Thiourea-Catalysed Conjugate Additions of Amines to Vinyl Phosphonates and Phosphinates

Supplementary Information

Peter E. McDermott,[a,b] Martin P. Ó Fearraigh,[b] Alexandra M. Horan,[b,c] and Eoghan M. McGarrigle*[a,b,c]

eoghanmcgarrigle@ucd.ie

[a] A2P CDT in Sustainable Chemistry and BiOrbic Bioeconomy SFI Research Centre, University College Dublin, Belfield, Dublin 4, Ireland. [b] Centre for Synthesis & Chemical Biology, UCD School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland. [c] SSPC, the SFI Research Centre for Pharmaceuticals, Centre for Synthesis & Chemical Biology, UCD School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland.

Table of Contents

General Experimental

Chemicals were purchased and used without further purification unless otherwise stated. Solvents were dried using a Grubbs-type still,[1] a Pure Solv-400-3-MD solvent purification system supplied by Innovative Technology Inc. design and stored in Strauss flasks over activated 4Å molecular sieves. Extracts were concentrated under reduced pressure using either a rotary evaporator (bath temperatures up to 55 °C), a high vacuum line at room temperature or a combination of both. Catalysts **1**,**4-9** were synthesised following literature procedures.[2–8]

Reaction monitoring by TLC was performed on Merck pre-coated Kieselgel 60 F254 aluminium plates. Visualization was accomplished under UV light (254 nm) or using the stains reported. Flash column chromatography (FCC) was performed using either silica gel [Davisil, 230-400 mesh (40-63 μm)] or using a Biotage Isolera® UV-VIS Flash Purification System Version 2.3.1 with Sfär Silica HC D (20 μm), or Sfär KP-Amino D (50 μm) prepacked silica cartridges.

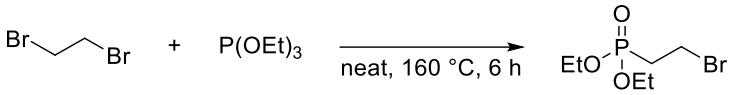
High-resolution mass spectra were run on a Waters Micromass GCT system or on an Agilent 6546 QTOF system in electrospray ionization mode (ESI).

High performance liquid chromatography (HPLC) analysis was performed using Agilent Technologies 1260 Infinity and 1200 Series systems equipped with an auto-sampler and Agilent UV-vis detector operating at 210, 230 and 254 nm. HPLC was carried out in normal phase using heptane and ethanol as solvents. For enantiomer separation, chiral columns Daicel Chiralpak® IA, IB, IC and Daicel Chiralcel® OJ-H, OB-H and ASH of 4.6 mm ID x 250 mm L and 5 μm particle size were used, coupled to a guard column of 4.6 mm ID x 50 mm L. Columns were positioned in an Agilent column switcher device.

^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were recorded on Varian VNMRs, measured in the solvent stated at 300 MHz, 400 MHz or 500 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to residual solvent peak (e.g., $CDCl_3$: ^{1}H – 7.26 ppm and ^{13}C – 77.16 ppm) or TMS (^{1}H – 0.00 ppm) and coupling constants (*J*) are given in Hertz. Multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof. Assignments were made, where necessary, with the aid of COSY, HSQC, HMBC and NOESY NMR experiments. ^{31}P NMR yields were measured using a 5s relaxation delay.

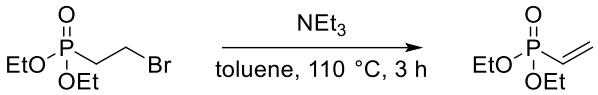
1. Synthesis of α,β-Unsaturated Phosph(in/on)ates

Synthesis of Diethyl Vinylphosphonate (2)



1,2-Dibromoethane (40 mL, 0.5 mol) was added to a flame-dried RBF with a reflux condenser attached under an atmosphere of N_2 and heated to 160 °C. Triethylphosphite (13 mL, 0.1 mol) was added dropwise and the solution was stirred for a further 6 h at 160 °C. The solution was allowed to cool to rt before being concentrated under reduced pressure. The crude product was purified by FCC (EtOAc:cHex 3:1 (R_f: 0.4), visualised using $KMnO_4$ stain), yielding diethyl (2-bromo)ethylphosphonate as a colourless oil (11.4 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 – 4.03 (m, 4H), 3.56 – 3.48 (m, 2H), 2.43 – 2.32 (m, 2H), 1.33 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.2 (d, J = 6.5 Hz), 30.9 (d, J = 134.6 Hz), 24.0, 16.6 (d, J = 6.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.5. NMR data were consistent with literature.[9]

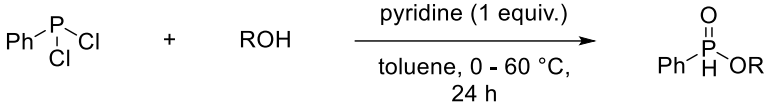


2

Diethyl (2-bromo)ethylphosphonate (8.532 g, 0.035 mol) was added to a flame-dried RBF, with a reflux condenser attached, under an atmosphere of N_2 and diluted with anhydrous toluene (20 mL). Triethylamine (7.7 mL, 0.05 mmol) was added, the solution was heated to 110 °C and stirred for 3 h. A white precipitate (Et_3NHBr) was formed over the course of the reaction. The suspension was allowed to cool to room temperature before the solid was removed by filtration. The solid was washed with EtOAc (3 x 5 mL) and the combined filtrate and washings were concentrated under reduced pressure. The crude material was purified by distillation at reduced pressure (B.P. 48-50 °C at 0.2 mbar) yielding **2** as a colourless liquid (3.971 g, 69%).

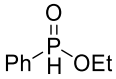
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 – 5.93 (m, 3H), 4.18 – 3.97 (m, 4H), 1.37 – 1.26 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5 (d, J = 2.0 Hz), 126.1 (d, J = 183.9 Hz), 62.0 (d, J = 5.6 Hz), 16.5 (d, J = 6.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.2. NMR data were consistent with literature.[10]

General Procedure A: Synthesis of Alkyl Phenyl-*H*-phosphinates



P,P-Dichlorophenylphosphine (6.8 mL, 50 mmol) was added to a flame-dried 250 mL Schlenk flask under an atmosphere of N_2. Anhydrous toluene (50 mL) was added and the solution was cooled to 0 °C in an ice-water bath. Alcohol (100 mmol) and pyridine (4.1 mL, 50 mmol) were added and the resulting suspension was stirred at 0 °C for 30 min before being allowed to warm to rt. The suspension was stirred at rt for 5 h before being heated to 60 °C in an oil bath and stirred for 18 h. Water (50 mL) was added and the resulting biphasic solution was stirred for 10 mins before sat. $NaHCO_3$ (75 mL) and EtOAc (75 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield the corresponding alkyl phenyl-*H*-phosphinates **(13a-c).**

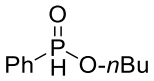
Ethyl Phenyl-*H*-phosphinate (13a):



13a

Synthesised following general procedure A: *P,P*-dichlorophenylphosphine (5.8 mL, 43 mmol), ethanol (5.0 mL, 86 mmol) and pyridine (3.5 mL, 43 mmol) were used. Concentration under reduced pressure yielded **13a** as a colourless oil (4.9 g, 81%), the product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 2H), 7.64 – 7.56 (m, 1H), 7.58 (d, *J* = 563.0 Hz, 1H), 7.55 – 7.47 (m, 2H), 4.23 – 4.06 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1 (d, *J* = 2.9 Hz), 130.7 (d, *J* = 11.6 Hz), 129.9 (d, *J* = 131.8 Hz), 128.7 (d, *J* = 13.7 Hz), 62.0 (d, *J* = 6.3 Hz), 16.2 (d, *J* = 6.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 24.6. NMR data were consistent with literature.[11]

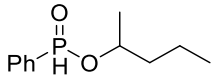
***n*-Butyl Phenyl-*H*-phosphinate (13b):**



13b

Synthesised following general procedure A: *P,P*-dichlorophenylphosphine (6.8 mL, 50 mmol), *n*-butanol (9.2 mL, 0.10 mol) and pyridine (4.0 mL, 50 mmol) were used. Concentration under reduced pressure yielded **13b** as a colourless oil (9.01 g, 91%), the product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.72 (m, 2H), 7.62 – 7.55 (m, 1H), 7.58 (d, *J* = 562.3 Hz, 1H), 7.54 – 7.47 (m, 2H), 4.16 – 4.00 (m, 2H), 1.77 – 1.60 (m, 2H), 1.49 – 1.32 (m, 2H), 0.97 – 0.87 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.2 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 11.8 Hz), 130.1 (d, *J* = 132.0 Hz), 128.9 (d, *J* = 13.7 Hz), 65.9 (d, *J* = 6.5 Hz), 32.6 (d, *J* = 6.5 Hz), 18.9, 13.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.8. NMR data were consistent with literature.[12]

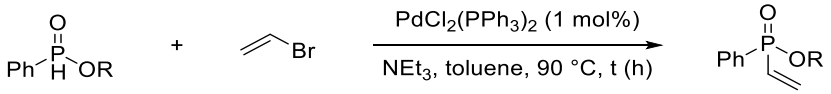
2-Pentanyl Phenyl-*H*-phosphinate (13c):



13c

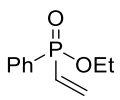
Synthesised following general procedure A: *P,P*-dichlorophenylphosphine (6.8 mL, 50 mmol), 2-pentanol (10.9 mL, 100 mmol) and pyridine (4.03 mL, 50 mmol) were used. Concentration under reduced pressure yielded a colourless oil (10.25 g) purification by FCC (Et_2O:pentane 4:1 R_f: 0.3, visualised using ninhydrin stain) yielded **13c** as a colourless oil (7.98 g, 67%). Isolated as a 1:1 mixture of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 556.8 Hz, 1H, P*H*), 7.83 – 7.69 (m, 2H, Ar*H*), 7.62 – 7.54 (m, 1H, Ar*H*), 7.54 – 7.45 (m, 2H, Ar*H*), 4.65 – 4.50 (m, 1H, OC*H*), 1.81 – 1.22 (m, 7H, 2xCH_2, CHCH_3), 0.95 (t, *J* = 7.3 Hz, CH_2CH_3), 0.86 (t, *J* = 7.3 Hz, CH_2CH_3), the signals at 0.95 and 0.86 ppm integrate for 3H. ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1 – 132.9 (m, *p*-Ar), 130.91 (d, *J* = 11.6 Hz, 2xAr), 130.86 (d, *J* = 133.9 Hz, *ipso*-Ar), 130.7 (d, *J* = 133.8 Hz, *ipso*-Ar) 128.8 (d, *J* = 13.9 Hz, 2xAr), 75.2 (d, *J* = 6.7 Hz, O*C*H), 74.6 (d, *J* = 6.8 Hz, O*C*H) 40.0 (CH*C*H_2), 39.9 (CH*C*H_2), 22.4 (d, *J* = 3.1 Hz, CH*C*H_3), 21.8 (d, *J* = 3.0 Hz, CH*C*H_3), 18.7 (*C*H_2CH_3), 18.5 (*C*H_2CH_3) 14.0 (CH_2*C*H_3), 13.9 (CH_2*C*H_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.5, 22.0. HRMS (ESI) *m/z* calc'd for $C_{11}H_{17}O_2P$ [M+H^+]: 213.1039; found: 213.1041.

General Procedure B: Synthesis of Alkyl Phenylvinylphosphinates (14a-c)



Based on a procedure developed by Hirao and co-workers.[13] $PdCl_2(PPh_3)_2$ (0.028 g, 0.040 mmol) was charged into an oven-dried crimp-top vial under an atmosphere of N_2. Alkyl phenyl-*H*-phosphinate (4.0 mmol) was added followed by anhydrous toluene (5 mL) and triethylamine (1.25 mL, 8.50 mmol). Vinyl bromide (1 M solution in THF, 6.0 mL, 6.0 mmol) was added in a single portion at 0 °C. The yellow solution was heated to 90 °C and stirred until consumption of phosphinate was observed by TLC (Et_2O:pentane, 4:1, visualised using ninhydrin stain). After the phosphinate had been consumed, the reaction was allowed to cool to rt. Et_2O (5 mL) was added and the suspension was filtered. The solid residue was washed with Et_2O (2 x 5 mL). The combined organic washes were concentrated under reduced pressure to yield crude alkyl phenylvinylphosphinates (**14a-c)**. The crude products were purified by FCC.

Ethyl Phenylvinylphosphinate (14a)

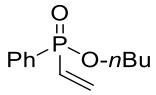


14a

Synthesised following general procedure B: ethyl phenyl-*H*-phosphinate (0.681 g, 4.00 mmol) was used. Reaction time: 40 h. Purified by FCC (Et_2O:pentane, 4:1, R_f: 0.4) to yield **14a** as a yellow oil (0.502 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 2H), 7.58 – 7.42 (m,

3H), 6.37 – 6.02 (m, 3H), 4.18 – 3.92 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5 (d, J = 2.1 Hz), 132.3 (d, J = 2.1 Hz), 131.4 (d, J = 10.2 Hz), 130.6 (d, J = 135.4 Hz), 129.8 (d, J = 133.3 Hz), 128.5 (d, J = 13.4 Hz), 60.7 (d, J = 6.1 Hz), 16.4 (d, J = 7.2 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.0. NMR data were consistent with literature.[14]

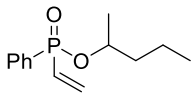
_n_-Butyl Phenylvinylphosphinate (14b)



14b

Synthesised following general procedure B: *n*-butyl phenyl-*H*-phosphinate (0.793 g, 4.00 mmol) was used. Reaction time: 40 h. Purified by FCC (Et_2O:pentane, 4:1, R_f: 0.4) to yield **14b** as a colourless oil (0.636 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 2H, ArH), 7.56 – 7.50 (m, 1H, ArH), 7.49 – 7.43 (m, 2H, ArH), 6.54 – 5.88 (m, 3H, *H*C=C*H*$_2$), 4.07 – 3.97 (m, 1H, OC*H*H), 3.95 – 3.86 (m, 1H, OCH*H*), 1.70 – 1.60 (m, 2H, OCH_2CH_2), 1.45 – 1.34 (m, 2H, CH_2CH_3), 0.90 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7 (d, J = 2.0 Hz, HC=*C*H$_2$), 132.4 (d, J = 2.9 Hz, *p*-Ar), 131.6 (d, J = 10.3 Hz, 2xAr), 130.8 (d, J = 136.2 Hz, *ipso*-C), 129.95 (d, J = 132.8 Hz, P*C*H), 128.7 (d, J = 13.0 Hz, 2xAr), 64.6 (d, J = 6.1 Hz, O*C*H$_2$), 32.7 (d, J = 6.5 Hz OCH_2CH_2), 18.9 (CH_2CH_3), 13.7 (CH_2CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.8. ESI HRMS: *m/z* calc'd for $C_{12}H_{17}O_2P$ [M + H^+]: 225.1039; found: 225.1041.

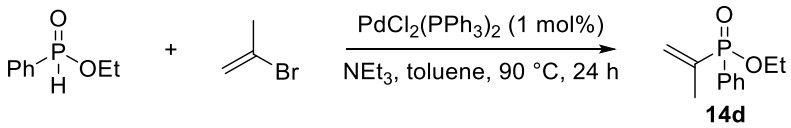
2-Pentanyl Phenylvinylphosphinate (14c)



14c

Synthesised following general procedure B: 2-pentanyl phenyl-*H*-phosphinate (0.849 g, 4.00 mmol) was used. Reaction time: 5 days. Purified by FCC (Et_2O:pentane, 4:1, R_f: 0.3) to yield **15c** as a colourless oil (0.795 g, 83%). Isolated as a 50:50 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H, 2xArH), 7.56 – 7.49 (m, 1H, ArH), 7.49 – 7.42 (m, 2H, 2xArH), 6.39 – 6.03 (m, 3H, *H*C=C*H*$_2$), 4.56 – 4.42 (m, 1H, OC*H*), 1.75 – 1.18 (m, 7H, C*H*$_2$C*H*$_2$ and OCHC*H*$_3$), 0.93 (t, J = 7.3 Hz, H_2CCH_3), 0.81 (t, J = 7.4 Hz, H_2CCH_3) the signals at 0.93 and 0.81 ppm integrate for 3H. ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (d, J = 1.9 Hz, HC=*C*H$_2$), 134.3 (d, J = 1.8 Hz, HC=*C*H$_2$), 132.2 (d, J = 2.8 Hz, *p*-Ar), 131.8 (d, J = 137.5, *ipso*-C) 131.51 (d, J = 10.1 Hz, 2xAr), 131.48 (d, J = 137.3 Hz, *ipso*-C) 130.7 (d, J = 132.5 Hz, P-*C*H) 130.5 (d, J = 132.0 Hz, P*C*H), 128.5 (d, J = 13.0 Hz, 2xAr), 73.4 (app. t, J = 6.0 Hz, O*C*H), 40.3 (d, J = 4.9 Hz, CH*C*H$_2$), 40.1 (d, J = 5.2 Hz, CH*C*H$_2$), 22.3 (app dd, J = 5.3, 2.8 CH*C*H$_3$), 18.7 (CH_2CH_3), 18.4 (CH_2CH_3), 14.0 (CH_2CH_3), 13.9 (CH_2CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.1. ESI HRMS *m/z* calc'd for $C_{13}H_{19}O_2P$ [M + H^+]: 239.1198; found: 239.1198.

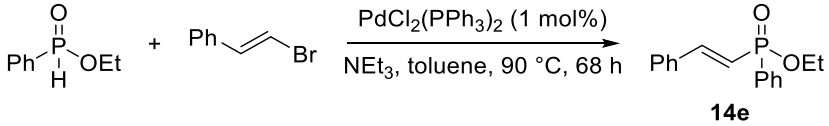
Synthesis of Ethyl Phenyl(prop-1-en-2-yl)phosphinate (14d)



Based on a procedure developed by Hirao and co-workers.[13] $PdCl_2(PPh_3)_2$ (0.021 g, 0.030 mmol) was added to an oven-dried crimp-top vial under an atmosphere of N_2. Ethyl phenyl-*H*-phosphinate (0.510 g, 3.00 mmol), 2-bromopropene (0.484 g, 4.00 mmol) and triethylamine (1.31 mL, 9.00 mmol) were added. The yellow suspension was dissolved in anhydrous toluene (5 mL), heated to 90 °C and stirred for 24 h. The reaction mixture was allowed to cool to rt. Et_2O (5 mL) was added and the suspension was filtered. The solid residue was washed with Et_2O (2 x 5 mL). The combined organic washes were concentrated under reduced pressure. The crude product was purified by FCC (Et_2O:pentane 5:1, R_f: 0.4) to yield **14d** as a colourless oil (0.372 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 2H, Ar*H*), 7.55 – 7.49 (m, 1H, Ar*H*), 7.48 – 7.40 (m, 2H, Ar*H*), 5.97 – 5.69 (m, 2H, C=CH_2), 4.15 – 3.95 (m, 2H, OCH_2), 1.92 – 1.82 (m, 3H, PCCH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (d, J = 125.1 Hz, P*C*=CH_2), 132.3 (d, J = 2.7 Hz, *p*-Ar), 131.8 (d, J = 10.0 Hz, 2xAr), 130.3 (d, J = 132.0 Hz, *ipso*-Ar), 129.7 (d, J = 9.2 Hz, PC=*C*H_2), 128.6 (d, J = 12.6 Hz, ArH), 60.9 (d, J = 6.0 Hz, O*C*H_2), 18.7 (d, J = 12.6 Hz, PC*C*H_3), 16.6 (d, J = 6.5 Hz, CH_2CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.7. ESI HRMS *m/z* calc'd for $C_{11}H_{15}O_2P$ [M + H^+]: 211.0882; found: 211.0881.

Synthesis of Ethyl (*E*)-Phenyl(styryl)phosphinate (14e)

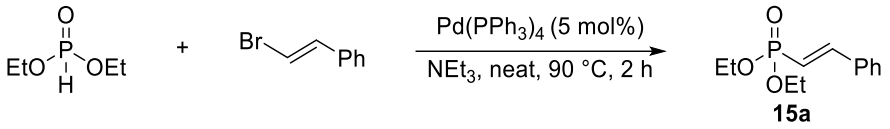


Based on a procedure developed by Hirao and co-workers.[13] $PdCl_2(PPh_3)_2$ (0.018 g, 0.026 mmol) was added to an oven-dried crimp-top vial under an atmosphere of N_2. Ethyl phenylvinylphosphinate (0.449 g, 2.64 mmol), β-bromostyrene (0.513 g, 2.80 mmol) and triethylamine (1.14 mL, 7.80 mmol) were added. The yellow suspension was dissolved in anhydrous toluene (4 mL), heated to 90 °C and stirred for 68 h. The reaction mixture was allowed to cool to rt before being diluted with Et_2O (5 mL). The suspension was filtered and the solid residue was washed with Et_2O (2 x 5 mL). The combined organic washes were concentrated under reduced pressure and the crude product was purified by FCC (cHex:EtOAc 90:10 – 20:80, R_f: 0.3 in cHex:EtOAc 20:80) to yield **14e** as a colourless oil (0.349 g, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 2H), 7.61 – 7.42 (m, 6H), 7.41 – 7.31 (m, 3H), 6.49 (dd, J = 20.4, 17.5 Hz, 1H), 4.22 – 3.98 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.9 (d, J = 5.6 Hz), 135.2 (d, J = 19.7 Hz), 132.6, 132.1, 131.5 (d, J =

10.0 Hz), 130.9, 130.5, 128.5 (d, J = 13.1 Hz), 128.4 (d, J = 106.0 Hz), 118.1 (d, J = 138.7 Hz), 60.9 (d, J = 5.9 Hz), 16.6 (d, J = 6.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ 31.1. NMR data were consistent with literature.[15]

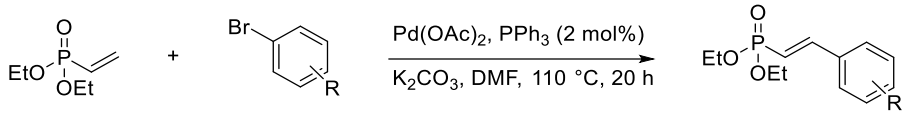
Synthesis of Diethyl (*E*)-Styrylphosphonate (15a)



15a

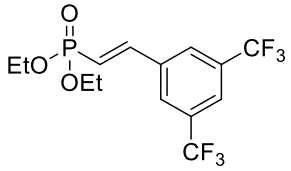
Based on a procedure developed by Hirao and co-workers.[13] $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol) was added to an oven-dried crimp-top vial under an atmosphere of Ar in a glovebox. The vial was removed from the glovebox and diethylphosphite (0.14 mL, 1.1 mmol), β-bromostyrene (0.13 mL, 1.0 mmol) and triethylamine (0.16 mL, 1.1 mmol) were added under a flow of N_2. The suspension was heated to 90 °C and stirred for 2 h. H_2O (5 mL) and EtOAc (5 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by FCC (Et_2O 100%, R_f: 0.3) to yield **15a** as a colourless oil (0.192 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.44 (m, 3H), 7.41 – 7.35 (m, 3H), 6.26 (app. t, J = 17.6 Hz, 1H), 4.19 – 4.07 (m, 4H), 1.35 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (d, J = 6.5 Hz), 135.0 (d, J = 23.3 Hz), 130.4, 129.0, 127.9, 114.1 (d, J = 191.3 Hz), 62.0 (d, J = 5.5 Hz), 16.6 (d, J = 6.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.5. NMR data were consistent with literature.[16]

General Procedure C: Synthesis of Substituted Diethyl Styrylphosphonates (15b and 15c)



Based on a procedure developed by Djakovitch and co-workers.[17] Triphenylphosphine (0.003 g, 0.01 mmol) and $Pd(OAc)_2$ (0.002 g, 0.01 mmol) were added to an oven-dried crimp-top vial under an atmosphere of N_2. Aryl bromide (0.50 mmol) and diethyl vinylphosphonate (0.08 g, 0.50 mmol) were added and the suspension was dissolved in anhydrous DMF (6 mL). N_2 was bubbled through the solution for 15 min before the solution was heated to 110 °C and stirred for 20 h. The reaction was allowed to cool to rt before H_2O (100 mL) was added. The aqueous solution was extracted with EtOAc (6 x 75 mL) and the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude products were purified by FCC to yield diethyl styrylphosphonates **15b** and **15c**.

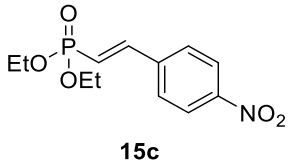
Diethyl (*E*)-(3,5-bis(trifluoromethyl)styryl)phosphonate (15b)



15b

Synthesised following general procedure C: 3,5-trifluoromethylbromobenzene (0.09 mL, 0.5 mmol) was used. Purified by FCC (90:10, EtOAC:cHex, R_f: 0.6) to yield **15b** as an orange amorphous solid (0.079 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.79 (m, 3H, 3xArH), 7.53 (dd, *J* = 22.2, 17.3, 1H, *H*C-Ar), 6.44 (dd, *J* = 17.5, 15.6, 1H, PC*H*), 4.32 – 3.94 (m, 4H, 2xOCH_2), 1.37 (t, *J* = 7.0 Hz, 6H, 2xCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (d, *J* = 7.1 Hz, H*C*-Ar), 137.1 (d, *J* = 24.1 Hz, *ipso*-Ar), 132.6 (q, *J* = 33.6 Hz, 2x*C*CF_3), 127.5 (d, *J* = 4.1 Hz, 2xAr), 123.48 (app. p, *J* = 3.8 Hz, Ar), 123.1 (q, *J* = 272.9 Hz, *C*F_3), 119.45 (d, *J* = 190.7 Hz, P*C*H), 62.4 (d, *J* = 5.7 Hz, 2xO*C*H_2), 16.5 (2x*C*H_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.8. ESI-HRMS *m/z* calc'd for $C_{14}H_{15}F_6O_3P$ [M + H^+]: 377.0736; found: 377.0736.

Diethyl (*E*)-(4-nitrostyryl)phosphonate (15c)

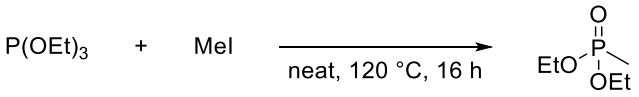


15c

Synthesised following general procedure C: 4-nitrobromobenzene (0.10 g, 0.50 mmol) was used. Purified by FCC (80:20, EtOAC:cHex, Rf: 0.35) to yield **15c** as a yellow amorphous solid (0.070 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.18 (m, 2H), 7.70 – 7.60 (m, 2H), 7.57 – 7.45 (m, 1H), 6.47 – 6.37 (m, 1H), 4.22 – 4.05 (m, 4H), 1.36 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 146.1 (d, *J* = 6.9 Hz), 140.9 (d, *J* = 23.3), 128.4, 124.4, 119.5 (d, *J* = 189.9 Hz), 62.6 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.2. NMR data were consistent with literature.[17]

Synthesis of Diethyl (*E*)-(3,3,3-trifluoroprop-1-en-1-yl)phosphonate (11)
Based on a procedure developed by Yuan and co-workers. [18]

Synthesis of Diethyl methylphosphonate

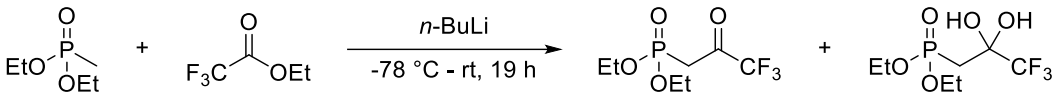


Triethylphosphite (10.4 mL, 60 mmol) was added to a flame-dried two-neck RBF with a reflux condenser attached under an atmosphere of N_2. Methyl iodide (3.7 mL, 60 mmol) was added and the mixture was heated to 120 °C for 16 h. The crude product was purified by distillation

under reduced pressure (B.P. range: 38 °C – 39 °C at 0.2 mBar) to yield diethyl methylphosphonate as a colourless oil (6.91 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 – 3.97 (m, 4H), 1.44 (d, J = 17.5 Hz, 3H), 1.30 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.5 (d, J = 6.1 Hz), 16.5 (d, J = 6.2 Hz), 11.3 (d, J = 144.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.4. NMR data were consistent with literature.[19]

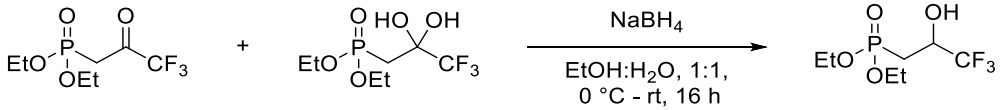
Synthesis of Diethyl (3,3,3-trifluoro-2-oxopropyl)phosphonate (A) and Diethyl (3,3,3-trifluoro-2,2-dihydroxypropyl)phosphonate (B)



To Et_2O (25 mL) in a flame-dried two-neck RBF was added *n*-BuLi (2.1 M solution in hexanes,11.4 mL, 24 mmol). The solution was cooled to -80 °C using a cooling bath and a solution of diethyl methylphosphonate (2.9 mL, 20 mmol) in Et_2O (20 mL) was added dropwise. The resulting solution was stirred at -80 °C for 1 h before a solution of ethyl trifluoroacetate (2.9 mL, 24 mmol) in Et_2O (20 mL) was added dropwise. After the addition was complete, the cooling bath was removed and the solution was stirred for a further 18 h at room temperature. $HCl_{(aq.)}$ (1 M, 50 mL) was added and the biphasic mixture was stirred for 10 min. Ethyl acetate (50 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield a 29:71 mixture of **A** and **B** as a colourless oil (3.97 g, 76%). The product was used in subsequent reactions without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 – 4.04 (m, 4H), 3.36 (d, J = 22.6 Hz, 0.59 H), 2.31 (d, J = 19.3 Hz, 1.41H), 1.35 (m, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.1, 15.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.8, -87.4. NMR data were consistent with literature.[20]

Synthesis of Diethyl (3,3,3-trifluoro-2-hydroxypropyl)phosphonate

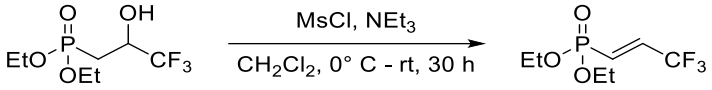


A 29:71 mixture of **A**:**B** (3.97 g, 4.47 mmol **A**, 10.75 mmol **B**) was dissolved in EtOH (25 mL). Water (25 mL) was added and the solution was cooled in an ice/water bath. $NaBH_4$ (0.69 g, 18 mmol) was added in small portions. Once addition was completed, the cooling bath was removed and the mixture was stirred at room temperature for a further 16 h. $HCl_{(aq.)}$ (1 M, 40 mL) was added in small portions. Brine (20 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield diethyl (3,3,3-trifluoro-2-

hydroxypropyl)phosphonate as a colourless oil (3.18 g, 83%). The product was used in subsequent reactions without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 – 4.29 (m, 1H), 4.24 – 4.05 (m, 4H), 2.18 – 2.07 (m, 2H), 1.35 (td, J = 7.0, 2.9 Hz, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.7 (d, J = 6.2 Hz). NMR data were consistent with literature.[21]

Synthesis of Diethyl (*E*)-(3,3,3-trifluoroprop-1-en-1-yl)phosphonate (11)



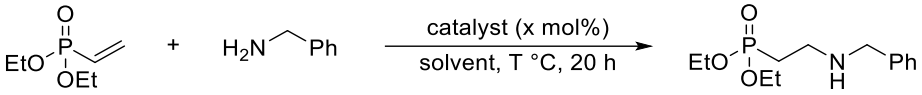
11

Diethyl (3,3,3-trifluoro-2-hydroxypropyl)phosphonate (3.18 g, 12.7 g) was added to a flame-dried Schlenk flask under an atmosphere of N_2. Triethylamine (5.5 mL, 38 mmol) and CH_2Cl_2 (30 mL) were added and the solution was chilled in an ice/water bath. Methanesulfonyl chloride (1.30 mL, 16.9 mmol) was added dropwise. After the addition was complete the ice/water bath was removed and the solution was stirred for 30 h at room temperature. CH_2Cl_2 (50 mL) and water (50 mL) were added. The layers were separated and the organic layer was washed with $HCl_{(aq)}$ (1 M, 50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by FCC (Et_2O:pentane 4:1, R_f: 0.3) to yield **11** as an orange oil (2.73 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 – 6.53 (m, 1H), 6.53 – 6.39 (m, 1H), 4.22 – 4.08 (m, 4H), 1.35 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9 (qd, J = 35.8, 6.8 Hz), 127.1 (dq, J = 186.5, 5.6 Hz), 121.5 (qd, J = 271.4, 30.0 Hz), 62.8 (d, J = 5.9 Hz), 16.3 (d, J = 6.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.8. NMR data were consistent with literature.[22]

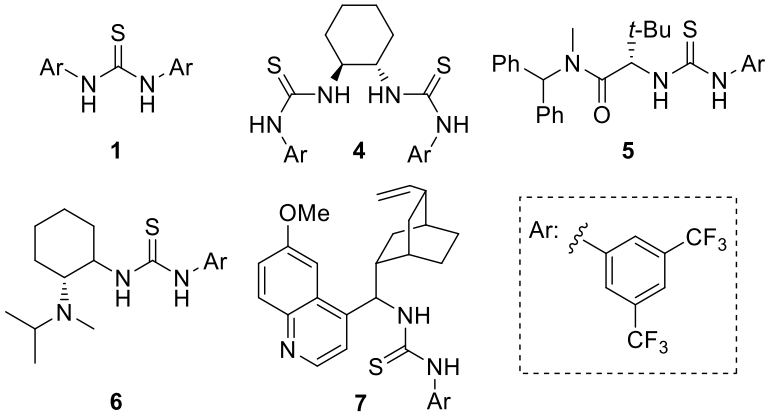
2. Thiourea-Catalysed Conjugate Addition of Amines to α,β-Unsaturated Phosph(in/on)ates

Optimisation of Conditions for Thiourea-Catalysed Conjugate Addition of Benzylamine to Diethyl Vinylphosphonate



Catalyst (x mol%) was added to an oven-dried crimp-top vial under an atmosphere of N_2. Diethyl vinylphosphonate (0.016 g, 0.10 mmol) was added, followed by solvent (0.20 mL) and benzylamine (0.011 g, 0.10 mmol). The reaction was stirred at temperature T °C for 20 h before the solvent was removed under reduced pressure. Conversion of **2** to **3a** was determined by ^{31}P NMR analysis of the crude reaction mixture in $CDCl_3$ with a 5 s relaxation delay (table S1).

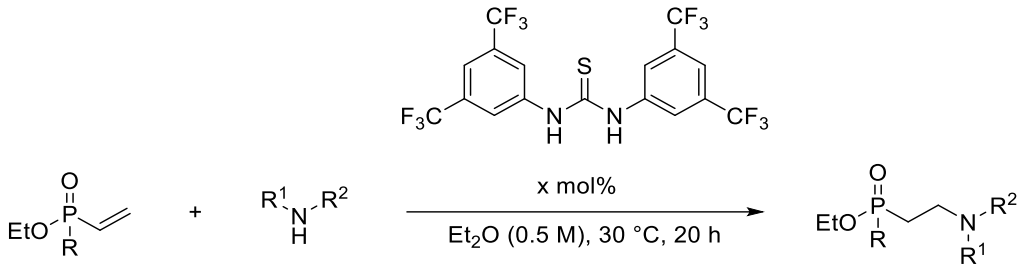
Table S1. Optimisation of reaction conditions for addition of benzylamine to diethyl vinylphosphonate.



Entry	Catalyst	Catalyst Loading (mol%)	Temperature (°C)	Solvent	Yield (%)[a]
1	-	-	rt	toluene	<1
2	1	10	rt	toluene	33
3	4	10	rt	toluene	20
4	5	10	rt	toluene	10
5	6	10	rt	toluene	12
6	7	10	rt	toluene	24
7	1	5	rt	toluene	29
8	1	20	rt	toluene	46
9	1	10	rt	THF	45
10	1	10	rt	CH_2Cl_2	30
11	1	10	rt	Et_2O	48
12	1	10	rt	MeCN	2
13	1	20	30	Et_2O	78

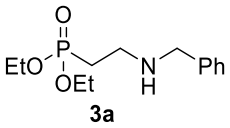
[a] Based on conversion of starting material to product determined by ^{31}P NMR analysis of the crude reaction mixture in $CDCl_3$ with a 5 s relaxation delay

General Procedure D: Thiourea-Catalysed Conjugate Additions of amines to α,β-Unsaturated Phosph(in/on)ates



Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) was added to an oven-dried crimp-top vial under an atmosphere of N_2. Phosph(in/on)ate (0.1 mmol) and anhydrous Et_2O (0.2 mL) were added followed by amine (0.1 mmol). The solution was stirred at 30 °C for 20 h before the solvent was removed under reduced pressure. The crude products were purified by FCC to yield β-aminophosph(in/on)ates **(3a-g** and **9a-c)**.

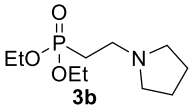
Diethyl (2-(benzylamino)ethyl)phosphonate (3a)



3a

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) benzylamine (0.011 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Purified by FCC on neutral alumina (95:5, CH_2Cl_2:MeOH, R_f: 0.4) to yield **3a** as a yellow oil (0.021 g ,78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 7.29 – 7.21 (m, 1H), 4.17 – 4.00 (m, 4H), 3.80 (s, 2H), 2.93 (dt, J = 15.7, 7.2 Hz, 2H), 2.00 (dt, J = 18.2, 7.2 Hz, 2H), 1.30 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 128.5, 128.2, 127.1, 61.7 (d, J = 6.5 Hz), 53.6, 42.8 (d, J = 3.8 Hz), 26.5 (d, J = 139.5 Hz), 16.5 (d, J = 6.1 Hz).^{31}P NMR (162 MHz, $CDCl_3$) δ 30.5. NMR data were consistent with literature.[23]

Diethyl (2-(pyrrolidin-1-yl)ethyl)phosphonate (3b)

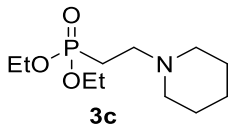


3b

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) pyrrolidine (0.007 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Isolated by liquid/liquid extractions. The crude material was dissolved in CH_2Cl_2 and $HCl_{(aq)}$ (1 M, 5 mL) was added. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The aqueous layer was basified to pH 14 with $NaOH_{(aq)}$ (1 M, 10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield **3b** as a brown oil (0.023 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 – 3.98 (m, 4H, OCH_2), 2.76 – 2.66 (m, 2H, PCH$_2$CH_2), 2.57 – 2.43 (m, 4H, 2xNCH_2), 2.05 – 1.92 (m, 2H, PCH_2), 1.83 – 1.67 (m, 4H, NCH$_2$CH_2), 1.30 (t, J = 7.0 Hz, 6H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.6 (d, J = 6.5 Hz, OCH$_2$), 53.9 (2xNCH$_2$), 49.4 (d, J = 1.2 Hz, PCH$_2$$CH_2$), 26.0 (d, J = 138.9 Hz,

P*C*H$_2$CH$_2$), 23.6 (2xNCH$_2$*C*H$_2$), 16.6 (d, *J* = 6.0 Hz, OCH$_2$*C*H$_3$). ^{31}P NMR (162 MHz, CDCl$_3$) δ 30.1. ESI-HRMS *m/z* calc'd for $C_{10}H_{22}NO_3P$ [M + H$^+$]: 236.1416; found: 236.1410.

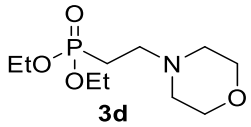
Diethyl (2-(piperidin-1-yl)ethyl)phosphonate (3c)



3c

Synthesised following general procedure D using diethyl vinylphosphonate (0.016 g, 0.10 mmol), piperidine (0.009 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol). Purified by FCC (CH$_2$Cl$_2$:MeOH, 95:5 – EtOAc:MeOH, 95:5, R_f: 0.1 in CH$_2$Cl$_2$:MeOH, 95:5) to yield **3c** as a yellow oil (0.023 g, 92%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.18 – 4.00 (m, 4H, 2xOC*H*$_2$), 2.70 – 2.60 (m, 2H, PCH$_2$C*H*$_2$), 2.42 (br s, 4H, 2xC*H*$_2$N), 2.07 – 1.93 (m, 2H, PC*H*$_2$), 1.65 – 1.55 (m, 4H, 2xC*H*$_2$CH$_2$N), 1.49 – 1.41 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 1.31 (t, *J* = 7.1 Hz, 6H, 2xC*H*$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ 61.7 (d, *J* = 6.4 Hz, O*C*H$_2$), 54.1 (2xN*C*H$_2$), 52.3 (*C*H$_2$CH$_2$P), 25.9 (2x*C*H$_2$CH$_2$N), 24.3 (*C*H$_2$CH$_2$CH$_2$N), 23.6 (d, *J* = 136.0 Hz, P*C*H$_2$), 16.6 (d, *J* = 6.1 Hz, *C*H$_3$). ^{31}P NMR (162 MHz, CDCl$_3$) δ 30.5. ESI-HRMS *m/z* calc'd for $C_{11}H_{24}NO_3P$ [M + Na$^+$]: 272.1386; found: 272.1385.

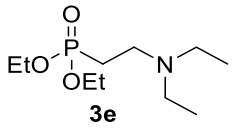
Diethyl (2-morpholinoethyl)phosphonate (3d)



3d

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) morpholine (0.009 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Isolated by liquid/liquid extractions. The crude material was dissolved in CH$_2$Cl$_2$ and HCl$_{(aq)}$ (1 M, 5 mL) was added. The layers were separated and the aqueous layer was washed with CH$_2$Cl$_2$ (2 x 5 mL). The aqueous layer was basified to pH 14 with NaOH$_{(aq)}$ (1 M, 10 mL) and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic fractions were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to yield **3d** as a colourless oil (0.23 g, 99%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.16 – 3.98 (m, 4H), 3.70 – 3.63 (m, 4H), 2.67 – 2.56 (m, 2H), 2.45 – 2.39 (m, 4H), 2.00 – 1.86 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 67.0, 61.7 (d, *J* = 6.5 Hz), 53.2, 52.0 (d, *J* = 1.0 Hz), 23.7 (d, *J* = 139.6 Hz), 16.5 (d, *J* = 5.7 Hz). ^{31}P NMR (162 MHz, CDCl$_3$) δ 30.2. NMR data were consistent with literature.[24]

Diethyl (2-(diethylamino)ethyl)phosphonate (3e)

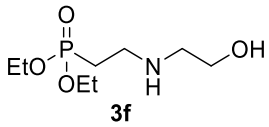


3e

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) morpholine (0.009 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Purified by FCC (95:5 – 90:10, CH$_2$Cl$_2$:MeOH, R_f: 0.05 in 95:5 CH$_2$Cl$_2$:MeOH) to yield **3e** as a waxy solid (0.17 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.19 – 4.01 (m, 4H), 2.90 –

2.80 (m, 2H), 2.58 (q, J = 7.2 Hz, 4H), 2.02 – 1.89 (m, 2H), 1.32 (t, J = 7.1 Hz, 6H), 1.07 (t, J = 7.2 Hz, 6H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 61.8 (d, J = 6.1 Hz), 46.8, 46.5, 22.6 (d, J = 137.3 Hz), 16.6 (d, J = 6.1 Hz), 11.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.3. NMR data were consistent with literature.[24]

Diethyl (2-((2-hydroxyethyl)amino)ethyl)phosphonate (3f)

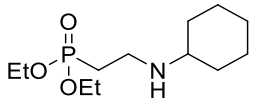


3f

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) ethanolamine (0.006 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Purified by FCC (95:5 – 90:10, CH_2Cl_2:MeOH, R_f: 0.15 in 95:5 CH_2Cl_2:MeOH) to yield **3f** as a colourless oil (0.018 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 – 4.04 (m, 4H), 3.61 – 3.55 (m, 2H), 2.86-2.78 (m, 2H), 2.59 – 2.54 (m, 2H), 1.96 (t, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.8 (d, J = 6.9 Hz), 59.1, 55.3, 46.5 (d, J = 3.1 Hz), 23.6 (d, J = 139.2 Hz), 16.60 (d, J = 6.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.4. NMR data were consistent with literature.[25]

Diethyl (2-(cyclohexylamino)ethyl)phosphonate (3g)

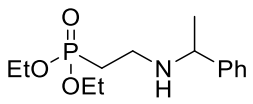


3g

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) cyclohexylamine (0.010 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Purified by FCC (100:0 – 90:10, EtOAc:MeOH, R_f: 0.05 in 90:10 EtOAc:MeOH) to yield **3g** as a colourless oil (0.017 g, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 – 4.02 (m, 4H, 2xOCH_2), 3.24 (br s, NH), 2.94 (dt, J = 14.6, 7.4 Hz, 2H, NCH_2), 2.53 – 2.43 (m, 1H, NCH), 1.99 (dt, J = 18.3, 7.4 Hz, 2H, PCH_2), 1.92 – 1.84 (m, 2H, 2xCHCHH), 1.77 – 1.67 (m, 2H, 2xCHCH$_2$CHH), 1.63 – 1.55 (m, 1H, CHCH$_2$CH$_2$CHH), 1.31 (t, J = 7.1 Hz, 6H, 2xOCH$_2$CH_3), 1.27 – 1.04 (m, 5H, cyHex). ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.8 (d, J = 6.5 Hz, OCH$_2$), 56.6 (NCH), 40.3 (d, J = 3.1 Hz, NCH$_2$), 33.0 (2xCHCH$_2$), 26.4 (d, J = 139.2 Hz, PCH$_2$), 26.1 (CHCH$_2$CH$_2$$CH_2$) 25.0 (2xCHCH$_2$$CH_2$), 16.6 (d, J = 6.1 Hz, OCH$_2$$CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.9. ESI-HRMS *m/z* calc'd for $C_{12}H_{26}NO_3P$ [M + H$^+$]:264.1723; found: 264.1725.

Diethyl (2-((1-phenylethyl)amino)ethyl)phosphonate (3h)

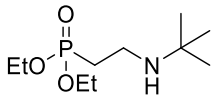


3h

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) α-methylbenzylamine (0.012 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Attempted purification by FCC was unsuccessful, ^{31}P NMR conversion 41%. The desired product **3h** was identified from the crude reaction mixture based on the following

signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (q, *J* = 6.6 Hz, 1H, NC*H*), 2.83 – 2.66 (m, 2H), 1.92 (dt, *J* = 18.0, 7.2 Hz, 2H, PCH_2), 1.27 (td, *J* = 7.1, 2.4 Hz, 6H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.3. NMR data were consistent with literature.[26]

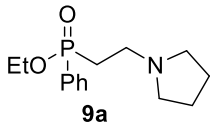
Diethyl (2-(tert-butylamino)ethyl)phosphonate



3i

Synthesised following general procedure D: diethyl vinylphosphonate (0.016 g, 0.10 mmol) tert-butylamine (0.008 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. Attempted purification by FCC was unsuccessful, ^{31}P NMR conversion 47%. The desired product **3i** was identified from the crude reaction mixture based on the following signals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.04 (m, 4H, OCH_2), 2.81 – 2.71 (m, 2H,NCH_2), 2.09 – 1.97 (m, 2H, PCH_2), 1.33 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3), 1.26 (s, 9H, 3xCH_3).^{31}P NMR (162 MHz, $CDCl_3$) δ 28.2. NMR data were consistent with literature.[26]

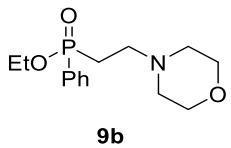
Ethyl phenyl(2-(pyrrolidin-1-yl)ethyl)phosphinate (9a)



9a

Synthesised following general procedure D: pyrrolidine (0.007 g, 0.100 mmol), ethyl phenylvinylphosphinate (0.020 g, 0.100 mmol) and Schreiner's thiourea catalyst (0.005 g, 0.01 mmol) were used. Purified by FCC on neutral alumina (CH_2Cl_2:MeOH 95:5, R_f: 0.25) to yield **9a** as a yellow oil (0.023 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 2H, Ar*H*), 7.59 – 7.52 (m, 1H, Ar*H*), 7.52 – 7.44 (m, 2H, Ar*H*), 4.18 – 3.75 (m, 2H, OCH_2), 2.79 – 2.60 (m, 2H, PCH_2CH_2), 2.50 – 2.36 (m, 4H, 2xNCH_2CH_2), 2.28 – 2.07 (m, 2H, CH_2P), 1.75 – 1.66 (m, 4H, 2xNCH_2CH_2), 1.29 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5 (d, *J* = 2.7 Hz, Ar), 131.7 (d, *J* = 9.9 Hz, *p*-Ar), 130.8 (d, *J* = 124.3 Hz, *ipso*-Ar), 128.8 (d, *J* = 12.5 Hz, Ar), 60.8 (d, *J* = 6.4 Hz, OCH_2), 53.8 (2xNCH_2CH_2), 48.7 (CH_2CH_2P), 29.9 (d, *J* = 99.4 Hz, PCH_2), 23.5 (2xNCH_2CH_2), 16.6 (d, *J* = 6.5 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.4. ESI-HRMS *m/z* calc'd for $C_{14}H_{22}NO_2P$ [M+H$^+$]: 268.1460; found: 268.1461.

Ethyl (2-morpholinoethyl)(phenyl)phosphinate (9b)

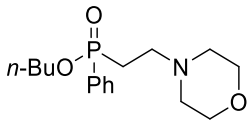


9b

Synthesised following general procedure D: morpholine (0.009 g, 0.100 mmol), ethyl phenylvinylphosphinate (0.020 g, 0.100 mmol) and Schreiner's thiourea catalyst (0.005 g, 0.01 mmol) were used. Purified by FCC on neutral alumina (CH_2Cl_2:MeOH 95:5, R_f: 0.4) to yield **9b** as a colourless oil (0.024 g, 86 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 2H, Ar*H*), 7.58 – 7.53 (m, 1H, Ar*H*), 7.51 – 7.46 (m, 2H, Ar*H*), 4.15 – 3.77 (m, 2H, OCH_2CH_3), 3.66 – 3.53 (m, 4H, 2xOCH_2CH_2N), 2.69 – 2.55 (m, 2H, CH_2CH_2P), 2.41 – 2.32 (m, 4H,

2xNCH_2CH$_2$O), 2.23 – 2.04 (m, 2H,CH_2P), 1.29 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.4 (d, J = 2.8 Hz, *p*-Ar), 131.7 (d, J = 10.0 Hz, Ar), 131.2 (d, J = 124.9 Hz, *ipso*-Ar), 128.7 (d, J = 12.5 Hz, Ar), 66.9 (O*C*H$_2$CH$_2$N), 60.7 (d, J = 6.2 Hz, O*C*H$_2$CH$_3$), 53.2 (N*C*H$_2$CH$_2$O), 51.4 (PCH$_2$*C*H$_2$), 27.6 (d, J = 99.8 Hz, P*C*H$_2$), 16.6 (d, J = 6.6 Hz, *C*H$_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.0. ESI-HRMS *m/z* calc'd for $C_{14}H_{22}NO_3P$ [M+H$^+$]: 284.1410; found: 284.1408.

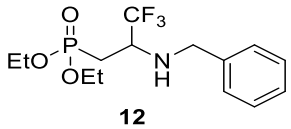
Butyl (2-morpholinoethyl)(phenyl)phosphinate (9c)



9c

Synthesised following general procedure D: morpholine (0.009 g, 0.100 mmol) n-butyl phenylvinylphosphinate (0.022 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.005 g, 0.01 mmol) were used. Reaction time: 40 h, room temperature. Purified by FCC on neutral alumina (CH_2Cl_2:MeOH 95:5, R_f: 0.4) to yield **9c** as a colourless oil (0.026 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H, Ar*H*), 7.57 – 7.51 (m, 1H, Ar*H*), 7.50 – 7.43 (m, 2H, Ar*H*), 4.08 – 3.69 (m, 2H, POCH_2), 3.64 – 3.51 (m, 4H, OCH_2CH$_2$N), 2.67 – 2.53 (m, 2H, CH_2CH$_2$P), 2.35 (t, J = 4.7 Hz, 4H, NCH_2CH$_2$O), 2.21 – 2.02 (m, 2H, PCH_2), 1.67 – 1.56 (m, 2H, OCH$_2$CH_2), 1.42 – 1.30 (m, 2H, CH_2CH$_3$), 0.88 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.4 (d, J = 2.7 Hz, *para*-Ar), 131.7 (d, J = 9.9 Hz, Ar), 131.1 (d, J = 124.7 Hz, Ar-*ipso*), 128.7 (d, J = 12.5 Hz, Ar), 66.9 (O*C*H$_2$CH$_2$N), 64.4 (d, J = 6.5 Hz, PO*C*H$_2$), 53.2 (N*C*H$_2$CH$_2$O), 51.4 (*C*H$_2$CH$_2$P), 32.7 (d, J = 6.5 Hz,POCH$_2$*C*H$_2$), 28.0 (d, J = 99.7 Hz, P*C*H$_2$), 18.9 (*C*H$_2$CH$_3$), 13.7 (*C*H$_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.9. ESI-HRMS *m/z* calc'd for $C_{16}H_{26}NO_3P$ [M+H$^+$]: 312.1723; found: 312.1724.

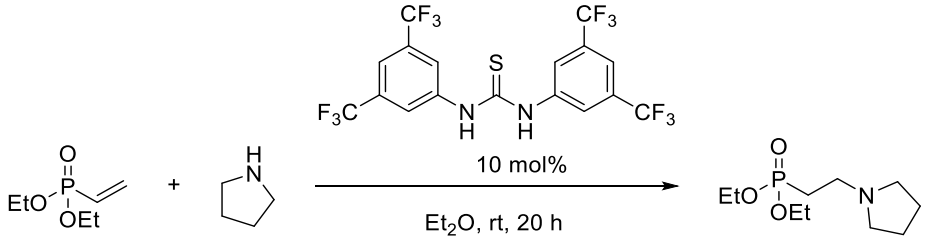
Diethyl (2-(benzylamino)-3,3,3-trifluoropropyl)phosphonate (12)



12

Synthesised following general procedure D: benzylamine (0.065 mL, 0.300 mmol), diethyl (*E*)-(3,3,3-trifluoroprop-1-en-1-yl)phosphonate (0.023 g, 0.100 mmol) and Schreiner's thiourea catalyst (0.005 g, 0.01 mmol) were used. Reaction time: 20 h, room temperature. Purified by FCC (cHex:EtOAc 1:1, R_f: 0.4) to yield **12** as a colourless oil (0.045 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 5H, 5xArH), 4.15 – 4.01 (m, 4H, OCH_2), 4.00 (d, J = 12.2 Hz, 1H, NC*H*H), 3.86 (d, J = 12.9 Hz, 1H, NCH*H*), 3.55 – 3.43 (m, 1H, NC*H*), 2.17 – 1.87 (m, 3H, PCH_2 and N*H*), 1.26 (td, J = 7.1, 1.8 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3 (*ipso*-Ar), 128.6 (Ar) , 128.5 (Ar), 127.4 (Ar), 127.0 (qd, J = 284.4, 22.9 Hz, CF_3), 62.3 (d, J = 6.5 Hz, OCH_2), 62.2 (d, J = 6.5 Hz, OCH_2), 55.1 (qd, J = 29.4, 3.8 Hz, N*C*H), 52.80 (br s, NCH_2), 26.1 (dq, J = 146.9, 2.4 Hz, PCH_2), 16.5 (d, J = 6.3 Hz, CH_2CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.8 (br s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.9 (d, J = 6.6 Hz). ESI-HRMS *m/z* calc'd for $C_{14}H_{21}F_3NO_3P$ [M+H$^+$]: 340.1289; found: 340.1287.

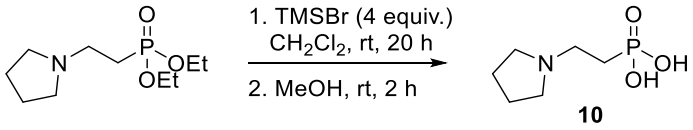
Gram Scale Synthesis of 3b



3b

Schreiner's thiourea catalyst (0.310 g) was added to a flame-dried 25 mL Schlenk tube under an atmosphere of N_2. Diethyl vinylphosphonate (0.94 mL, 6.1 mmol) was added followed by anhydrous Et_2O (10 mL). Pyrrolidine (0.51 mL, 6.1 mmol) was added and the solution was stirred at room temperature for 20 h. Et_2O (20 mL) and $HCl_{(aq)}$ (1 M, 20 mL) were added and the layers were separated. The aqueous layer was washed with Et_2O (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield Schreiner's thiourea catalyst as a white solid (0.300 g, 97% recovery). The aqueous layer was basified to pH 14 using $NaOH_{(aq)}$ (1 M, 40 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **3b** as a brown oil (1.41 g, 99%). NMR data were consistent with those previously obtained for **3b**.

Synthesis of (2-(pyrrolidin-1-yl)ethyl)phosphonic acid 10.



Diethyl (2-(pyrrolidin-1-yl)ethyl)phosphonate (0.100 g, 0.43 mmol) was added to a flame-dried Schlenk flask under an atmosphere of N_2 and was dissolved in anhydrous CH_2Cl_2 (2 mL). TMSBr (0.23 mL, 1.7 mmol) was added dropwise and the solution was stirred at rt for 20 h. After 20 h ^{31}P NMR analysis of the reaction mixture showed the starting material had been consumed. The solvent was removed under reduced pressure and the resulting solid was dissolved in MeOH (2 mL). The solution was stirred at rt for 2 h before the solvent was removed under reduced pressure to yield an orange wax. The wax was dissolved in water (2 mL) and washed with Et_2O (3 x 5 mL). The water was removed by lyophilization to yield **10** as a purple solid (0.082 g, quant) which rapidly became a purple oil at atmospheric pressure.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.41 – 3.10 (m, 6H, 2 x NCH_2, PCH$_2$CH_2), 2.10 – 1.88 (m, 6H, PCH_2, NCH$_2$CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 52.8 (2xNCH$_2$), 49.3 (PCH$_2$$CH_2$), 24.9 (d, J = 134.3 Hz, PCH$_2$), 22.6 (2xNCH$_2$$CH_2$). ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.3. ESI-HRMS *m/z* calc'd for $C_6H_{14}NO_3P$ [M + H$^+$]: 18.0790; found: 180.0787.

Incompatible Substrates

Following general procedure D: α,β-unsaturated phosph(in/on)ate **-14d, 14e, 15a-c** (0.1 mmol) pyrrolidine (0.007 g, 0.10 mmol) and Schreiner's thiourea catalyst (0.010 g, 0.02 mmol) were used. No conversion of starting material was observed by ^{31}P NMR analysis after 24 h using any of phosph(in/on)ates **14d, 14e, 15a-c**. No conversion was observed when the procedure was repeated with toluene as solvent at 110 °C.

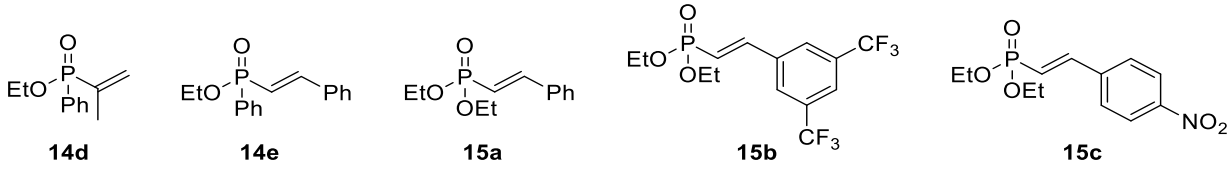
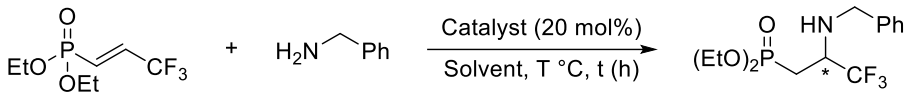


Figure S1. Electrophiles that failed to react with pyrrolidine under standard conditions or at 110 °C in toluene

3. Attempted Thiourea-Catalysed Asymmetric Additions to Diethyl (3,3,3-trifluoro)propylphosphonate

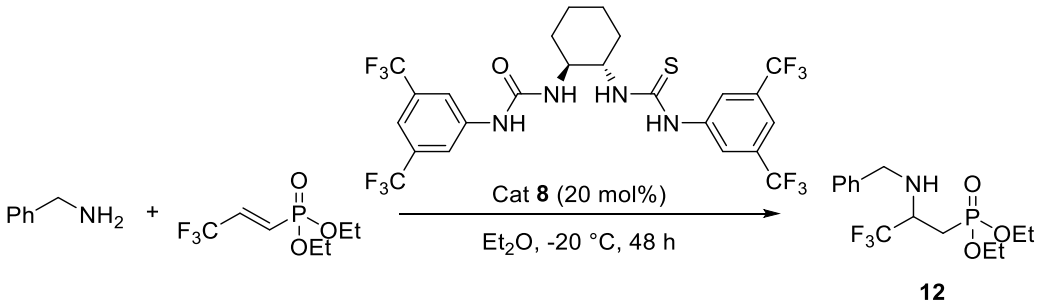
Table S2: Optimisation of asymmetric addition of benzylamine to **11.**[a]



11 **12**

Entry	Amine equiv.	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	1	**1**	Et_2O	30	20	34	-
2	5	**4**	Et_2O	5.5	48	>99	0
3	5	**4**	Et_2O	-20	48	59	10
4	5	**4**	toluene	-20	48	33	10
5	5	**4**	CH_2Cl_2	-20	48	0	-
6	1	**4**	Et_2O	5.5	64	68	10
7	1	**7**	Et_2O	5.5	64	55	0
8	1	**9**	Et_2O	5.5	64	72	19
10	1	**4**	Et_2O	-20	64	16	20
11	1	**4**	Et_2O	-40	64	6	20
12	1	**9**	Et_2O	-20	64	19	22

[a] Reaction conditions: diethyl (3,3,3-trifluoro)propylphosphonate (0.1 mmol) catalyst (0.02 mmol) benzylamine (0.1 or 0.5 mmol) Et_2O (0.2 mL). [b] Measured by ^{31}P NMR analysis based on conversion of starting material. [c] Measured by chiral phase HPLC.

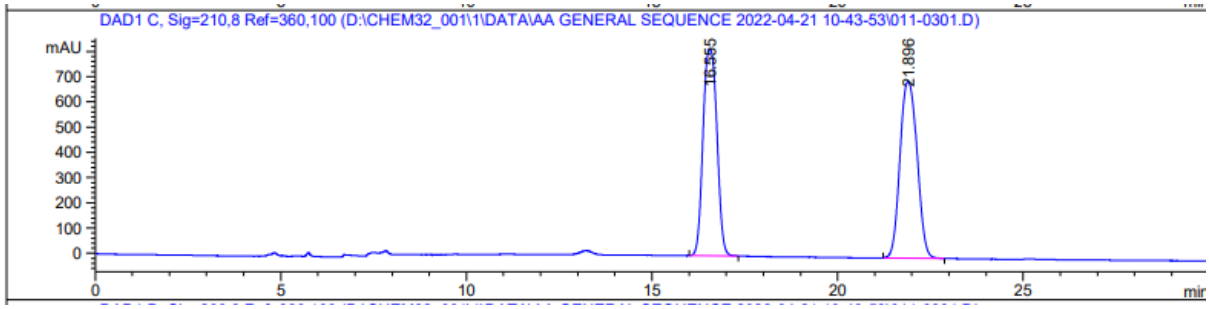


12

Diethyl (3,3,3-fluoro)propylphosphonate (0.012 g, 0.05 mmol) and catalyst **8** (0.006 g, 0.01 mmol) were added to an oven-dried crimp-top vial under an atmosphere of N_2 and dissolved in anhydrous Et_2O (0.1 mL). The solution was cooled to -20 °C and benzylamine (0.006 mL, 0.05 mmol) was added. The solution was stirred at -20 °C for 4 days before $CDCl_3$ (0.5 mL) was added. The yield and ee of **12** were measured by ^{31}P NMR analysis and chiral phase HPLC, respectively.

ee: 22%, determined by chiral phase HPLC. HPLC conditions: ChiralPak® IC column (length 25 cm, diameter 0.46 cm), heptane:EtOH 98:2, 0.7 mL/min, t_R = 16.56, 21.90.

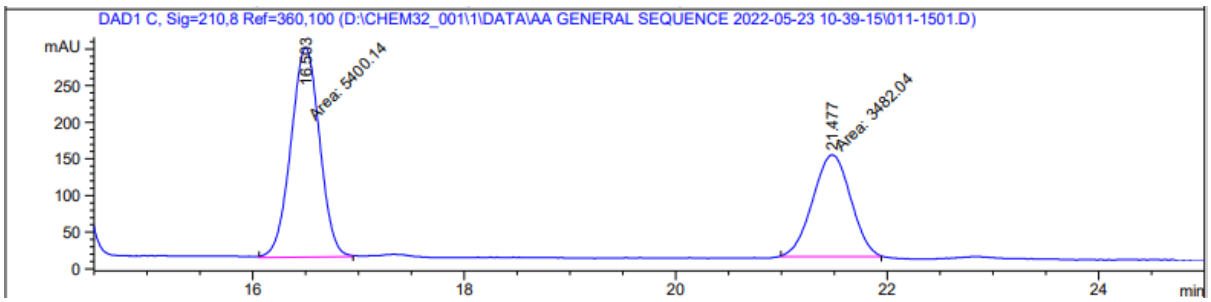
Racemic **12**



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.555	BB	0.4170	2.11877e4	821.13177	48.6124
2	21.896	BB	0.5210	2.23973e4	700.58978	51.3876
Totals :				4.35851e4	1521.72156	

Scalemic **12**

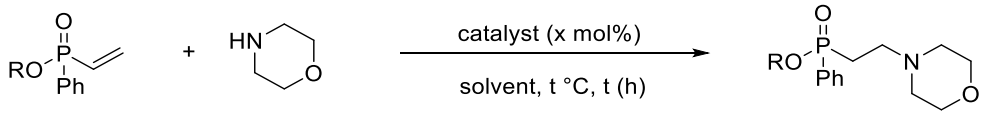


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.503	MM	0.3146	5400.14014	286.04782	60.7975
2	21.477	MM	0.4179	3482.03809	138.87677	39.2025
Totals :				8882.17822	424.92459	

4. Attempted Kinetic Resolution of Vinyl Phosphinates

Optimisation of Reaction Conditions for Kinetic Resolution



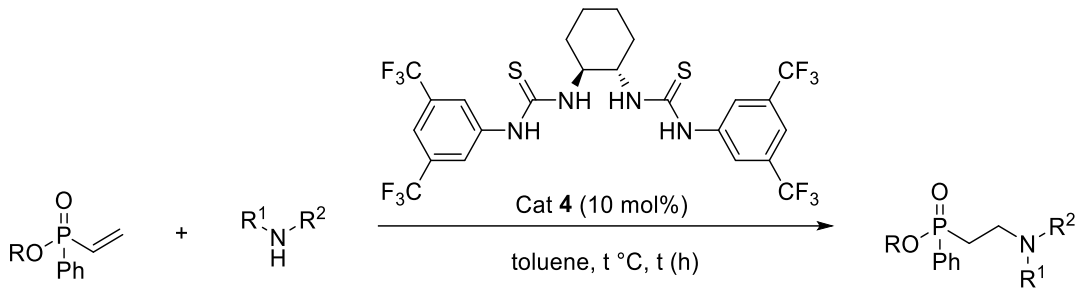
Catalyst (x mol%) was added to an oven-dried crimp-top vial under an atmosphere of N_2. Phosphinate (0.1 mmol) was added followed by solvent (0.1 mL) and morpholine (0.009 mL, 0.1 mmol). The solution was stirred at temperature (T °C) for time (h) before sat. NH_4Cl:brine 1:1 (2 mL) was added. EtOAc (2 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 2 mL) and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield crude phosphinates. Ee was determined using chiral phase HPLC after purification *via* FCC. De was measured *via* ^{31}P NMR analysis of the crude product.

Table S3: Optimisation of thiourea-catalysed kinetic resolution of vinyl phosphinates

R	Amine	Amine equiv.	Catalyst	Catalyst Loading (mol%)	Solvent	Temp (°C)	time (h)	Yield[a] (%)	Ee[b]/de[c] (%)
Et	morpholine	1.0	**4**	10	toluene	rt	20	52	4
Et	morpholine	1.0	**5**	10	toluene	rt	20	45	2
Et	morpholine	1.0	**6**	10	toluene	rt	20	43	0
Et	morpholine	1.0	**7**	10	toluene	rt	20	48	0
2-MeBu	morpholine	1.0	**4**	10	toluene	rt	32	32	12
2-MeBu	morpholine	0.50	**4**	10	toluene	rt	32	34	10
2-MeBu	morpholine	0.75	**4**	10	toluene	rt	32	34	10
2-MeBu	morpholine	1.0	**4**	10	MeCN	rt	32	24	6
2-MeBu	morpholine	1.0	**4**	10	Et_2O	rt	32	45	8
2-MeBu	morpholine	1.0	**4**	10	$CHCl_3$	rt	32	19	8
2-MeBu	morpholine	1.0	**4**	10	CH_2Cl_2	rt	32	34	10
2-MeBu	pyrrolidine	1.0	**4**	10	toluene	0	2	41	14
2-MeBu	pyrrolidine	1.0	**4**	20	toluene	0	2	53	12

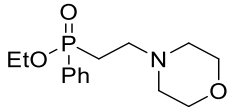
[a] Measured by ^{31}P NMR analysis of the crude material based on conversion of starting material. [b] Measured by chiral phase HPLC analysis of the purified reaction product. [c] Measured by ^{31}P NMR analysis of the crude material.

General Procedure E: Kinetic Resolution of Vinyl Phosphinates



Catalyst **4** (0.007 g, 10 mol%) was added to an oven-dried crimp-top vial under an atmosphere of N_2. Phosphinate (0.1 mmol) and amine (0.1 mmol) were added followed by anhydrous toluene (0.1 mL). The solution was stirred at T °C, for t (h) before sat. NH_4Cl:brine 1:1 (2 mL) was added. EtOAc (2 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 2 mL) and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield crude phosphinates. Ee was measured using chiral phase HPLC after purification *via* FCC. De was measured *via* ^{31}P NMR analysis of the crude product.

Ethyl (2-morpholinoethyl)(phenyl)phosphinate (9b)

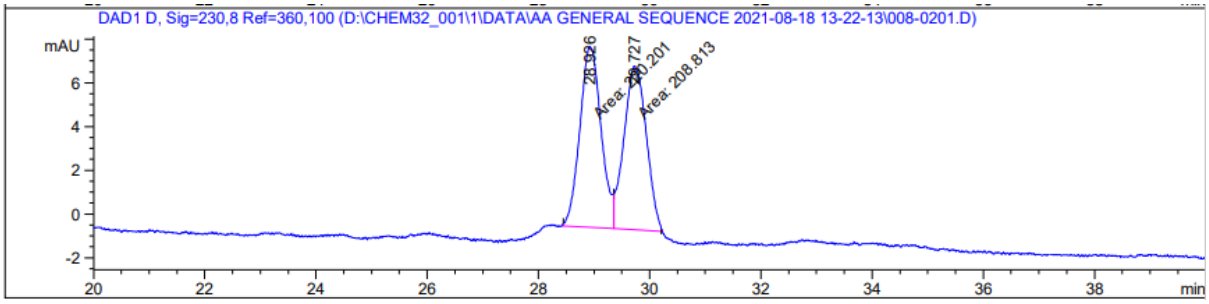


9b

Synthesised following general procedure E: morpholine (0.009 g, 0.100 mmol) and ethyl phenylvinylphosphinate (0.020 g, 0.100 mmol). Reaction time: 20 h, room temperature. Purified by FCC on neutral alumina (CH_2Cl_2:MeOH 95:5, R_f: 0.4) to yield **9b** as a colourless oil (0.012 g, 43%). NMR spectra were consistent with those previously obtained for **9b**.

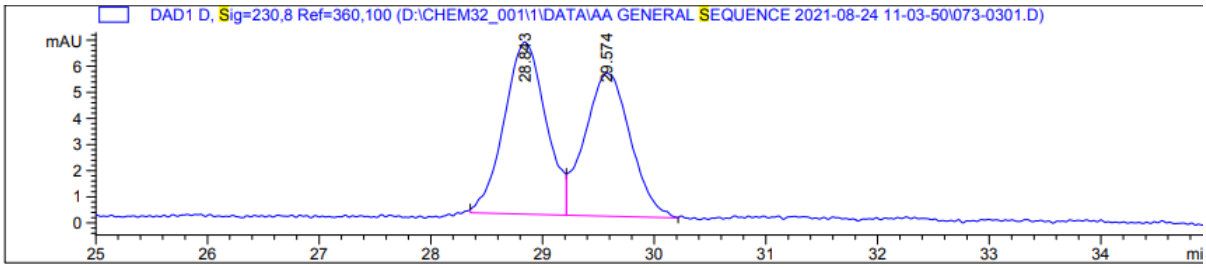
ee: 2%, determined by chiral phase HPLC. HPLC conditions: ChiralPak® O-JH column (length 25 cm, diameter 0.46 cm), heptane:EtOH 99:1 – 97:3 over 45 min, 1 mL/min, t_R = 28.8, 29.6.

Racemic **9b**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.926	MF	0.4439	220.20134	8.26692	51.3273
2	29.727	FM	0.4648	208.81281	7.48681	48.6727

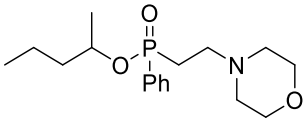
Scalemic **9b**



Signal 3: DAD1 D, Sig=230,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.843	BV	0.3484	171.10422	6.60049	52.3681
2	29.574	VB	0.3649	155.62918	5.48647	47.6319

Pentan-2-yl (2-morpholinoehtyl)(phenyl)phosphinate (9d)



9d

Synthesised following general procedure E: using morpholine (0.009 g, 0.100 mmol) and 2-methylbutyl phenylvinylphosphinate (0.024 g, 0.100 mmol). Reaction time 70 h, room temperature. Purified by FCC on neutral alumina (CH_2Cl_2:MeOH 95:5, R_f: 0.2) to yield **9d** as a colourless oil (0.006 g, 18%). De of crude product: 12%, measured by ^{31}P NMR. Isolated as a 53:47 mixture of diastereoisomers as determined by ^{31}P NMR analysis of isolated product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H), 7.53 (m, 1H), 7.50 – 7.43 (m, 2H), 4.51 – 4.30 (m, 1H), 3.66 – 3.51 (m, 4H), 2.75 – 2.50 (m, 2H), 2.37 (m, 4H), 2.22 – 1.98 (m, 2H), 1.77 – 1.04 (m, 7H), 0.93 (t, J = 7.3 Hz), 0.76 (t, J = 7.3 Hz) the signals at 0.93 and 0.76

integrate for 3H when combined. ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.4 (d, *J* = 125.2 Hz, *ipso*-C), 132.2 (app. t, *J* = 3.5 Hz, *p*-Ar), 131.8 (d, *J* = 125.7 Hz, *ipso*-C), 131.6 (d, *J* = 9.8 Hz, Ar), 128.5 (d, *J* = 13.0 Hz, 2xAr) 73.2 (d, *J* = 6.7 Hz, O*C*H), 72.9 (d, *J* = 6.7 Hz, O*C*H), 66.9 (O*C*H_2), 53.2 (d, *J* = 1.9 Hz, OCH$_2$*C*H$_2$), 51.5 (d, *J* = 3.6 Hz, NCH$_2$CH$_2$P), 40.4 (d, *J* = 4.3 Hz, OCH*C*H$_2$), 39.9 (d, *J* = 5.8 Hz, OCH*C*H$_2$), 27.9 (d, *J* = 99.7 Hz, P*C*H$_2$), 22.5 (d, *J* = 2.4 Hz, CH*C*H$_3$), 21.8 (d, *J* = 3.4 Hz, CH*C*H$_3$), 18.6 (*C*H$_2$CH$_3$), 18.3 (*C*H$_2$CH$_3$), 14.1 (CH$_2$*C*H$_3$), 13.9 (CH$_2$*C*H$_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.4, 41.1. ESI-HRMS *m/z* calc'd for $C_{17}H_{28}NO_3P$ [M+H$^+$]: 326.1880; found: 326.1881. De of crude product: 12%, measured by ^{31}P NMR.

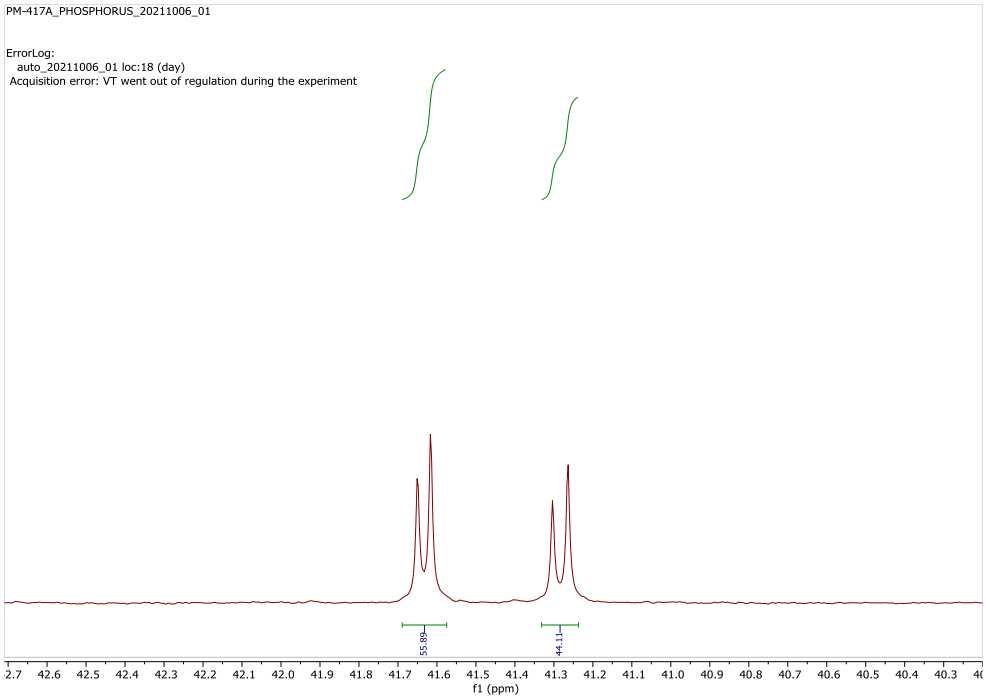
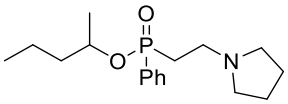


Figure S2. ^{31}P NMR spectrum of crude reaction mixture after 20 h, showing signals corresponding to **9d** in the presence of catalyst **2** (10 mol%).

Ethyl phenyl(2-pyrrolidin-l-yl)ethyl)phosphinate (9e)



9e

Synthesised following general procedure E: pyrrolidine (0.007 g, 0.100 mmol) and 2-pentanyl phenylvinylphosphinate (0.024 g, 0.100 mmol). Reaction time: 2 h, 0 °C. Purified by FCC on neutral alumina (CH_2Cl_2:MeOH 95:5, R_f: 0.15) to yield **9e** as a yellow oil (0.011 g, 37%). De of crude product: 14%, measured by ^{31}P NMR analysis. Isolated as a 56:43 mixture of diastereoisomers as determined by ^{31}P NMR analysis of the isolated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 2H, Ar*H*), 7.55 – 7.48 (m, 1H, Ar*H*), 7.48 – 7.40 (m, 2H, Ar*H*), 4.50 – 4.28 (m, 1H, POC*H*), 2.81 – 2.59 (m, 2H, C*H*$_2$CH$_2$P), 2.52 – 2.43 (m, 4H, 2xNC*H*$_2$CH$_2$), 2.29 – 2.04 (m, 2H, PC*H*$_2$), 1.79 – 1.71 (m, 4H, 2xNCH$_2$C*H*$_2$), 1.70 – 1.04 (m, 7H, OCHC*H*$_2$, CHC*H*$_3$ and C*H*$_2$CH$_3$), 0.91 (t, *J* = 7.3 Hz, CH$_2$C*H*$_3$), 0.74 (t, *J* = 7.3 Hz, CH$_2$C*H*$_3$) the signals at 0.91 and 0.74 combined integrate for 3H. ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0 (d, *J* = 125.2 Hz, *ipso*-C), 131.6 (d, *J* = 9.9 Hz, *p*-Ar), 131.4 (d, *J* = 125.2 Hz, *ipso*-C), 128.7 (d, *J* = 1.9 Hz, 2xAr), 128.5 (d, *J* = 1.9 Hz, 2xAr), 73.3 (d, *J* = 6.6 Hz, O*C*H) 73.1 (d, *J* = 6.7 Hz, O*C*H), 53.7

(2xN*C*H$_2$), 48.8 (d, *J* = 4.4 Hz, PCH$_2$*C*H$_2$), 40.3 (d, *J* = 4.3 Hz, OCH*C*H$_2$), 39.9 (d, *J* = 5.7 Hz, OCH*C*H$_2$), 29.91 (d, *J* = 99.7 Hz, P*C*H$_2$), 29.87 (d, *J* = 99.7 Hz, P*C*H$_2$), 23.5 (NCH$_2$*C*H$_2$) 22.5 (d, *J* = 2.3 Hz, CH*C*H$_3$), 21.8 (d, *J* = 3.4 Hz, CH*C*H$_3$), 18.5 (*C*H$_2$CH$_3$), 18.3 (*C*H$_2$CH$_3$), 14.1 (CH$_2$*C*H$_3$), 13.9 (CH$_2$*C*H$_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.8, 40.5. ESI-HRMS *m/z* calc'd for $C_{17}H_{28}NO_2P$ [M+Na$^+$]: 332.1750 found: 332.1749. De of crude product: 14%, measured by ^{31}P NMR analysis.

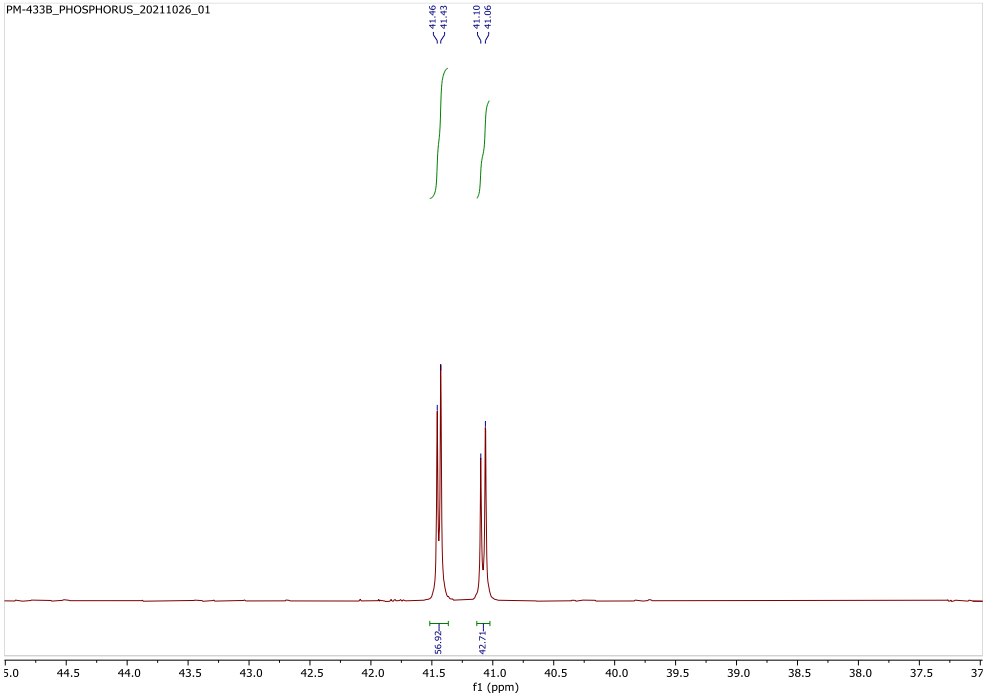


Figure S3. ^{31}P NMR spectrum of crude reaction mixture after 2h, showing signals corresponding to **9e** in the presence of catalyst **4** (10 mol%).

5. NMR Studies

NMR Study of Diethyl Vinylphosphonate and Methyl Acrylate in the Presence of Schreiner's Catalyst

A stock solution of diethyl vinylphosphonate (0.2 M in $CDCl_3$) was made up in an oven-dried crimp-top vial under an atmosphere of N_2 and dried over activated 4 Å molecular sieves. An aliquot of this stock solution (0.5 mL) was added to an NMR tube and ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded (solution A). Schreiner's thiourea catalyst **1** (0.012 g) was dissolved in an aliquot of the stock solution (0.1 mL) and added to the NMR tube. ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded (Solution B). Schreiner's thiourea catalyst **1** (0.023 g) was dissolved in an aliquot of the stock solution (0.1 mL) and added to the NMR tube. ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded (solution C) to produce spectra with 0, 20 and 50 mol% catalyst present. This process was repeated using a solution of methyl acrylate (0.2 M in $CDCl_3$) as substrate with two sequential additions of Schreiner's thiourea catalyst **1** (0.007 g). To produce spectra with 0, 10 and 20 mol% catalyst present.

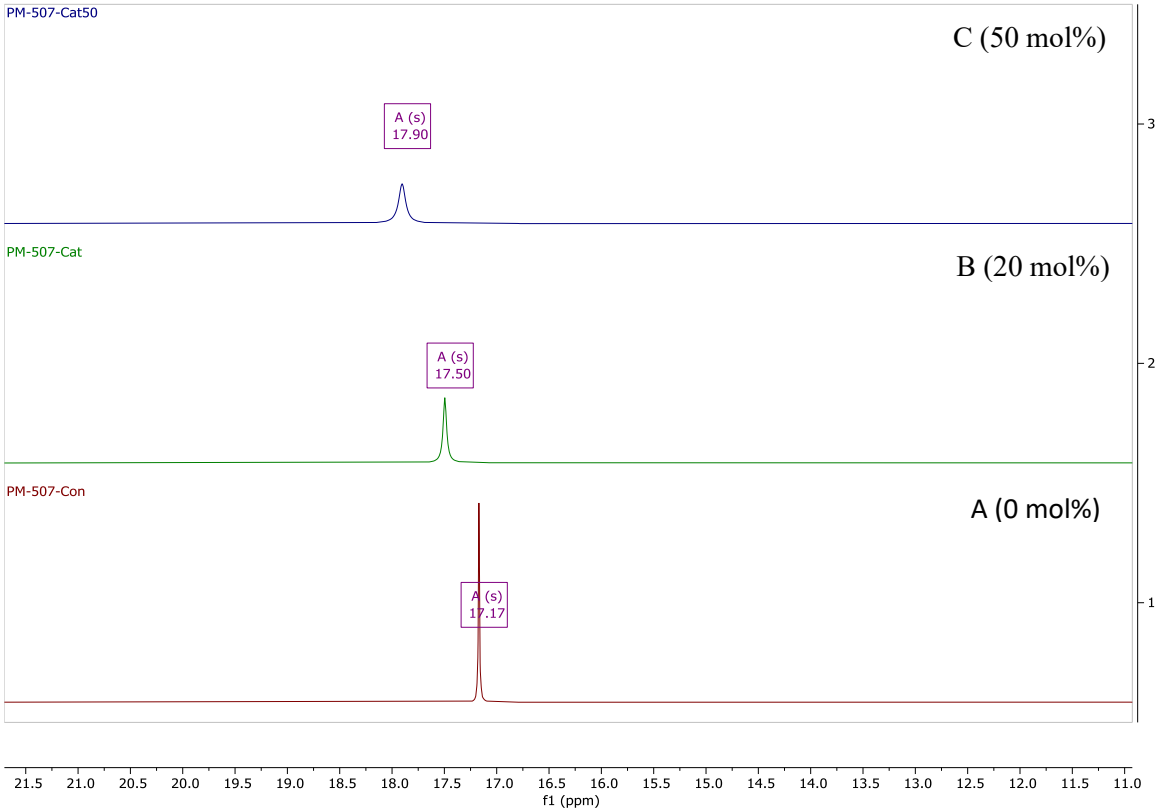


Figure S4. ^{31}P NMR spectra of solutions A,B and C prepared as described above **Bottom:** ^{31}P NMR spectra of diethyl vinylphosphonate, 0 mol% catalyst (**solution A**). **Middle:** ^{31}P NMR spectra of diethyl vinylphosphonate in the presence of 20 mol% catalyst **1** (**solution B**). **Top:** ^{31}P NMR spectra of diethyl vinylphosphonate in the presence of 50 mol% catalyst **1** (**solution C**).

The increasing downfield shift and broadening of the signal observed as catalyst concentration is increased is in line with previous reports of hydrogen-bonding between thioureas and phosphoryl compounds.[27]

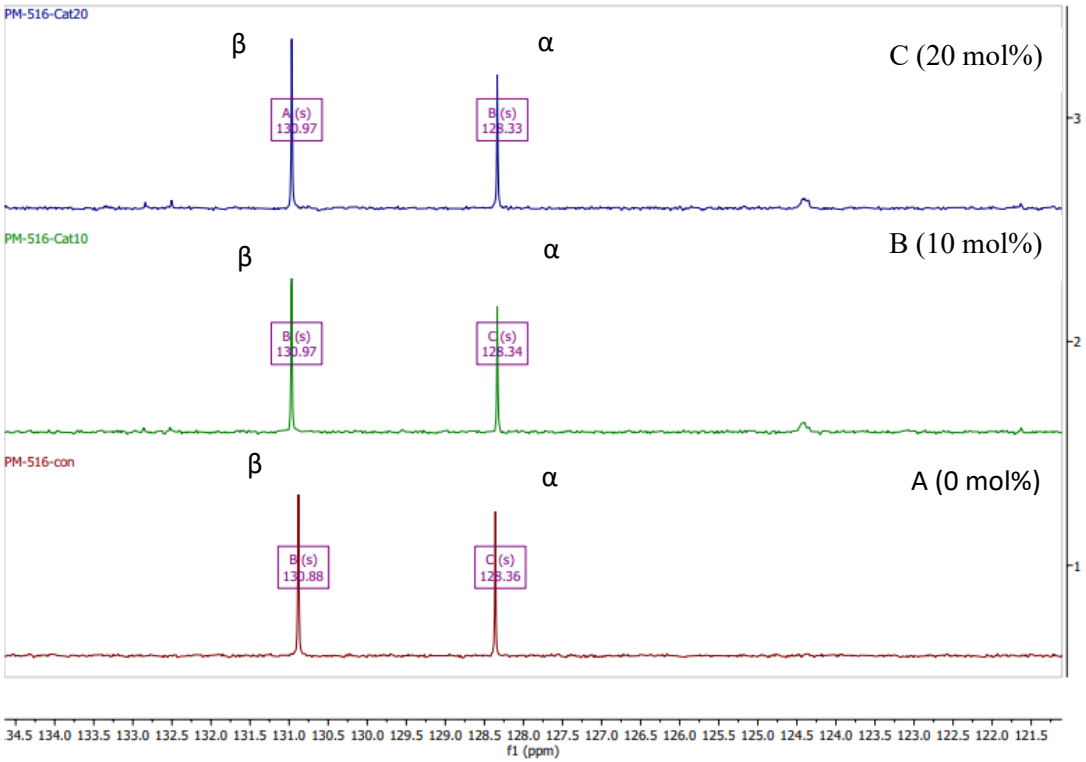


Figure S5. ^{13}C NMR spectra of solutions containing methyl acrylate and Schreiner's catalyst **1** showing signals corresponding to the α,β-carbons. **Bottom:** ^{13}C NMR spectrum of methyl with 0 mol% catalyst. **Middle:** ^{13}C NMR spectrum of methyl with 10 mol% catalyst **1**. **Top:** ^{13}C NMR spectrum of methyl with 20 mol% catalyst **1**.

NMR analysis of reaction mixture under standard conditions

Having observed an increase in polarity of the double bond in diethyl vinylphosphonate in the presence of Schreiner's catalyst **1** by ^{13}C NMR analysis (Figure 5), we wanted to test if this interaction would still occur in the presence of amine. To test this a ^{13}C NMR spectrum was recorded of diethyl vinylphosphonate in the presence of benzylamine (1.0 equiv.) and Schreiner's thiourea catalyst (0.2 equiv.) at 0.5 M concentration. Again the same trend was observed, the signal corresponding to the β-carbon shifted downfield and the signal corresponding to the α-carbon shifted upfield (Figure S5). This observation shows that the catalyst can still increase the polarity of diethyl vinylphosphonate in the presence of benzylamine.

Diethyl vinylphosphonate (0.051 mL, 0.300 mmol), Schreiner's catalyst (0.030 g, 0.060 mmol) and benzylamine (0.033 mL, 0.300 mmol) were dissolved in $CDCl_3$ (0.6 mL) and transferred to an NMR tube. ^{1}H NMR and ^{13}C NMR spectra were recorded.

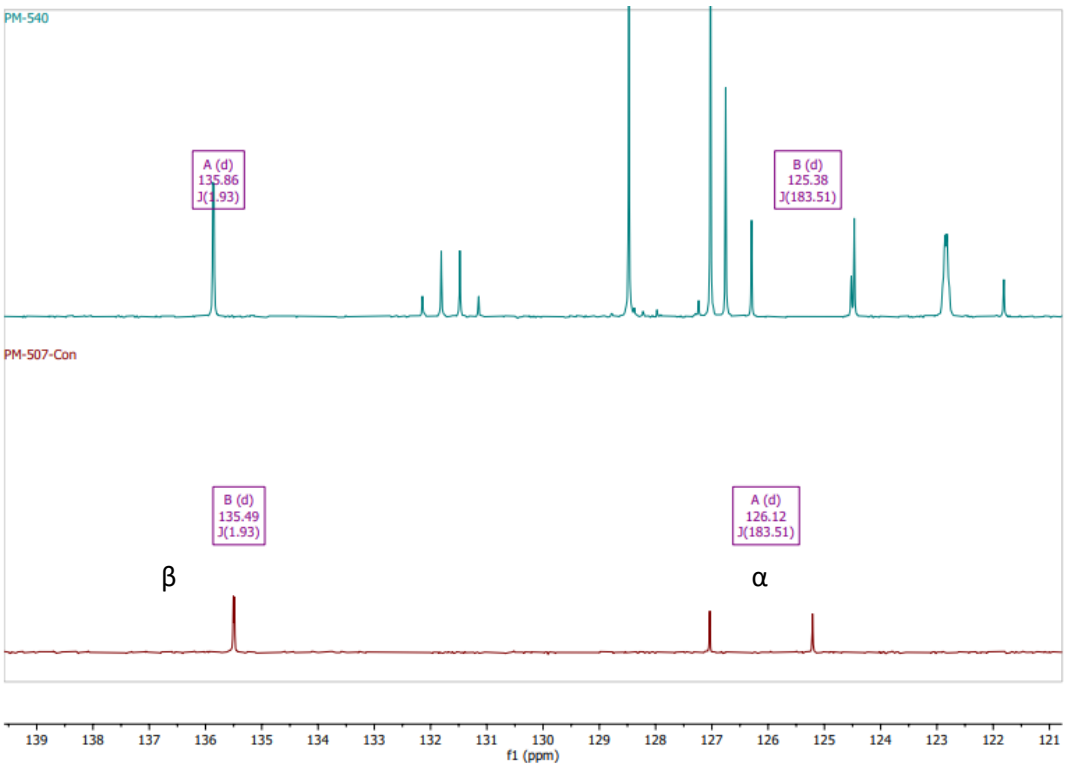
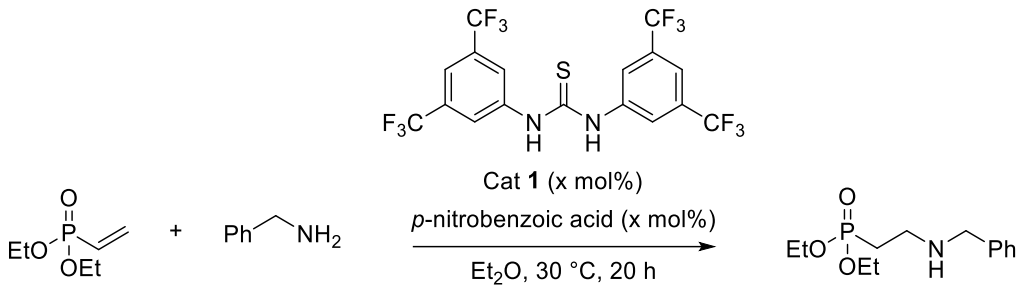


Figure S6. ^{13}C NMR spectra of the reaction mixture in $CDCl_3$ **(top)** compared to ^{13}C NMR spectrum of diethyl vinylphosphonate **(bottom)**.

6. Acid Catalysis Study



Schreiner's thiourea catalyst **1** (0.010 g, 0.02 mmol) and/or *p*-nitrobenzoic acid (0.003 g, 0.02 mmol) were added to a flame-dried crimp-top vial under an atmosphere of N_2. Diethyl vinylphosphonate (0.016 g, 0.10 mmol) was added followed by anhydrous Et_2O (0.2 mL). Benzylamine (0.011 mL, 0.10 mmol) was added and the solution was heated to 30 °C and stirred for 20 h. The solution was concentrated under reduced pressure and the yield was determined by ^{31}P NMR analysis of the crude mixture.

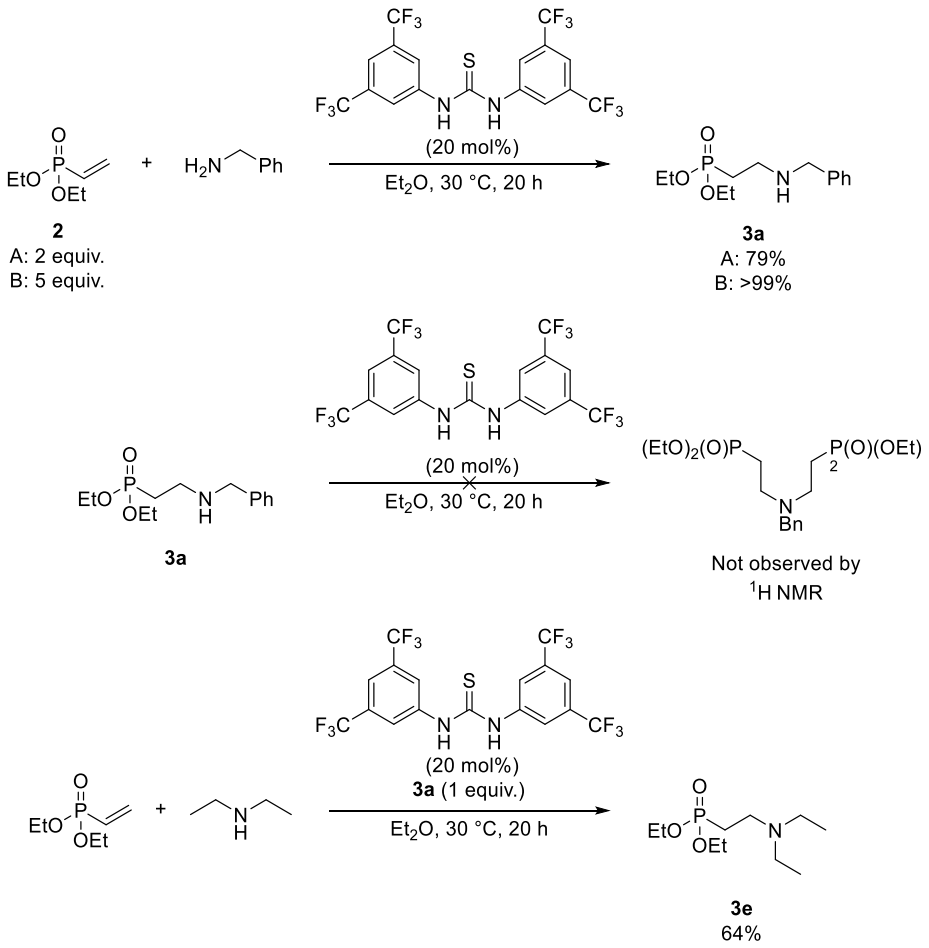
Table S4. Results of acid catalysis studies

Entry	Catalyst **1** (mol%)	$(4\text{-}NO_2)C_6H_4CO_2H$ (mol%)	yield[a] (%)
1	0	0	<1
2	20	0	78
3	0	20	27
4	20	20	79

[a] Measured by ^{31}P NMR based on conversion of starting material.

.

7. Monoalkylation Studies



In an attempt to dialkylated benzylamine increased equivalences of diethyl vinylphosphonate were used in the reaction. Following general procedure D the reaction was attempted with 2 and 5 equiv. of **2**. In both cases **3a** was the major product and when 5 equiv. of **2** were used full conversion was observed. To investigate if the lack of dialkylated product was due to increased steric hinderance or inhibition of the catalys caused by the presence of **3a,** two control experiments were carried out. First, isolated **3a** was resubmitted to standard conditions following general procedure D. No conversion dialkylation was observed after 20 h. Second, the addition of diethylamine to **2** was carried out following general procedure D with the addition of 1 equiv. of **3a.** A reduced yield of 64% of **3e** compared to 88% in the absence of **3a** was observed by ^{31}P NMR analysis.

References

[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

[2] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, *2012*, 5919–5927.

[3] Y. Sohtome, N. Takemura, R. Takagi, Y. Hashimoto, K. Nagasawa, *Tetrahedron* **2008**, *64*, 9423–9429.

[4] M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 1891–1894.

[5] N. R. Amarasinghe, P. Turner, M. H. Todd, *Adv. Synth. Catal.* **2012**, *354*, 2954–2958.

[6] C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre, *Nat. Protoc.* **2013**, *8*, 325–344.

[7] W. Yang, D. M. Du, *Org. Lett.* **2010**, *12*, 5450–5453.

[8] E. G. Klauber, C. K. De, T. K. Shah, D. Seidel, *J. Am. Chem. Soc.* **2010**, *132*, 13624–13626.

[9] A. Baber, J. G. De Vries, A. G. Orpen, P. G. Pringle, K. Von Der Luehe, *Dalton Trans.* **2006**, 4821–4828.

[10] M. Lukáč, M. Garajová, M. Mrva, F. Devínsky, F. Ondriska, J. Kubincová, *J. Fluor. Chem.* **2014**, *164*, 10–17.

[11] K. Dziuba, M. Lubańska, K. M. Pietrusiewicz, *Synthesis* **2020**, *52*, 909–916.

[12] A. Mohd, T. Anitha, K. R. Reddy, J. Wencel-Delord, F. Colobert, *Eur. J. Org. Chem.* **2019**, *2019*, 7836–7841.

[13] T. Hirao, T. Masunaga, Y. Ohshiro, T. Agawa, *Tetrahedron Lett.* **1980**, *21*, 3595–3598.

[14] T. Chen, C. Q. Zhao, L. B. Han, *J. Am. Chem. Soc.* **2018**, *140*, 3139–3155.

[15] K. Juhász, B. Varga, P. Bagi, Z. Hell, *Catal. Lett.* **2022**, *152*, 1100–1108.

[16] U. S. Dakarapu, A. Bokka, P. Asgari, G. Trog, Y. Hua, H. H. Nguyen, N. Rahman, J. Jeon, *Org. Lett.* **2015**, *17*, 5792–5795.

[17] W. Al-Maksoud, J. Mesnager, F. Jaber, C. Pinel, L. Djakovitch, *J. Organomet. Chem.* **2009**, *694*, 3222–3231.

[18] C. Yuan, J. Li, W. Zhang, *J. Fluor. Chem.* **2006**, *127*, 44–47.

[19] A. Jasiak, G. Mielniczak, K. Owsianik, M. Koprowski, D. Krasowska, J. Drabowicz, *J. Org. Chem.* **2019**, *84*, 2619–2625.

[20] F. Palacios, A. M. Ochoa De Retana, J. M. Alonso, *J. Org. Chem.* **2006**, *71*, 6141–6148.

[21] S. Zhou, J. Pan, K. M. Davis, I. Schaperdoth, B. Wang, A. K. Boal, C. Krebs, J. M. Bollinger, *J. Am. Chem. Soc.* **2019**, *141*, 20397–20406.

[22] T. E. Nickson, *J. Org. Chem.* **2002**, *53*, 3870–3872.

[23] D. Solé, F. Pérez-Janer, Y. García-Rodeja, I. Fernández, *Eur. J. Org. Chem.* **2017**, *2017*, 799–805.

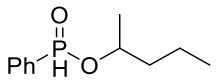
[24] R. A. Cherkasov, V. I. Galkin, N. G. Khusainova, O. A. Mostovaya, A. R. Garifzyanov, G. K. Nuriazdanova, N. S. Krasnova, E. A. Berdnikov, *Russ. J. Org. Chem.* **2005**, *41*, 1481–1484.

[25] N. Khusainova, O. Mostovaya, E. Berdnikov, S. Rybakov, R. Cherkasov, *Phosphorus Sulfur Silicon Relat. Elem.* **2009**, *184*, 865–871.

[26] E. V. Matveeva, P. V. Petrovskii, I. L. Odinets, *Tetrahedron Lett.* **2008**, *49*, 6129–6133.

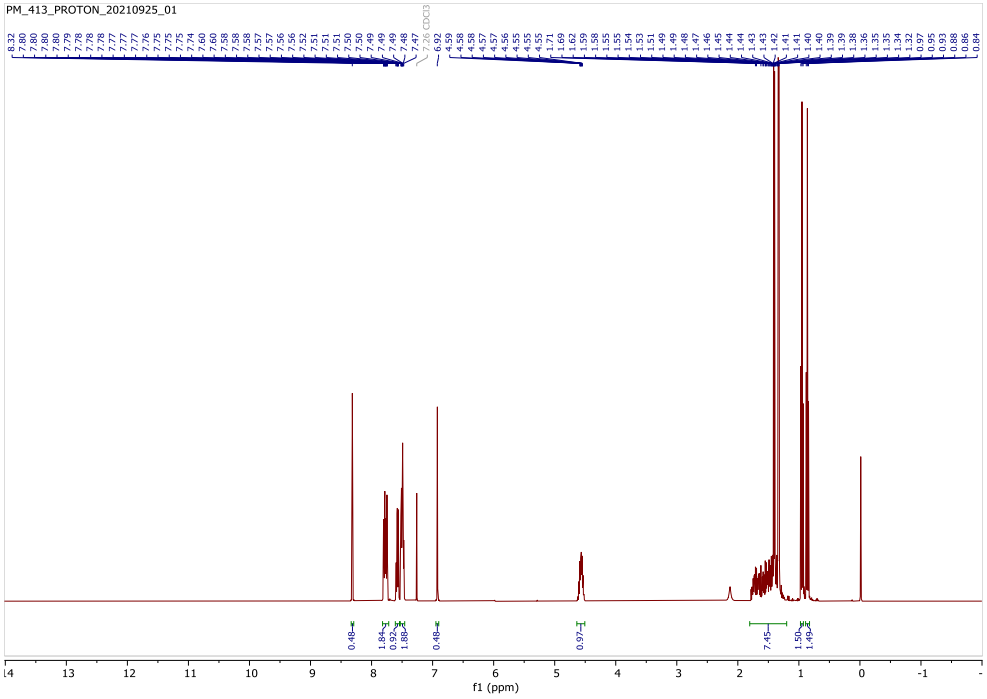
[27] A. R. Nödling, G. Jakab, P. R. Schreiner, G. Hilt, *Eur. J. Org. Chem.* **2014**, *2014*, 6394–6398.

NMR spectra of selected compounds

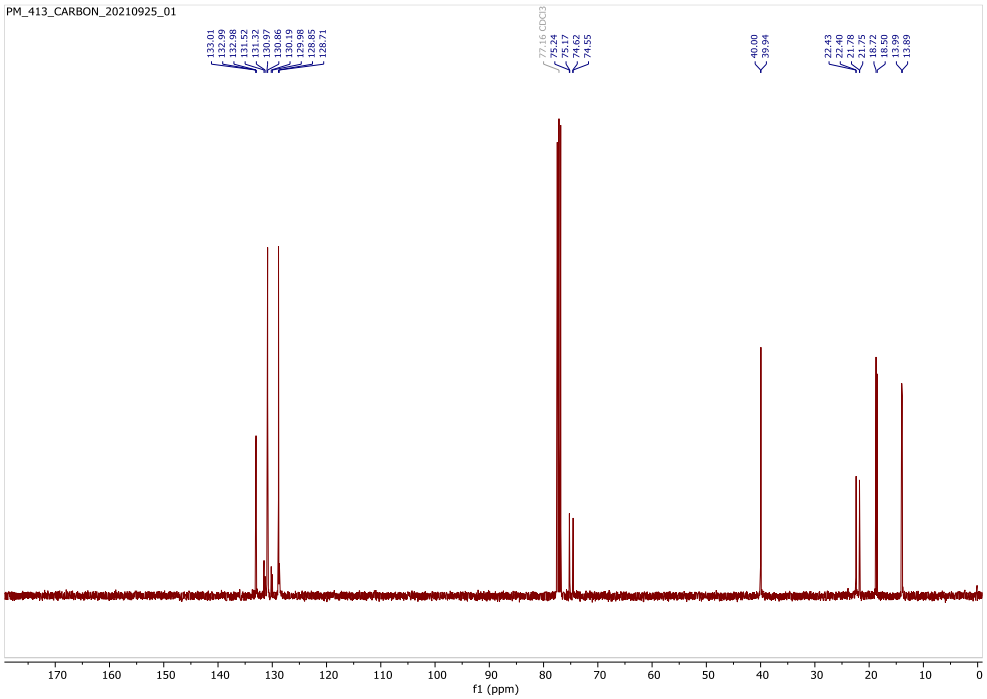


13c

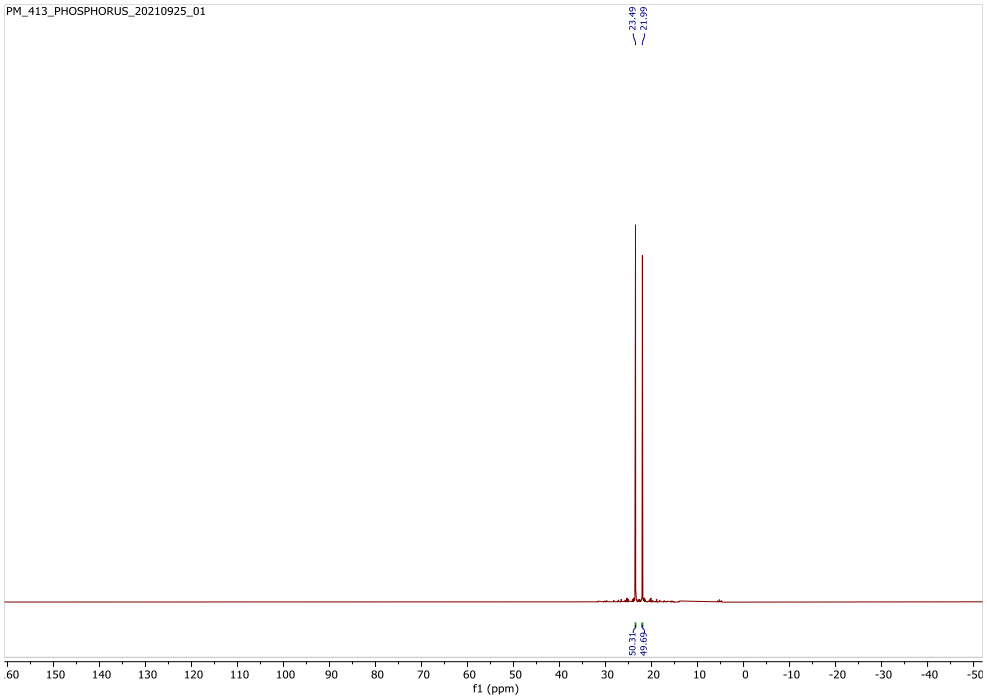
^{1}H-NMR (400 MHz, $CDCl_3$)

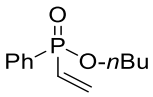


^{13}C-NMR (101 MHz, $CDCl_3$)



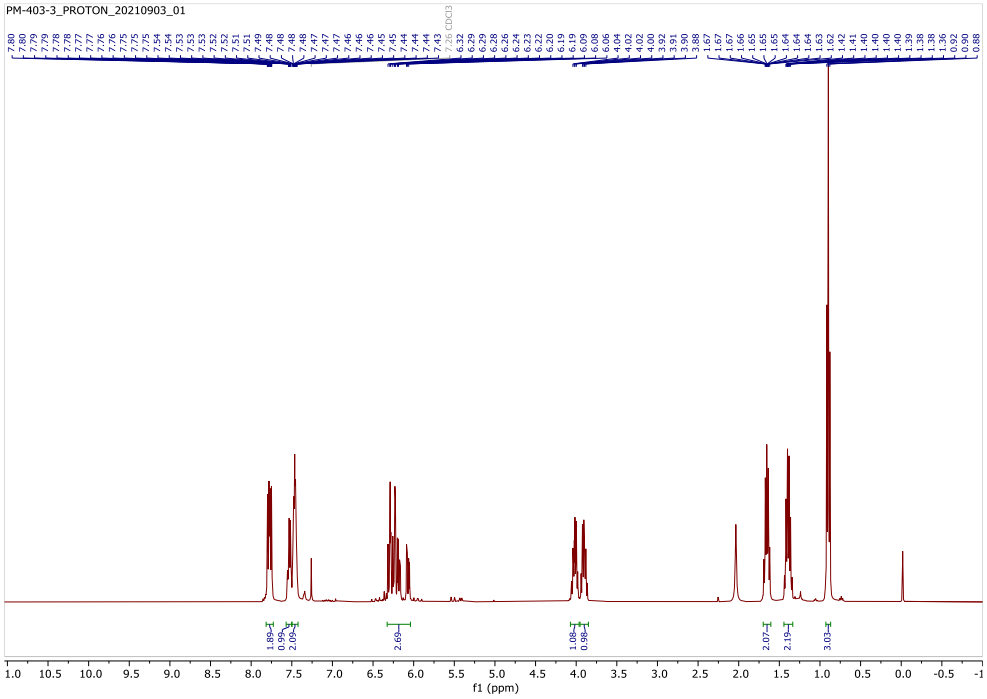
^{31}P-NMR (162 MHz, $CDCl_3$)



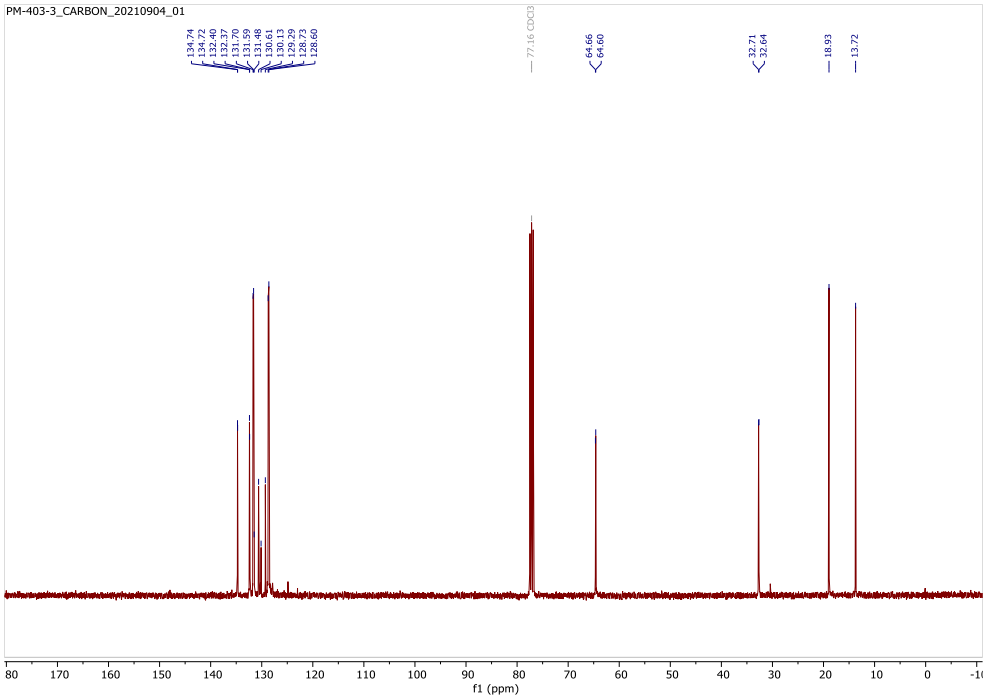


14b

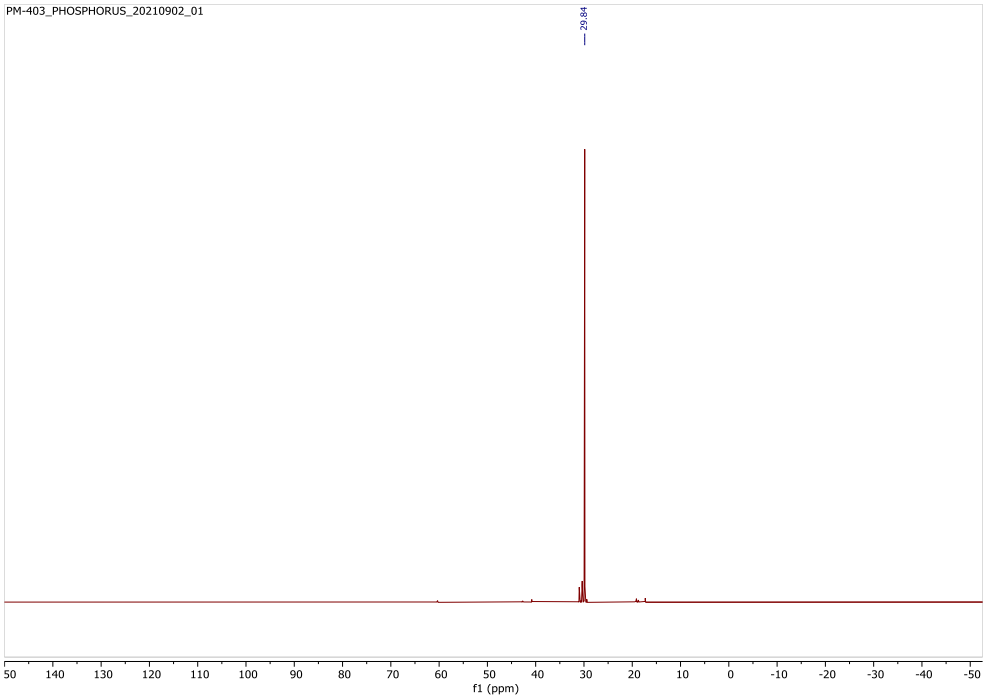
^{1}H-NMR (400 MHz, $CDCl_3$)

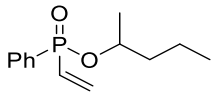


^{13}C-NMR (101 MHz, $CDCl_3$)



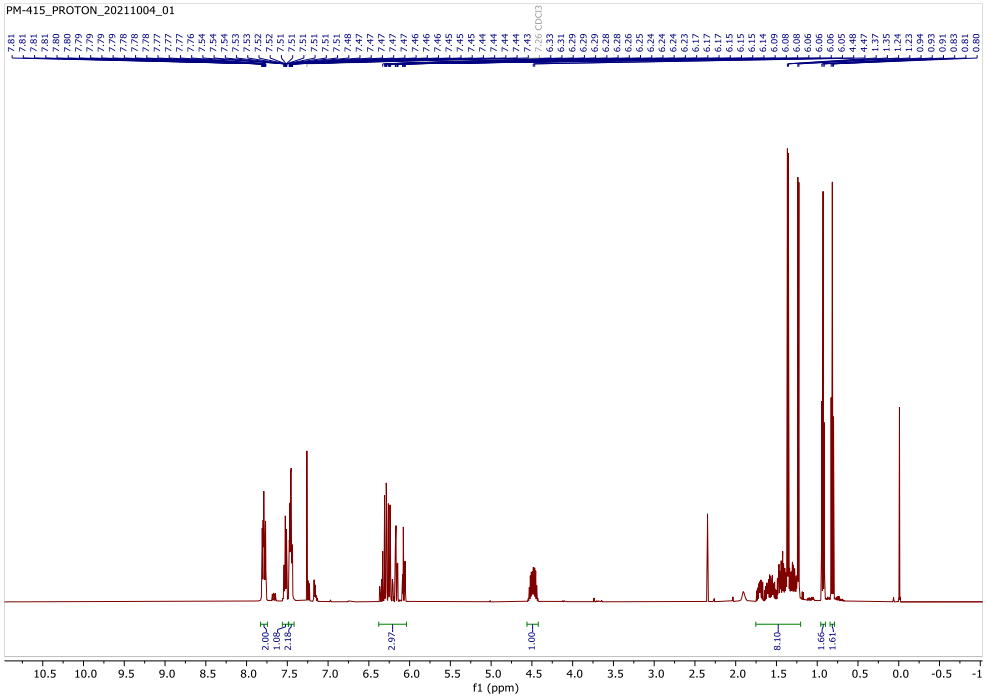
^{31}P-NMR (162 MHz, $CDCl_3$)



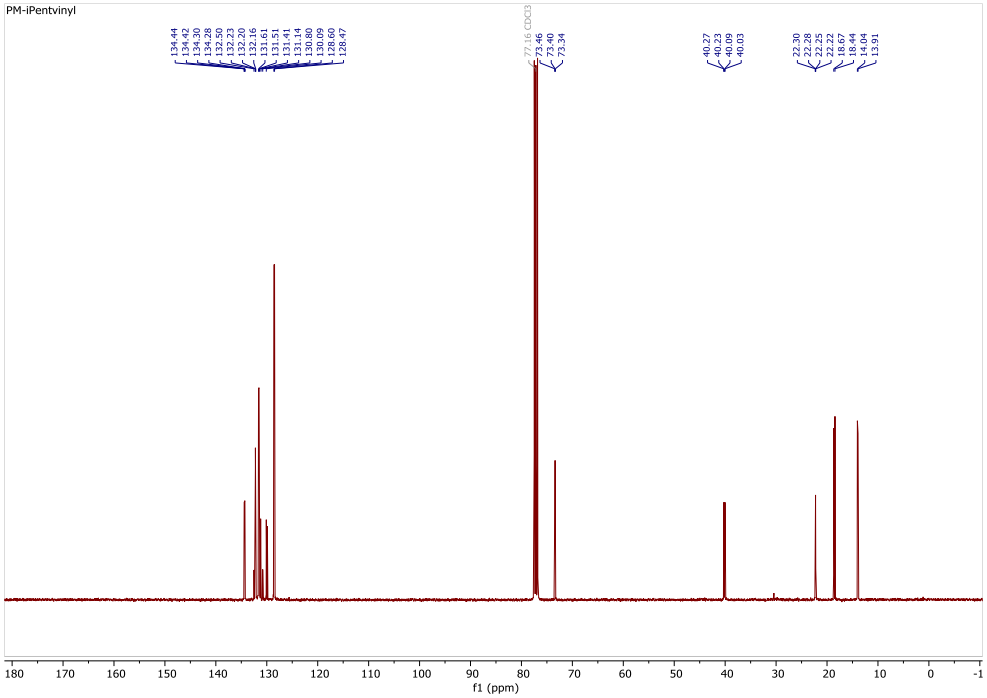


14c

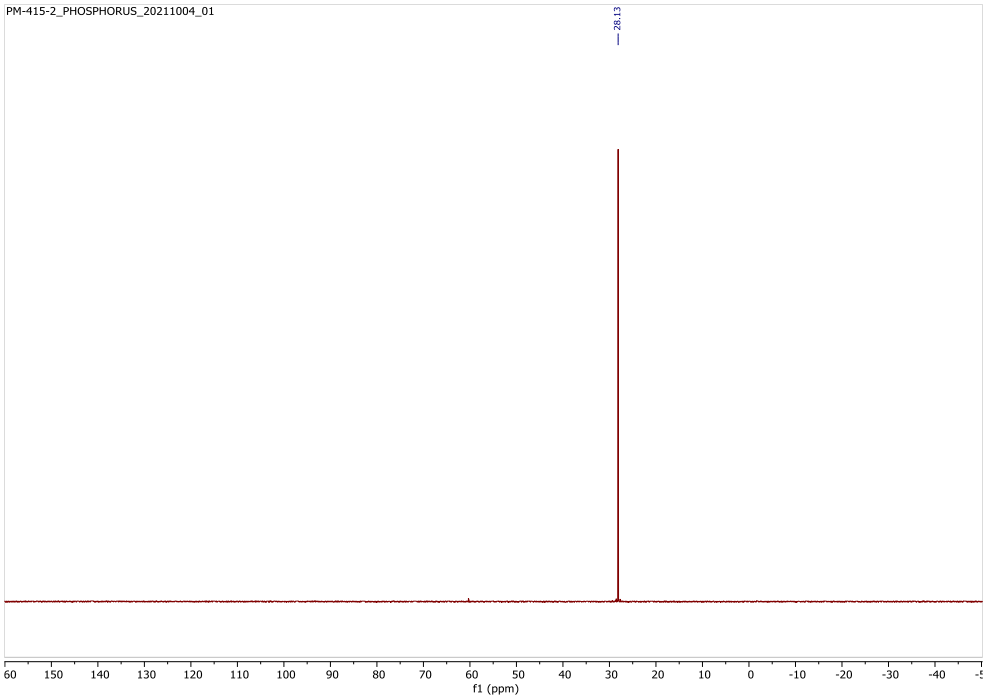
^{1}H-NMR (400 MHz, $CDCl_3$)

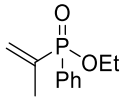


^{13}C-NMR (101 MHz, $CDCl_3$)



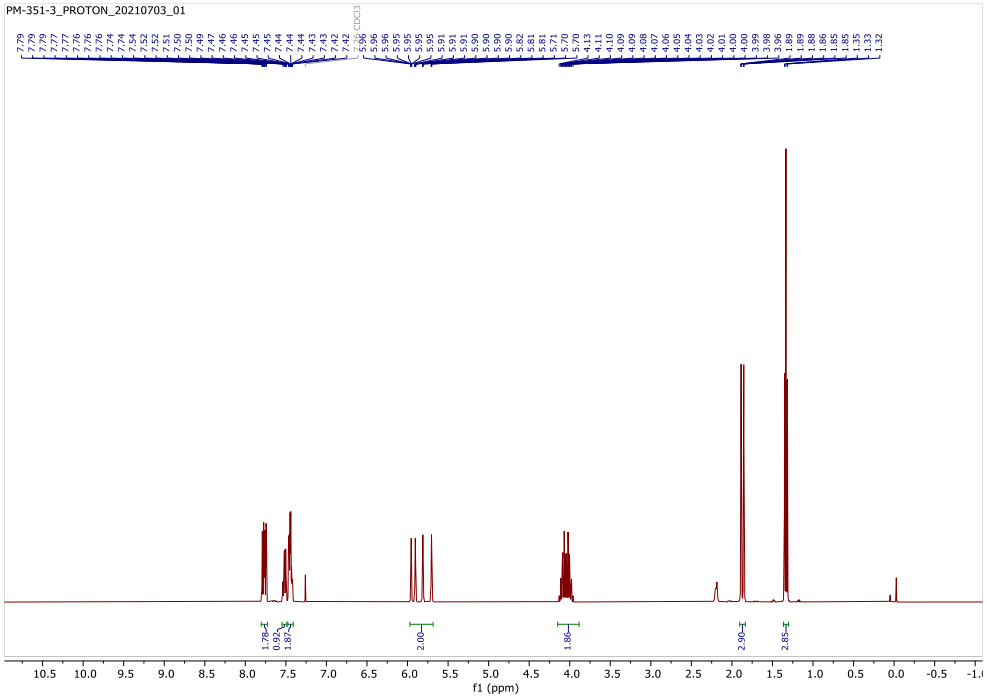
^{31}P-NMR (162 MHz, $CDCl_3$)



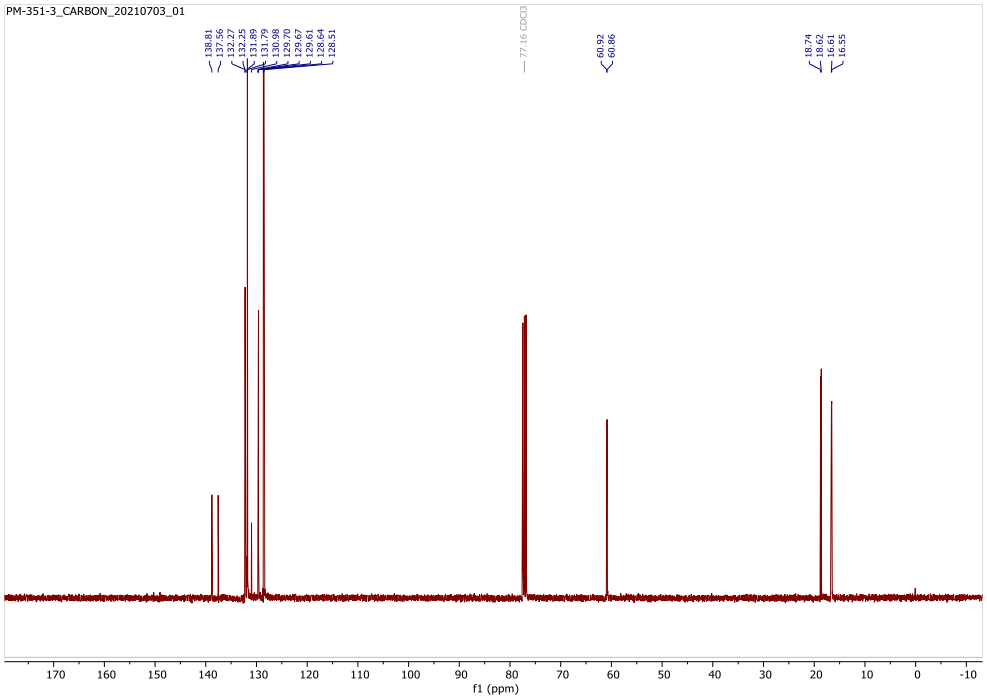


14d

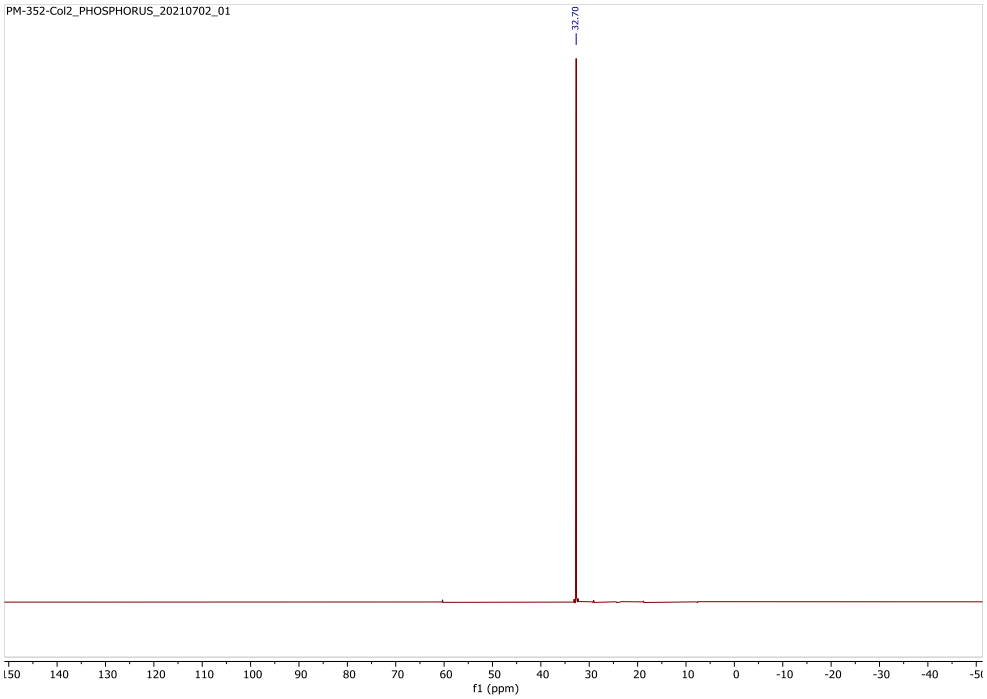
^{1}H-NMR (400 MHz, $CDCl_3$)

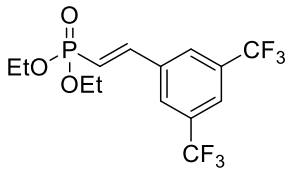


^{13}C-NMR (101 MHz, $CDCl_3$)



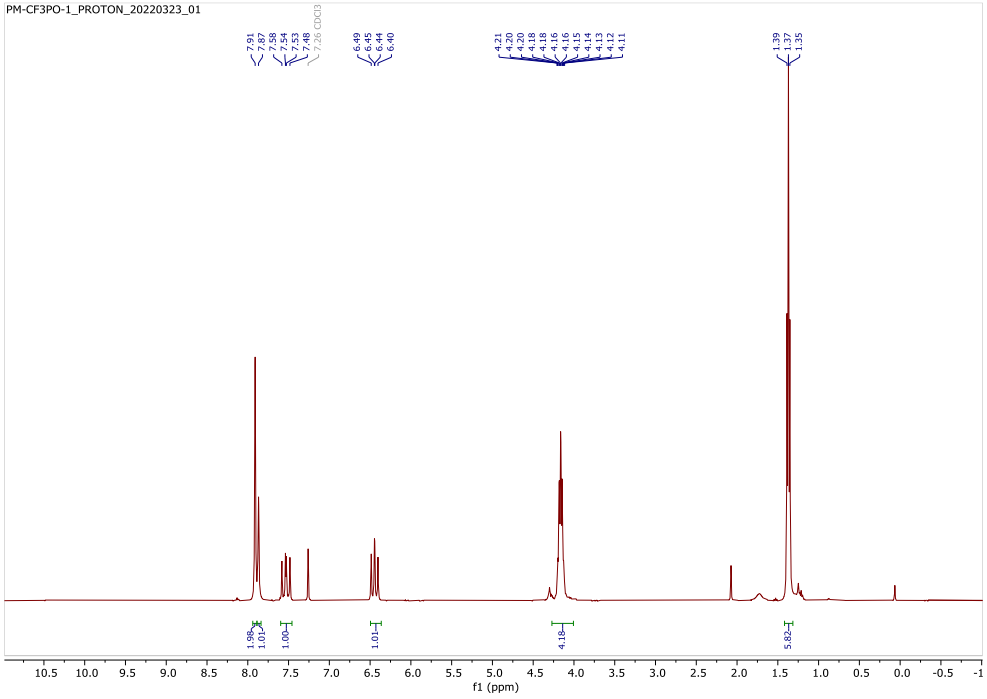
^{31}P-NMR (162 MHz, $CDCl_3$)



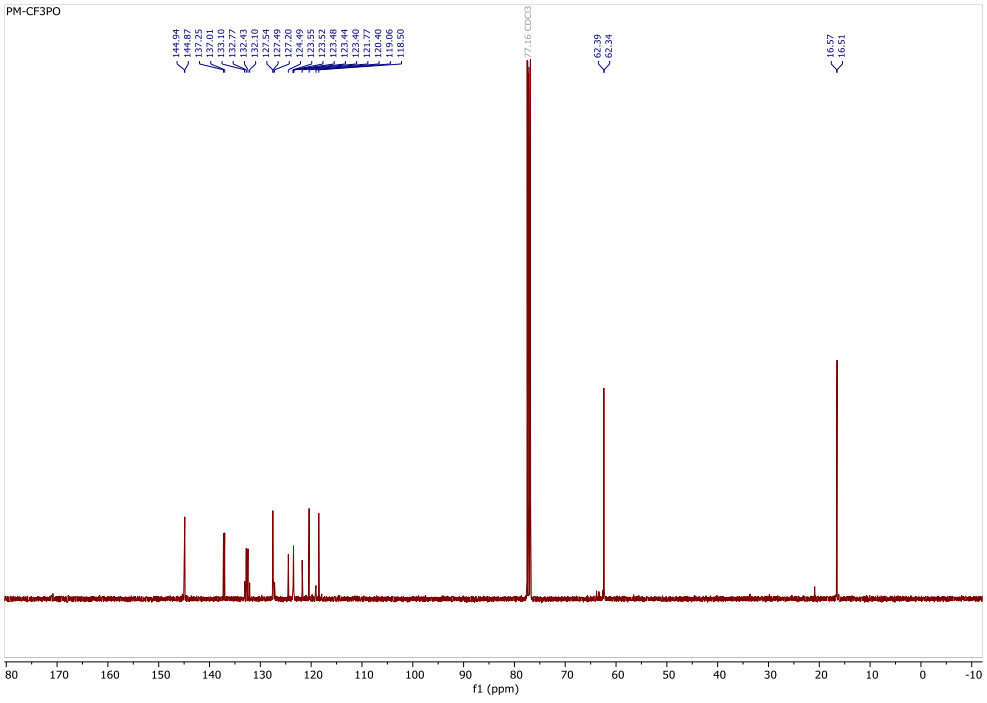


15b

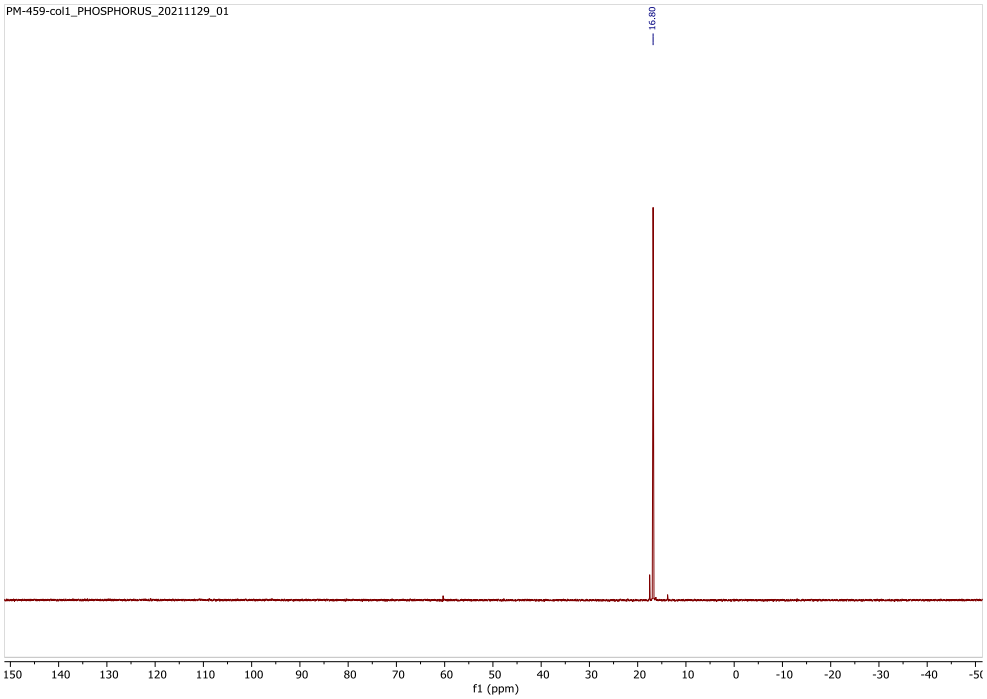
^{1}H-NMR (400 MHz, $CDCl_3$)

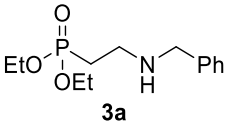


^{13}C-NMR (101 MHz, $CDCl_3$)



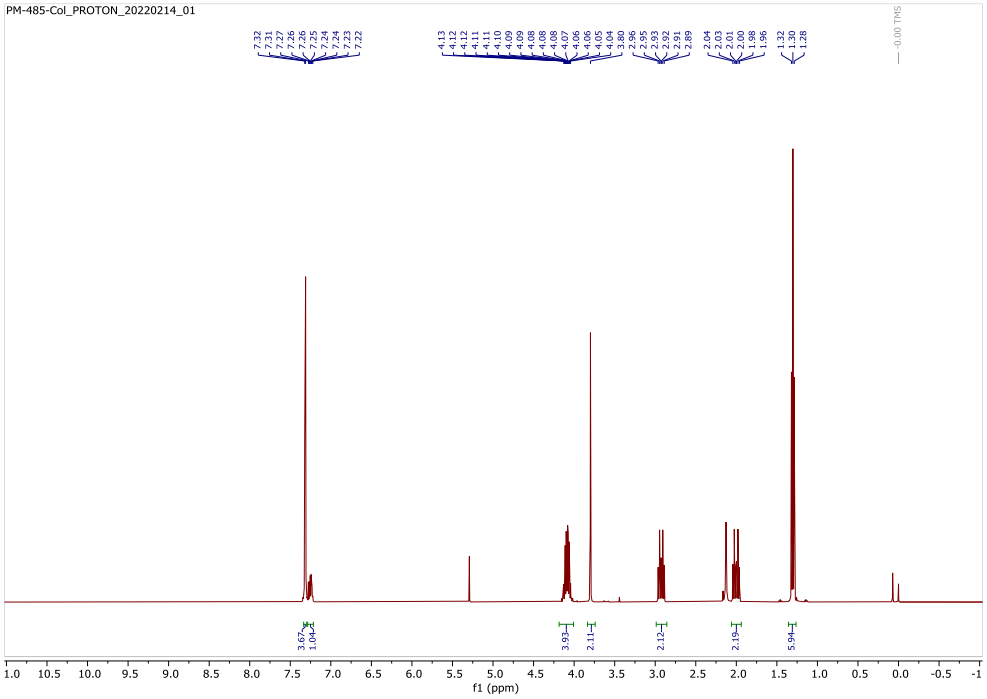
^{31}P-NMR (162 MHz, $CDCl_3$)



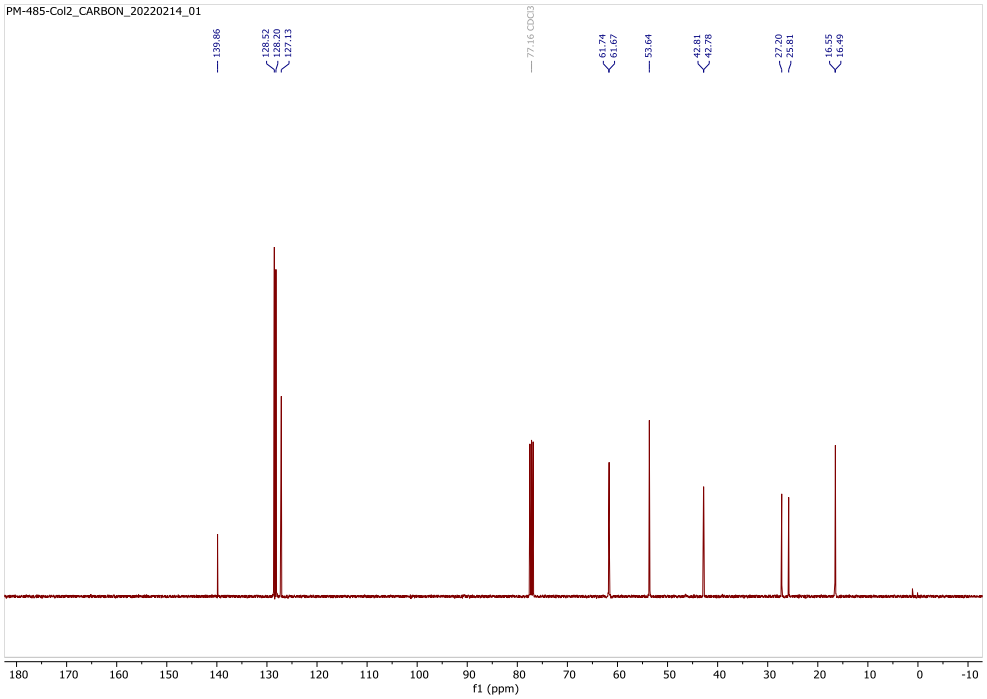


3a

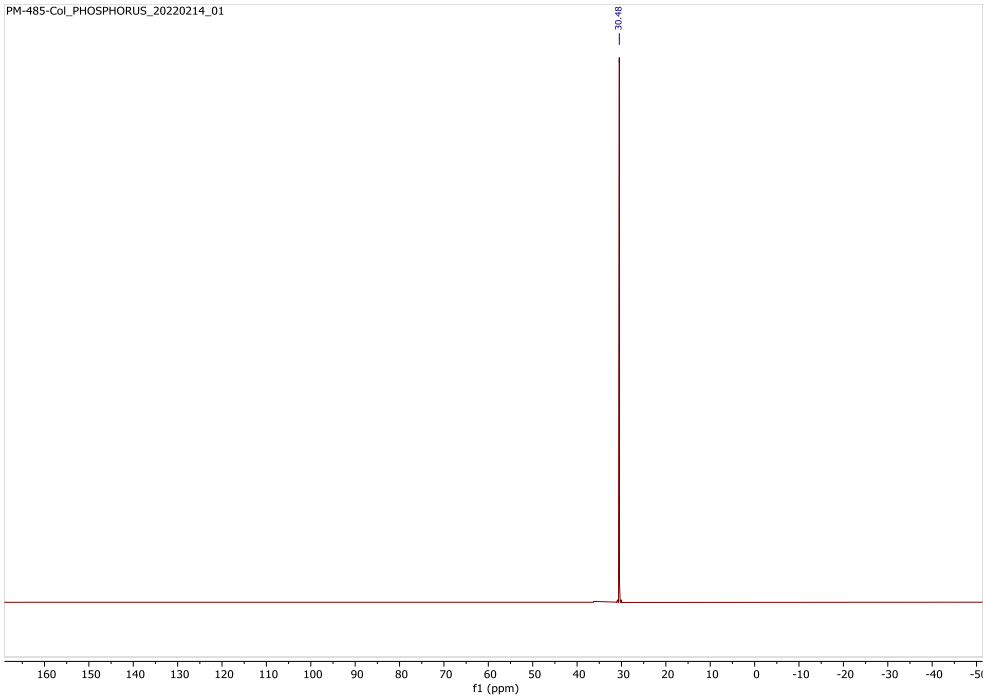
^{1}H NMR (400 MHz, $CDCl_3$)

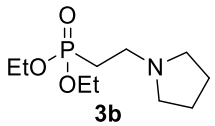


^{13}C NMR (101 MHz, $CDCl_3$)



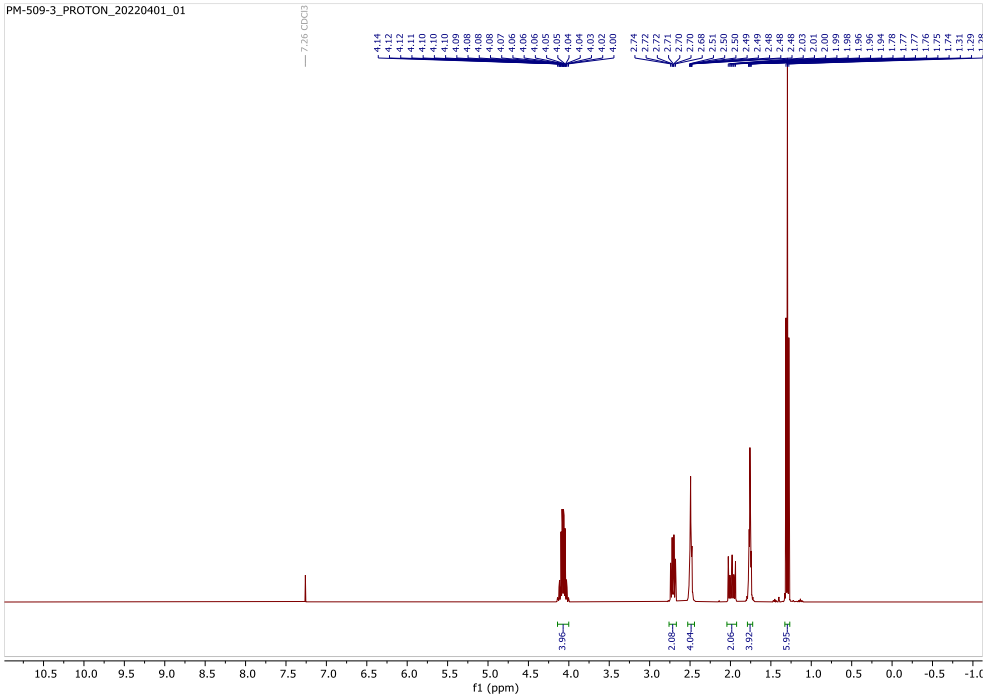
^{31}P NMR (162 MHz, $CDCl_3$)



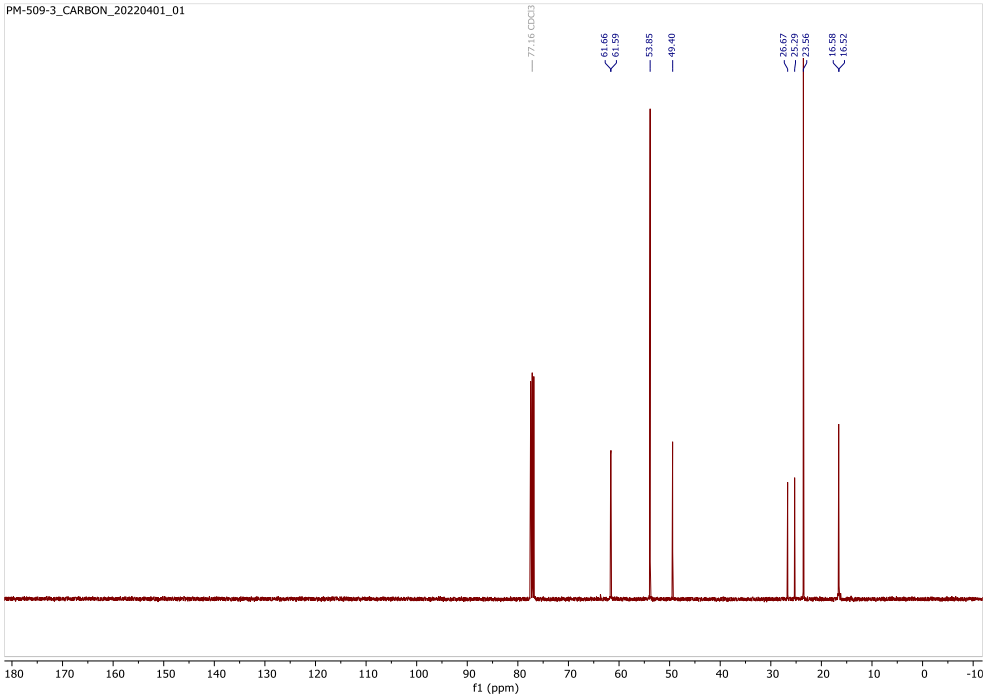


3b

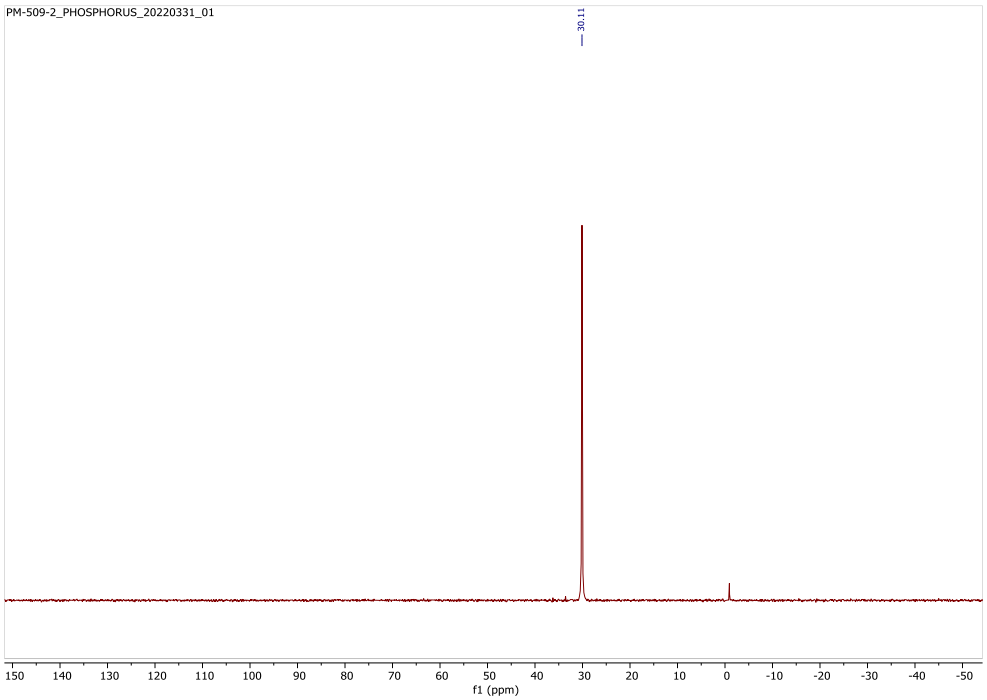
^{1}H NMR (400 MHz, $CDCl_3$)

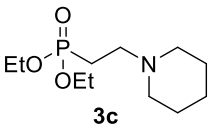


^{13}C NMR (101 MHz, $CDCl_3$)



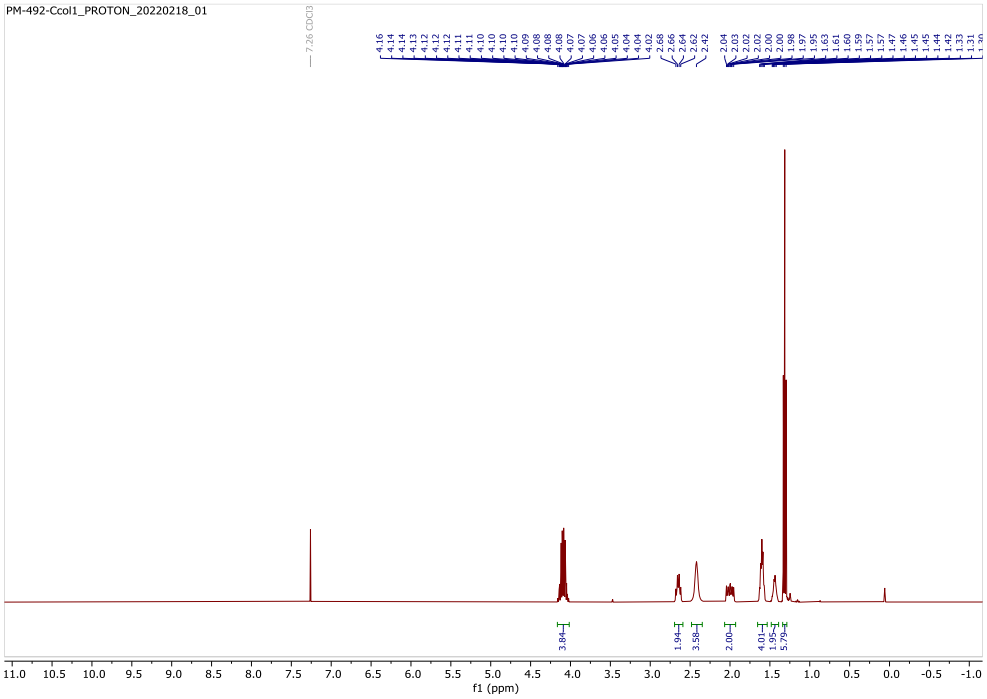
^{31}P NMR (162 MHz, $CDCl_3$)



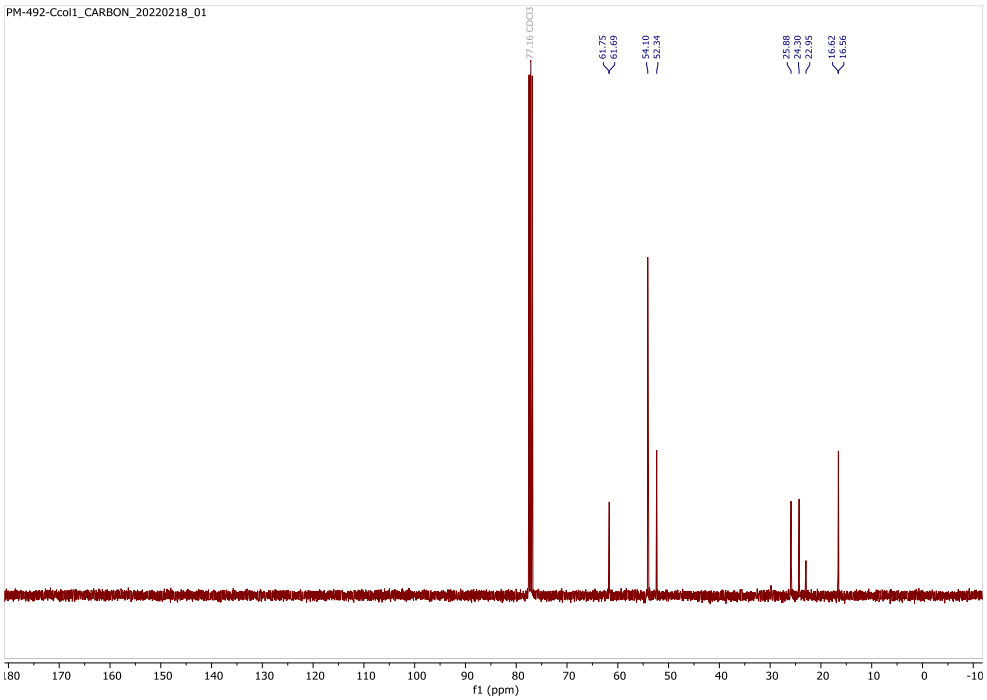


3c

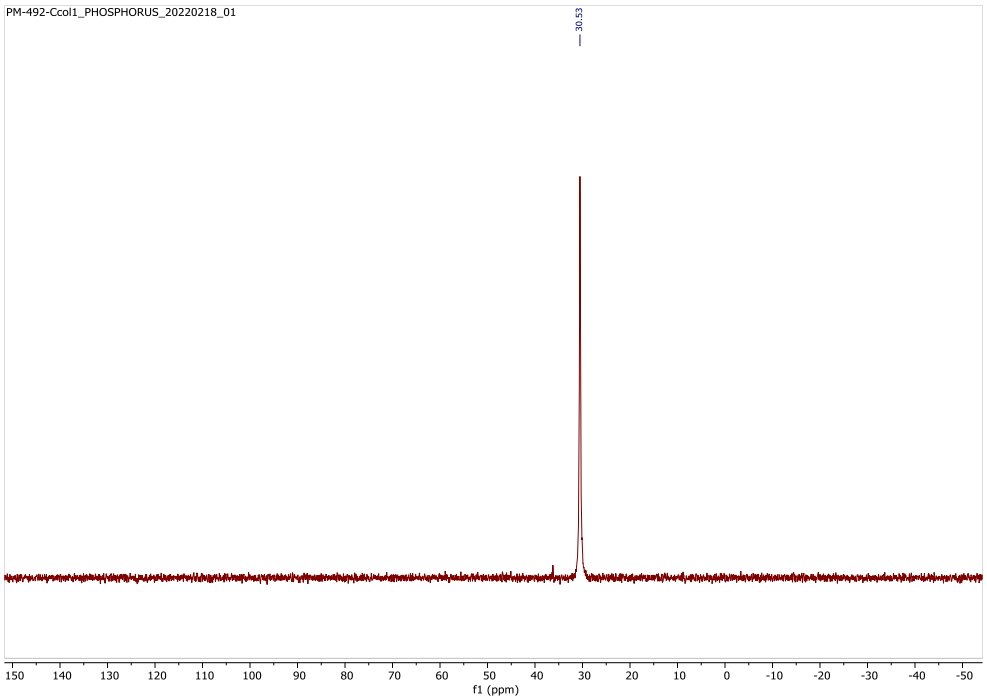
^{1}H NMR (400 MHz, $CDCl_3$)

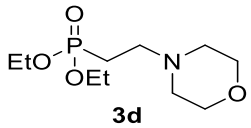


^{13}C NMR (101 MHz, $CDCl_3$)



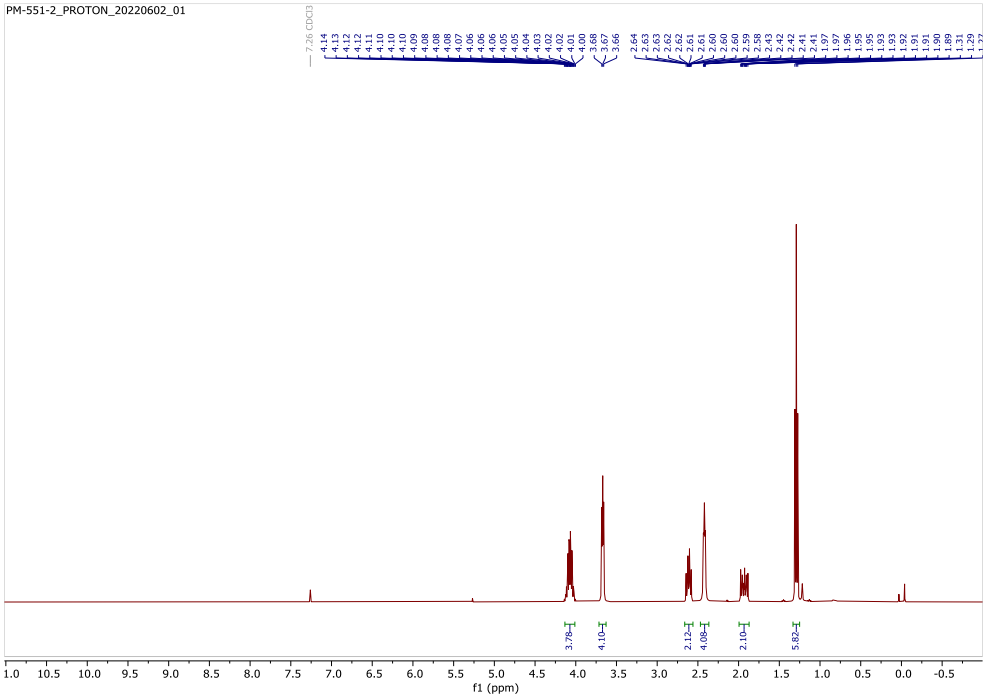
^{31}P NMR (162 MHz, $CDCl_3$)



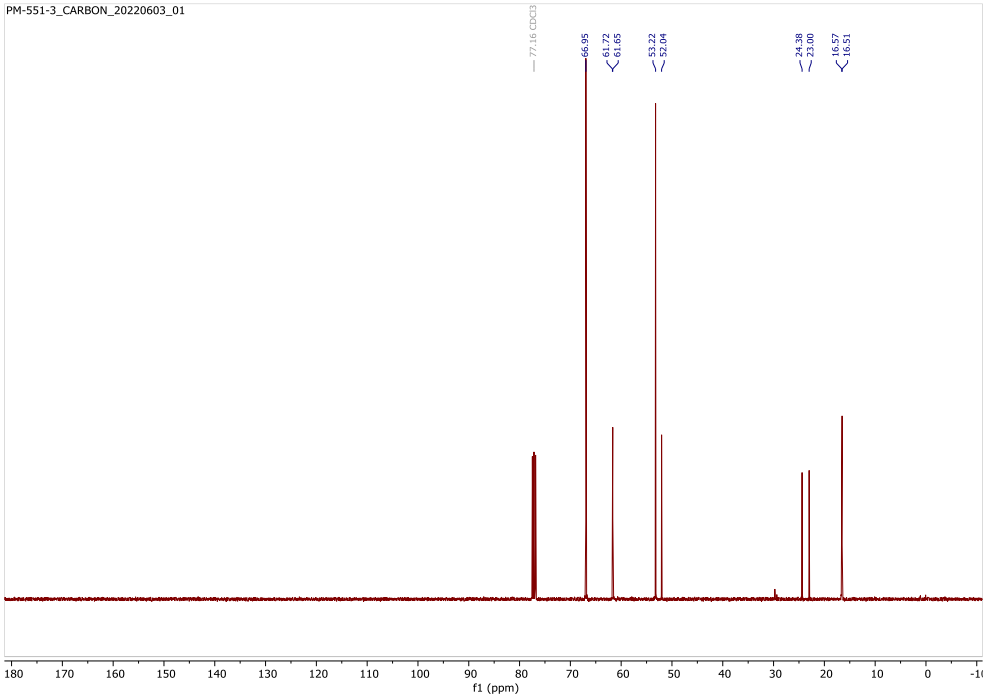


3d

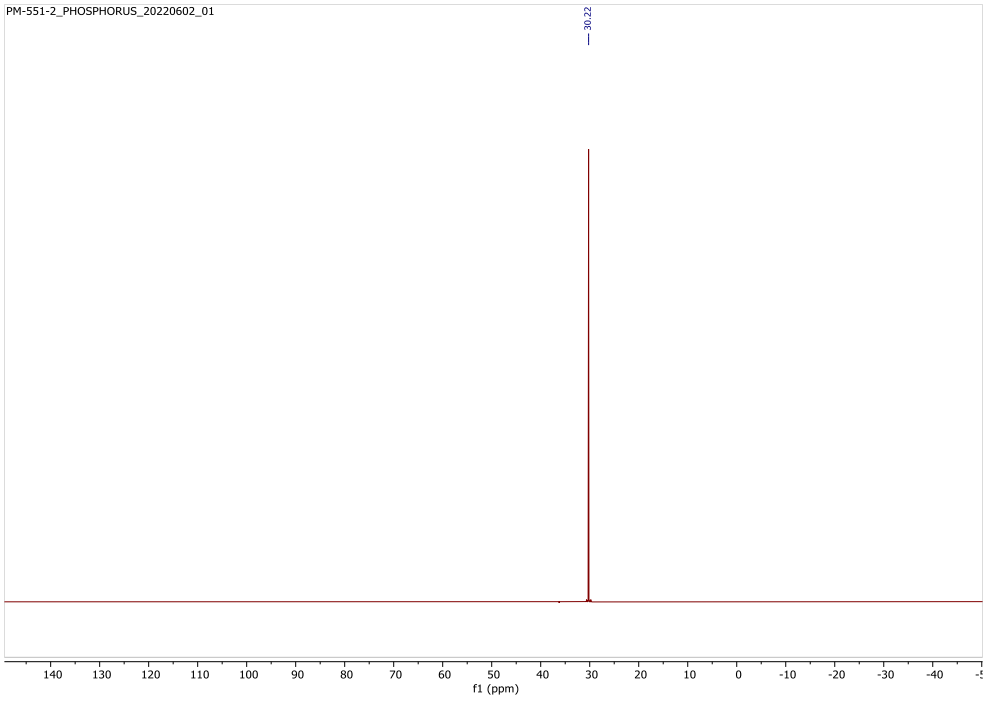
^{1}H NMR (400 MHz, $CDCl_3$)

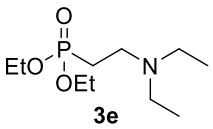


^{13}C NMR (101 MHz, $CDCl_3$)



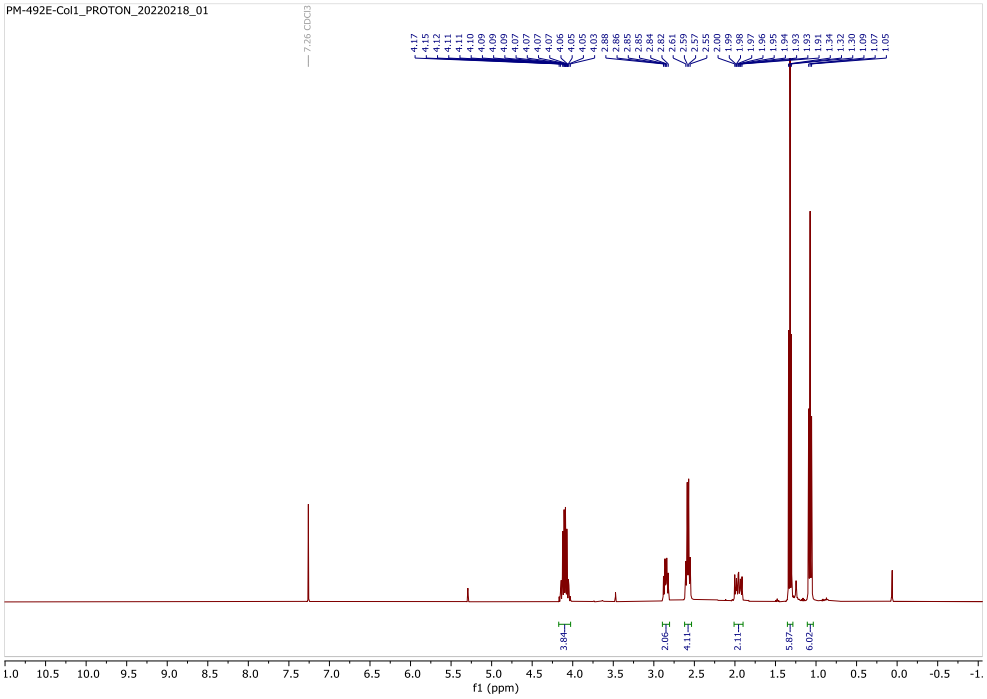
^{31}P NMR (162 MHz, $CDCl_3$)



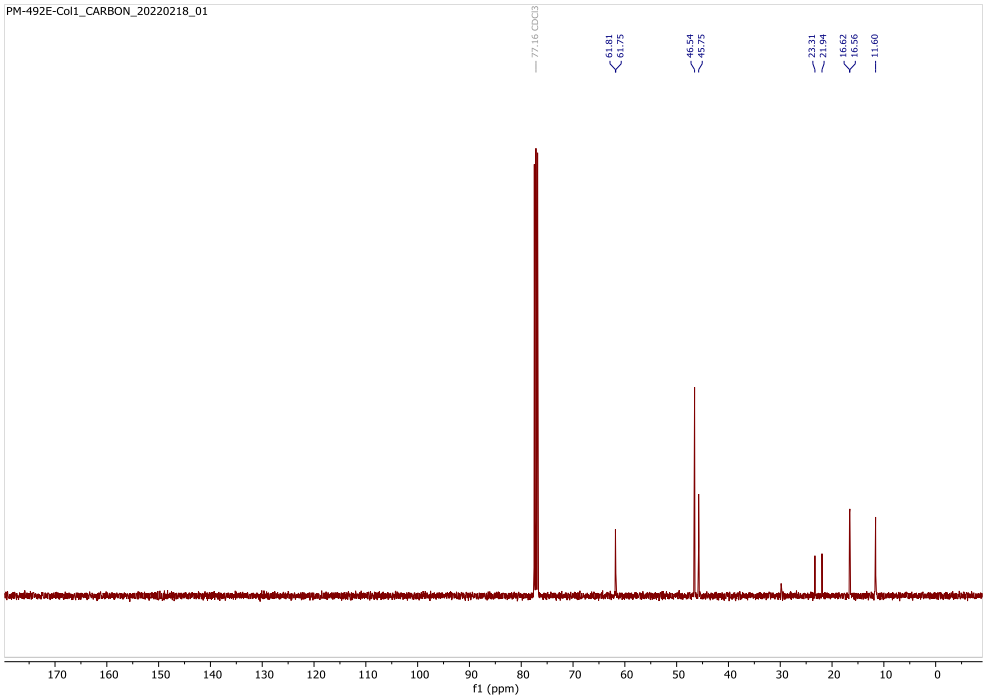


3e

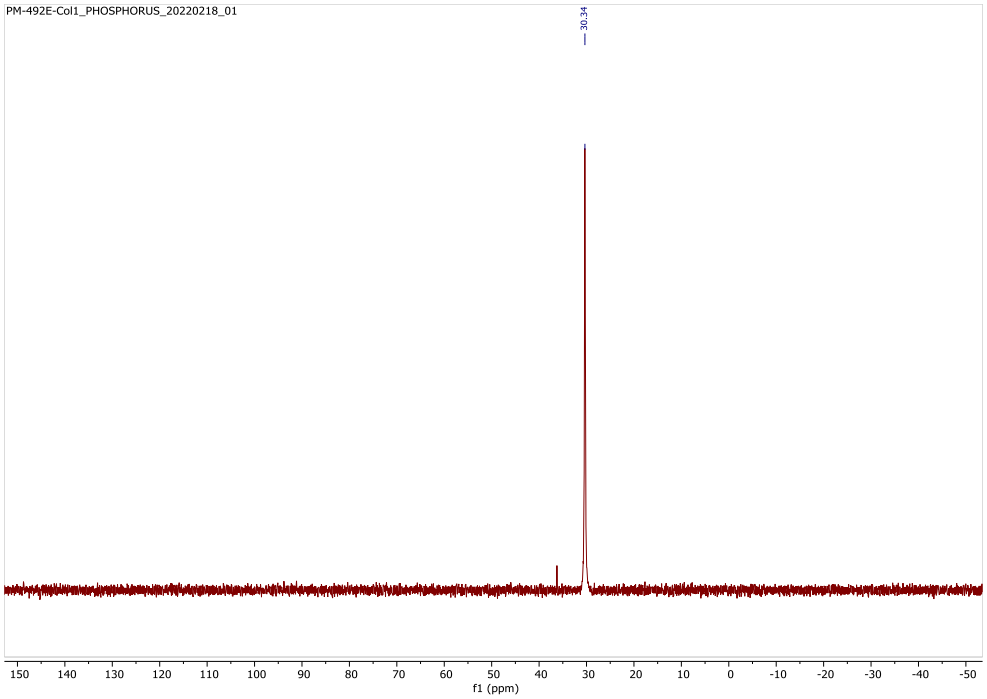
^{1}H NMR (400 MHz, $CDCl_3$)

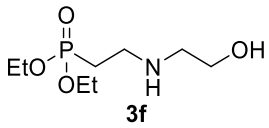


^{13}C NMR (101 MHz, $CDCl_3$)



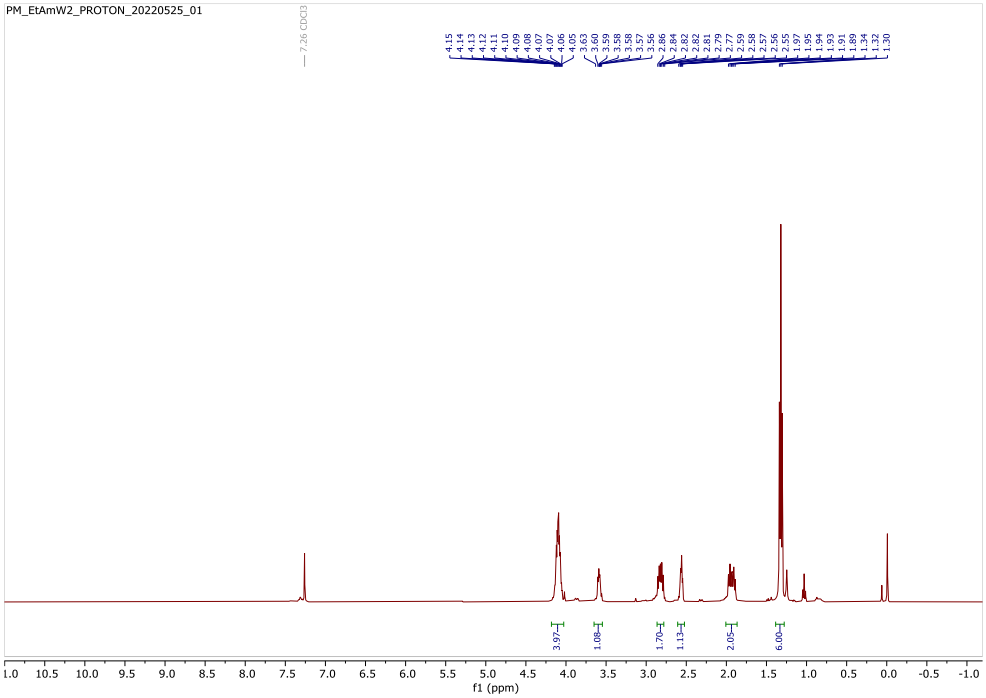
^{31}P NMR (162 MHz, $CDCl_3$)



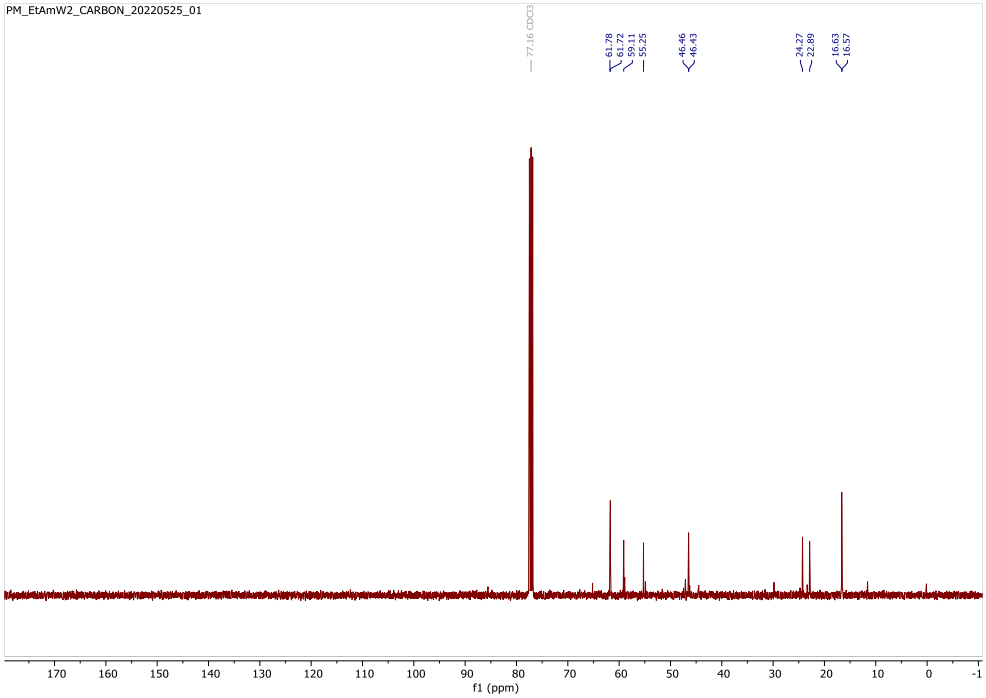


3f

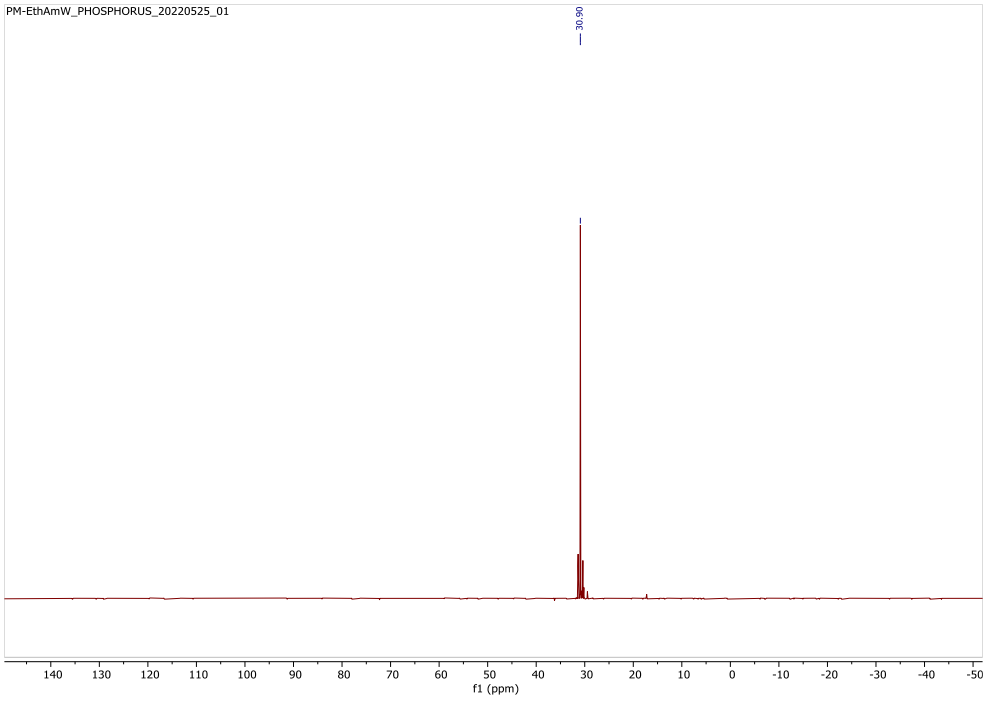
^{1}H NMR (400 MHz, $CDCl_3$)

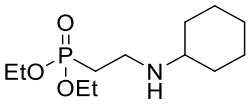


^{13}C NMR (101 MHz, $CDCl_3$)



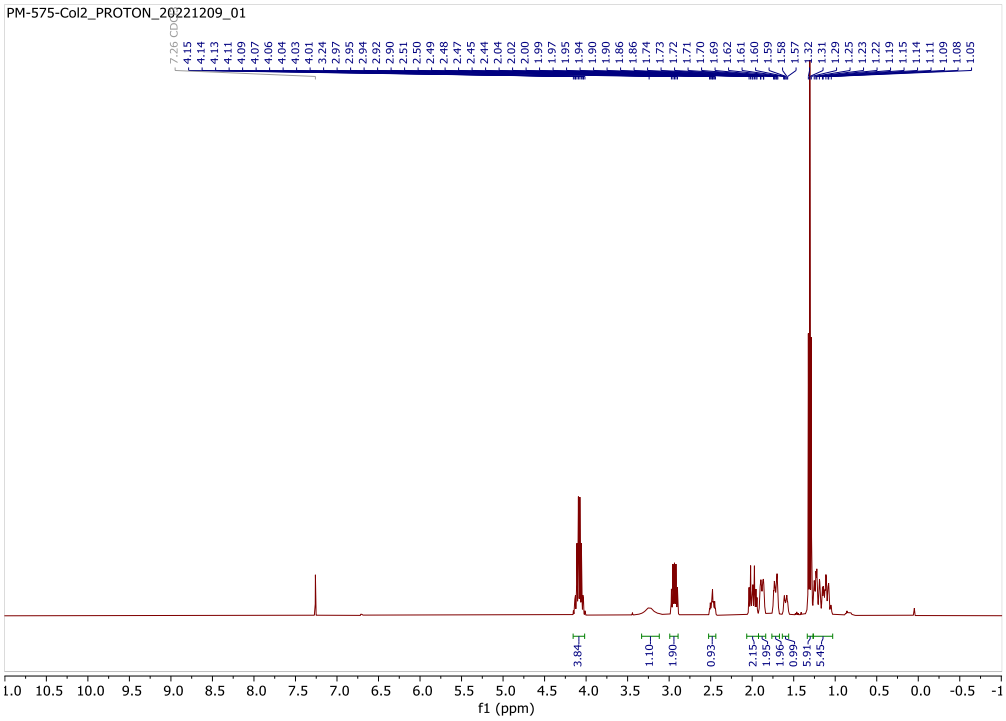
^{31}P NMR (162 MHz, $CDCl_3$)



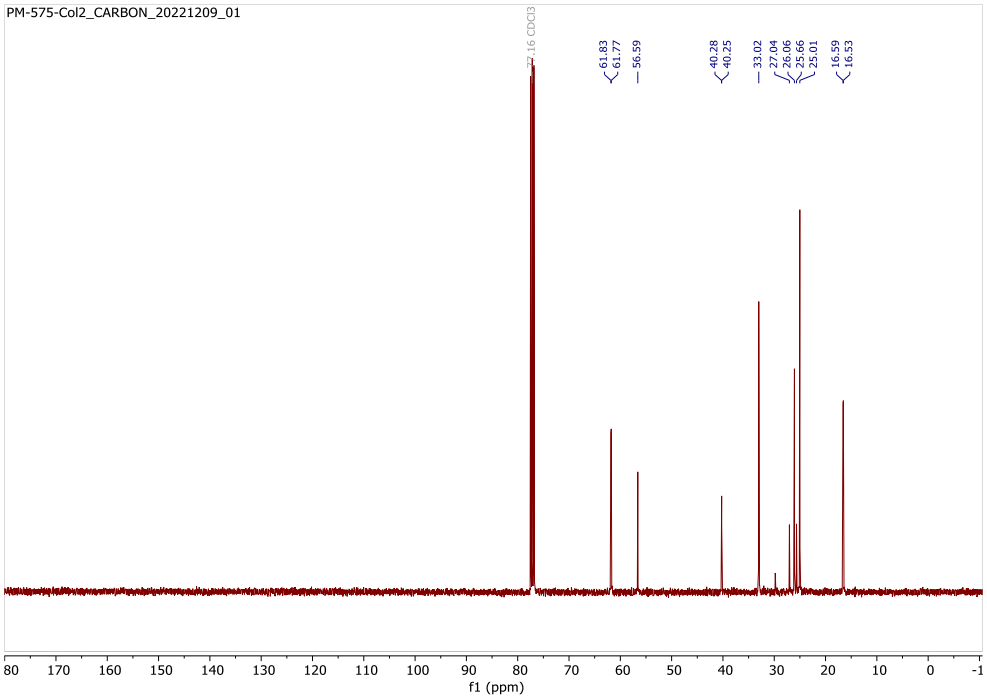


3g

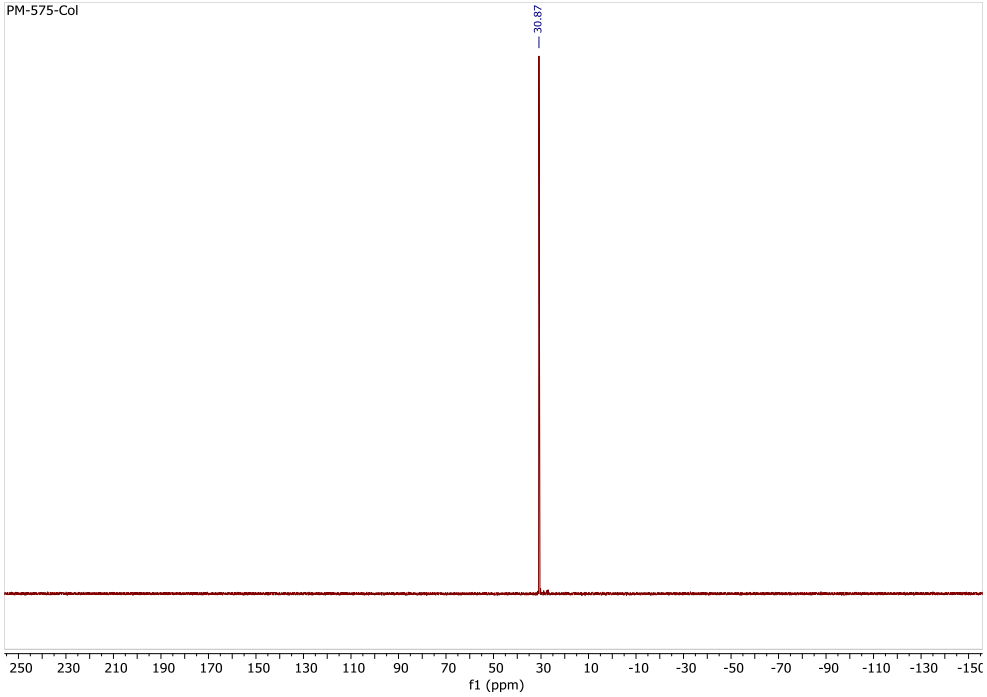
^{1}H NMR (400 MHz, $CDCl_3$)

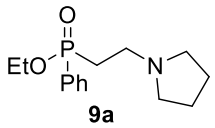


^{13}C-NMR (101 MHz, $CDCl_3$)



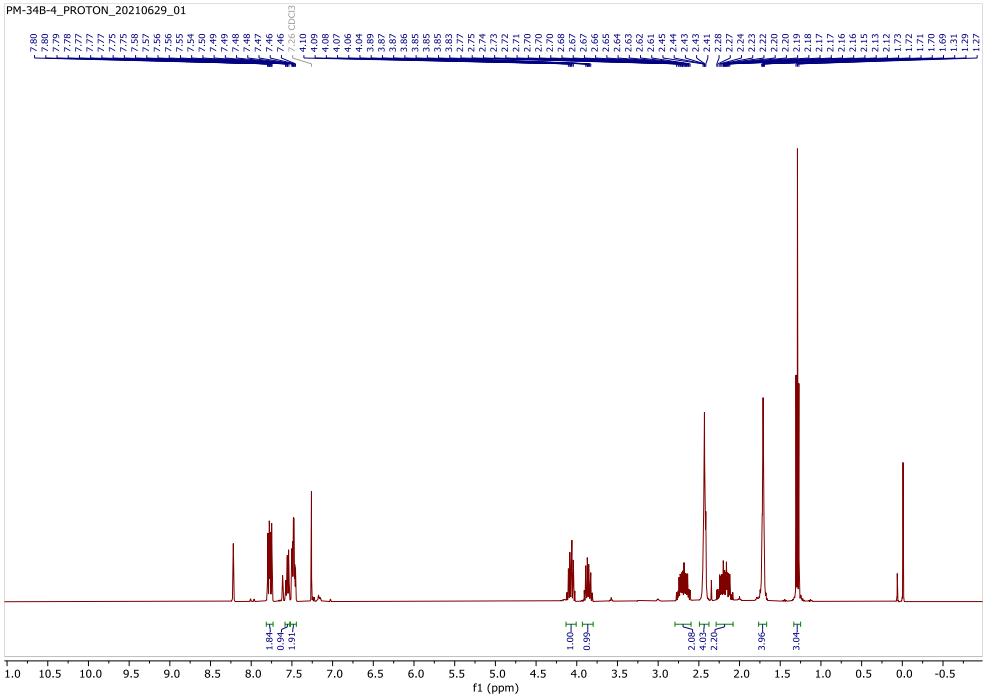
^{31}P-NMR (162 MHz, $CDCl_3$)



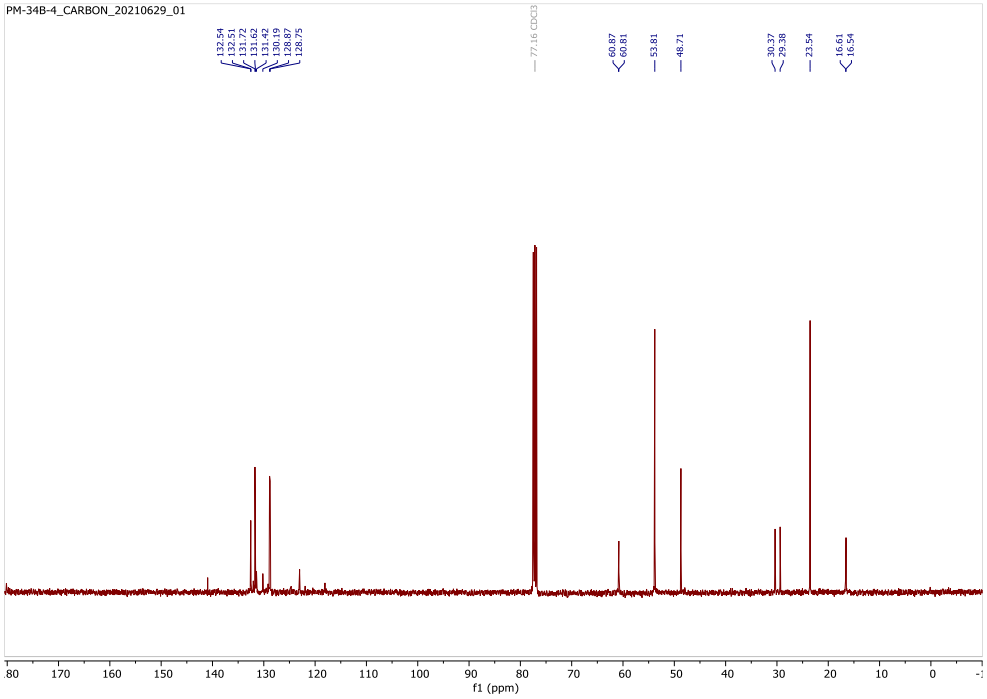


9a

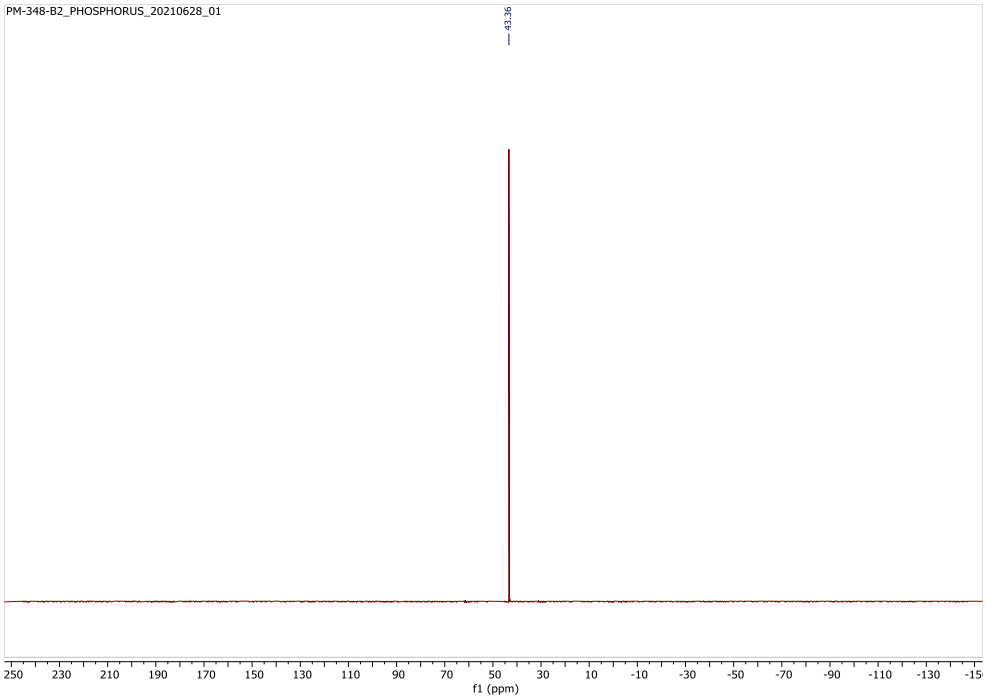
^{1}H NMR (400 MHz, $CDCl_3$)

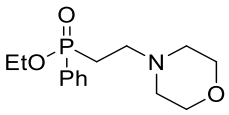


^{13}C-NMR (101 MHz, $CDCl_3$)



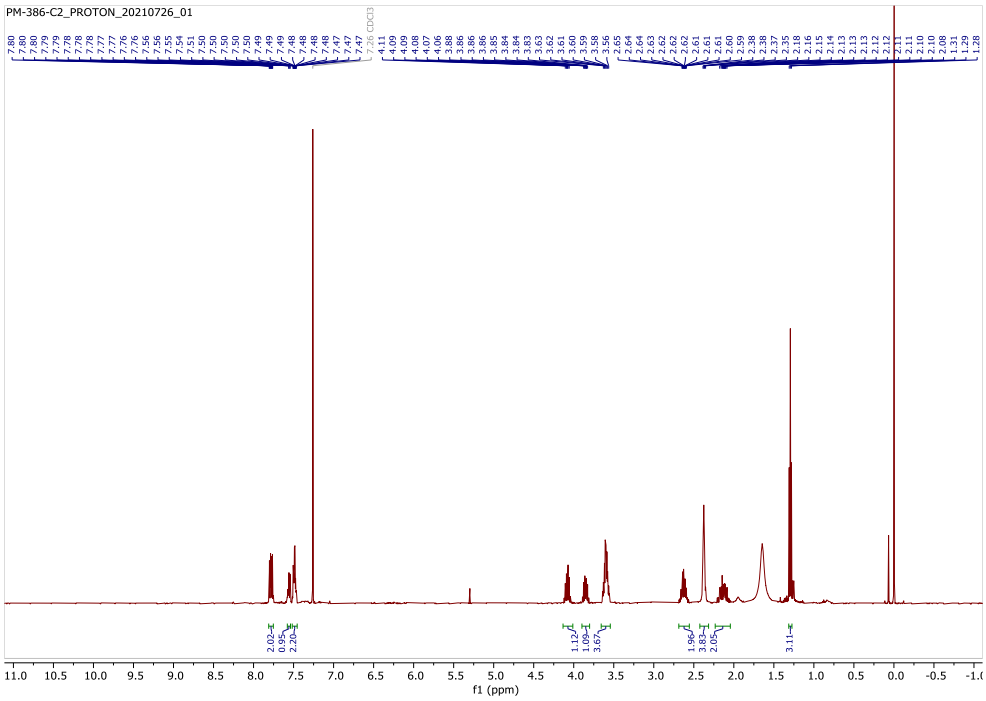
^{31}P-NMR (162 MHz, $CDCl_3$)



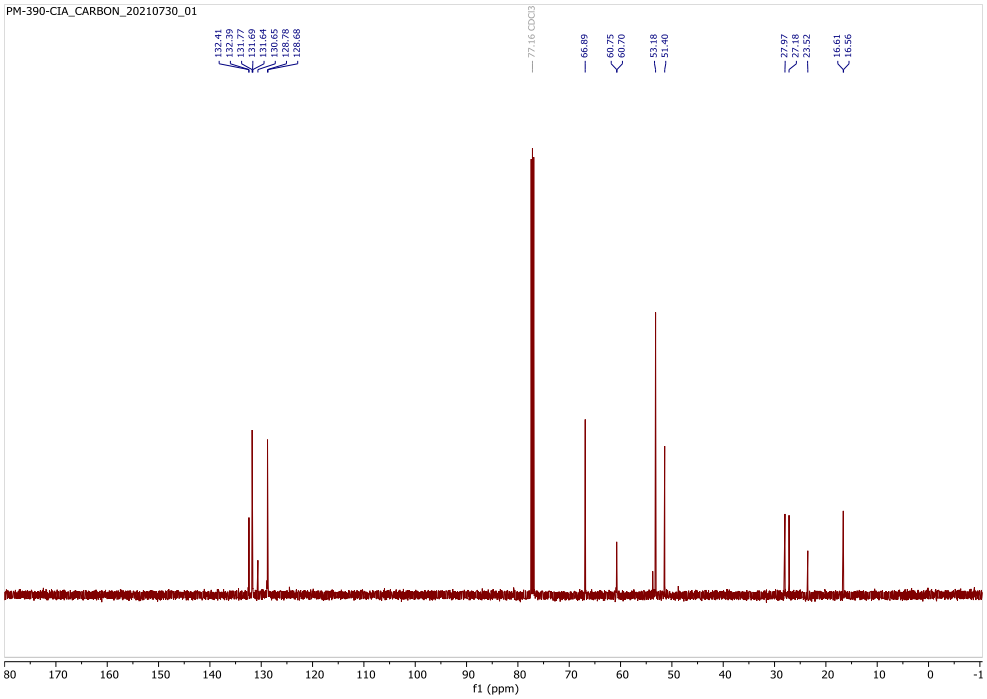


9b

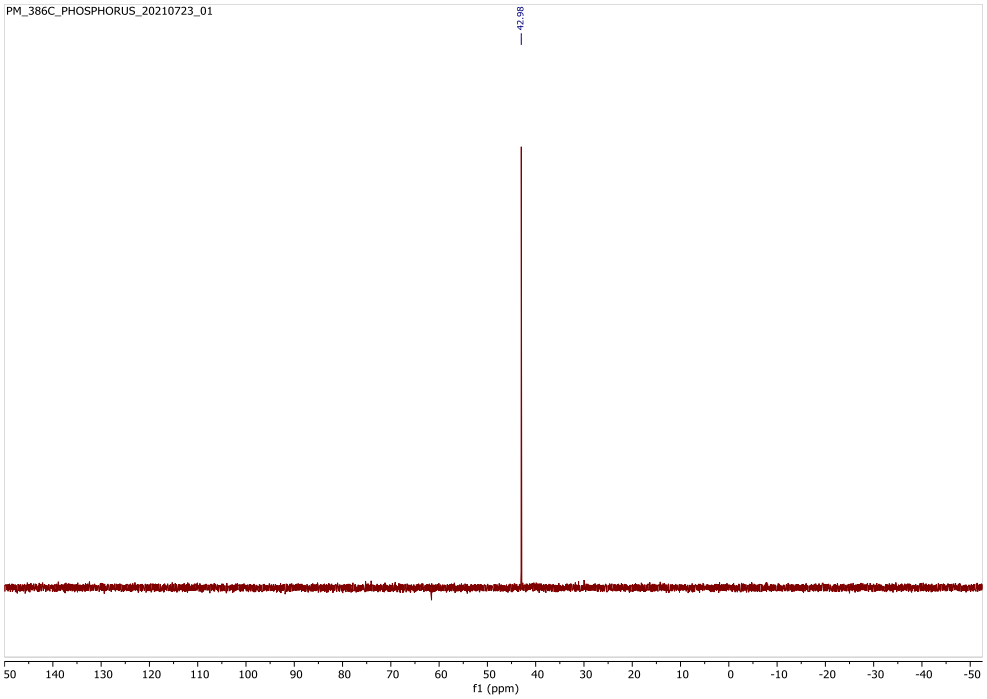
^{1}H-NMR (500 MHz, $CDCl_3$)

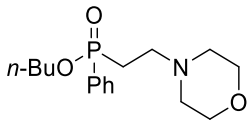


^{13}C-NMR (126 MHz, $CDCl_3$)



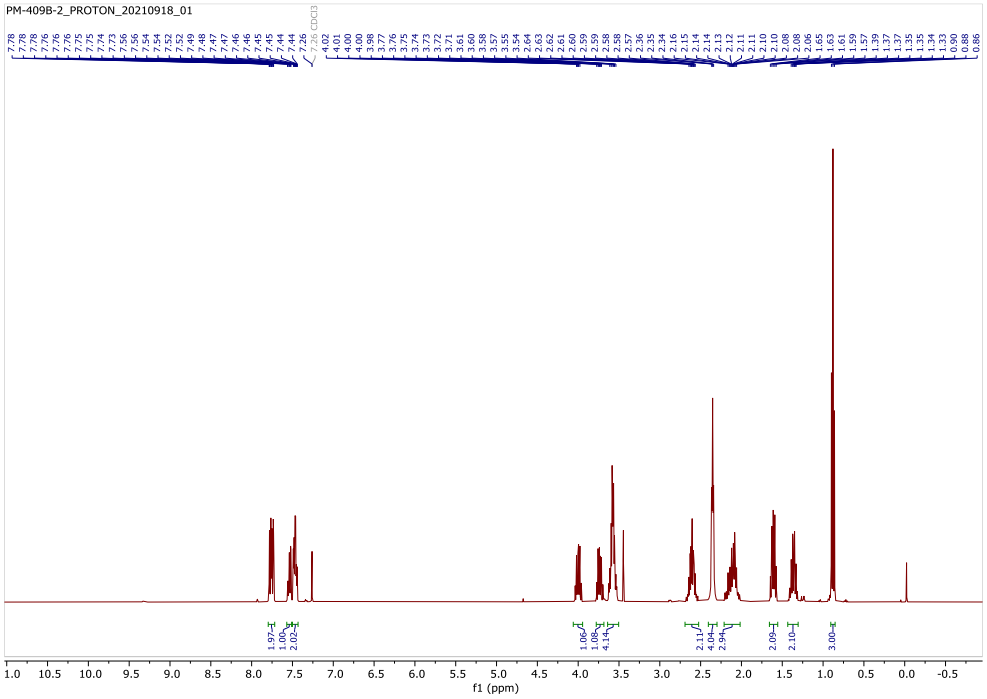
^{31}P-NMR (162 MHz, $CDCl_3$)



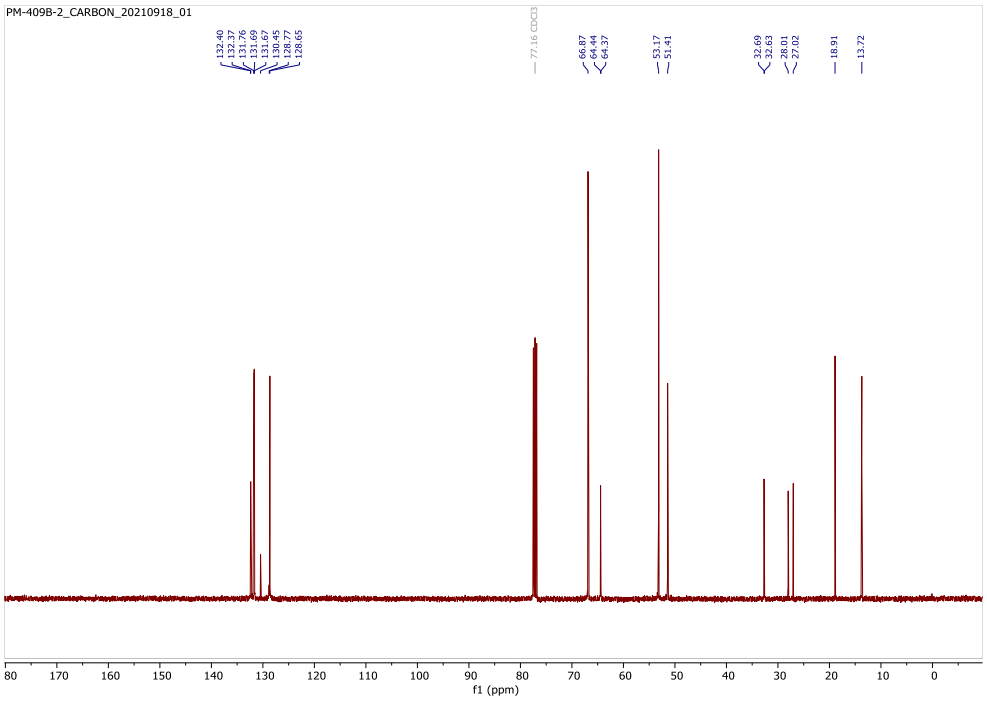


9c

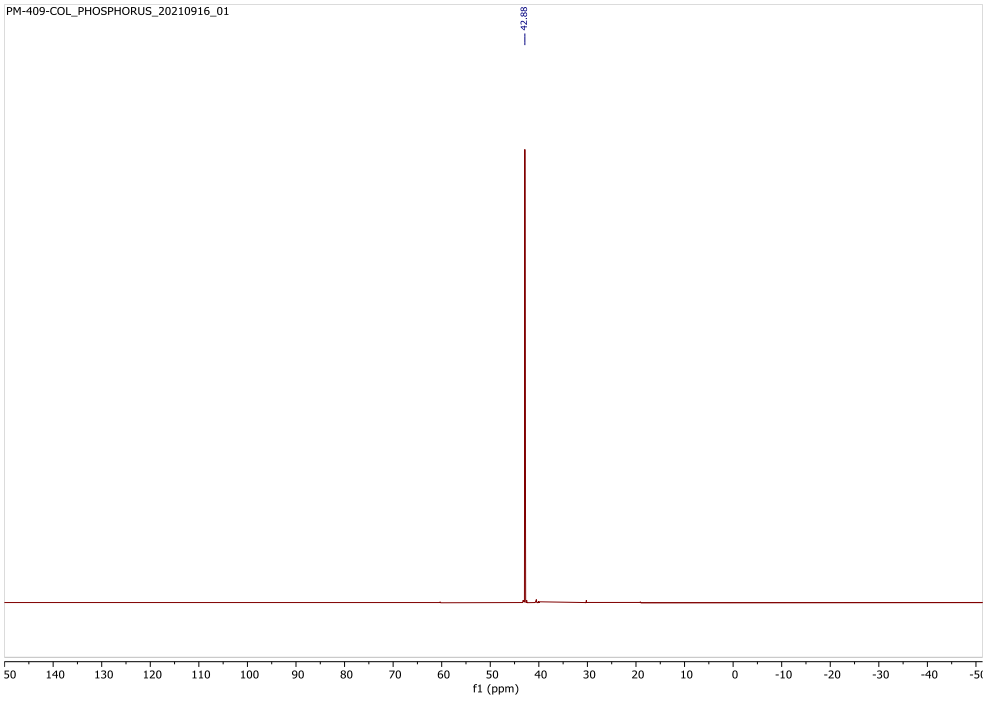
^{1}H NMR (400 MHz, $CDCl_3$)

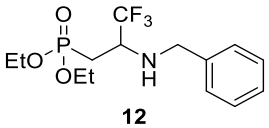


^{13}C NMR (101 MHz, $CDCl_3$)



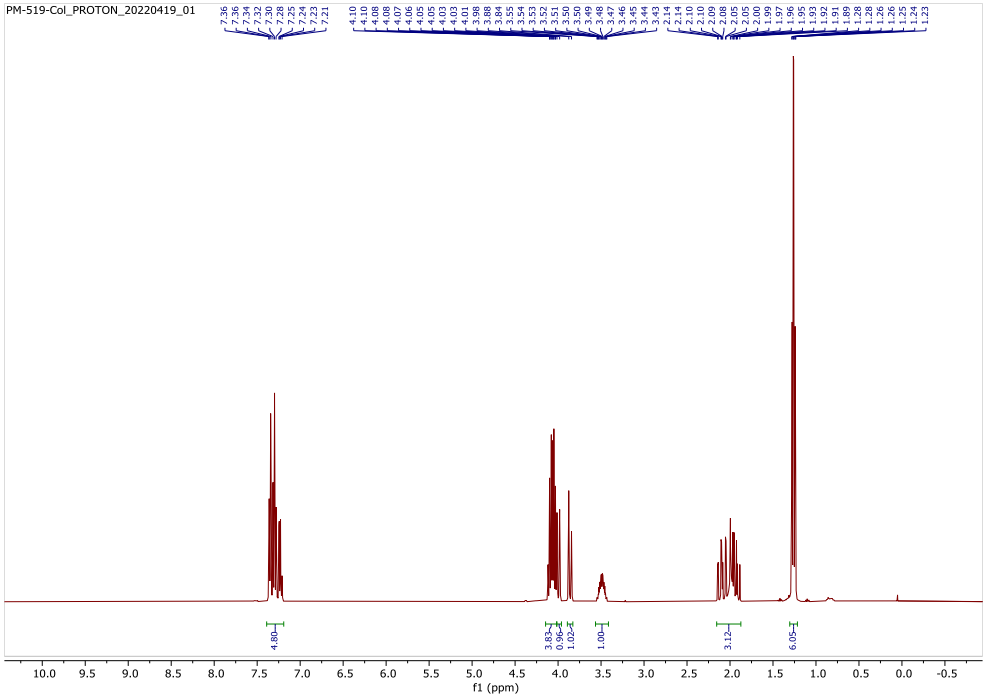
^{31}P NMR (162 MHz, $CDCl_3$)



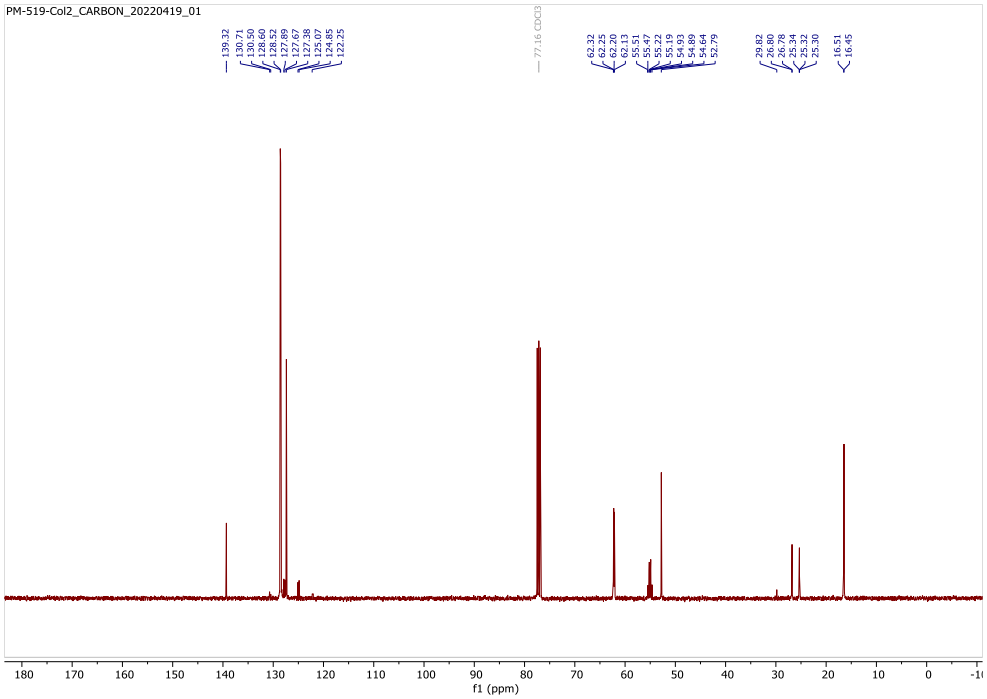


12

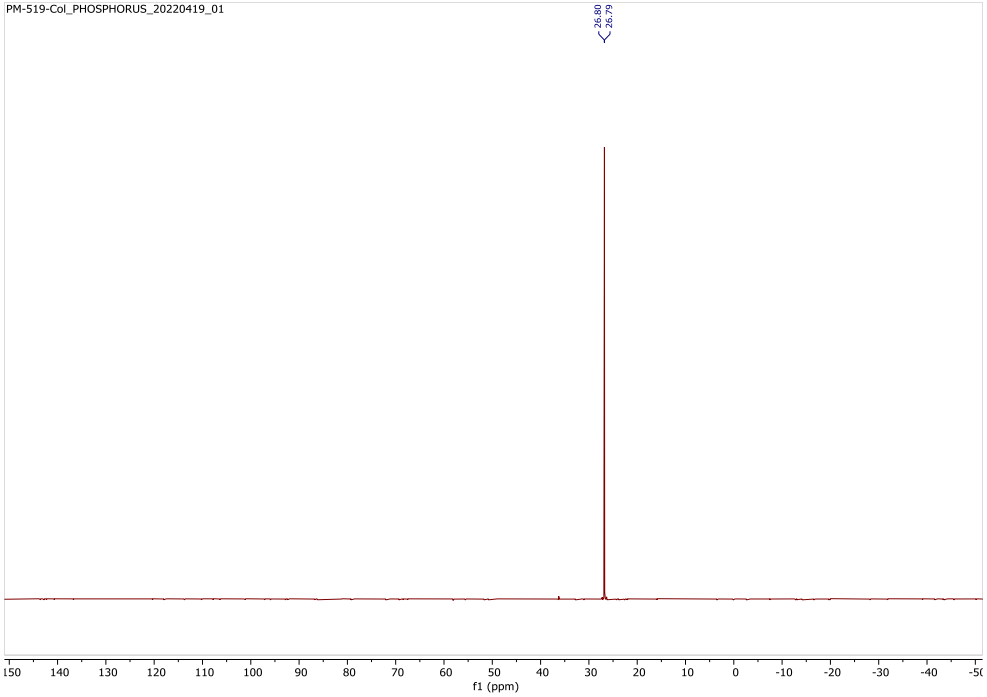
^{1}H NMR (400 MHz, $CDCl_3$)



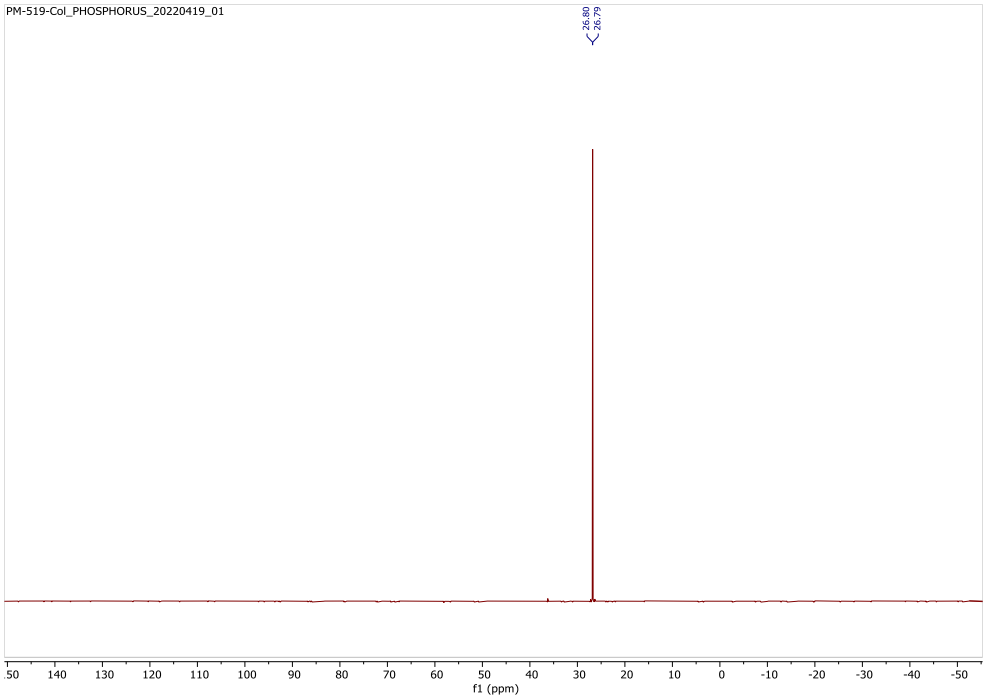
^{13}C NMR (126 MHz, $CDCl_3$)

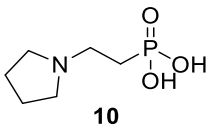


^{31}P NMR (162 MHz, $CDCl_3$)



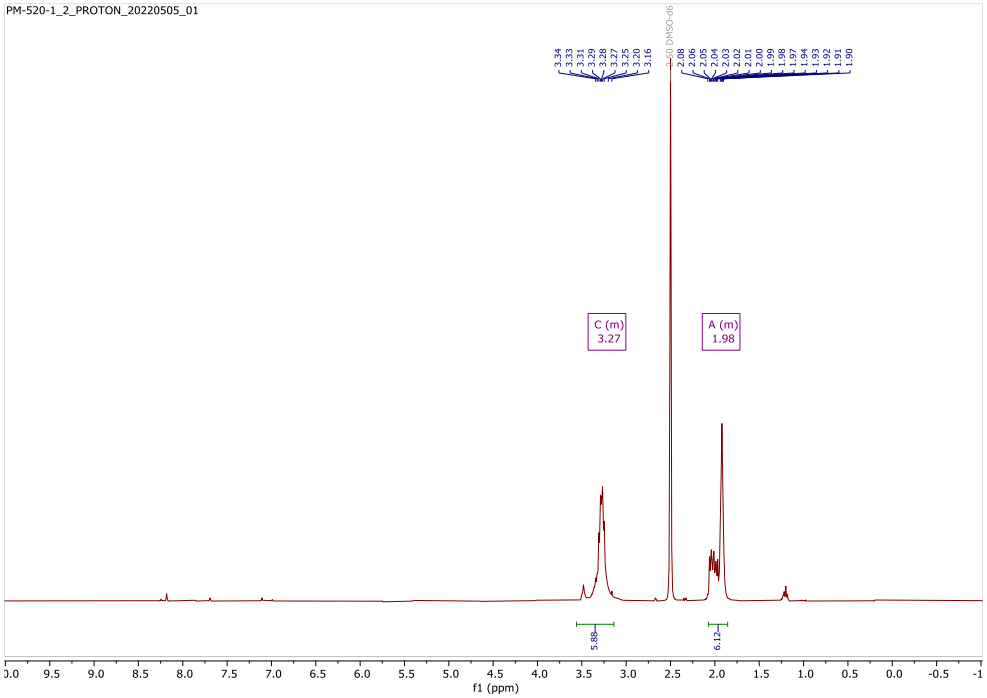
^{19}F NMR (376 MHz, $CDCl_3$)



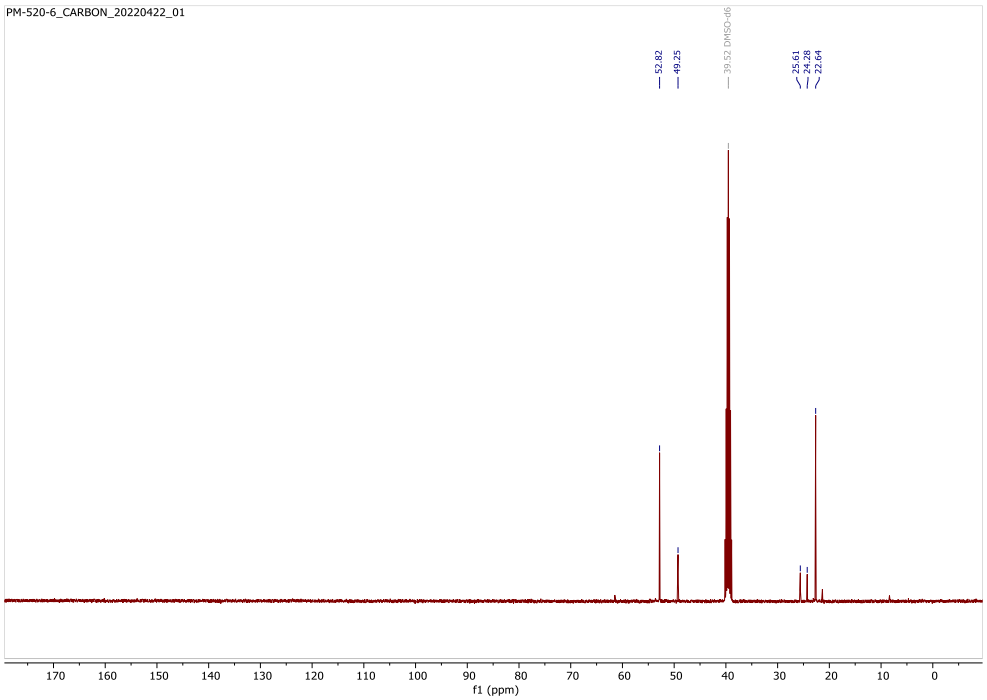


10

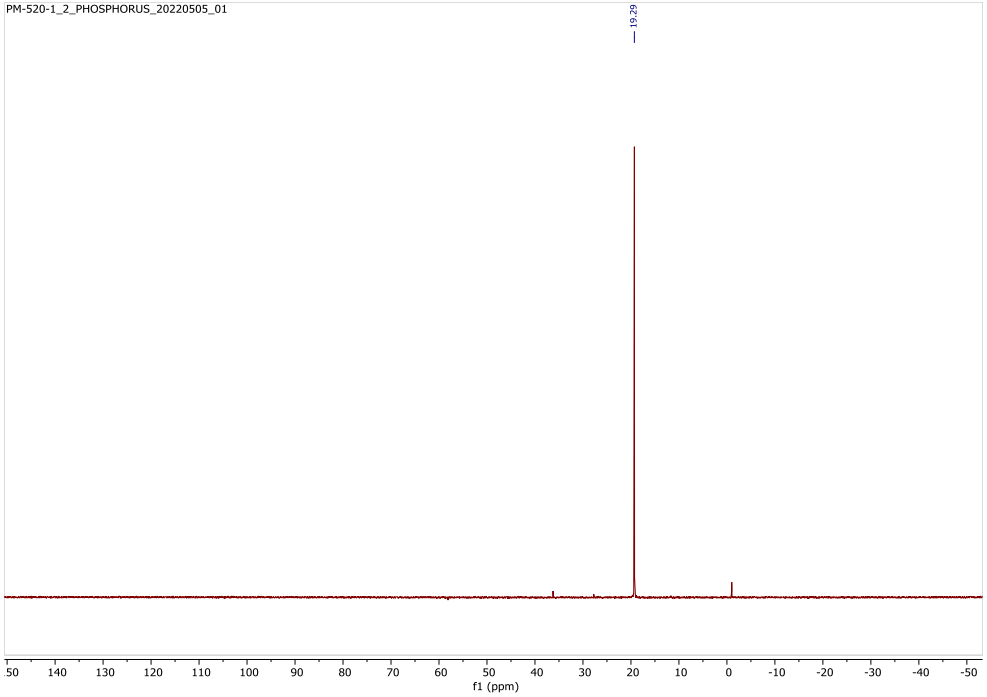
^{1}H NMR (400 MHz, DMSO-d_6)

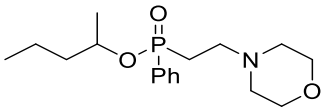


^{13}C NMR (101 MHz, DMSO-d_6)



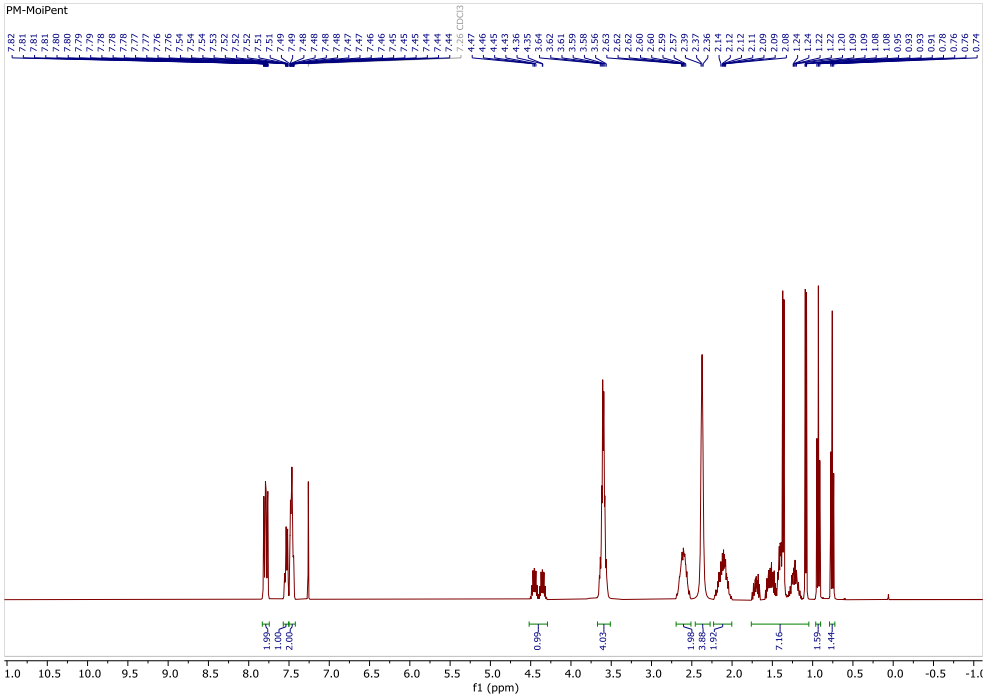
^{31}P NMR (162 MHz, DMSO-d_6)



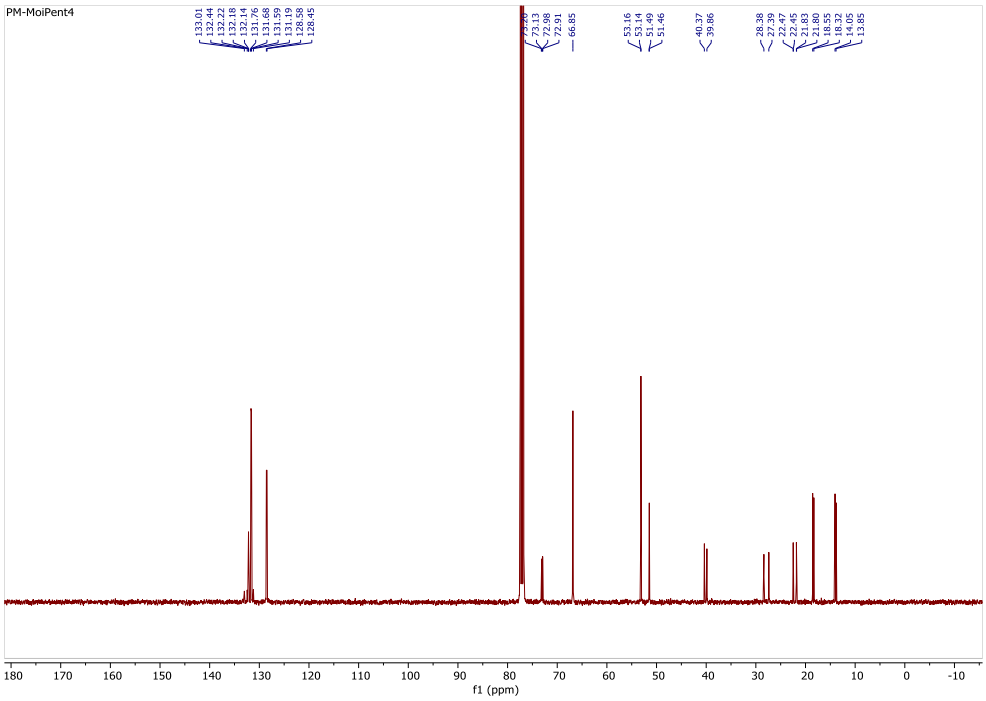


9d

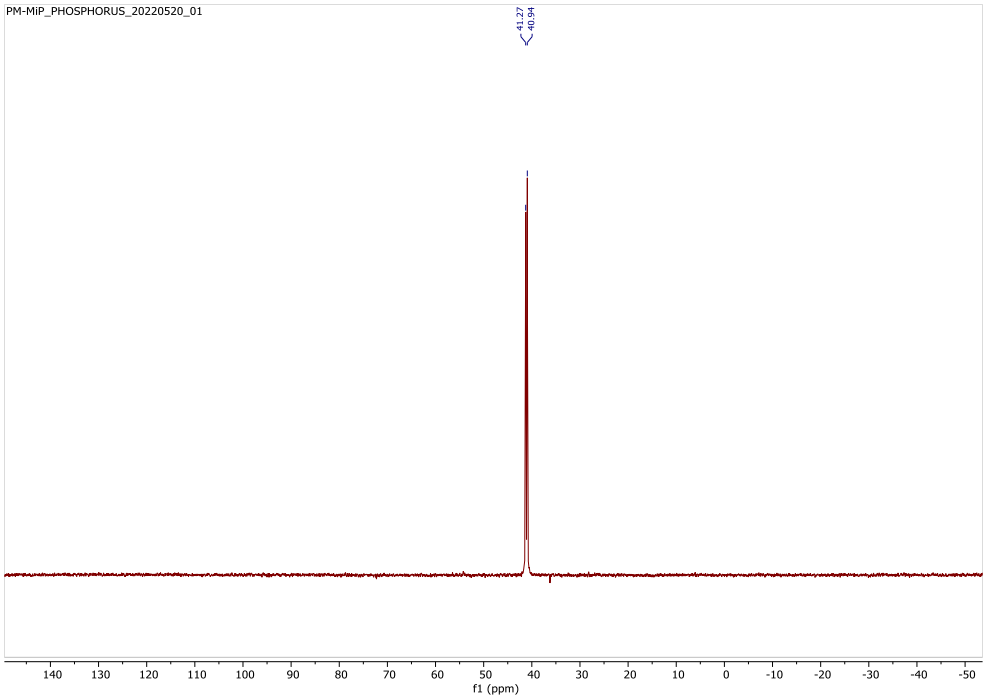
^{1}H-NMR (400 MHz, $CDCl_3$)

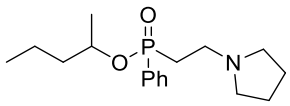


^{13}C-NMR (101 MHz, $CDCl_3$)



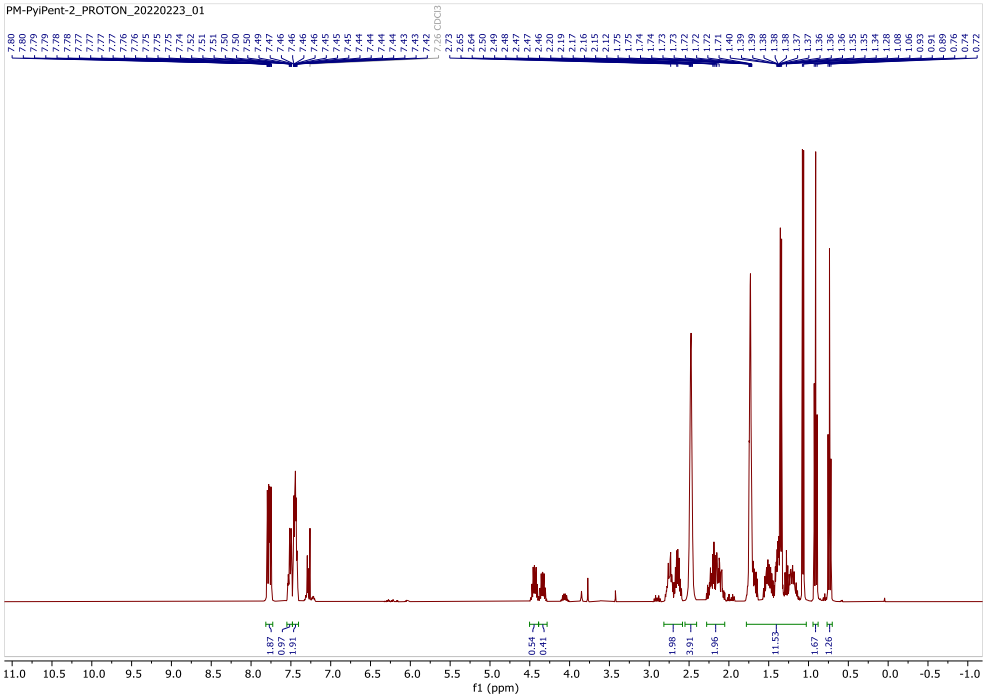
^{31}P NMR (162 MHz, $CDCl_3$)



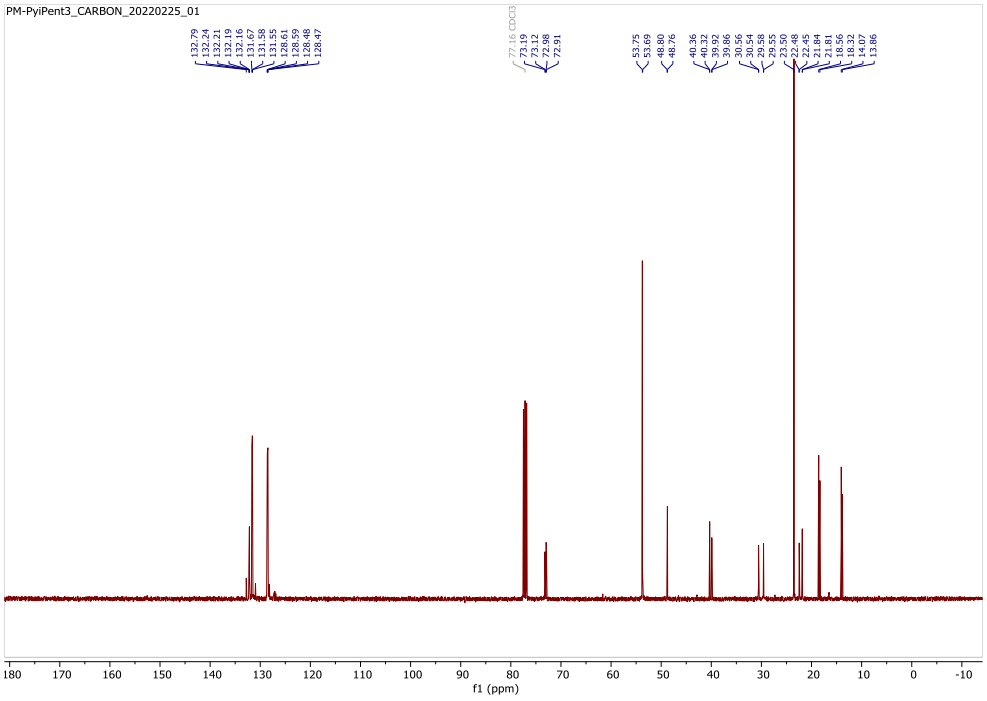


9e

^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (101 MHz, $CDCl_3$)



^{31}P-NMR (162 MHz, $CDCl_3$)