127.0, 127.2, 127.5 (two peaks), 127.9, 128.2, 128.3, 128.6, 129.2, 129.4, 129.5, 129.6 (two peaks), 130.4, 130.6, 132.1, 132.2, 133.3, 133.4, 133.6, 133.7, 133.8, 133.9 (two peaks), 134.1, 134.2, 134.3 (two peaks), 134.4 (two peaks). ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 37.2. (KBr) 772, 1158, 1554, 3058 cm^{-1}. LRMS (ESI) m/z 486.1 ($M+H^+$), HRMS (ESI) m/z 486.1047. ($M+H^+$), calc. for $C_{28}H_{22}ClNO_3P$ 486.1026.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 19.7 min and 27.2 min.

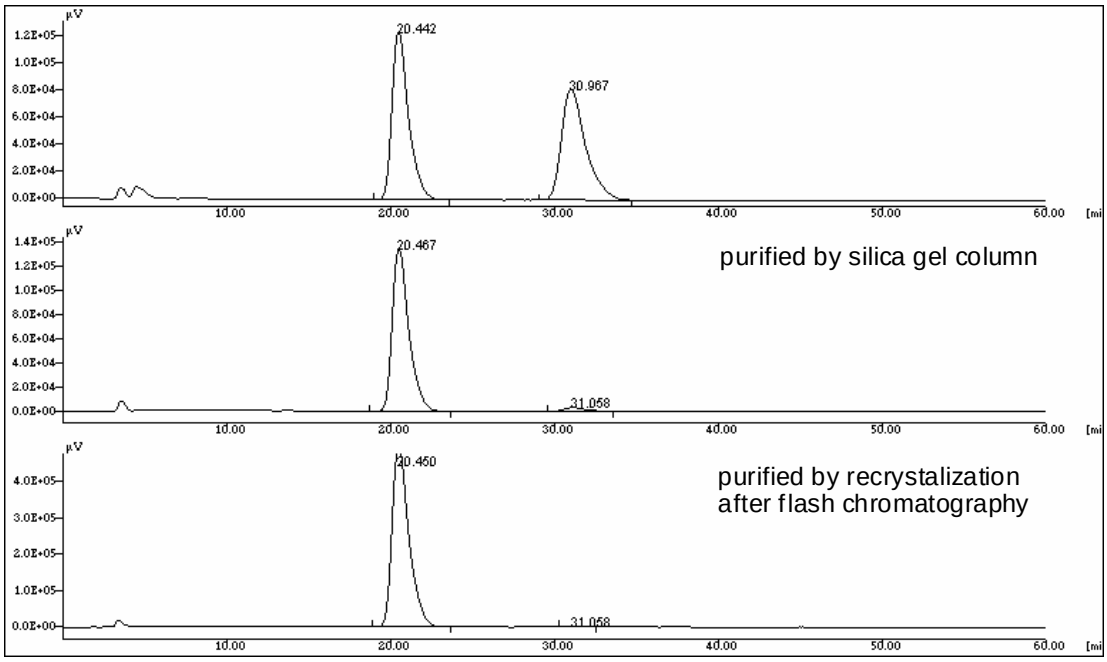


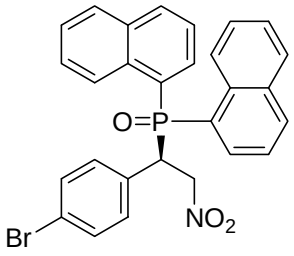


(4c) (2-Nitro-1-(2-chlorophenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 249.3-250.5 ^{o}C. 98% yield, 93% ee; after recrystallization 99% ee. $[\alpha]_D^{25}$ -102.4 (*c* 2.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.14-5.21 (m, 1H), 5.29-5.38 (m, 1H), 5.63-5.72 (m, 1H), 6.87-8.79 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 40.4, 41.3, 76.2, 76.3, 123.8, 124.0, 124.4, 124.6, 125.7, 126.1, 126.2, 126.6, 126.7, 126.9 (two peaks), 127.1, 127.4, 127.5, 127.9, 128.2, 128.3, 129.2 (two peaks), 129.5 (two peaks), 130.2 (two peaks), 130.3 (two peaks), 130.9, 131.0, 132.4, 132.5, 133.1, 133.2, 133.5, 133.6 (two peaks), 133.7, 133.9, 134.0, 134.1 (two peaks), 134.3, 134.4, 134.7, 134.8. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 38.9. IR (KBr) 764, 1161, 1565, 2923 cm^{-1}. LRMS (ESI) m/z 486.1 ($M+H^+$), HRMS (ESI) m/z 486.1044 ($M+H^+$), calc. for $C_{28}H_{22}ClNO_3P$ 486.1026.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 60/40; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 20.5 min and 31.1 min.



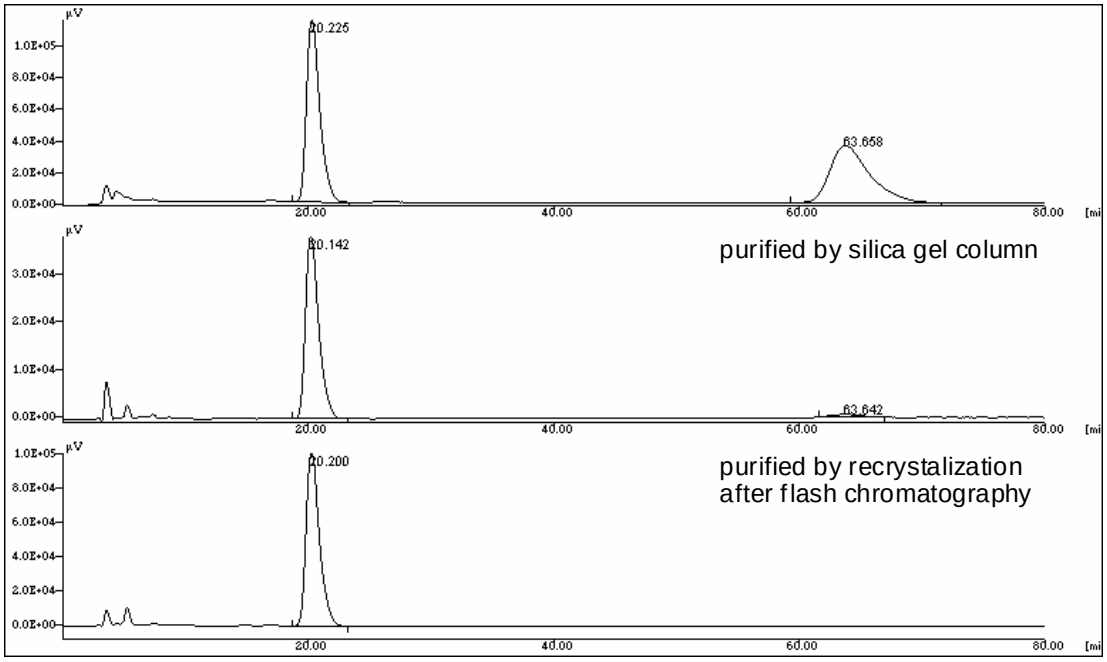


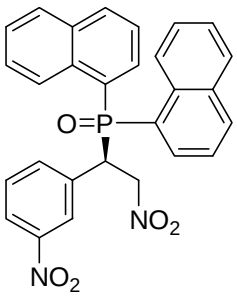
(4d) (2-Nitro-1-(4-bromophenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 250.7-252.1 ^{o}C. 99% yield; 93% ee, after recrystallization >99% ee. $[\alpha]_D^{26}$ -61.3 (*c* 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.80-4.89 (m, 1H), 5.11-5.19 (m, 1H), 5.26-5.35 (m, 1H), 7.12-8.76 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 44.8, 45.6, 76.2, 76.3, 122.4, 122.5, 124.0, 124.2, 124.4, 124.6, 125.6 (two peaks), 126.1, 126.3, 126.5 (two peaks), 126.9, 127.4, 127.5, 127.9, 128.2, 128.8, 129.2, 130.6, 130.8, 130.9, 131.0 (two peaks), 131.7, 132.3, 132.4, 133.3, 133.4 (two peaks), 133.6 (two peaks), 133.8, 134.1, 134.2 (two peaks), 134.4. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.6. IR (KBr) 770, 1158, 1549, 3052 cm^{-1}. LRMS (ESI) m/z 552.0 ($M+Na^+$), HRMS (ESI) m/z 552.0332 ($M+Na^+$)

554.0317 ($M+Na^+$), calc. for $C_{28}H_{21}{}^{79}BrNO_3PNa$ 552.0335 and $C_{28}H_{21}{}^{81}BrNO_3PNa$ 554.0314.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 50/50; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 20.1 min and 63.6 min.



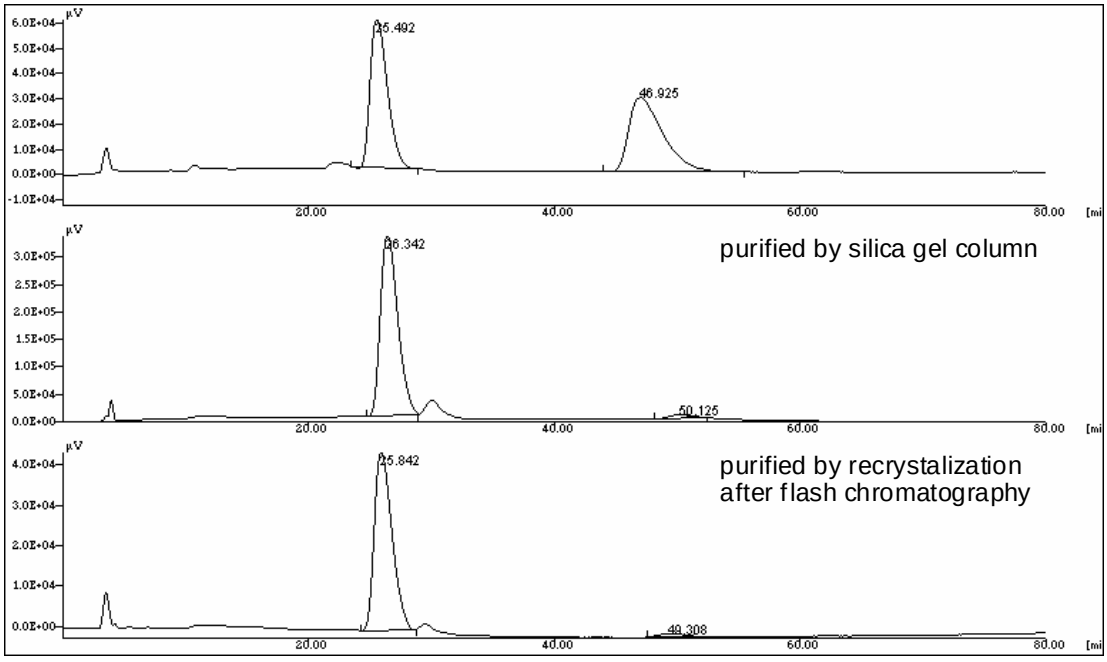


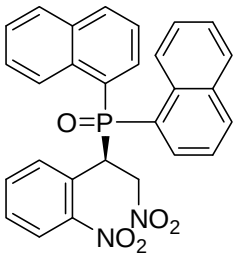
(4e) (2-Nitro-1-(3-nitrophenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 196.3-198.0 °C. 95% yield, 96% ee; after recrystallization 96% ee. $[\alpha]_D^{26}$ -124.6 (*c* 2.59, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 4.94-5.02 (m, 1H), 5.23-5.30 (m, 1H), 5.36-5.46 (m, 1H), 7.16-8.72 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.1, 45.9, 75.6, 75.7, 123.0, 124.1, 124.3, 124.4, 124.5, 124.6, 125.4 (two peaks), 125.7, 126.4, 126.5, 126.6, 127.0, 127.1, 127.5, 127.7, 128.1, 128.7, 129.2, 129.4, 130.3, 130.4, 132.1, 132.2, 133.2, 133.3, 133.6 (two peaks), 133.7, 133.9 (two peaks), 134.1, 134.2, 134.4 (two peaks), 134.5, 134.9, 135.0, 147.7. ^{31}P NMR (121MHz, $CDCl_3$,

ppm): δ 37.4. IR (KBr) 732, 1157, 1556, 3064 cm^{-1}. LRMS (ESI) m/z 497.1 ($M+H^+$), HRMS (ESI) m/z 497.1291 ($M+H^+$) calc. for $C_{28}H_{22}N_2O_5P$ 497.1266

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 26.3 min and 50.1 min.



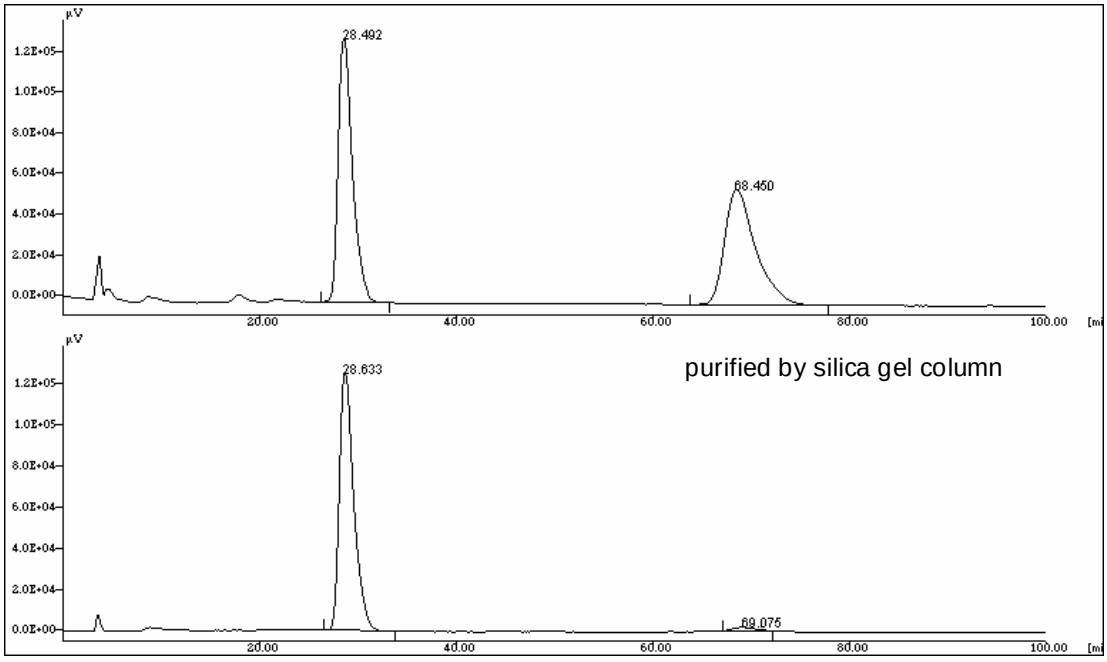


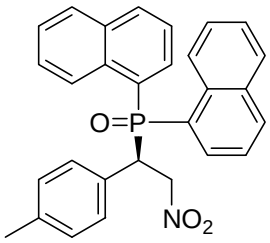
(4f) (2-Nitro-1-(2-nitrophenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 206.3-208.1 °C. 99% yield, 96% ee. $[\alpha]_D^{25}$ -77.8 (*c* 3.46, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 5.16-5.24 (m, 1H), 5.36-5.45 (m, 1H), 6.33-6.41 (m, 1H), 7.13-8.77 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 38.2, 39.0, 76.2 (two peaks), 124.1, 124.3, 124.6, 124.7, 125.2, 125.4, 125.7, 125.8, 126.2, 126.4, 126.5, 126.9, 127.2, 127.6, 128.0, 128.1, 128.2, 128.5, 128.8, 129.2, 130.7, 130.8, 131.1, 131.2, 132.4, 132.6, 133.2, 133.3, 133.5, 133.6, 133.7, 133.8, 134.3 (two peaks), 134.4, 148.9 (two peaks). ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 39.3. IR (KBr) 775, 1183, 1555, 3081 cm^{-1}. LRMS

(ESI) m/z 519.1 ($M+Na^+$), HRMS (ESI) m/z 519.1077 ($M+Na^+$), calc. for $C_{28}H_{21}N_2O_5PNa$ 519.1080.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 60/40; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 28.6 min and 69.1 min.



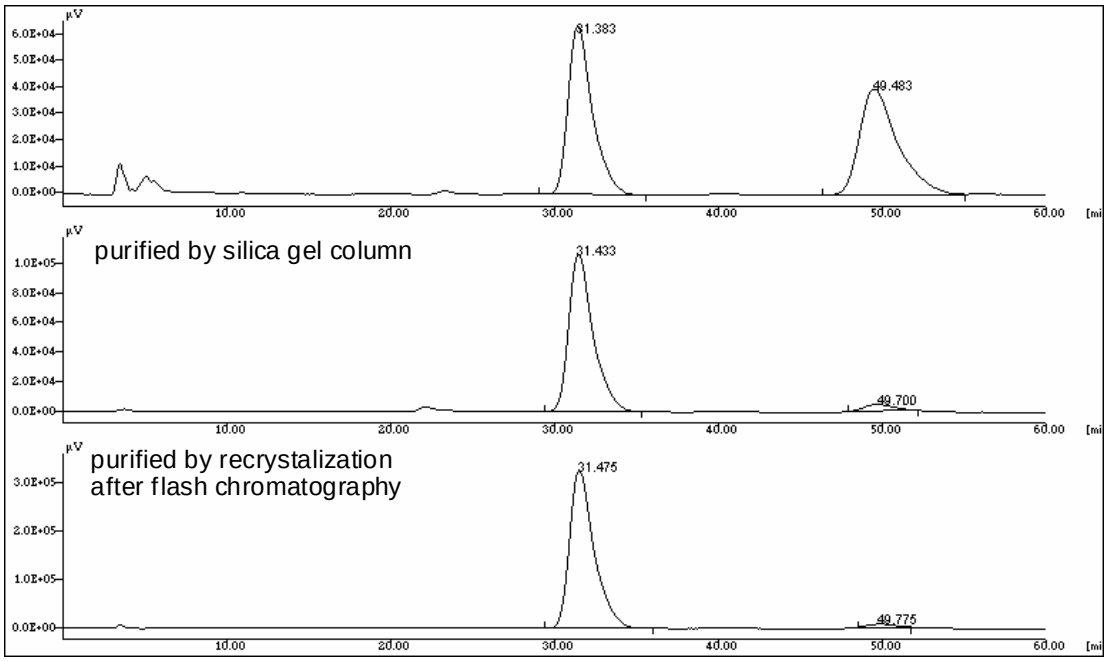


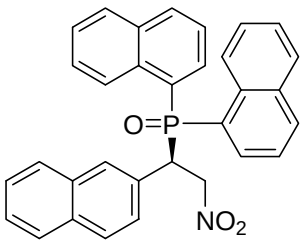
(4g) (2-Nitro-1-(4-methyl-phenyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 229.1-229.9 °C. 90% yield, 90% ee; after recrystallization, 96% ee. $[\alpha]_D^{26}$ -68.5 (*c* 2.73, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm) : δ 2.11 (s, 3H), 4.81-4.89 (m, 1H), 5.08-5.16 (m, 1H), 5.28-5.37 (m, 1H), 6.81-8.79 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.9, 45.0, 45.9, 76.6, 76.7, 123.9, 124.1, 124.4, 124.6, 126.0 (two peaks), 126.1, 126.5, 126.6, 126.8, 127.1, 127.6, 127.8, 128.0, 128.6, 128.7, 128.8, 129.1, 129.2, 129.3, 130.8, 130.9, 132.2, 132.4, 133.3, 133.4, 133.6, 133.7, 133.8, 133.9 (two peaks), 134.2, 134.3, 137.9 (two

peaks). ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.8. IR 773, 1158, 1550, 3052 cm^{-1}. LRMS (ESI) m/z 488.1 ($M+Na^+$), HRMS (ESI) m/z 488.1387 ($M+Na^+$), calc. for $C_{29}H_{24}NO_3PNa$ 488.1386.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 70/30; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 31.4 min and 49.7 min.



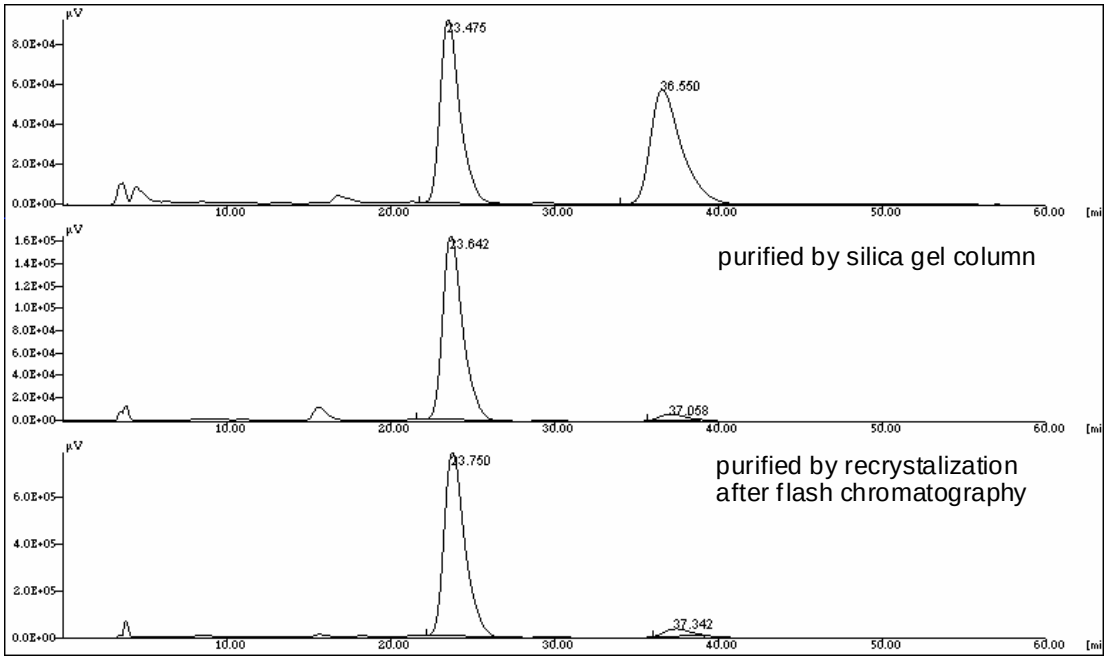


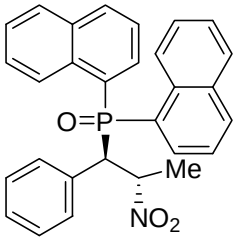
(4h) (2-Nitro-1-(2-naphthyl)ethyl)di-1-naphthyl phosphine oxide

White solid. mp 246.1-247.5 ^{o}C. 75% yield, 92% ee; after recrystallization, 92% ee. $[\alpha]_D^{27}$ -67.7 (*c* 0.33, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.01-5.09 (m, 1H), 5.18-5.26 (m, 1H), 5.41-5.51 (m, 1H), 7.13-8.80 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.4, 46.3, 76.6 (two peaks), 123.9, 124.1, 124.5, 124.6, 125.7 (two peaks), 126.1, 126.2, 126.4, 126.6 (two peaks), 126.8 (two peaks), 126.9, 127.0, 127.3, 127.4, 127.7, 127.9, 128.3, 128.5, 128.7, 128.8, 128.9, 129.2, 129.5, 129.5, 130.9, 131.0, 132.2, 132.3, 132.7, 133.0, 133.2, 133.4

(two peaks), 133.5, 133.6, 133.8, 133.9, 134.0 (two peaks), 134.3, 134.4. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.9. IR (KBr) 765, 1161, 1565, 2923 cm^{-1}. LRMS (ESI) m/z 502.2 ($M+H^+$), HRMS (ESI) m/z 502.1594 ($M+H^+$), calc. for $C_{32}H_{25}NO_3P$ 502.1572.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 60/40; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 23.6 min and 37.1 min.



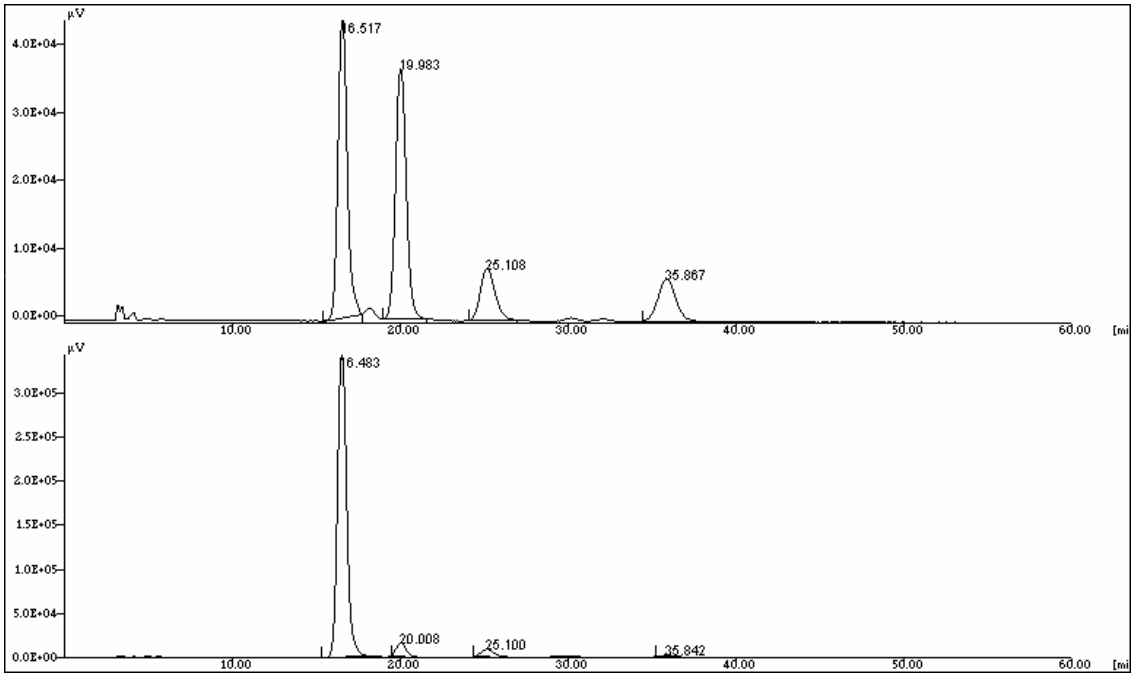


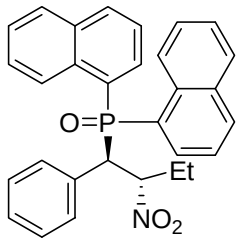
(6a) (2-Methyl-2-nitro-1-phenylethyl)di-1-naphthyl phosphine oxide

White solid. mp 197.4-198.7 ^{o}C. 70% yield, 90% ee, 95:5 dr. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.73 (d, J=6.8 Hz, 3H), 4.93-5.04 (m, 1H), 5.10 (dd, J=2.9, 11.7 Hz, 1H), 7.19-8.96 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 15.3, 48.7, 49.6, 82.8, 82.9, 123.8, 124.0, 124.7, 124.8, 125.7, 125.8, 126.0 (two peaks), 126.3, 126.6, 127.3, 127.4, 127.5, 127.8, 128.3, 128.7 (two peaks), 128.9, 129.3, 131.0, 131.1, 131.3, 131.9, 132.0, 132.2, 132.3, 133.2 (two peaks), 133.8 (two peaks), 134.0, 134.1. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.5. IR (KBr) 775, 1158, 1553, 3060

cm^{-1}. LRMS (ESI) m/z 488.1 ($M+Na^+$), HRMS (ESI) m/z 488.1386 ($M+Na^+$), calc. for $C_{29}H_{24}O_3NPNa$ 488.1386.

The ee was determined by chiral HPLC; CHIRALCEL IA (4.6 mm i.d. x 250 mm); hexane/2-propanol 85/15; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 16.5 min and 20.0 min; 25.1 min and 35.8 min.



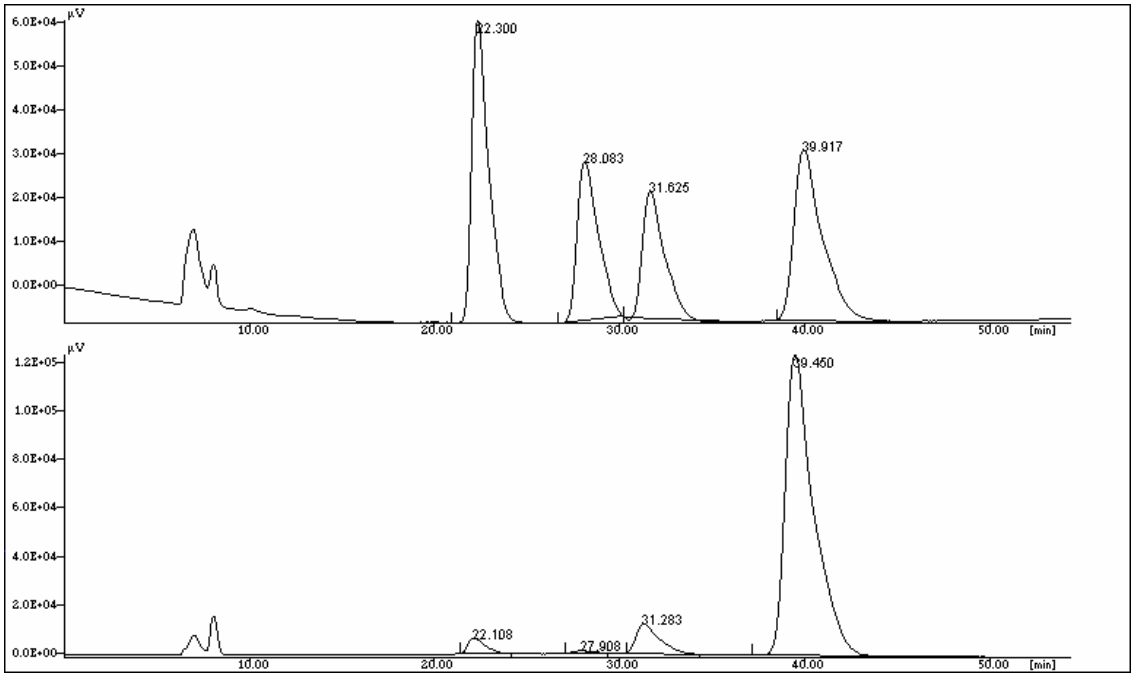


(6b) (2-Ethyl-2-nitro-1-phenylethyl)di-1-naphthyl phosphine oxide

White solid. mp 214.2-215.5 °C. 70% yield, 93% ee, 95:5 dr. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.75 (t, J=7.3 Hz, 3H), 1.78-1.94 (m, 1H), 2.53-2.65 (m, 1H), 4.75-4.86 (m, 2H), 6.74-8.98 (m, 19H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 11.0, 23.2, 49.4, 50.3, 89.8, 89.9, 123.8, 124.0, 124.6, 124.8, 125.8 (two peaks), 125.9, 126.0, 126.1, 126.3, 126.6, 127.3, 127.5, 127.8, 128.3, 128.6, 128.7, 128.9, 129.3, 130.8, 130.9, 131.8, 131.9, 132.2, 132.3, 132.8, 133.1, 133.2, 133.4, 133.7, 133.8 (two peaks), 134.1. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 36.9. IR (KBr) 772, 1157,

1554, 3055 cm^{-1}. LRMS (ESI) m/z 480.0 ($M+H^+$), HRMS (ESI) m/z 480.1726 ($M+H^+$), calc. for $C_{30}H_{27}NO_3P$ 480.1729.

The ee was determined by chiral HPLC; CHIRALCEL AD-H (4.6 mm i.d. x 250 mm); hexane/2-propanol 80/20; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 22.3 min and 39.9 min, 27.9 min and 31.3min.



4. Preparation and characterization of donors

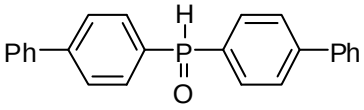
Donor **2a** was purchased from Sigma-Aldrich and used without purification. **2b-f** were prepared using the literature protocol.[1] Data for **2b** was consistent with data reported in the literature.

(2c) Di-4-phenylphenyl phosphine oxide

White solid. mp 159.7-161.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.39-7.85 (m, 18H), 8.29 (d, J=418.9Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 127.0, 127.2, 127.4, 128.0, 128.7, 129.0, 130.4, 130.9, 131.4, 139.4, 145.1 (two peaks). ^{31}P NMR (121MHz,

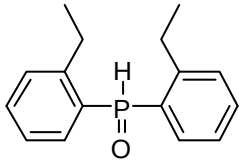
[1] Busacca, C. A.; Lorenz, J. C.; Gringerg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayke, C. H. *Org. Lett.* **2005**, *7*, 4277-4280.

$CDCl_3$, ppm): δ 21.5. IR (KBr) 760, 1128, 3025 cm^{-1}. LRMS ESI m/z 354.9 (M^+), HRMS ESI m/z 355.1246 ($M+H^+$), calc. for $C_{24}H_{20}OP$ 355.1252.



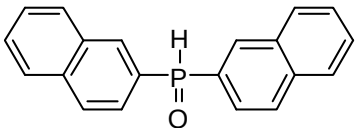
(2d) Di-2-ethylphenyl phosphine oxide

White solid. mp 67.6-68.1 ^oC. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.04 (t, J=7.5Hz, 6H), 2.72 (q, J=7.5, 15.0Hz, 4H), 7.27-7.73 (m, 8H), 8.27 (d, J=474.8Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.9, 26.3, 26.4, 125.9, 126.0, 128.5, 129.2, 129.3, 129.9, 132.2, 132.3, 132.6 (two peaks), 147.1, 147.3. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 17.7. IR (KBr) 754, 1180, 3054 cm^{-1}. LRMS ESI m/z 259.2 ($M+H^+$), HRMS ESI m/z 259.1247 ($M+H^+$), calc. for $C_{16}H_{20}OP$ 259.1252.



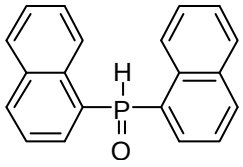
(2e) Di-2-naphthyl phosphine oxide

White solid. mp 90.4-92.0 ^oC. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.51-8.40 (m, 14H), 8.33 (d, 1H, J = 480.9Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 124.9, 125.1, 127.0, 127.7, 127.8, 128.3, 128.7, 128.9, 129.0, 132.3, 132.5, 132.7, 132.8, 134.9 (two peaks). ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 22.3. IR (KBr) 748, 1188, 3050 cm^{-1}. LRMS EI m/z 301.9 ($M-H^+$), HRMS EI m/z 302.0847 (M^+), calc. for $C_{20}H_{15}OP$ 302.0861.



(2f) Di-1-naphthyl phosphine oxide

White solid. mp 164.9-165.6 ^oC. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.43-8.41 (m, 14H), 8.89(d, 1H, J = 481.4Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 124.8, 125.0, 125.2, 126.5, 126.7, 127.8, 127.9, 129.1, 132.7, 132.8, 133.0, 133.4, 133.6 (two peaks), 133.7. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 19.2. (KBr) 773, 1179, 3045 cm^{-1}. LRMS EI m/z 302.0 (M^+), HRMS EI m/z 302.0850 (M^+), calc. for $C_{20}H_{15}OP$ 302.0861.

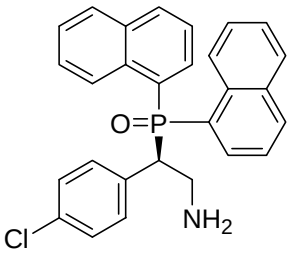


5. Reduction of adducts

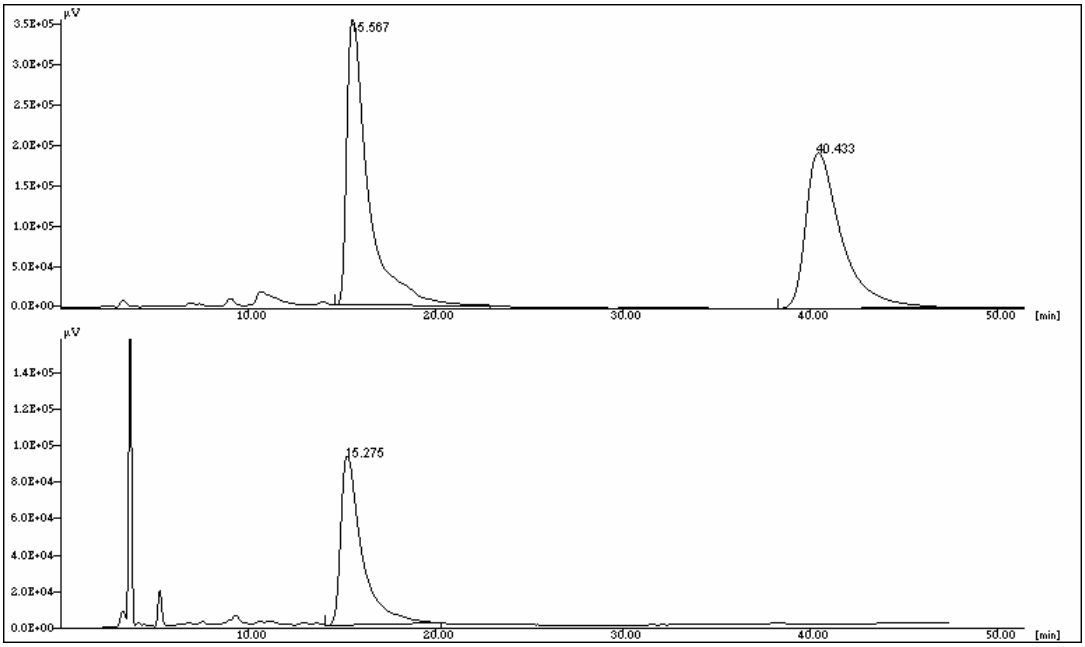
(7) 2-(4-Chlorophenyl)-2-(dinaphthalen-1-ylphosphoryl)ethanamine

In a seal tube containing adduct **4a** (46.8 mg, 0.1 mmol), zinc (45.8 mg, 0.7 mmol, 7eq.) and a stirring bar, 0.6 ml MeOH, 0.3ml THF, 0.6 ml 6M HCl, were added in this sequence and refluxed until TLC showed the completion of reaction. After cooling down to room temperature, saturated $NaHCO_3$ solution was added dropwise until pH=8. The solution was then filtered through Celite and extracted with CH_2Cl_2 (x 3 times). The organic phase was dried with $MgSO_4$ and the organic solvent was removed. The crude product was loaded onto a short silica gel column. Flash chromatography (gradient elution with CH_2Cl_2/MeOH mixtures; 100/1 to 20/1) led to product **7** (34.2 mg) as a white foam in 89 % yield.

mp 99.4-100.5 ^oC. 89% yield, >99% ee. $[\alpha]_D^{27}$ -20.1 (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 3.42-3.50 (m, 1H), 3.56-3.66 (m, 1H), 3.97-4.04 (m, 1H), 7.04-8.80 (m, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 43.1, 49.2, 50.0, 123.9, 124.1, 124.3, 124.5, 126.0, 126.5, 126.6, 126.7, 127.0, 127.4, 128.2, 128.5, 128.6, 128.7, 129.0, 129.4, 129.7, 131.2, 131.3, 131.4, 131.6, 131.9, 132.0, 132.8, 132.8, 133.3 (two peaks), 133.5 (two peaks), 133.6, 133.7, 133.8, 133.9, 134.0, 134.1. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ 37.1. IR (KBr) 772, 1158, 1490, 3055 cm^{-1}. LRMS (ESI) m/z 456.1 ($M+H^+$), HRMS (ESI) m/z 456.1285 ($M+H^+$), calc. for $C_{28}H_{24}ClNOP$ 456.1279.



The ee was determined by chiral HPLC; CHIRALCEL IA (4.6 mm i.d. x 250 mm); hexane/2-propanol 60/40; flow rate 1.0 ml/min; temp 25 °C; detection UV 210 nm; retention time: 15.8 min and 40.4 min.

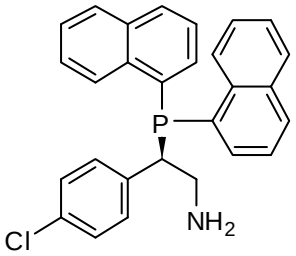


(8) 2-(4-Chlorophenyl)-2-(dinaphthalen-1-ylphosphino)ethanamine

In a seal tube containing phosphine oxide **7** (36.5mg, 0.08 mmol), triphenyl phosphine (42.1mg, 0.16 mmol, 2eq.) and a stiring bar, 1ml toluene and distilled Et_3N (0.22ml, 1.6mmol, 20eq.) were added and cooled down to 0 ^oC. $HSiCl_3$ (0.32ml, 3.2mmol, 40eq.) was then added dropwise to the seal tube. After purging with N_2, the tube was sealed and refluxed. After 12h, the reaction was cooled down to 0 ^oC and diluted with 3ml diethyl ether. 1M NaOH aq. solution was added dropwise. The solution was washed with sat. $NaHCO_3$, brine and water in this sequence. After acidifying the organic layer with 1M HCl, the aqueous layer was washed with diethyl ether (x5 times) and extracted with dichloromethane (x3 times) after re-basification with 1M NaOH aq. solution. The organic extracts were dried with $MgSO_4$ and removed to provide the product **8** (24.2 mg) as a white solid in 70 % yield.

White solid. 70% yield, >99% ee. $[\alpha]_D^{25}$ -62.3 (*c* 0.44, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.94-3.05 (m, 1H), 3.10-3.19 (m, 1H), 3.66-3.72 (m, 1H), 6.99-8.85 (m,

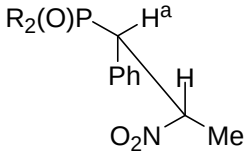
18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 49.3, 45.4, 49.2, 49.3, 125.1, 125.6, 125.8, 125.9, 126.0, 126.4, 126.9, 127.4, 128.3, 128.5, 128.7, 129.3, 129.8, 130.4, 130.5, 131.0, 131.2, 131.9, 132.0, 132.2, 132.8, 133.2, 133.6, 133.8, 134.1, 134.3, 135.6, 135.9, 136.2, 136.5, 137.9, 138.0. ^{31}P NMR (121MHz, $CDCl_3$, ppm): δ -34.8. IR (KBr) 774, 1504, 3050 cm^{-1}. HRMS (ESI) m/z 440.1348 ($M+H^+$), calc. for $C_{28}H_{24}ClNP$ 440.1335.



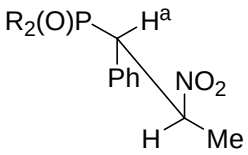
The ee of **8** was determined by converting back to **7** using H_2O_2.

6. Determination of relative configuration of **6a** through NMR and Chemdraw prediction.

The stable conformations of the diastereomers were predicted by Chem3D Ultra MM2 minimization. The relative stereochemistry of the major diastereoisomer is predicted using the coupling constants of H^a obtained with ^{1}H NMR.



Major diastereoisomer: H^a δ 5.10 (dd, J=2.9, 11.7 Hz, 1H)

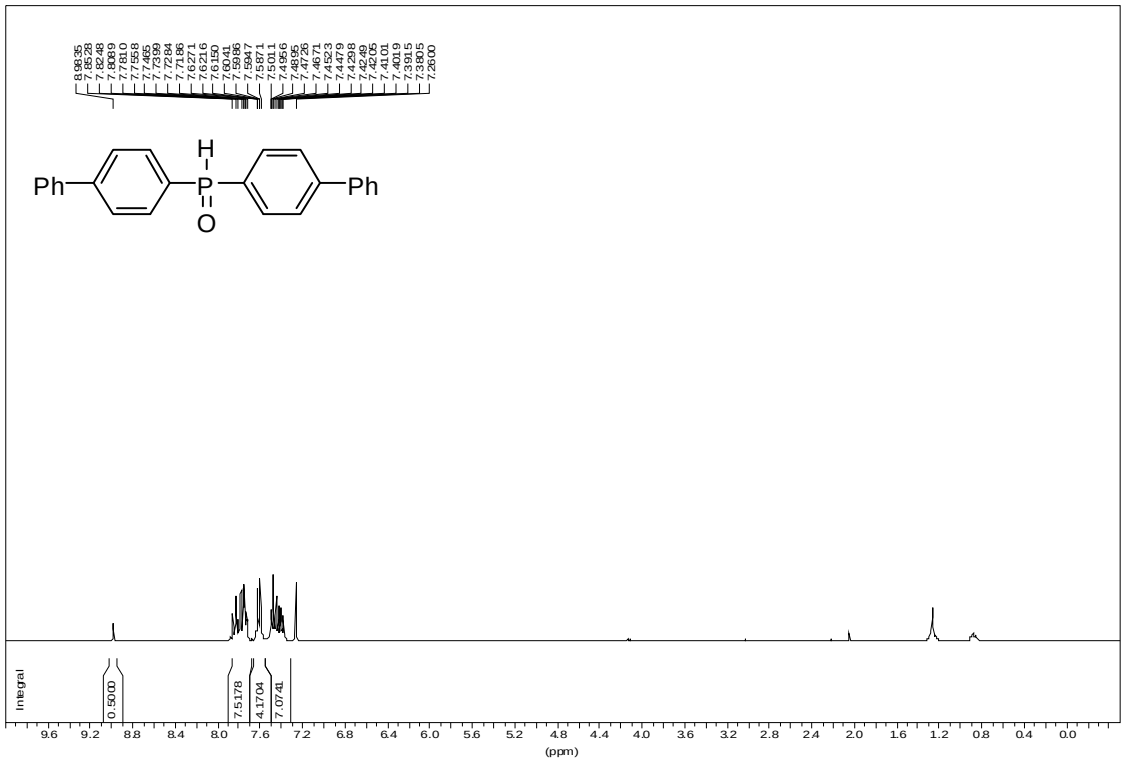


Minor diastereoisomer: H^a δ 4.86 (dd, J=8.2, 10.2Hz)

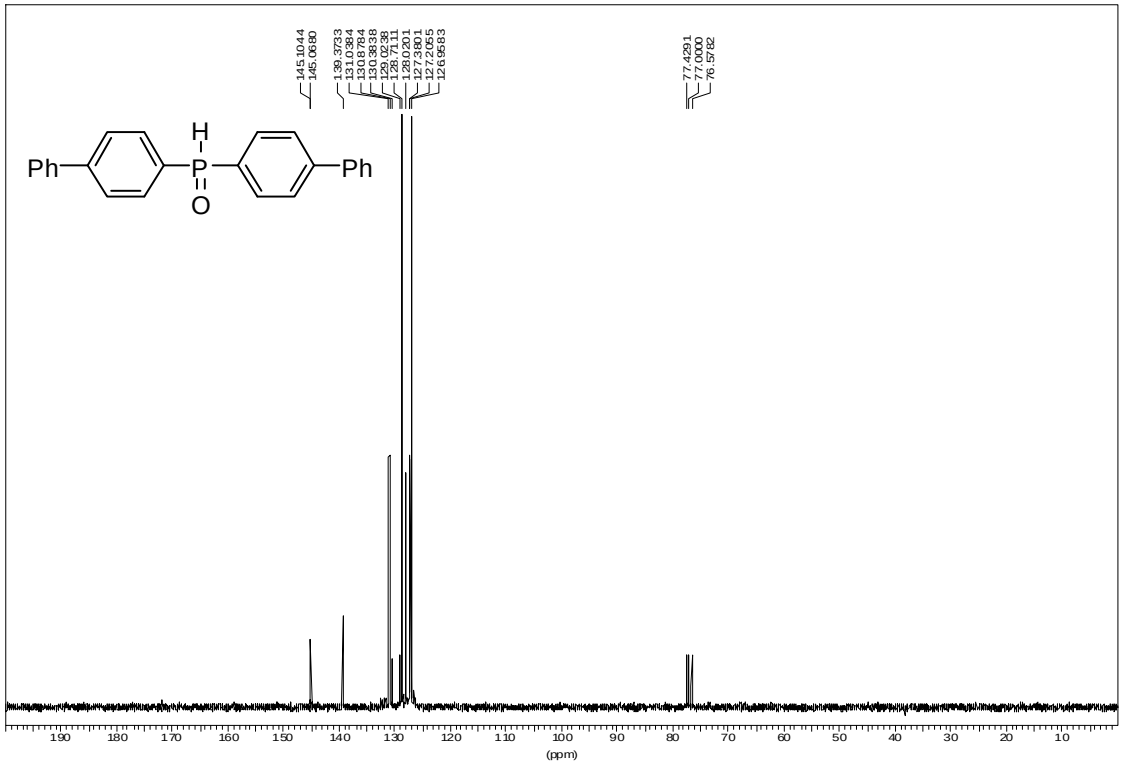
7. Copy of NMR spectrum

(2c) Di-4-phenylphenyl phosphine oxide

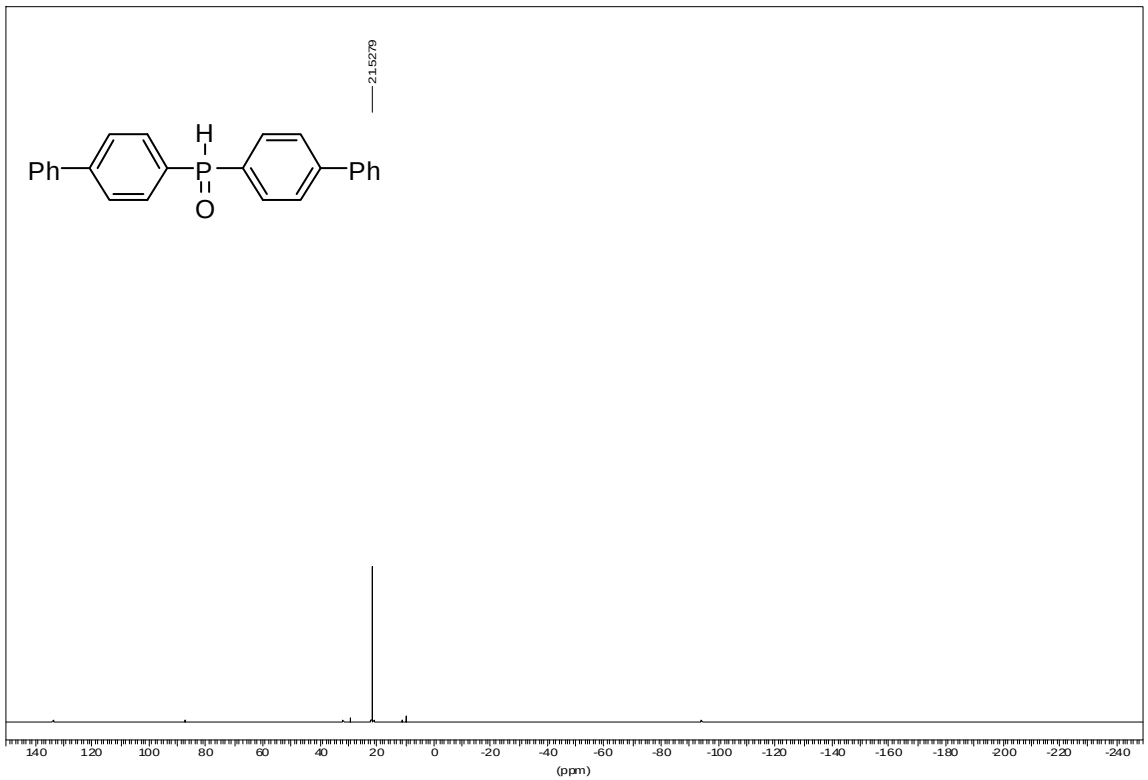
1H normal range AC300 my28fux1.1.1 FuX9124



13C Standard AC300 my29fux1.1.3.1 FuX9124

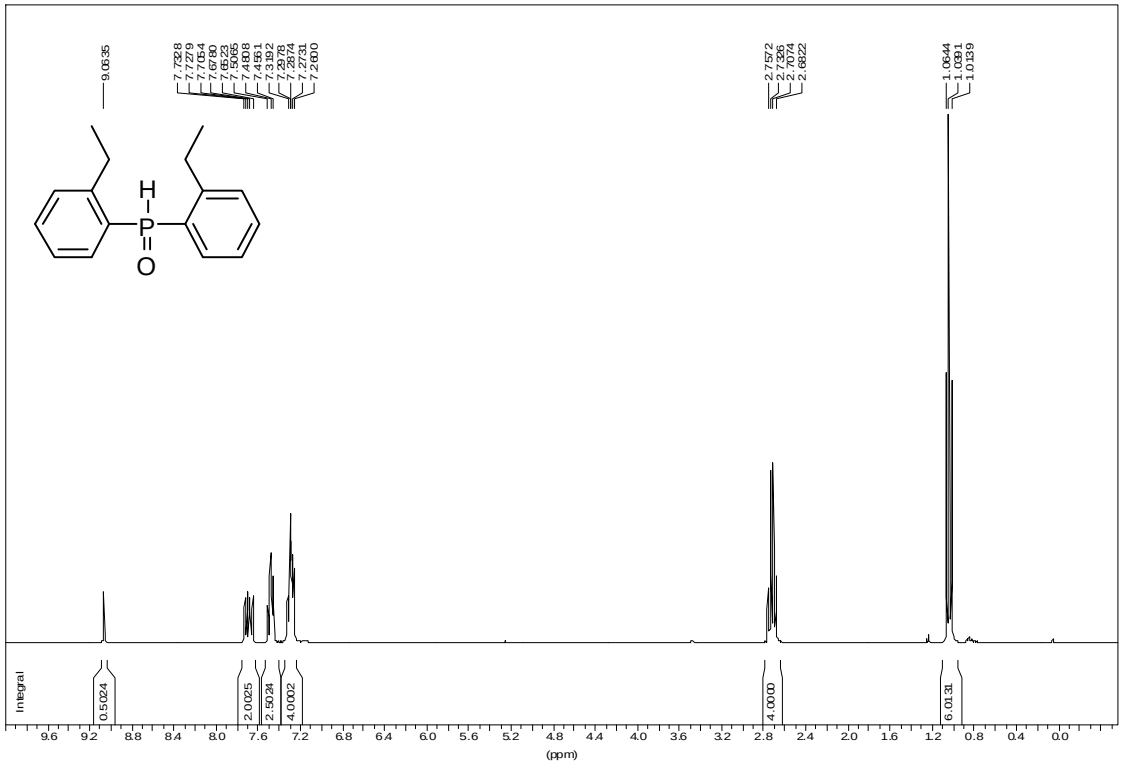


31P AC300 my28fux1 2 1.1 FuX9124

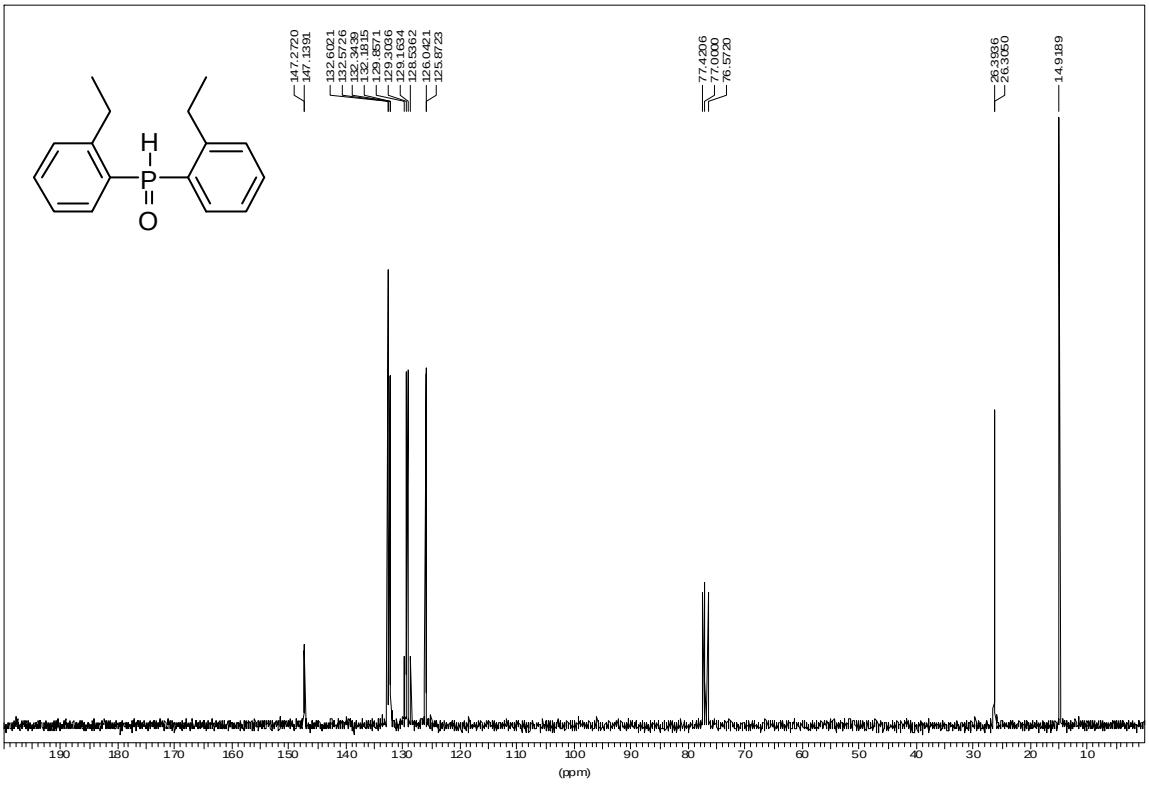


(2d) Di-2-ethylphenyl phosphine oxide

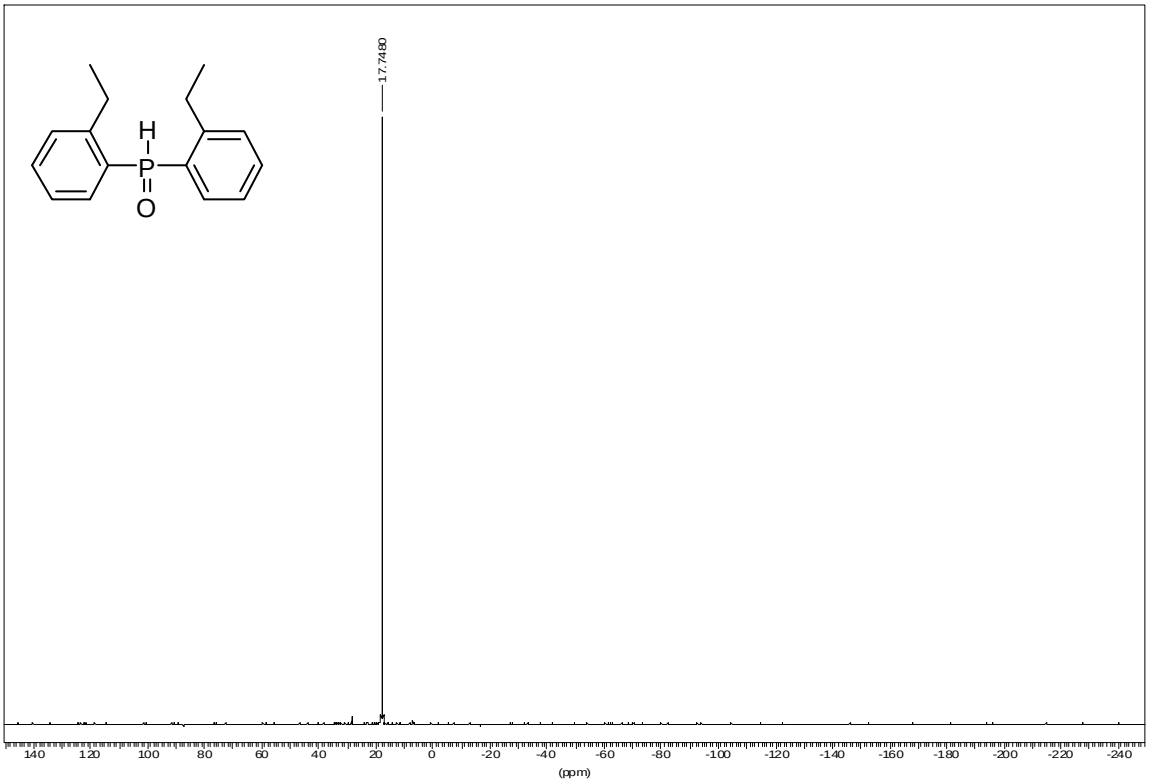
1H normal range AC300 my03fux1 1 1.1 FuX9049



my03fux1.1.1.1.FuX9049

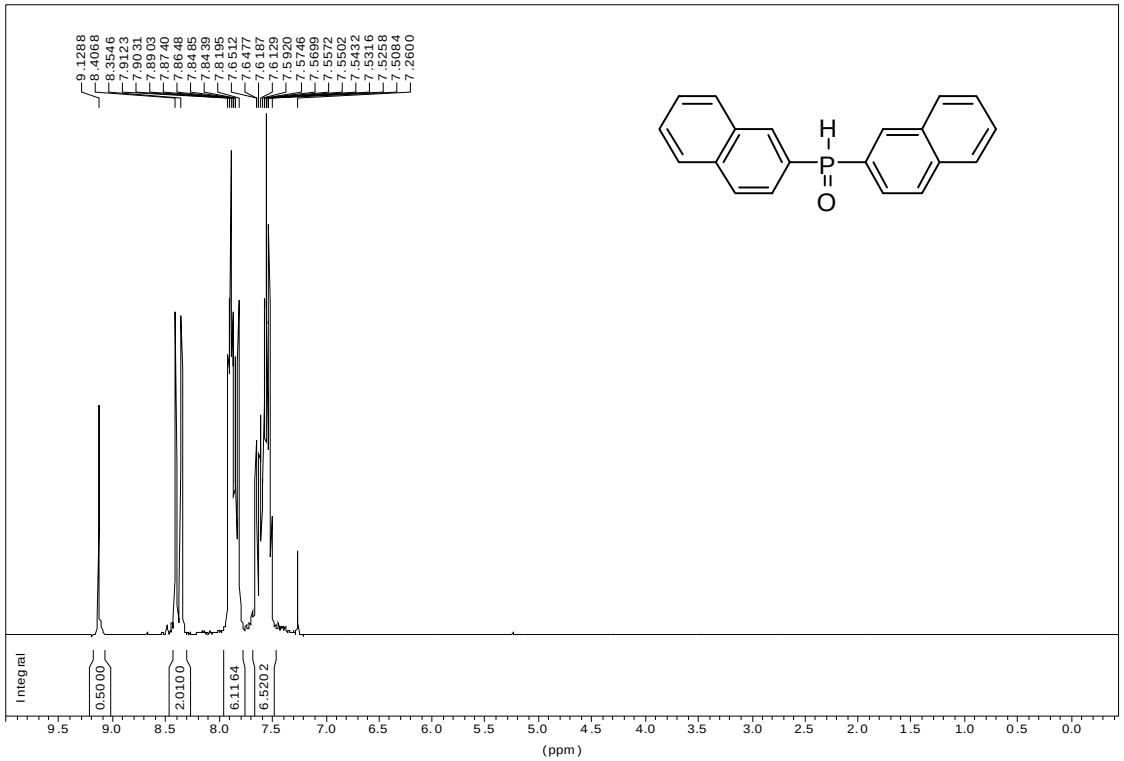


31P AC300 my03fux1.2.1.1 FuX9049

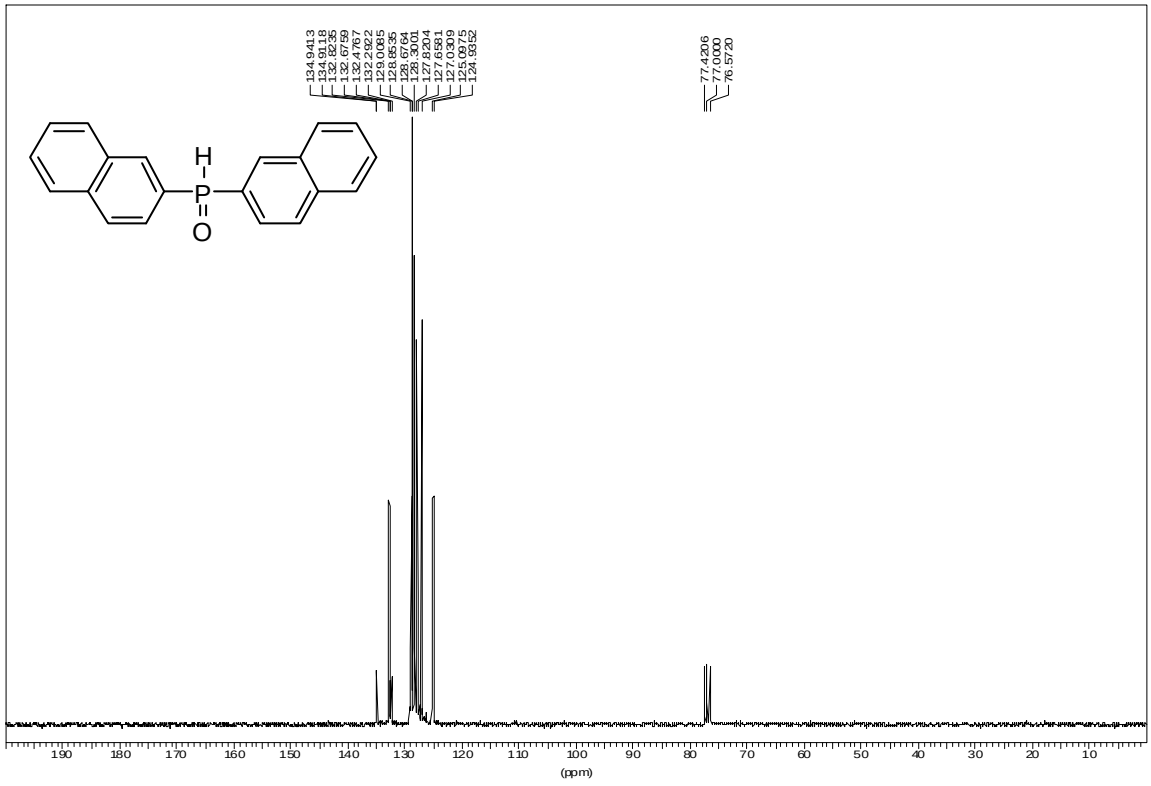


(2e) Di-2-naphthyl phosphine oxide

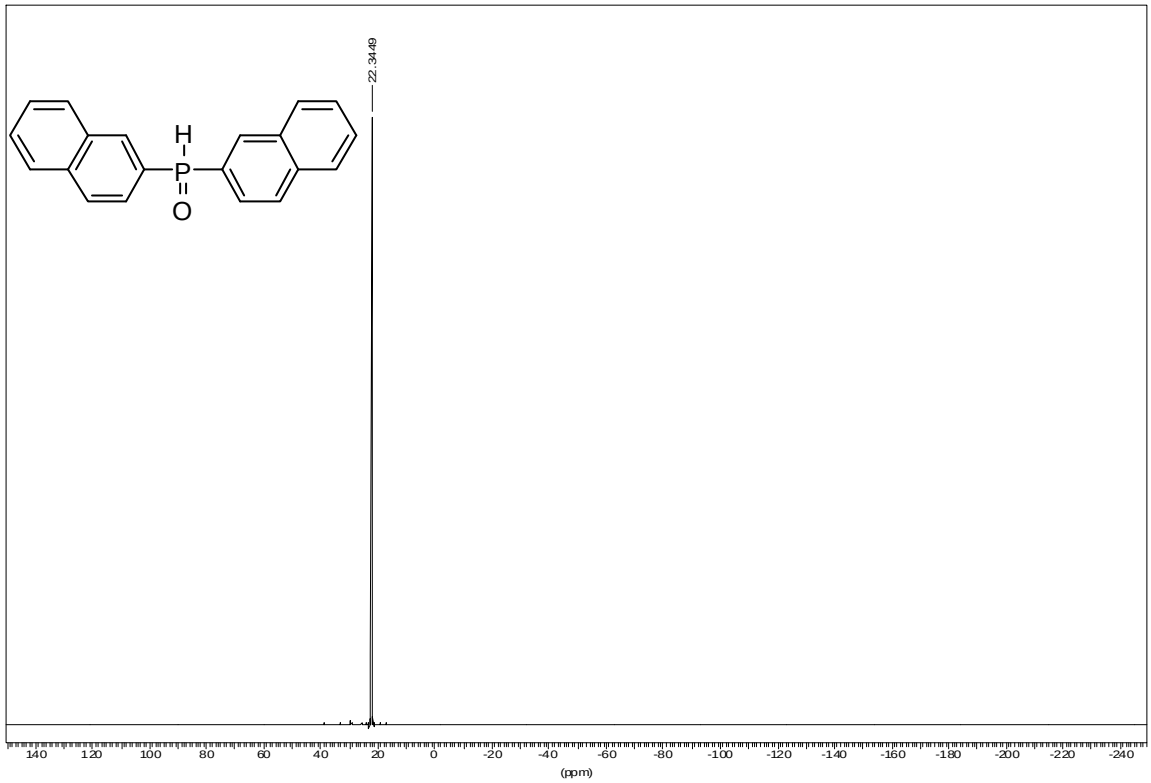
my01fux1.5.1 FuX8199



my01fux1.1.5.1 FuX8199

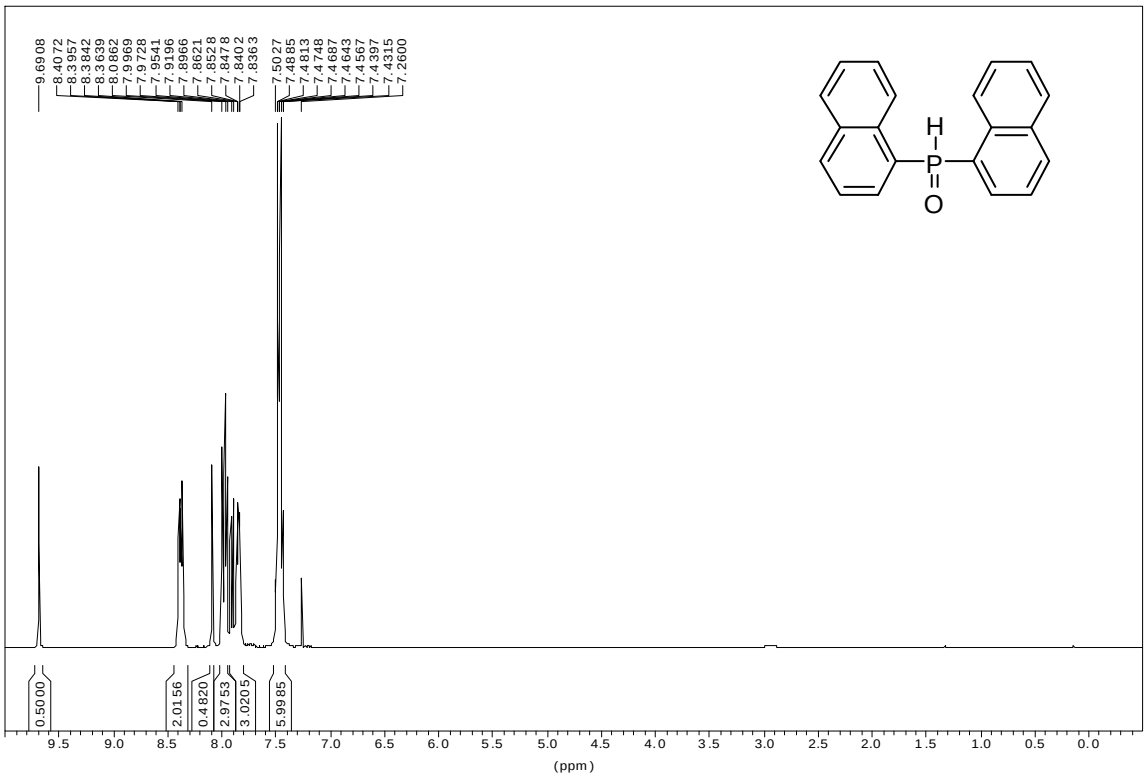


31P AC300 my01fux1.24.1 FuX8199

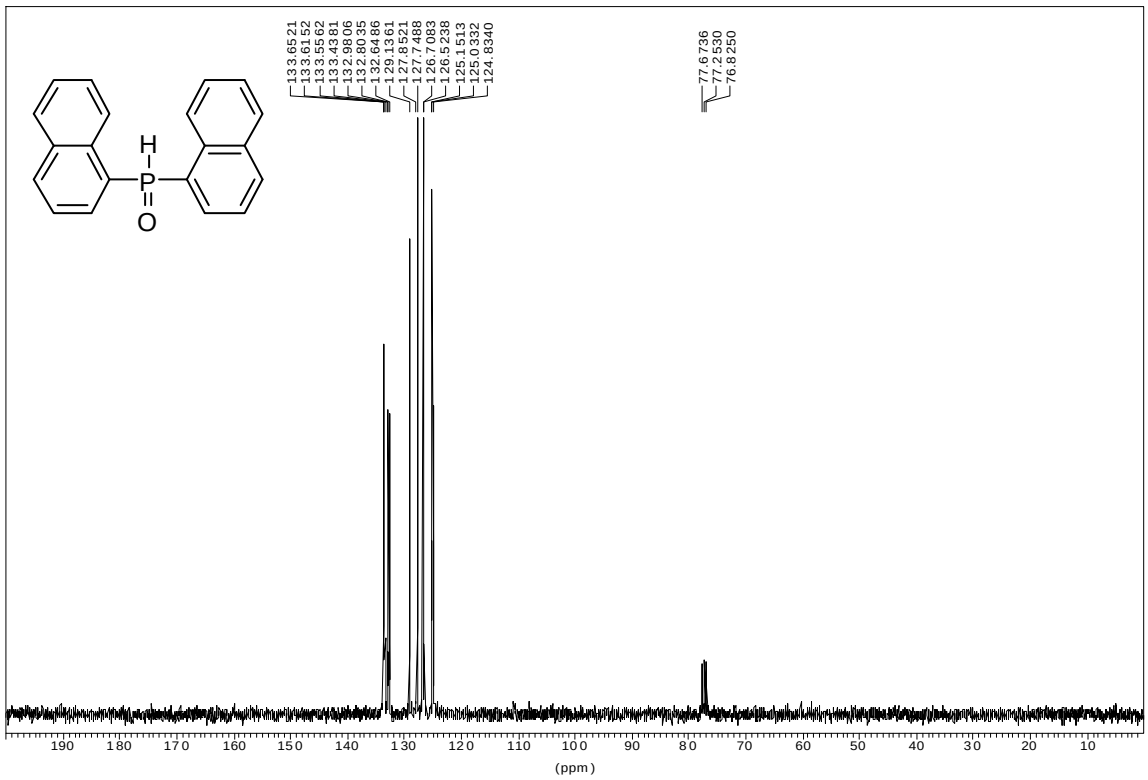


(2f) Di-1-naphthyl phosphine oxide

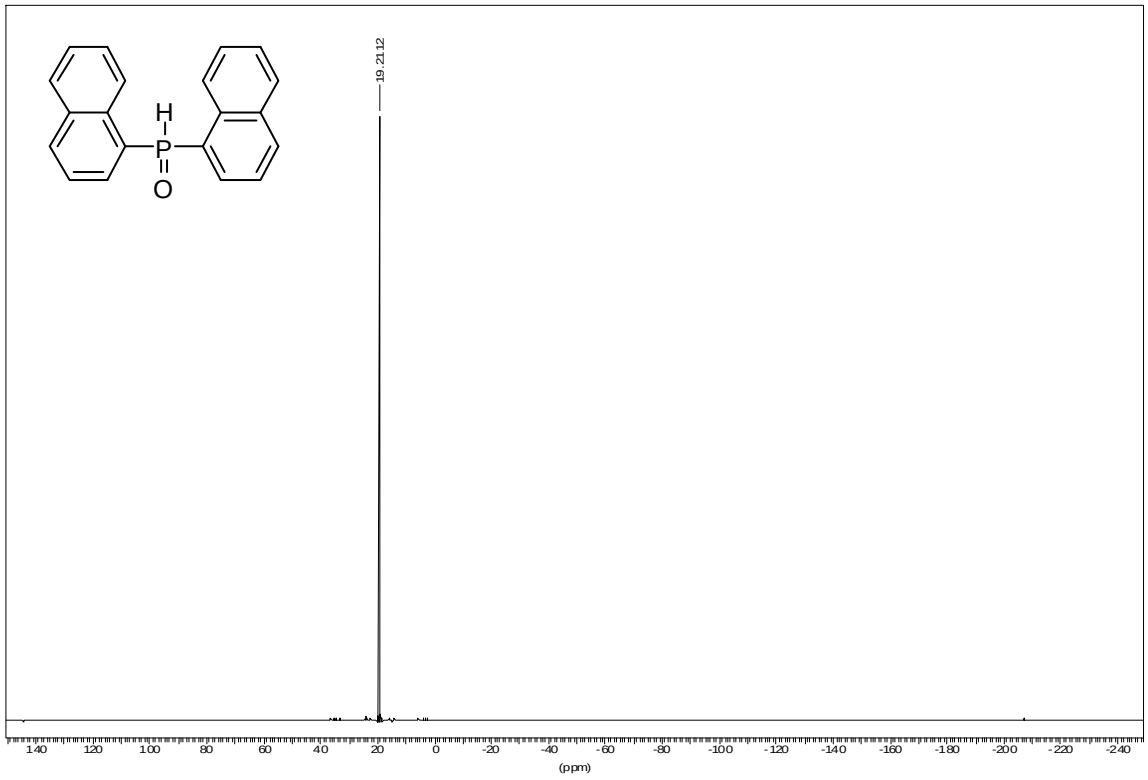
1H normal range AC300 ma07fux1.1.1 FuX8285



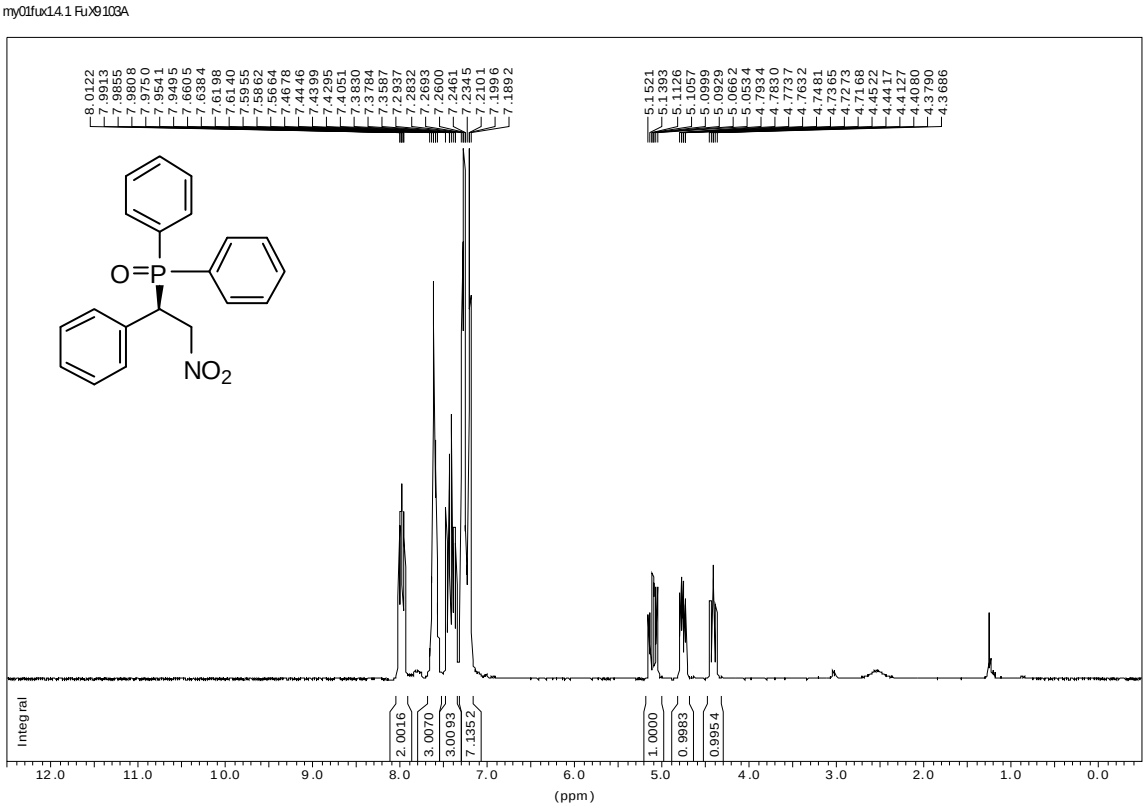
ma07fux1.11.1.FuX8285

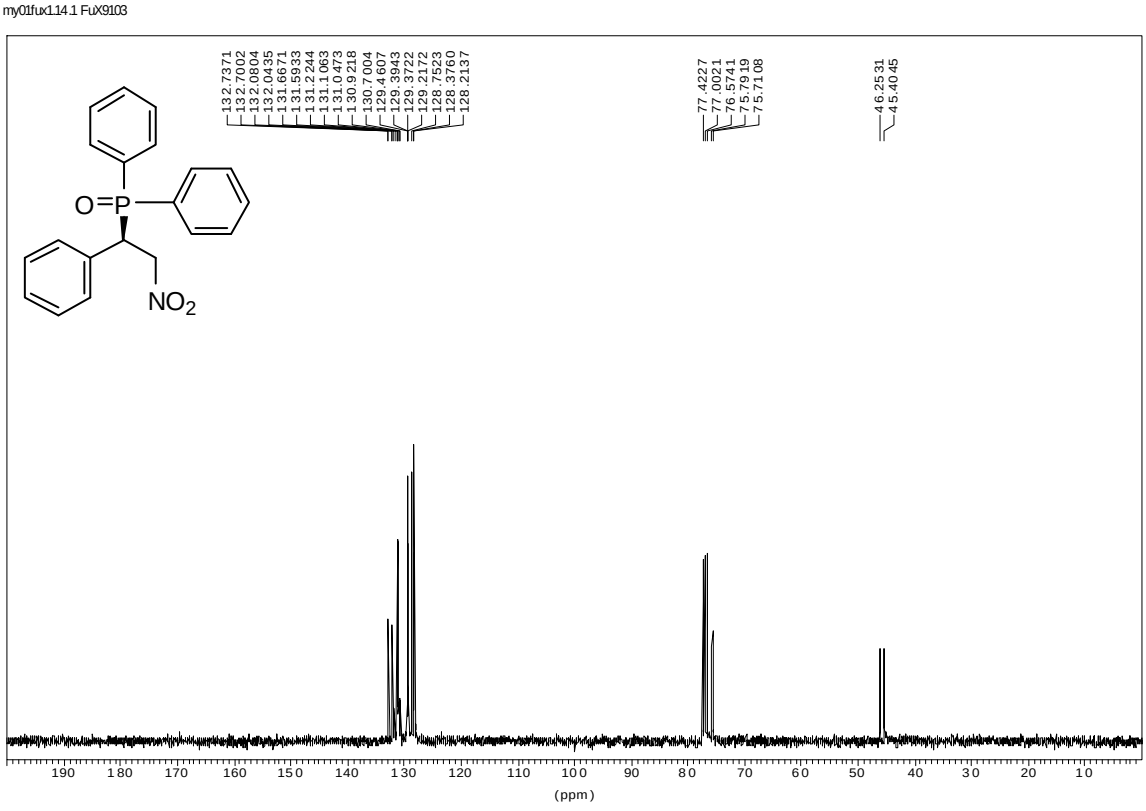


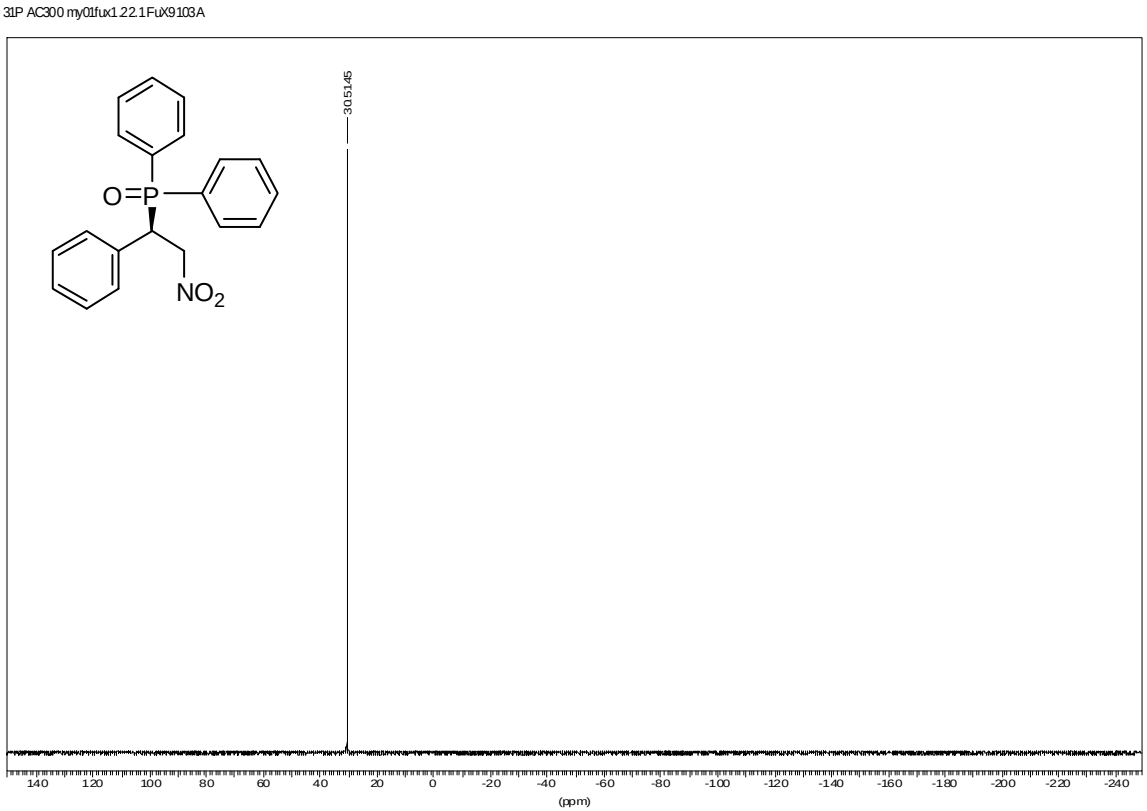
31P AC300 ma06fux1.2.1.1 FuX8285 I



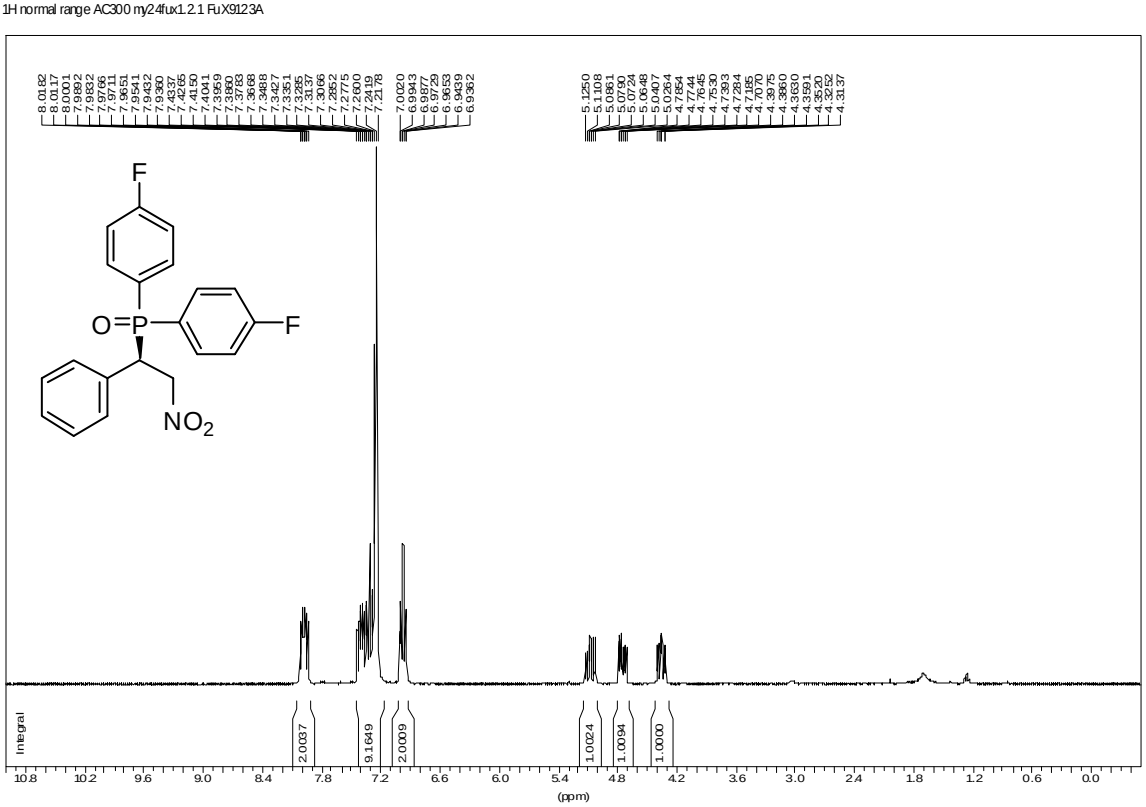
(3a) (2-Nitro-1-phenylethyl)diphenyl phosphine oxide



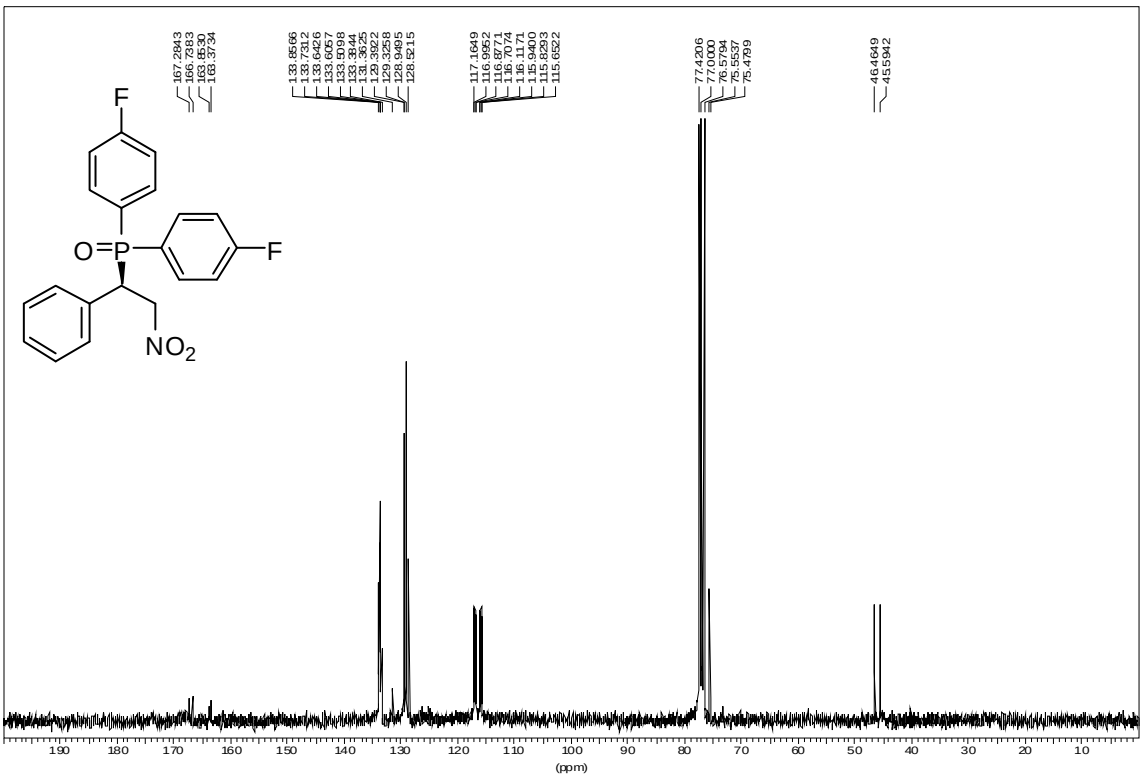




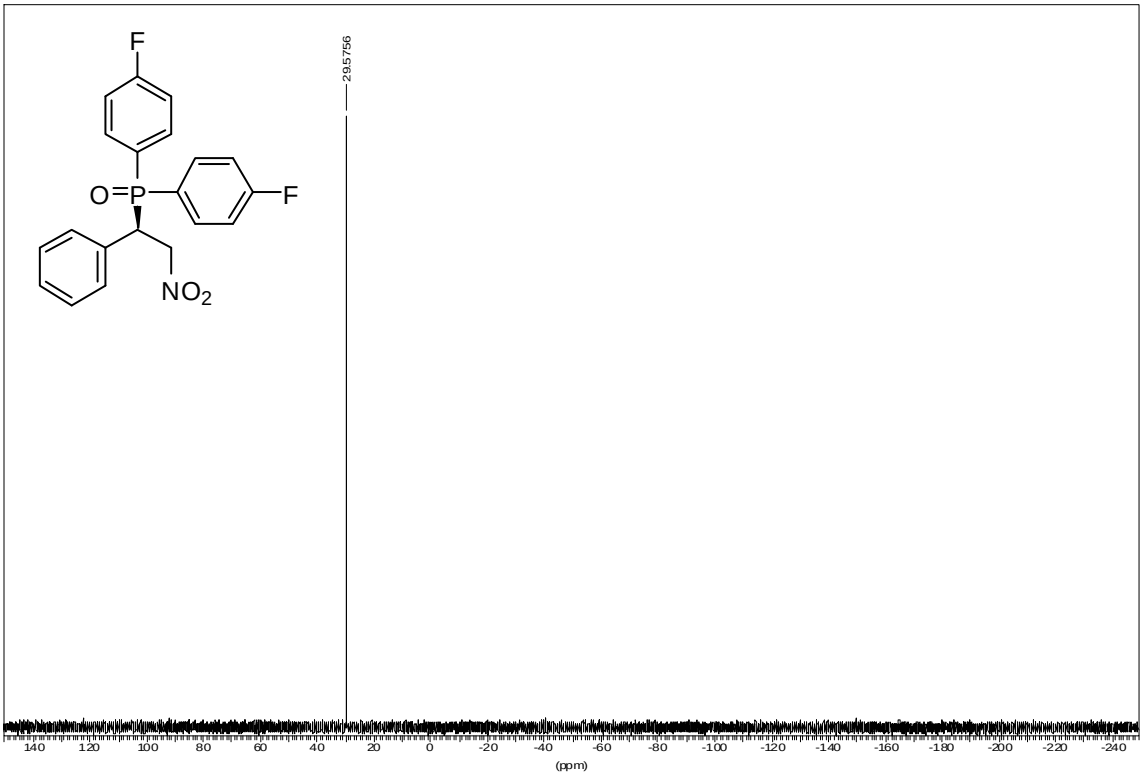
(3b) (2-Nitro-1-phenylethyl)di-4-fluorophenyl phosphine oxide



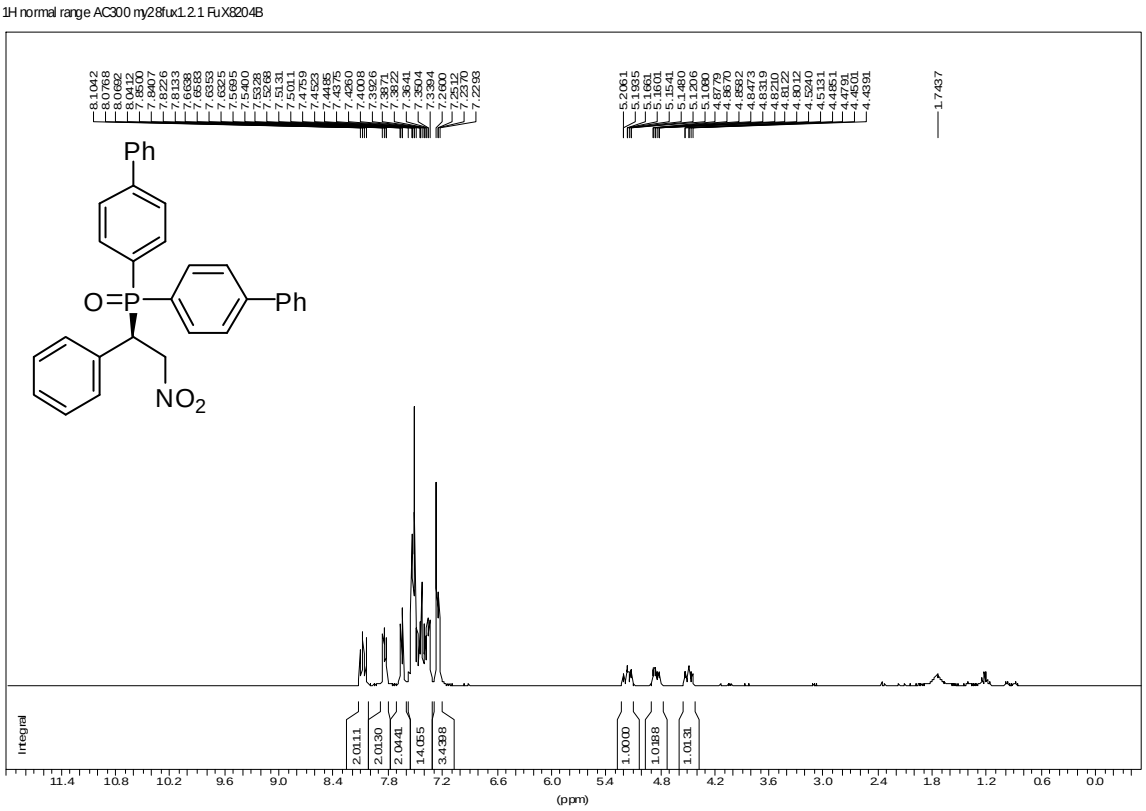
my24fux1.11.1FuX9123A

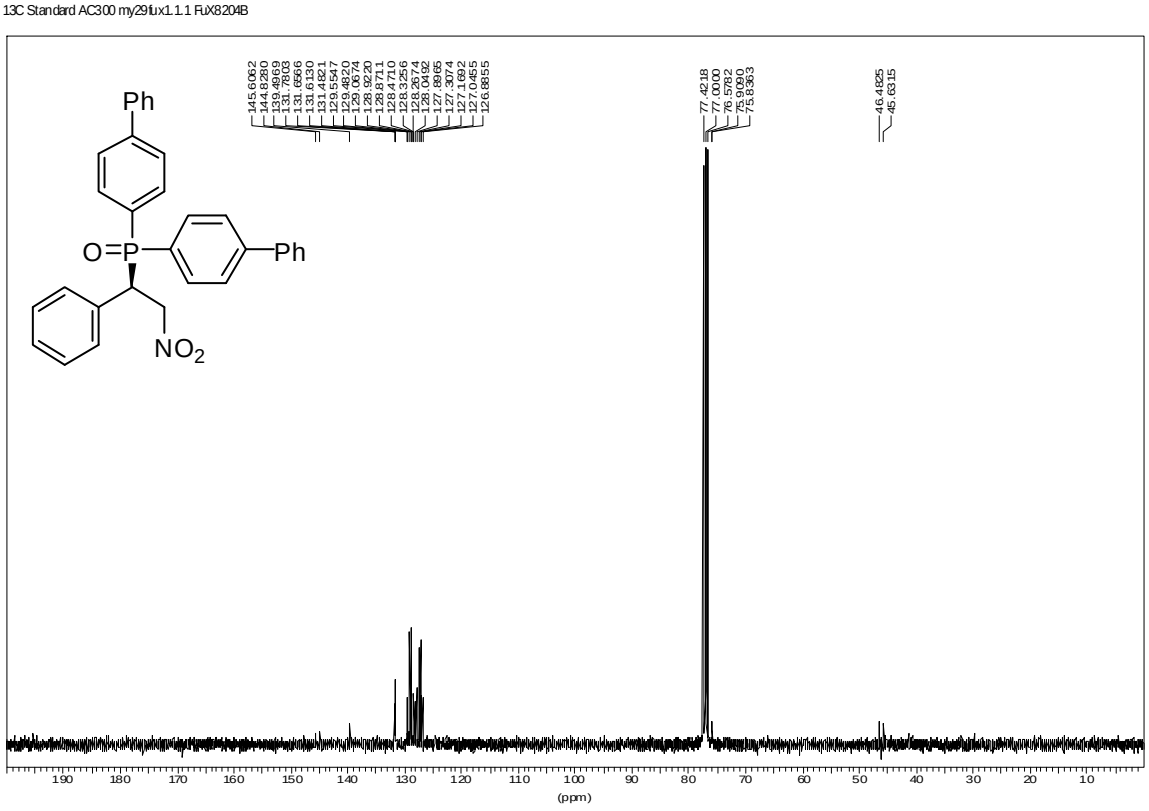


31P AC300 my24fux1.22.1FuX9123A

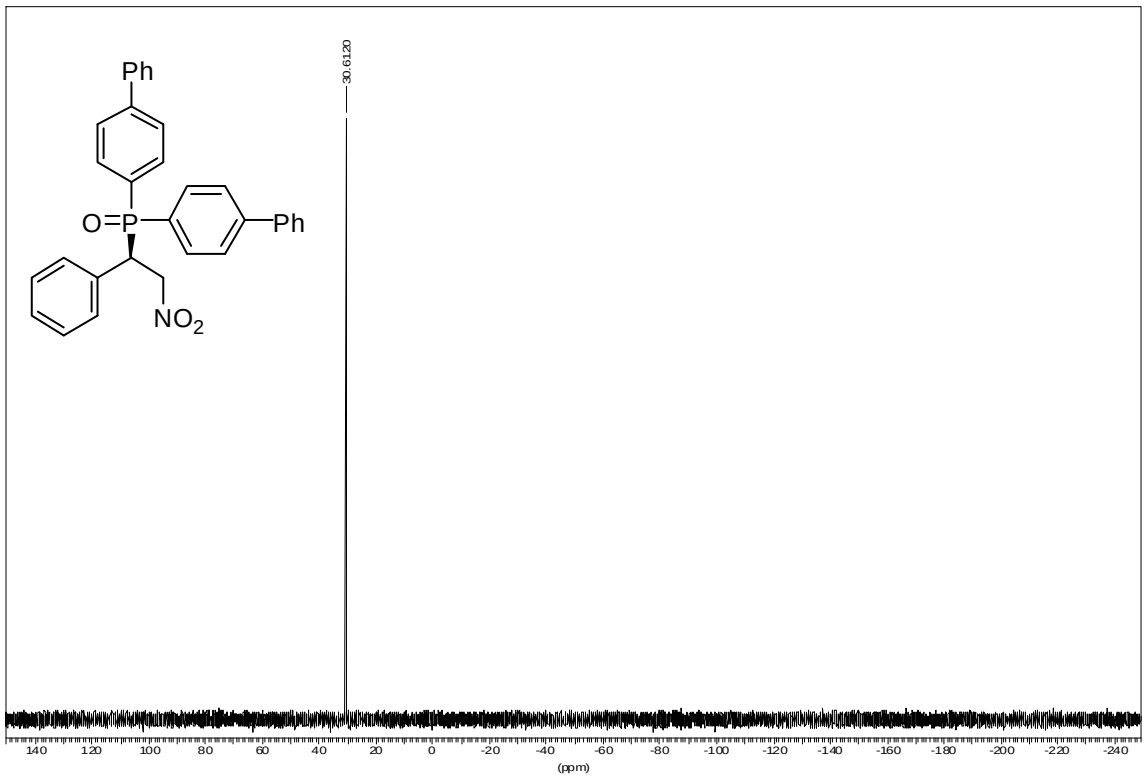


(3c) (2-Nitro-1-phenylethyl)di-4-phenylphenyl phosphine oxide



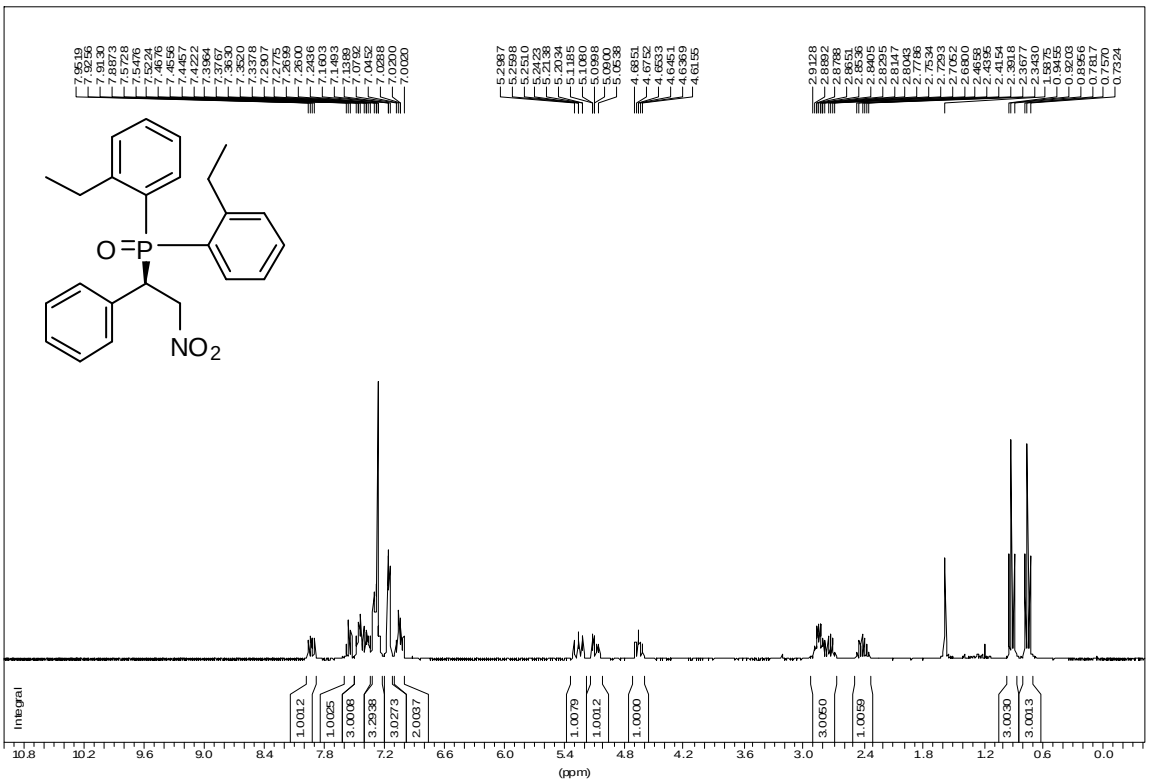


31P AC300 my28fux1 2 2.1 FuX8204B

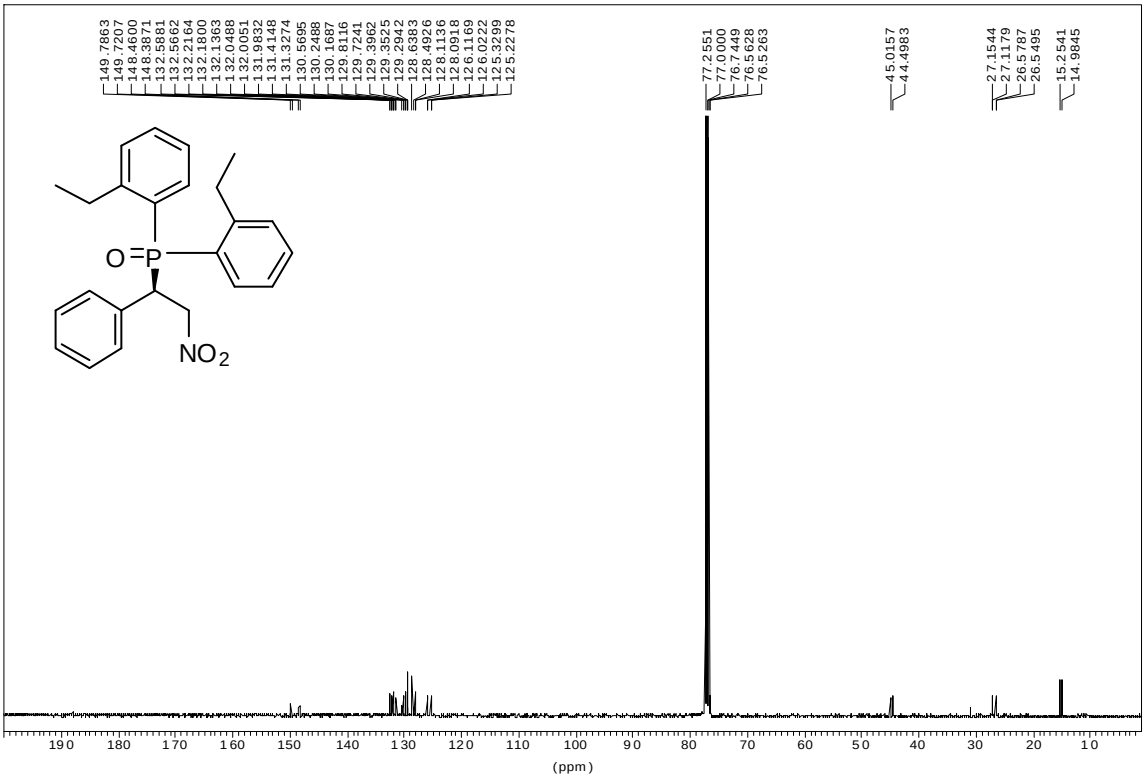


(3d) (2-Nitro-1-phenylethyl)di-2-ethylphenyl phosphine oxide

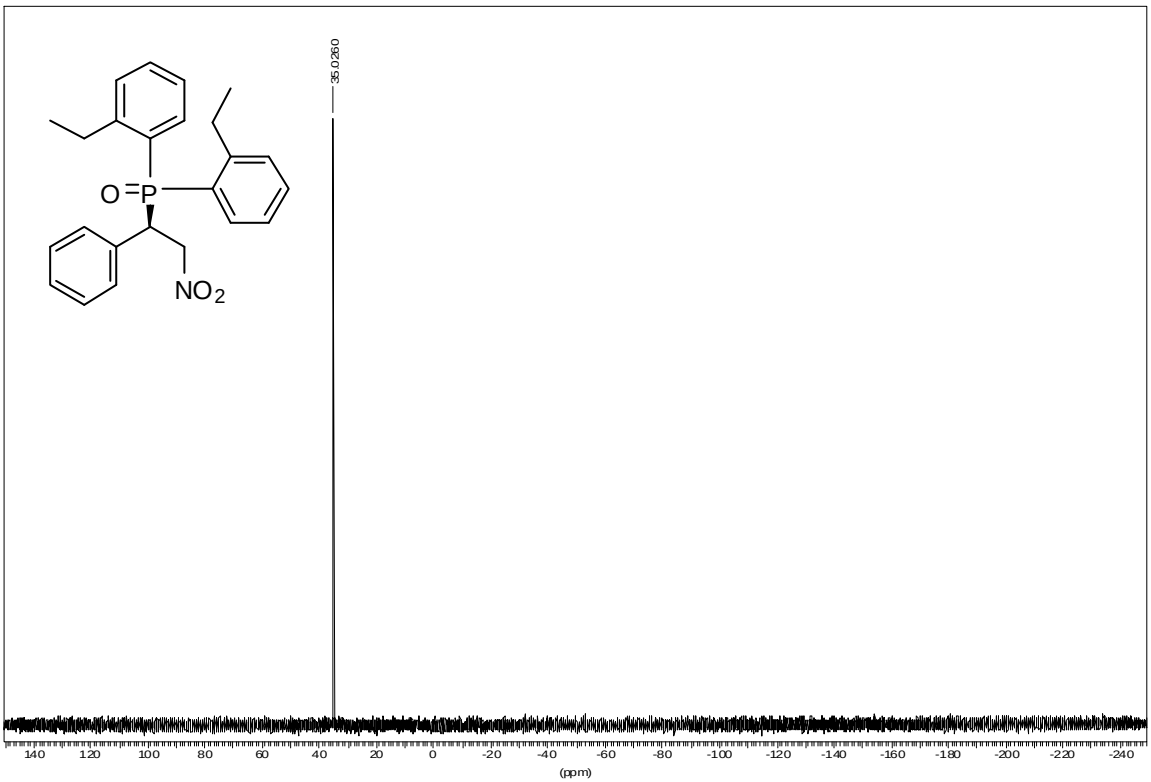
1H normal range AC300 my03fux1.2.1 FuX9050



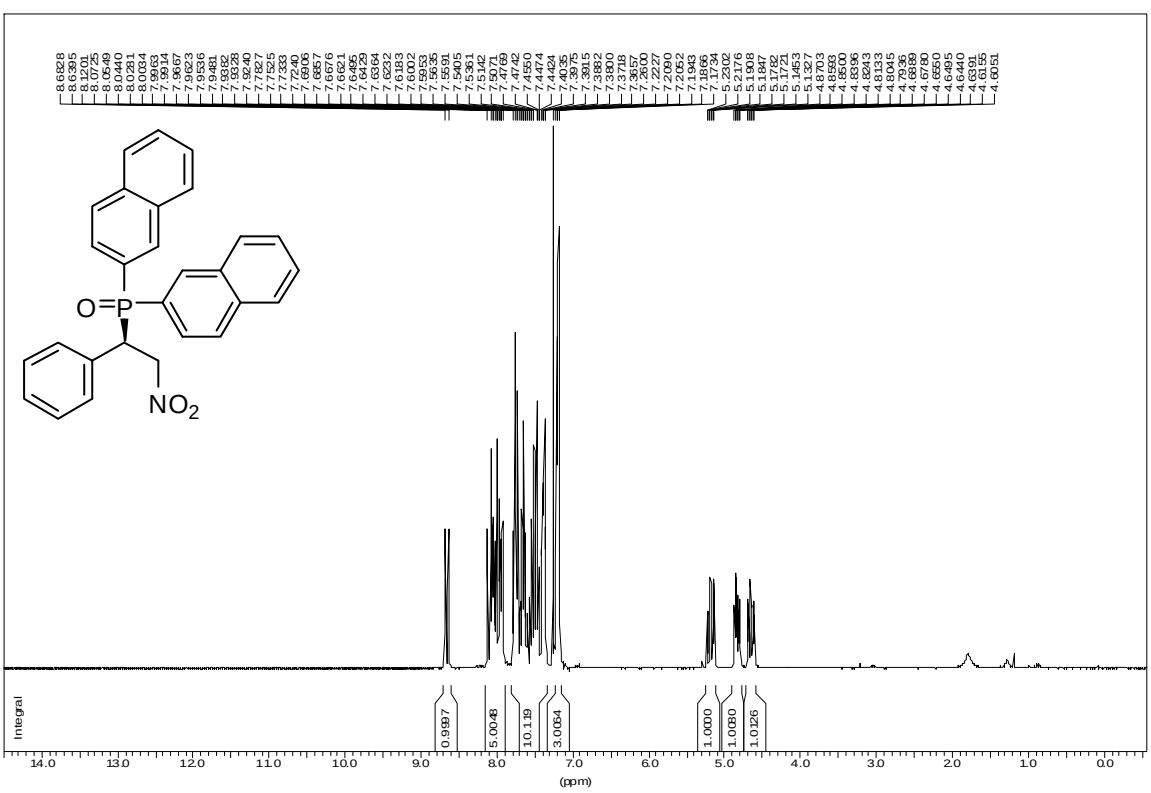
13C AMX500 fx0506fux1.12.1 FuX9050

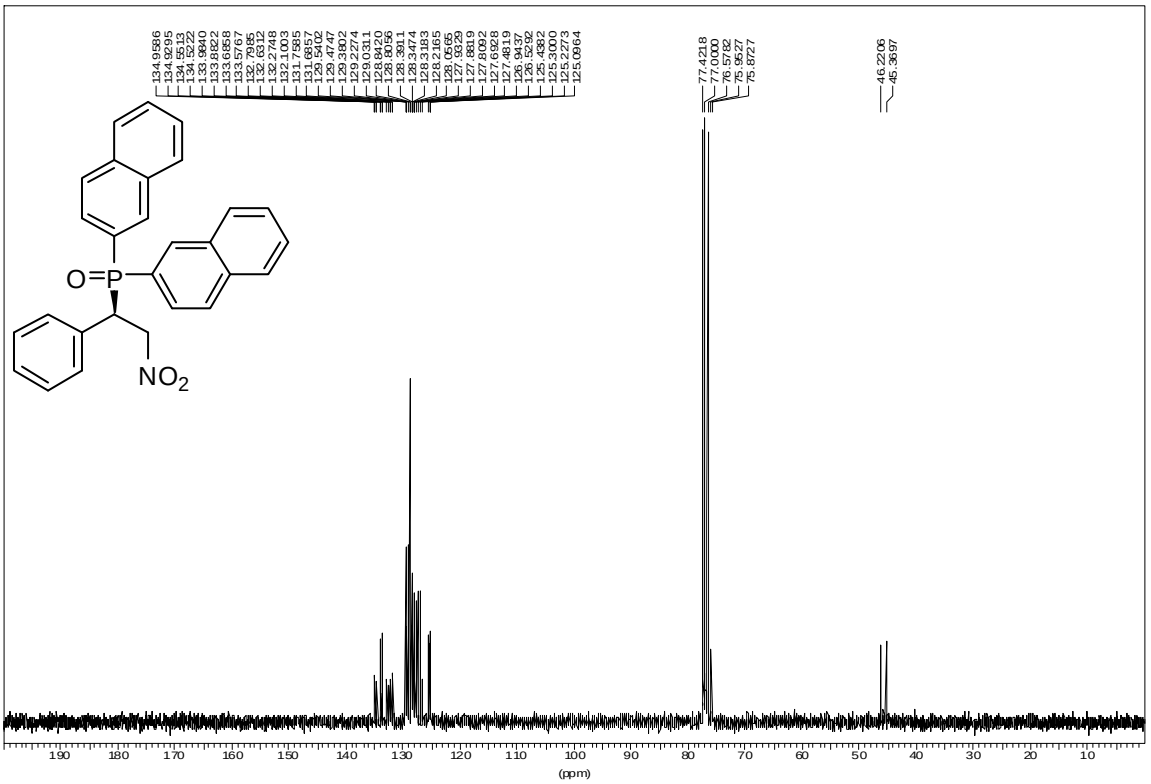


31P AC300 my03fux1.22.1 FuX9050

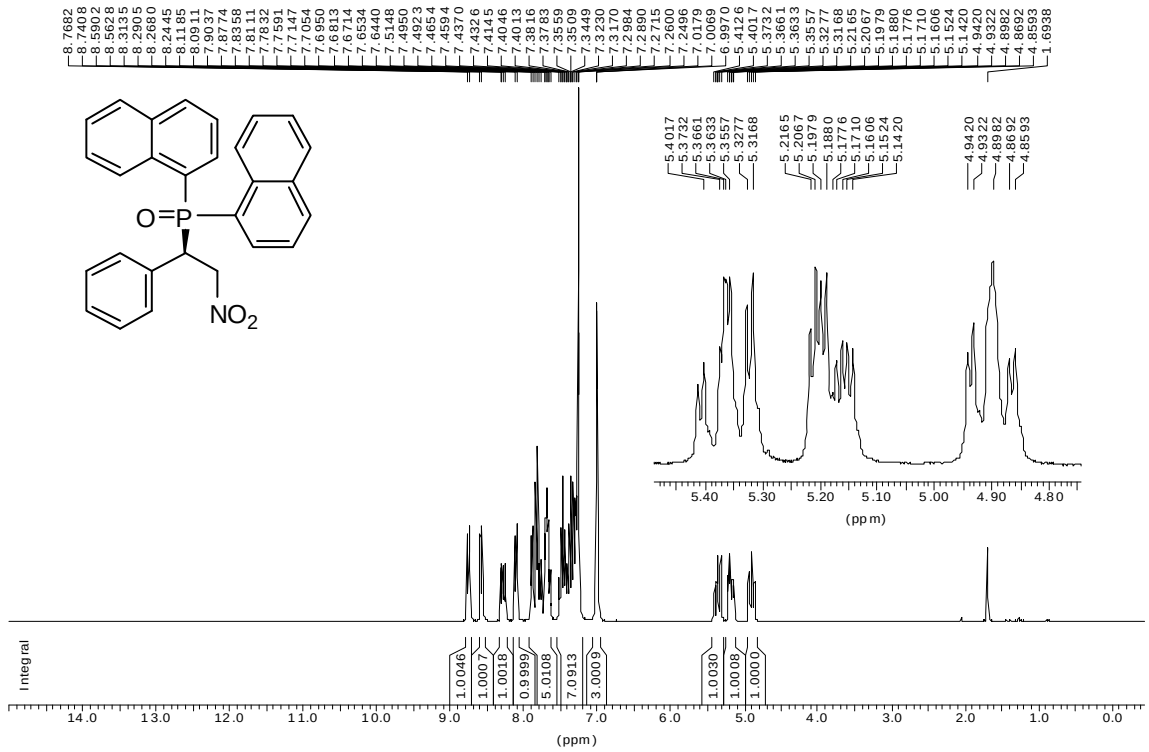


(3e) (2-Nitro-1-phenylethyl)di-2-naphthyl phosphine oxide

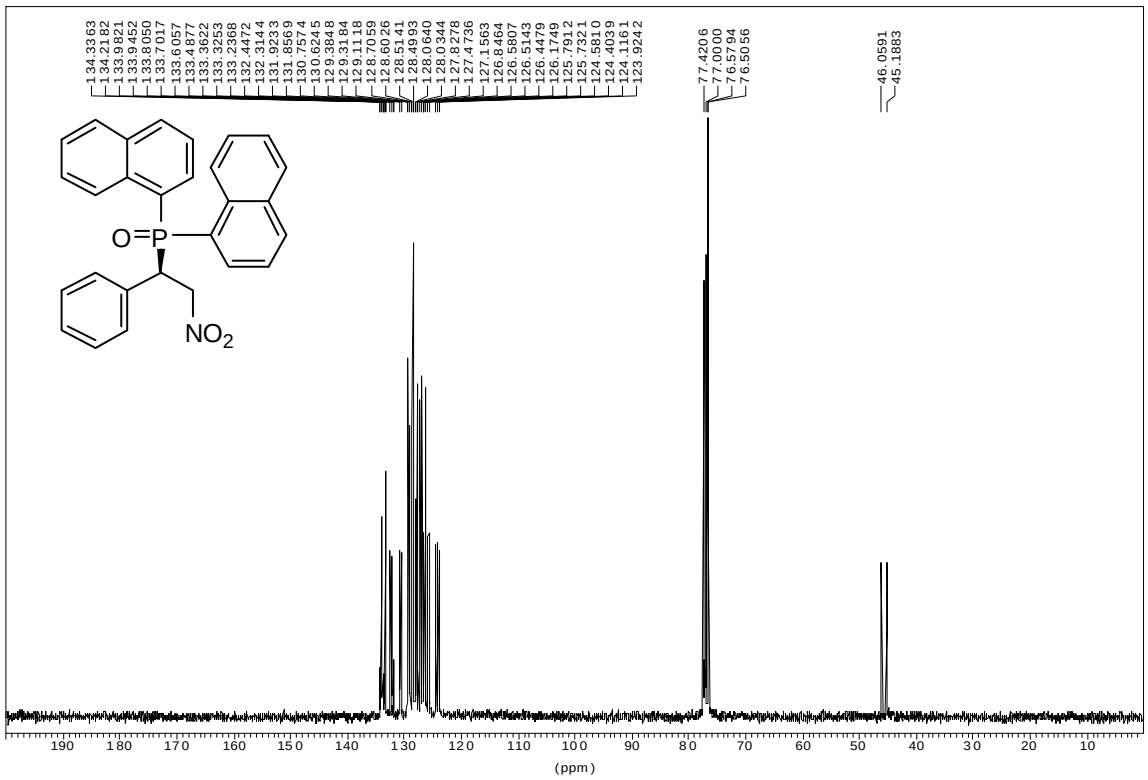




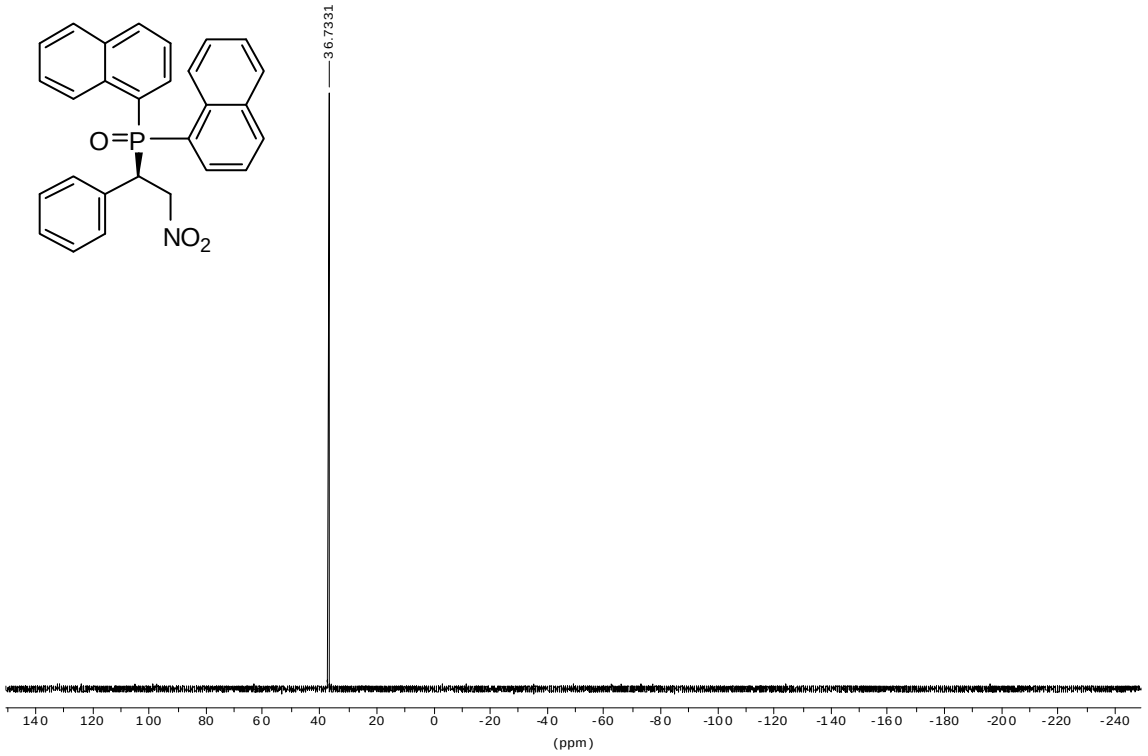
(3f) (2-Nitro-1-phenyl)ethyl)di-1-naphthyl phosphine oxide



ma30fux1.11.1.FuX9041

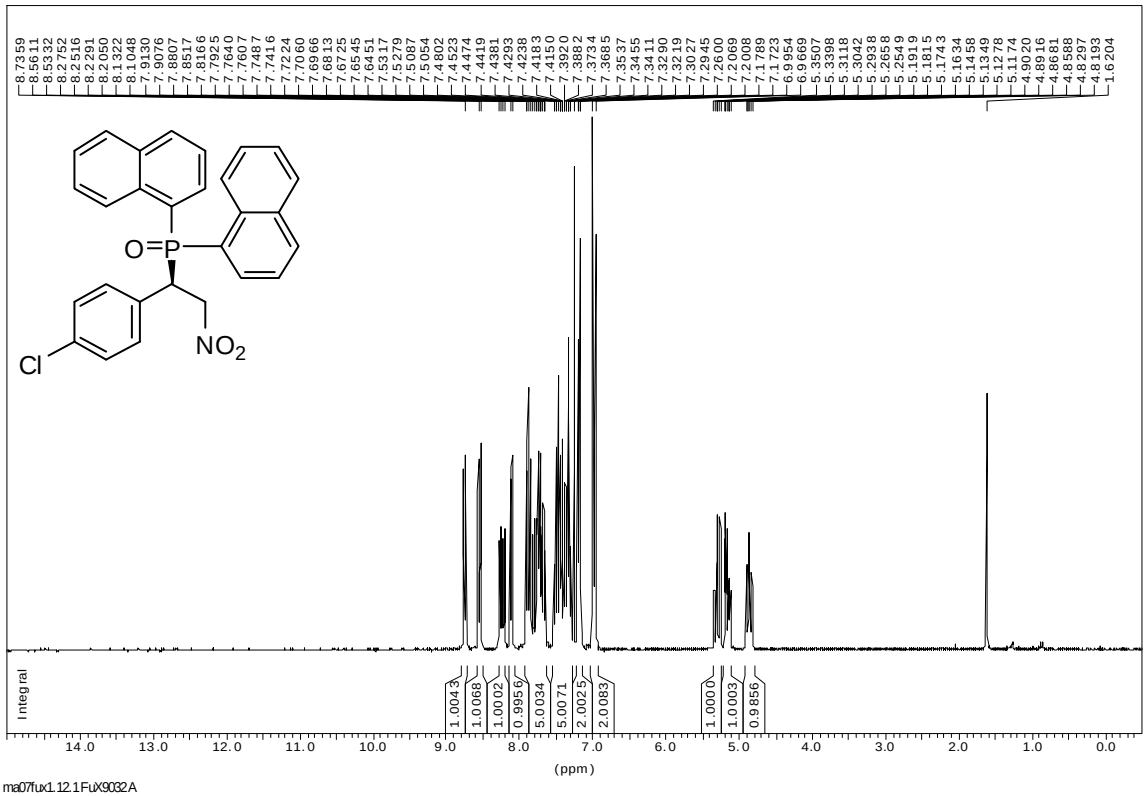


31P AC300 ma29fux1.2.1.1 FuX9041

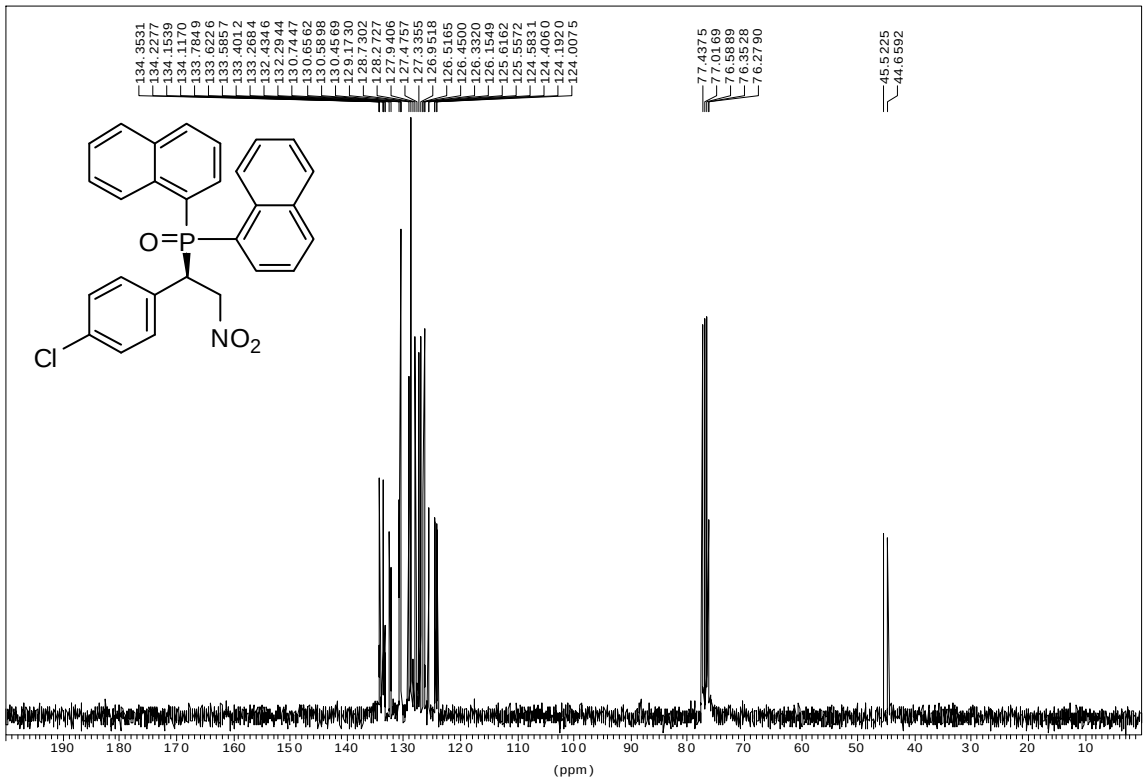


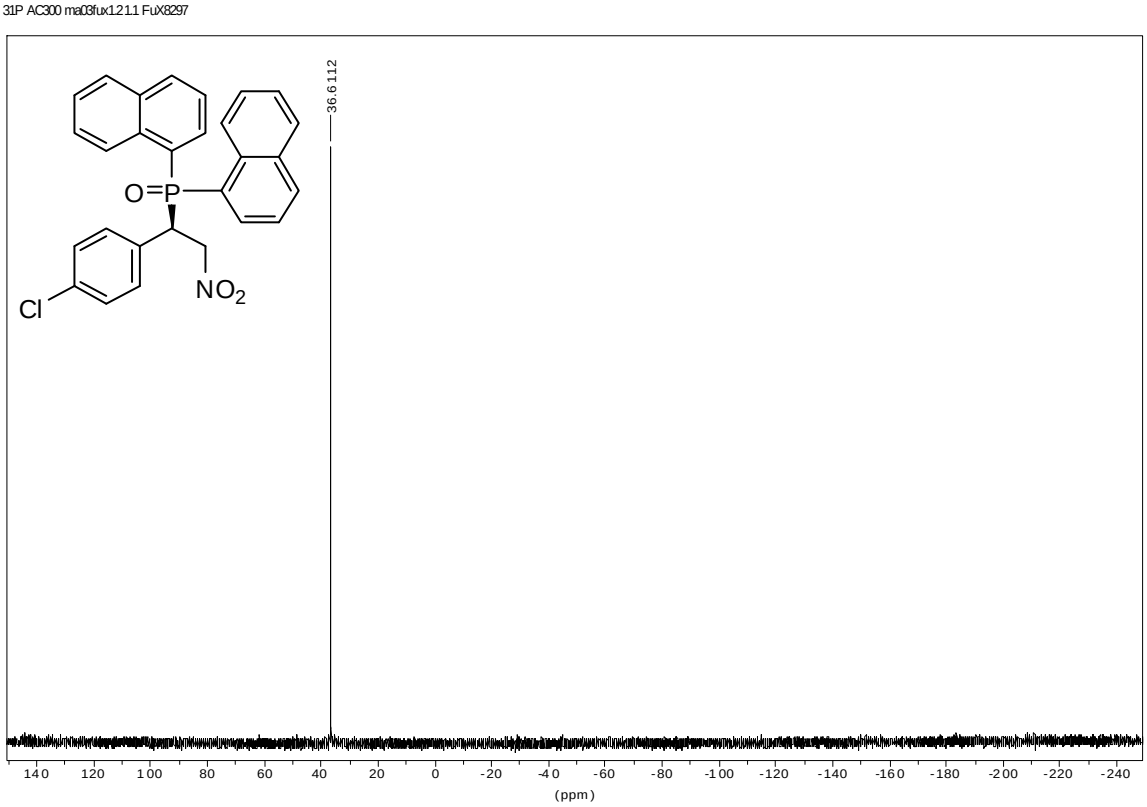
(4a) (2-Nitro-1-(4-chlorophenyl)ethyl)di-1-naphthyl phosphine oxide

1H normal range AC300 ma22fux1.2.1.FuX9032.AI

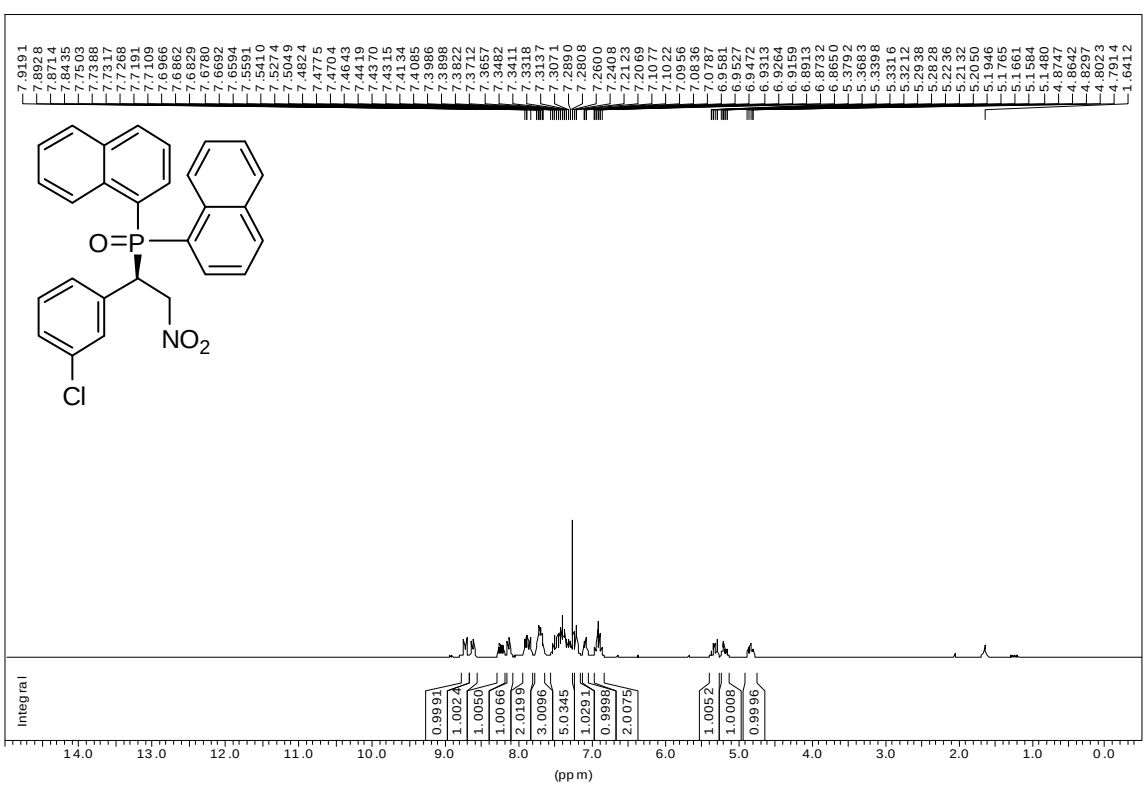


ma07fux1.12.1.FuX9032.A

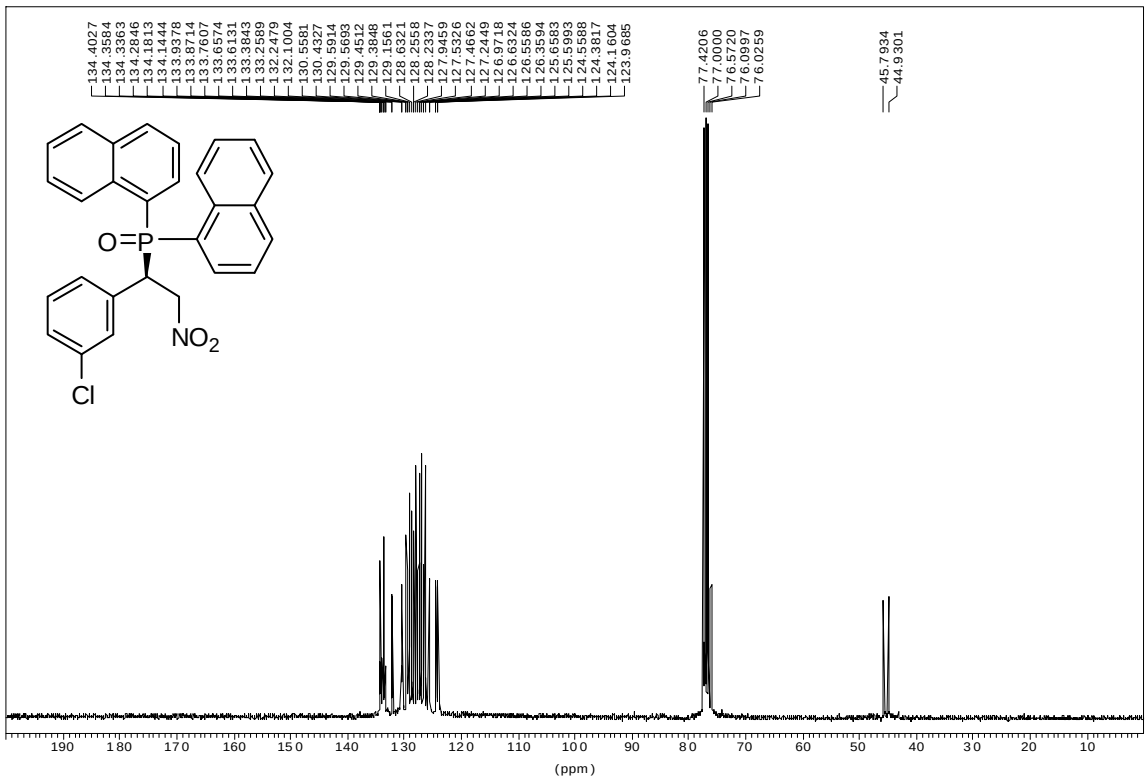




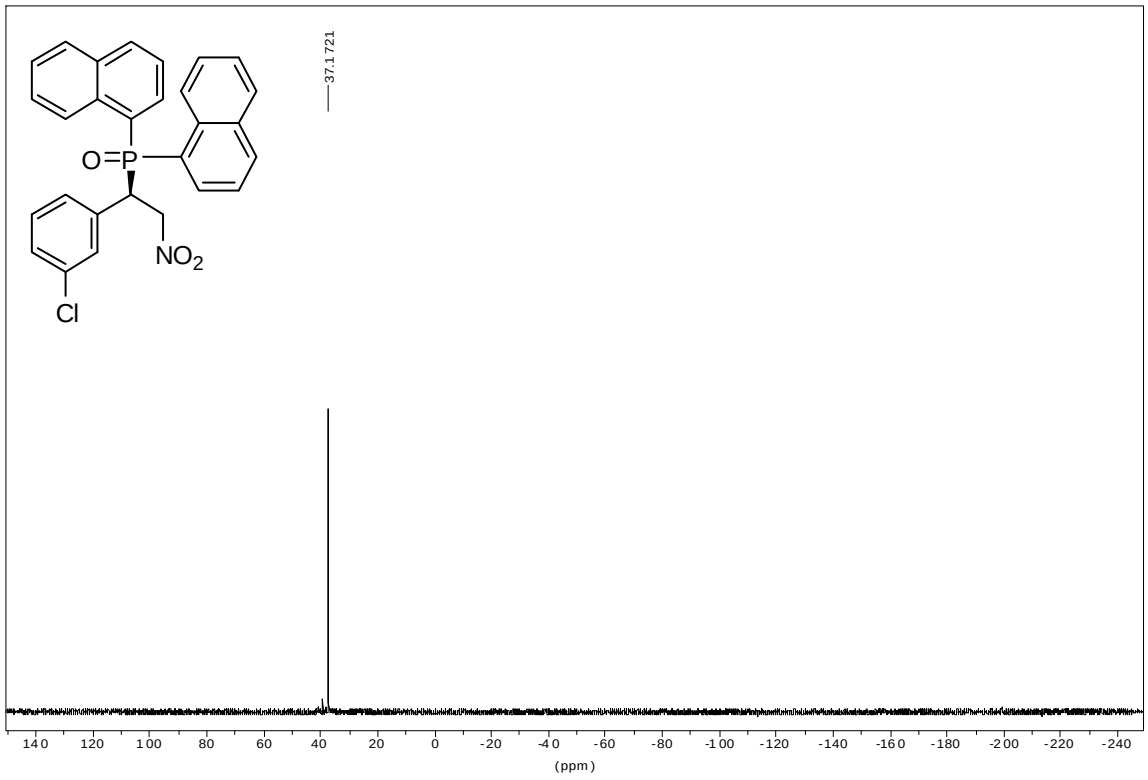
(4b) (2-Nitro-1-(2-nitrophenyl)ethyl)di-1-naphthyl phosphine oxide



ma30fux1.12.1.FuX9047.A

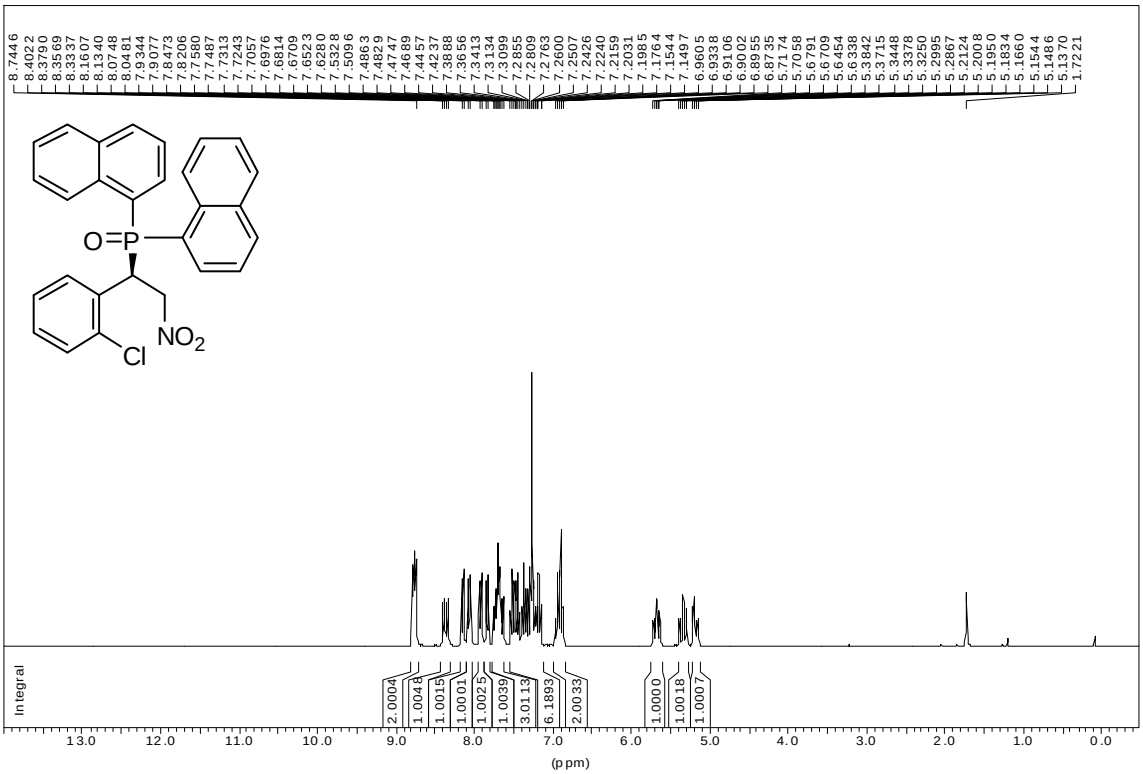


31P AC300 ma30fux1.2.1.1 FuX9047.A

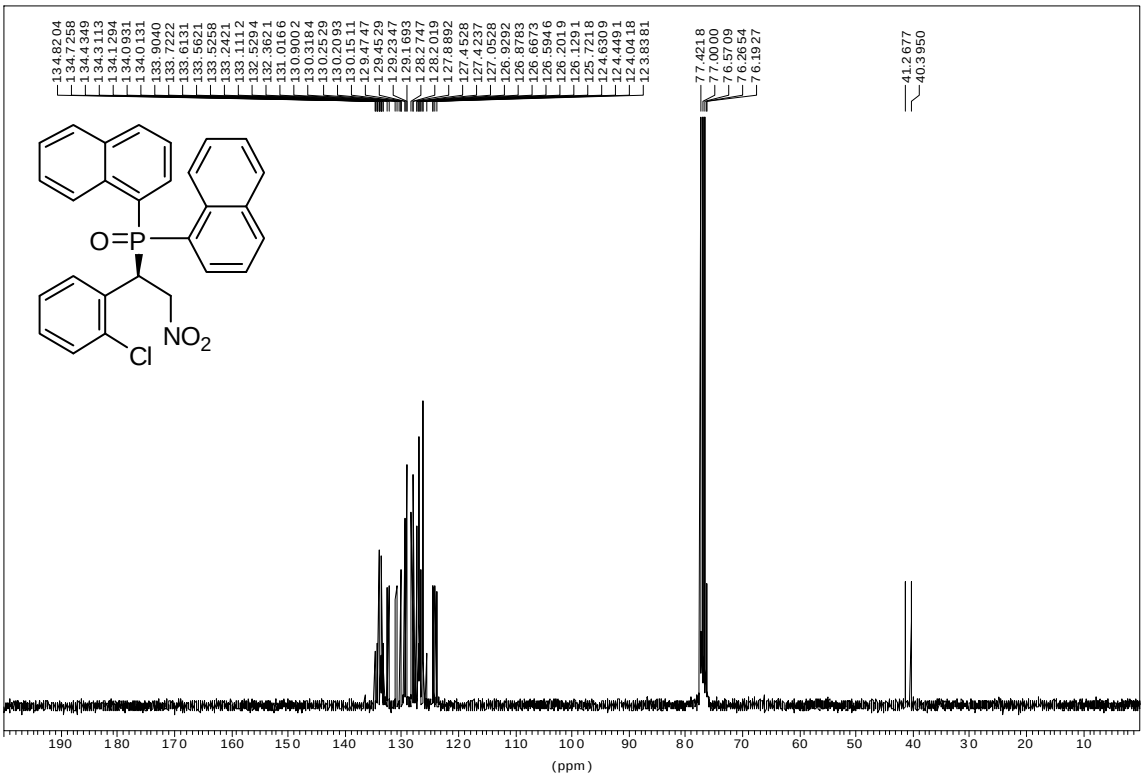


(4c) (2-Nitro-1-(2-chlorophenyl)ethyl)di-1-naphthyl phosphine oxide

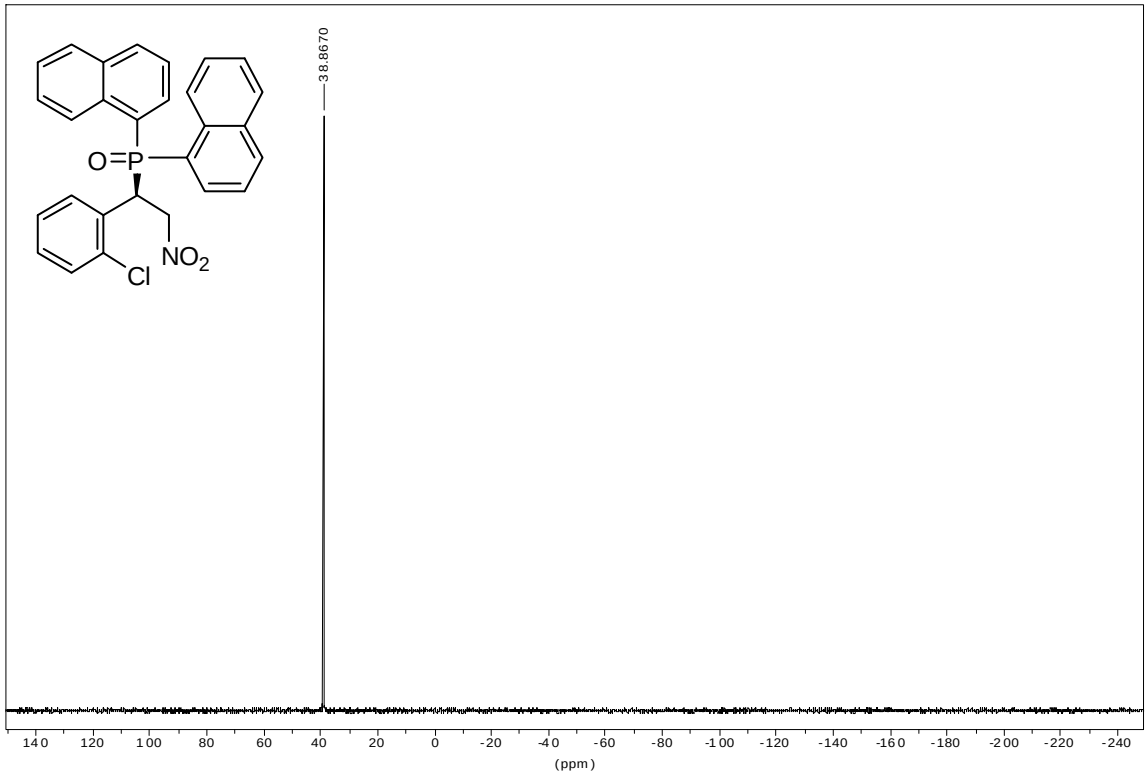
ap14fux1.2.1 FuX9078B



13C Standard AC300 ap14fux1.11.1 FuX9078B

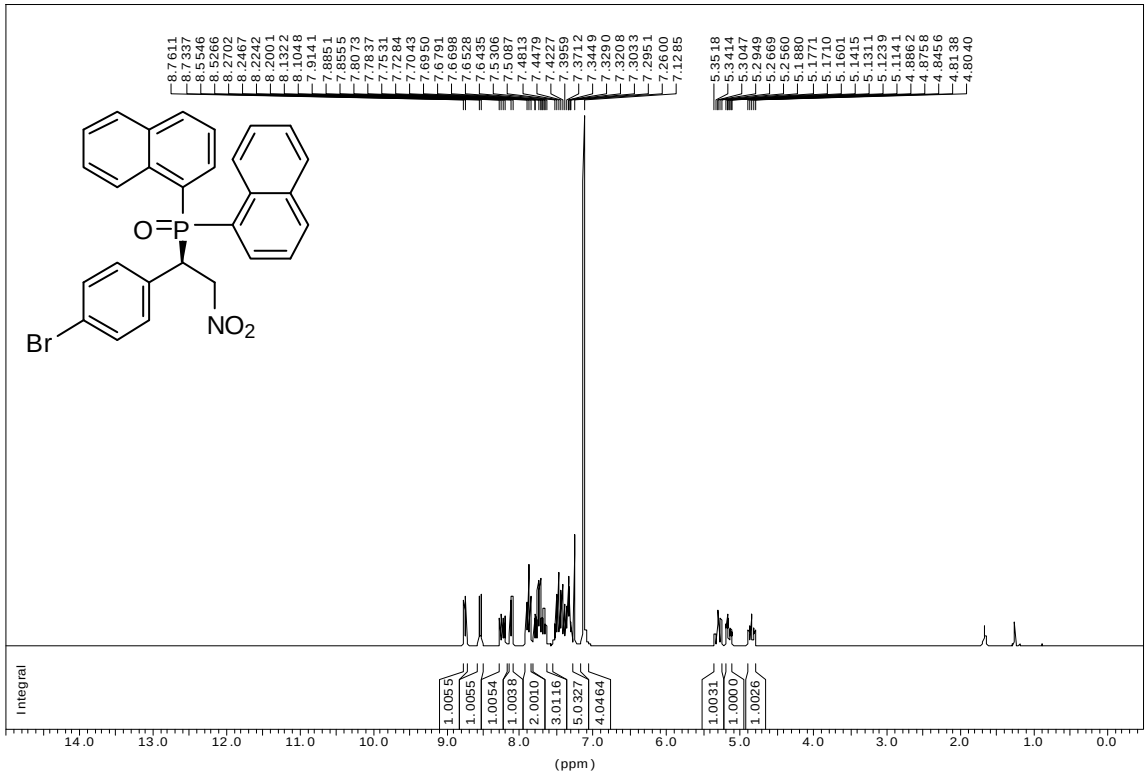


31P AC300 ap14fux1.21.1 FuX9078B

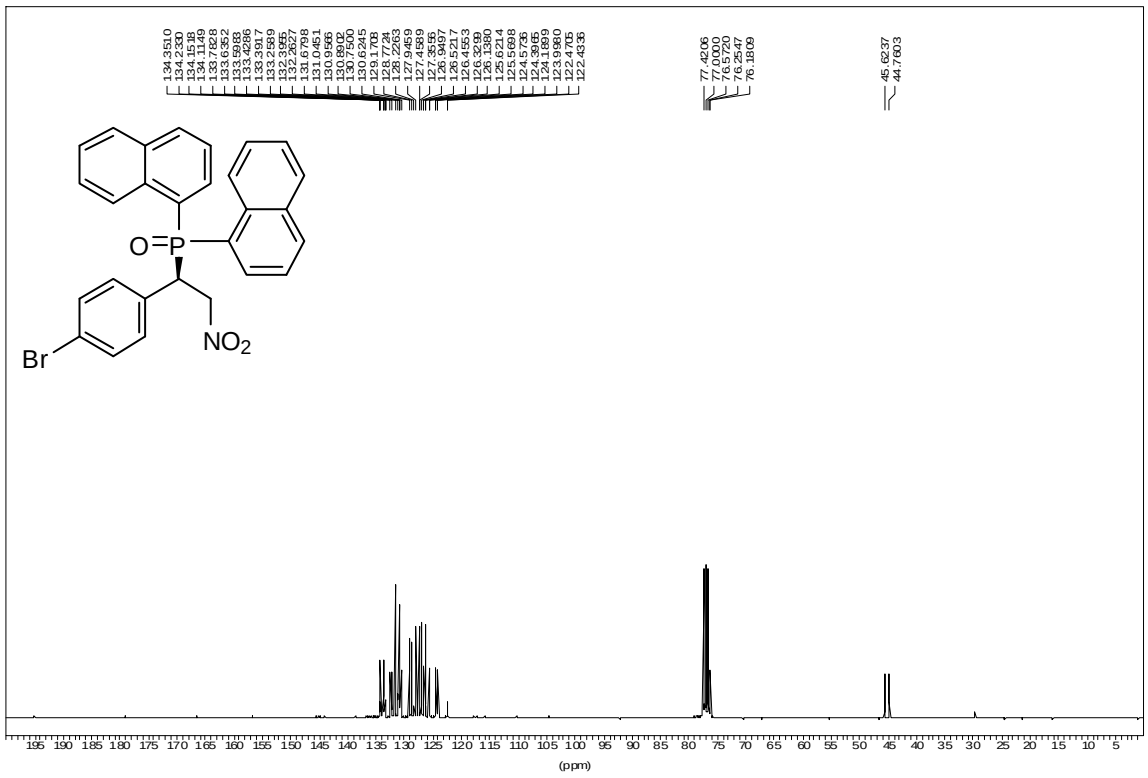


(4d) (2-Nitro-1-(4-bromophenyl)ethyl)di-1-naphthyl phosphine oxide

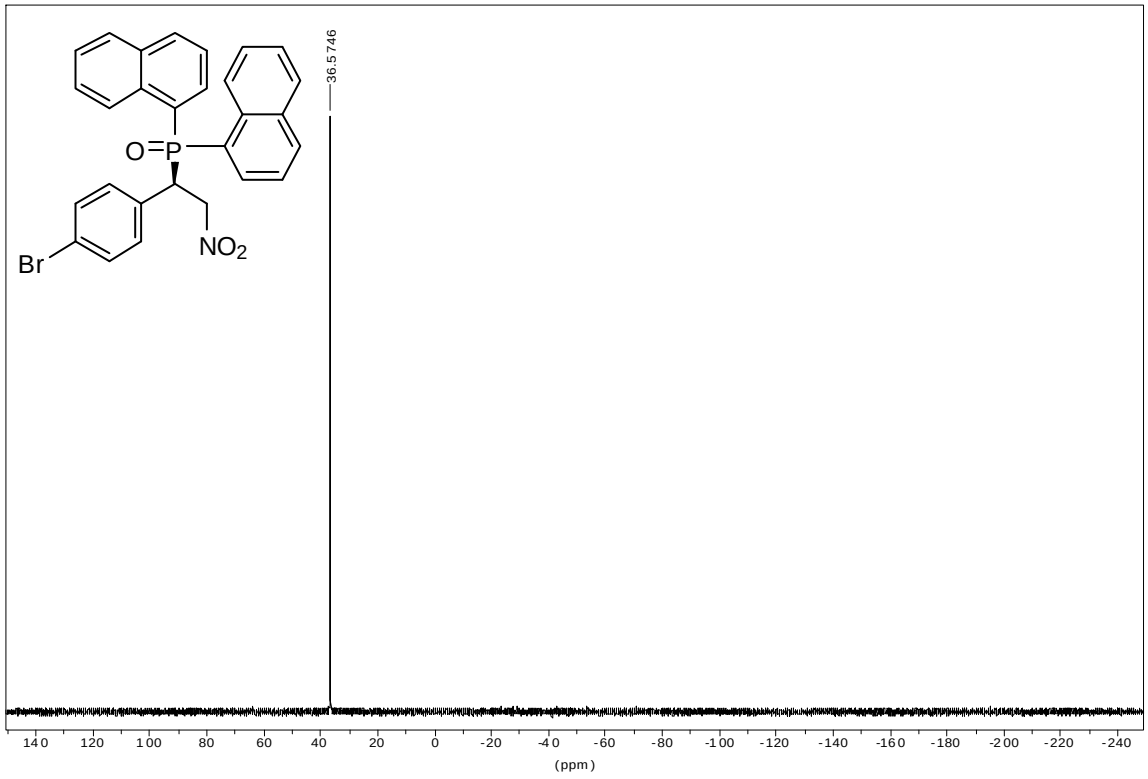
1H normal range AC300 ap01fux1.1.1 FuX9060A



ap01fux1.11.1 FuX9060A

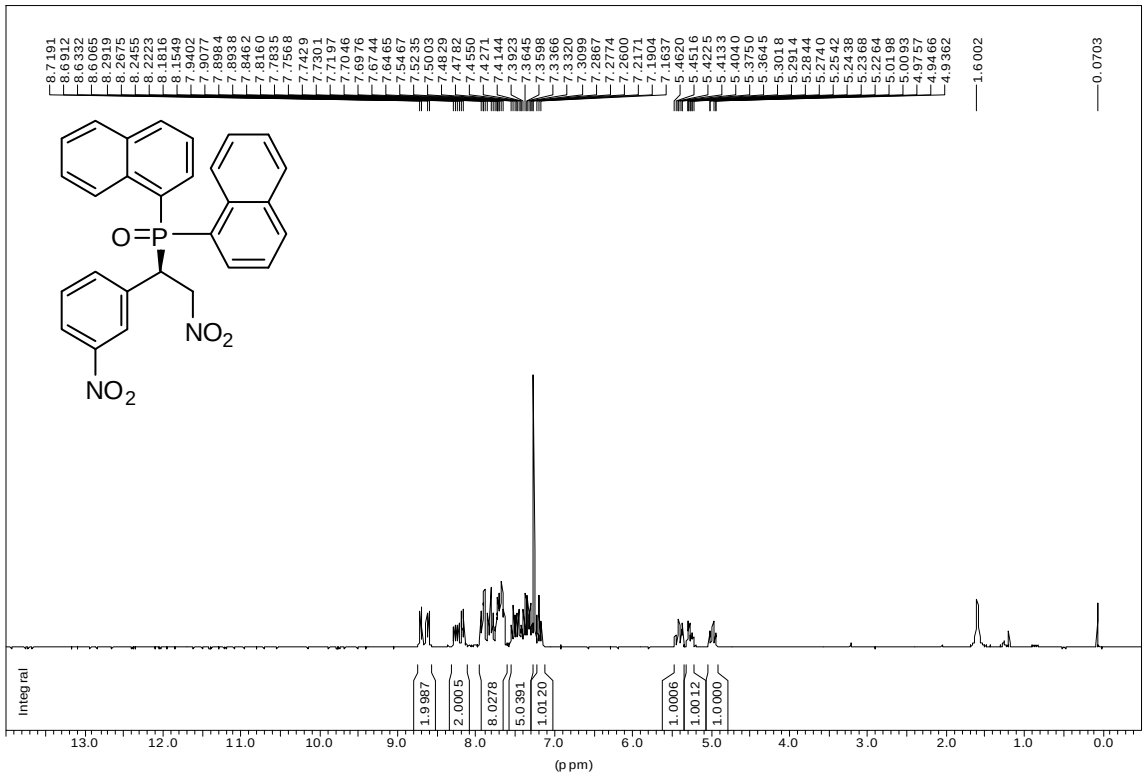


31P AC300 ap01fux1.21.1 FuX9060A

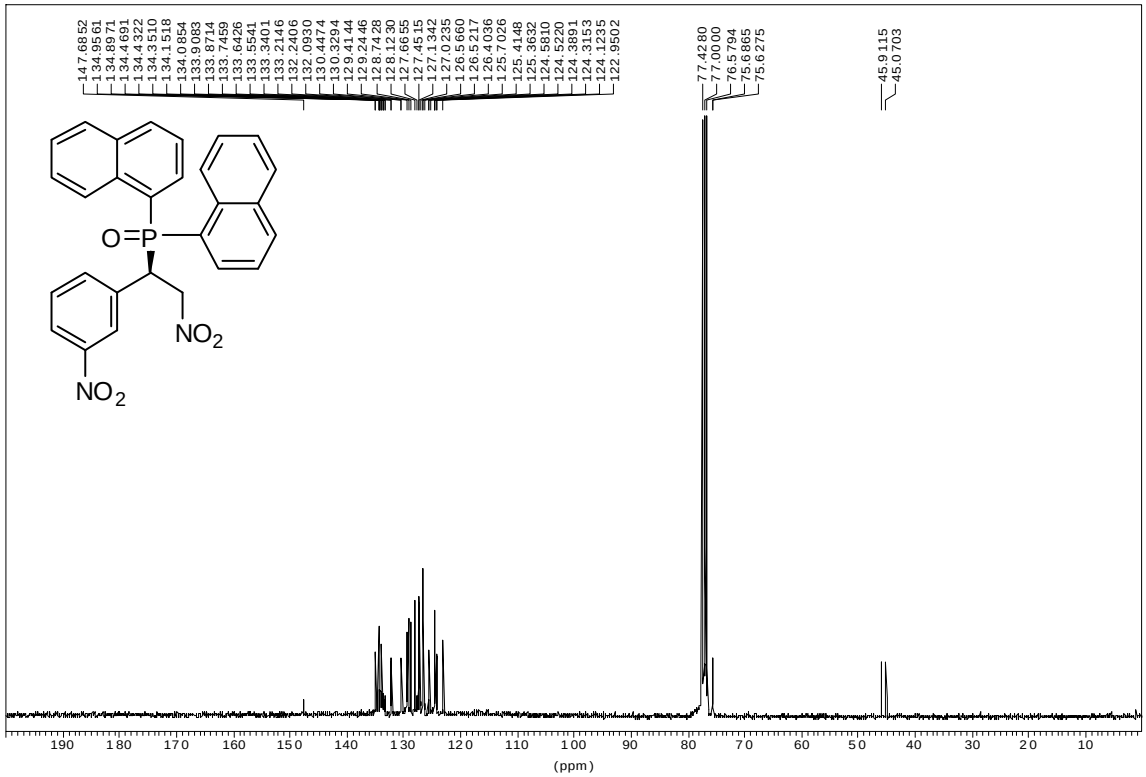


(4e) (2-Nitro-1-(3-nitrophenyl)ethyl)di-1-naphthyl phosphine oxide

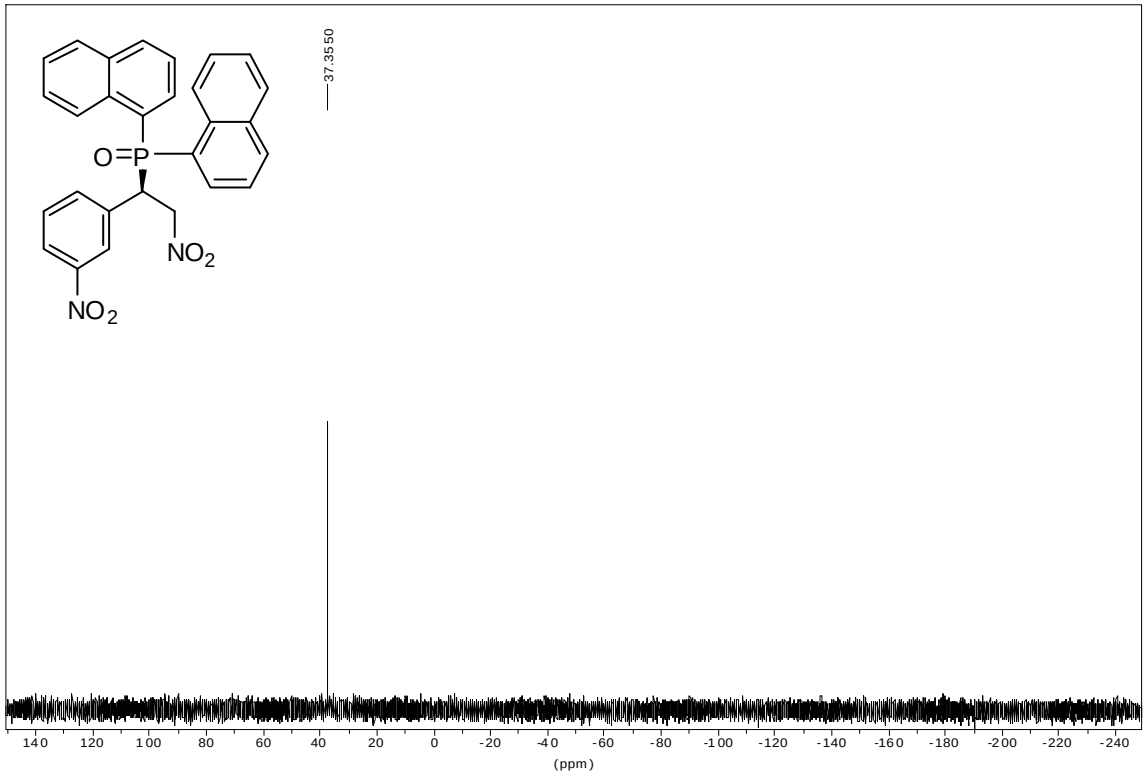
ap13fux1.1.1 FuX9075



ap13fux1.11.1 FuX9075

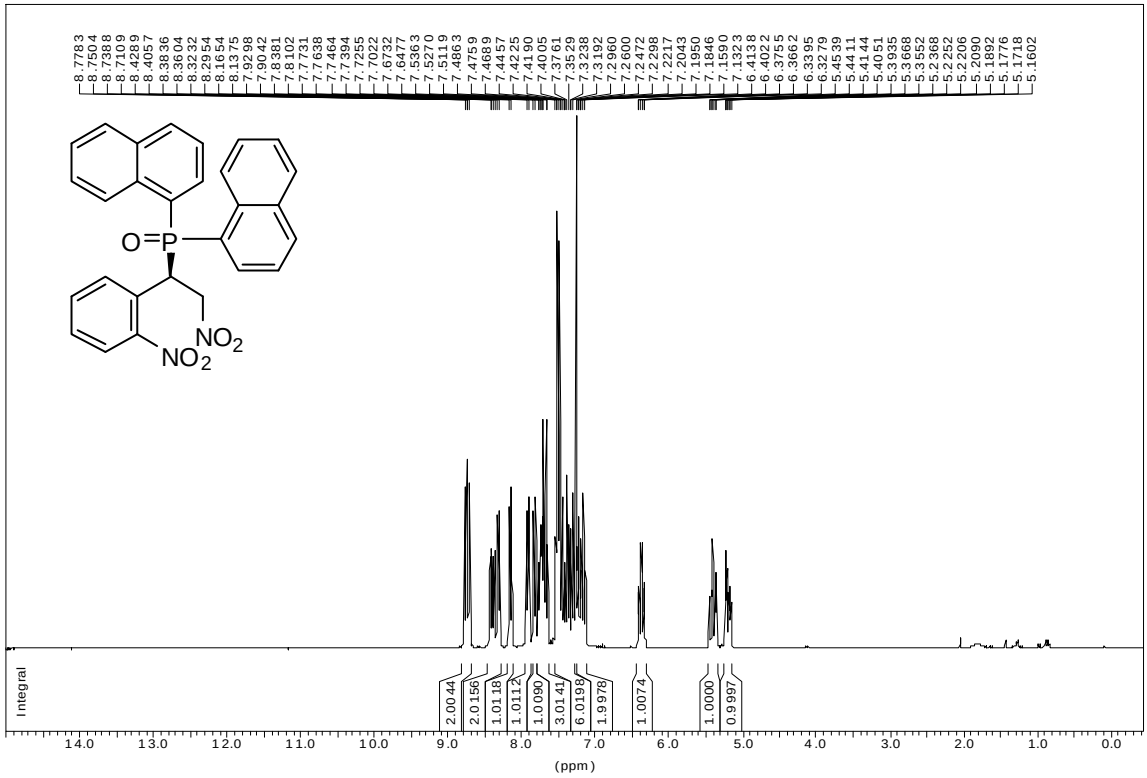


31P AC300 de13fux1.23.1 FuX8178B

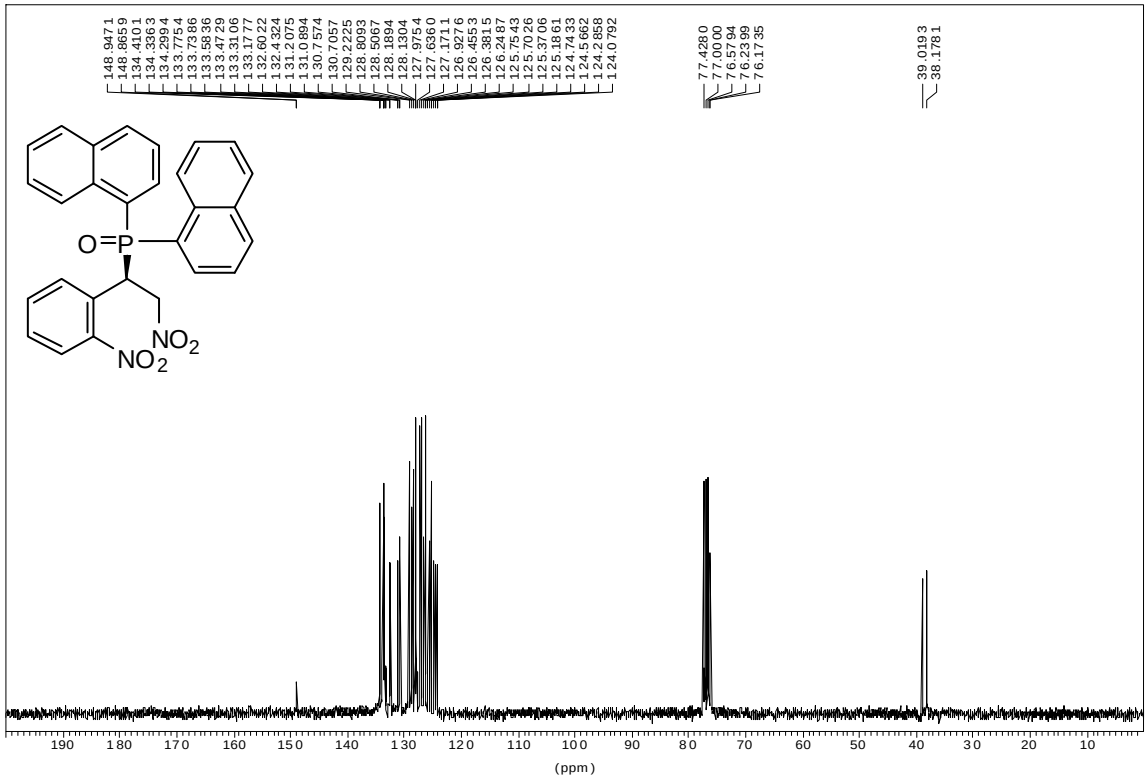


(4f) (2-Nitro-1-(2-nitrophenyl)ethyl)di-1-naphthyl phosphine oxide

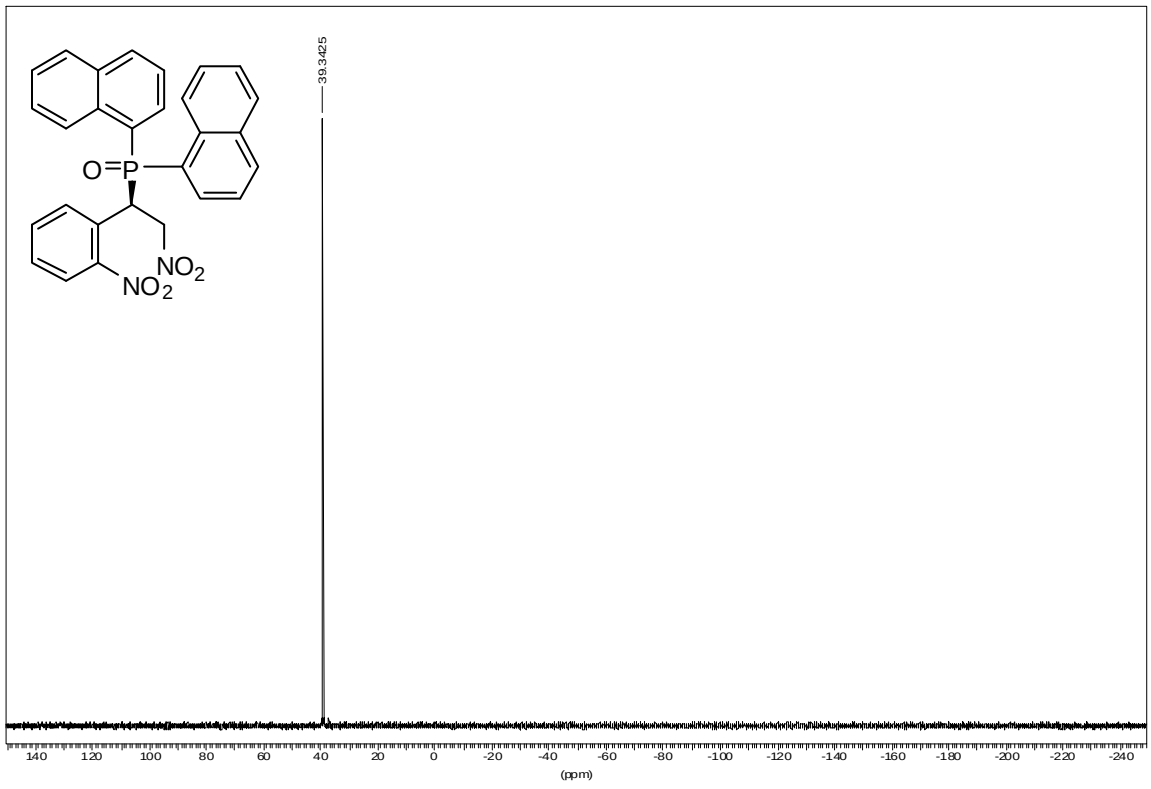
ma26fux1.2.1 FuX9037AI



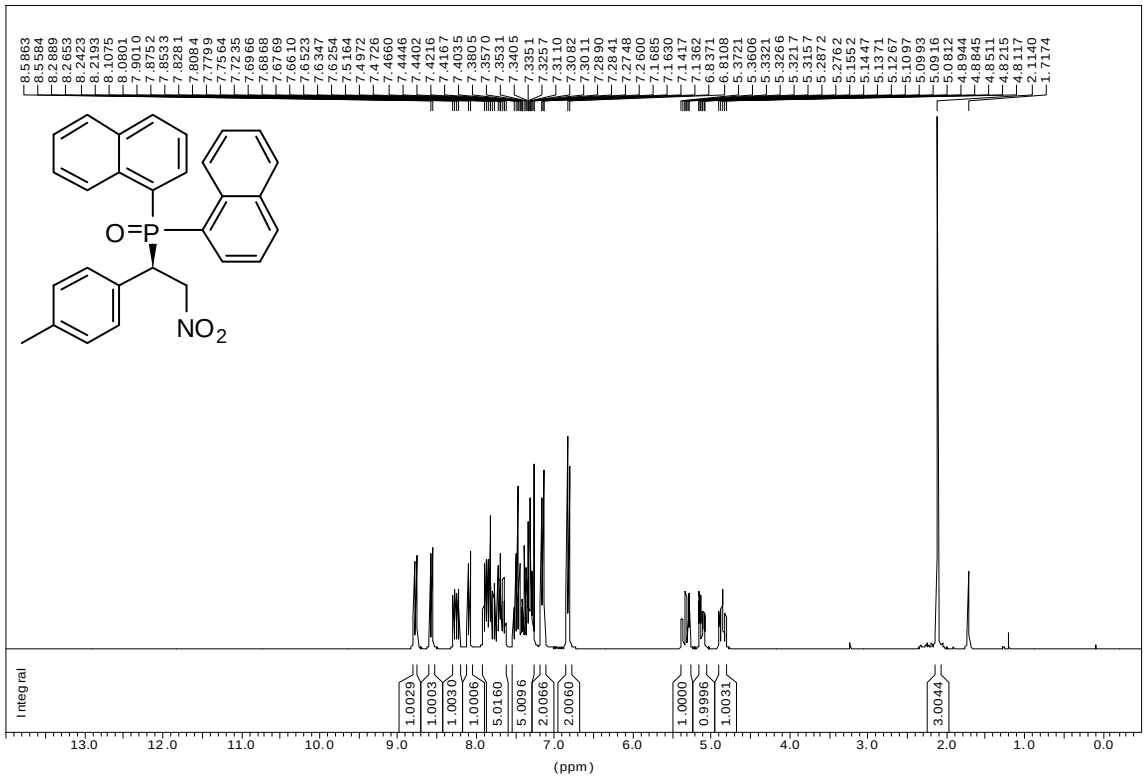
ma26fux1.11.1.FuX9037.Al

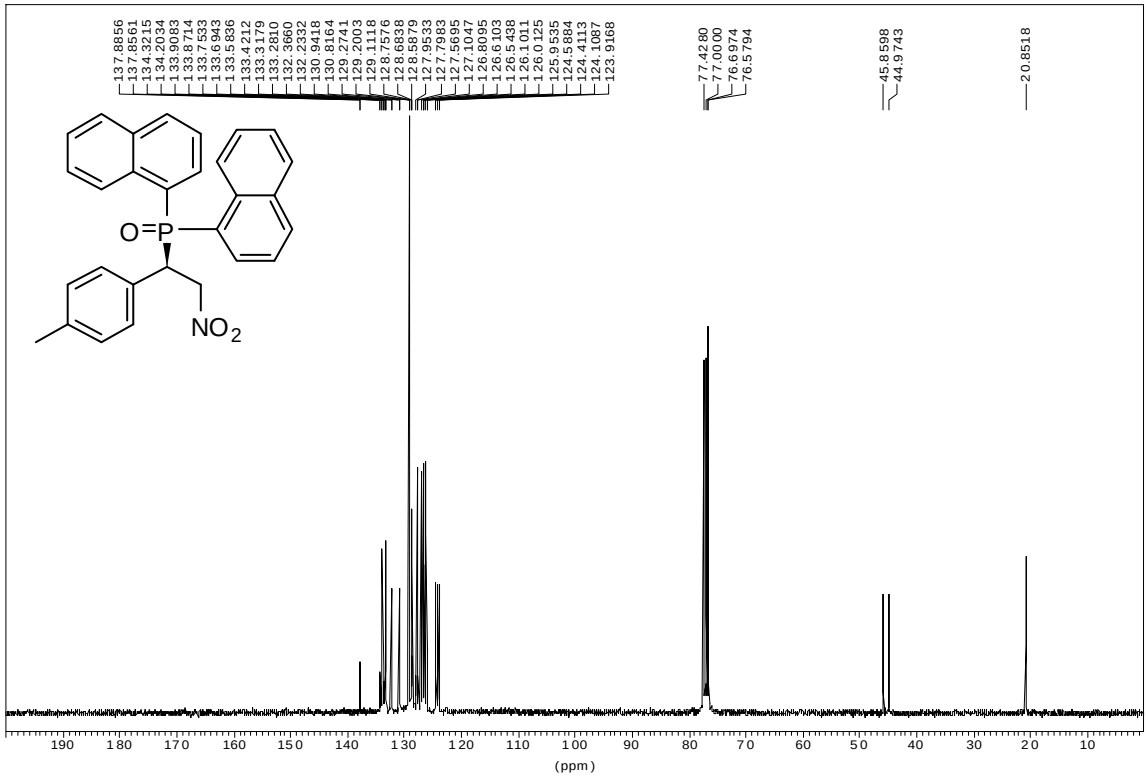


31P AC300 ma24fux 2 1 fux9037A

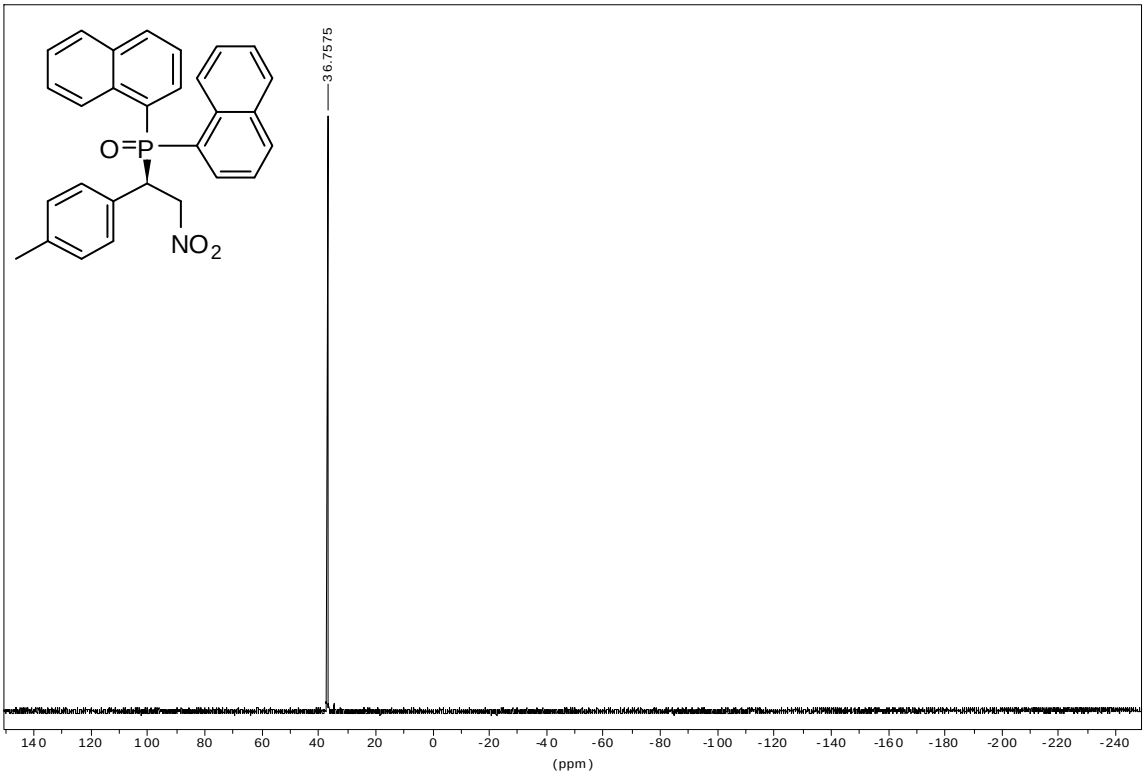


(4g) (2-Nitro-1-(4-methyl-phenyl)ethyl)di-1-naphthyl phosphine oxide



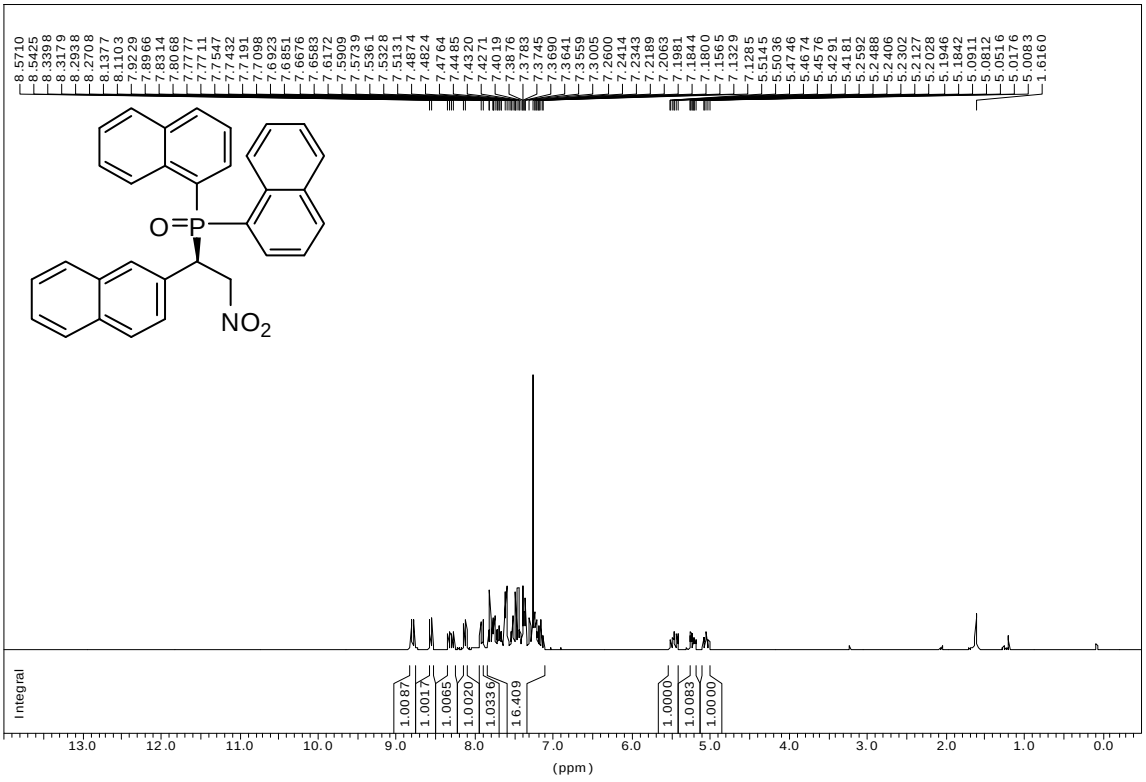


31P AC300 ap16flux1.21.1 FuX90804

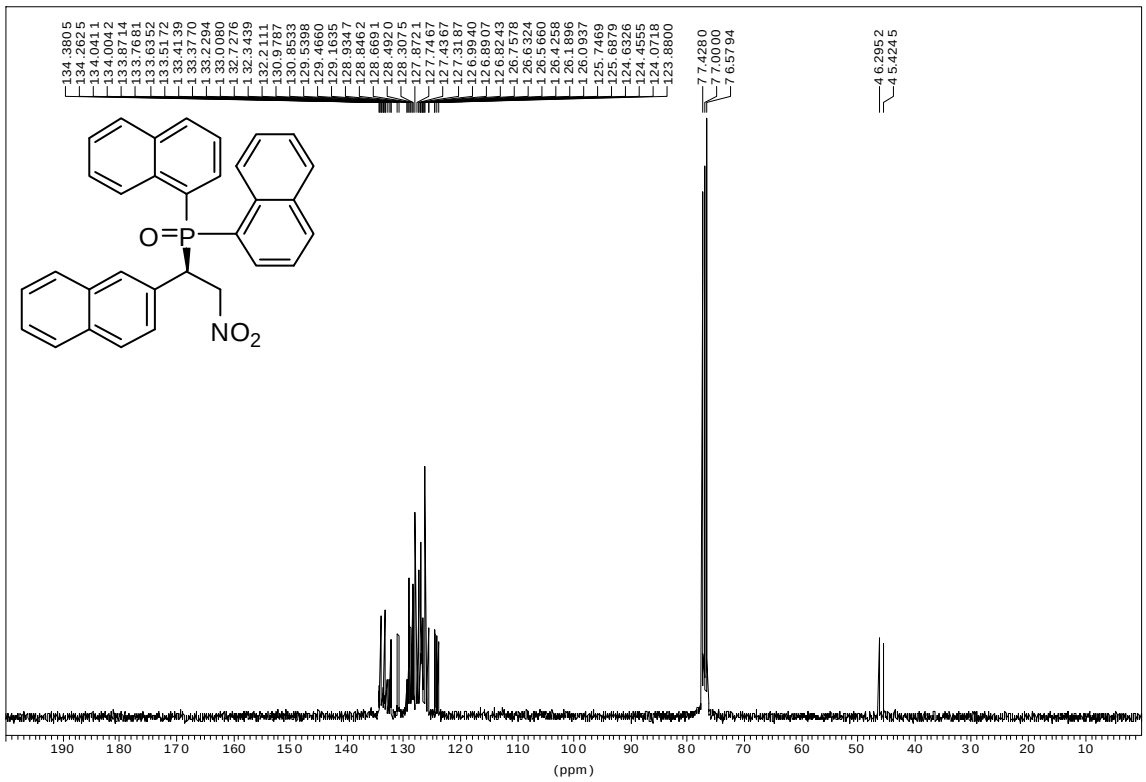


(4h) (2-Nitro-1-(2-naphthyl)ethyl)di-1-naphthyl phosphine oxide

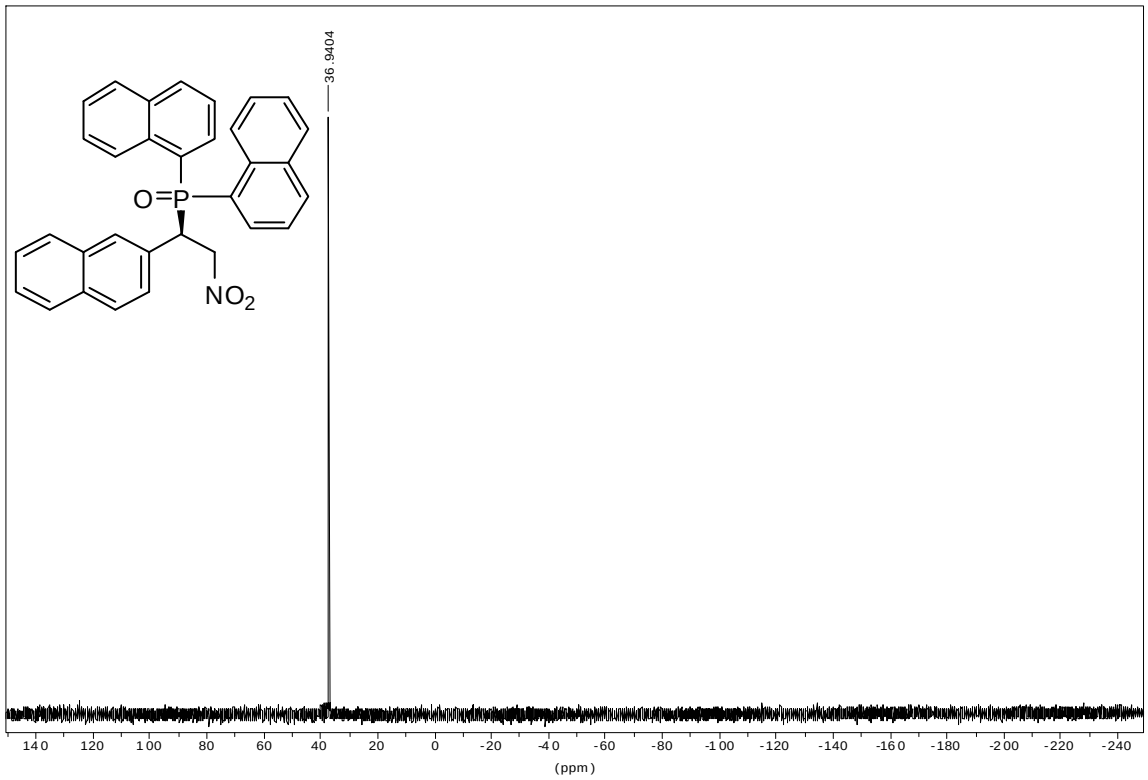
1H normal range AC300 ap16flux1.2.1 FuX90808



ap16fux1.12.1 FuX9080B

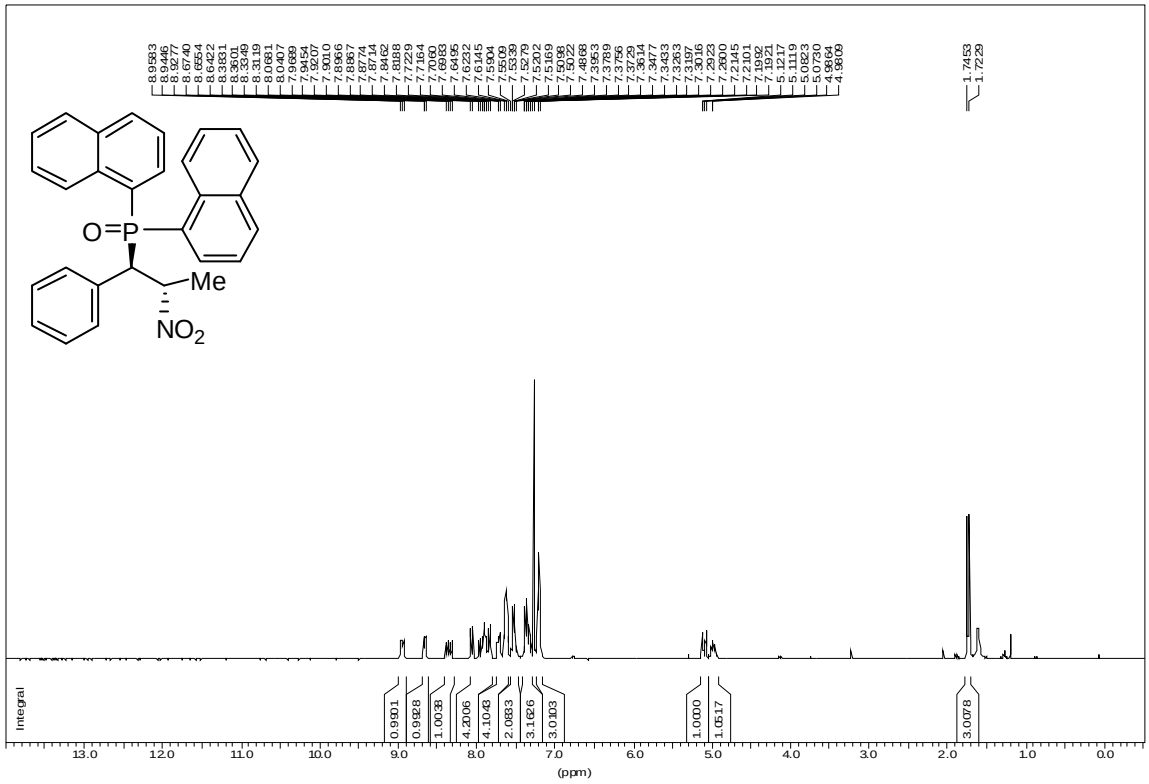


31P AC300 ap16fux1.22.1 FuX9080B

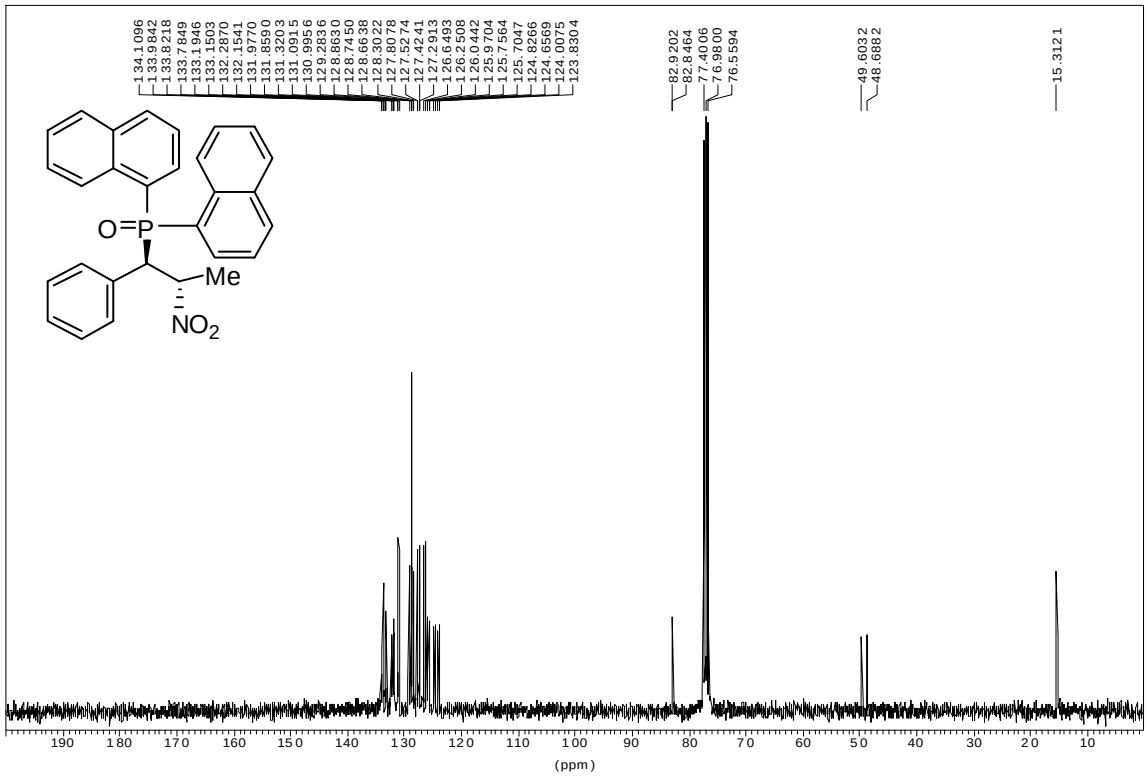


(6a) (2-Methyl-2-nitro-1-phenylethyl)di-1-naphthyl phosphine oxide

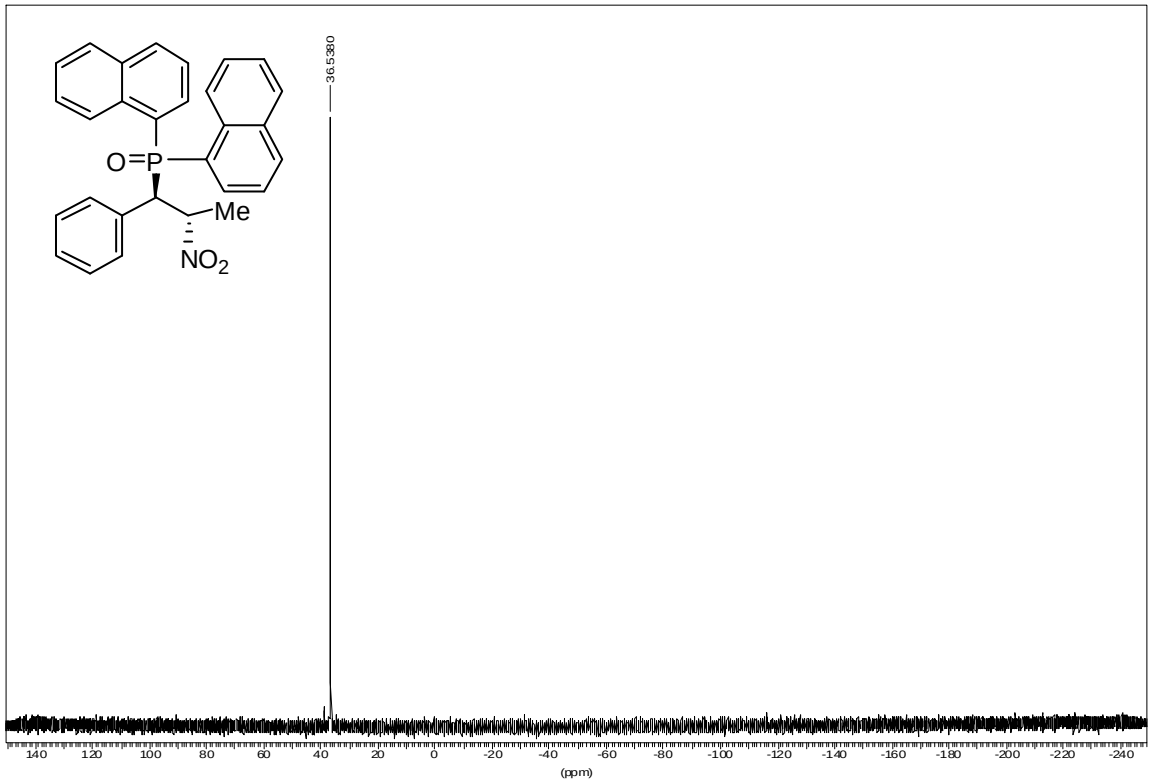
1H normal range AC300 ap24fux1.1.1 FuX9084B



ap25fux1.12.1 FuX9084B

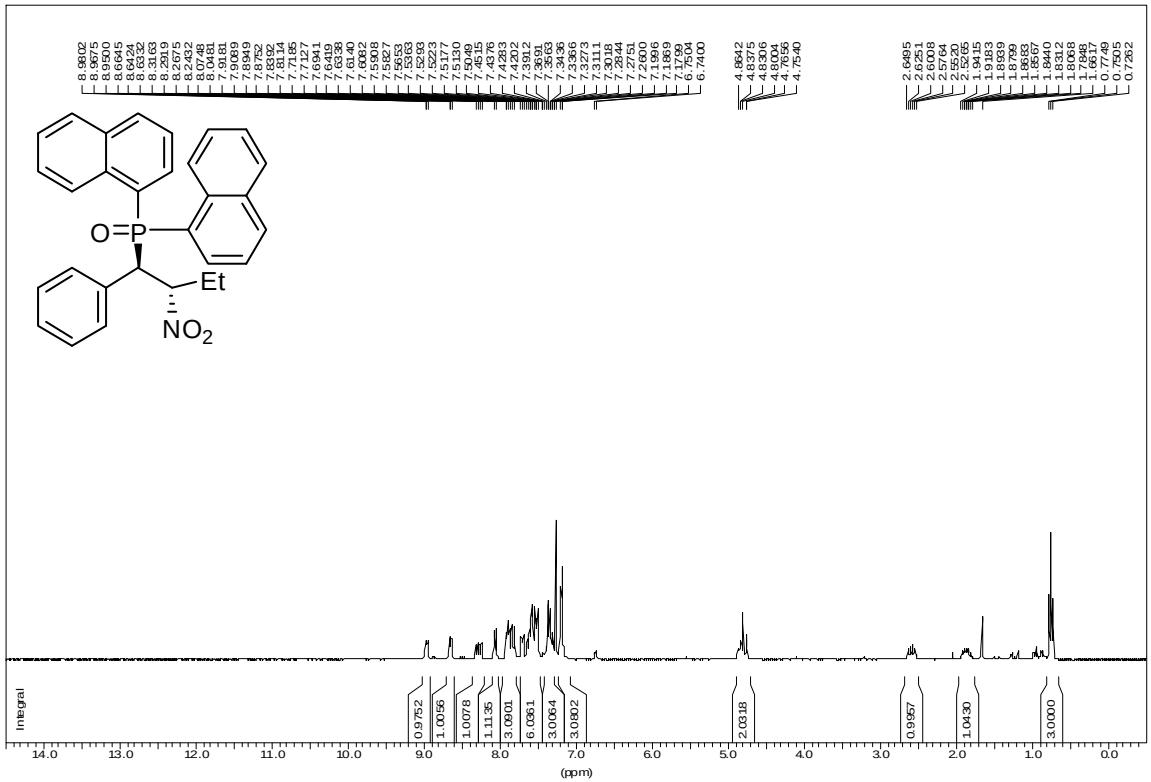


31P AC300 ap24fux1.21.1 FuX9084

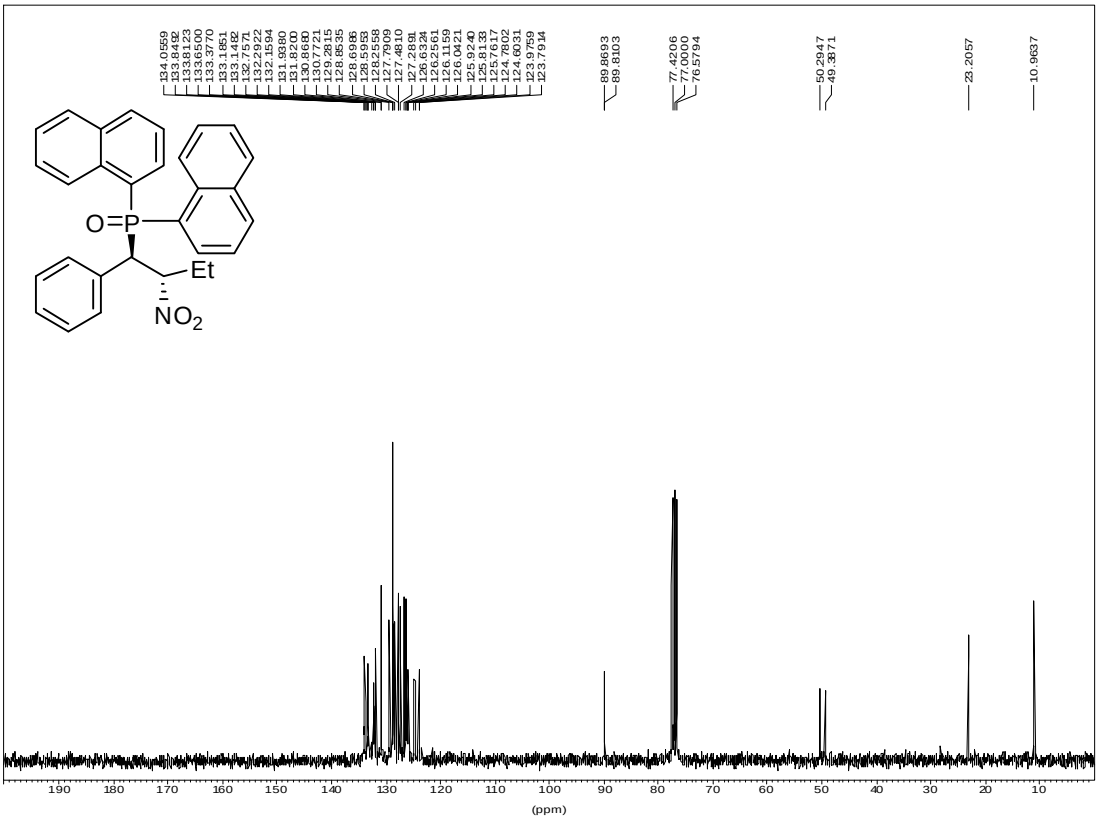


(6b) (2-Ethyl-2-nitro-1-phenylethyl)di-1-naphthyl phosphine oxide

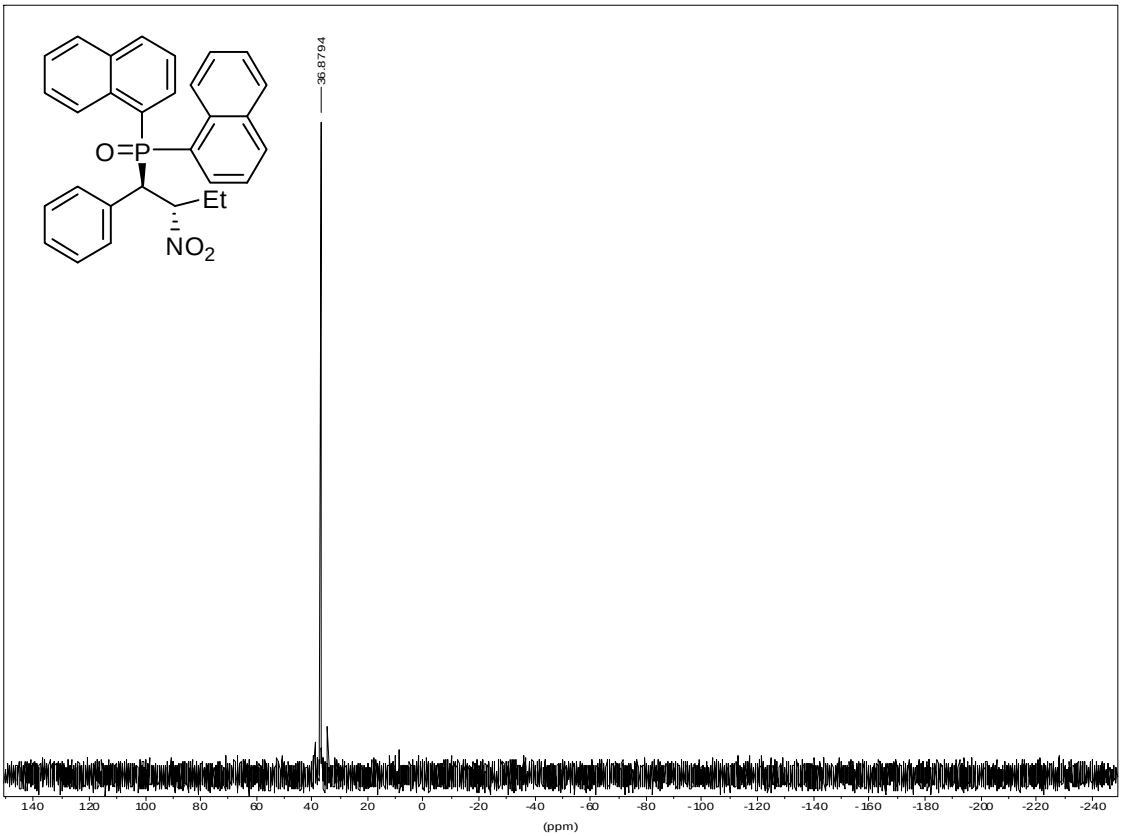
my17fux1.2.1 FuX9103B



my18fux 1.11.1 FuX9103B

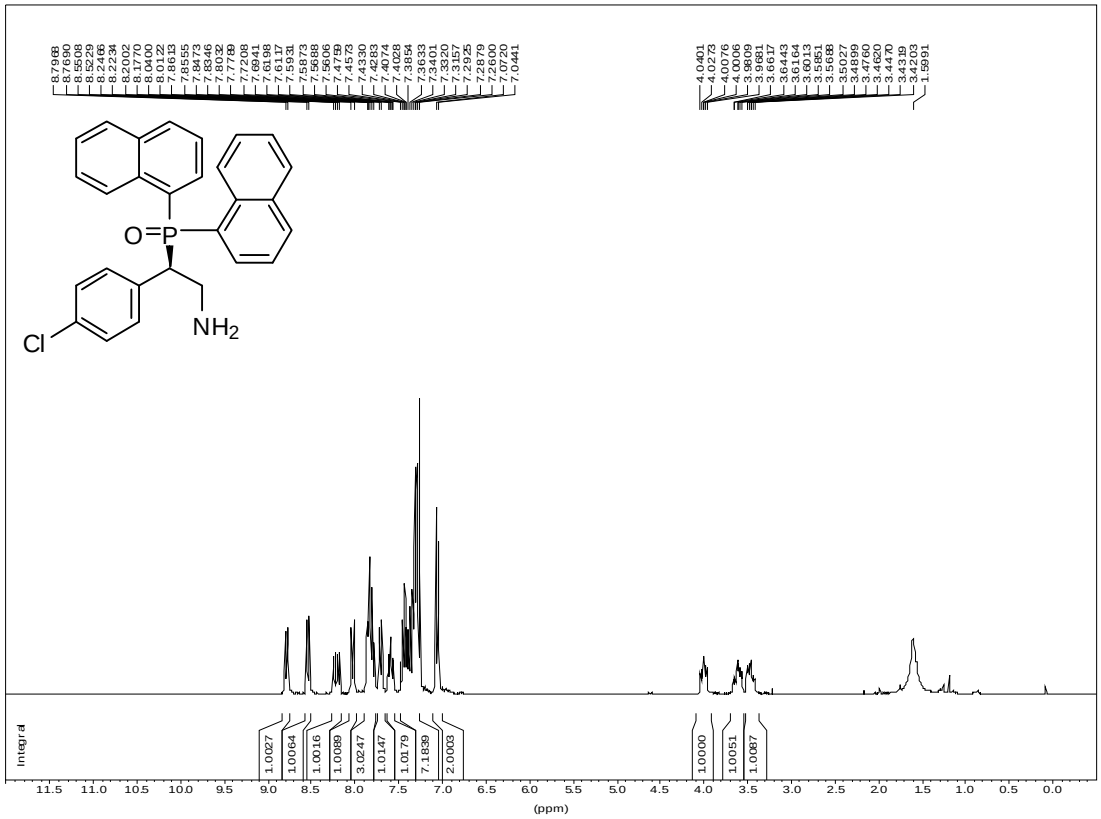


31P AC300 my18fux1.24.1 FUX9103B

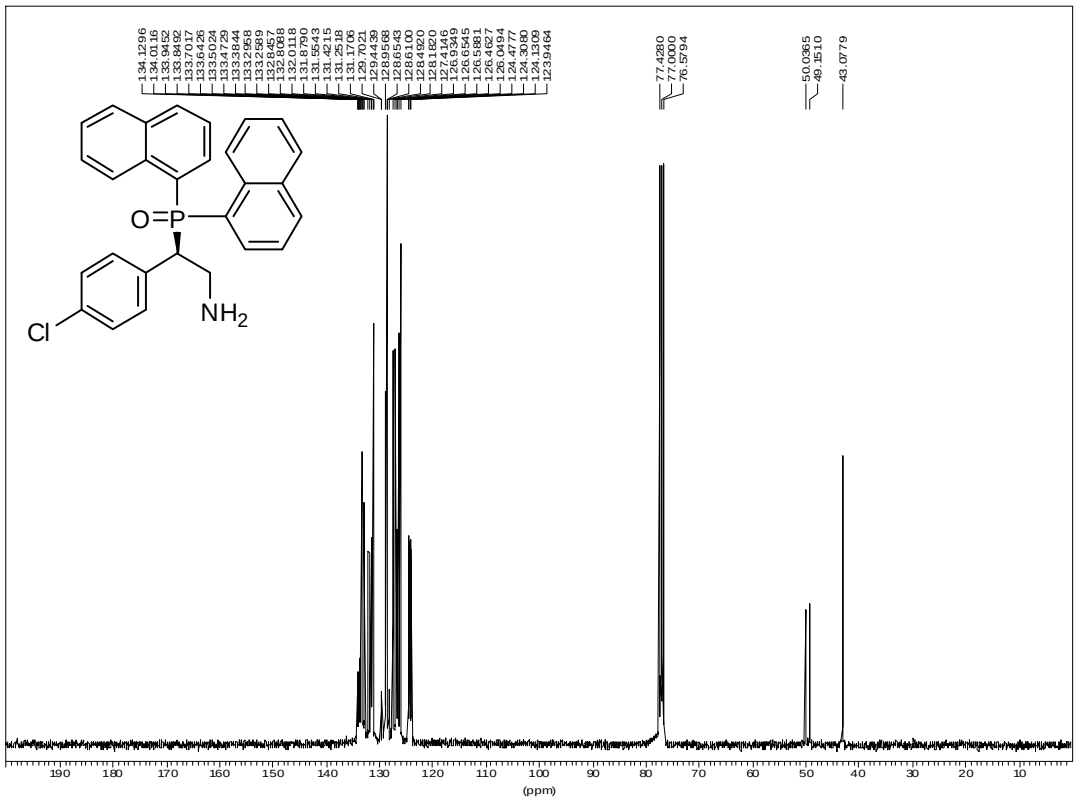


(7) 2-(4-Chlorophenyl)-2-(dinaphthalen-1-ylphosphoryl)ethanamine

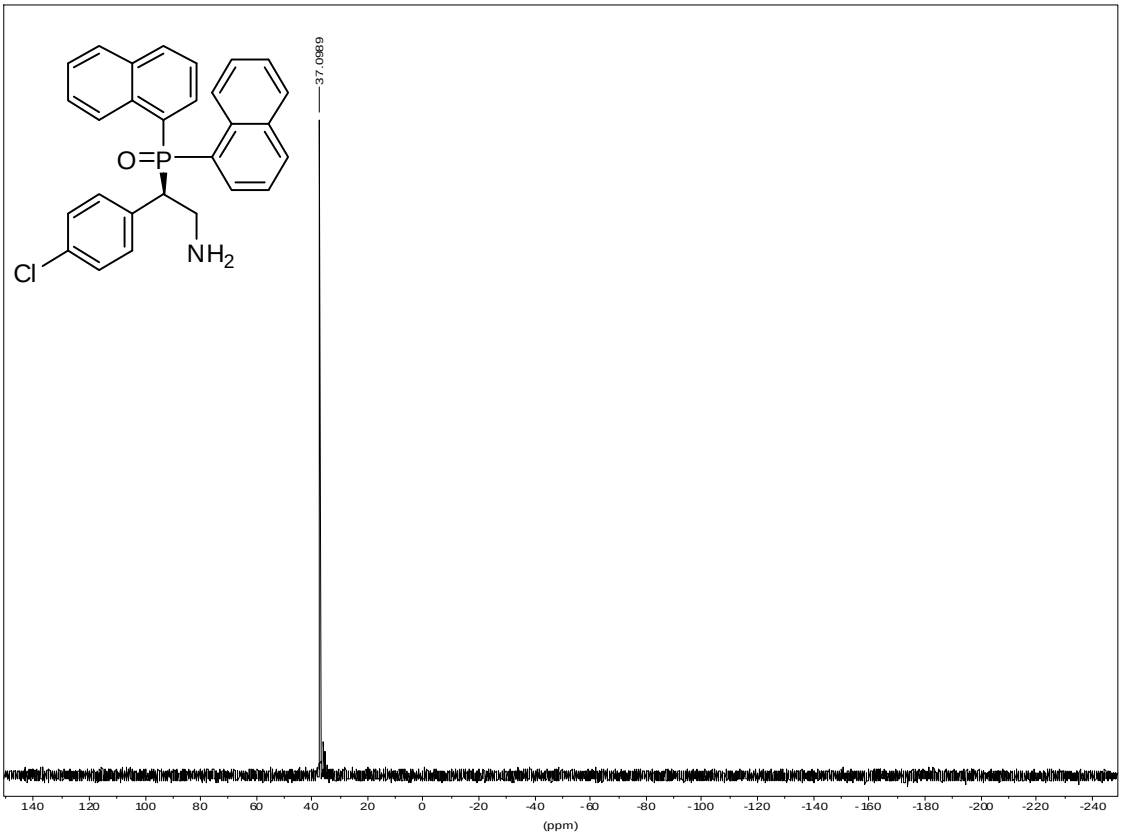
my13fux 1.1.1 FuX9100 14,15



my13fux1.11.1 FUX9100 14,15

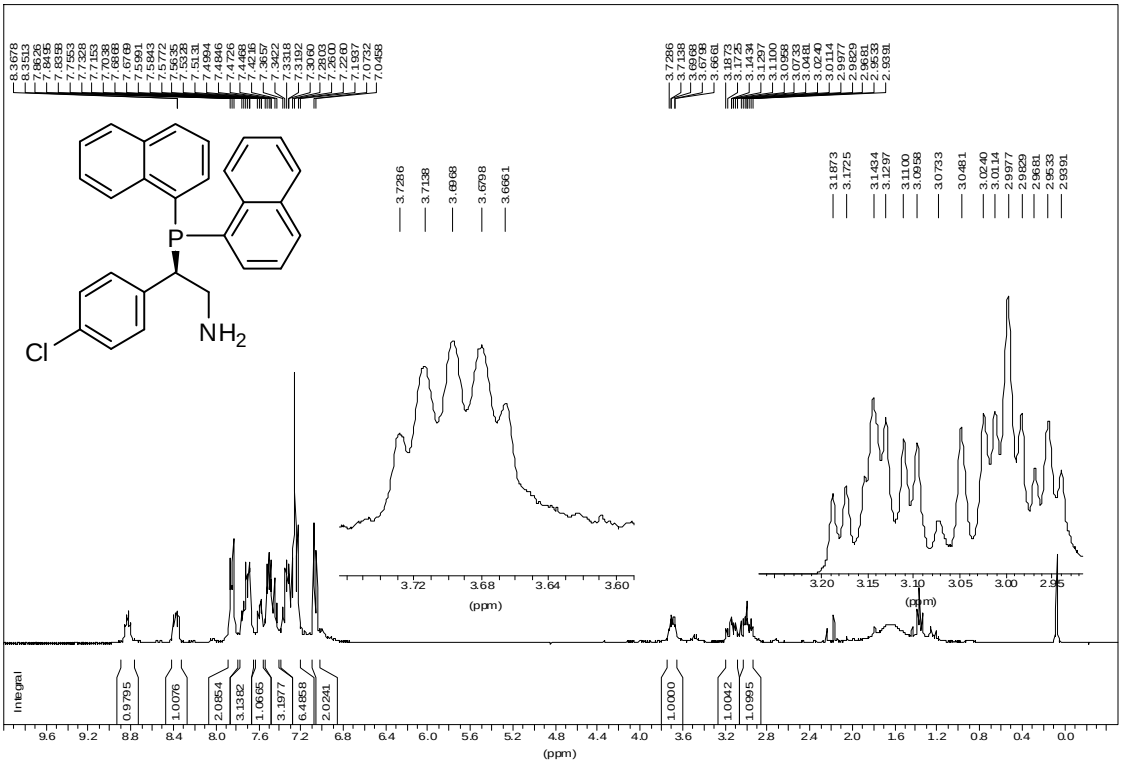


31P AC300 my12flux1.21.1 FuX9100 14,15



(8) 2-(4-chlorophenyl)-2-(dinaphthalen-1-ylphosphino)ethanamine

1H normal range AC300 jl09flux1.1.1 FuX9184 l



31P AC300 j9fux1.21.1 FuX9184 1