Supplementary Materials

Enantioselective hydrogen-bond-donor catalysis to access diverse stereogenic-at-P(V) compounds

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General Information

Methods:

All reactions were performed in standard, oven-dried glassware fitted capped with rubber septa under a N_2 atmosphere. Concentration of solutions was carried out under reduced pressure using house vacuum (40 torr) at 35 °C unless otherwise described. Concentrations refer to solution volumes at room temperature (~22 °C). High-vacuum was achieved using a vacuum pump at 400 mTorr. Flash column chromatography was performed using a Biotage Isolera One system. Thin layer chromatography was used for product detection using Silica Gel 60 F254 plates, with visualization effected via exposure to UV Light (λ_{ex} = 254 nm) or staining and heating with $KMnO_4$ or cerium ammonium molybdate.

Materials and Reagents:

Catalyst **1a** ((R)-N-[(1R,2R)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)cyclohexyl]-tert-butyl-sulfinamide ; CAS = 934762-68-2) and phenyl phosphonic dichloride **2a** (CAS = 824-72-6) were purchased from Sigma-Aldrich and used as received. Diisoamylamine (CAS = 544-00-3) and 4-methoxyphenyl phosphonic dichloride **4g** (CAS = 37632-18-1) were purchased from TCI America and used as received. All other reagents and solvents were purchased from commercial suppliers including Sigma-Aldrich, TCI, Alfa Aesar, Acros Organics, Matrix Scientific, Cambridge Isotope Laboratories, or Strem and used as received. Anhydrous solvents (diethyl ether, toluene, tetrahydrofuran (THF), dichloromethane (DCM), and dimethylformamide (DMF)) were dried using activated alumina columns. Deuterated solvents were purchased from Cambridge Isotope Laboratories.

Special Note:

Aryl phosphonic dichlorides (**2a-g**) are hydrolytically sensitive and undergo decomposition when exposed to air. These reagents should be stored under an anhydrous/inert atmosphere. Optimal results were achieved by using phosphonyl dichlorides immediately after preparation or freshly distilled under inert atmosphere. Similarly, aryl chlorophosphonamidate **3** and its analogues are susceptible to decomposition and/or racemization upon attempted purification. These intermediates are best used immediately via in situ addition of a nucleophile or via filtration and partial concentration according to the procedures reported herein. Alternatively, the aryl chlorophosphonamidate intermediates may be stored as crude mixtures at –78 °C.

Instrumentation:

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE NEO 400 or Bruker AVANCE NEO 400B spectrometer. Proton NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced using the NMR solvent ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Proton-decoupled ^{13}C NMR spectra are reported in ppm downfield from tetramethylsilane, and are referenced using the NMR solvent ($CDCl_3$: 77.16 ppm, C_6D_6: 128.06 ppm). Proton-decoupled ^{31}P NMR spectra are reported in ppm downfield from 85% H_3PO_4. ^{19}F NMR spectra are reported in ppm downfield from chlorotrifluoromethane. Splitting patterns for peaks on NMR spectra are represented as: (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, m = multiplet). Coupling constants are measured in Hertz (Hz). High-resolution Mass Spectrometry (HRMS) data were acquired by the Harvard FAS Division of Science Small Molecule Mass Spectrometry facility. Gas chromatography (GC) analysis was performed on an Agilent 7890A series GC system outfitted with a commercially available Cyclodex B (60 m) column. Chiral high-performance liquid chromatography (HPLC) analysis

was performed using an Agilent 1200 series quaternary HPLC system with commercially available CHIRALCEL and CHIRALPAK analytical columns (4.6 x 250 mm). Optical rotations ([α]) were obtained using a Jasco DIP 370 digital polarimeter at 589 nm using sodium D line at 22 °C in a 1 mL cell with a 0.5 dm path length.

Abbreviations Used:

Ar = aryl, Bn = benzyl, c= concentration, Bz = Benzoyl, Cbz = benzyloxycarbonyl, DCM = dichloromethane, DMF = dimethylformamide, d.r. = diastereomer ratio, ds = diastereospecificity (i.e. stereospecificity for reaction of a chiral compound to another chiral compound), ee = enantiomeric excess, es = enantiospecificity, Et = ethyl, equiv = equivalents, Et_2O = diethyl ether, EtOAc = ethyl acetate, EtOH = ethanol, g = grams, h = hours, HPLC = high-performance liquid chromatography, HRMS = high-resolution mass spectrometry, mg = milligrams, Hz = Hertz, ^{i}Am = isoamyl, ^{i}Bu = isobutyl, ^{i}Pr = ispropyl, iPrOH = isopropyl alcohol, MeOH = methanol, NaHMDS = sodium hexamethyldisilazide, Me = methyl, min = minutes, m/z = mass to charge ratio, ^{n}Bu = *n*-butyl, NMR = nuclear magnetic resonance, Ph = phenyl, ppm = parts per millon, *p*-TsOH = para-toluenesulfonic acid, TBME = *tert*-butyl methyl ether, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = para-tolylsulfonyl.

General procedures for catalytic, enantioselective nucleophilic substitution reaction and sequential enantiospecific substitution reactions:

General Procedure A describes the procedure for the enantioselective substitution by amine followed by direct substitution by a second nucleophile *in situ*.

General Procedure B describes the procedure for the enantioselective substitution by amine followed by filtration and addition by a second nucleophile in a separate step.

General Procedure C describes a procedure for the enantioselective substitution by amine followed by direct substitution by methoxide using a prepared sodium methoxide solution.

General Procedure D describes a procedure for the synthesis of racemic amine substitution products.

General Procedure E describes a procedure for the displacement of the diisoamylamino group with alcohols.

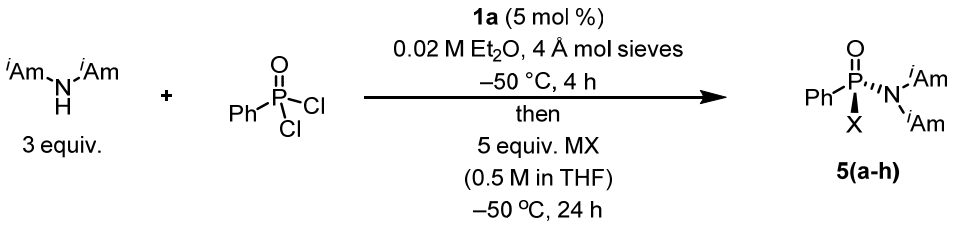
General Procedure F describes a procedure for the phosphonylation of alcohols with compound **6d**.

General Procedure G describes a procedure for the addition of Grignard reagents to compound **6b**.

General Procedure H describes a procedure for the synthesis of non-commercial phosphonyl dichlorides.

General Procedure I describes the procedure used for preparation of 4 Å molecular sieves.

General Procedure A



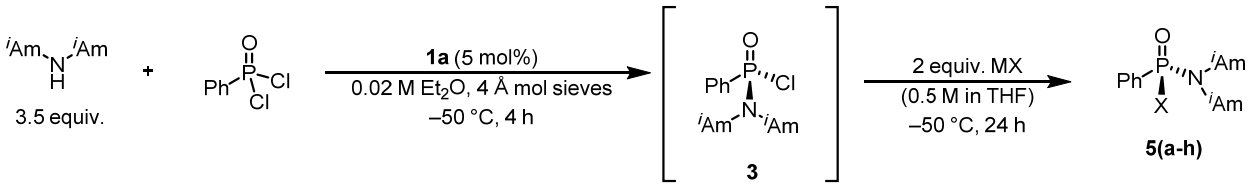
Note: The success of this reaction relies on vigorous stirring and use of properly activated molecular sieves (see* **General Procedure I*).*

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol), 4 Å mol sieves (200 mg), and diisoamylamine (140 μL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. Phenyl phosphonic dichloride (28 μL, 0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 4 to 24 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with 120 mg of sodium hydride (3 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and the resulting mixture was subjected to stirring at room temperature for 1 minute. The nucleophile (5 equiv., 1 mmol) dissolved in THF (0.5 mL) was then added dropwise over 2 min. via a syringe to the stirring sodium hydride mixture, and stirring was continued at room temperature for 30 minutes after addition. The resultant mixture was then added in a single portion directly to the catalytic reaction mixture generated as described above at –50 °C. The resultant mixture was then subjected to stirring for 24 hours at –50 °C. The mixture was then concentrated under reduced pressure and

purified by flash column chromatography on silica gel.

General Procedure B

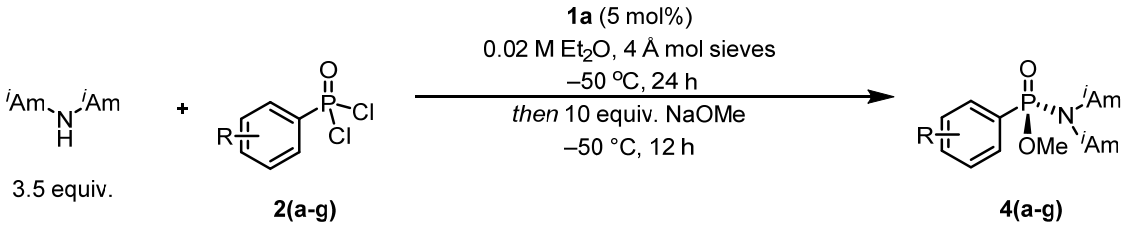


Note: The success of this reaction relies on vigorous stirring and use of properly activated molecular sieves (see* **General Procedure I*).*

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol, 0.05 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. A solution of phenyl phoshonic dichloride (28 µL, 0.2 mmol, 1 equiv.) in toluene (0.5 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 4 hours. The mixture was filtered at room temperature through ~10 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained (**Note: this product undergoes racemization when concentrated above room temperature**). The crude toluene solution of product **3** was then diluted with THF (1.5 mL) and transferred to an oven-dried 2-dram vial equipped with a magnetic stir bar and a septum cap. The vial was sealed with parafilm and put under N_2 atmosphere and allowed to stir at –50 °C for 20 minutes.

A separate oven-dried 2-dram vial equipped with a magnetic stir bar was charged with sodium hydride (48 mg,1.2 mmol, 6 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. THF (0.5 mL) was then added, and the resulting mixture was subjected to stirring at room temperature for ~1 minute. The nucleophile (2 equiv., 0.4 mmol) dissolved in THF (0.1 mL) was then added dropwise via a syringe through the septum to the stirring mixture over a 2-minute period. The mixture was then allowed to stir at room temperature for 30 minutes to ensure full deprotonation of the nucleophile. The resultant mixture was then added directly to the stirred solution of chlorophosphonamidate produced as described above at –50 °C and stirring was continued at –50 °C for 24 hours. The mixture was then concentrated under reduced pressure and purified by flash column chromatography on silica gel.

General Procedure C



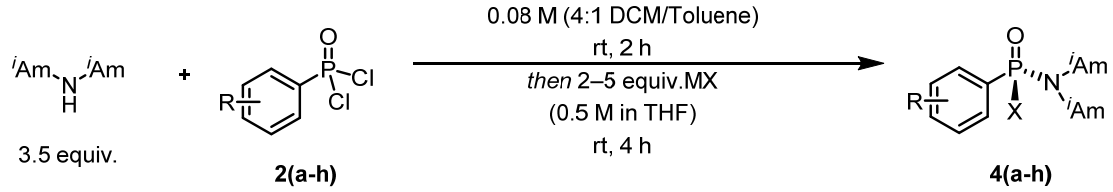
Note: The success of this reaction relies on vigorous stirring and use of properly activated molecular sieves (see* **General Procedure I*).*

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol, 0.05 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. The aryl phosphonic

dichloride (0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 24 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and the mixture was allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum over a 2-minute period to the stirring mixture, and stirring was continued at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly in a single portion to the solution of chlorophosphonamidate produced as described immediately above at –50 °C. The resulting reaction mixture was then subjected to stirring for 12 hours at –50 °C, and then concentrated under reduced pressure and purified by flash column chromatography on silica gel.

General Procedure for Racemic Reference Samples



An oven-dried 20 mL vial equipped with a magnetic stir bar was charged with diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with DCM (2 mL), followed by 0.2 mmol of aryl phosphonic dichloride (**2a-g**) dissolved in toluene (0.5 mL), and the reaction mixture was subjected to stirring at room temperature for 2 hours, or until reaction completion. The reaction was then quenched according to one of the following procedures:

For racemic standards of **4a**–**g**:

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with 80 mg of sodium hydride (2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum to the stirring mixture over a 2-minute period, and the solution was subjected to stirring at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly in a single portion to the solution of chlorophosphonamidate produced as described immediately above. The reaction mixture was then subjected to stirring for 4 hours at room temperature, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

For racemic standards of **5a**–**e**:

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (120 mg, 3 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and allowed to stir at room temperature for 1 minute. The nucleophile (5 equiv., 1 mmol) dissolved in THF (0.5 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature for 30 minutes. The resultant mixture was then added directly as a single portion directly to the solution of chlorophosphonamidate **3** stirring in DCM. The resultant mixture was then subjected to stirring for 4 hours at room temperature. Afterwards, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

For racemic standard of **5f**:

Upon reaction completion, the mixture was filtered through ~10 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained. The crude phosphonamidate in toluene (**3**) was then dissolved in THF (2 mL) and transferred to an oven-dried 2-dram vial equipped with a magnetic stir bar and capped with a septum. The vial was sealed with parafilm and put under a N_2 atmosphere and allowed to stir at room temperature for ~1 minute.

A separate oven-dried 2-dram vial equipped with a magnetic stir bar was charged with sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. THF (0.5 mL) was then added, and the mixture was allowed to stir at room temperature for ~1 minute. Benzyl carbamate (60 mg, 0.4 mmol, 2 equiv.) dissolved in THF (0.2 mL) was then added dropwise via a syringe through the septum to the stirring mixture over a 2-minute period. The mixture was then allowed to stir at room temperature for 30 minutes to ensure full deprotonation of the nucleophile. The resultant mixture was then added directly in a single portion to the solution of chlorophosphonamidate produced as described immediately above. The resultant mixture was subjected to stirring at room temperature for 4 hours. Upon completion, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

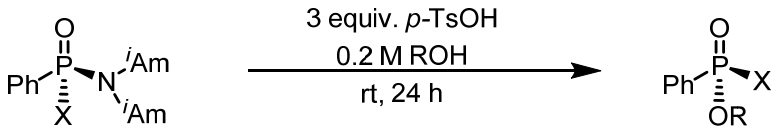
For racemic standards of **5g–h**:

Upon reaction completion, the mixture was filtered through ~10 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature

of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained. The crude product in toluene (**3**) was then dissolved in THF (2 mL) and transferred to an oven-dried 2-dram vial equipped with a magnetic stir bar and capped with a septum. The vial was sealed with parafilm and put under N_2 atmosphere and allowed to stir at room temperature for ~1 minute.

The Grignard reagent (5 equiv., 0.4 mmol) was then added in a single portion to the solution of chlorophosphonamidate **3** stirring in THF. The reaction was subsequently subjected to stirring at room temperature for 4 hours. Upon completion, the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

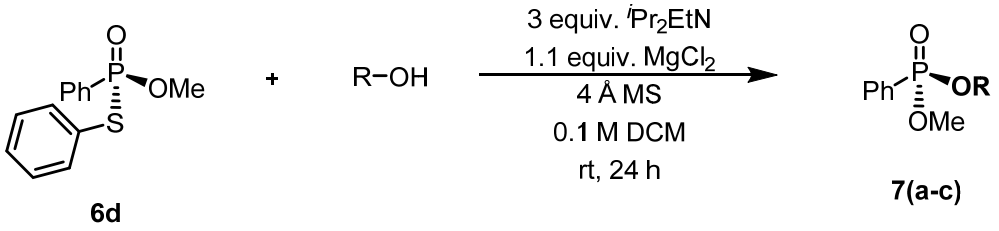
General Procedure E



6(a-i)

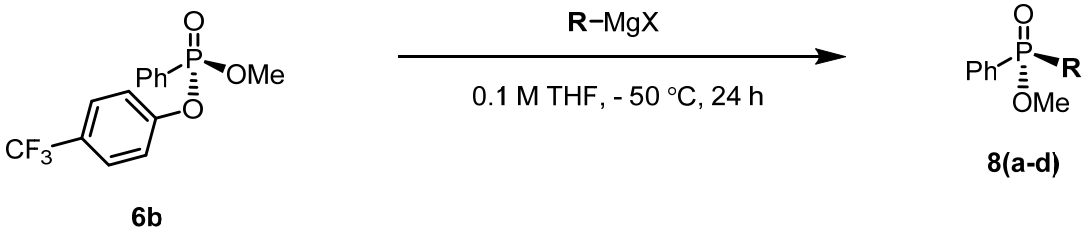
An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with the substrate (**5a-h**). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. A 0.6 M solution of *para*-tolylsulfonic acid monohydrate (3 equiv.) in the corresponding alcohol was then added through the septum, and the reaction was allowed to stir at room temperature for 24 hours. *Do not concentrate*. After 24 hours, the methanol solution was loaded directly onto a silica gel column that had been packed and equilibrated with solvent and purified via flash column chromatography.

General Procedure F



An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with $MgCl_2$ (10 mg, 0.11 mmol, 1.1 equiv.), 4 Å mol sieves (50 mg), and the alcohol to be phosphonylated. The vial was capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with DCM (0.7 mL) followed by *N*,*N*-diisopropylethylamine (52 µL, 0.3 mmol, 3 equiv.). The solution was allowed to stir at room temperature for ~1 minute. Then phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) dissolved in DCM (0.3 mL) was added in one portion through the septum cap. The reaction was then allowed to stir at room temperature for 24 hours. *Do not concentrate*. After 24 hours, the solution was loaded directly onto a silica gel column that had been packed and equilibrated with solvent and purified via flash column chromatography.

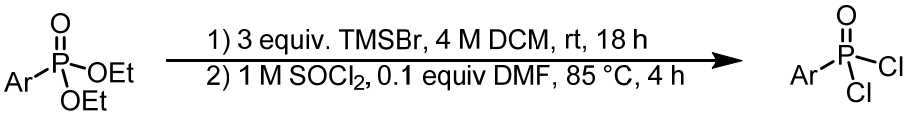
General Procedure G



An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with phosphonate **6b** (1 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (0.1 M) and allowed to stir at room temperature for ~1 minute. The solution was then cooled and subjected to stirring at –50 °C for 20 minutes. Next, the Grignard reagent was added through the septum cap, and the reaction mixture was then

allowed to stir at –50 °C for 24 hours. After 24 hours had elapsed, isopropanol (50 μL) was added to the solution at –50 °C to quench any remaining Grignard reagent. *Do not concentrate*. The resultant solution was loaded directly onto a silica gel column that had been packed and equilibrated with solvent and purified via flash column chromatography.

General Procedure H:



Conditions were adapted from a reported procedure for synthesis of phosphonyl dichlorides *(49)*. An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with the aryl phosphonate ester (0.4 mmol, 1 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with DCM (0.1 mL) and allowed to stir at room temperature for ~1 minute. Bromotrimethylsilane (158 μL, 1.2 mmol, 3 equiv.) was then added to the stirring solution via syringe through the septum. The resulting solution was then subjected to stirring 18 hours at room temperature. After subjection to stirring for 18 hours, the solution was concentrated under reduced pressure in the same vial, then subjected to high vacuum to remove the remaining bromotrimethylsilane and solvent. The vial was then capped with a new septum, sealed with electrical tape, and evacuated/backfilled three times with N_2. $SOCl_2$ (0.4 mL) and DMF (3 μL, 0.04 mmol, 0.1 equiv.) were then added to the vial via a syringe through the septum. The top of the vial was then sealed tightly with electrical tape. The solution was then subjected to stirring at 85 °C for 4 hours. Afterwards, the solution was cooled to room temperature. Without exposing the mixture to the atmosphere, the $SOCl_2$, HCl, and other volatiles were removed via a syringe needle inserted through the septum cap positioned above the

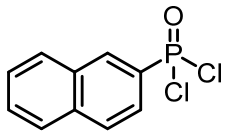
solution and attached to a high-vacuum line. The resulting crude phosphonyl dichloride was used immediately without further purification.

General Procedure I:

Powdered 4 Å molecular sieves (50 grams, 325 mesh, activated; CAS = 70955-01-0) were added to a 500 mL round bottom flask equipped with a large magnetic stir bar. The flask size was chosen such that the sieves filled no more than ~1/4 of the volume of the flask. The flask was then fitted with an adapter with an inlet and placed under vacuum. The flask was then submerged in an oil bath, insulated with foil, and heated to 220 °C over a magnetic stir plate. The flask was maintained under constant vacuum for 5 days while the sieves were subjected to stirring continuously at 220 °C. Afterwards, the dried molecular sieves were stored in a sealed container under N_2.

Scope of catalytic enantioselective substitution of phosphonyl dichlorides by diisoamylamine

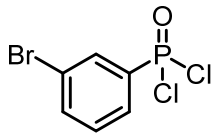
Naphthalen-2-ylphosphonic dichloride (2b)



2b

Following **General Procedure H**, phosphonic dichloride **2b** was prepared from diethyl naphthalen-2-ylphosphonate (106 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2b** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or detectable byproducts. ^{1}H NMR (400 MHz, C_6D_6) δ 8.39 (d, *J* = 18.5 Hz, 1H), 7.55 (ddd, *J* = 15.4, 8.6, 1.7 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.02 (m, 2H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 135.34 (d, *J* = 3.5 Hz), 132.99 (d, *J* = 13.1 Hz), 132.06 (d, *J* = 59.4 Hz), 131.19 (d, *J* = 75.2 Hz), 129.41, 129.34, 129.32, 129.16, 127.38 (d, *J* = 1.8 Hz), 123.94 (d, *J* = 14.9 Hz) ; ^{31}P NMR (162 MHz, C_6D_6) δ 33.31.

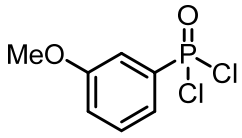
(3-bromophenyl)phosphonic dichloride (2c)



2c

Following **General Procedure H**, phosphonic dichloride **2c** was prepared from diethyl (3-bromophenyl)phosphonate (118 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2c** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.89 (dt, *J* = 18.0, 1.7 Hz, 1H), 7.41 (dd, *J* = 17.3, 7.6 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.56 (q, *J* = 7.6 Hz, 1H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 137.03 (d, *J* = 3.7 Hz), 136.52 (d, *J* = 153.5 Hz), 132.58 (d, *J* = 14.9 Hz), 130.44 (d, *J* = 19.6 Hz), 128.51 (d, *J* = 13.0 Hz), 123.06 (d, *J* = 24.0 Hz); ^{31}P NMR (162 MHz, C_6D_6) δ 30.18.

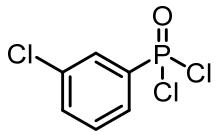
(3-methoxyphenyl)phosphonic dichloride (2d)



2d

Following **General Procedure H**, phosphonic dichloride **2d** was prepared from diethyl (3-methoxyphenyl)phosphonate (98 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2d** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.39 – 7.24 (m, 2H), 6.85 (q, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 3.10 (s, 3H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 159.61 (d, *J* = 23.2 Hz), 135.81 (d, *J* = 153.2 Hz), 130.19 (d, *J* = 22.1 Hz), 122.28 (d, *J* = 13.4 Hz), 120.75 (d, *J* = 4.0 Hz), 114.39 (d, *J* = 15.6 Hz), 54.71 ; ^{31}P NMR (162 MHz, C_6D_6) δ 33.57.

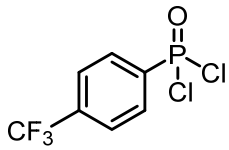
(3-chlorophenyl)phosphonic dichloride (2e)



2e

Following **General Procedure H**, phosphonic dichloride **2e** was prepared from diethyl (3-chlorophenyl)phosphonate (100 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2e** by ^{1}H and ^{31}P, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.71 (dt, *J* = 18.4, 1.8 Hz, 1H), 7.36 (ddt, *J* = 17.3, 7.7, 1.3 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.60 (q, *J* = 7.7 Hz, 1H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 136.33 (d, *J* = 154.6 Hz), 135.14 (d, *J* = 24.8 Hz), 134.05 (d, *J* = 3.7 Hz), 130.23 (d, *J* = 20.0 Hz), 129.78 (d, *J* = 15.2 Hz), 128.10 (d, *J* = 12.7 Hz) ; ^{31}P NMR (162 MHz, C_6D_6) δ 30.53.

(4-(trifluoromethyl)phenyl)phosphonic dichloride (2f)

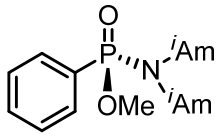


2f

Following **General Procedure H**, phosphonic dichloride **2f** was prepared from diethyl (4-(trifluoromethyl)phenyl)phosphonate (113 mg, 0.4 mmol) and used directly without further purification in the catalytic reaction. Analysis of phosphonic dichloride **2f** by ^{1}H and ^{31}P, ^{19}F, and ^{13}C NMR confirmed clean conversion with no remaining starting material or significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (dd, *J* = 17.4, 8.0 Hz, 2H), 7.03 (dd, *J* =

8.2, 5.4 Hz, 2H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 137.87 (d, *J* = 154.5 Hz), 134.91 (qd, *J* = 33.0, 4.3 Hz), 130.55 (d, *J* = 14.4 Hz), 125.59 (dq, *J* = 18.9, 3.7 Hz), 123.21 (dd, *J* = 273.2, 1.8 Hz) ; ^{19}F NMR (376 MHz, C_6D_6) δ -63.43 ; ^{31}P NMR (162 MHz, C_6D_6) δ 30.34.

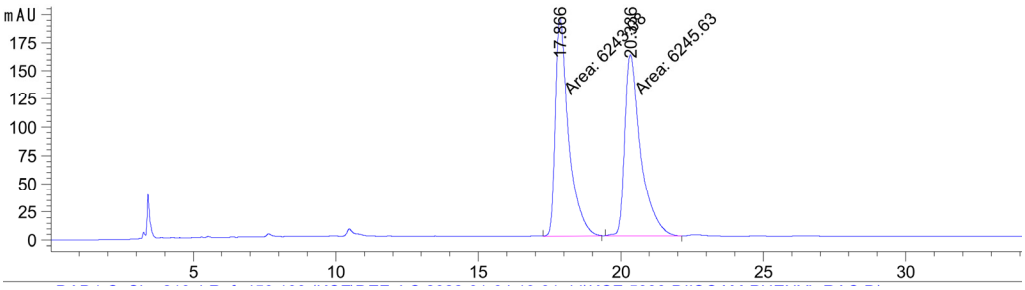
Methyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidate (4a)



4a

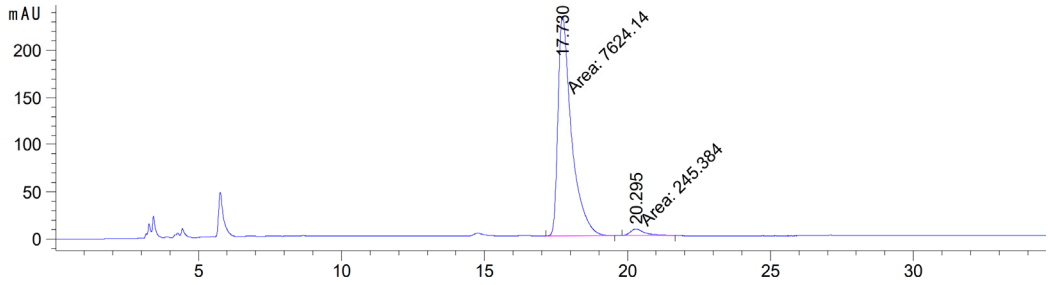
Following **General Procedure C**, phosphonamidate **4a** (59 mg, 94% yield, 94% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 μL, 0.2 mmol). The product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (ddd, *J* = 12.7, 8.2, 1.5 Hz, 2H), 7.53 – 7.35 (m, 3H), 3.72 (d, *J* = 11.0 Hz, 3H), 3.11 – 2.76 (m, 4H), 1.48 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.42 – 1.26 (m, 4H), 0.84 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.42 (d, *J* = 2.9 Hz), 131.41 (d, *J* = 9.4 Hz), 131.23 (d, *J* = 174.9 Hz), 128.30 (d, *J* = 14.1 Hz), 50.84 (d, *J* = 5.9 Hz), 43.26 (d, *J* = 4.6 Hz), 37.60 (d, *J* = 2.0 Hz), 26.01, 22.55 (d, *J* = 4.0 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.89 ; HRMS (ESI) m/z calcd for $C_{17}H_{31}NO_2P$ $(M+H)^+$: 312.2087; found: 312.2088. Phosphonamidate **4a** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 20.3 min, t_R(major) = 17.7 min).

Racemic sample:



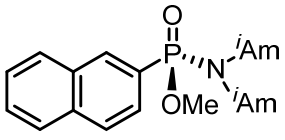
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.866	MM	0.5371	6243.07959	193.73647	49.9898
2	20.336	MM	0.6483	6245.62842	160.57492	50.0102

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.730	MM	0.5462	7624.14453	232.64314	96.8819
2	20.295	MM	0.5946	245.38354	6.87788	3.1181

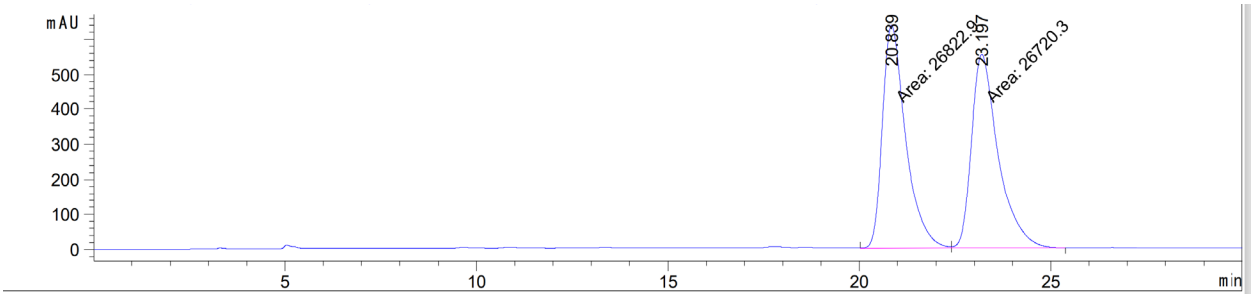
Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(naphthalen-2-yl)phosphonamidate (4b)



4b

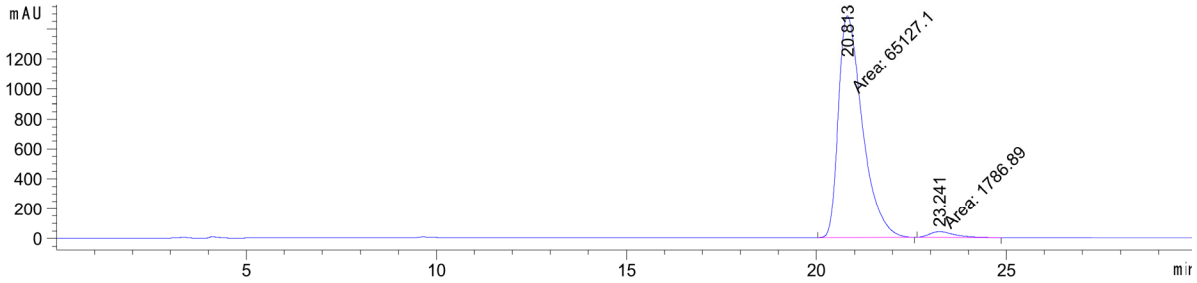
Following **General Procedure C**, phosphonamidate **4b** (62 mg, 85% yield, 95% ee) was produced as a colorless oil from **2b** (0.2 mmol). The product was purified using flash chromatography on silica gel (0 to 100% EtOAc in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 14.6 Hz, 1H), 7.89 (dt, J = 12.1, 7.5 Hz, 2H), 7.73 (ddd, J = 10.3, 8.4, 1.5 Hz, 2H), 7.56 (pd, J = 7.0, 1.6 Hz, 2H), 3.77 (d, J = 11.1 Hz, 3H), 3.28 – 2.69 (m, 4H), 1.49 (dq, J = 13.5, 6.8 Hz, 2H), 1.44 – 1.28 (m, 4H), 0.84 (d, J = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.57 (d, J = 2.6 Hz), 133.08 (d, J = 9.1 Hz), 132.53 (d, J = 15.4 Hz), 128.82, 128.41 (d, J = 174.9 Hz), 128.10 (d, J = 13.7 Hz), 127.76, 126.75, 126.66, 126.63 (d, J = 1.2 Hz), 50.98 (d, J = 5.9 Hz), 43.37 (d, J = 4.6 Hz), 37.67 (d, J = 2.0 Hz), 26.03, 22.56 (d, J = 4.2 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.91 ; HRMS (ESI) m/z calcd for $C_{21}H_{33}NO_2P$ $(M+H)^+$: 362.2243; found: 362.2245. Phosphonamidate **4b** was determined to be 95% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 23.2 min, t_R(major) = 20.8 min).

Racemic Sample:



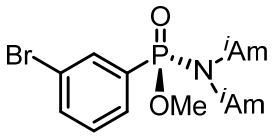
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.839	MF	0.7028	2.68229e4	636.09015	50.0958
2	23.197	FM	0.8058	2.67203e4	552.65314	49.9042

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.813	MM	0.7331	6.51271e4	1480.64075	97.3296
2	23.241	MM	0.7609	1786.88892	39.14061	2.6704

Methyl (*R*)-*P*-(3-bromophenyl)-*N*,*N*-diisopentylphosphonamidate (4c)

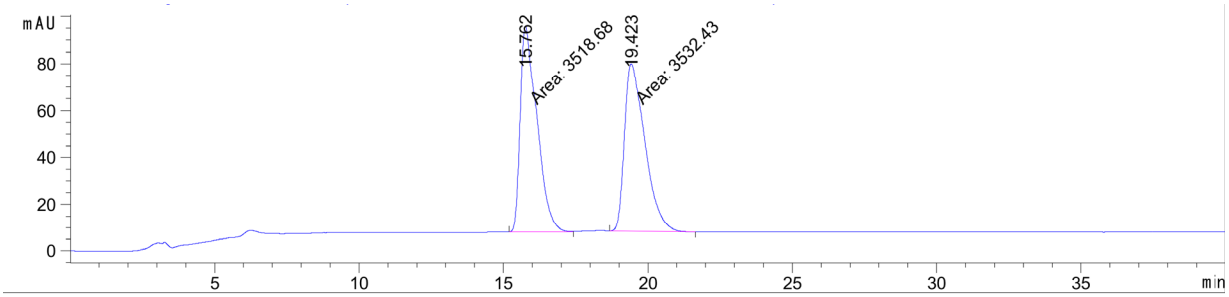


4c

Following **General Procedure C**, phosphonamidate **4c** (57.5 mg, 74% yield, 94% ee) was produced as a colorless oil from phosphonic dichloride **2c** (0.2 mmol). The product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, *J* = 12.9, 1.7 Hz, 1H), 7.69 – 7.55 (m, 2H), 7.31 (td, *J* = 7.8, 4.4 Hz, 1H), 3.73 (d, *J* = 11.2 Hz, 3H), 3.00 (ddd, *J* = 10.4, 8.9, 7.1 Hz, 4H), 1.49 (dq, *J* = 13.1, 6.6 Hz, 2H), 1.34 (ttt, *J* = 12.7, 6.0, 3.4 Hz, 4H), 0.86 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.41 (d, *J* = 2.9 Hz), 134.19 (d, *J* = 10.1 Hz), 134.08 (d, *J* = 173.0 Hz), 130.02 (d, *J* = 15.0 Hz), 129.80 (d, *J* = 8.9 Hz), 122.75 (d, *J* = 18.6 Hz), 50.96 (d, *J* = 6.1 Hz), 43.25 (d, *J* = 4.7 Hz), 37.59 (d, *J* = 1.9 Hz), 26.00, 22.54 (d, *J* = 3.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.33 ; HRMS (ESI) m/z calcd for $C_{17}H_{30}BrNO_2P$ $(M+H)^+$: 390.1192; found: 390.1193. Phosphonamidate **4c** was determined to be

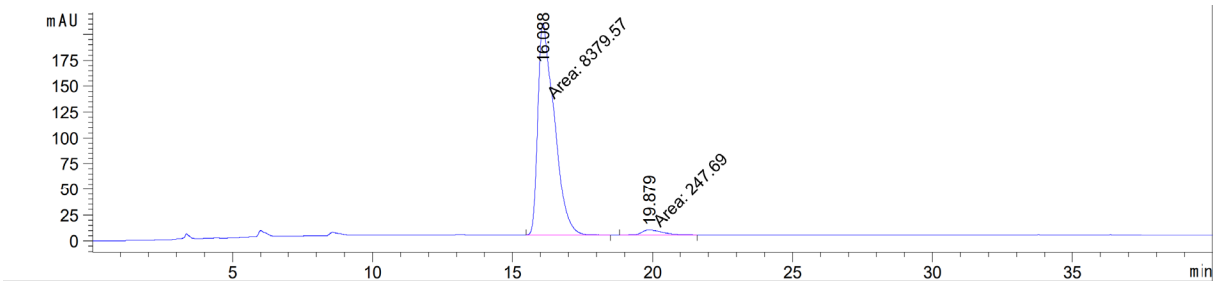
94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 19.9 min, t_R(major) = 16.1 min).

Racemic Sample:



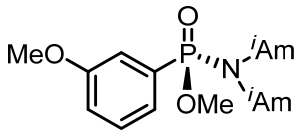
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.762	MM	0.6677	3518.68286	87.83620	49.9025
2	19.423	MM	0.8226	3532.43042	71.56898	50.0975

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.088	MM	0.6801	8379.56836	205.35091	97.1290
2	19.879	MM	0.8337	247.69002	4.95151	2.8710

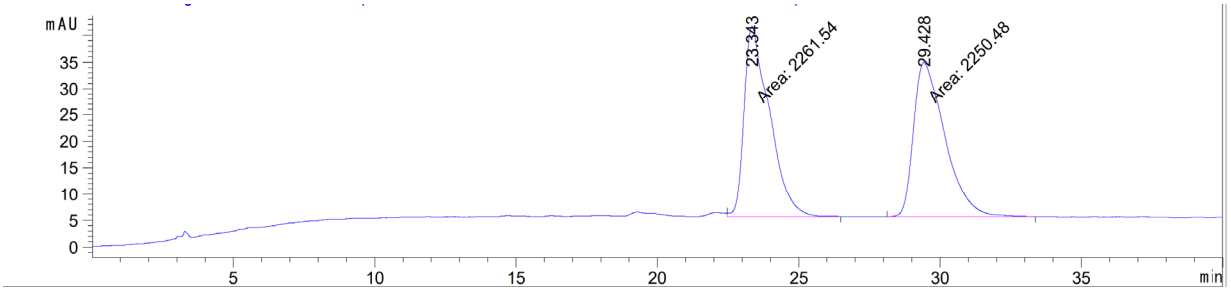
Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(3-methoxyphenyl)phosphonamidate (4d)



4d

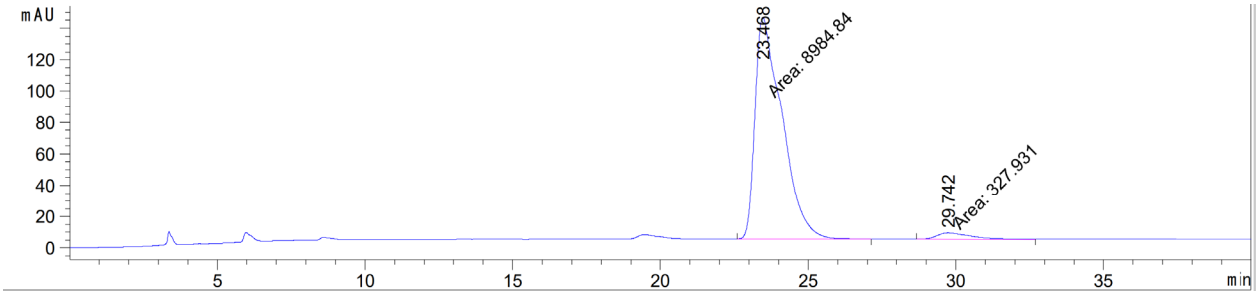
Following **General Procedure C**, phosphonamidate **4d** (63 mg, 92% yield, 94% ee) was produced as a colorless oil from **2d** (0.2 mmol). The product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 3H), 7.01 (ddd, *J* = 8.7, 2.3, 0.9 Hz, 1H), 3.83 (s, 3H), 3.72 (d, *J* = 11.1 Hz, 3H), 3.35 – 2.74 (m, 4H), 1.49 (dq, *J* = 13.1, 6.6 Hz, 4H), 1.41 – 1.28 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40 (d, *J* = 17.8 Hz), 132.55 (d, *J* = 173.9 Hz), 129.53 (d, *J* = 16.5 Hz), 123.65 (d, *J* = 9.0 Hz), 117.68 (d, *J* = 3.0 Hz), 116.20 (d, *J* = 10.7 Hz), 55.40, 50.92 (d, *J* = 6.0 Hz), 43.27 (d, *J* = 4.7 Hz), 37.59 (d, *J* = 1.9 Hz), 26.02, 22.57 (d, *J* = 4.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.72; HRMS (ESI) m/z calcd for $C_{18}H_{33}NO_3P$ $(M+H)^+$: 342.2193; found: 342.2193. Phosphonamidate **4d** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 29.7 min, t_R(major) = 23.5 min).

Racemic Sample:



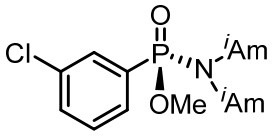
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.343	FM	1.0472	2261.53540	35.99278	50.1225
2	29.428	MM	1.2840	2250.48462	29.21214	49.8775

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.468	MM	1.0602	8984.83594	141.24014	96.4787
2	29.742	MM	1.3275	327.93115	4.11700	3.5213

Methyl (*R*)-*P*-(3-chlorophenyl)-*N*,*N*-diisopentylphosphonamidate (4b)

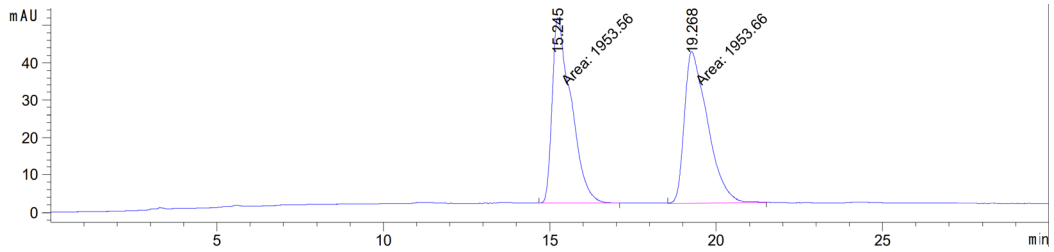


4e

Following **General Procedure C**, phosphonamidate **4e** (63 mg, 87% yield, 89% ee) was produced as a colorless oil from phosphonic dichloride **2e** (0.2 mmol). Product was purified by flash chromatography on silica gel (0 to 50% Et_2O in DCM). ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 13.0, 1.8 Hz, 1H), 7.61 (ddt, *J* = 12.4, 7.5, 1.3 Hz, 1H), 7.45

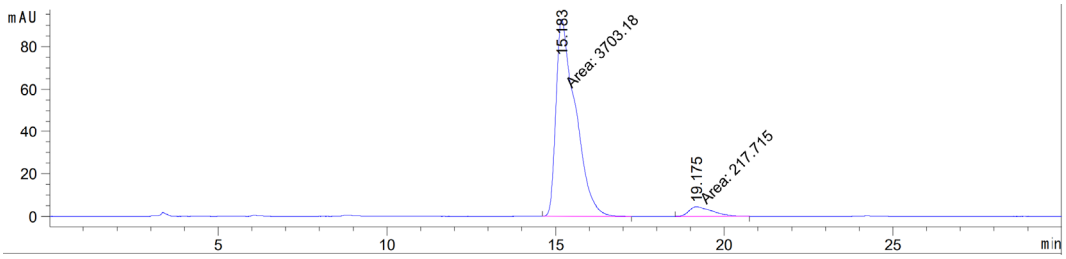
(ddt, J = 8.1, 2.2, 1.1 Hz, 1H), 7.37 (td, J = 7.7, 4.3 Hz, 1H), 3.73 (d, J = 11.1 Hz, 3H), 3.00 (dddd, J = 10.8, 8.7, 6.7, 1.5 Hz, 4H), 1.49 (dq, J = 13.1, 6.6 Hz, 2H), 1.34 (dddd, J = 19.2, 12.8, 8.7, 6.1 Hz, 4H), 0.86 (d, J = 6.6 Hz, 12H); δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.66 (d, J = 7.1 Hz), 133.71 (d, J = 162.1 Hz), 131.50 (d, J = 2.9 Hz), 131.33 (d, J = 10.0 Hz), 129.78 (d, J = 15.4 Hz), 129.37 (d, J = 8.9 Hz), 50.95 (d, J = 6.0 Hz), 43.25 (d, J = 4.7 Hz), 37.59 (d, J = 1.9 Hz), 26.00, 22.54 (d, J = 3.3 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.63 ; HRMS (ESI) m/z calcd for $C_{17}H_{30}ClNO_2P$ $(M+H)^+$: 346.1697; found: 346.1698. Phosphonamidate **4e** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 19.2 min, t_R(major) = 15.2 min).

Racemic sample:



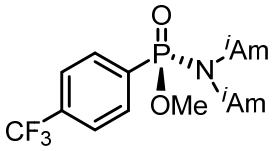
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.245	MM	0.6579	1953.55896	49.49269	49.9987
2	19.268	MM	0.8041	1953.65906	40.49458	50.0013

Enriched sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.183	MM	0.6660	3703.18311	92.66764	94.4473
2	19.175	MM	0.8050	217.71455	4.50762	5.5527

Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(4-(trifluoromethyl)phenyl)phosphonamidate (4f)



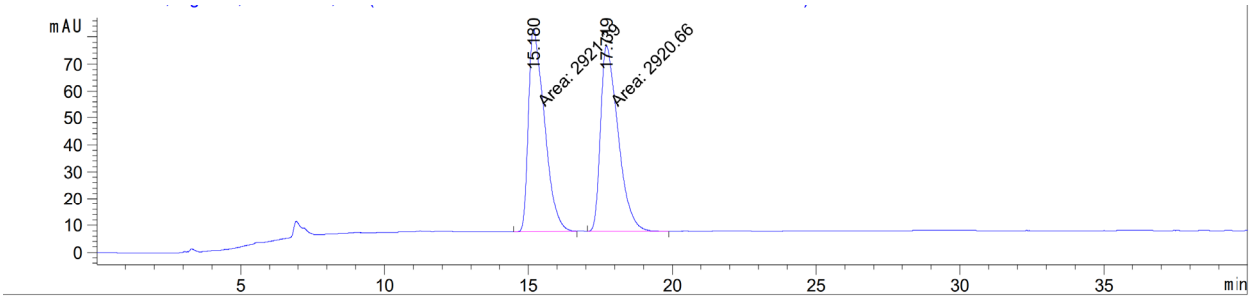
4f

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (20 mg, 0.04 mmol, 0.2 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 μL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –78 °C and subjected to stirring at that temperature for 20 minutes. Phosphonic dichloride **2f** (0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction was subjected to stirring at –78 °C for 18 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with 80 mg of sodium hydride (2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and the solution was subjected to stirring at room temperature until clear. If the mixture remained

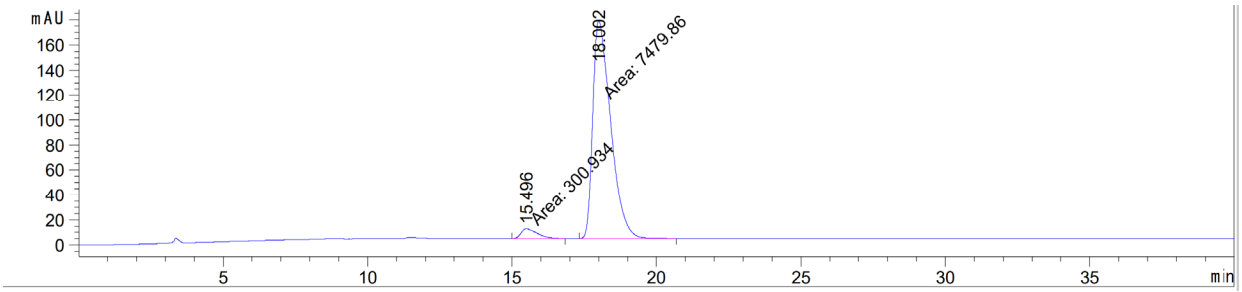
cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly to the catalytic reaction at –78 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 12 hours at –50 °C, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 50% Et_2O in DCM) to afford the product. Phosphonamidate **4f** (76 mg, 89% yield, 92% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 12.3, 7.9 Hz, 2H), 7.69 (dd, *J* = 8.1, 3.2 Hz, 2H), 3.74 (d, *J* = 11.1 Hz, 3H), 3.18 – 2.80 (m, 4H), 1.56 – 1.23 (m, 6H), 0.85 (dd, *J* = 6.6, 1.0 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.86 (d, *J* = 173.0 Hz), 133.13 (qd, *J* = 32.6, 3.2 Hz), 131.77 (d, *J* = 9.5 Hz), 125.14 (dq, *J* = 14.2, 3.7 Hz), 123.70 (q, *J* = 818.0 Hz), 50.94 (d, *J* = 5.9 Hz), 43.24 (d, *J* = 4.7 Hz), 37.57 (d, *J* = 1.8 Hz), 25.99, 22.50 (d, *J* = 3.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.33 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.13 ; HRMS (ESI) m/z calcd for $C_{18}H_{30}F_3NO_2P$ $(M+H)^+$: 380.1961; found: 380.1960. Phosphonamidate **4f** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 15.5 min, t_R(major) = 18.0 min).

Racemic Sample:



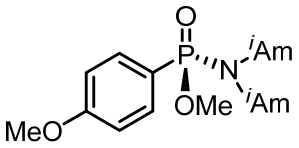
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.180	MM	0.6453	2921.39429	75.45140	50.0063
2	17.719	MM	0.7071	2920.65942	68.84431	49.9937

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.496	MM	0.6362	300.93442	7.88329	3.8677
2	18.002	MM	0.7159	7479.85596	174.13049	96.1323

Methyl (*R*)-*N*,*N*-diisopentyl-*P*-(4-methoxyphenyl)phosphonamidate (4g)



4g

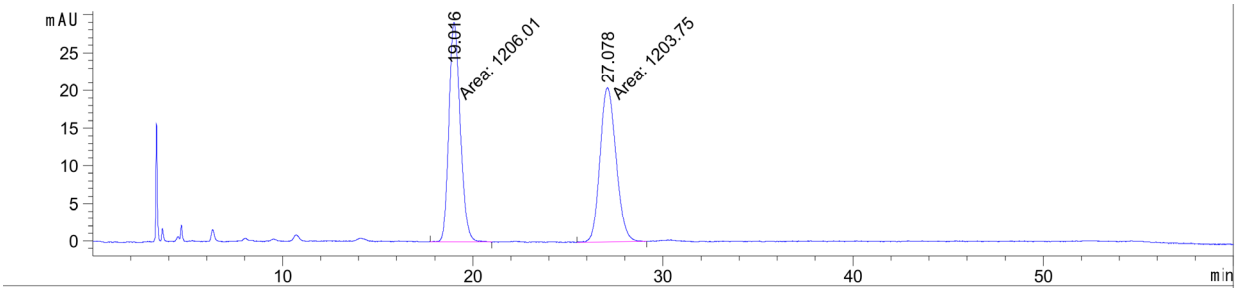
An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (5 mg, 0.01 mmol, 0.05 equiv.), 4 Å mol sieves (200 mg), and diisoamylamine (140 µL, 0.7 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –40 °C and subjected to stirring at that temperature for 20 minutes. 4-methoxyphenyl

phosphonic dichloride (32 μL, 0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL) was then added in one portion, and the reaction was subjected to stirring at –40 °C for 24 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and the solution was subjected to stirring at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly to the catalytic reaction at –40 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 12 hours at –40 °C, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 100% Et_2O in DCM) to afford the product. Phosphonamidate **4g** (63 mg, 92% yield, 90% ee) was afforded as a colorless oil.

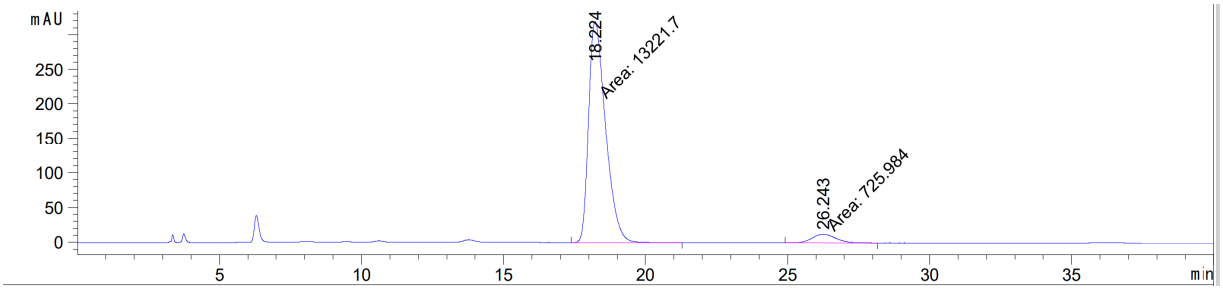
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.51 (m, 2H), 6.93 (dd, *J* = 8.8, 3.0 Hz, 2H), 3.84 (s, 3H), 3.69 (d, *J* = 11.0 Hz, 3H), 3.09 – 2.89 (m, 4H), 1.54 – 1.41 (m, 2H), 1.34 (ddt, *J* = 16.2, 12.9, 6.3 Hz, 4H), 0.85 (d, *J* = 6.5 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.08 (d, *J* = 3.2 Hz), 133.35 (d, *J* = 10.8 Hz), 122.53 (d, *J* = 181.8 Hz), 113.80 (d, *J* = 15.2 Hz), 55.28, 50.80 (d, *J* = 6.0 Hz), 43.29 (d, *J* = 4.7 Hz), 37.64 (d, *J* = 2.0 Hz), 26.03, 22.58 (d, *J* = 4.8 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.71 ; HRMS (ESI) m/z calcd for $C_{18}H_{33}NO_3P$ $(M+H)^+$: 342.2193; found: 342.2193. Phosphonamidate **4g** was determined to be 90% ee by chiral HPLC analysis (Chiralcel OD-H, 3% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 26.2 min, t_R(major) = 18.2 min).

Racemic Sample:



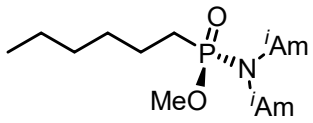
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.016	MM	0.6900	1206.00720	29.12862	50.0469
2	27.078	MM	0.9805	1203.74585	20.46228	49.9531

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.224	MM	0.6904	1.32217e4	319.17303	94.7950
2	26.243	MM	0.9627	725.98444	12.56860	5.2050

Methyl (*R*)-*P*-hexyl-*N*,*N*-diisopentylphosphonamidate (4h)



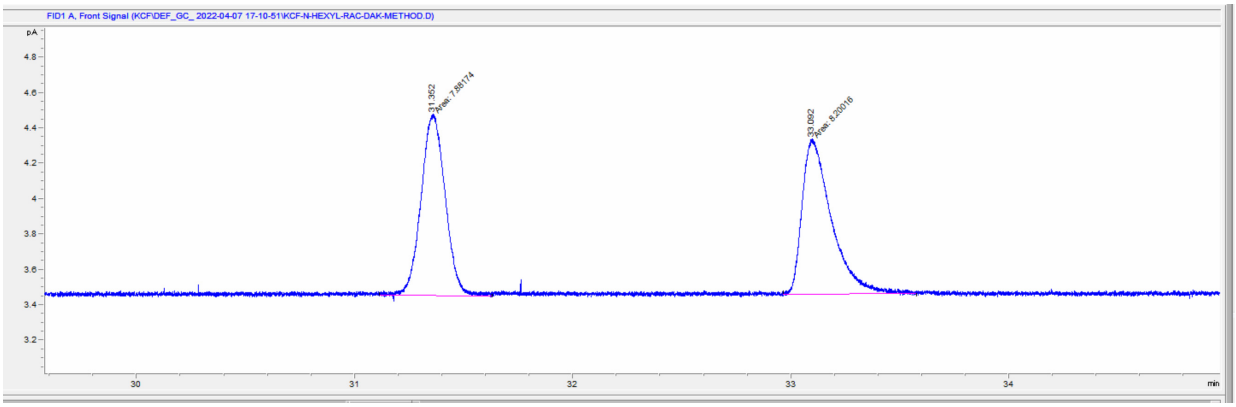
4h

Following **General Procedure C**, phosphonamidate **4h** (32.1 mg, 50% yield, 26% ee) was produced as a colorless oil from hexylphosphonic dichloride (34 µL, 0.2 mmol). Product **4h** was purified by flash chromatography on silica gel (0 to 60% Et_2O in Hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, *J* = 10.9 Hz, 3H), 2.97 (td, *J* = 10.1, 6.5 Hz, 4H), 1.75 – 1.48 (m, 6H), 1.45 – 1.31 (m, 6H), 1.35 – 1.19 (m, 4H), 0.91 (d, *J* = 6.6 Hz, 12H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 49.72 (d, *J* = 6.9 Hz), 42.96 (d, *J* = 4.3 Hz), 37.88 (d, *J* = 1.7 Hz), 31.40, 30.55 (d, *J* = 17.2 Hz), 26.53 (d, *J* = 131.1 Hz), 26.15, 22.64, 22.46, 22.35 (d, *J* = 4.1 Hz), 14.04; ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.97; HRMS (ESI) m/z calcd for $C_{17}H_{39}N_1O_2P_1$ $(M+H)^+$: 320.2713; found: 320.2712.

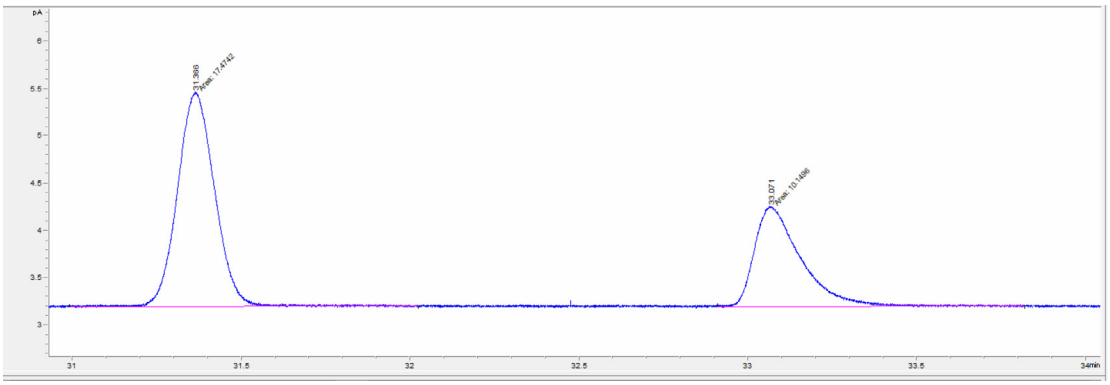
Phosphonamidate **4h** was determined to be 26% ee by chiral GC analysis (Cyclodex B 60 m x 0.25 mm x 0.25 µm, 1.0 °C/min, 100 °C to 200 °C, 7 psi), t_R(minor) = 33.1 min, t_R(major) = 31.4 min.

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.352	MM	0.1289	7.88174	1.01915	49.01002
2	33.092	MM	0.1565	8.20016	8.73491e-1	50.98998

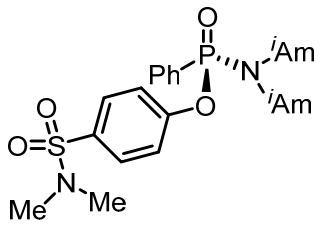
Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.366	MM	0.1286	17.47416	2.26527	63.25772
2	33.071	MM	0.1606	10.14960	1.05304	36.74228

Scope of enantiospecific nucleophile substitution of phenyl chlorophosphonamidate 3 by various nucleophiles

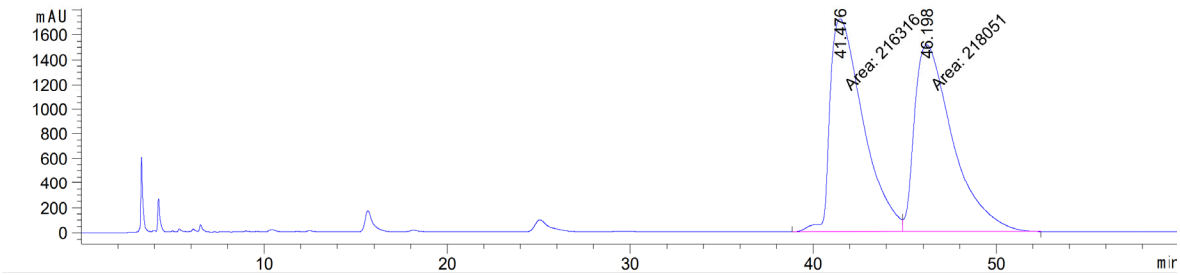
4-(*N*,*N*-dimethylsulfamoyl)phenyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidate (5a)



5a

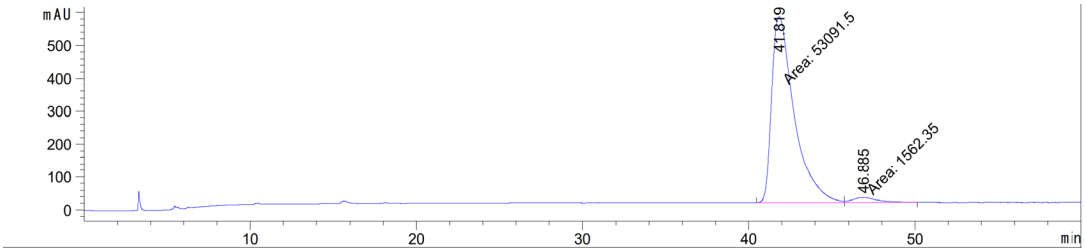
Following **General Procedure B**, phosphonamidate **5a** (70 mg, 73% yield, 94% ee) was produced as a white solid from phenyl phosphonic dichloride (28 μL, 0.2 mmol), sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil), and 4-hydroxy-*N*,*N*-dimethylbenzenesulfonamide (81 mg, 0.4 mmol, 2 equiv.). *NOTE: after addition of phenoxide solution, reaction was subjected to stirring at –30 °C instead of –50 °C.* The product was purified via flash chromatography on silica gel (0 to 100% Et_2O in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 2H), 7.78 – 7.66 (m, 2H), 7.62 – 7.53 (m, 1H), 7.49 (tdd, *J* = 7.0, 3.1, 1.8 Hz, 2H), 7.46 – 7.39 (m, 2H), 3.24 – 2.94 (m, 4H), 2.69 (s, 6H), 1.44 (h, *J* = 6.6 Hz, 2H), 1.37 – 1.17 (m, 4H), 0.81 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.94 (d, *J* = 7.6 Hz), 132.22 (d, *J* = 3.3 Hz), 131.50 (d, *J* = 9.9 Hz), 131.04 (d, *J* = 1.7 Hz), 129.68, 128.64 (d, *J* = 14.8 Hz), 128.46 (d, *J* = 164.2 Hz), 120.81 (d, *J* = 5.3 Hz), 43.16 (d, *J* = 4.5 Hz), 37.94, 37.27 (d, *J* = 2.2 Hz), 25.92, 22.50 (d, *J* = 7.7 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.44 ; HRMS (ESI) m/z calcd for $C_{24}H_{38}N_2O_4P$ $(M+H)^+$: 481.2284; found: 481.2282. Phosphonamidate **5a** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 46.9 min, t_R(major) = 41.8 min).

Enriched Sample:



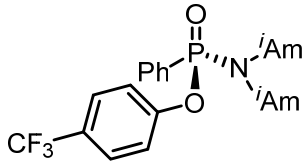
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.476	MF	2.1002	2.16316e5	1716.62000	49.8002
2	46.198	FM	2.4101	2.18051e5	1507.92786	50.1998

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.819	MF	1.5668	5.30915e4	564.75763	97.1414
2	46.885	FM	1.7079	1562.35327	15.24649	2.8586

4-(trifluoromethyl)phenyl (R)-N,N-diisopentyl-P-phenylphosphonamidate (5b)



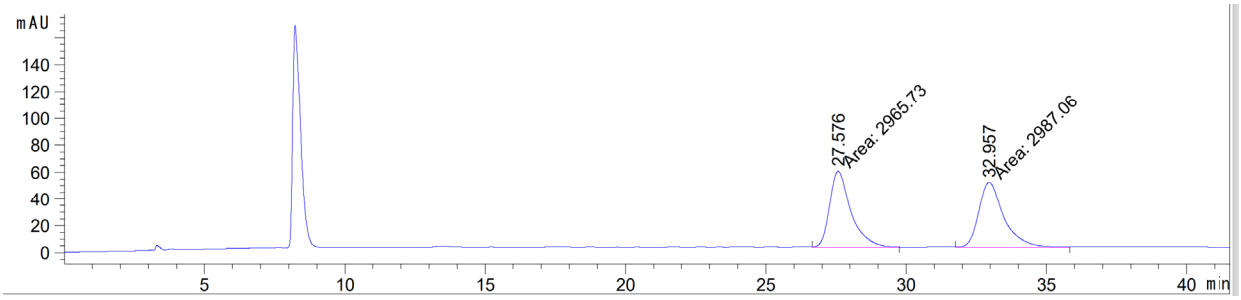
5b

An oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with catalyst **1a** (23 mg, 0.045 mmol), 4 Å mol sieves (800 mg), and diisoamylamine (0.65 mL, 3.15 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (45 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring for 20 minutes. Phenyl phosphonic dichloride (126 µL, 0.9 mmol, 1 equiv.) dissolved in toluene (1 mL) was then added in one portion, and the reaction was subjected to stirring at –50 °C for 4 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (0.54 g, 15 equiv, 13.5 mmol, 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (9 mL) and allowed to stir at room temperature for 1 minute. 4-(trifluoromethyl)phenol (729 mg, 4.5 mmol, 5 equiv.) dissolved in THF (1 mL) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 5-minute period, and stirring was continued at room temperature for 30 minutes. The resultant 4-(trifluoromethyl)phenoxide mixture was then added directly to the catalytic reaction at –50 °C after it had been stirred for 4 hours. The reaction was then subjected to stirring for 24 hours at –50 °C, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (0 to 40% Et_2O in Hexanes) to afford the product. Phosphonamidate **5b** (251 mg, 63% yield, 93% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.73 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.48 (ddd, *J* = 8.5, 6.5, 4.2 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.06 (dddd, *J* = 11.4, 8.9, 6.4, 2.0 Hz, 4H), 1.49 – 1.36 (m, 2H), 1.34 – 1.11 (m, 4H), 0.80 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.98 (d, *J* = 7.6 Hz), 132.07 (d, *J* = 3.1 Hz), 131.53 (d, *J* = 9.6 Hz), 130.41 (d, *J* = 179.1 Hz), 128.56 (d, *J* = 14.8 Hz), 126.95 (q, *J* = 3.8 Hz), 126.47 (q, *J* = 32.9 Hz), 124.02 (q, *J* = 271.7 Hz),

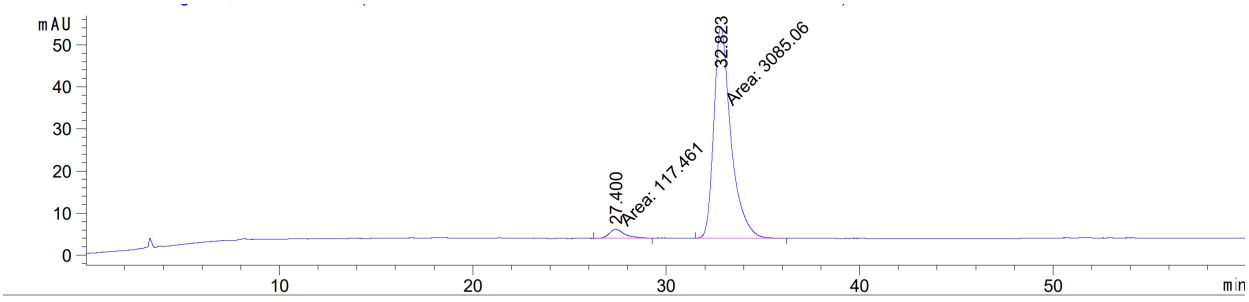
120.78 (d, J = 5.1 Hz), 43.10 (d, J = 4.6 Hz), 37.23 (d, J = 2.1 Hz), 25.91, 22.47 (d, J = 8.2 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.16 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.04 ; HRMS (ESI) m/z calcd for $C_{23}H_{32}F_3NO_2P$ $(M+H)^+$: 442.2117; found: 442.2117. Phosphonamidate **5b** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 27.4 min, t_R(major) = 32.8 min).

Racemic Sample:



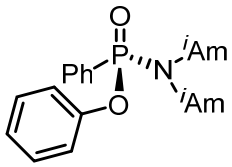
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.576	MM	0.8733	2965.72803	56.60071	49.8209
2	32.957	MM	1.0233	2987.05566	48.64917	50.1791

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.400	MM	0.9142	117.46119	2.14139	3.6678
2	32.823	MM	1.0238	3085.05737	50.22353	96.3322

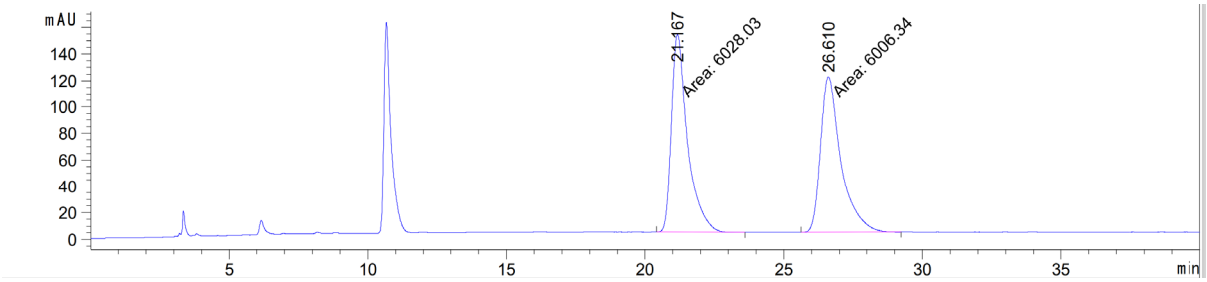
Phenyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidate (5c)



5c

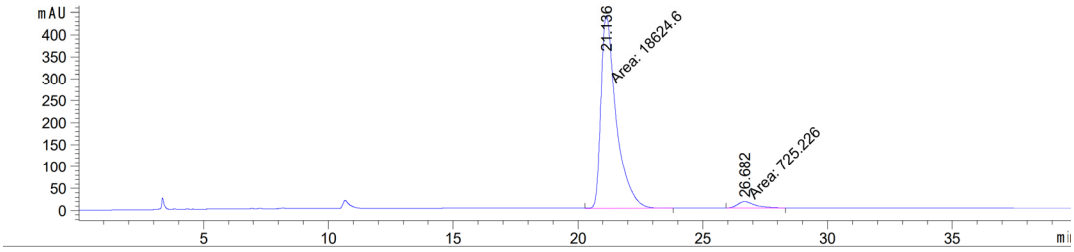
Following **General Procedure B**, phosphonamidate **5c** (64 mg, 86% yield, 93% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 μL, 0.2 mmol), sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil), and phenol (38 mg, 0.4 mmol, 2 equiv.). The product was purified via flash chromatography on silica gel (0 to 50% Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.76 (m, 2H), 7.61 – 7.38 (m, 3H), 7.38 – 7.20 (m, 4H), 7.16 – 7.03 (m, 1H), 3.05 (dddd, *J* = 10.9, 8.7, 6.5, 1.5 Hz, 4H), 1.54 – 1.34 (m, 2H), 1.34 – 1.00 (m, 4H), 0.79 (d, *J* = 6.6 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.23 (d, *J* = 8.2 Hz), 131.70 (d, *J* = 3.0 Hz), 131.58 (d, *J* = 9.5 Hz), 131.15 (d, *J* = 179.2 Hz), 129.53, 128.39 (d, *J* = 14.5 Hz), 124.21, 120.54 (d, *J* = 5.0 Hz), 43.11 (d, *J* = 4.4 Hz), 37.20 (d, *J* = 2.1 Hz), 25.95, 22.51 (d, *J* = 7.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.20 ; HRMS (ESI) m/z calcd for $C_{22}H_{33}NO_2P$ $(M+H)^+$: 374.2243; found: 374.2242. Phosphonamidate **5c** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 26.6 min, t_R(major) = 21.1 min).

Racemic Sample:



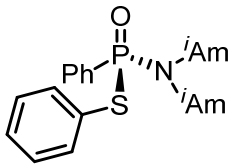
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.167	MM	0.6734	6028.03271	149.20413	50.0901
2	26.610	MM	0.8510	6006.33594	117.62879	49.9099

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.136	MM	0.7091	1.86246e4	437.77039	96.2520
2	26.682	MM	0.8215	725.22614	14.71269	3.7480

***S*-phenyl (*R*)-*N*,*N*-diisopentyl-*P*-phenylphosphonamidothioate (5d)**



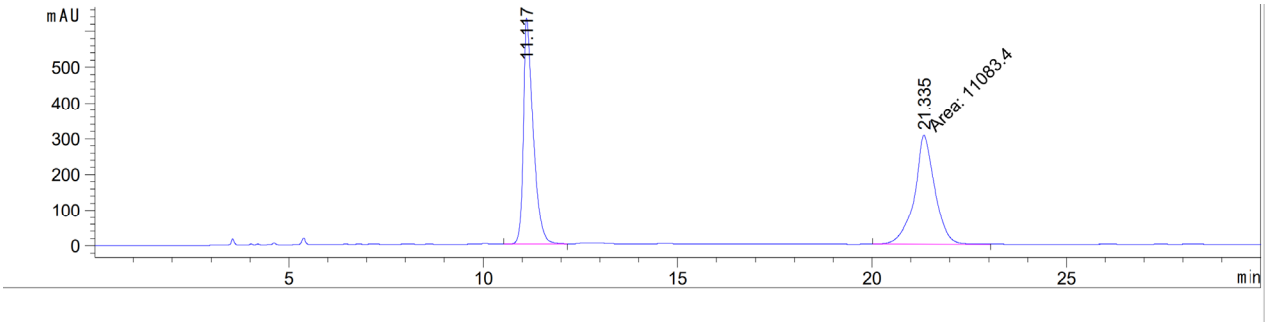
5d

An oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with catalyst **1a** (24 mg, 0.05 mmol), 4 Å mol sieves (800 mg), and diisoamylamine (0.72 mL, 3.5 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (50 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring for 20 minutes at that temperature. Phenyl phosphonic dichloride (140 µL, 1 mmol, 1 equiv.) dissolved in toluene (1 mL) was then added in one portion, and the reaction was subjected to stirring at –50 °C for 4 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (0.6 g, 15 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (10 mL) and allowed to stir at room temperature for 1 minute. Thiophenol (509 µL, 5 mmol, 5 equiv.) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature for 30 minutes. The resultant thiophenoxide mixture was then added directly to the catalytic reaction at –50 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 24 hours at –50 °C, concentrated under reduced pressure, and purified by flash column chromatography on silica gel (0 to 40% Et_2O in Hexanes) to afford the product. Phosphonamidothioate **5d** (366 mg, 90% yield, 94% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.74 (m, 2H), 7.55 (ddt, *J* = 6.8, 3.0, 1.5 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.42 (tdd, *J* = 6.7, 3.8, 1.5 Hz, 2H), 7.25 – 7.19 (m, 3H), 3.25 – 2.80 (m, 4H), 1.53 – 1.29 (m, 4H), 1.18 (ddt, *J* = 12.7, 10.2, 6.3 Hz, 2H), 0.80 (dd, *J* = 6.6, 2.2 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.62 (d, *J* = 4.3 Hz), 133.03 (d, *J* = 136.0 Hz), 131.98 (d, *J* = 3.1 Hz), 131.80 (d, *J* = 10.0 Hz), 128.99 (d, *J* = 1.4 Hz), 128.34 (d, *J* = 14.1 Hz), 128.34 (d, *J* = 5.3 Hz), 128.19 (d, *J* = 2.1 Hz), 43.77 (d, *J* = 3.6 Hz), 37.53 (d, *J* = 2.6 Hz), 26.00,

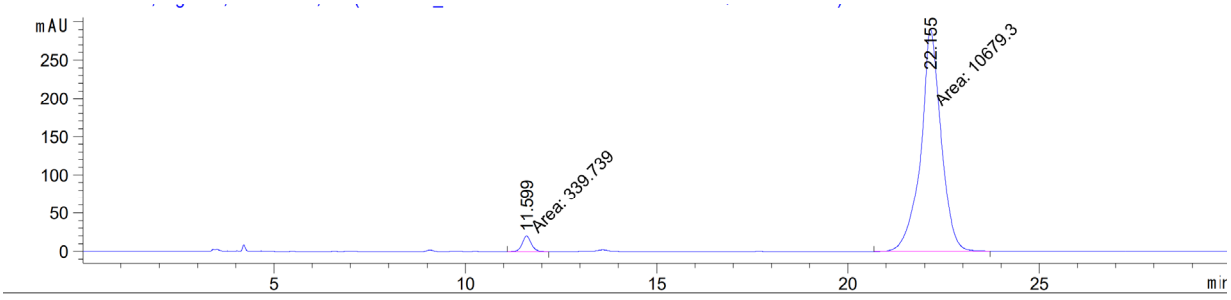
22.51 (d, J = 8.9 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.82 ; HRMS (ESI) m/z calcd for $C_{22}H_{33}NOPS$ $(M+H)^+$: 390.2015; found: 390.2013. Phosphonamidothioate **5d** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 11.6 min, t_R(major) = 22.2 min).

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.117	BB	0.2551	1.11106e4	631.90796	50.0613
2	21.335	MM	0.6057	1.10834e4	304.99411	49.9387

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.599	MM	0.2766	339.73944	20.46908	3.0832
2	22.155	MM	0.6115	1.06793e4	291.07159	96.9168

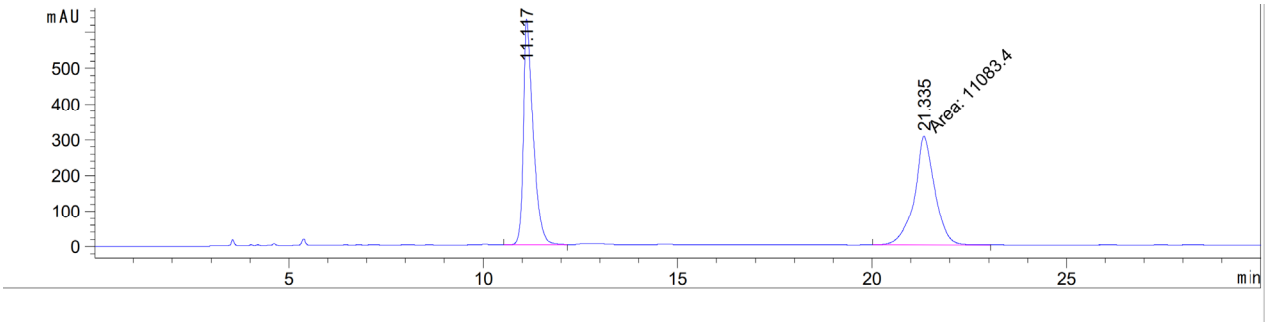
Gram-scale synthesis of 5d*:*

An oven-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with catalyst **1a** (71 mg, 0.15 mmol), 4 Å mol sieves (2.6 g), and diisoamylamine (1.85 mL, 9 mmol, 3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (125 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring for 20 minutes at that temperature. Phenyl phosphonic dichloride (0.42 mL, 3 mmol, 1 equiv.) was then added in one portion, and the reaction was subjected to stirring at –50 °C for 12 hours.

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (1.8 g, 45 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (30 mL) and allowed to stir at room temperature for 1 minute. Thiophenol (1.6 mL, 5 mmol, 5 equiv.) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 5-minute period, and stirring was continued at room temperature for 30 minutes. The resultant thiophenoxide mixture was then added directly to the catalytic reaction at –50 °C after it had been stirred for 24 hours. The reaction was then subjected to stirring for 12 hours at –50 °C then warmed to room temperature while subjected to stirring. The reaction as then filtered through a fritted funnel packed

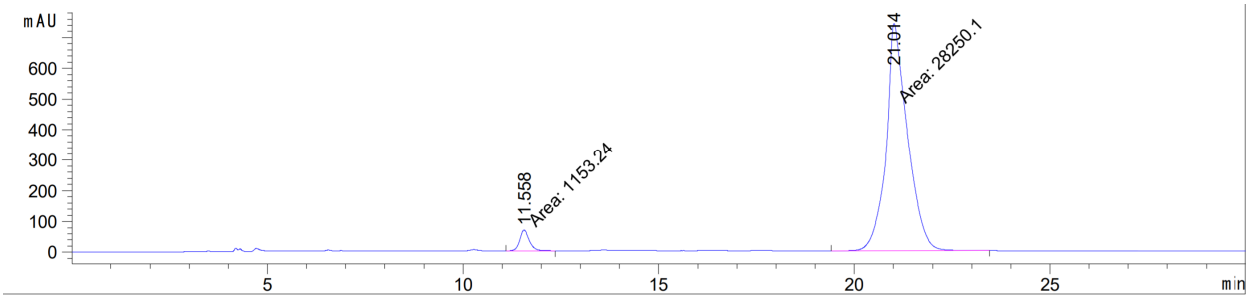
with ~2 inches of silica gel to remove the solids, which was then washed with diethyl ether (250 mL). The filtrate was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 25% EtOAc in Hexanes) to afford the product. Phosphonamidothioate **5d** (1.1095 g, 95% yield, 92% ee) was afforded as a colorless oil. Phosphonamidothioate **5d** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 11.6 min, t_R(major) = 21 min).

Racemic Sample:



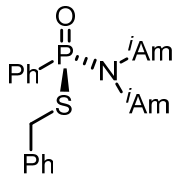
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.117	BB	0.2551	1.11106e4	631.90796	50.0613
2	21.335	MM	0.6057	1.10834e4	304.99411	49.9387

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.558	MM	0.2839	1153.24304	67.70479	3.9221
2	21.014	MM	0.6354	2.82501e4	741.01544	96.0779

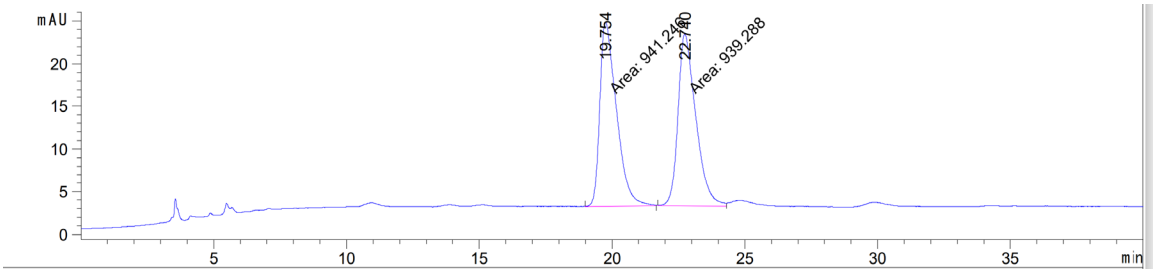
_S_-benzyl (_R_)-_N_,_N_-diisopentyl-_P_-phenylphosphonamidothioate (5e)



5e

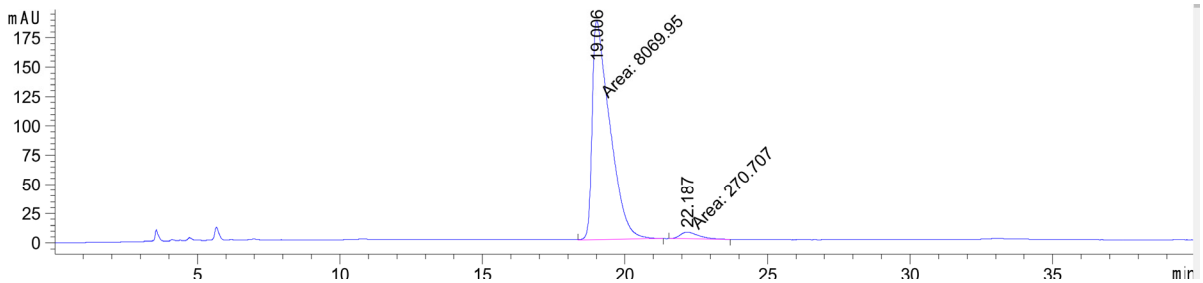
Following **General Procedure A**, phosphonamidothioate **5e** (73 mg, 91% yield, 94% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 μL, 0.2 mmol), sodium hydride (120 mg, 3 mmol, 15 equiv., 60% in mineral oil), and benzyl mercaptan (117 μL, 1 mmol, 5 equiv.). The product was purified via flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.81 (m, 2H), 7.55 – 7.38 (m, 3H), 7.29 – 7.13 (m, 5H), 4.14 – 3.77 (m, 2H), 3.08 – 2.89 (m, 4H), 1.51 – 1.19 (m, 6H), 0.80 (dd, J = 6.5, 4.7 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.83, 133.24 (d, J = 135.6 Hz), 131.99 (d, J = 10.6 Hz), 131.91 (d, J = 2.8 Hz), 129.01, 128.48, 128.37 (d, J = 14.1 Hz), 127.17, 43.79 (d, J = 3.8 Hz), 37.70 (d, J = 2.7 Hz), 34.48 (d, J = 2.5 Hz), 26.00, 22.49 (d, J = 7.2 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.57 ; HRMS (ESI) m/z calcd for $C_{23}H_{35}NOPS$ $(M+H)^+$: 404.2171; found: 404.2170. Phosphonamidothioate **5e** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK IB, 2% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 22.2 min, t_R(major) = 19.0 min).

Racemic Sample:



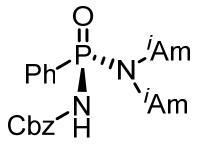
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.754	MM	0.7251	941.24573	21.63447	50.0521
2	22.740	MF	0.7760	939.28778	20.17343	49.9479

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.006	MM	0.7196	8069.95459	186.90515	96.7544
2	22.187	MM	0.7659	270.70706	5.89054	3.2456

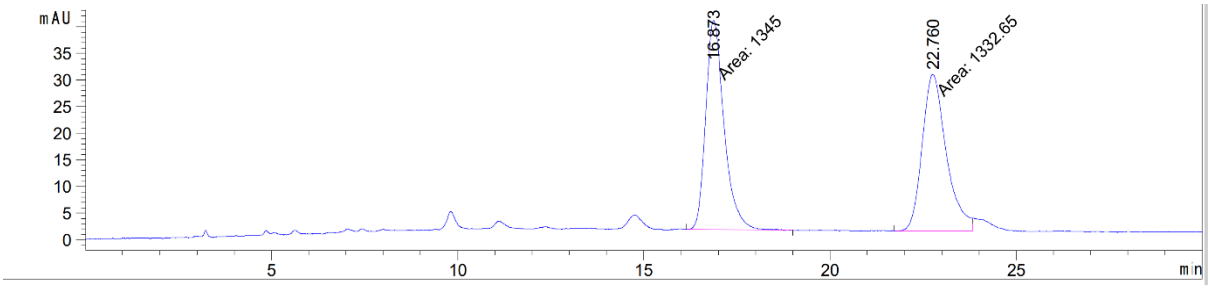
Benzyl (*R*)-((diisopentylamino)(phenyl)phosphoryl)carbamate (5f)



5f

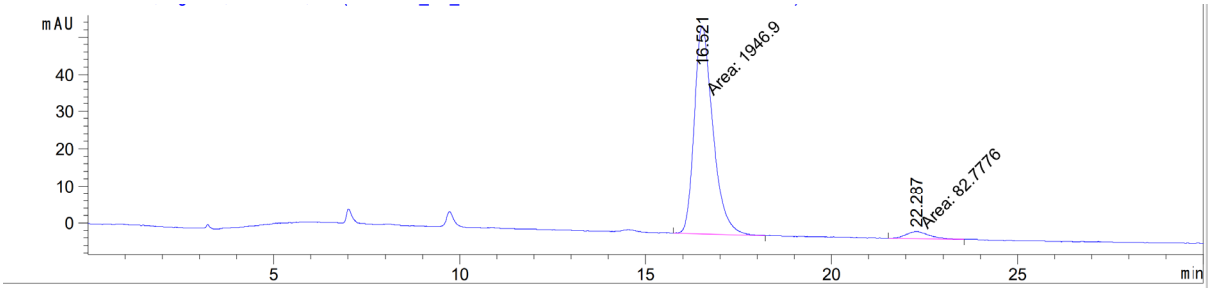
Following **General Procedure B**, compound **5f** (64 mg, 75% yield, 92% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol), sodium hydride (48 mg, 1.2 mmol, 6 equiv., 60% in mineral oil), and benzyl carbamate (60 mg, 0.4 mmol, 2 equiv.). The product was purified via flash column chromatography (0 to 100% EtOAc in DCM). *NOTE: after addition of sodium benzyl carbamide mixture, reaction was subjected to stirring at –30 °C instead of –50 °C.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddd, *J* = 13.5, 8.3, 1.4 Hz, 2H), 7.58 – 7.49 (m, 1H), 7.49 – 7.40 (m, 2H), 7.40 – 7.27 (m, 5H), 5.96 (s, 1H), 5.21 – 5.01 (m, 2H), 3.17 – 2.86 (m, 4H), 1.49 – 1.34 (m, 4H), 1.34 – 1.18 (m, 2H), 0.77 (t, *J* = 6.1 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.91 (d, *J* = 3.2 Hz), 135.49, 132.35 (d, *J* = 3.2 Hz), 132.02 (d, *J* = 10.3 Hz), 128.92 (d, *J* = 385.5 Hz), 128.46 (d, *J* = 7.4 Hz), 128.44 (d, *J* = 153.6 Hz), 128.42 (d, *J* = 34.3 Hz), 128.26 (d, *J* = 18.9 Hz), 67.67, 43.64 (d, *J* = 4.7 Hz), 37.35 (d, *J* = 2.6 Hz), 26.04, 22.47 (d, *J* = 10.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.96 ; HRMS (ESI) m/z calcd for $C_{24}H_{36}N_2O_3P$ $(M+H)^+$: 431.2458; found: 431.2454. Compound **5f** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 22.3 min, t_R(major) = 16.5 min).

Racemic Sample:



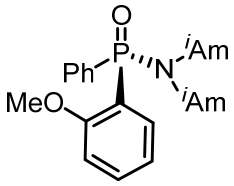
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.873	MM	0.5710	1345.00012	39.25836	50.2306
2	22.760	MF	0.7542	1332.65039	29.45085	49.7694

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.521	MM	0.5804	1946.89990	55.90345	95.9216
2	22.287	MM	0.7176	82.77764	1.92254	4.0784

(*R*)-*N*,*N*-diisopentyl-*P*-(2-methoxyphenyl)-*P*-phenylphosphinic amide (5g)

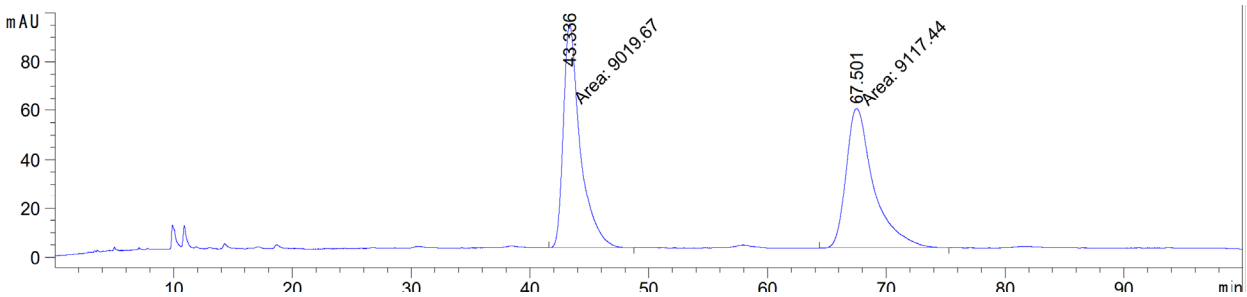


5g

Following **General Procedure B**, phosphinamidate **5g** (75 mg, 97% yield, 91% ee) was produced as a colorless oil from phenyl phosphonic dichloride (42 mg, 0.2 mmol) and 2-methoxyphenyl magnesium bromide (1 mL, 1 M solution in THF, 5.0 equiv.). The product was purified via flash

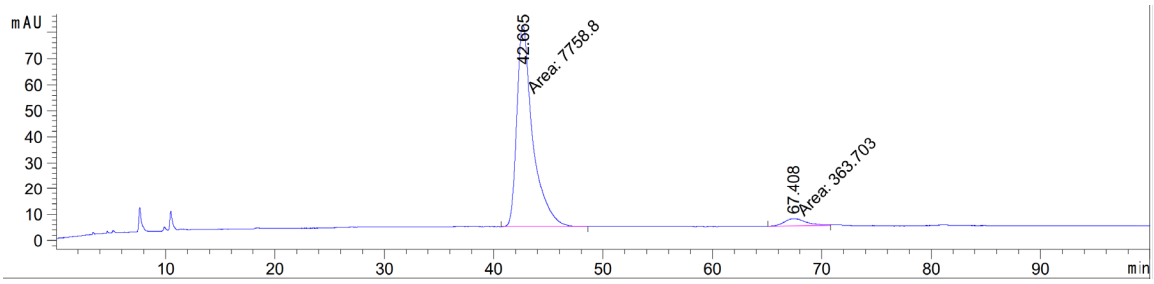
column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 13.5, 7.6, 1.8 Hz, 1H), 7.93 – 7.74 (m, 2H), 7.55 – 7.33 (m, 4H), 7.06 (tdd, *J* = 7.5, 2.1, 0.9 Hz, 1H), 6.91 – 6.82 (m, 1H), 3.74 (s, 3H), 3.19 – 2.80 (m, 4H), 1.53 – 1.29 (m, 6H), 0.74 (d, *J* = 6.2 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.44 (d, *J* = 3.2 Hz), 136.03 (d, *J* = 6.8 Hz), 134.07, 133.73 (d, *J* = 2.0 Hz), 132.67 (d, *J* = 10.2 Hz), 131.14 (d, *J* = 2.9 Hz), 127.77 (d, *J* = 12.9 Hz), 120.73 (d, *J* = 11.9 Hz), 120.38 (d, *J* = 123.5 Hz), 110.65 (d, *J* = 7.2 Hz), 54.95, 43.82 (d, *J* = 4.1 Hz), 37.61 (d, *J* = 3.0 Hz), 26.15, 22.53 (d, *J* = 2.7 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.34 ; HRMS (ESI) m/z calcd for $C_{23}H_{35}NO_2P$ $(M+H)^+$: 388.2400; found: 388.2397. Phosphinamidate **5g** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK AD-H, 4% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 67.4 min, t_R(major) = 42.7 min).

Racemic Sample:



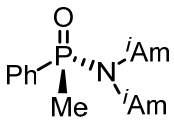
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.336	MM	1.6402	9019.67285	91.65068	49.7305
2	67.501	MM	2.6826	9117.43652	56.64543	50.2695

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.665	MM	1.6717	7758.80078	77.35439	95.5223
2	67.408	MM	2.2708	363.70343	2.66937	4.4777

(*S*)-*N*,*N*-diisopentyl-*P*-methyl-*P*-phenylphosphinic amide (5h)

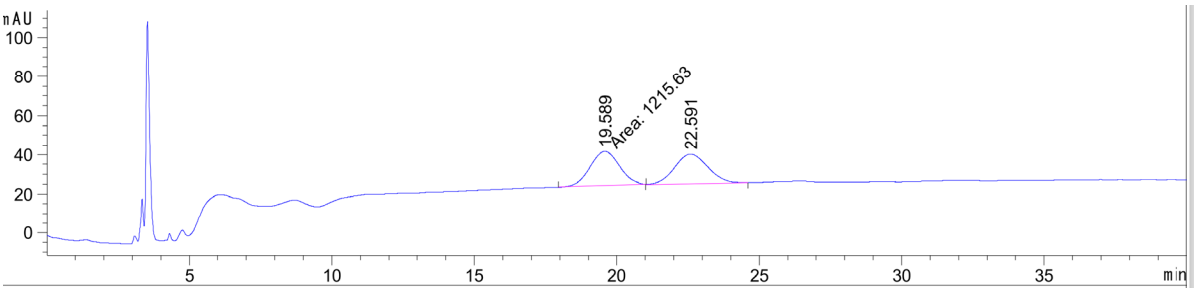


5h

Following **General Procedure B**, phosphinamidate **5h** (55 mg, 94% yield, 94% ee) was produced as a colorless oil from phenyl phosphonic dichloride (28 µL, 0.2 mmol), methylmagnesium chloride (0.5 mL, 2 M solution in THF, 5 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (ddt, *J* = 11.8, 8.3, 1.8 Hz, 2H), 7.46 (dddd, *J* = 14.0, 9.0, 6.7, 2.1 Hz, 3H), 2.94 (tdd, *J* = 10.9, 5.6, 2.9 Hz, 4H), 1.70 (dd, *J* = 13.6, 3.1 Hz, 3H), 1.53 – 1.29 (m, 6H), 0.81 (dt, *J* = 6.4, 2.2 Hz, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.90 (d, *J* = 125.8 Hz), 131.46, 131.39 (d, *J* = 9.4 Hz), 128.38 (d, *J* = 12.3 Hz), 43.99 (d, *J* = 3.2 Hz), 38.06 (d, *J* = 3.2 Hz), 26.09, 22.51 (d, *J* = 7.4 Hz), 15.30 (d, *J* = 93.4 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.81 ; HRMS (ESI) m/z calcd for $C_{17}H_{31}NOP$ $(M+H)^+$:

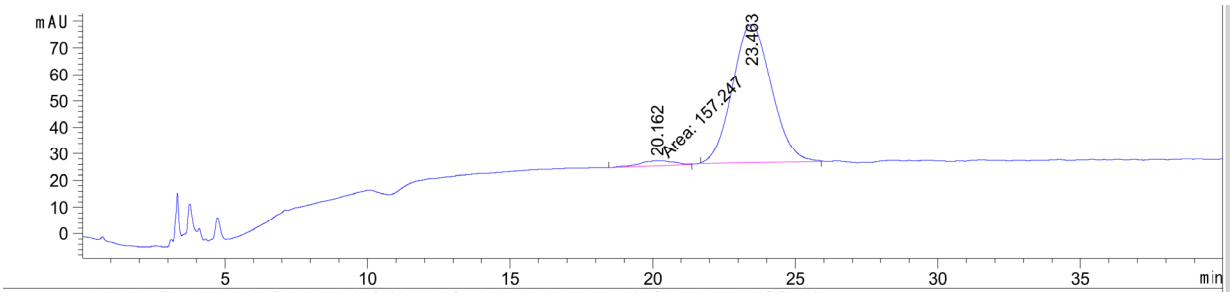
296.2138; found: 296.2138. Phosphinamidate **5h** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AS-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 20.2 min, t_R(major) = 23.5 min).

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.589	MM	1.1803	1215.62708	17.16542	49.9831
2	22.591	VB	1.0058	1216.44971	15.10050	50.0169

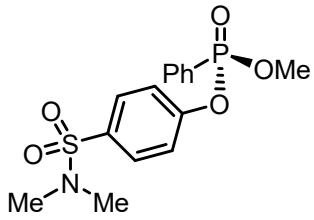
Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.162	MM	1.4032	157.24745	1.86771	3.0860
2	23.463	BB	1.2952	4938.28516	51.93941	96.9140

Scope of Enantiospecific Displacement of Diisoamylamino Group with Alcohols

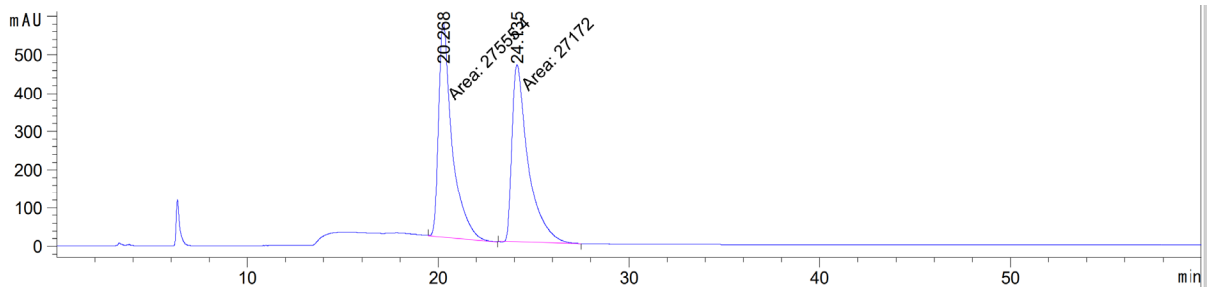
4-(*N*,*N*-dimethylsulfamoyl)phenyl methyl (*R*)-phenylphosphonate (6a)



6a

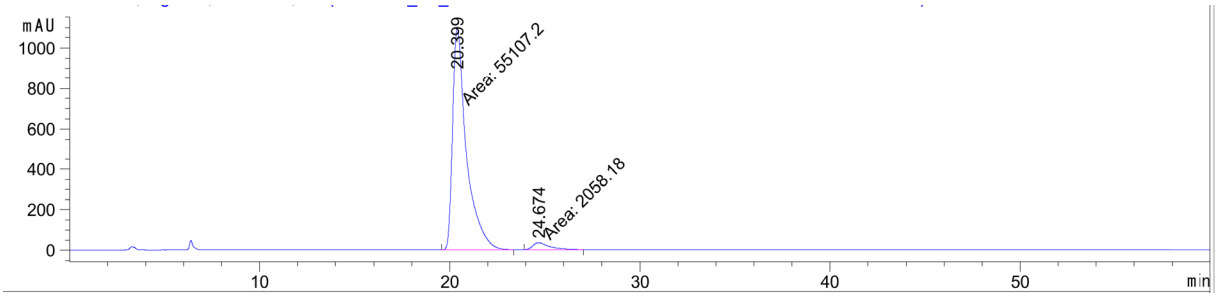
Following **General Procedure E**, phosphonate **6a** (33 mg, 93% yield, 93% ee) was produced as a colorless oil from phosphonamidate **5a** (48 mg, 0.1 mmol, 94% ee), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddt, *J* = 13.9, 6.9, 1.4 Hz, 2H), 7.80 – 7.67 (m, 2H), 7.67 – 7.57 (m, 1H), 7.51 (ddd, *J* = 8.6, 7.0, 4.6 Hz, 2H), 7.41 – 7.29 (m, 2H), 3.90 (d, *J* = 11.4 Hz, 3H), 2.69 (s, 6H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.97 (d, *J* = 6.8 Hz), 133.42 (d, *J* = 3.1 Hz), 132.04 (d, *J* = 10.3 Hz), 132.03, 129.74, 128.83 (d, *J* = 15.7 Hz), 126.14 (d, *J* = 191.6 Hz), 120.96 (d, *J* = 4.8 Hz), 53.34 (d, *J* = 5.9 Hz), 37.89 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.34 ; HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_5PS$ $(M+H)^+$: 356.0716; found: 356.0716. Phosphonate **6a** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 20% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 24.7 min, t_R(major) = 20.4 min).

Racemic Sample:



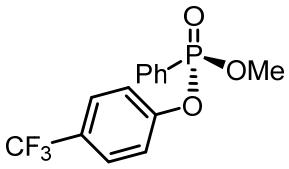
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.268	MM	0.8207	2.75554e4	559.59259	50.3503
2	24.135	MM	0.9792	2.71720e4	462.48834	49.6497

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.399	MM	0.8395	5.51072e4	1094.08679	96.3996
2	24.674	MM	1.0070	2058.18286	34.06351	3.6004

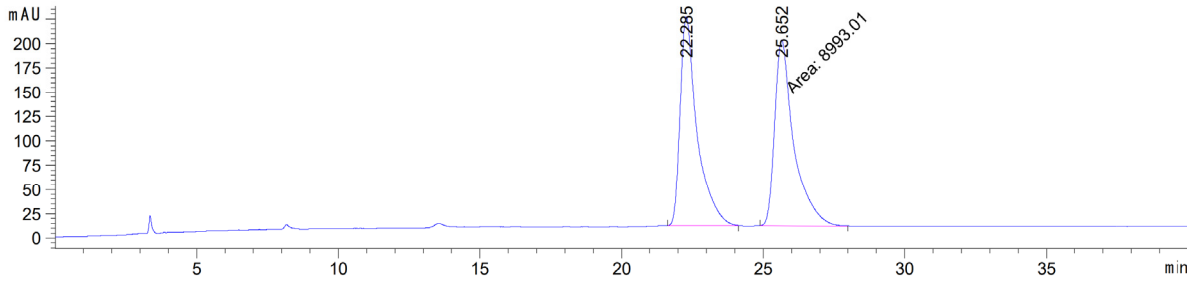
Methyl (4-(trifluoromethyl)phenyl) (*R*)-phenylphosphonate (6b)



6b

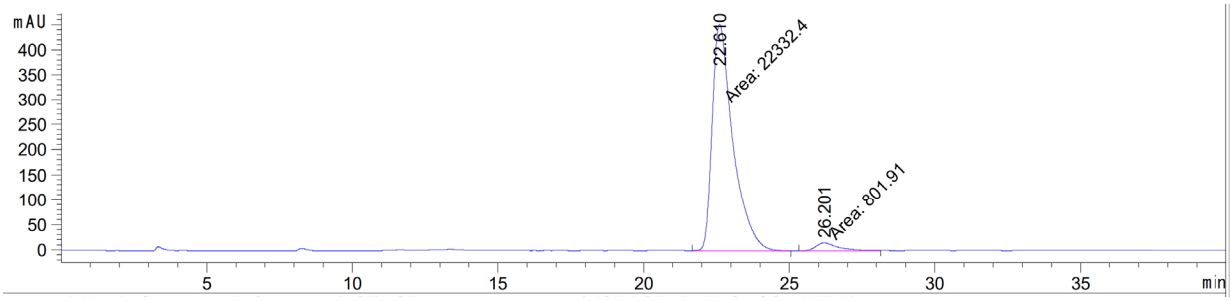
Following **General Procedure E**, phosphonate **6b** (132 mg, 74% yield, 93% ee) was produced as a colorless oil from phosphonamidate **5b** (251 mg, 0.57 mmol), methanol (2.8 mL), and *para*-tolylsulfonic acid monohydrate (325 mg, 1.71 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 50% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (ddd, J = 13.8, 8.3, 1.4 Hz, 2H), 7.67 – 7.44 (m, 5H), 7.29 (d, J = 8.6 Hz, 2H), 3.89 (d, J = 11.4 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.13 (d, J = 6.5 Hz), 133.29 (d, J = 3.1 Hz), 132.05 (d, J = 10.2 Hz), 128.76 (d, J = 15.6 Hz), 127.19 (q, J = 32.5 Hz), 127.11 (q, J = 3.8 Hz), 126.33 (d, J = 191.5 Hz), 123.86 (q, J = 271.8 Hz), 120.83 (d, J = 4.6 Hz), 53.26 (d, J = 5.8 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.18 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.21 ; HRMS (ESI) m/z calcd for $C_{14}H_{13}F_3O_3P$ $(M+H)^+$: 317.0549; found: 317.0550. Phosphonate **6b** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 26.2 min, t_R(major) = 22.6 min).

Racemic Sample:



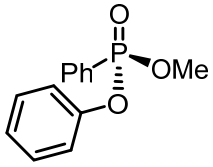
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.285	BB	0.6077	8970.52344	214.58705	49.9374
2	25.652	MM	0.7846	8993.00977	191.02090	50.0626

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.610	MM	0.8225	2.23324e4	452.50851	96.5337
2	26.201	MM	0.8649	801.91028	15.45306	3.4663

Methyl phenyl (*R*)-phenylphosphonate (6c)

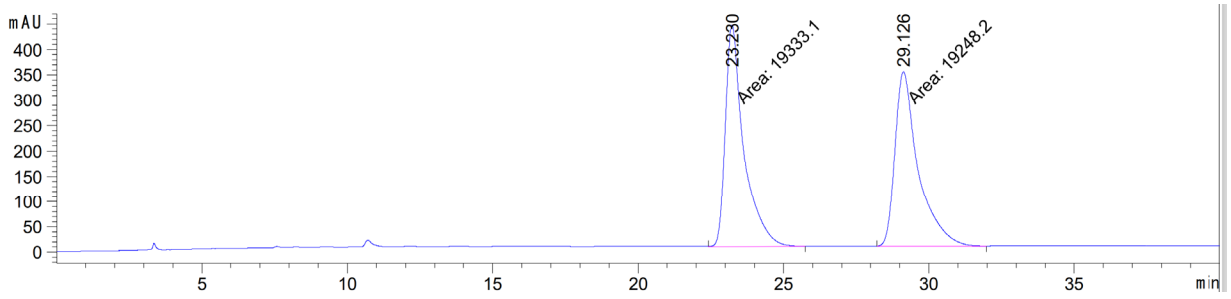


6c

Following **General Procedure E**, phosphonate **6c** (55 mg, 92%; 93% ee) was produced as a colorless oil from phosphonamidate **5c** (90 mg, 0.24 mmol, 93% ee), methanol (1.2 mL), and *para*-tolylsulfonic acid monohydrate (137 mg) with a 24-hour reaction time. The product was purified

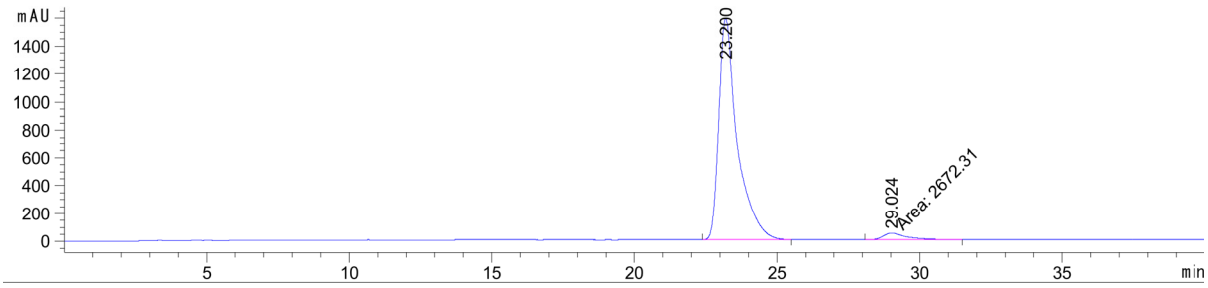
via flash column chromatography (0 to 60% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.67 – 7.54 (m, 1H), 7.53 – 7.43 (m, 2H), 7.33 – 7.24 (m, 3H), 7.17 – 7.09 (m, 2H), 3.87 (d, J = 11.3 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.56 (d, J = 7.2 Hz), 132.92 (d, J = 3.1 Hz), 132.08 (d, J = 10.2 Hz), 129.69, 128.59 (d, J = 15.5 Hz), 126.98 (d, J = 191.1 Hz), 124.90, 120.51 (d, J = 4.5 Hz), 53.10 (d, J = 5.9 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.82 ; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_3P$ $(M+H)^+$: 249.0675; found: 249.0675. Phosphonate **6c** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 29.0 min, t_R(major) = 23.2 min).

Racemic Sample:



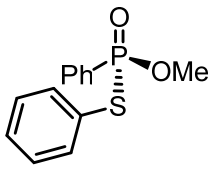
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.230	MM	0.7373	1.93331e4	436.99603	50.1099
2	29.126	MM	0.9302	1.92482e4	344.85953	49.8901

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.200	BB	0.6597	7.14970e4	1586.84241	96.3970
2	29.024	MM	0.9334	2672.30884	47.71827	3.6030

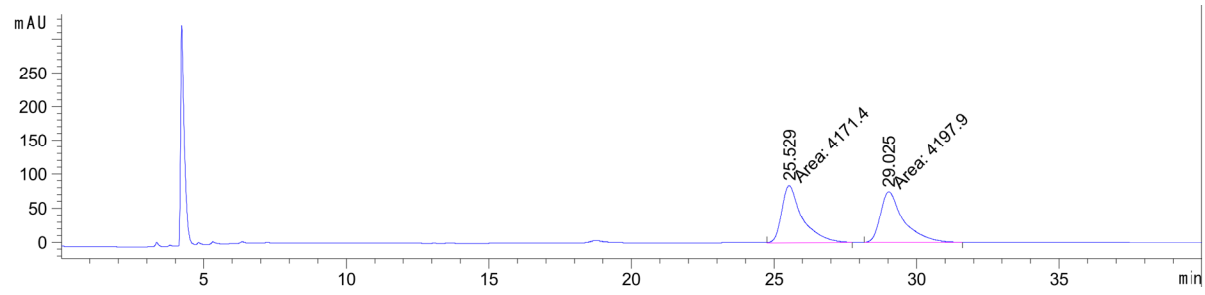
_O_-methyl _S_-phenyl (_R_)-phenylphosphonothioate (6d)



6d

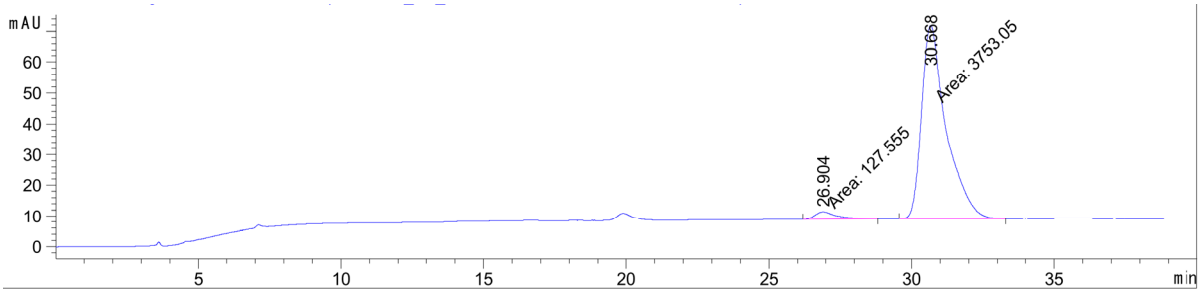
Following **General Procedure E**, phosphonothioate **6d** (197 mg, 82% yield, 93% ee) was produced as a colorless oil from phosphonamidothioate **5d** (350 mg, 0.9 mmol, 94% ee), methanol (3 mL), and *para*-tolylsulfonic acid monohydrate (513 mg, 27 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 60% Et_2O in Hexanes). *Note: this product must be stored under inert atmosphere below 0 °C, preferably at –80 °C.* ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 2H), 7.55 – 7.45 (m, 1H), 7.37 (ddd, *J* = 8.9, 7.0, 4.6 Hz, 2H), 7.29 (ddt, *J* = 7.0, 3.8, 1.4 Hz, 3H), 7.24 – 7.17 (m, 2H), 3.95 (d, *J* = 12.3 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.53 (d, *J* = 4.3 Hz), 132.61 (d, *J* = 3.3 Hz), 131.47 (d, *J* = 10.6 Hz), 131.00 (d, *J* = 151.1 Hz), 129.20 (d, *J* = 2.3 Hz), 129.05 (d, *J* = 2.9 Hz), 128.23 (d, *J* = 15.1 Hz), 126.48 (d, *J* = 5.7 Hz), 52.44 (d, *J* = 7.0 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.65 ; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_2PS$ $(M+H)^+$: 265.0447; found: 265.0448. Phosphonothioate **6d** was determined to be 93% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 26.9 min, t_R(major) = 30.7 min).

Racemic Sample:



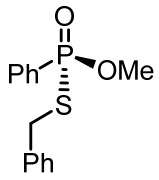
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.529	MM	0.8282	4171.40186	83.94846	49.8417
2	29.025	MM	0.9353	4197.89648	74.80561	50.1583

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.904	MM	0.8621	127.55495	2.46610	3.2870
2	30.668	MM	0.9956	3753.04932	62.82982	96.7130

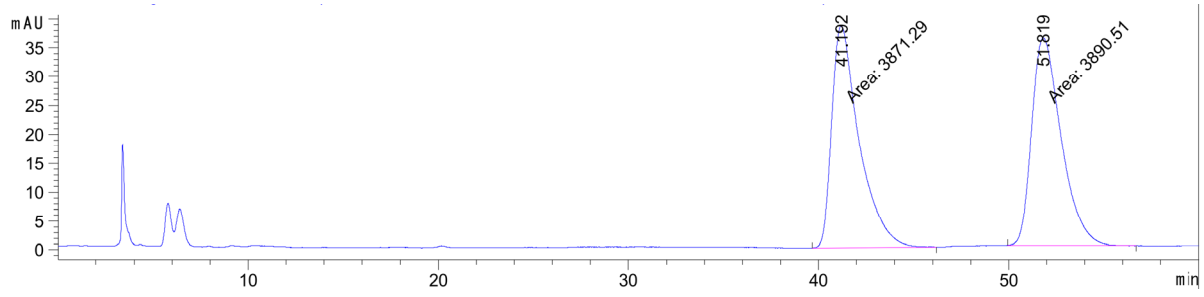
***S*-benzyl *O*-methyl (*R*)-phenylphosphonothioate (6e)**



6e

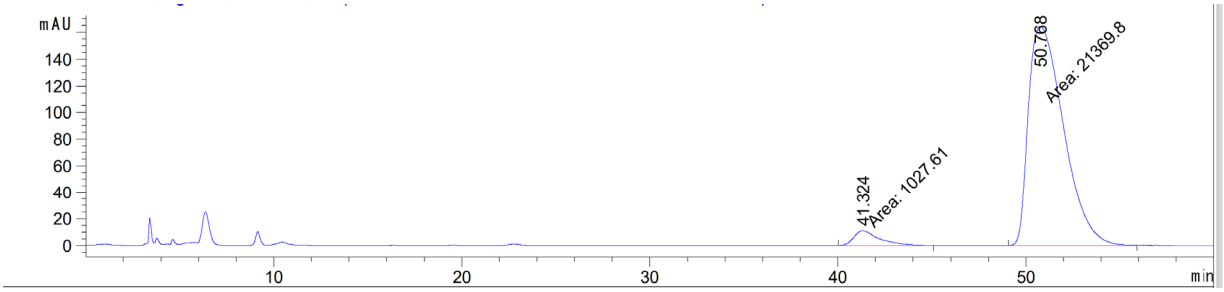
Following **General Procedure E**, phosphonothioate **6e** (21 mg, 79% yield, 92% ee) was produced as a colorless oil from phosphonamidothioate **5e** (40 mg, 0.1 mmol, 94% ee, prepared via **General Procedure B**), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 60% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.72 (m, 2H), 7.64 – 7.53 (m, 1H), 7.48 (ddd, *J* = 8.4, 6.8, 4.4 Hz, 2H), 7.32 – 7.09 (m, 5H), 4.11 – 3.89 (m, 2H), 3.81 (d, *J* = 12.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.23 (d, *J* = 5.1 Hz), 132.62 (d, *J* = 3.3 Hz), 132.07 (d, *J* = 151.1 Hz), 131.19 (d, *J* = 10.9 Hz), 128.74 (d, *J* = 29.5 Hz), 128.63, 128.48, 127.49, 52.23 (d, *J* = 6.9 Hz), 34.49 (d, *J* = 2.9 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.65 ; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2PS$ $(M+H)^+$: 279.0603; found: 279.0604. Phosphonothioate **6e** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK AS-H, 5% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 41.3 min, t_R(major) = 50.8 min).

Racemic Sample:



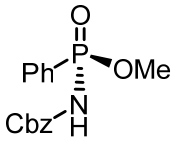
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.192	MM	1.6746	3871.28516	38.52939	49.8761
2	51.819	MM	1.8013	3890.51367	35.99757	50.1239

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.324	MM	1.5635	1027.60706	10.95381	4.5881
2	50.768	MM	2.1658	2.13698e4	164.44994	95.4119

Benzyl (*R*)-(methoxy(phenyl)phosphoryl)carbamate (6f)

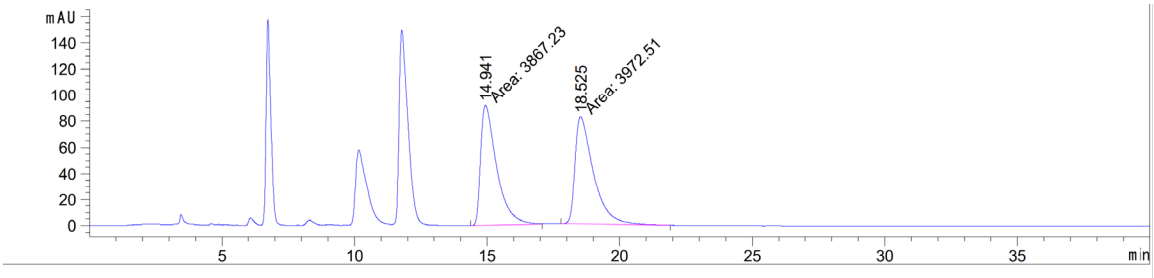


6f

Following **General Procedure E**, phosphonamidate **6f** (27 mg, 86% yield, 92% ee) was produced as a colorless solid from compound **5f** (43 mg, 0.1 mmol, 92% ee), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (ddt, *J*

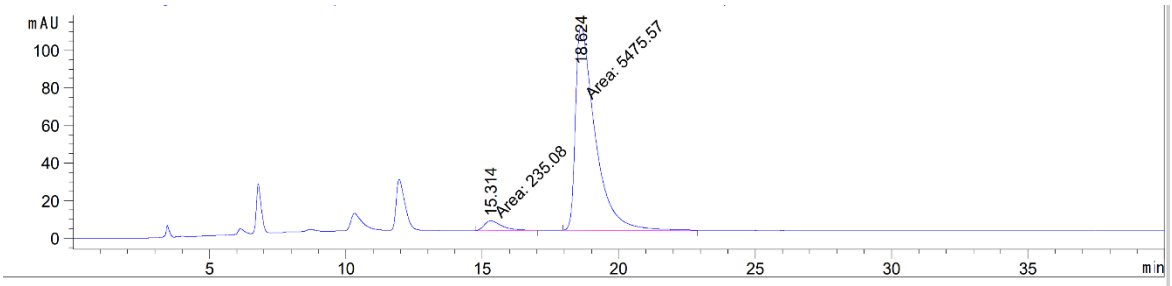
= 14.0, 6.8, 1.4 Hz, 2H), 7.57 (td, *J* = 7.4, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.7, 7.0, 4.4 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.23 (dd, *J* = 6.7, 3.0 Hz, 2H), 6.30 (d, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 2.3 Hz, 2H), 3.84 (d, *J* = 11.7 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.86 (d, *J* = 5.3 Hz), 135.11, 132.92 (d, *J* = 3.2 Hz), 132.06 (d, *J* = 10.7 Hz), 128.59, 128.49, 128.34, 128.21, 128.02 (d, *J* = 182.0 Hz), 67.96, 52.04 (d, *J* = 6.3 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.09 ; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_4P$ $(M+H)^+$: 306.0890; found: 306.0890. Phosphonamidate **6f** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK IB, 10% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 15.3 min, t_R(major) = 18.6 min).

Racemic Sample:



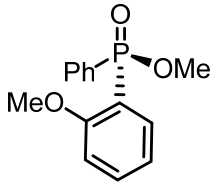
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.941	MM	0.7028	3867.23462	91.71310	49.3286
2	18.525	MM	0.8071	3972.50635	82.03683	50.6714

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.314	MM	0.7620	235.08018	5.14141	4.1165
2	18.624	MM	0.8362	5475.56934	109.13271	95.8835

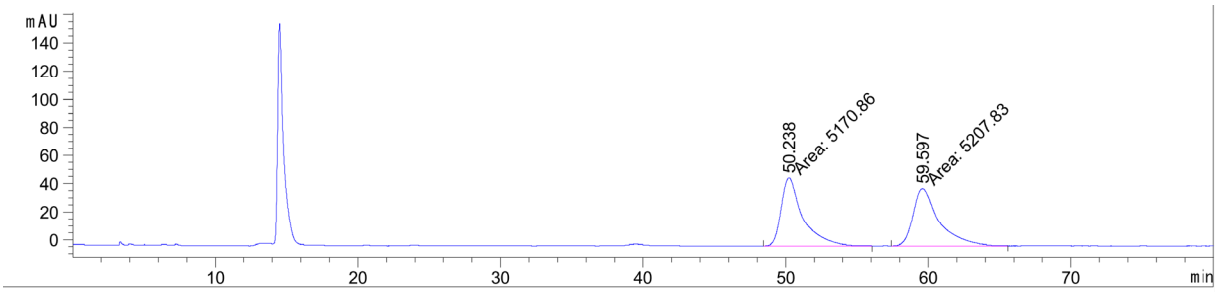
Methyl (*R*)-(2-methoxyphenyl)(phenyl)phosphinate (6g)



6g

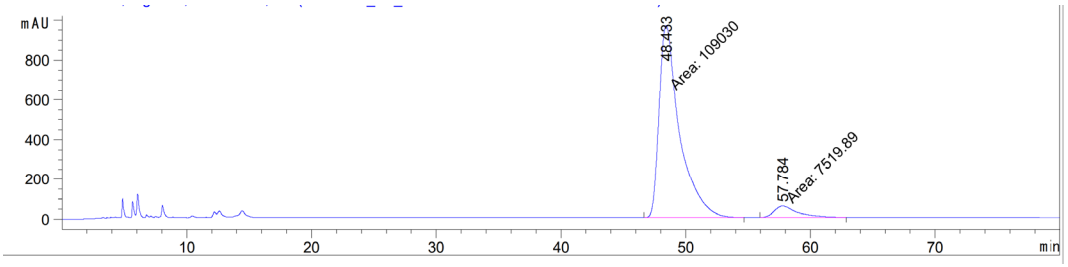
Following **General Procedure E**, phosphinate **6g** (18 mg, 70% yield, 87% ee) was produced as a colorless oil from phosphinamidate **5g** (39 mg, 0.1 mmol), methanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.). The product was purified via flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 13.3, 7.6, 1.8 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.50 (dddd, *J* = 9.5, 6.7, 2.3, 1.1 Hz, 2H), 7.46 – 7.36 (m, 2H), 7.07 (tdd, *J* = 7.5, 2.6, 0.9 Hz, 1H), 6.87 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 3H), 3.71 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.01 (d, *J* = 3.9 Hz), 134.81 (d, *J* = 6.3 Hz), 134.46 (d, *J* = 2.0 Hz), 132.00 (d, *J* = 142.6 Hz), 131.86, 131.79, 131.76, 128.04 (d, *J* = 13.6 Hz), 120.66 (d, *J* = 12.3 Hz), 111.26 (d, *J* = 7.9 Hz), 55.53, 51.42 (d, *J* = 6.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.72 ; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_3P$ $(M+H)^+$: 263.0832; found: 263.0833. Phosphinate **6g** was determined to be 87% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 57.8 min, t_R(major) = 48.4 min).

Racemic Sample:



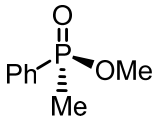
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.238	MM	1.7740	5170.85547	48.58001	49.8219
2	59.597	MM	2.1236	5207.82520	40.87336	50.1781

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.433	MM	1.8838	1.09030e5	964.60413	93.5479
2	57.784	MM	2.1621	7519.89063	57.96749	6.4521

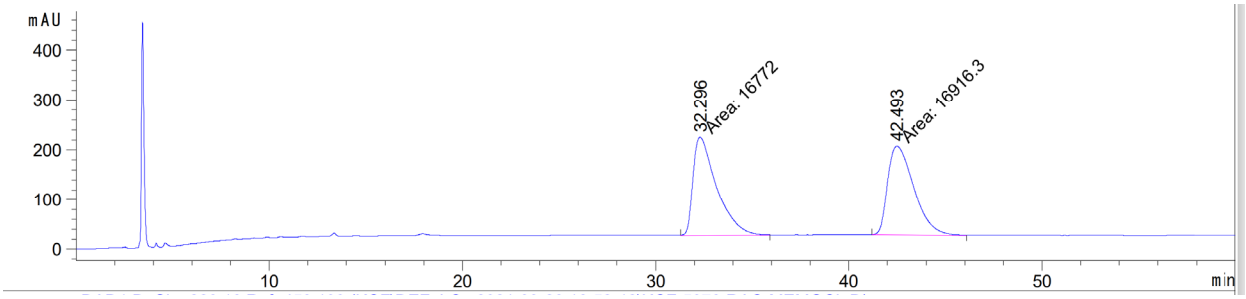
Methyl (*S*)-methyl(phenyl)phosphinate (6h)



6h

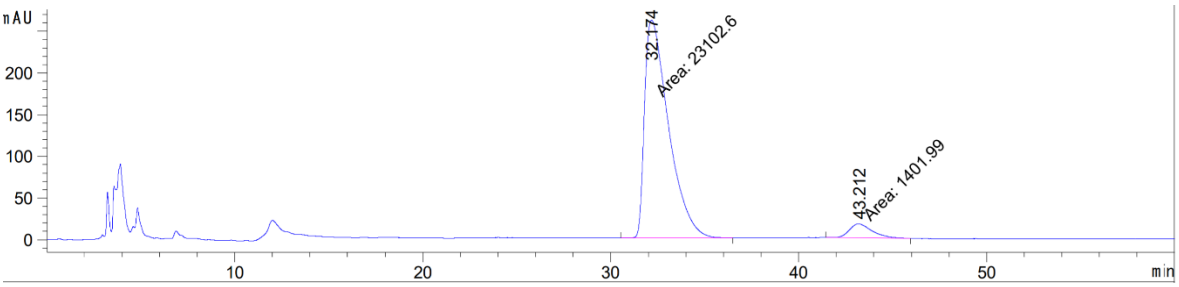
Phosphinamidate **5h** (29.5 mg, 0.1 mmol, 1 equiv.) was added to a 1-dram vial equipped with a magnetic stir bar. 25 mg of H_3PO_3 (0.3 mmol, 3 equiv.) was then dissolved in methanol (1 mL) and added to the vial, which was then capped with a septum and sealed with parafilm. The resulting solution was subjected to stirring at room temperature for 48 hours. The product was then purified via flash column chromatography on silica gel (0 to 10% MeOH in DCM). Phosphinate **6h** (8 mg, 48% yield, 89% ee) was afforded as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.72 (m, 2H), 7.62 – 7.52 (m, 1H), 7.55 – 7.42 (m, 2H), 3.61 (d, J = 11.3 Hz, 3H), 1.67 (d, J = 14.6 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.37 (d, J = 2.8 Hz), 131.33 (d, J = 10.2 Hz), 131.04 (d, J = 126.8 Hz), 128.72 (d, J = 12.6 Hz), 51.04 (d, J = 6.2 Hz), 15.53 (d, J = 103.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.07 ; HRMS (ESI) m/z calcd for $C_8H_{12}O_2P$ $(M+H)^+$: 171.0569; found: 171.0569. Phosphinate **6h** was determined to be 89% ee by chiral HPLC analysis (CHIRALPAK AS-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 43.2 min, t_R(major) = 32.2 min).

Racemic Sample:



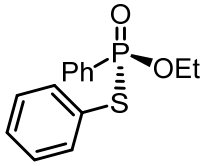
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.296	MM	1.4131	1.67720e4	197.81993	49.7858
2	42.493	MM	1.5762	1.69163e4	178.87239	50.2142

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.174	MM	1.4762	2.31026e4	260.83728	94.2787
2	43.212	MM	1.3991	1401.99255	16.70129	5.7213

_O_-ethyl _S_-phenyl (_R_)-phenylphosphonothioate (6i)

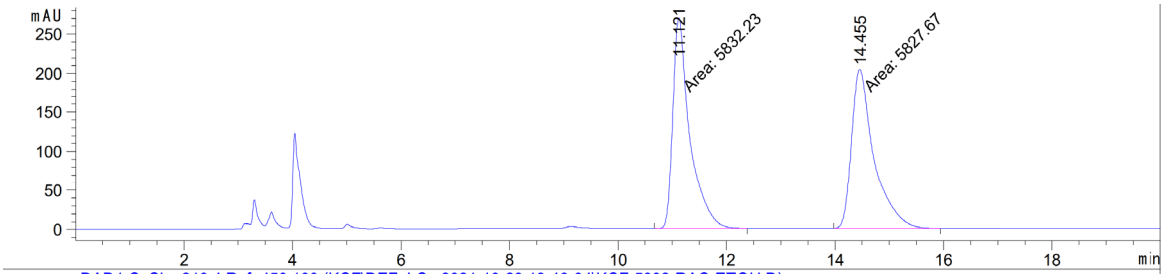


6i

Following **General Procedure E**, phosphonothioate **6i** (14 mg, 58% yield, 92% ee) was produced as a colorless oil from phosphonamidothioate **5d** (39 mg, 0.1 mmol, 93% ee), ethanol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.) for a 72-hour reaction time. The product was purified via flash column chromatography (slow gradient of 0 to 60% Et_2O in Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddt, J = 13.6, 6.8, 1.4 Hz, 2H), 7.56 – 7.44 (m, 1H), 7.44 – 7.32 (m, 2H), 7.32 – 7.25 (m, 3H), 7.20 (dd, J = 8.3, 6.3 Hz, 2H), 4.64 – 4.14 (m, 2H), 1.49 – 1.34 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.52 (d, J = 4.3 Hz), 132.49 (d, J = 3.2 Hz), 131.56 (d, J = 150.6 Hz), 131.46 (d, J = 10.7 Hz), 129.12 (d, J = 2.3 Hz), 128.97 (d, J = 2.7 Hz), 128.20 (d, J = 14.9 Hz), 126.68 (d, J = 5.6 Hz), 62.47 (d, J = 6.9 Hz), 16.35 (d, J = 6.8 Hz) ;

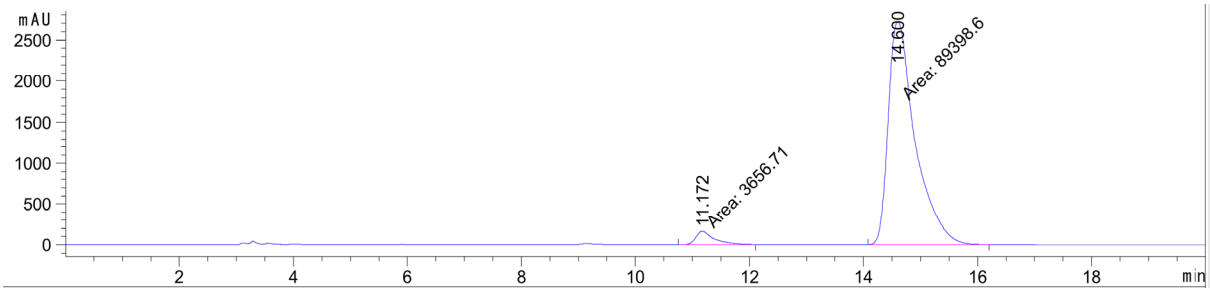
^{31}P NMR (162 MHz, $CDCl_3$) δ 41.66 ; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2PS$ $(M+H)^+$: 279.0603; found: 279.0604. Phosphonothioate **6i** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 11.2 min, t_R(major) = 14.6 min).

Racemic Sample:



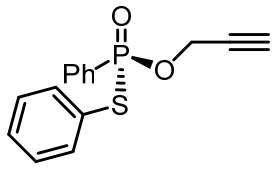
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.121	MM	0.3613	5832.23145	269.06909	50.0196
2	14.455	MM	0.4759	5827.66846	204.07596	49.9804

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.172	MM	0.3710	3656.70728	164.25067	3.9296
2	14.600	MM	0.5490	8.93986e4	2714.03076	96.0704

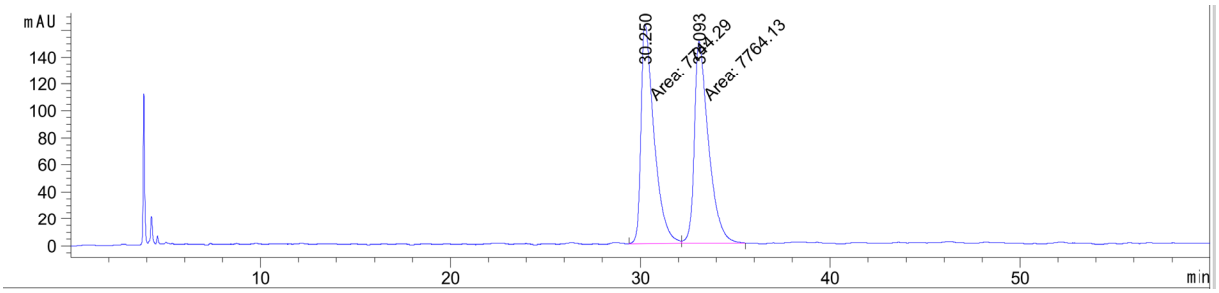
***S*-phenyl *O*-(prop-2-yn-1-yl) (*R*)-phenylphosphonothioate (6j)**



6j

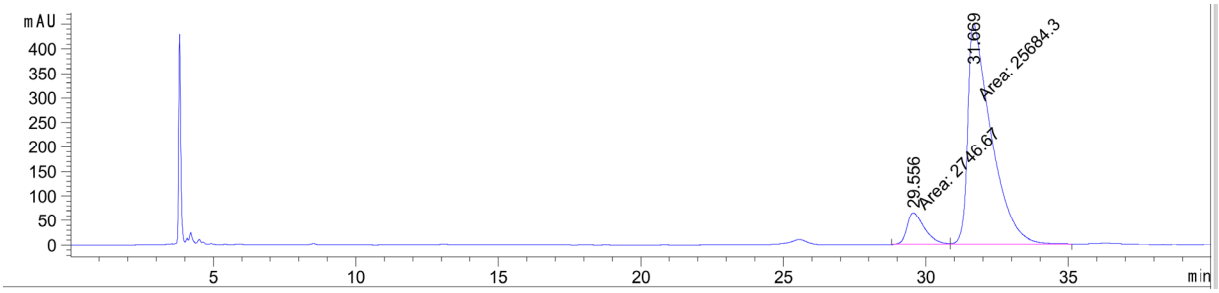
Following **General Procedure E**, phosphonothioate **6j** (14 mg, 49% yield, 81% ee) was produced as a colorless oil from phosphonamidothioate **5d** (39 mg, 0.1 mmol, 93% ee), propargyl alcohol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.) for a 48-hour reaction time. The product was purified via flash column chromatography (slow gradient of 0 to 50% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (ddt, *J* = 13.9, 6.8, 1.4 Hz, 2H), 7.58 – 7.44 (m, 1H), 7.41 – 7.27 (m, 5H), 7.22 (dd, *J* = 8.3, 6.9 Hz, 2H), 5.07 – 4.68 (m, 2H), 2.58 (t, *J* = 2.5 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.73 (d, *J* = 4.3 Hz), 132.83 (d, *J* = 3.3 Hz), 131.49 (d, *J* = 10.9 Hz), 130.68 (d, *J* = 148.8 Hz), 129.25 (d, *J* = 1.9 Hz), 129.22 (d, *J* = 2.5 Hz), 128.28 (d, *J* = 15.0 Hz), 125.91 (d, *J* = 5.7 Hz), 77.66 (d, *J* = 9.2 Hz), 76.27, 53.32 (d, *J* = 5.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.39 ; HRMS (ESI) m/z calcd for $C_{15}H_{14}O_2PS$ $(M+H)^+$: 289.0447; found: 289.0447. Phosphonothioate **6j** was determined to be 81% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 29.6 min, t_R(major) = 31.7 min).

Racemic Sample:



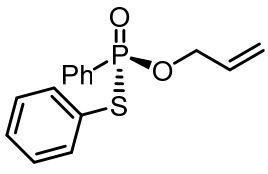
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.250	MF	0.7928	7744.29395	162.80408	49.9360
2	33.093	FM	0.8633	7764.13330	149.89427	50.0640

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.556	MF	0.7082	2746.66553	64.64251	9.6608
2	31.669	FM	0.9521	2.56843e4	449.61768	90.3392

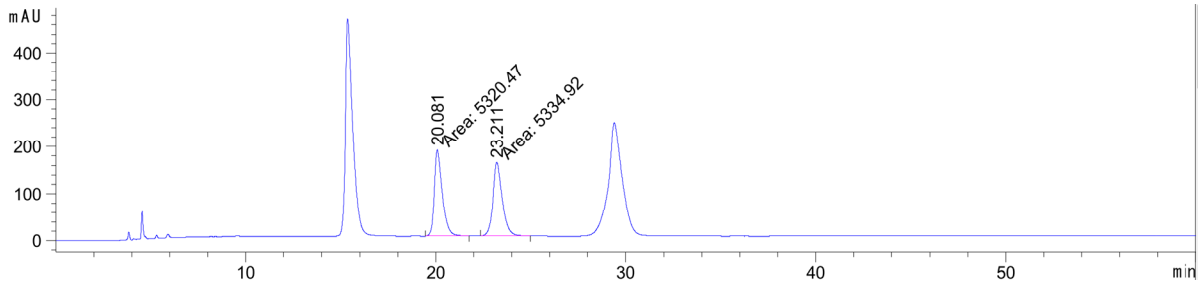
***O*-allyl *S*-phenyl (*R*)-phenylphosphonothioate (6k)**



6k

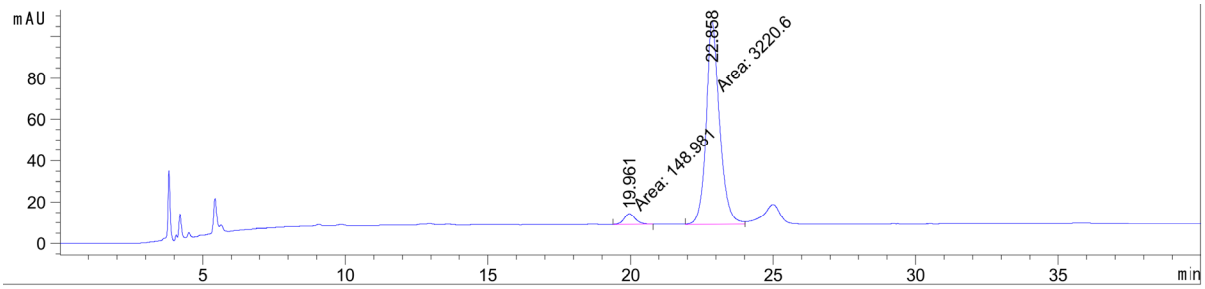
Following **General Procedure E**, phosphonothioate **6k** (16 mg, 55% yield, 91% ee) was afforded as a colorless oil from phosphonamidothioate **5d** (39 mg, 0.1 mmol, 93% ee), allyl alcohol (0.5 mL), and *para*-tolylsulfonic acid monohydrate (57 mg, 0.3 mmol, 3 equiv.) for a 48-hour reaction time. The product was purified via flash column chromatography on silica gel (slow gradient of 0 to 50% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (ddt, *J* = 13.6, 6.9, 1.3 Hz, 2H), 7.51 – 7.40 (m, 1H), 7.34 (tdd, *J* = 7.8, 5.5, 3.1 Hz, 2H), 7.30 – 7.22 (m, 3H), 7.17 (dd, *J* = 8.5, 6.6 Hz, 2H), 5.96 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.35 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.74 (ddt, *J* = 8.4, 5.5, 1.4 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.61 (d, *J* = 4.2 Hz), 132.60 (d, *J* = 3.3 Hz), 132.51 (d, *J* = 7.5 Hz), 131.47 (d, *J* = 10.6 Hz), 131.30 (d, *J* = 150.1 Hz), 129.16 (d, *J* = 2.3 Hz), 129.05 (d, *J* = 2.9 Hz), 128.24 (d, *J* = 15.0 Hz), 126.44 (d, *J* = 5.7 Hz), 118.46, 66.41 (d, *J* = 6.6 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.47 ; HRMS (ESI) m/z calcd for $C_{15}H_{16}O_2PS$ $(M+H)^+$: 291.0603; found: 291.0605. Phosphonothioate **6k** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK IB, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 19.9 min, t_R(major) = 22.9 min).

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.081	MM	0.4866	3925.65991	134.46416	49.8875
2	23.211	MM	0.5716	3943.36353	114.98200	50.1125

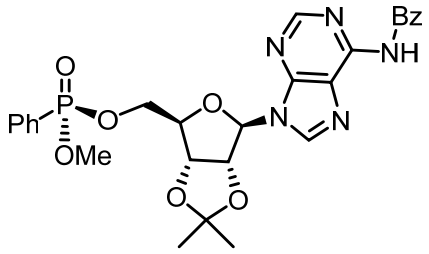
Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.961	MM	0.4631	148.98062	5.36222	4.4213
2	22.858	MF	0.5458	3220.59521	98.34910	95.5787

Stereospecific phosphonylation of precious alcohols with phosphonothioate 6d

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-benzamido-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl methyl (*S*)-phenylphosphonate (7a)

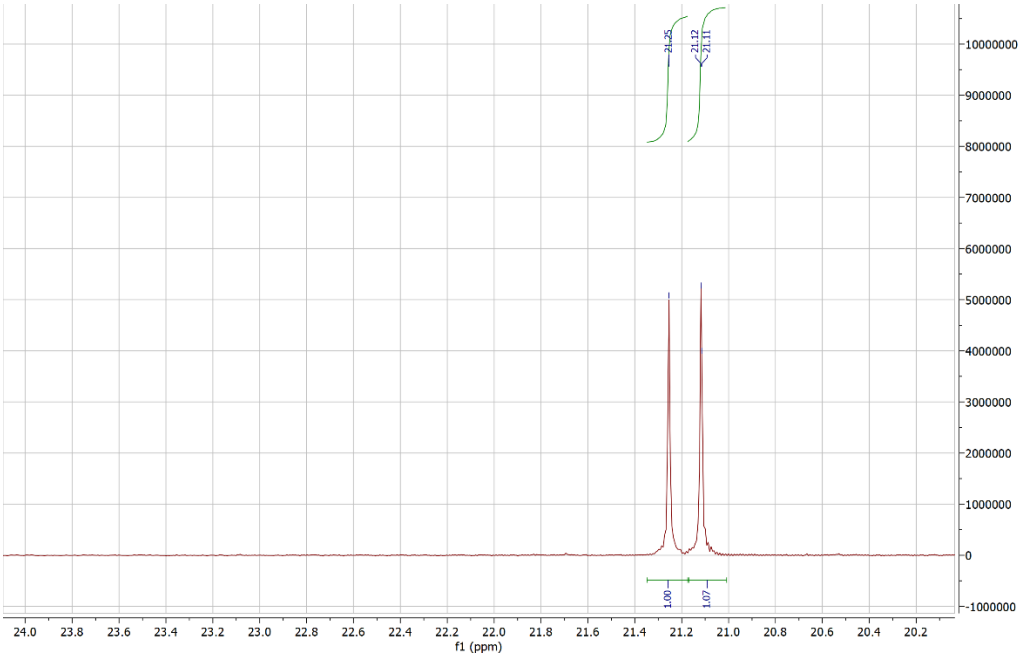


7a

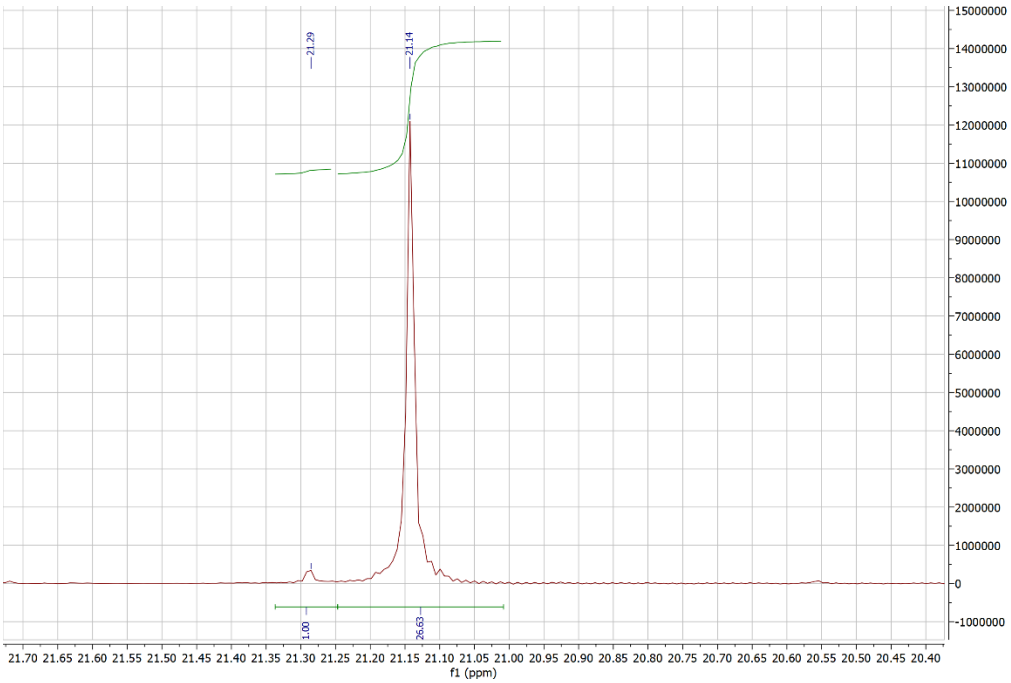
Following **General Procedure F**, phosphonate **7a** (32.3 mg, 57% yield, 27:1 dr) was produced as a white solid from phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) and N6-Benzoyl-2',3'-isopropylideneadenosine (41 mg, 0.1 mmol, 1 equiv.). The product was purified via flash chromatography on silica gel. First, ten column volumes of 100% ethyl acetate were passed through the column to remove thiophenol and any remaining starting materials. Then, a gradient of 0 to 10% MeOH in DCM was used to elute the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.74 (s, 1H), 8.17 (s, 1H), 8.07 – 7.99 (m, 2H), 7.77 – 7.65 (m, 2H), 7.64 – 7.59 (m, 1H), 7.58 – 7.49 (m, 3H), 7.40 (td, *J* = 7.7, 4.4 Hz, 2H), 6.19 (d, *J* = 2.4 Hz, 1H), 5.43 (dd, *J* = 6.2, 2.5 Hz, 1H), 5.10 (dd, *J* = 6.3, 2.8 Hz, 1H), 4.55 (td, *J* = 4.4, 2.6 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.68 (d, *J* = 11.2 Hz, 3H), 1.62 (s, 3H), 1.41 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.72, 151.13, 149.59, 141.89, 133.59, 133.00 (d, *J* = 3.0 Hz), 132.89, 131.81 (d, *J* = 10.1 Hz), 128.93, 128.62 (d, *J* = 15.2 Hz), 127.88, 126.21 (d, *J* = 188.2 Hz), 123.41, 114.70, 91.54, 85.59 (d, *J* = 7.4 Hz), 84.34, 81.51, 65.23 (d, *J* = 5.2 Hz), 52.95 (d, *J* = 5.2 Hz), 27.16, 25.38 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.14. HRMS (ESI) m/z calcd for $C_{27}H_{29}N_5O_7P$ $(M+H)^+$: 566.1799; found: 566.1794. D.r. of

phosphonate **7a** was determined to be 27:1 by ^{31}P NMR 162 MHz, $CDCl_3$ with a 10-second relaxation delay. (Major: δ 21.14, Minor: δ 21.29).

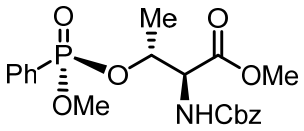
1:1 Mixture of Diastereomers:



Compound 7a:



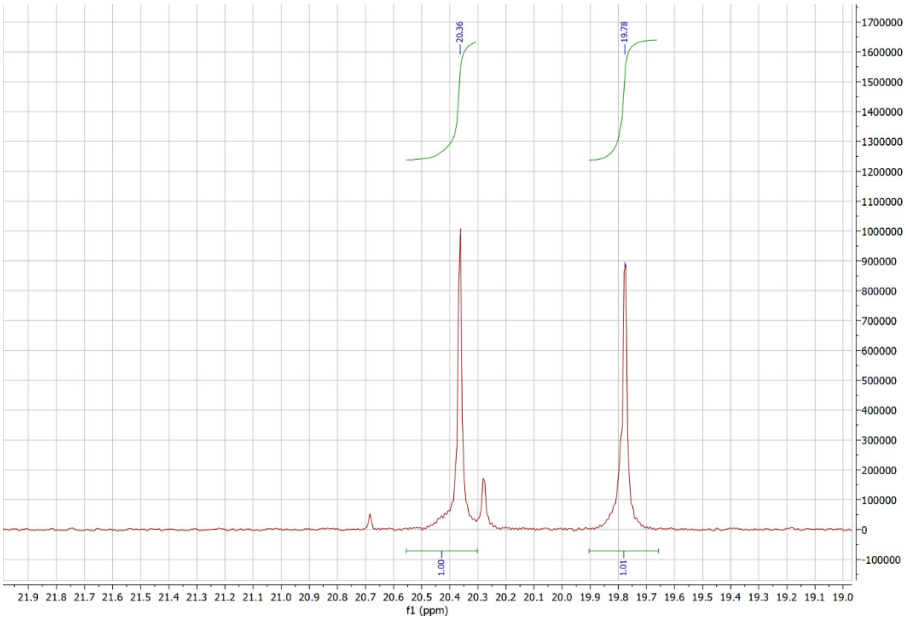
Methyl *N*-((benzyloxy)carbonyl)-*O*-((*S*)-methoxy(phenyl)phosphoryl)-*L*-threoninate (7b)



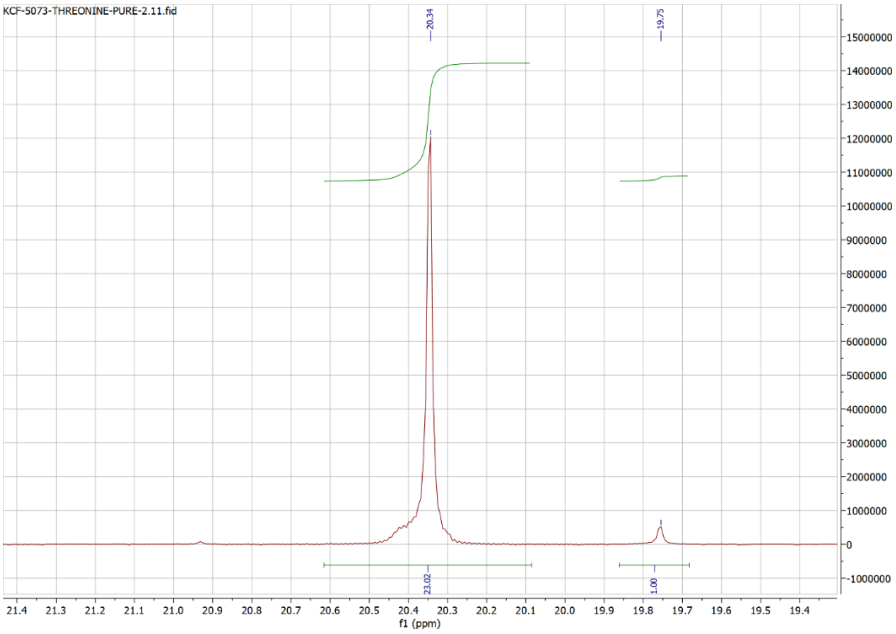
7b

Following **General Procedure F**, phosphonate **7b** (29 mg, 70% yield, 23:1 dr) was produced as a colorless liquid from phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) and *N*-Z-L-threonine methyl ester (33 mg, 0.125 mmol, 1.25 equiv.). The product was purified via flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes with 50% DCM additive throughout). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (ddd, *J* = 13.5, 8.2, 1.4 Hz, 2H), 7.50 – 7.40 (m, 1H), 7.35 (ddd, *J* = 8.4, 7.0, 4.5 Hz, 2H), 7.33 – 7.08 (m, 5H), 5.48 (d, *J* = 9.6 Hz, 1H), 5.07 – 4.94 (m, 3H), 4.32 (dt, *J* = 9.6, 2.2 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 3H), 3.31 (s, 3H), 1.38 (d, *J* = 6.3 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.87, 156.56, 136.05, 132.71 (d, *J* = 3.1 Hz), 131.81 (d, *J* = 10.0 Hz), 128.61, 128.58, 128.37 (d, *J* = 16.8 Hz), 128.15, 125.90 (d, *J* = 74.8 Hz), 73.85 (d, *J* = 5.6 Hz), 67.35, 58.60 (d, *J* = 6.8 Hz), 52.56 (d, *J* = 5.6 Hz), 52.43, 19.31 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.35; HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_7P$ $(M+H)^+$: 422.1363; found: 422.1362. Phosphonate **7b** was determined to be 23:1 d.r. by ^{31}P NMR 162 MHz, $CDCl_3$ with a 10-second relaxation delay (Major: δ 20.34, Minor: δ 19.75).

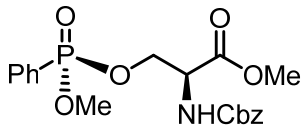
1:1 Mixture of Diastereomers:



Compound 7b:



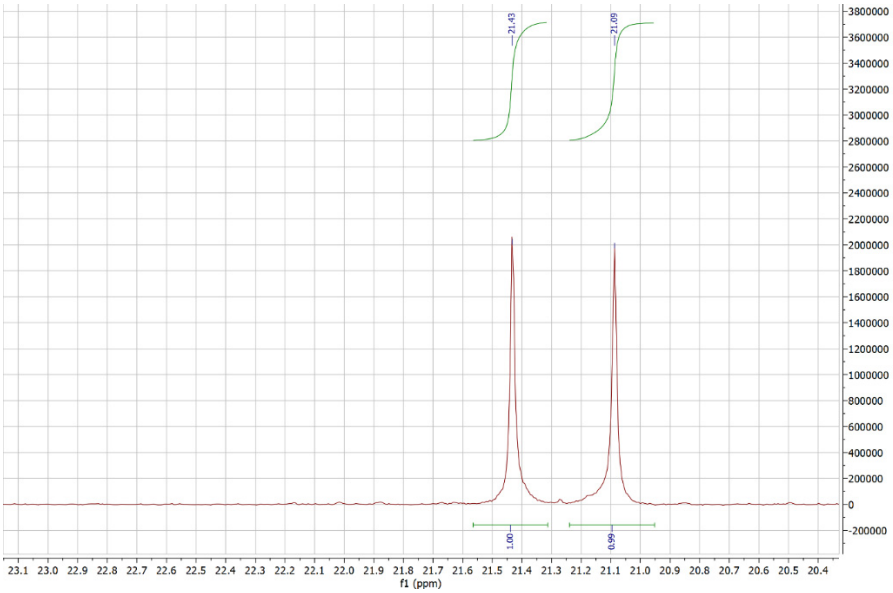
Methyl *N*-((benzyloxy)carbonyl)-*O*-((*S*)-methoxy(phenyl)phosphoryl)-*L*-serinate (7c)



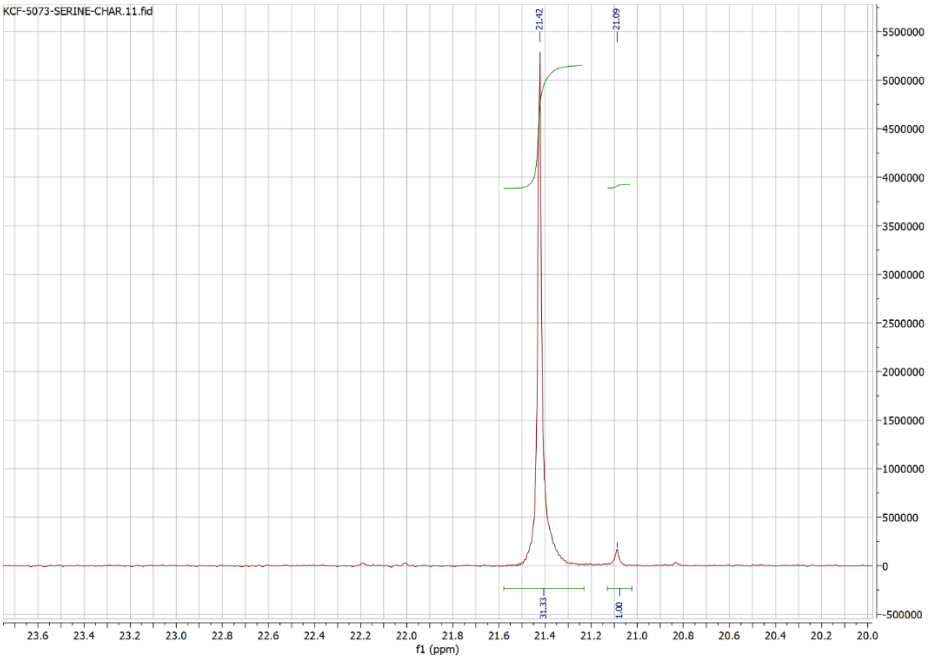
7c

Following **General Procedure F**, phosphonate **7c** (21 mg, 52% yield, 31:1 dr) was produced as a colorless liquid from phosphonothioate **6d** (26.2 mg, 0.1 mmol, 1 equiv.) and *N*-Z-L-serine methyl ester (32 mg, 0.125 mmol, 1.25 equiv.). The product was purified via flash column chromatography on silica gel (slow gradient of 0 to 100% Et_2O in Hexanes with 50% DCM additive throughout). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (ddd, *J* = 13.5, 8.3, 1.4 Hz, 2H), 7.65 – 7.53 (m, 1H), 7.46 (ddd, *J* = 8.6, 6.9, 4.4 Hz, 2H), 7.40 – 7.28 (m, 5H), 6.01 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 4.57 (dd, *J* = 6.9, 3.7 Hz, 1H), 4.44 (ddd, *J* = 10.9, 8.9, 3.4 Hz, 1H), 4.33 (ddd, *J* = 10.8, 6.5, 2.9 Hz, 1H), 3.74 (d, *J* = 11.2 Hz, 3H), 3.68 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.52, 155.89, 136.15, 132.96 (d, *J* = 3.1 Hz), 131.88 (d, *J* = 10.1 Hz), 128.65 (d, *J* = 15.3 Hz), 128.55, 128.23, 128.14, 126.44 (d, *J* = 190.0 Hz), 67.18, 65.84 (d, *J* = 4.9 Hz), 54.55 (d, *J* = 6.0 Hz), 52.88 (d, *J* = 5.6 Hz), 29.72 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.42 ; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_7P$ $(M+H)^+$: 408.1207; found: 408.1204. Phosphonate **7c** was determined to be 31:1 d.r. by ^{31}P NMR (162 MHz, $CDCl_3$) with a 10-second relaxation delay (Major: δ 21.42, Minor: δ 21.09).

1:1 Mixture of Diastereomers:

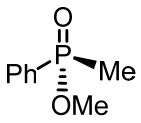


Compound 7c:



Enantiospecific Substitution of Phosphonate 6b with Organomagnesium Reagents

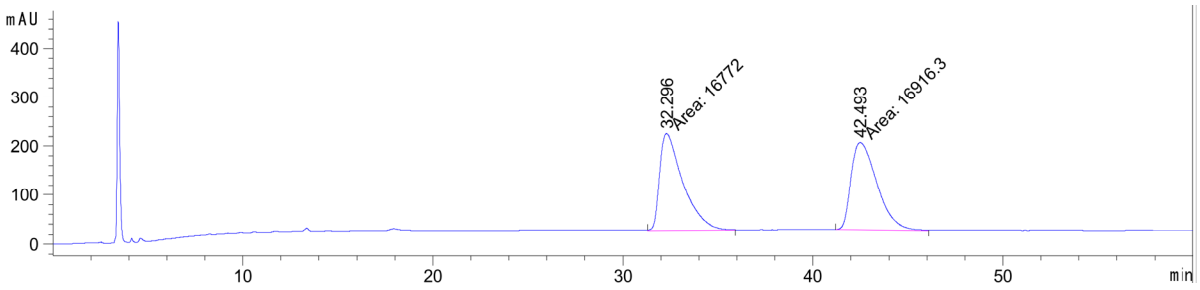
Methyl (*R*)-methyl(phenyl)phosphinate (8a)



8a

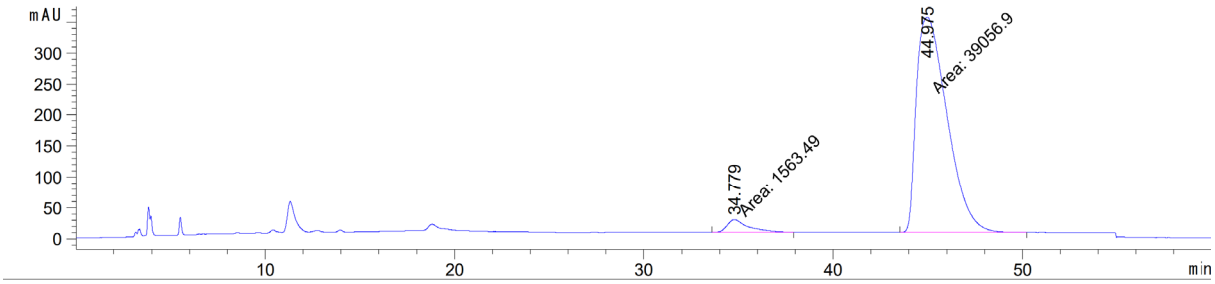
Following **General Procedure G**, phosphinate **8a** (15 mg, 88% yield, 92% ee) was produced as a colorless oil from phosphonate **6b** (32 mg, 0.1 mmol, 93% ee) and methylmagnesium chloride (50 µL, 0.1 mmol, 1 equiv., 2 M solution in THF). The product was purified using flash column chromatography on silica gel (0 to 10% MeOH in DCM). Phosphinate **8a** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK AS-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 34.8 min, t_R(major) = 45.0 min). $[\alpha]^{22}$= +87.5 (c = 4 mg/mL, C_6H_6). Absolute stereochemistry was assigned by comparison to literature value (*14*).

Racemic Sample:



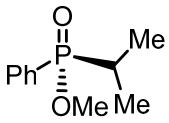
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.296	MM	1.4131	1.67720e4	197.81993	49.7858
2	42.493	MM	1.5762	1.69163e4	178.87239	50.2142

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.779	MM	1.2892	1563.48840	20.21192	3.8490
2	44.975	MM	1.8771	3.90569e4	346.79221	96.1510

Isopropyl (*R*)-methyl(phenyl)phosphinate (8b)

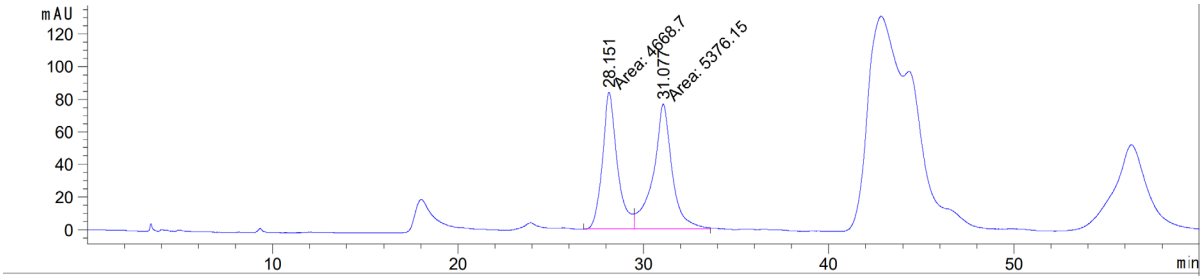


8b

Following **General Procedure G**, phosphinate **8b** (9.4 mg, 95% yield, 91% ee) was produced as a colorless oil from phosphonate **6b** (16 mg, 0.05 mmol, 92% ee) and isopropylmagnesium chloride lithium chloride complex (120 µL, 0.06 mmol, 1.2 equiv., 0.5 M solution in THF). The product was purified using flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.71 (m, 2H), 7.61 – 7.51 (m, 1H), 7.46 (tdd, *J* = 7.1, 4.2, 1.9 Hz, 2H), 4.74 (dhept, *J* = 7.7, 6.2 Hz, 1H), 3.72 (d, *J* = 11.2 Hz, 3H), 1.39 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* =

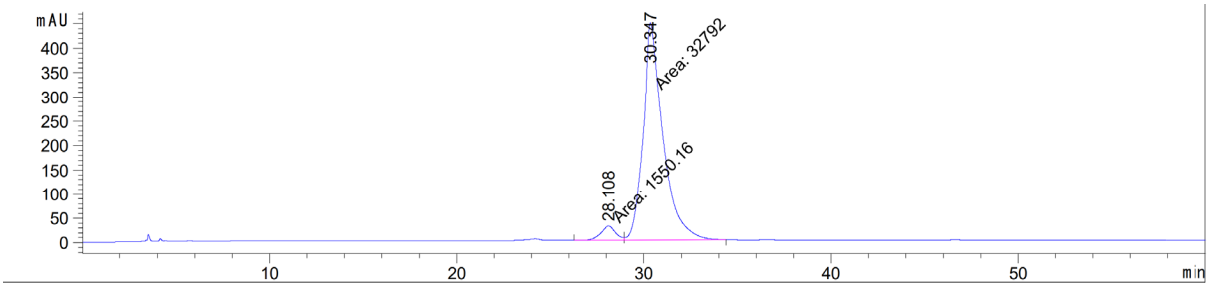
6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.35 (d, J = 3.1 Hz), 131.80 (d, J = 9.8 Hz), 128.45 (d, J = 188.7 Hz), 128.45 (d, J = 15.0 Hz), 71.13 (d, J = 5.7 Hz), 52.39 (d, J = 5.5 Hz), 23.97 (dd, J = 22.9, 4.4 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.12 ; HRMS (ESI) m/z calcd for $C_{10}H_{16}O_2P$ $(M+H)^+$: 199.0882; found: 199.0882. Phosphinate **8b** was determined to be 91% ee by chiral HPLC analysis (CHIRALPAK IA, 1.0% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 28.1 min, t_R(major) = 30.3 min.

Racemic Sample:



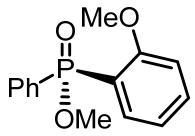
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.151	MF	0.9290	4668.70068	83.76037	46.4786
2	31.077	FM	1.1727	5376.14551	76.40487	53.5214

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.108	MF	0.8843	1550.15649	29.21516	4.5139
2	30.347	FM	1.2249	3.27920e4	446.17682	95.4861

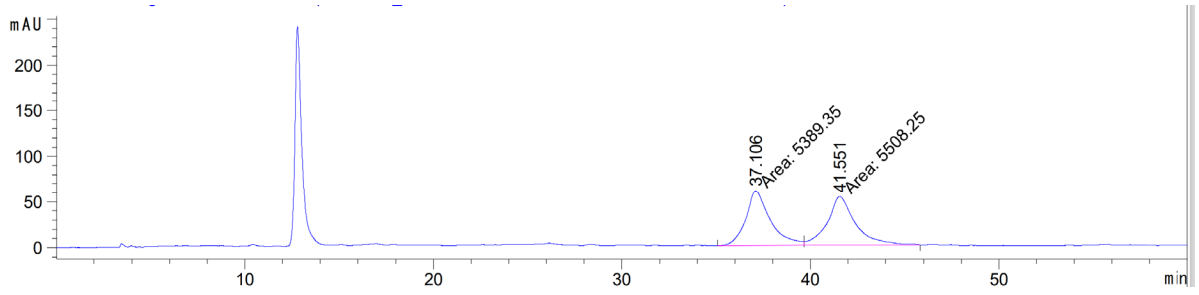
Methyl (*S*)-(2-methoxyphenyl)(phenyl)phosphinate (8c)



8c

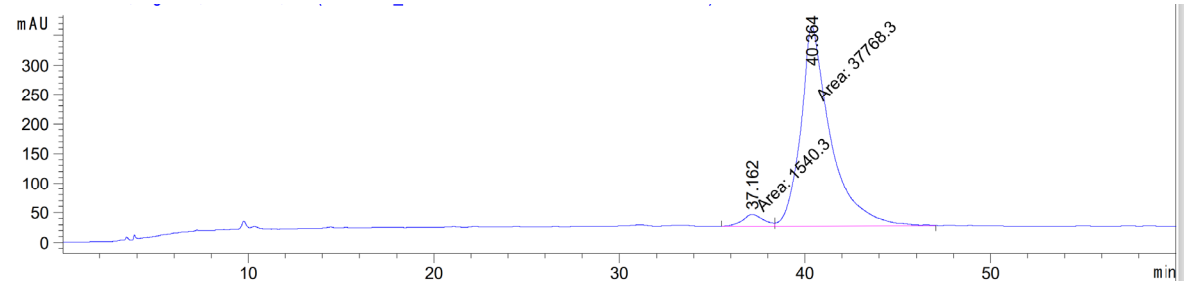
Following **General Procedure G**, phosphinate **8c** (13.7 mg, 97% yield, 92% ee) was produced as a colorless oil from **6b** (16mg, 0.05 mmol, 93% ee). *Note: this reaction was subjected to stirring at –30 °C for 48 hours instead of –50 °C.* Product was purified using flash column chromatography (0 to 10% MeOH in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 13.3, 7.6, 1.8 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.50 (dddd, *J* = 9.5, 6.7, 2.3, 1.1 Hz, 2H), 7.46 – 7.36 (m, 2H), 7.07 (tdd, *J* = 7.5, 2.6, 0.9 Hz, 1H), 6.87 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 3H), 3.71 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.01 (d, *J* = 3.9 Hz), 134.81 (d, *J* = 6.3 Hz), 134.46 (d, *J* = 2.0 Hz), 132.00 (d, *J* = 142.6 Hz), 131.86, 131.79, 131.76, 128.04 (d, *J* = 13.6 Hz), 120.66 (d, *J* = 12.3 Hz), 111.26 (d, *J* = 7.9 Hz), 55.53, 51.42 (d, *J* = 6.1 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.72 ; HRMS (CI-TOF) m/z calcd for $(M+H)^+$, found. Phosphinate **8c** was determined to be 92% ee by chiral HPLC analysis (CHIRALPAK IA, 5% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 37.2 min, t_R(major) = 40.4 min.

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.106	MF	1.5027	5389.35400	59.77253	49.4545
2	41.551	FM	1.7373	5508.25195	52.84269	50.5455

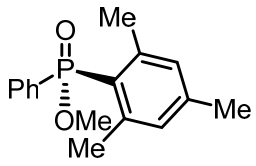
Enriched Sample:



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.162	MF	1.2999	1540.30176	19.74917	3.9185
2	40.364	FM	1.8628	3.77683e4	337.91623	96.0815

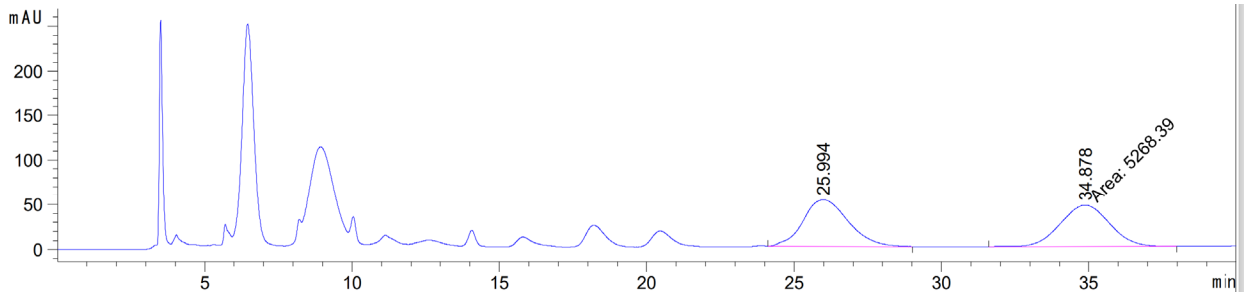
Methyl (*S*)-mesityl(phenyl)phosphinate (8d)



8d

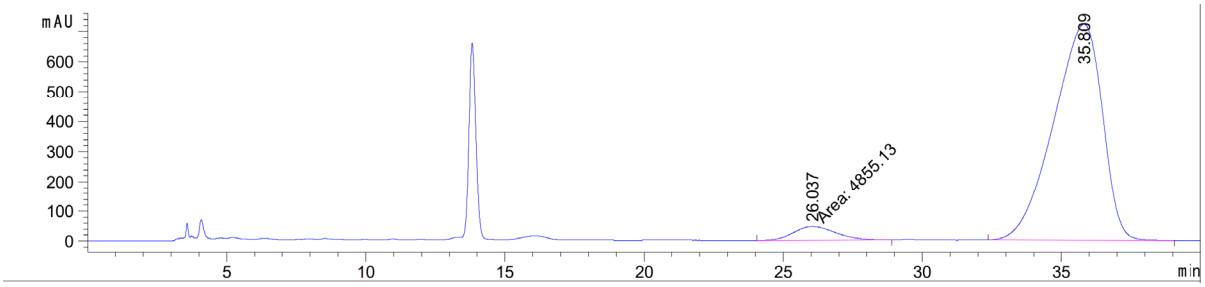
Following **General Procedure G**, phosphinate **8d** (8.4 mg, 31% yield, 89% ee) was produced as a colorless oil via reaction of phosphonate **6b** (16 mg, 0.1 mmol, 93% ee) with 2-mesityl magnesium bromide (0.1 mL, 0.1 mmol, 1 equiv., 1 M in THF). *Note: this reaction was subjected to stirring at room temperature for 36 hours instead of –50 °C.* Product was purified using flash column chromatography (0 to 5% MeOH in DCM). ^{1}H NMR (300 MHz; $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.58 (m, 2H), 7.58 – 7.33 (m, 3H), 6.91 (d, *J* = 4.3 Hz, 2H), 3.74 (d, *J* = 11.3 Hz, 3H), 2.49 (d, *J* = 1.4 Hz, 6H), 2.30 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.92 (d, *J* = 11.3 Hz), 142.22 (d, *J* = 2.8 Hz), 133.24 (d, *J* = 4.8 Hz), 131.74 (d, *J* = 3.1 Hz), 130.86 (d, *J* = 13.1 Hz), 130.50 (d, *J* = 10.9 Hz), 128.46 (d, *J* = 13.4 Hz), 115.53, 50.65 (d, *J* = 5.9 Hz), 23.37 (d, *J* = 3.3 Hz), 21.11 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.42; HRMS (ESI) m/z calcd for $C_{16}H_{19}O_2P$ $(M+H)^+$: 275.1195; found: 275.1195. Phosphinate **8d** was determined to be 89% ee by chiral HPLC analysis (CHIRALCEL OJ-H, 4% iPrOH/hexanes, 1.0 mL/min, 230 nm, t_R(minor) = 26.0 min, t_R(major) = 35.8 min.

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.994	BB	1.2554	5447.34033	51.35950	50.8350
2	34.878	MM	1.9254	5268.38525	45.60527	49.1650

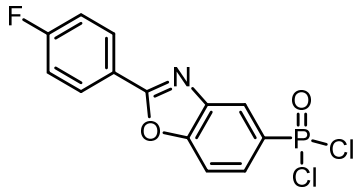
Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.037	MM	1.7604	4855.13037	45.96743	5.2031
2	35.809	BB	1.7129	8.84577e4	722.23193	94.7969

Synthesis of (+)-SMT022332

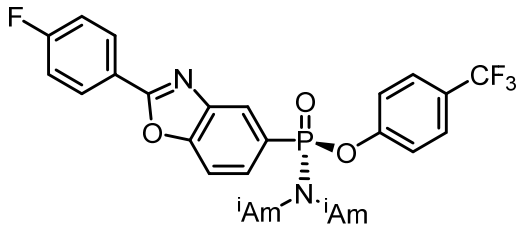
(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)phosphonic dichloride



9

Phosphonic dichloride **9** was prepared according to **General Procedure H** and used directly without further purification in the catalytic reaction. Crude phosphonic dichloride **9** was found to be pure by ^{1}H, ^{31}P, ^{19}F, and ^{13}C NMR with no significant byproducts observed. ^{1}H NMR (400 MHz, C_6D_6) δ 8.25 (dd, *J* = 18.5, 1.6 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.60 (ddd, *J* = 16.9, 8.4, 1.7 Hz, 1H), 6.92 (dd, *J* = 8.4, 4.9 Hz, 1H), 6.77 – 6.67 (m, 2H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 165.34, 162.80 (d, *J* = 3.0 Hz), 152.80 (d, *J* = 4.3 Hz), 141.51 (d, *J* = 26.7 Hz), 130.08 (d, *J* = 158.3 Hz), 129.11 (d, *J* = 9.0 Hz), 126.09 (d, *J* = 16.3 Hz), 121.87 (d, *J* = 16.3 Hz), 121.37 (d, *J* = 3.2 Hz), 115.06 (d, *J* = 22.3 Hz), 110.07 (d, *J* = 21.7 Hz) ; ^{31}P NMR (162 MHz, C_6D_6) δ 33.00 ; ^{19}F NMR (376 MHz, C_6D_6) δ -105.73.

4-(trifluoromethyl)phenyl (*R*)-*P*-(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)-*N*,*N*-diisopentylphosphonamidate (10)



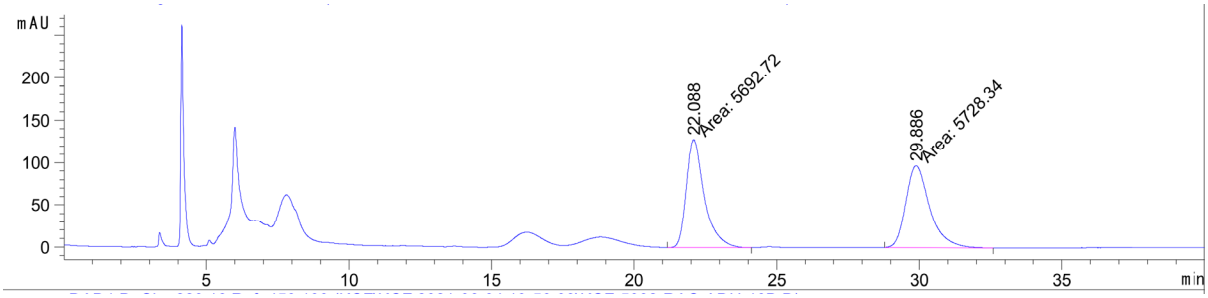
10

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (14 mg, 0.03 mmol, 0.1 equiv.), 4 Å mol sieves (300 mg), and diisoamylamine (0.31 mL, 1.5 mmol, 5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (15 mL) and the reaction mixture was cooled to –40 °C and subjected to stirring for 20 minutes at that temperature. Phosphonic dichloride **9** (0.3 mmol) was then added to the stirring reaction mixture in one portion as a stock solution in toluene (0.5 mL), and the reaction was subjected to stirring at –40 °C for 48 hours.

A separate oven-dried 20 mL vial with a magnetic stir bar was charged with sodium hydride (180 mg, 4.5 mmol, 15 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (3 mL) and allowed to stir at room temperature for 1 minute. 4-trifluoromethylphenol (243 mg, 1.5 mmol, 5 equiv.) was dissolved in THF (0.5 mL) and then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period. Stirring was continued at room temperature for 30 minutes. The resultant mixture was then added directly to the catalytic reaction at –40 °C after it had been stirred for 48 hours. The reaction mixture was then subjected to stirring for 24 hours at –40 °C, and then concentrated under reduced pressure. Purification via flash column

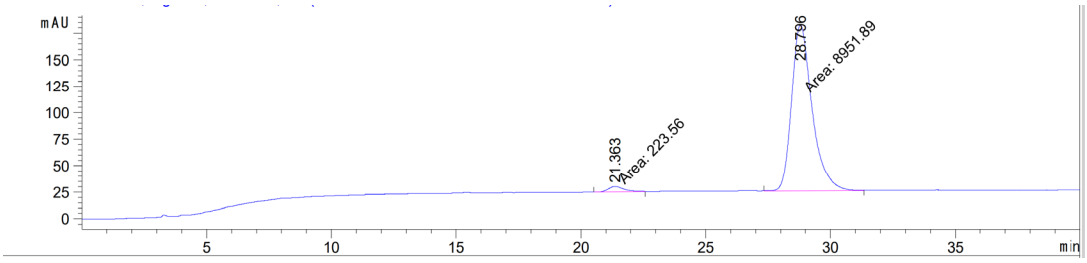
chromatography on silica gel (0 to 100% Et_2O in Hexanes) afforded phosphonamidate **10** (118 mg, 68% yield, 95% ee) as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.18 (m, 3H), 7.88 (ddd, *J* = 12.7, 8.4, 1.5 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.21 (m, 2H), 3.29 – 2.91 (m, 4H), 1.43 (dq, *J* = 13.1, 6.6 Hz, 2H), 1.36 – 1.16 (m, 4H), 0.81 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.16 (d, *J* = 253.9 Hz), 163.47, 153.91 (d, *J* = 8.1 Hz), 152.96 (d, *J* = 3.6 Hz), 142.24 (d, *J* = 20.5 Hz), 130.15 (d, *J* = 9.0 Hz), 128.72 (d, *J* = 11.8 Hz), 127.12 (d, *J* = 181.0 Hz), 127.03 (q, *J* = 3.7 Hz), 126.57 (q, *J* = 32.7 Hz), 123.99 (q, *J* = 271.6 Hz), 123.78 (d, *J* = 10.9 Hz), 122.87 (d, *J* = 3.3 Hz), 120.69 (d, *J* = 5.1 Hz), 116.41 (d, *J* = 22.2 Hz), 111.17 (d, *J* = 17.1 Hz), 43.28 (d, *J* = 4.4 Hz), 37.29 (d, *J* = 2.1 Hz), 25.94, 22.48 (d, *J* = 8.4 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.06, -106.25; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.75 ; HRMS (ESI) m/z calcd for $C_{30}H_{34}F_4N_2O_3P$ $(M+H)^+$: 577.2238; found: 577.2237. A crystal suitable for X-ray diffraction formed spontaneously via vapor diffusion: a saturated solution of phosphonamidate **10** in *tert*-butyl methyl ether was placed in a chamber filled ~2 cm high with hexanes, covered, and left to stand at room temperature for ~24 hours. Phosphonamidate **10** was determined to be 95% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 21.4 min, t_R(major) = 28.8 min.

Racemic Sample:



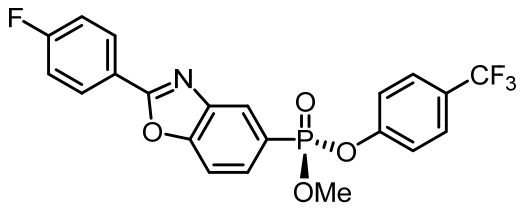
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.088	MM	0.7398	5692.72314	128.25186	49.8441
2	29.886	MM	0.9803	5728.34180	97.38958	50.1559

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.363	MM	0.7163	223.56013	5.20191	2.4365
2	28.796	MM	0.9518	8951.89258	156.74986	97.5635

Methyl (4-(trifluoromethyl)phenyl) (*R*)-(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)phosphonate (11)

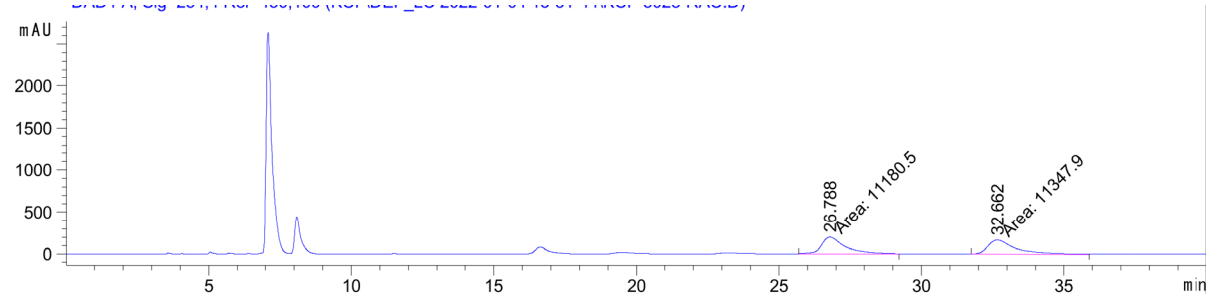


11

Following the **General Procedure E**, phosphonate **11** (55 mg, 65% yield, 94% ee) was produced as a colorless oil from phosphonamidate **10** (108 mg, 0.188 mmol, 95% ee), methanol (1 mL), and *para*-tolylsulfonic acid monohydrate (107 mg, 0.564 mmol, 3 equiv.). The product was purified

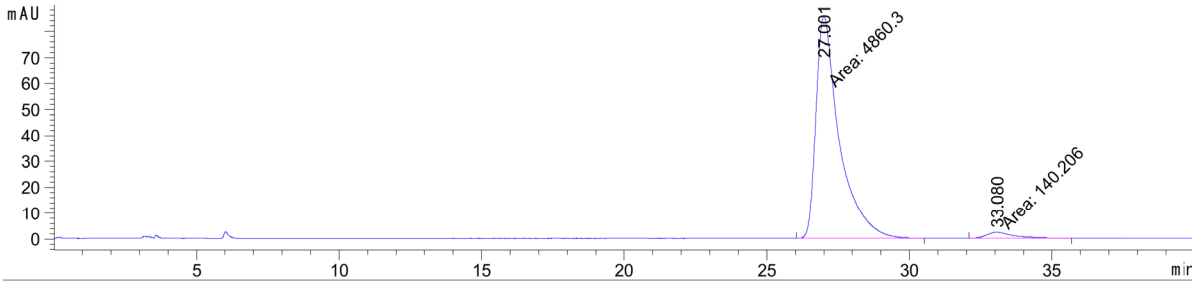
using flash column chromatography on silica gel (0 to 100% Et_2O in Hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.17 (m, 4H), 7.90 (ddd, *J* = 13.3, 8.3, 1.5 Hz, 1H), 7.70 (ddd, *J* = 8.4, 3.6, 0.7 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 3.93 (d, *J* = 11.4 Hz, 3H) ; δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.52, 163.99, 163.73, 153.76 (d, *J* = 3.6 Hz), 153.07 (d, *J* = 6.8 Hz), 142.48 (d, *J* = 21.9 Hz), 130.26 (d, *J* = 9.0 Hz), 129.13 (d, *J* = 12.2 Hz), 127.18 (q, *J* = 3.9 Hz), 124.56 (d, *J* = 11.6 Hz), 123.82 (q, *J* = 272.1 Hz), 122.75 (d, *J* = 194.0 Hz), 122.69 (d, *J* = 3.3 Hz), 120.79 (d, *J* = 4.7 Hz), 116.45 (d, *J* = 22.2 Hz), 111.37 (d, *J* = 18.1 Hz), 53.45 (d, *J* = 5.8 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.20, -105.98; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.98; HRMS (ESI) m/z calcd for $C_{21}H_{15}F_4NO_4P$ $(M+H)^+$: 452.0669; found: 452.0668. Phosphonate **11** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 10% iPrOH/hexanes, 1.0 mL/min, 254 nm, t_R(minor) = 33.1 min, t_R(major) = 27.0 min.

Racemic Sample:



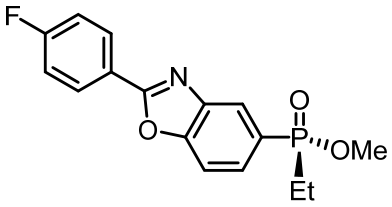
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.788	MM	0.9402	1.11805e4	198.20406	49.6286
2	32.662	MM	1.1347	1.13479e4	166.68651	50.3714

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.001	MM	0.9499	4860.29736	85.27512	97.1962
2	33.080	MM	1.0681	140.20575	2.18772	2.8038

Methyl (*R*)-ethyl(2-(4-fluorophenyl)benzo[d]oxazol-5-yl)phosphinate (12)

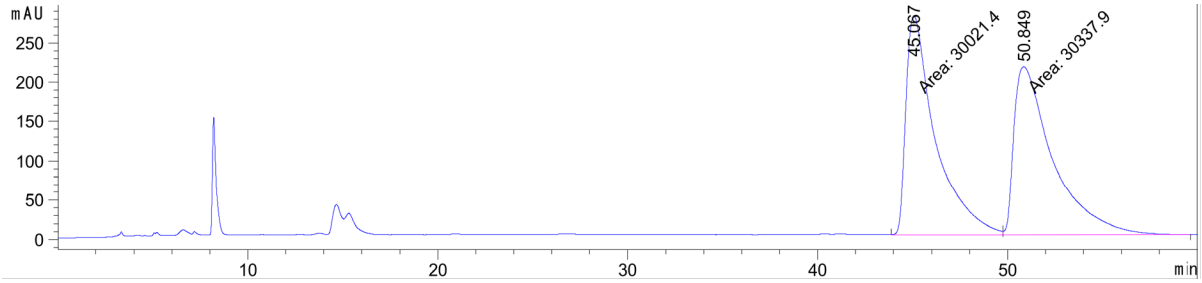


(+)-SMT022332

An oven-dried 2-dram vial with a magnetic stir bar was charged with phosphonate **11** (42 mg, 0.094 mmol, 1 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1 mL) and allowed to stir at room temperature for 1 minute. The vial was then cooled to –50 °C for 20 minutes. EtMgCl (280 µL, 0.282 mmol, 3 equiv., 1.0 M solution in THF) was then added through the septum in one portion, and the reaction was subjected to stirring for 24 hours at –50 °C. After 24 hours had elapsed, isopropanol (50 µL) was added via a syringe at –50 °C and subjected to stirring for 1 minute at –50 °C to quench any remaining EtMgCl. Immediate purification of the mixture via flash column

chromatography on a 10-gram silica gel column (0 to 10% MeOH in DCM) afforded phosphinate **12** (30 mg, 98% yield, 94% ee) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.23 (m, 2H), 8.15 (ddd, *J* = 11.7, 1.4, 0.7 Hz, 1H), 7.83 (ddd, *J* = 10.9, 8.3, 1.4 Hz, 1H), 7.71 (ddd, *J* = 8.3, 2.5, 0.7 Hz, 1H), 7.32 – 7.16 (m, 1H), 7.22 (dd, *J* = 212.9, 8.5 Hz, 1H), 3.68 (d, *J* = 11.0 Hz, 3H), 2.11 – 1.80 (m, 2H), 1.14 (dt, *J* = 19.1, 7.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.31 (d, *J* = 2.9 Hz), 130.18 (d, *J* = 8.9 Hz), 129.03 (d, *J* = 11.0 Hz), 127.01 (d, *J* = 2.7 Hz), 125.78, 123.96, 123.85, 122.88 (d, *J* = 3.4 Hz), 116.42 (d, *J* = 22.2 Hz), 115.53, 111.24 (d, *J* = 14.0 Hz), 51.26 (d, *J* = 6.9 Hz), 22.78 (d, *J* = 103.1 Hz), 5.93 (d, *J* = 4.8 Hz) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.31; ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.84 ; HRMS (ESI) m/z calcd for $C_{16}H_{16}FNO_3P$ $(M+H)^+$: 320.0846; found: 320.0847. $[\alpha]^{22}$ = +32.2 (c = 1.0, THF). Absolute stereochemistry was assigned by comparison to literature value (*36*). Phosphinate **12** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 52.0 min, t_R(major) = 45.0 min.

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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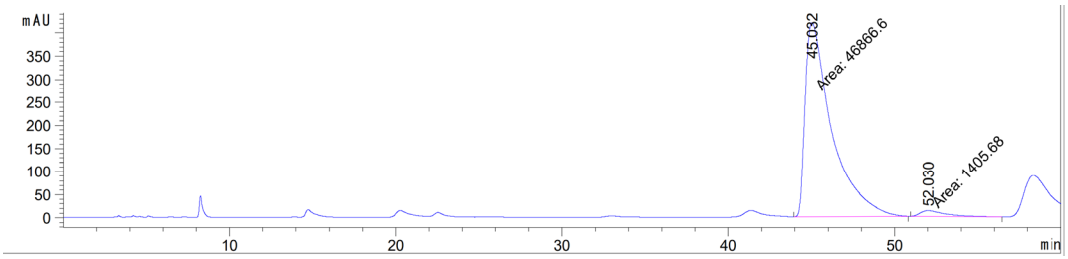
2	50.849	FM	2.3655	3.03379e4	213.75435	50.2622

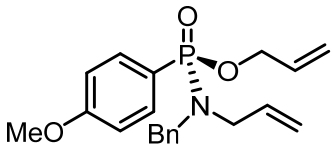
Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.032	MM	1.8576	4.68666e4	420.50204	97.0880
2	52.030	MM	1.8085	1405.68286	12.95427	2.9120

Formal Synthesis of Matrix Metalloproteinase Inhibitor (17)

Allyl (*R*)-*N*-allyl-*N*-benzyl-*P*-(4-methoxyphenyl)phosphonamidate (13)



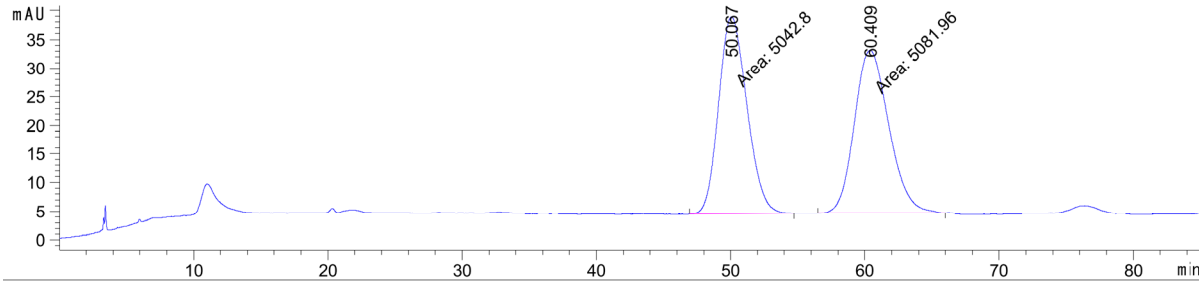
13

An oven-dried 40 mL vial equipped with a magnetic stir bar was charged with catalyst **1a** (20 mg, 0.04 mmol), 4 Å mol sieves (200 mg), and *N*-allyl benzylamine (103 μL, 0.66 mmol, 3.3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (10 mL), and the reaction mixture was cooled to –40 °C and subjected to stirring for 20 minutes at that temperature. Then, 4-methoxyphenylphosphonic dichloride (32 μL, 0.2 mmol, 1 equiv.) was then added in one portion as a stock solution in toluene (0.5 mL), and the reaction was subjected to stirring at –40 °C for 60 hours.

A separate oven-dried 20 mL vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (2 mL) and allowed to stir at room temperature for 1 minute. Allyl alcohol (136 μL, 2 mmol, 10 equiv.) was then added dropwise via a syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature for 30 minutes. The resultant allyl alkoxide mixture was then added directly to the catalytic reaction at –40 °C after it had been stirred for 60 hours. The reaction mixture was then subjected to stirring for 24 hours at –40 °C, and then concentrated under reduced pressure. Purification via flash column chromatography on silica gel (0 to 40% Et_2O in DCM) afforded phosphonamidate **13** (63 mg, 88% yield, 89% ee) as a colorless

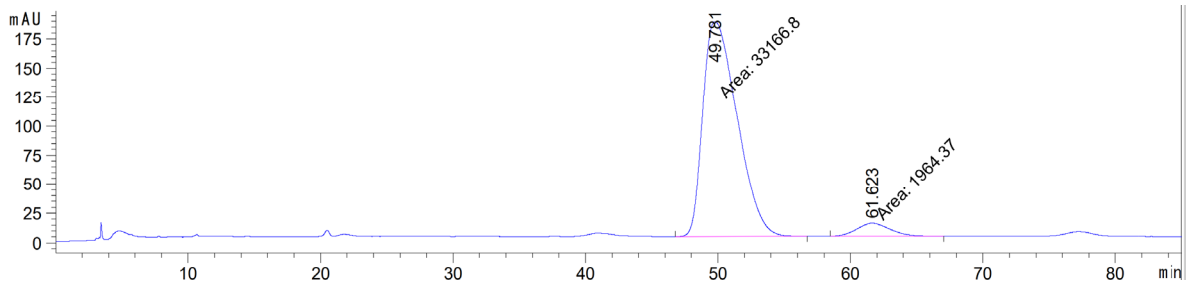
oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.36 – 7.21 (m, 5H), 7.04 – 6.79 (m, 2H), 5.97 (ddt, *J* = 17.1, 10.6, 5.3 Hz, 1H), 5.70 – 5.48 (m, 1H), 5.35 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.6 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.62 – 4.43 (m, 2H), 4.31 – 4.16 (m, 2H), 3.85 (s, 3H), 3.57 – 3.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.35 (d, *J* = 3.1 Hz), 137.92 (d, *J* = 3.4 Hz), 134.21 (d, *J* = 1.7 Hz), 133.58 (d, *J* = 11.0 Hz), 133.38 (d, *J* = 7.6 Hz), 128.54 (d, *J* = 34.0 Hz), 127.25, 122.01 (d, *J* = 182.4 Hz), 118.37, 117.31, 114.07, 113.92, 64.96 (d, *J* = 5.4 Hz), 55.31, 47.90 (d, *J* = 4.9 Hz), 47.10 (d, *J* = 5.0 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.48 ; HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_3P$ $(M+H)^+$: 358.1567; found: 358.1566. Phosphonamidate **13** was determined to be 89% ee by chiral HPLC analysis (CHIRALPAK AS-H, 5% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 61.6 min, t_R(major) = 49.8 min.

Racemic Sample:



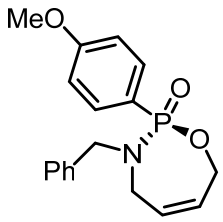
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.067	MM	2.4425	5042.80322	34.41081	49.8066
2	60.409	MM	2.9711	5081.96289	28.50823	50.1934

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.781	MM	2.9965	3.31668e4	184.47664	94.4085
2	61.623	MM	2.9433	1964.36536	11.12346	5.5915

(*R*)-3-benzyl-2-(4-methoxyphenyl)-3,4,7-trihydro-1,3,2-oxazaphosphepine 2-oxide (14)

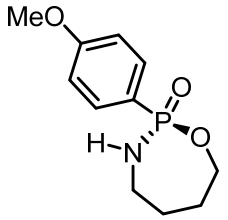


14

An oven-dried 100 mL flask with a magnetic stir bar was charged with Hoveyda-Grubbs 2nd Generation M720 (18 mg, 0.028 mmol 0.04 equiv.). The flask was then sealed with a septum cap, sealed with parafilm, and put under N_2 atmosphere. The flask was then charged with DCM (30 mL). Phosphonamidate **13** (250 mg, 0.7 mmol, 1 equiv.) dissolved in DCM (5 mL) was then added to the flask via syringe through the septum. The resulting solution was then degassed with N_2 for 30 minutes. The reaction was then subjected to stirring at 40 °C for 24 hours, at which point Hoveyda-Grubbs 2nd Generation M720 (15 mg, 0.025 mmol, 0.035 equiv.) dissolved in DCM (1 mL) was added via a syringe through the septum. The reaction was then subjected to stirring at 40

°C for an additional 24 hours. Upon completion, the crude mixture was dry loaded onto silica gel (~5 grams) and purified via flash column chromatography on silica gel (0 to 40% Et_2O in DCM) to afford the product. Phosphonamidate **14** was obtained as a colorless oil (217 mg, 0.66 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.56 (m, 2H), 7.49 – 7.10 (m, 5H), 6.97 (dd, *J* = 8.8, 3.2 Hz, 2H), 5.65 (ddt, *J* = 13.4, 5.3, 2.4 Hz, 2H), 5.23 (dddd, *J* = 13.1, 8.5, 4.3, 2.1 Hz, 1H), 4.65 (dd, *J* = 15.0, 7.9 Hz, 1H), 4.54 – 4.32 (m, 1H), 4.23 (dd, *J* = 15.1, 5.8 Hz, 1H), 3.85 (s, 3H), 3.68 (dd, *J* = 16.8, 5.0 Hz, 1H), 3.24 – 2.96 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.42 (d, *J* = 3.3 Hz), 138.72 (d, *J* = 4.6 Hz), 133.18 (d, *J* = 10.7 Hz), 128.80, 128.46, 128.23, 127.01 (d, *J* = 50.6 Hz), 120.98 (d, *J* = 187.7 Hz), 114.07, 113.92, 62.35 (d, *J* = 6.5 Hz), 55.33, 50.69 (d, *J* = 4.4 Hz), 43.41 (d, *J* = 4.3 Hz) ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.34; HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_3P$ $(M+H)^+$: 330.1254; found: 330.1254.

(*R*)-2-(4-methoxyphenyl)-1,3,2-oxazaphosphepane 2-oxide (15)



15

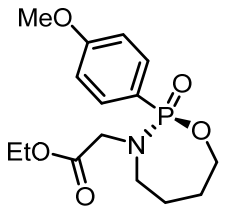
**Note: successful hydrogenolysis is dependent on efficient sparging with H_2 at 30 °C and subjection to vigorous stirring.*

To a 1-dram vial equipped with a magnetic stir bar, phosphonamidate **14** (18.0 mg, 0.0547 mmol, 1 equiv.), $Pd(OH)_2/C$ (6 mg, 0.0082 mmol, 0.15 equiv., 20%), and Pd/C (9 mg, 0.0082 mmol, 0.15 equiv., 10%) were added. The vial was then capped with a septum and sealed with parafilm.

The vial was evacuated and backfilled three times with N_2, then evacuated and backfilled once with H_2. Isopropanol (0.55 mL) and trifluoroacetic acid (12 μL, 0.164 mmol, 3 equiv.) were introduced sequentially via a syringe through the septum. The mixture was then sparged with H_2 for 10 minutes while subjected to vigorous stirring at 30 °C. The reaction was then subjected to stirring under an H_2 balloon for 20 hours at 30 °C, after which point an additional portion of trifluoroacetic acid (12 μL, 0.164 mmol, 3 equiv.) was added and the reaction was sparged with H_2 again for 5 minutes. The reaction was subjected to stirring under an H_2 balloon for an additional 8 hours at 30 °C, after which point it was sparged with H_2 for an additional 5 minutes. Reaction completion was confirmed after 41 hours by TLC analysis by visualization with $KMnO_4$. The crude mixture was then loaded directly onto a silica gel column and purified using flash column chromatography (0 to 10% MeOH in DCM) to afford the product. Phosphonamidate **15** (9.1 mg, 0.0377 mmol, 69% yield) was afforded as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.63 (m, 2H), 6.94 (dq, *J* = 9.3, 2.7 Hz, 2H), 4.54 (qd, *J* = 11.6, 1.2 Hz, 1H), 4.16 (ddtd, *J* = 19.9, 11.8, 3.7, 3.3, 1.4 Hz, 1H), 3.84 (s, 3H), 3.36 – 2.95 (m, 1H), 2.81 (q, *J* = 9.3, 7.9 Hz, 1H), 2.02 – 1.71 (m, 4H), 1.70 – 1.45 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.25 (d, *J* = 3.3 Hz), 132.82 (d, *J* = 10.9 Hz), 122.69 (d, *J* = 190.0 Hz), 113.87 (d, *J* = 15.6 Hz), 65.28 (d, *J* = 6.7 Hz), 55.31, 41.23, 32.01, 29.97; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.00; HRMS (ESI) m/z calcd for $C_{11}H_{17}NO_3P$ $(M+H)^+$: 242.0941; found: 242.0940.

Ethyl (*R*)-2-(2-(4-methoxyphenyl)-2-oxido-1,3,2-oxazaphosphepan-3-yl)acetate (16)



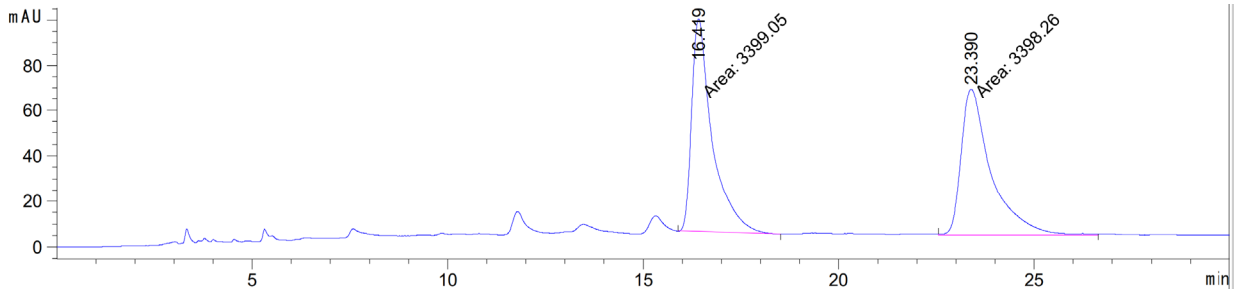
16

An oven-dried 2-dram vial with a magnetic stir bar was charged with phosphonamidate **15** (40 mg, 0.165 mmol, 1 equiv.). The vial was then capped with a septum and sealed with parafilm. The vial was then put under N_2 atmosphere, charged with THF (1.2 mL), and subjected to stirring at 0 °C for 10 minutes. NaHMDS (180 µL, 0.18 mmol, 1.1 equiv, 1.0 M in THF) was then added dropwise via a syringe through the septum to the stirring solution over a 5-minute period. The resulting yellow solution was subjected to stirring for 1 hour at 0 °C. Ethyl bromoacetate (44 µL, 0.36 mmol, 2.2 equiv.,) dissolved in THF (0.2 mL) was then slowly added dropwise via a syringe through the septum to the stirring solution over a 1-minute period. The mixture was then subjected to stirring at 0 °C for 4 hours. The crude mixture was then purified by flash column chromatograph using silica gel (0 to 10% MeOH in DCM) to afford the product. Phosphonamidate **16** (47 mg, 87% yield, 90% ee) was afforded as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 12.7, 8.7 Hz, 2H), 7.14 – 6.78 (m, 2H), 4.62 – 4.44 (m, 1H), 4.35 (ddd, *J* = 18.1, 9.6, 1.3 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 3.94 – 3.67 (m, 1H), 3.16 (dq, *J* = 16.1, 6.1 Hz, 1H), 2.99 – 2.83 (m, 1H), 1.88 – 1.71 (m, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.02 – 6.78 (m, 2H), 4.62 – 4.43 (m, 1H), 4.35 (ddd, *J* = 18.1, 9.6, 1.3 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 3.80 (d, *J* = 9.1 Hz, 1H), 3.16 (ddd, *J* = 16.3, 11.0, 6.0 Hz, 1H), 3.03 – 2.77 (m, 1H), 1.95 – 1.71 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.45 (d, *J* = 2.9 Hz), 162.23 (d, *J* = 3.4 Hz),

133.21 (d, J = 11.3 Hz), 122.07 (d, J = 191.0 Hz), 113.77 (d, J = 15.9 Hz), 65.16 (d, J = 6.7 Hz), 60.96, 55.27, 48.51 (d, J = 6.0 Hz), 47.33 (d, J = 5.2 Hz), 29.51, 26.51, 14.19 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.57; HRMS (ESI) m/z calcd for $C_{15}H_{23}NO_5P$ $(M+H)^+$: 328.1308; found: 328.1309. Phosphonamidate **16** was determined to be 90% ee by chiral HPLC analysis (CHIRALPAK AD-H, 15% iPrOH/hexanes, 1.0 mL/min, 210 nm, t_R(minor) = 23.3 min, t_R(major) = 16.1 min.

Racemic Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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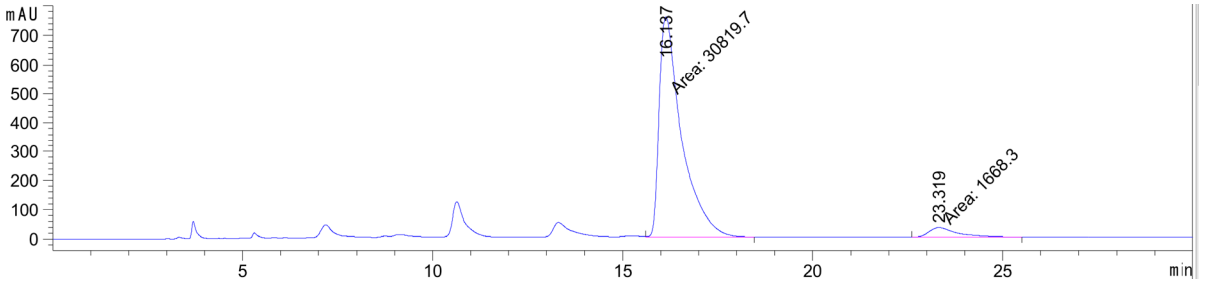
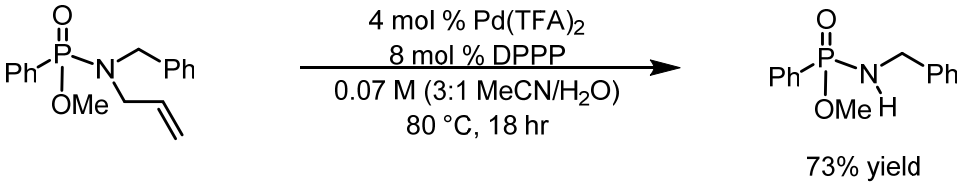
2	23.390	MM	0.8815	3398.26294	64.25117	49.9942

Enriched Sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.137	MM	0.6800	3.08197e4	755.38434	94.8649
2	23.319	MM	0.8591	1668.30176	32.36551	5.1351

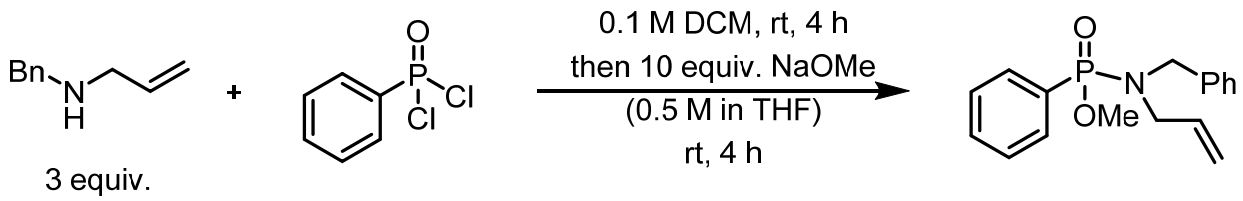
Deallylation of methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate



Procedure:

Conditions were adapted from a reported procedure for deallylation of amides *(50)*. $Pd(TFA)_2$ (2 mg, 0.006 mmol, 0.04 equiv.), 1,3-Bis(diphenylphosphino)propane (DPPP) (5 mg, 0.012 mmol, 0.08 equiv.), and methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate (45.2 mg, 0.15 mmol, 1 equiv.) were added to a 2-dram vial equipped with a magnetic stir bar. The vial was then capped with a septum and sealed with electrical tape. The vial was then evacuated and backfilled three times with N_2. MeCN (1.6 mL) and H_2O (0.5 mL) of water were then added to the vial via syringe. The resulting solution was subjected to stirring at room temperature for ~1 minute, and then subjected to stirring at 80 °C for 18 hours. After 18 hours, the crude mixture was cooled to room temperature, concentrated under reduced pressure until ~1 mL of solvent remained, and then purified via flash column chromatography on silica gel (0 to 10% MeOH in DCM). Methyl *N*-benzyl-*P*-phenylphosphonamidate was afforded as a colorless oil (28.7 mg, 73% yield).

Synthesis of Methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate



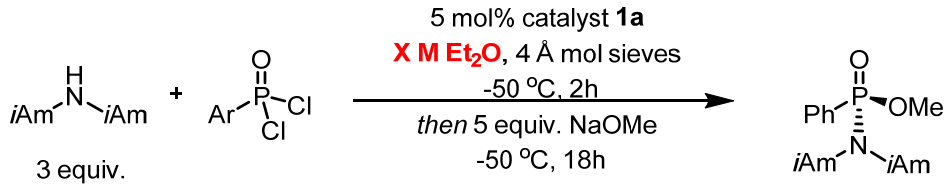
An oven-dried 20 mL vial equipped with a magnetic stir bar was charged with *N*-allyl benzylamine (94 μL, 0.6 mmol, 3 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with DCM (2 mL), followed by phenyl phosphonic dichloride (28 μL, 0.2 mmol, 1 equiv.) dissolved in toluene (0.5 mL), and the reaction was subjected to stirring at room temperature for 4 hours. The reaction was quenched with sodium methoxide prepared according to the following procedure:

A separate oven-dried 2-dram vial with a magnetic stir bar was charged with sodium hydride (80 mg, 2 mmol, 10 equiv., 60% in mineral oil). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was then charged with THF (1.5 mL) and allowed to stir at room temperature for 1 minute. Methanol (0.5 mL) was then added dropwise via syringe through the septum to the stirring sodium hydride mixture over a 2-minute period, and stirring was continued at room temperature until clear. If the mixture remained cloudy after 10 minutes, additional methanol (0.1 mL) was introduced to ensure complete dissolution of sodium methoxide. The resultant sodium methoxide solution was then added directly in a single portion to the reaction stirring in DCM at room temperature. Upon addition of sodium methoxide, the reaction was subjected to stirring for 4 hours at room temperature, after which point it was concentrated under reduced pressure and purified by flash column chromatography on silica gel (0 to 50% Et_2O in DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 12.8, 8.3, 1.5 Hz, 2H), 7.61 – 7.47 (m, 1H), 7.44 (ddd, *J* = 8.6, 6.5, 3.9 Hz, 2H), 7.34 – 7.13 (m, 5H), 5.60 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.12 (dd, *J* = 10.1, 1.5 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.24 (d, *J* = 9.0 Hz, 2H), 3.75 (d, *J* = 11.1 Hz, 3H), 3.49 (dtdd, *J* = 9.1, 7.7, 3.4, 2.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.75 (d, *J* = 3.3 Hz), 134.02 (d, *J* = 1.7 Hz), 131.74 (d, *J* = 3.0 Hz), 131.56 (d, *J* = 9.5 Hz), 130.70 (d, *J* = 175.7 Hz), 128.56 (d, *J* = 32.0 Hz), 128.50 (d, *J* = 36.0 Hz), 128.49 (d, *J* = 14.2 Hz), 127.31,

118.49, 51.37 (d, J = 5.9 Hz), 47.89 (d, J = 4.8 Hz), 47.02 (d, J = 4.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.59. HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_2P$ $(M+H)^+$: 302.1304 ; found: 302.1306.

Reaction Optimization

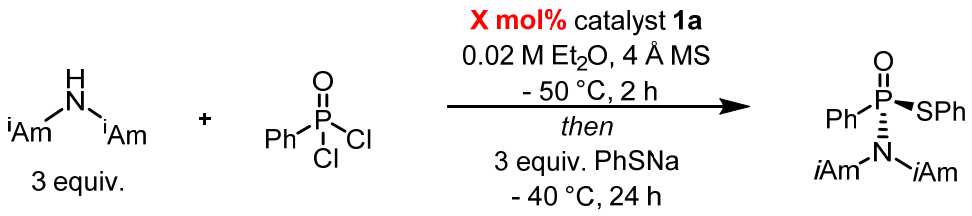
Concentration



concentration	% ee	% yield
0.02 M	95	93
0.05 M	94	100
0.1 M	91	98
0.2 M	90	94

Table S1. Effect of reaction concentration on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

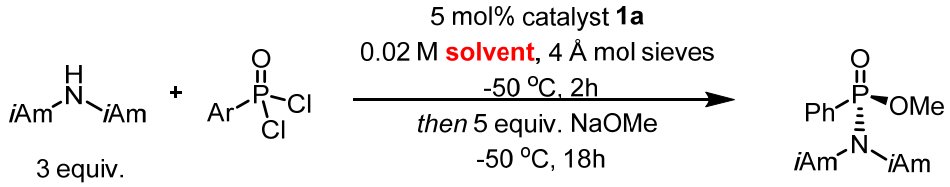
Catalyst Loading



X	% ee	% conversion	% yield
2	94	89	84
5	94	100	100
10	94	100	100

Table S2. Effect of catalyst loading on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

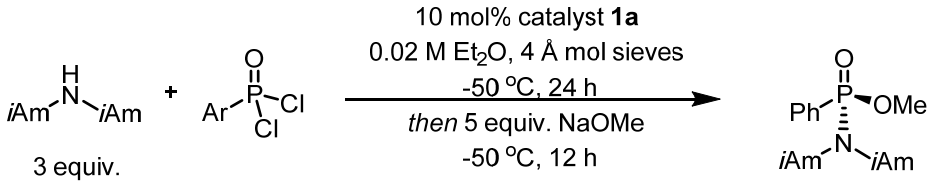
Solvent Effects



Solvent	% ee	% yield
Et_2O	95	93
TBME	93	96
THF	68	89
DCM	5	98
Toluene	91	100

Table S3. Effect of solvent on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

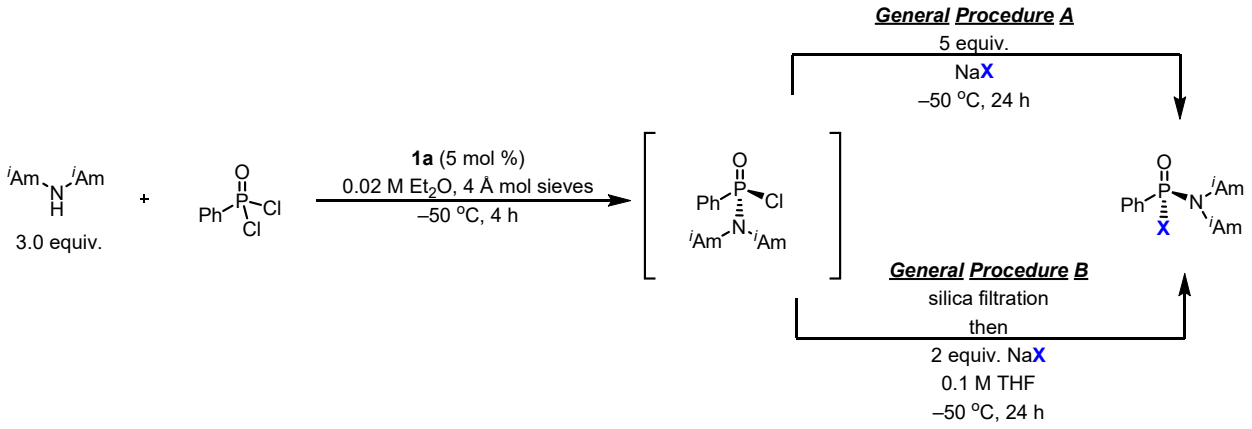
Effect of Molecular Sieves

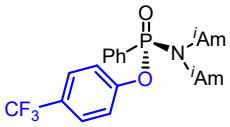


Deviation from Conditions	% ee	% yield
--	95	100
No mol sieves	89	94

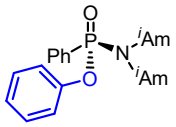
Table S4. Effect of molecular sieves on enantioselectivity. Reactions were carried out on a 0.06 mmol scale. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.

Comparison of General Procedure A and General Procedure B for various nucleophiles

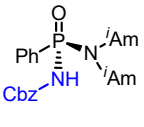




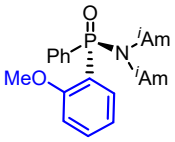
A: 93% ee, 63% yield
B: 93% ee, 59% yield



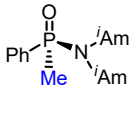
A: 93% ee, 100% yield
B: 93% ee, 86% yield



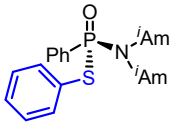
A: product not observed
B: 92% ee, 75% yield



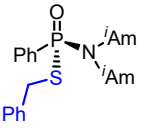
A: 70% ee, 36% yield*
B: 91% ee, 97% yield**



A: 93% ee, 59% yield*
B: 94% ee, 94% yield**



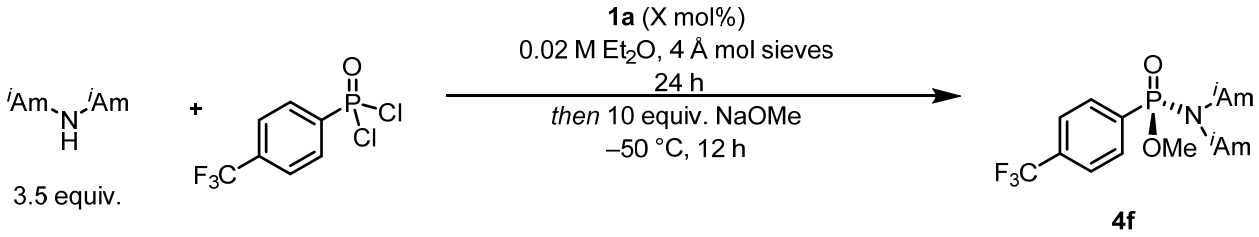
A: 94% ee, 90% yield
B: 93% ee, 62% yield



A: 94% ee, 91% yield
B: 92% ee, 72% yield

Reactions were carried out on 0.2 mmol scale. Yield values reflect isolated yields. *Reaction was carried out on 0.06 mmol scale. **5 equivalents of Grignard reagent used.

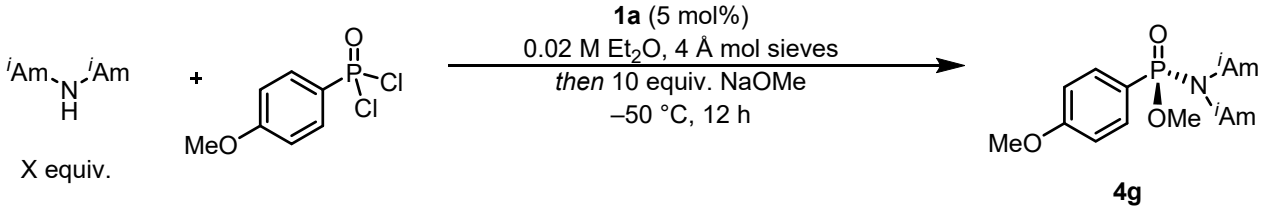
Comparison of conditions for synthesis of compound 4f



Catalyst Loading (mol%)	Temperature (°C)	% yield	% ee
5	–78	96	88
20	–78	89	92

Table S5. Yield values reflect isolated yields. Reactions were performed on 0.2 mmol scale.

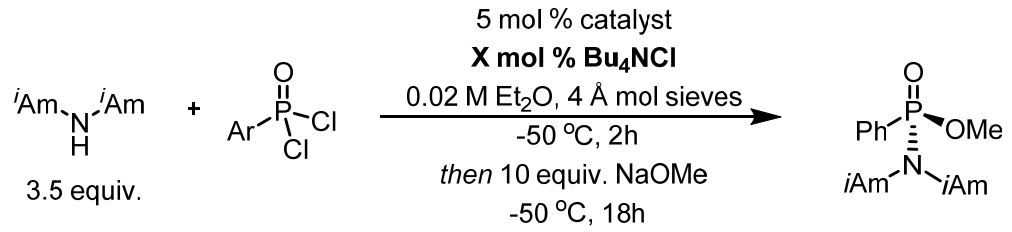
Comparison of conditions for synthesis of compound 4g



Conditions	% yield	% ee
Standard (3.5 equiv. $^{i}Am_2NH$, –50 °C, 24 h)	54	90
Optimal (4.5 equiv. $^{i}Am_2NH$, –40 °C, 48 h)	92	90

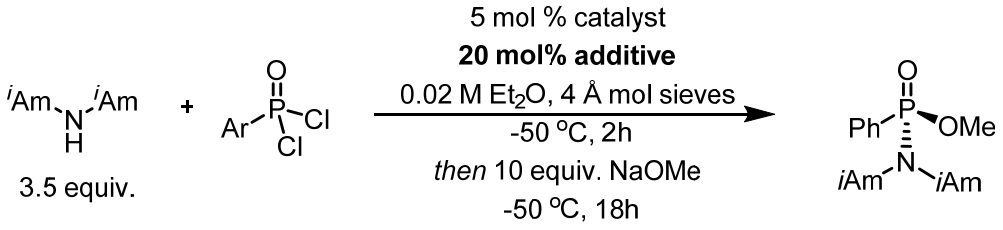
Table S6. Yield values reflect isolated yields. Reactions were performed on 0.2 mmol scale.

Effect of ammonium chloride additives on catalytic and racemic reaction



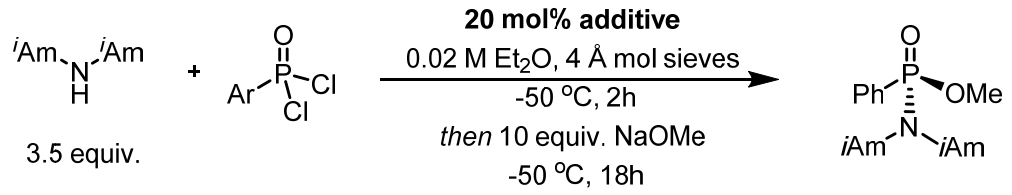
mol % Bu_4NCl	% ee	% yield	% conversion
0	95	93	100
5	92	92	92
10	83	78	84
20	20	73	79
40	9	82	89
80	5	87	90

Table S7. Enantioselectivity of catalytic reaction decreases with increasing amounts of BuN_4Cl. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



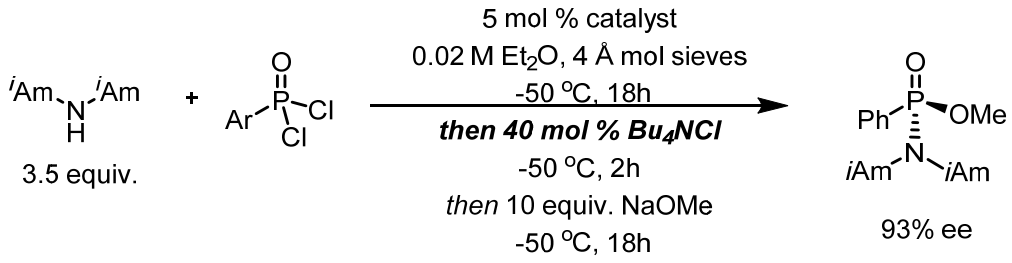
Additive (20 mol%)	% ee	% yield	% conversion
--	95	93	100
$^{i}Am_2NH_2Cl$	93	93	100
Bn_2NH_2Cl	92	97	100

Table S8. Effect of dialkylammonium chloride additives on enantioselectivity of catalytic reaction. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



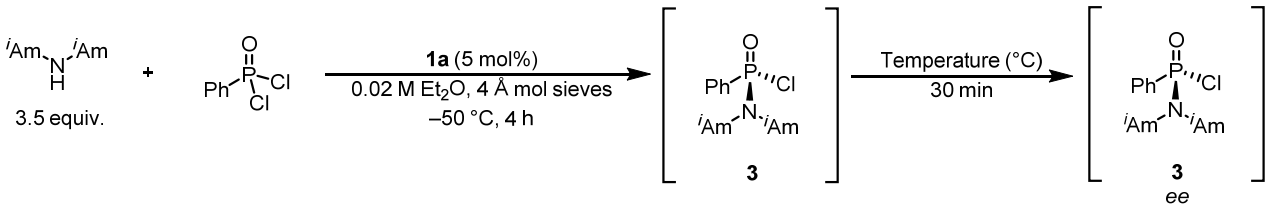
Additive	% yield	% conversion
None	21	38
$^{i}AmNH_2Cl$	23	44
Bn_2NH_2Cl	32	65
Bu_4NCl	83	83
Bu_4NBzO	96	100
Bu_4NPF_6	18	48
Bu_4NBF_4	22	54

Table S9. Effect of ammonium chloride additives on racemic background reaction in the absence of catalyst. Yield values reflect product quantification by ^{31}P NMR relative to an internal standard.



Scheme S1. Enantioenriched chlorophosphonamidate **3** formed under reaction conditions does not undergo racemization in the presence of BuN_4Cl.

Racemization studies of chlorophosphonamidate 3



Temperature (°C)	% ee
0	94
25	93
35	92
25 (16 h)	82

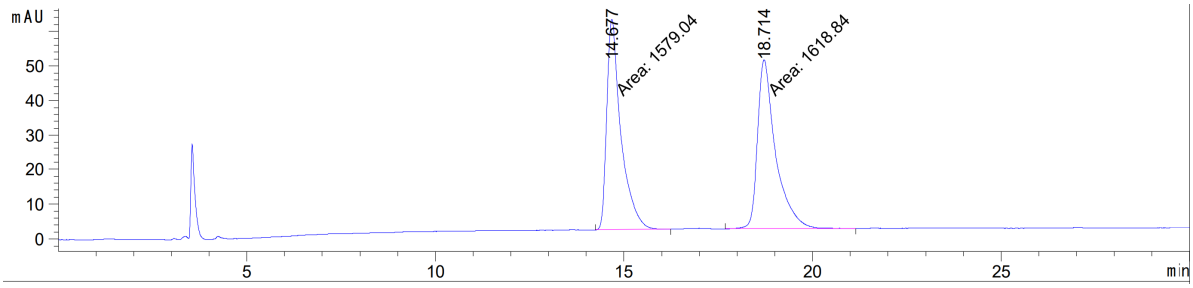
Table S10.

An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with catalyst **1a** (1.4 mg, 0.003 mmol, 0.05 equiv.), 4 Å mol sieves (60 mg), and diisoamylamine (44 μL, 0.21 mmol, 3.5 equiv.). The vial was then capped with a septum, sealed with parafilm, and put under N_2 atmosphere. The vial was charged with diethyl ether (3 mL), and the reaction mixture was cooled to –50 °C and subjected to stirring at that temperature for 20 minutes. A solution of phenyl phoshonic dichloride (8.4 μL, 0.06 mmol, 1 equiv.) in toluene (0.2 mL) was then added in one portion, and the reaction mixture was subjected to stirring at –50 °C for 4 hours. The mixture was filtered at room temperature through ~3 grams of silica to remove remaining amine, ammonium chloride byproduct, and catalyst. The filtered solution of **3** was then transferred to a 20 mL vial and concentrated under reduced pressure while kept at a temperature of 0 °C or below to remove the Et_2O until ~0.5 mL toluene remained. After this procedure, chlorophosphonamidate **3** was determined to be 94% ee by chiral HPLC analysis (CHIRALPAK AD-H, 3% iPrOH/hexanes, 1.0 mL/min, 220 nm, t_R(minor) = 14.7 min, t_R(major) = 18.8 min). Subsequently, the same solution of

3 was heated to 25 °C for 30 min, after which point chlorophosphonamidate **3** was determined to be 93% ee by chiral HPLC analysis. Subsequently, the same solution of **3** was heated to 35 °C for 30 min, after which point chlorophosphonamidate **3** was determined to be 92% ee by chiral HPLC analysis. Then, upon letting the same solution of **3** stand at 25 °C for 16 hours, chlorophosphonamidate **3** was determined to be 82% ee by chiral HPLC analysis.

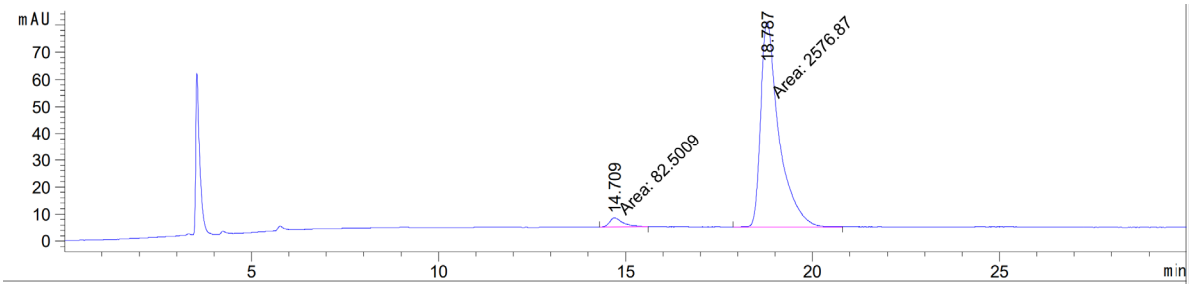
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (ddt, J = 14.9, 6.4, 1.8 Hz, 1H), 7.17 – 6.94 (m, 3H), 3.29 – 2.97 (m, 4H), 1.58 – 1.31 (m, 6H), 0.82 (dd, J = 9.7, 6.3 Hz, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.00.

Racemic Sample



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.677	MM	0.4328	1579.03784	60.81334	49.3776
2	18.714	MM	0.5528	1618.84204	48.80572	50.6224

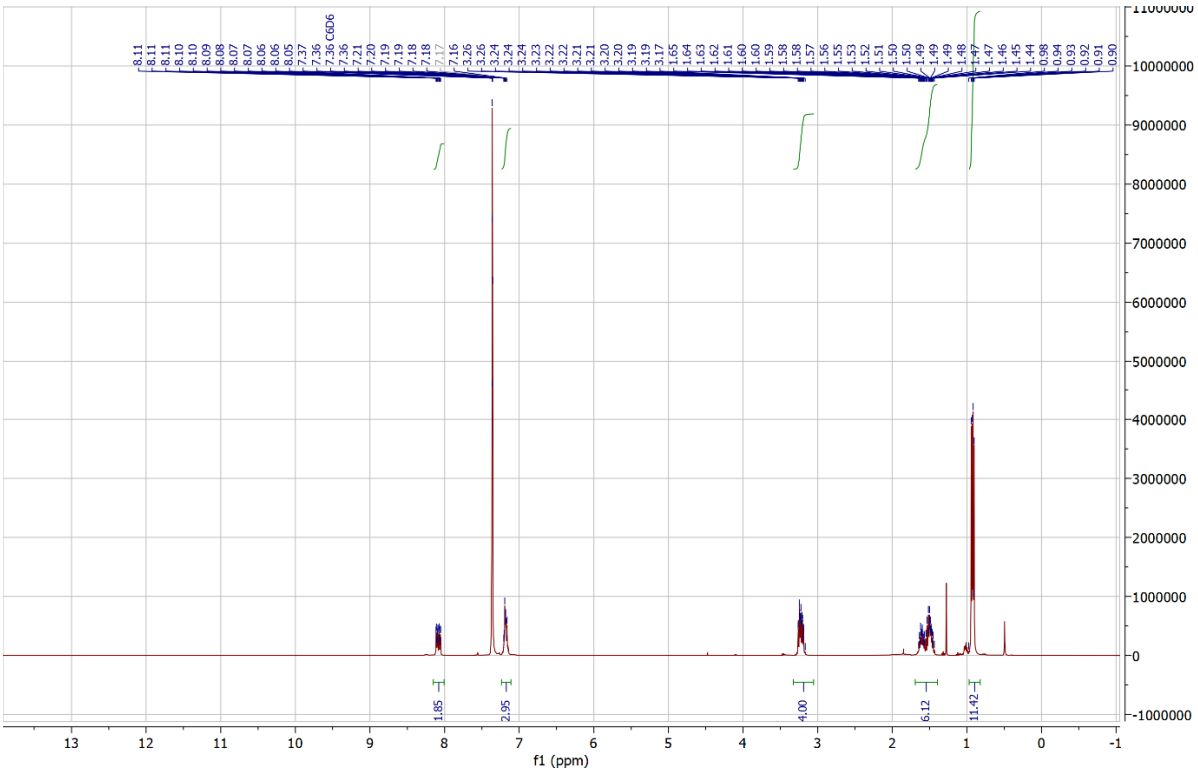
Enriched Sample (94% ee)



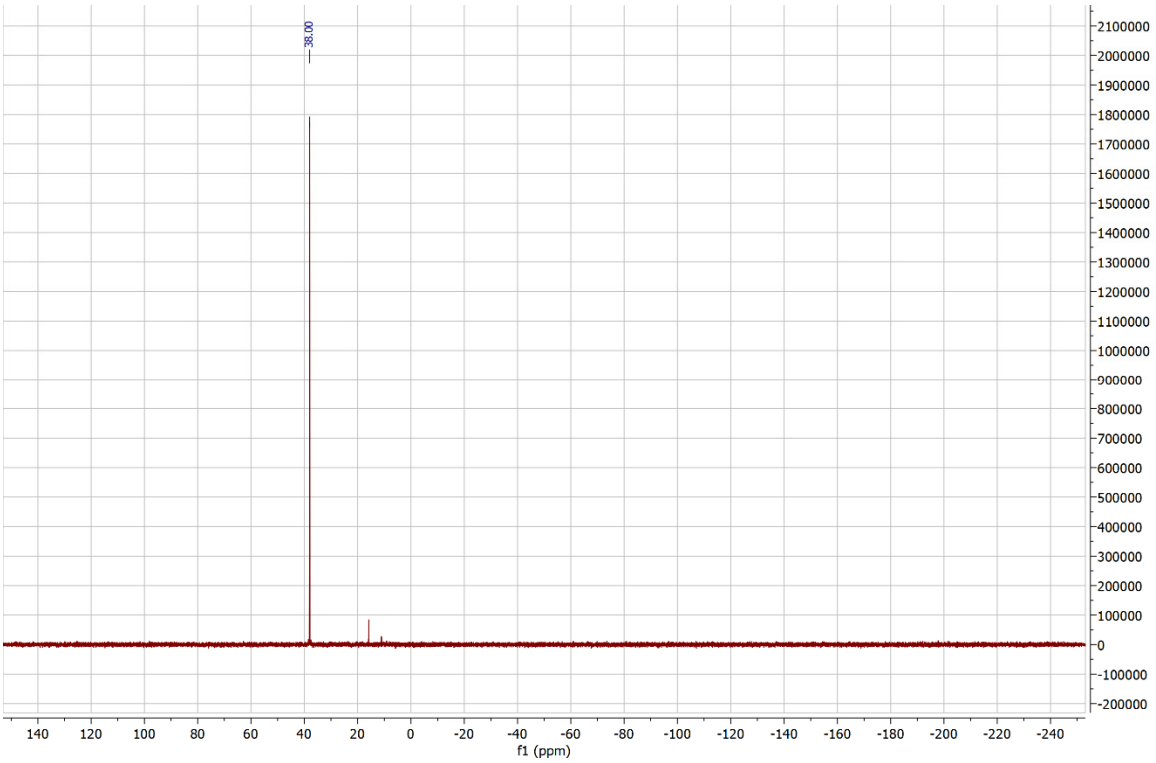
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.709	MM	0.4145	82.50092	3.31699	3.1023
2	18.787	MM	0.5651	2576.87476	75.99724	96.8977

NMR spectra of chlorophosphonamidate 3 in C_6D_6

^1H



^{31}P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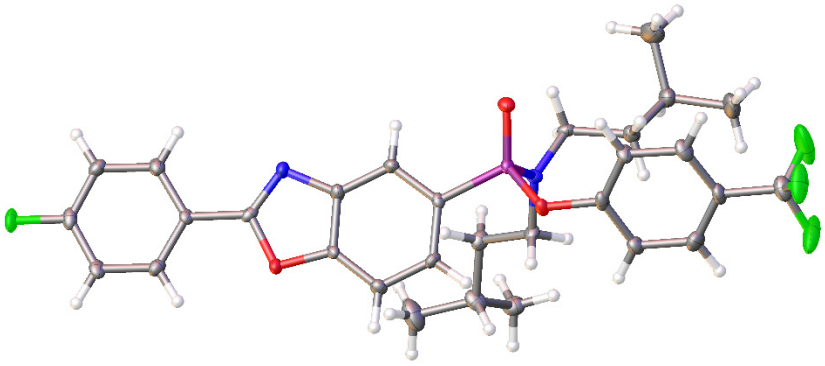
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

X-ray crystallography



10

X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.77 Å resolution was carried out using SAINT V8.37A *(51)* with reflection spot size optimization. Absorption corrections were made with the program SADABS *(51,52)*. The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014 *(53)* and SHELXL-2014 *(54)* with OLEX 2 interface *(55)*. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table S10, and geometric parameters are shown in Table S11. The Ortep plots were produced with SHELXL-2014 program, and the three-dimensional supramolecular architecture drawing was produced with Accelrys DS Visualizer 2.06 *(56)*.

Table S10. Experimental details

Crystal data	
Chemical formula	$C_{30}H_{33}F_4N_2O_3P$
M_r	576.55
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	14.0169 (7), 5.9557 (3), 18.0856 (10)
β (°)	103.9371 (17)
V (Å^3)	1465.35 (13)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.15
Crystal size (mm)	0.14 × 0.08 × 0.06
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.728, 0.801

No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	15725, 6211, 5220
R_{int}	0.039
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.650
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.059, 0.117, 1.13
No. of reflections	6211
No. of parameters	376
No. of restraints	40
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.43, -0.39
Absolute structure	Flack x determined using 1819 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.05 (8)

Computer programs: *SAINT* 8.37A (Bruker-AXS, 2015), *SHELXT2014* (Sheldrick, 2015), *SHELXL2014* (Sheldrick, 2015), Bruker *SHELXTL* (Sheldrick, 2015).

Table S11. Geometric parameters (Å, º)

P1—O2	1.471 (3)	C17—C20	1.494 (6)
P1—O3	1.614 (3)	C18—C19	1.390 (6)
P1—N2	1.628 (4)	C18—H18	0.9500
P1—C4	1.790 (4)	C19—H19	0.9500
F1—C11	1.358 (4)	C21—C22	1.528 (5)
O1—C1	1.370 (4)	C21—H21A	0.9900
O1—C7	1.379 (5)	C21—H21B	0.9900
O3—C14	1.399 (5)	C22—C23	1.527 (6)
N1—C7	1.286 (5)	C22—H22A	0.9900
N1—C6	1.400 (5)	C22—H22B	0.9900
N2—C26	1.472 (5)	C23—C24	1.522 (6)
N2—C21	1.475 (5)	C23—C25	1.523 (6)
C1—C2	1.373 (6)	C23—H23	1.0000
C1—C6	1.391 (6)	C24—H24A	0.9800
C2—C3	1.397 (5)	C24—H24B	0.9800
C2—H2	0.9500	C24—H24C	0.9800
C3—C4	1.403 (6)	C25—H25A	0.9800
C3—H3	0.9500	C25—H25B	0.9800

C4—C5	1.386 (6)	C25—H25C	0.9800
C5—C6	1.386 (5)	C26—C27	1.529 (5)
C5—H5	0.9500	C26—H26A	0.9900
C7—C8	1.468 (5)	C26—H26B	0.9900
C8—C9	1.393 (6)	C27—C28	1.521 (6)
C8—C13	1.393 (6)	C27—H27A	0.9900
C9—C10	1.393 (6)	C27—H27B	0.9900
C9—H9	0.9500	C28—C29	1.521 (6)
C10—C11	1.375 (6)	C28—C30	1.533 (7)
C10—H10	0.9500	C28—H28	1.0000
C11—C12	1.372 (6)	C29—H29A	0.9800
C12—C13	1.383 (5)	C29—H29B	0.9800
C12—H12	0.9500	C29—H29C	0.9800
C13—H13	0.9500	C30—H30A	0.9800
C14—C19	1.377 (6)	C30—H30B	0.9800
C14—C15	1.383 (6)	C30—H30C	0.9800
C15—C16	1.386 (5)	C20—F4	1.303 (5)
C15—H15	0.9500	C20—F2	1.310 (6)

C16—C17	1.389 (6)	C20—F3	1.337 (6)
C16—H16	0.9500	C20A—F4A	1.258 (15)
C17—C18	1.378 (6)	C20A—F2A	1.298 (16)
C17—C20A	1.494 (6)	C20A—F3A	1.36 (2)
O2—P1—O3	114.21 (17)	N2—C21—H21A	109.0
O2—P1—N2	112.07 (18)	C22—C21—H21A	109.0
O3—P1—N2	108.00 (17)	N2—C21—H21B	109.0
O2—P1—C4	114.10 (18)	C22—C21—H21B	109.0
O3—P1—C4	99.22 (17)	H21A—C21—H21B	107.8
N2—P1—C4	108.35 (18)	C23—C22—C21	113.1 (3)
C1—O1—C7	103.3 (3)	C23—C22—H22A	109.0
C14—O3—P1	120.0 (2)	C21—C22—H22A	109.0
C7—N1—C6	104.0 (3)	C23—C22—H22B	109.0
C26—N2—C21	116.6 (3)	C21—C22—H22B	109.0
C26—N2—P1	122.5 (3)	H22A—C22—H22B	107.8
C21—N2—P1	120.7 (3)	C24—C23—C25	110.5 (4)
O1—C1—C2	128.0 (4)	C24—C23—C22	111.5 (4)

O1—C1—C6	108.0 (3)	C25—C23—C22	110.9 (4)
C2—C1—C6	124.0 (3)	C24—C23—H23	107.9
C1—C2—C3	116.1 (4)	C25—C23—H23	107.9
C1—C2—H2	122.0	C22—C23—H23	107.9
C3—C2—H2	122.0	C23—C24—H24A	109.5
C2—C3—C4	120.8 (4)	C23—C24—H24B	109.5
C2—C3—H3	119.6	H24A—C24—H24B	109.5
C4—C3—H3	119.6	C23—C24—H24C	109.5
C5—C4—C3	121.8 (3)	H24A—C24—H24C	109.5
C5—C4—P1	116.1 (3)	H24B—C24—H24C	109.5
C3—C4—P1	121.9 (3)	C23—C25—H25A	109.5
C4—C5—C6	117.5 (4)	C23—C25—H25B	109.5
C4—C5—H5	121.3	H25A—C25—H25B	109.5
C6—C5—H5	121.3	C23—C25—H25C	109.5
C5—C6—C1	119.9 (4)	H25A—C25—H25C	109.5
C5—C6—N1	131.5 (4)	H25B—C25—H25C	109.5
C1—C6—N1	108.6 (3)	N2—C26—C27	112.9 (3)
N1—C7—O1	116.1 (3)	N2—C26—H26A	109.0

N1—C7—C8	128.2 (4)	C27—C26—H26A	109.0
O1—C7—C8	115.6 (3)	N2—C26—H26B	109.0
C9—C8—C13	120.5 (4)	C27—C26—H26B	109.0
C9—C8—C7	119.1 (4)	H26A—C26—H26B	107.8
C13—C8—C7	120.3 (4)	C28—C27—C26	114.9 (4)
C8—C9—C10	119.7 (4)	C28—C27—H27A	108.5
C8—C9—H9	120.2	C26—C27—H27A	108.5
C10—C9—H9	120.2	C28—C27—H27B	108.5
C11—C10—C9	117.8 (4)	C26—C27—H27B	108.5
C11—C10—H10	121.1	H27A—C27—H27B	107.5
C9—C10—H10	121.1	C29—C28—C27	110.4 (4)
F1—C11—C12	118.0 (4)	C29—C28—C30	110.4 (4)
F1—C11—C10	118.0 (4)	C27—C28—C30	112.1 (4)
C12—C11—C10	124.0 (4)	C29—C28—H28	107.9
C11—C12—C13	118.0 (4)	C27—C28—H28	107.9
C11—C12—H12	121.0	C30—C28—H28	107.9
C13—C12—H12	121.0	C28—C29—H29A	109.5
C12—C13—C8	120.0 (4)	C28—C29—H29B	109.5

C12—C13—H13	120.0	H29A—C29—H29B	109.5
C8—C13—H13	120.0	C28—C29—H29C	109.5
C19—C14—C15	122.0 (4)	H29A—C29—H29C	109.5
C19—C14—O3	117.9 (4)	H29B—C29—H29C	109.5
C15—C14—O3	120.0 (4)	C28—C30—H30A	109.5
C14—C15—C16	118.5 (4)	C28—C30—H30B	109.5
C14—C15—H15	120.7	H30A—C30—H30B	109.5
C16—C15—H15	120.7	C28—C30—H30C	109.5
C15—C16—C17	120.2 (4)	H30A—C30—H30C	109.5
C15—C16—H16	119.9	H30B—C30—H30C	109.5
C17—C16—H16	119.9	F4—C20—F2	107.5 (4)
C18—C17—C16	120.3 (4)	F4—C20—F3	104.6 (4)
C18—C17—C20A	120.8 (4)	F2—C20—F3	104.9 (4)
C16—C17—C20A	118.9 (4)	F4—C20—C17	113.5 (4)
C18—C17—C20	120.8 (4)	F2—C20—C17	112.7 (4)
C16—C17—C20	118.9 (4)	F3—C20—C17	112.9 (4)
C17—C18—C19	120.1 (4)	F4A—C20A—F2A	108.0 (14)
C17—C18—H18	119.9	F4A—C20A—F3A	104.9 (13)

C19—C18—H18	119.9	F2A—C20A—F3A	103.9 (13)
C14—C19—C18	118.8 (4)	F4A—C20A—C17	115.7 (10)
C14—C19—H19	120.6	F2A—C20A—C17	111.3 (10)
C18—C19—H19	120.6	F3A—C20A—C17	112.3 (10)
N2—C21—C22	113.1 (3)		
O2—P1—O3—C14	-67.5 (3)	C9—C10—C11—F1	-179.9 (3)
N2—P1—O3—C14	57.9 (3)	C9—C10—C11—C12	-1.3 (6)
C4—P1—O3—C14	170.8 (3)	F1—C11—C12—C13	178.9 (3)
O2—P1—N2—C26	13.7 (4)	C10—C11—C12—C13	0.3 (6)
O3—P1—N2—C26	-112.9 (3)	C11—C12—C13—C8	0.6 (6)
C4—P1—N2—C26	140.5 (3)	C9—C8—C13—C12	-0.5 (6)
O2—P1—N2—C21	-171.4 (3)	C7—C8—C13—C12	177.7 (4)

O3—P1—N2—C21	61.9 (3)	P1—O3—C14—C19	-109.6 (4)
C4—P1—N2—C21	-44.7 (3)	P1—O3—C14—C15	72.3 (4)
C7—O1—C1—C2	-179.9 (4)	C19—C14—C15—C16	0.9 (6)
C7—O1—C1—C6	0.5 (4)	O3—C14—C15—C16	178.9 (4)
O1—C1—C2—C3	-178.8 (4)	C14—C15—C16—C17	-0.4 (6)
C6—C1—C2—C3	0.7 (6)	C15—C16—C17—C18	-0.2 (6)
C1—C2—C3—C4	-0.9 (6)	C15—C16—C17—C20A	179.9 (4)
C2—C3—C4—C5	0.6 (6)	C15—C16—C17—C20	179.9 (4)
C2—C3—C4—P1	-174.6 (3)	C16—C17—C18—C19	0.3 (7)
O2—P1—C4—C5	31.7 (4)	C20A—C17—C18—C19	-179.9 (4)

O3—P1—C4—C5	153.5 (3)	C20—C17—C18—C19	-179.9 (4)
N2—P1—C4—C5	-93.9 (3)	C15—C14—C19—C18	-0.8 (6)
O2—P1—C4—C3	-152.9 (3)	O3—C14—C19—C18	-178.9 (4)
O3—P1—C4—C3	-31.1 (4)	C17—C18—C19—C14	0.2 (6)
N2—P1—C4—C3	81.5 (4)	C26—N2—C21—C22	-90.9 (4)
C3—C4—C5—C6	0.0 (6)	P1—N2—C21—C22	94.0 (4)
P1—C4—C5—C6	175.4 (3)	N2—C21—C22—C23	-177.3 (3)
C4—C5—C6—C1	-0.2 (6)	C21—C22—C23—C24	-82.4 (4)
C4—C5—C6—N1	179.4 (4)	C21—C22—C23—C25	154.0 (4)
O1—C1—C6—C5	179.4 (4)	C21—N2—C26—C27	-82.0 (4)
C2—C1—C6—C5	-0.2 (6)	P1—N2—C26—C27	93.1 (4)

O1—C1—C6—N1	-0.2 (4)	N2—C26—C27—C28	166.9 (4)
C2—C1—C6—N1	-179.8 (4)	C26—C27—C28—C29	-177.3 (4)
C7—N1—C6—C5	-179.8 (4)	C26—C27—C28—C30	59.2 (6)
C7—N1—C6—C1	-0.2 (4)	C18—C17—C20—F4	-122.4 (6)
C6—N1—C7—O1	0.6 (4)	C16—C17—C20—F4	57.4 (6)
C6—N1—C7—C8	178.3 (4)	C18—C17—C20—F2	115.1 (6)
C1—O1—C7—N1	-0.8 (4)	C16—C17—C20—F2	-65.1 (6)
C1—O1—C7—C8	-178.7 (3)	C18—C17—C20—F3	-3.6 (7)
N1—C7—C8—C9	5.6 (6)	C16—C17—C20—F3	176.2 (5)
O1—C7—C8—C9	-176.8 (3)	C18—C17—C20A—F4A	71.3 (17)
N1—C7—C8—C13	-172.6 (4)	C16—C17—C20A—F4A	-108.9 (17)
O1—C7—C8—C13	5.1 (5)	C18—C17—C20A—F2A	-52 (2)
C13—C8—C9—C10	-0.6 (6)	C16—C17—C20A—F2A	127 (2)

C7—C8—C9—C10	-178.8 (4)	C18—C17—C20A—F3A	-168.4 (18)
C8—C9—C10—C11	1.5 (6)	C16—C17—C20A—F3A	11.4 (19)

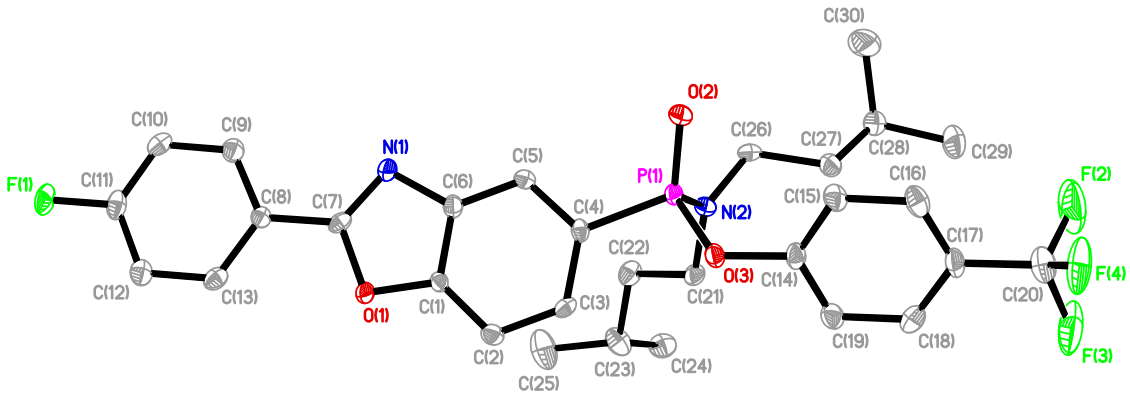


Figure S1. Perspective views showing 50% probability displacement

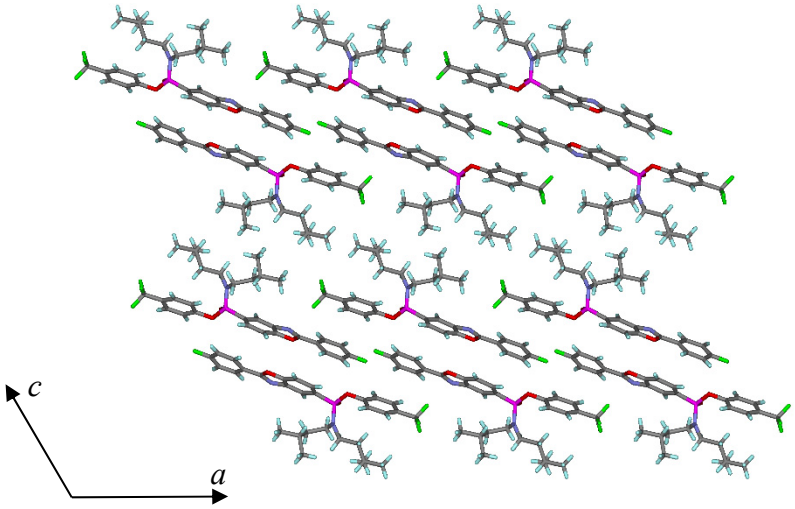
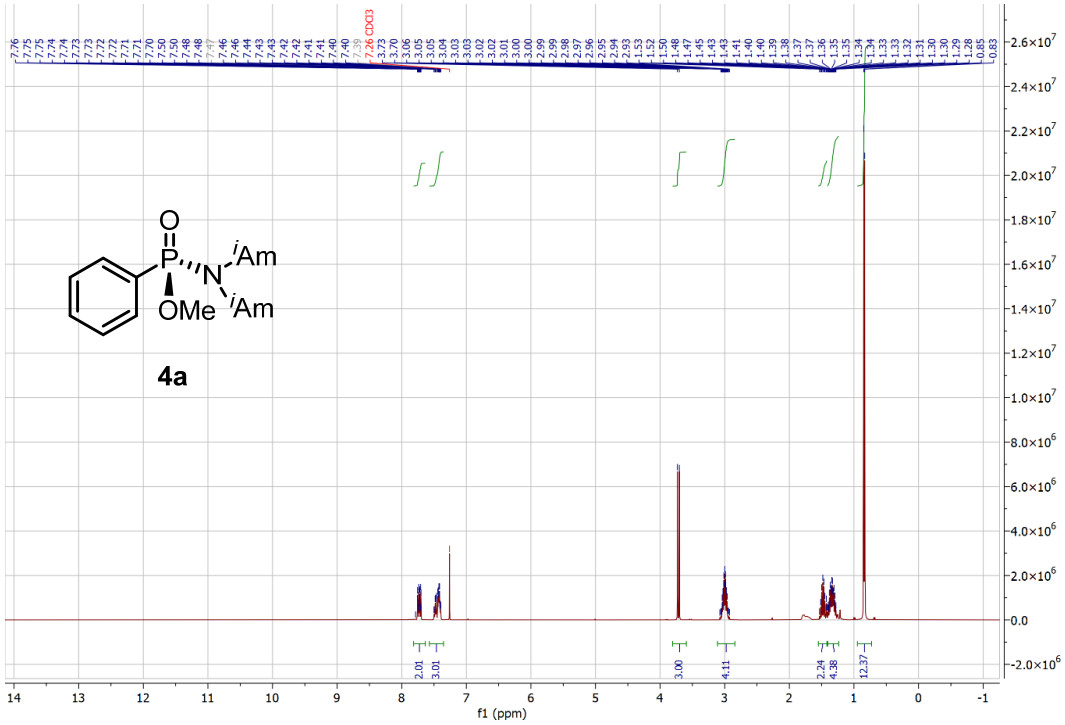


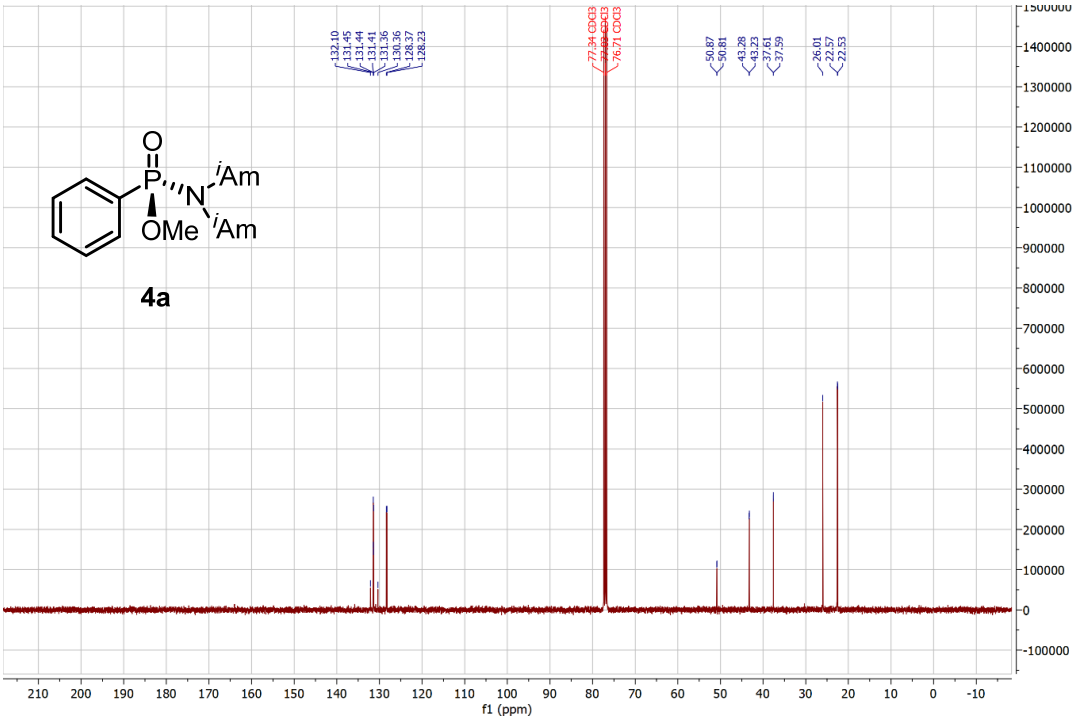
Figure S2. Three-dimensional supramolecular architecture viewed along the *b*-axis direction.

NMR Spectra

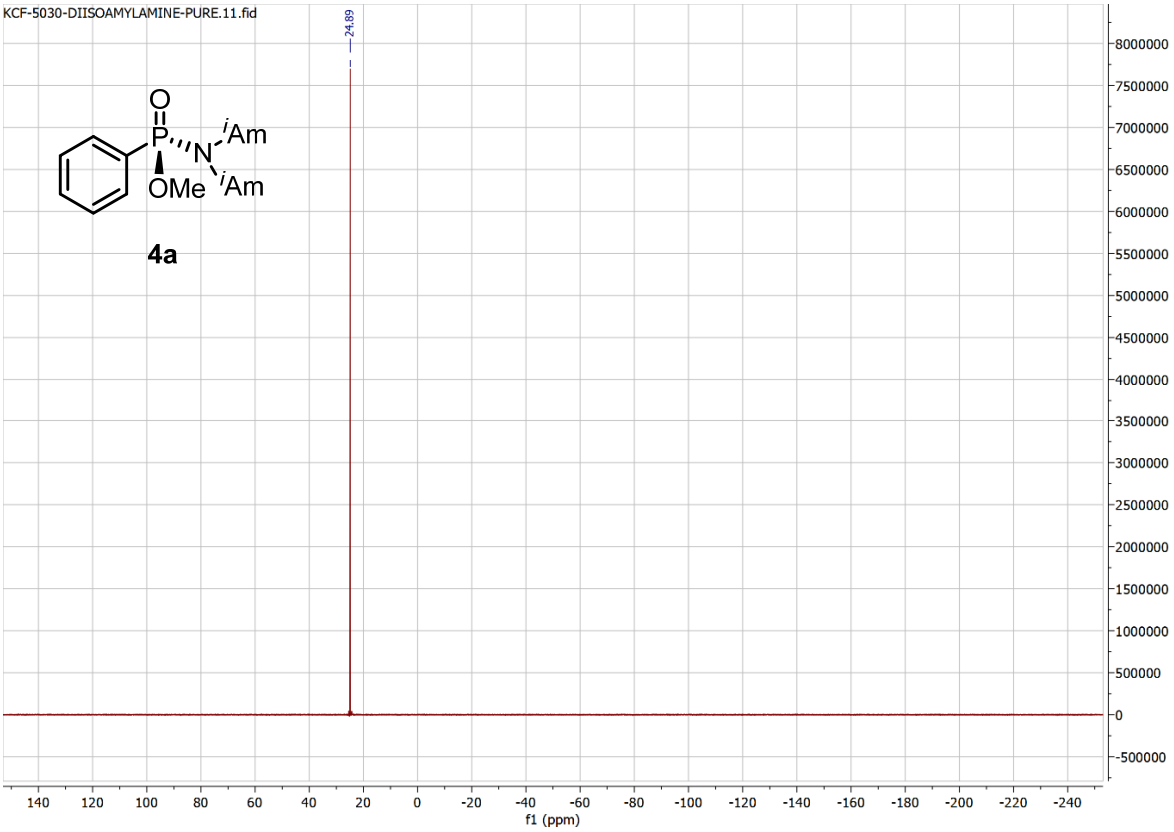
^{1}H NMR



^{13}C NMR



^{31}P NMR


KCF-5030-DIISOAMYLAMINE-PURE.11.fid
24.89
O
P
N
iAm
OMe
iAm
4a
8000000
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7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
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-80
-100
-120
-140
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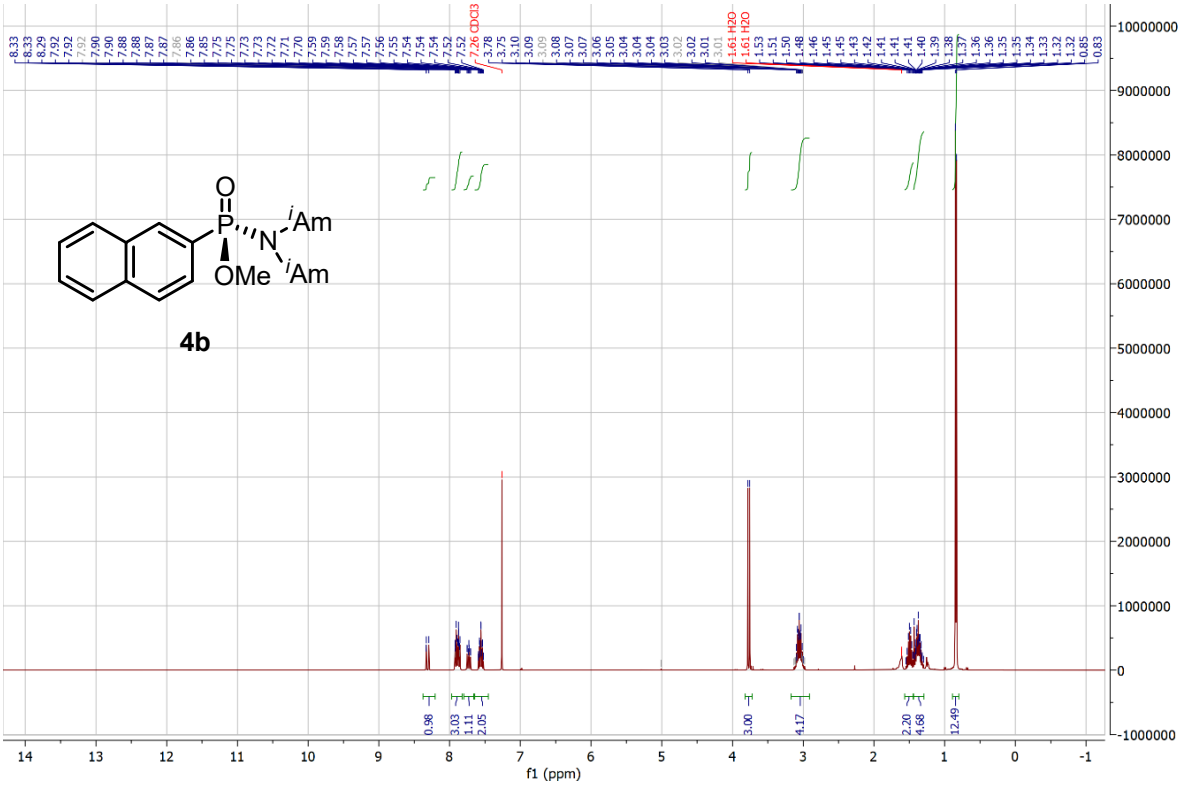
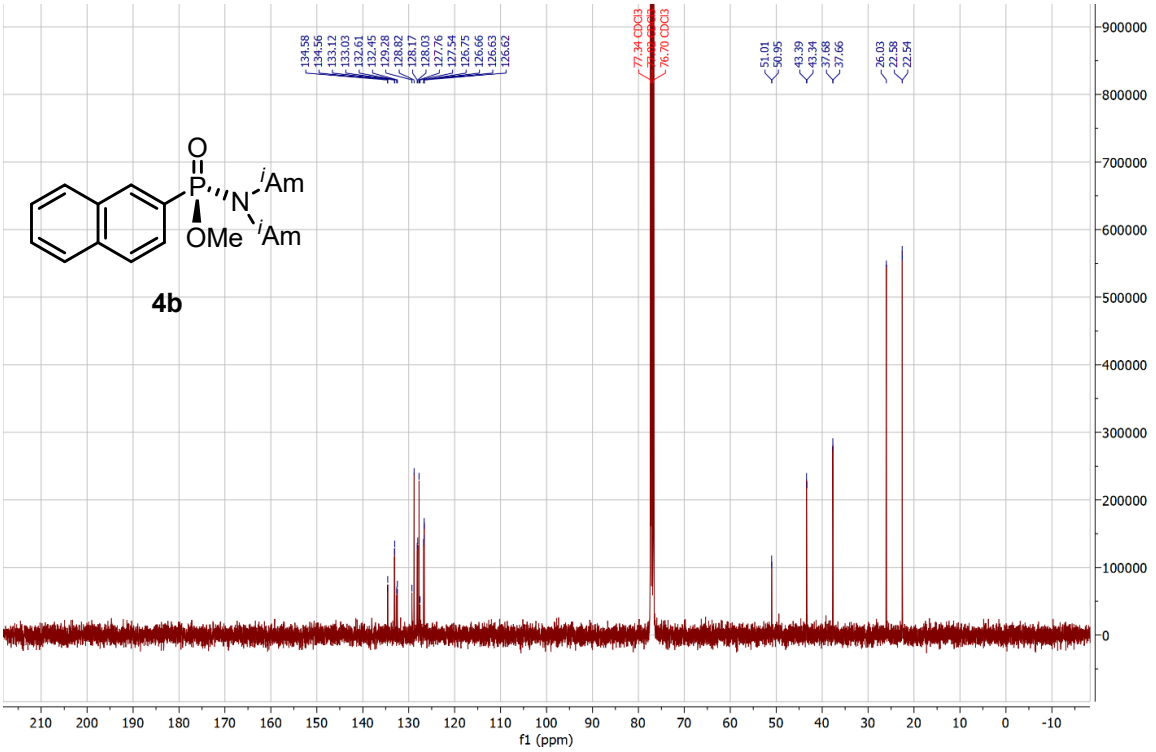
-180
-200
-220
-240
f1 (ppm)

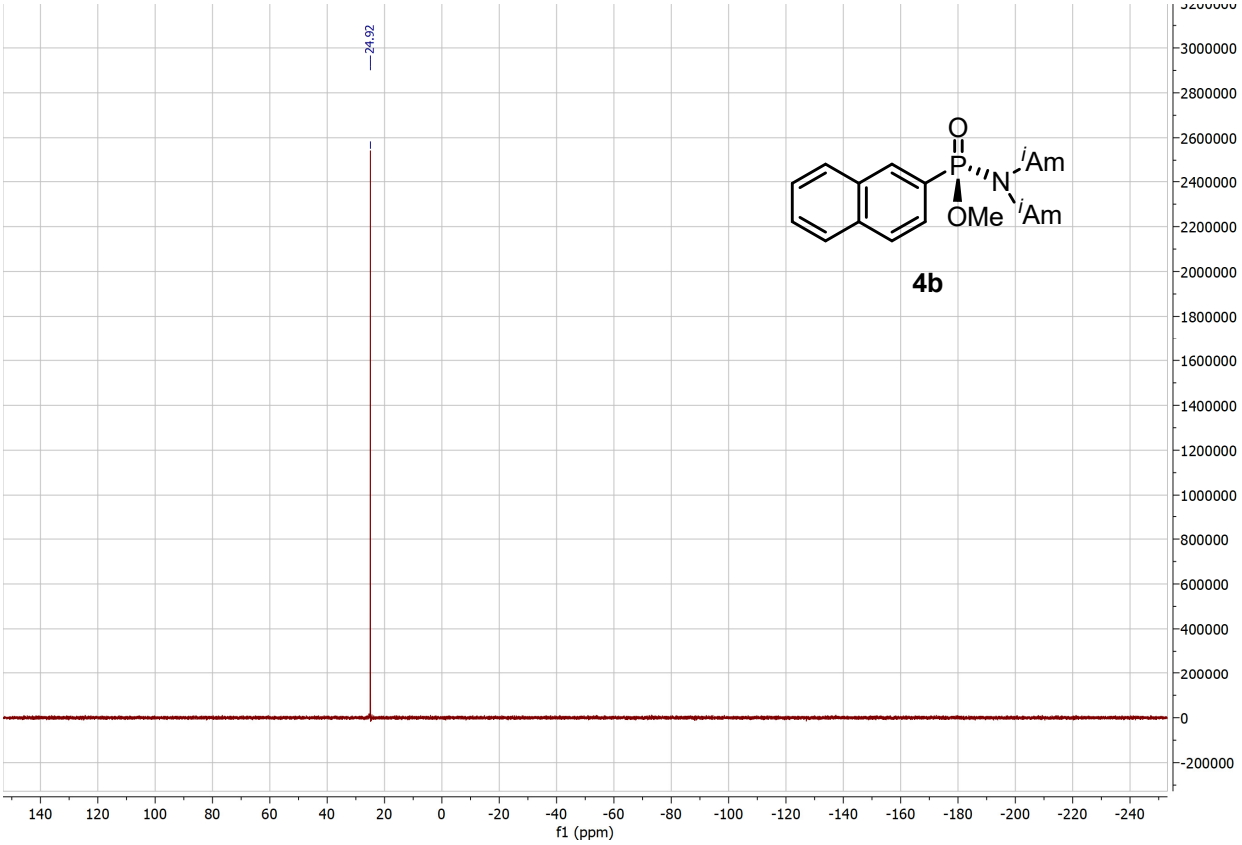
^{1}H NMR



^{13}C NMR



^{31}P NMR


24.92
O
P
N
iAm
OMe
iAm
4b
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
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-140
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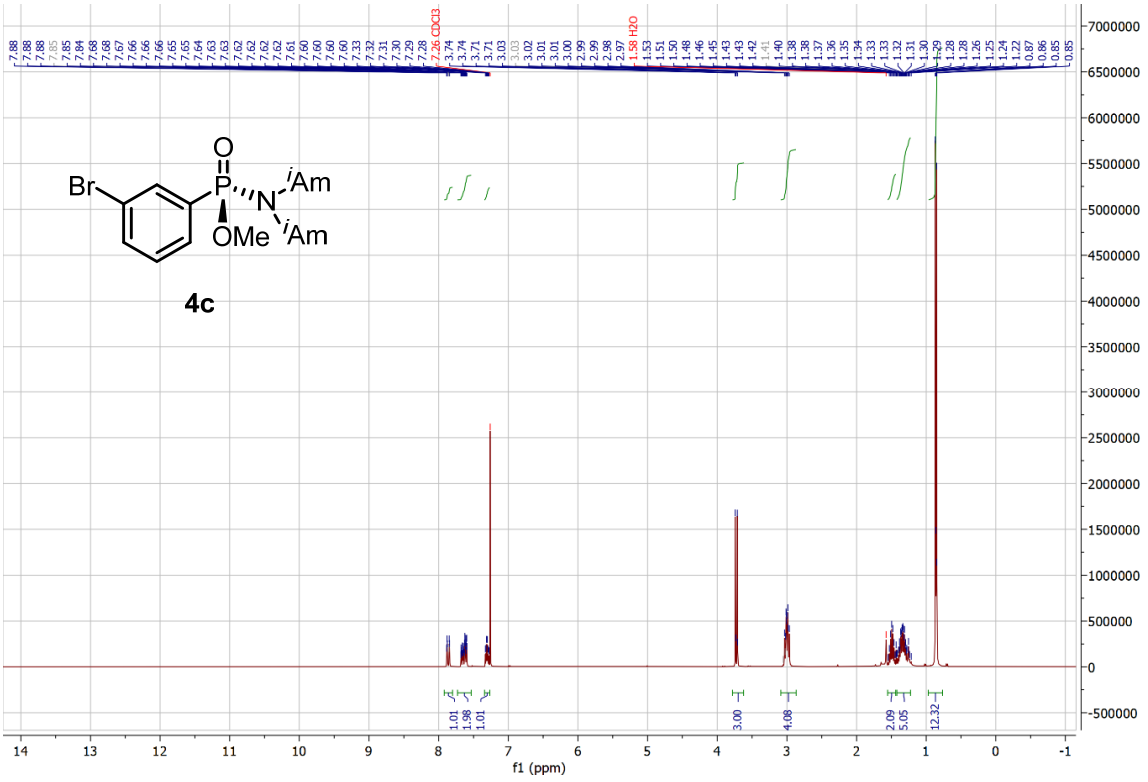
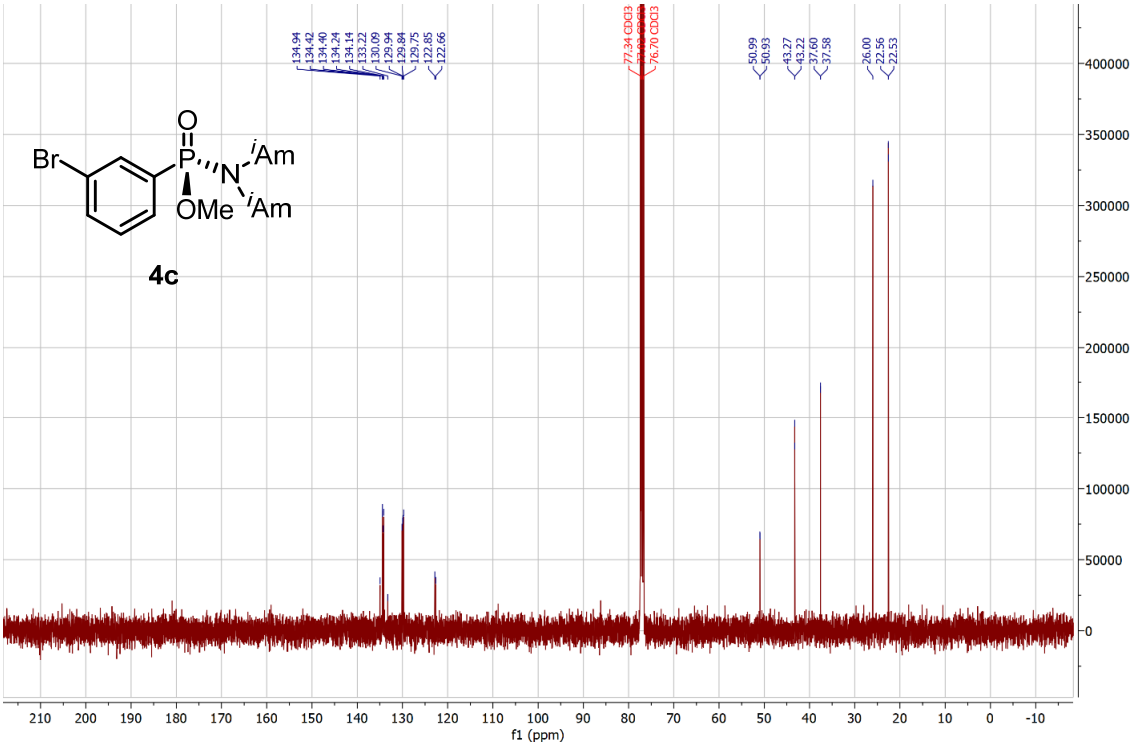
-180
-200
-220
-240
f1 (ppm)

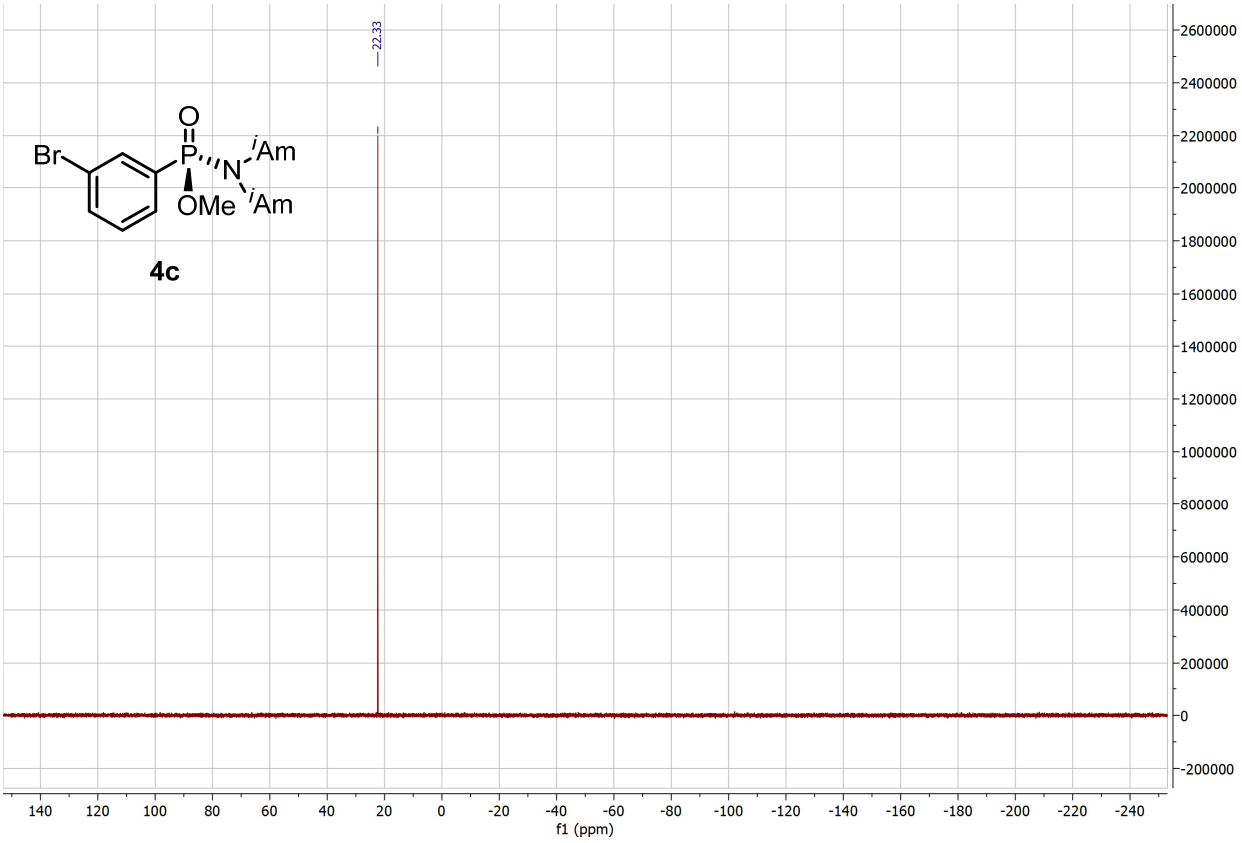
^{1}H NMR



^{13}C NMR



^{31}P NMR


22.33
Br
O
P
N
iAm
OMe
iAm
4c
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
-20
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-140
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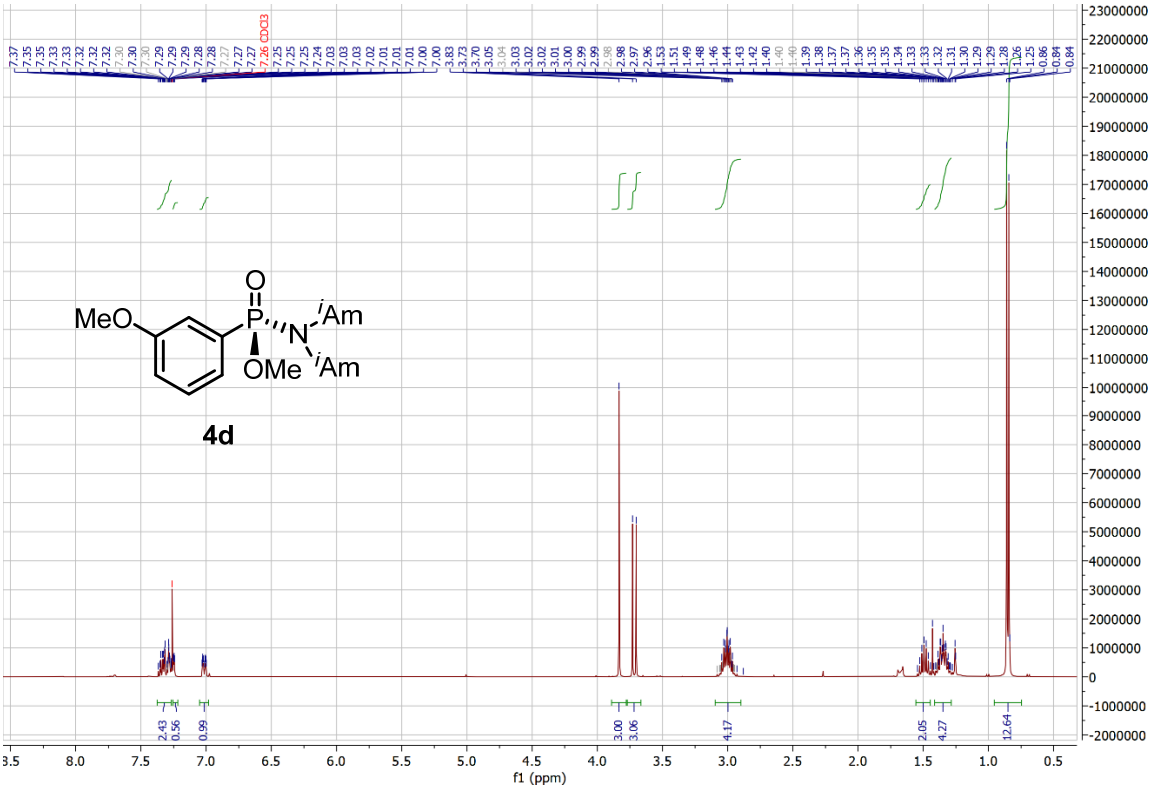
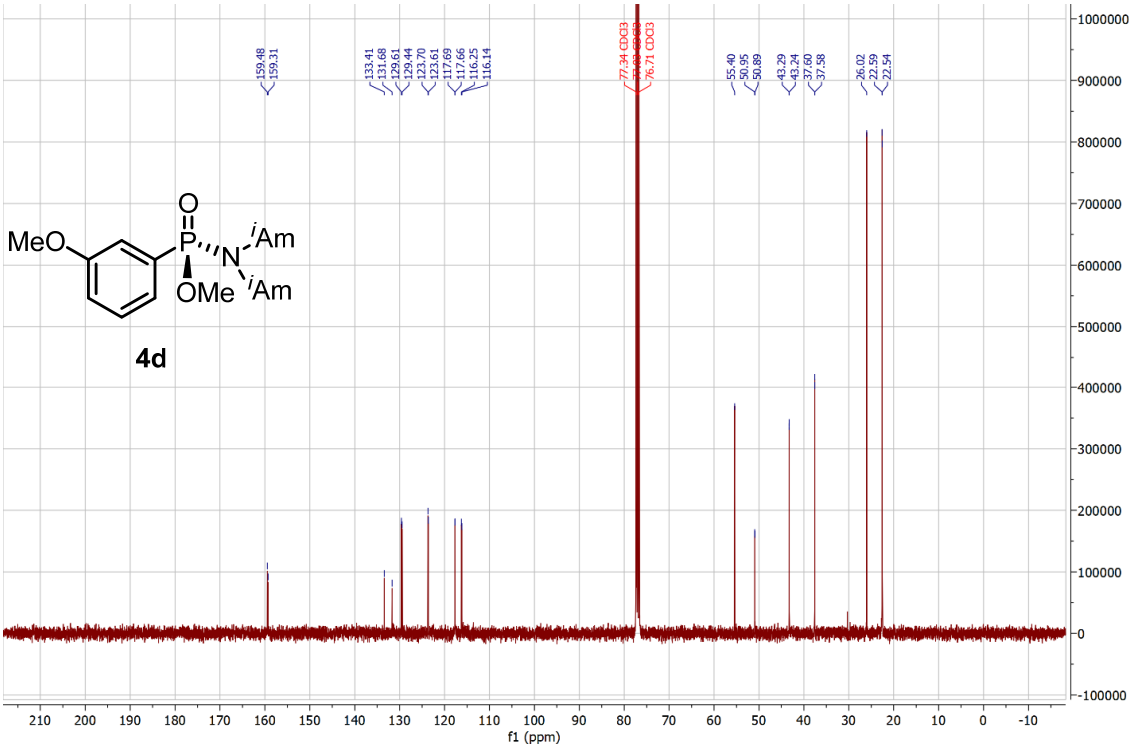
-200
-220
-240
f1 (ppm)

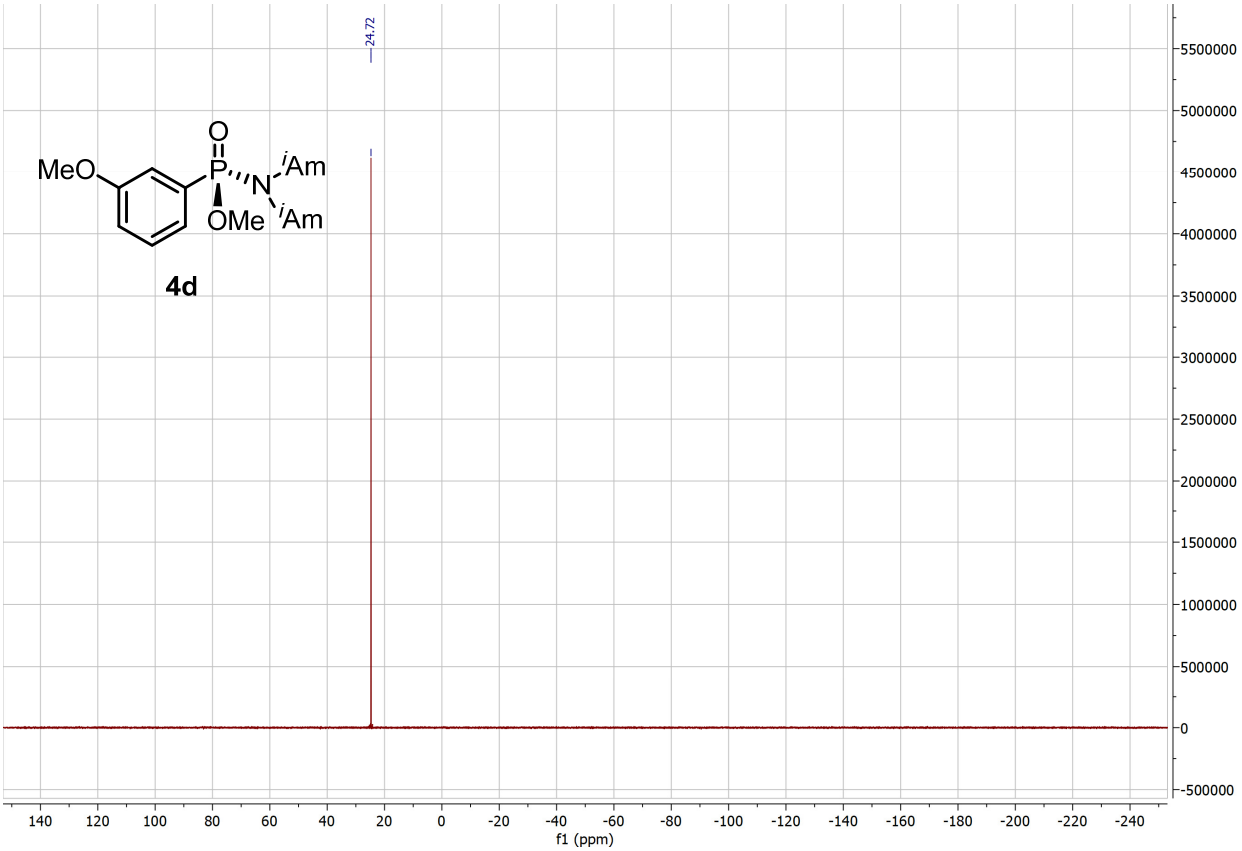
^{1}H NMR



^{13}C NMR



^{31}P NMR


24.72
MeO
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P
N
OMe
iAm
iAm
4d
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4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
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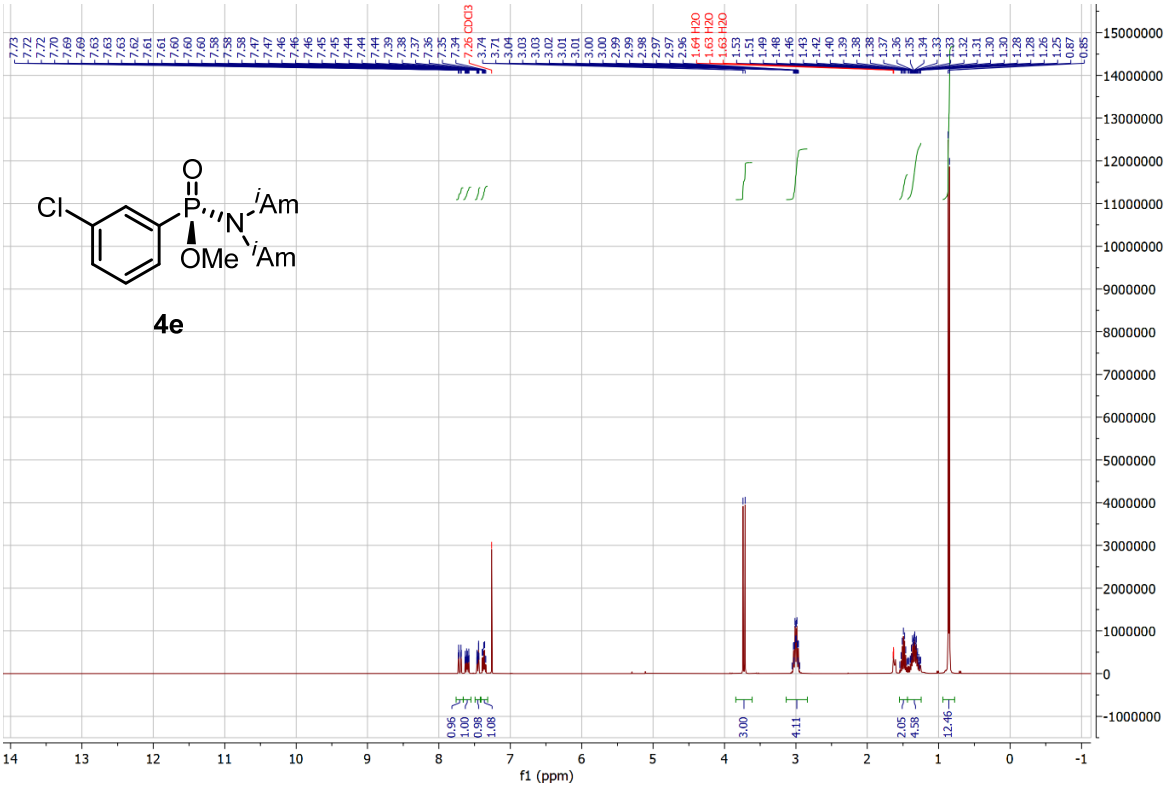
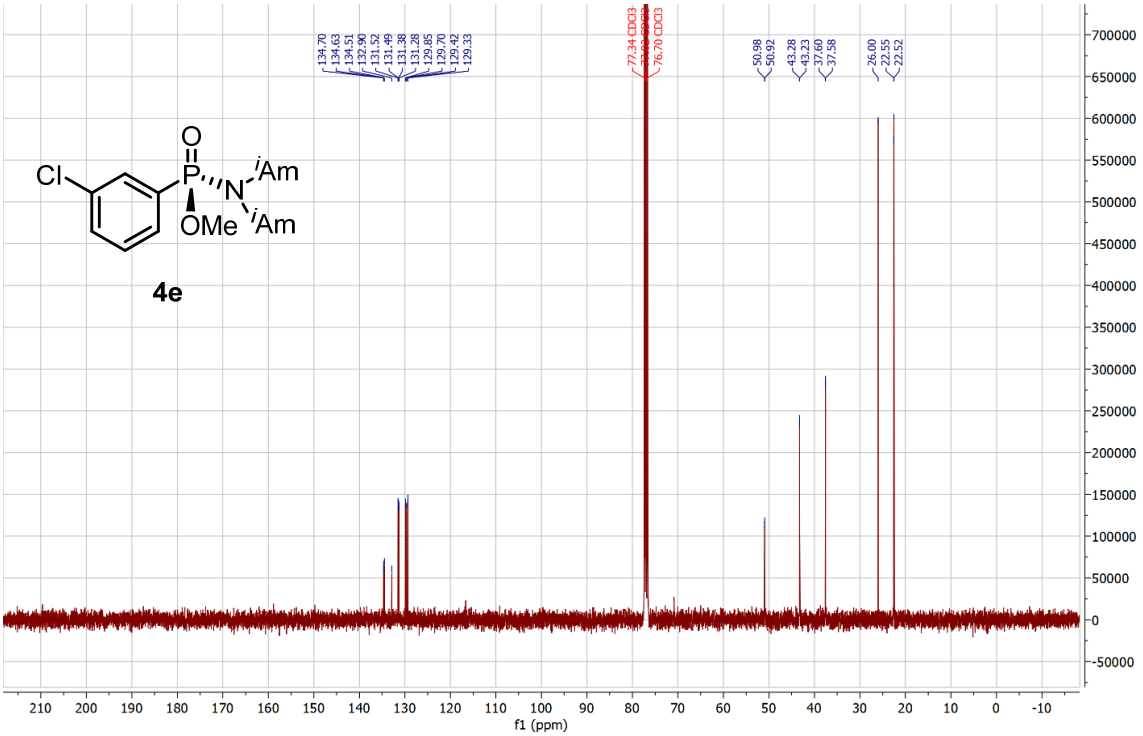
-200
-220
-240
f1 (ppm)

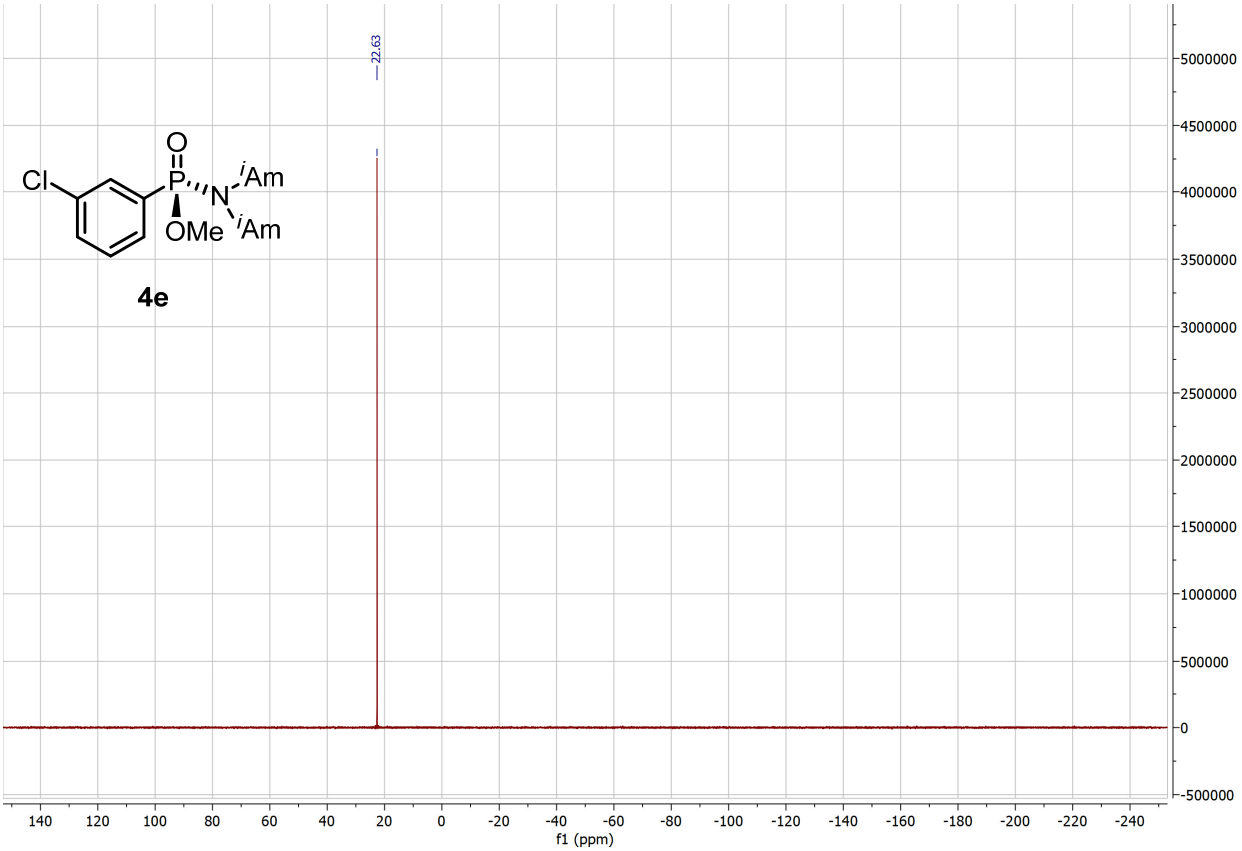
^{1}H NMR



^{13}C NMR



^{31}P NMR


22.63
Cl
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P
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OMe
iAm
4e
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4000000
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3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
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-200
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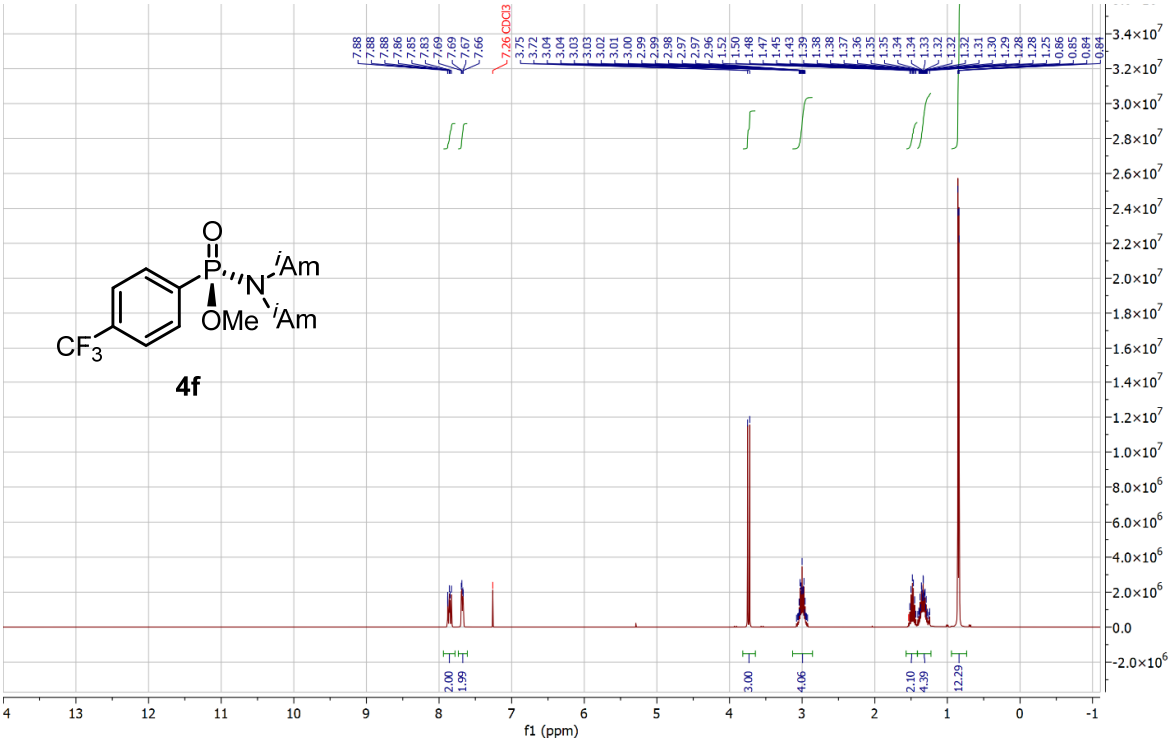
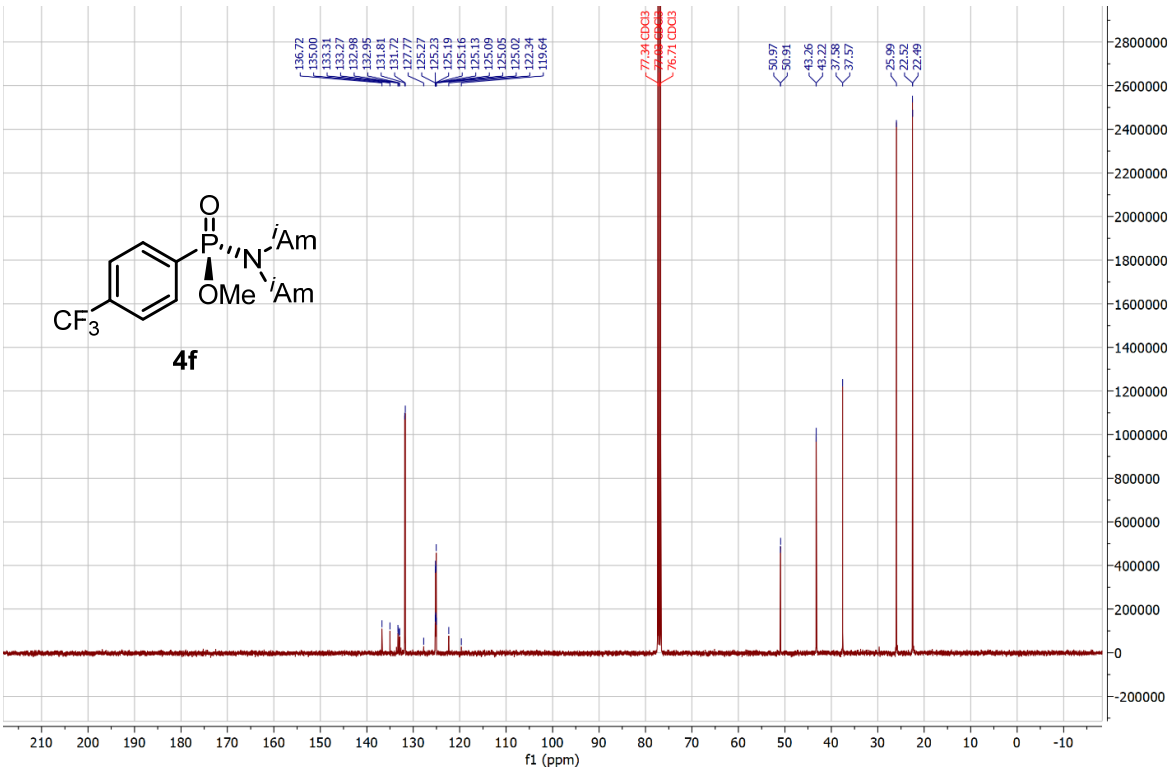
-240
f1 (ppm)

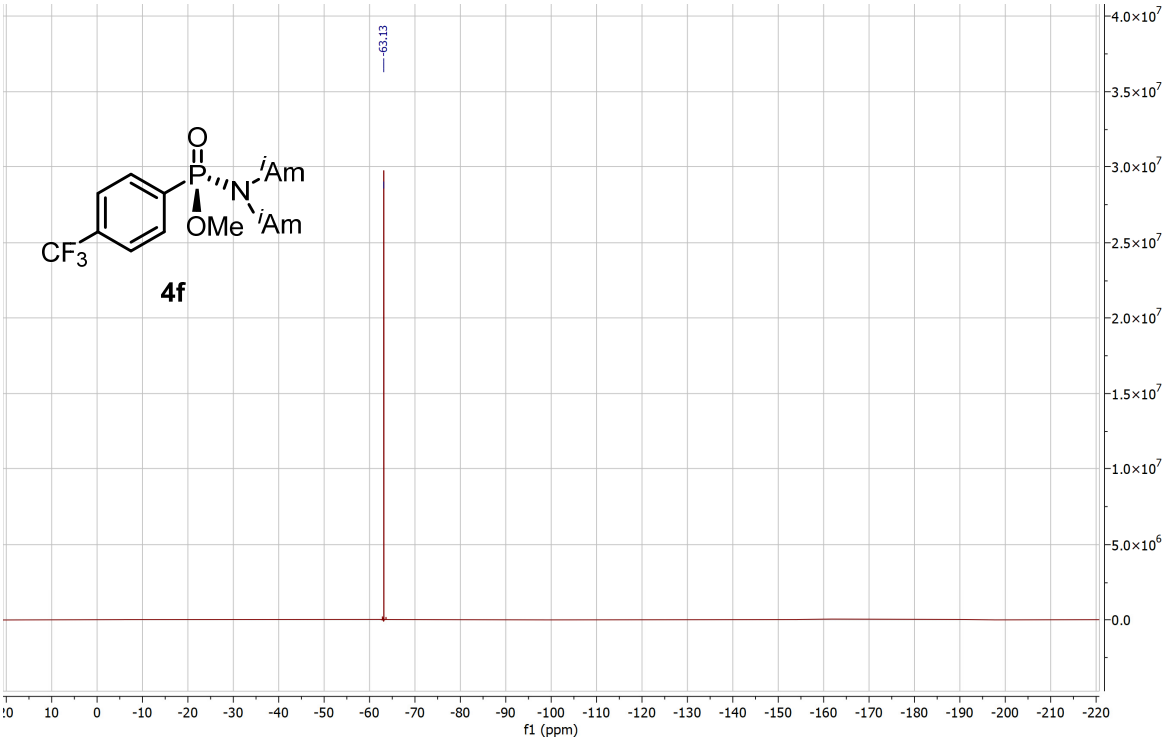
^{1}H NMR



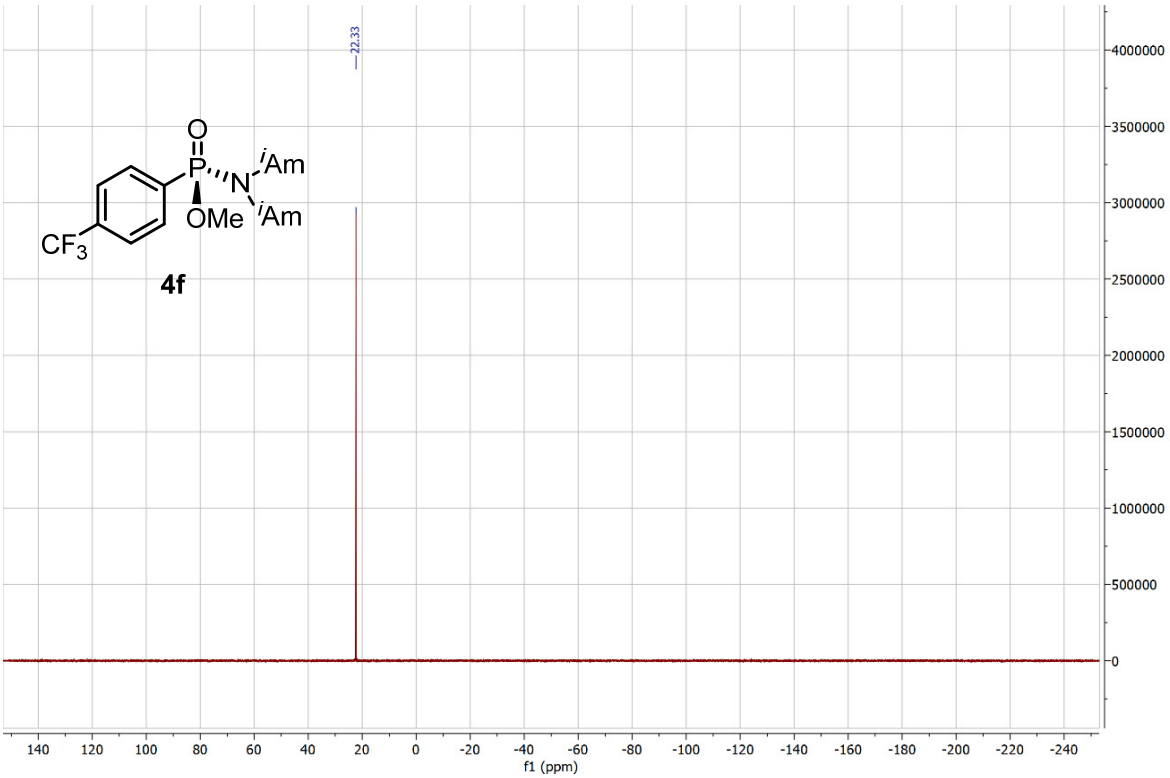
^{13}C NMR



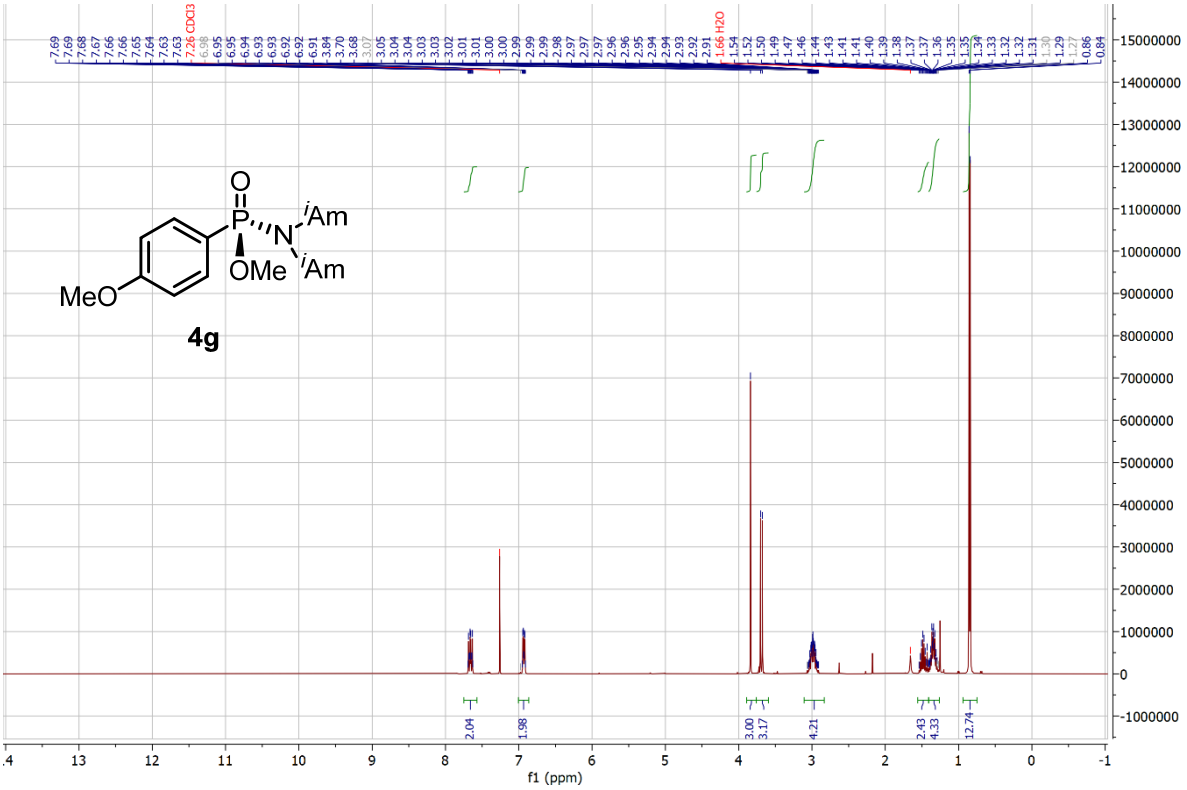
^{19}F NMR



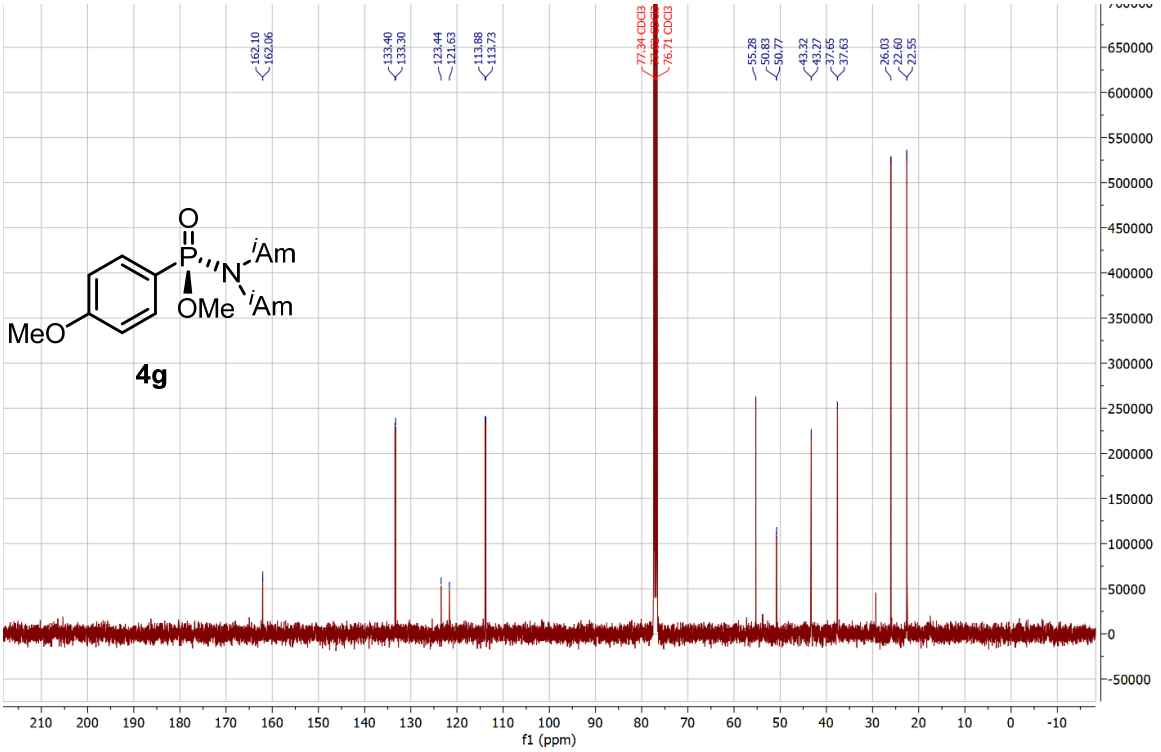
^{31}P NMR



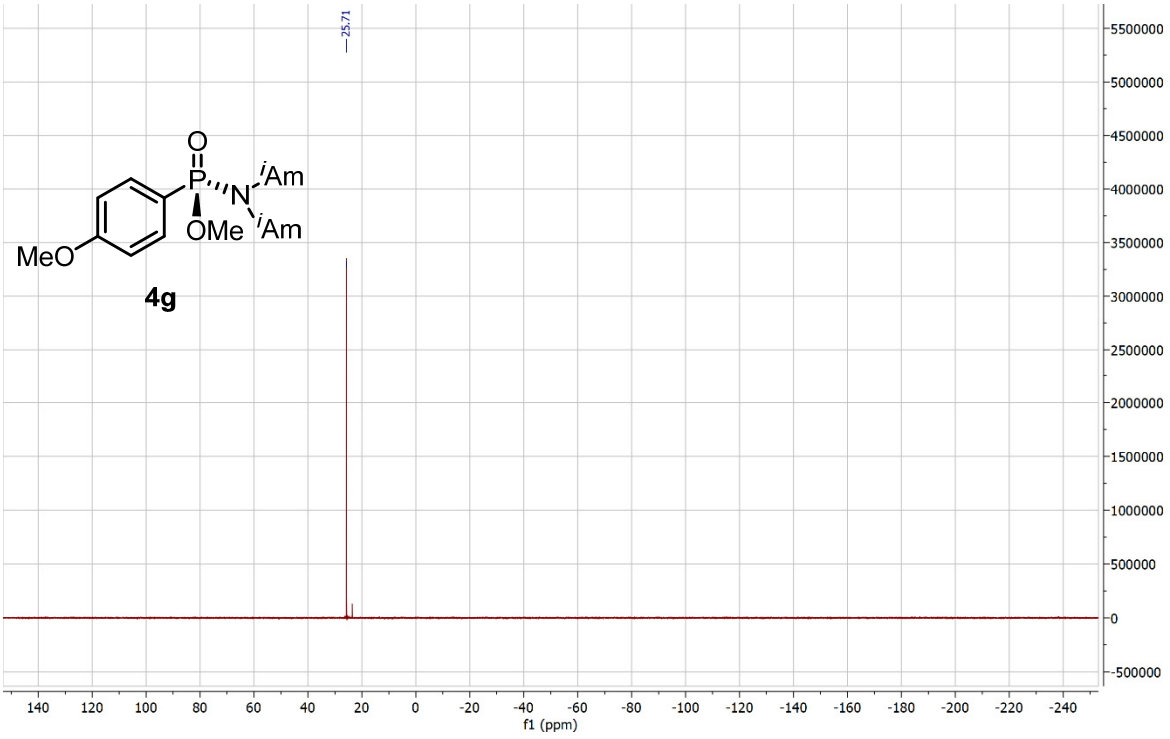
^{1}H NMR



^{13}C NMR



^{31}P NMR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1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
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-40
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-140
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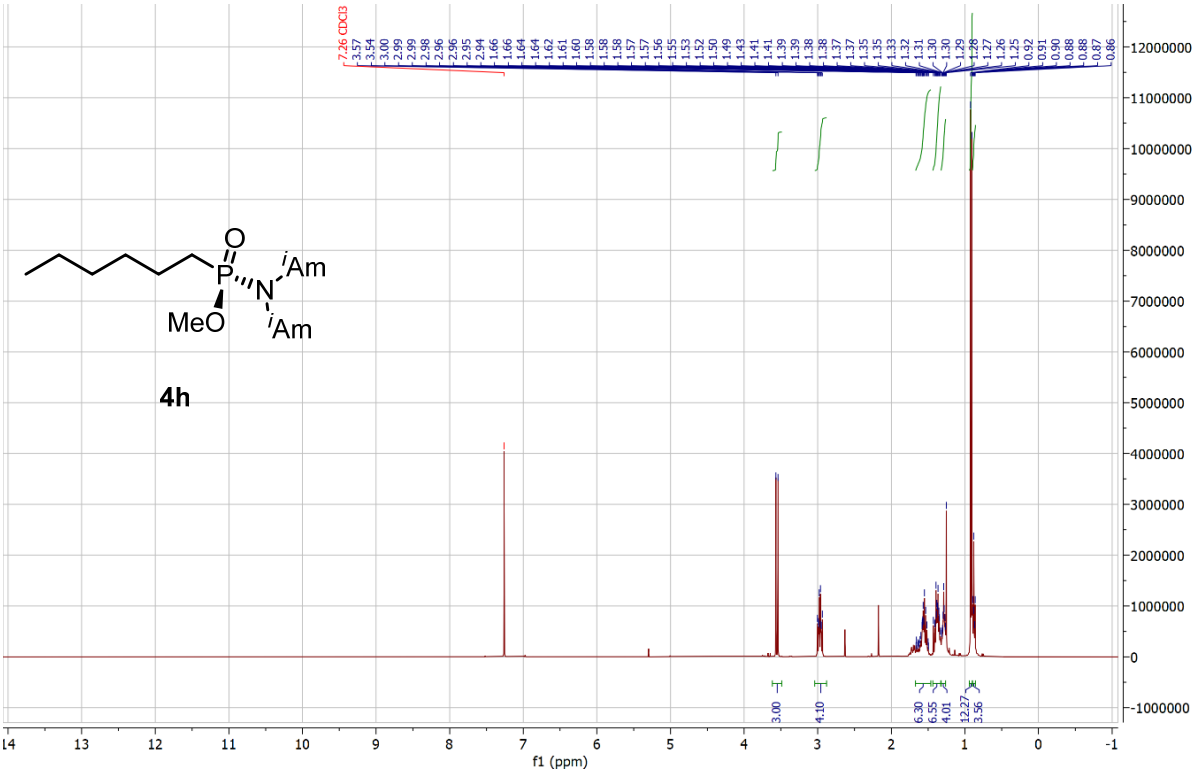
-180
-200
-220
-240
f1 (ppm)

^{1}H NMR



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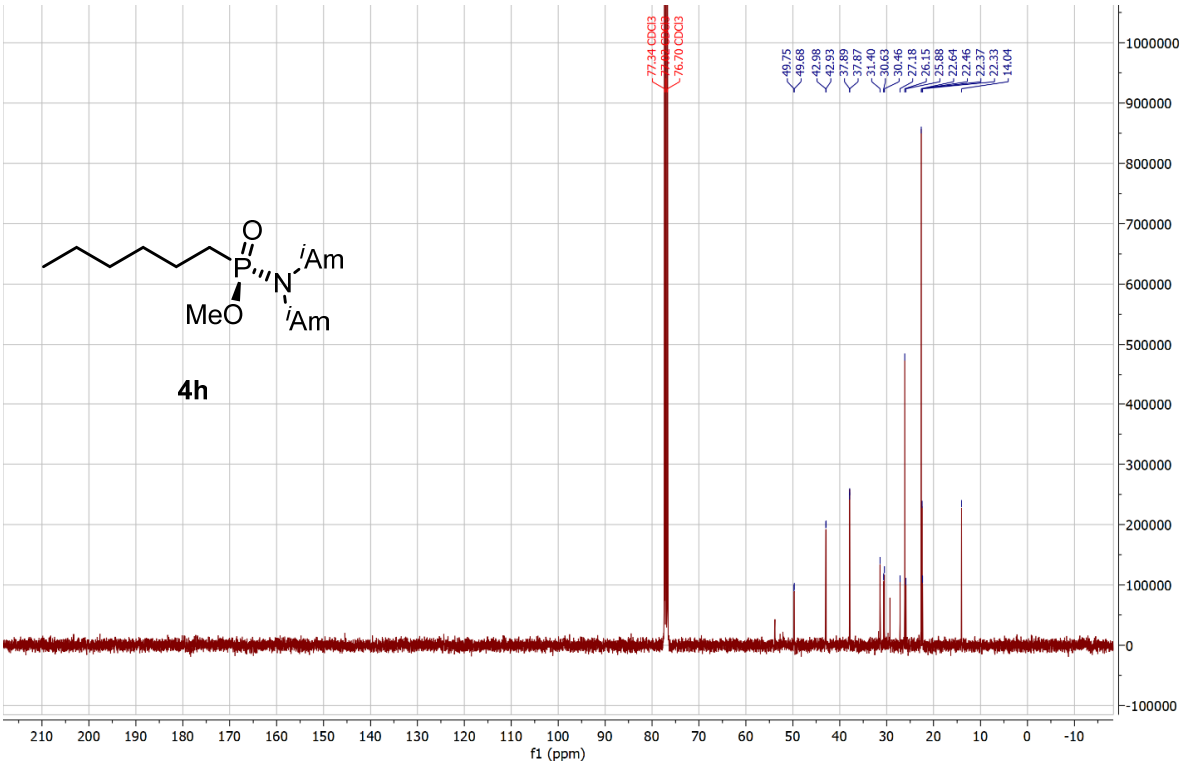

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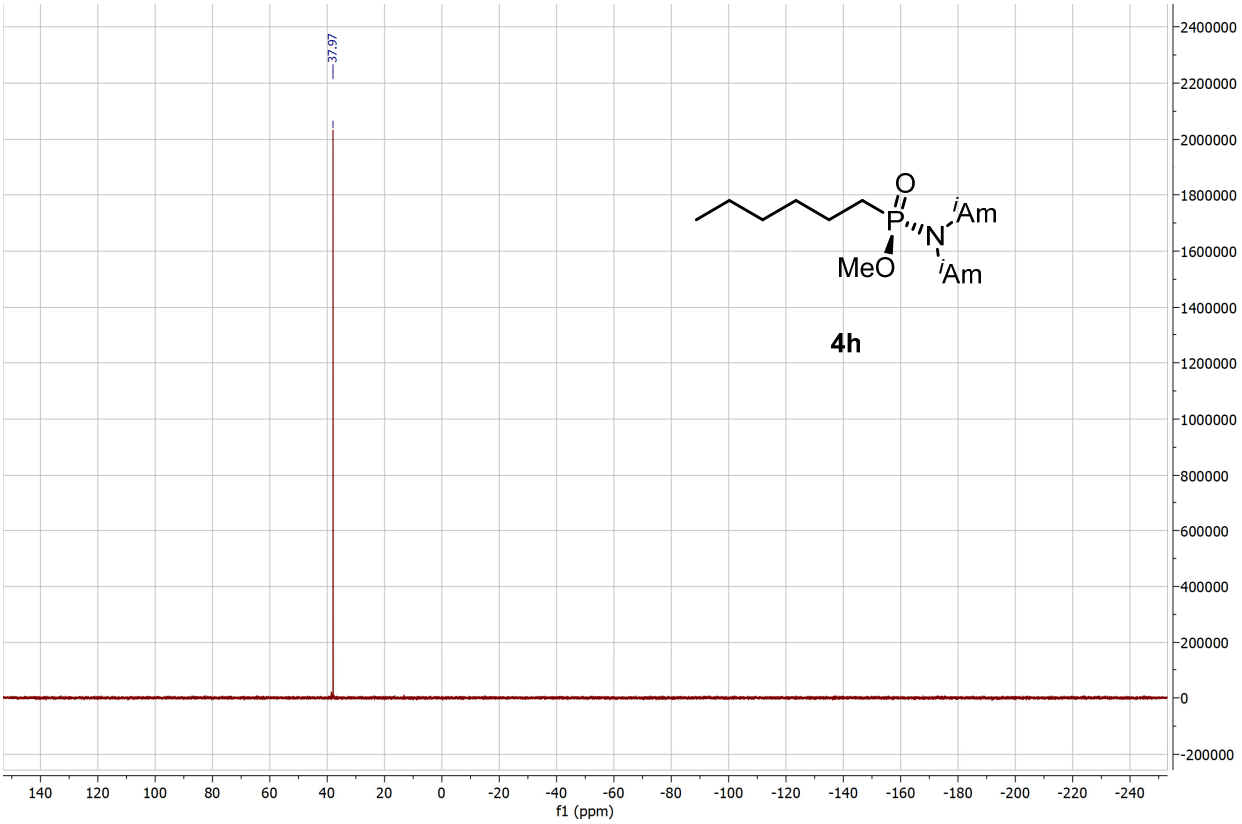
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P
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MeO
iAm
iAm
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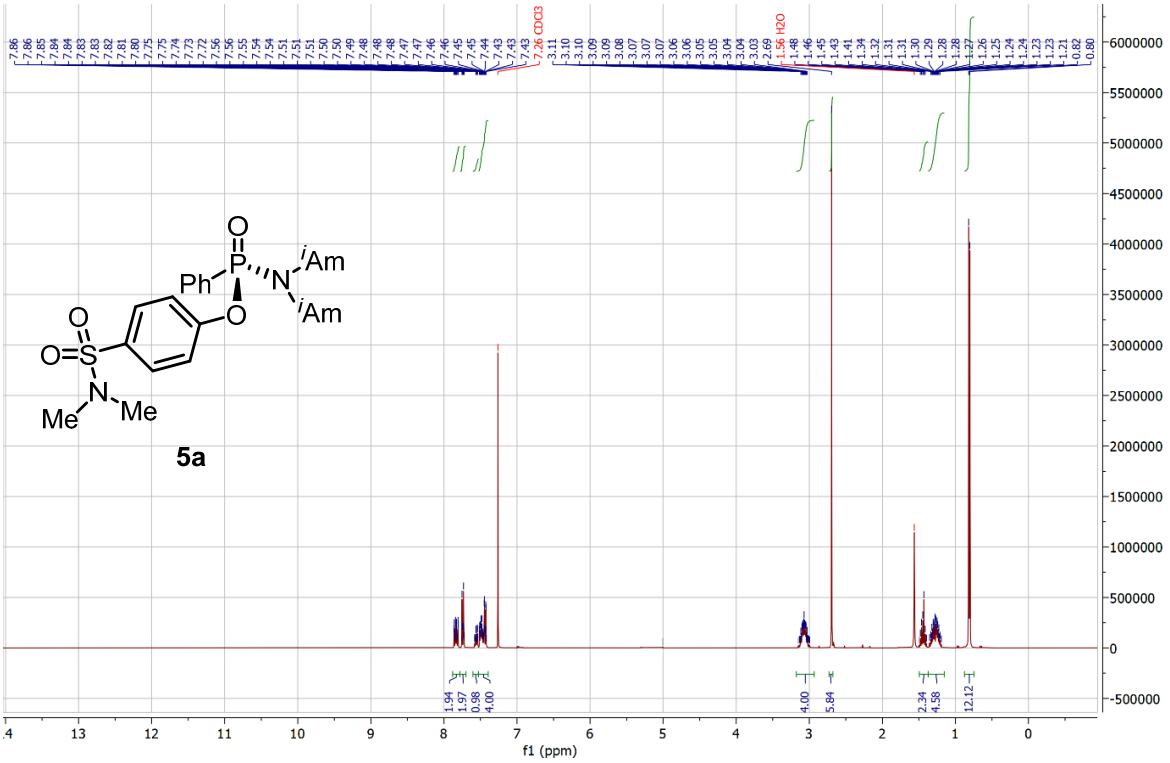
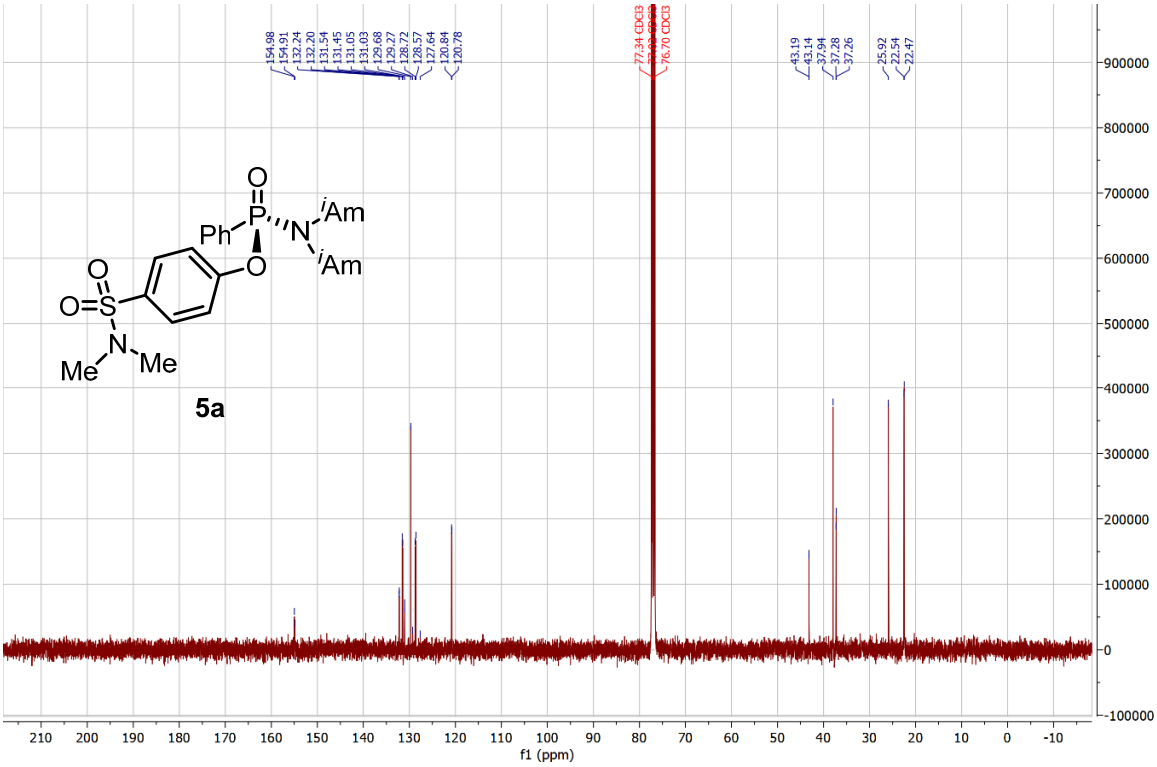
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

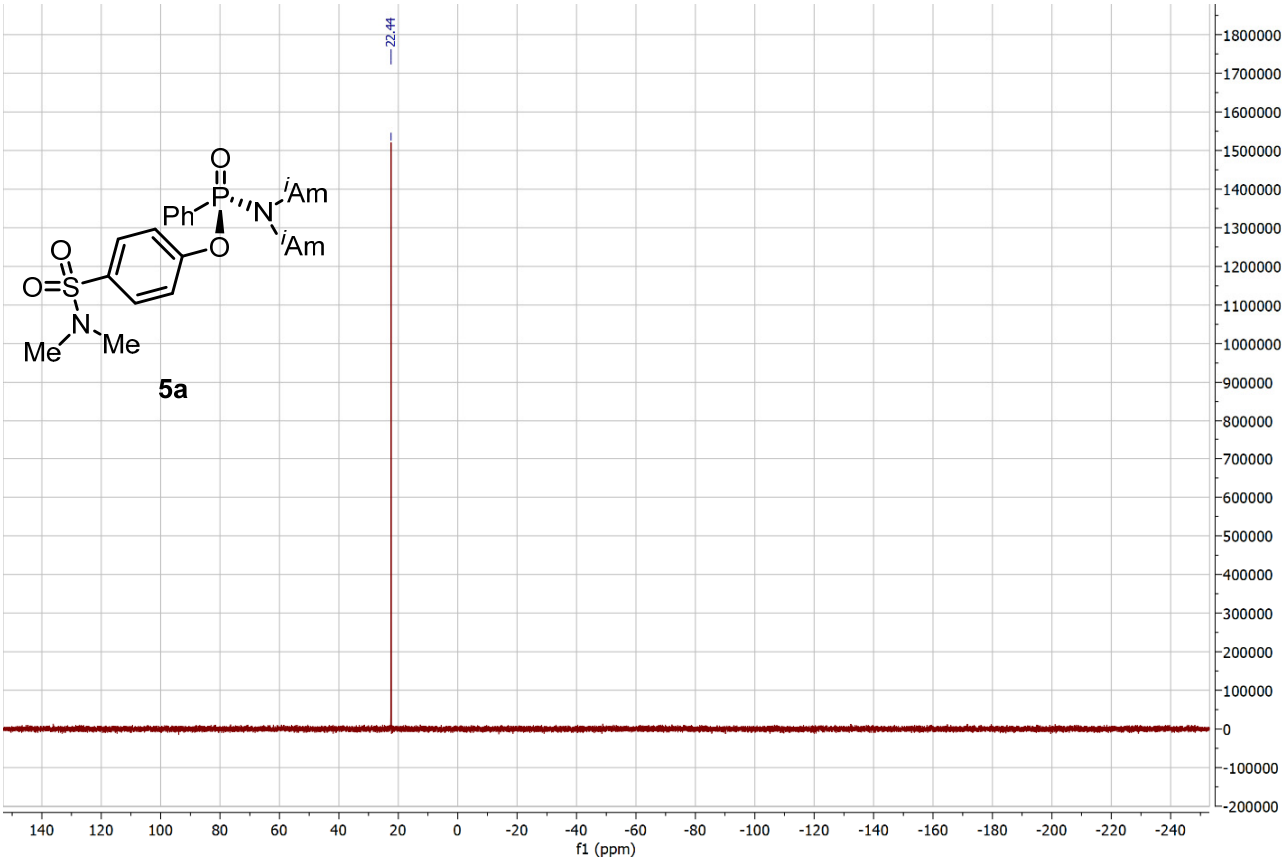
^{1}H NMR



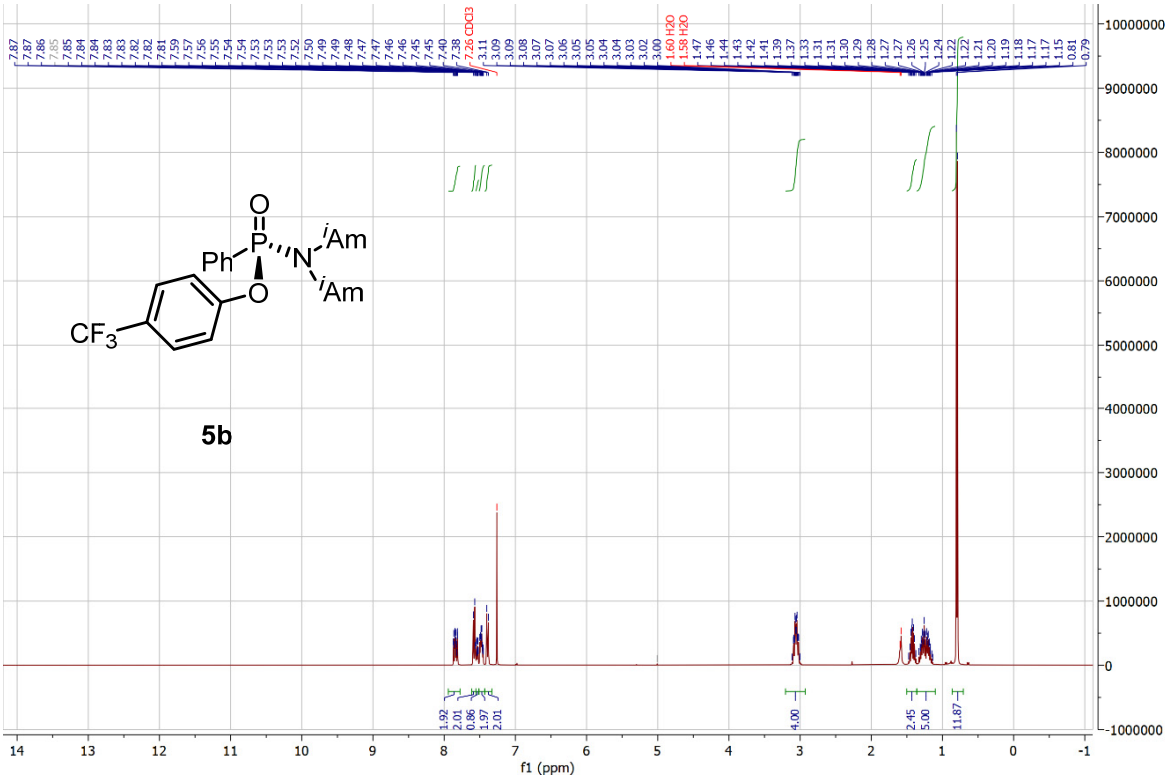
^{13}C NMR



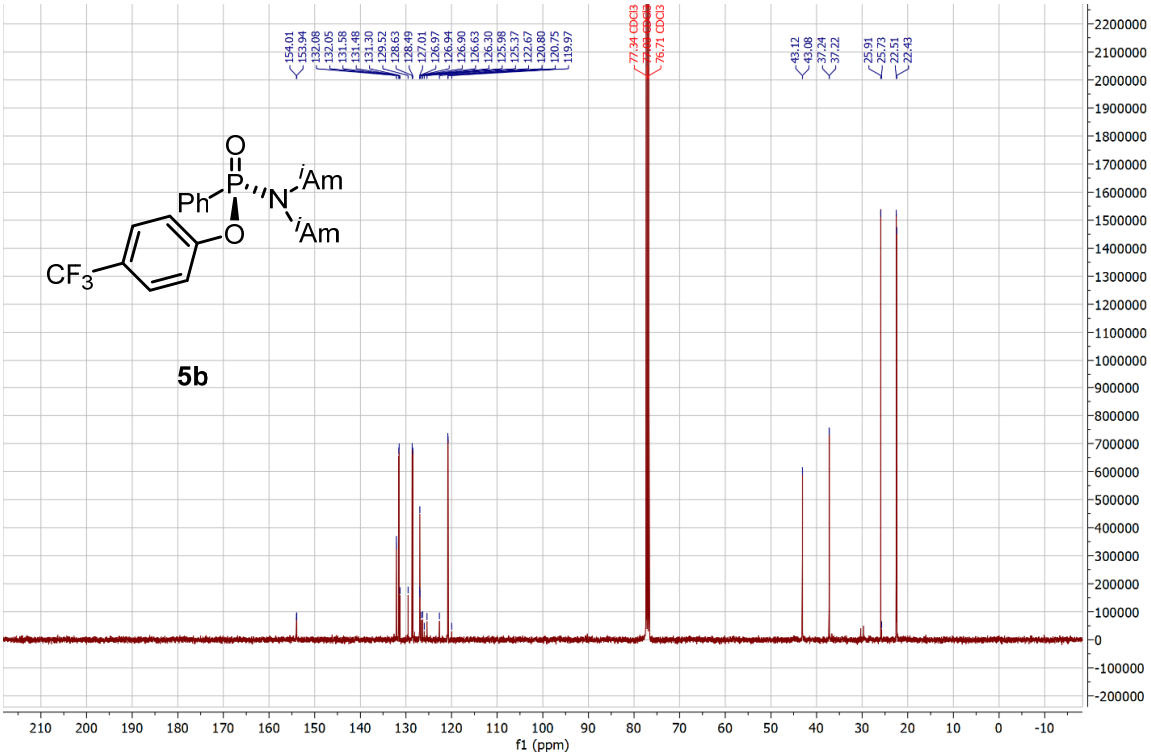
^{31}P NMR


22.44
O
P
Ph
N
iAm
iAm
O
O
O=S
N
Me
Me
5a
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

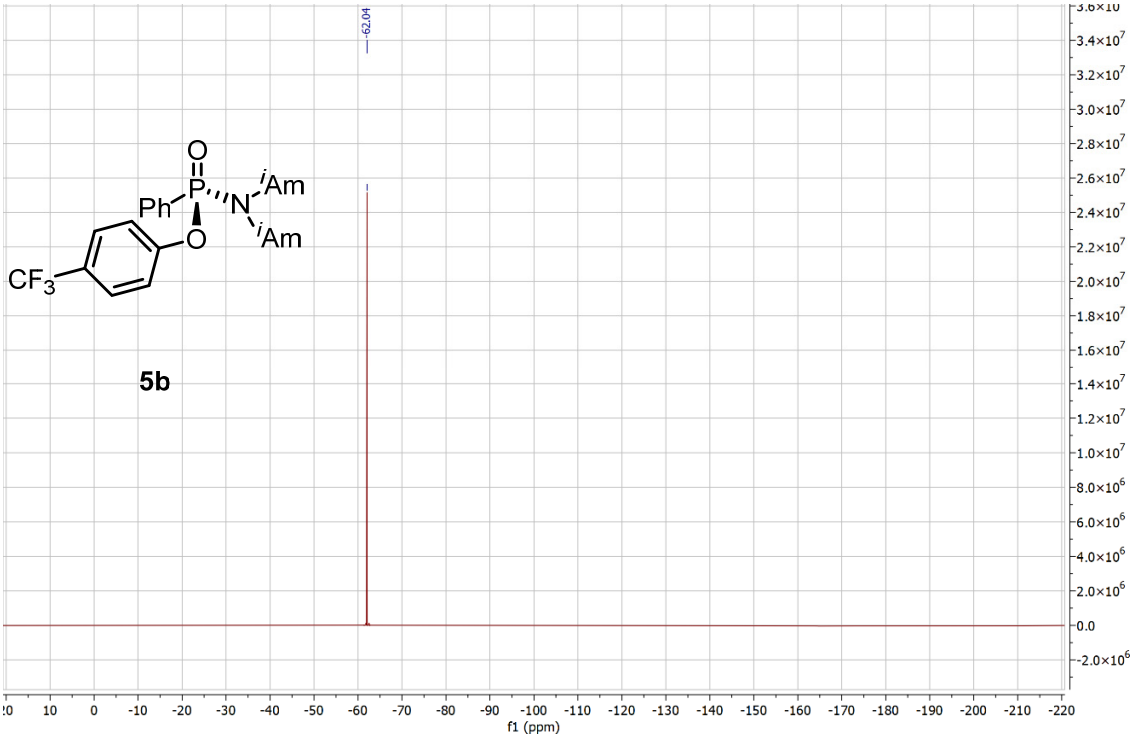
^{1}H NMR



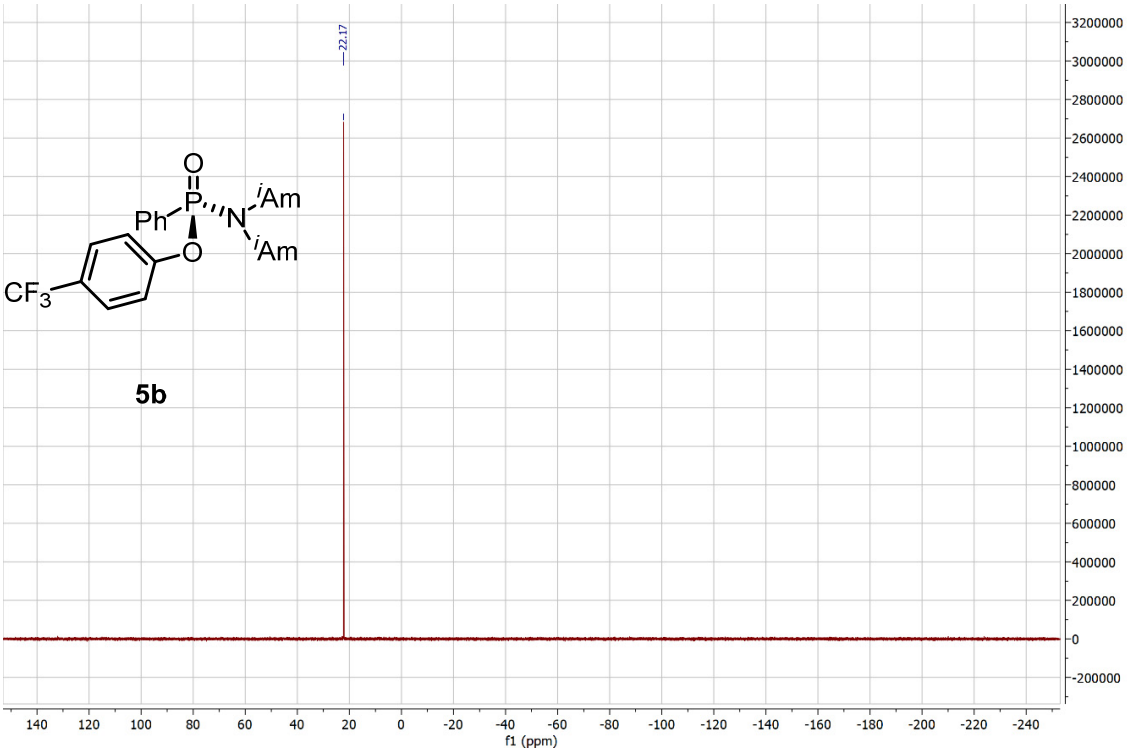
^{13}C NMR



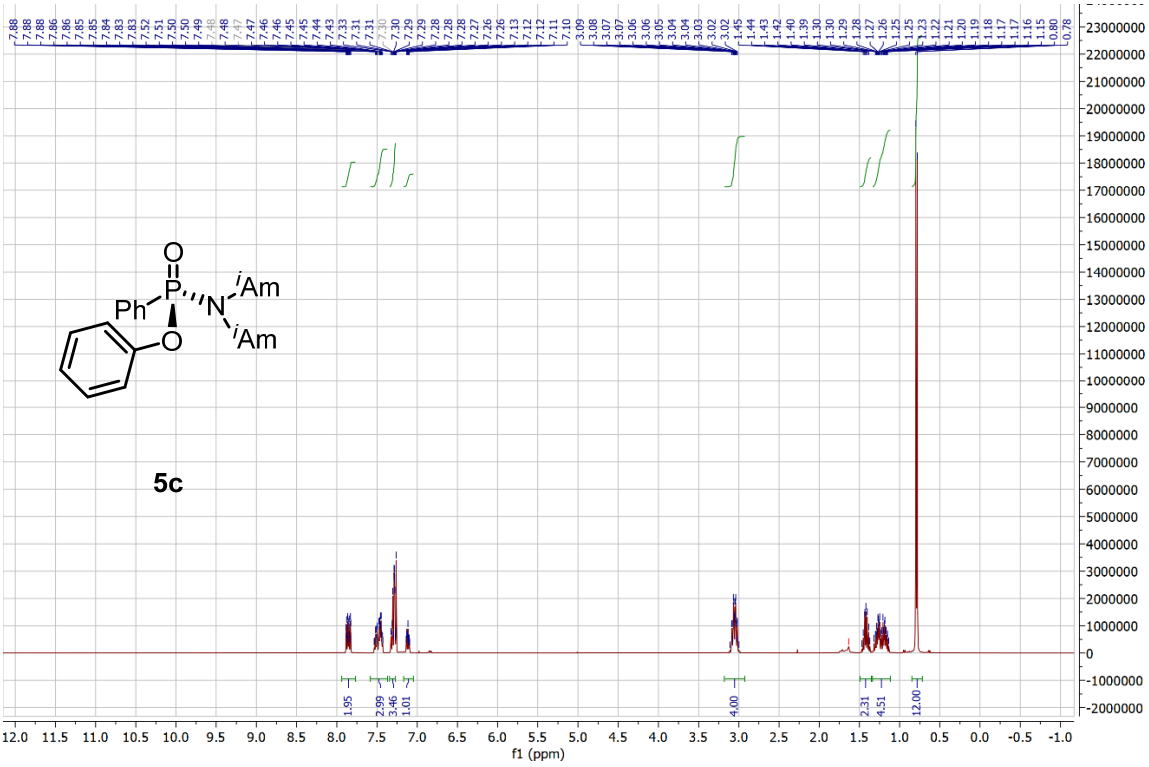
^{19}F NMR



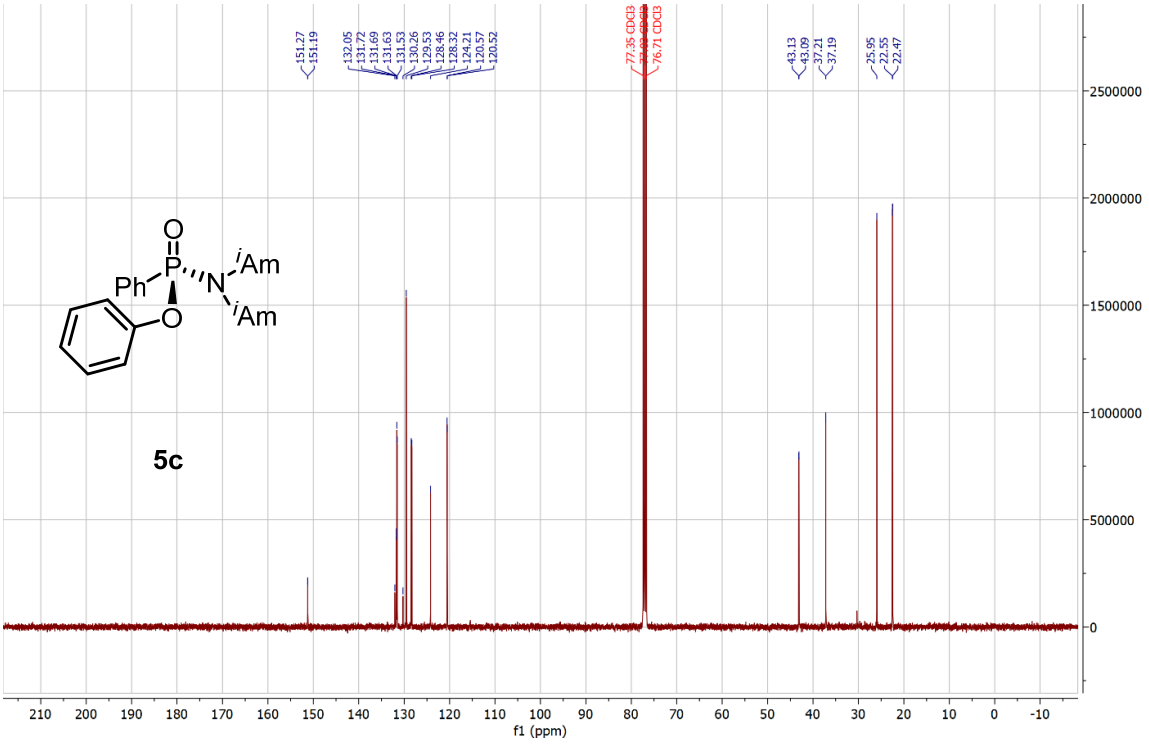
^{31}P NMR



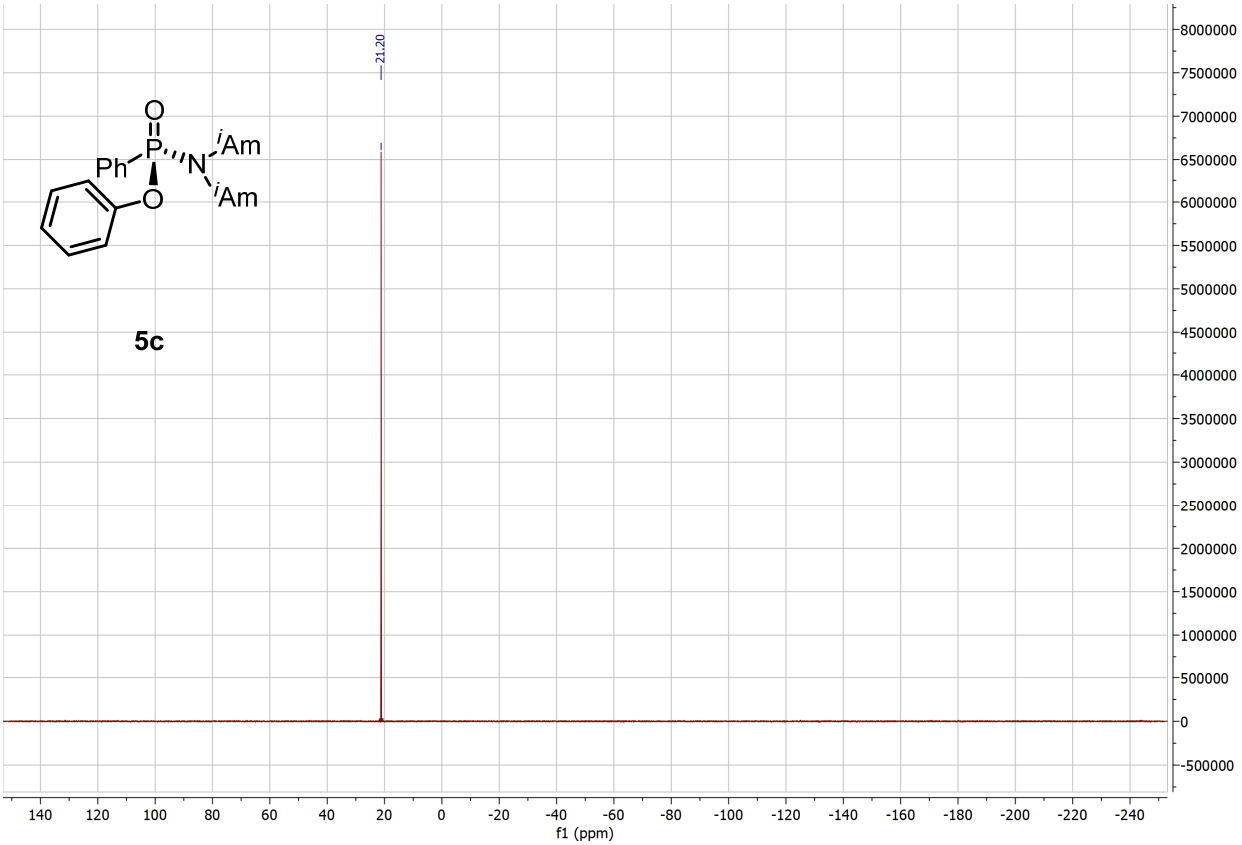
^{1}H NMR



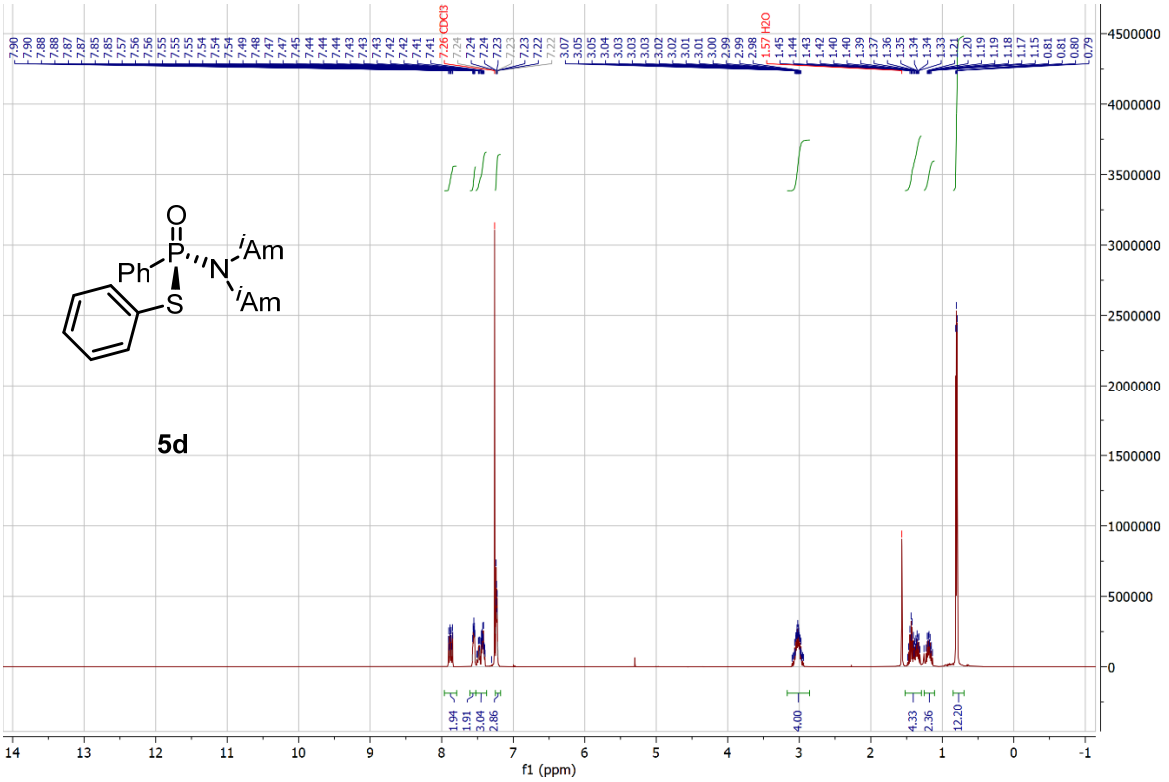
^{13}C NMR



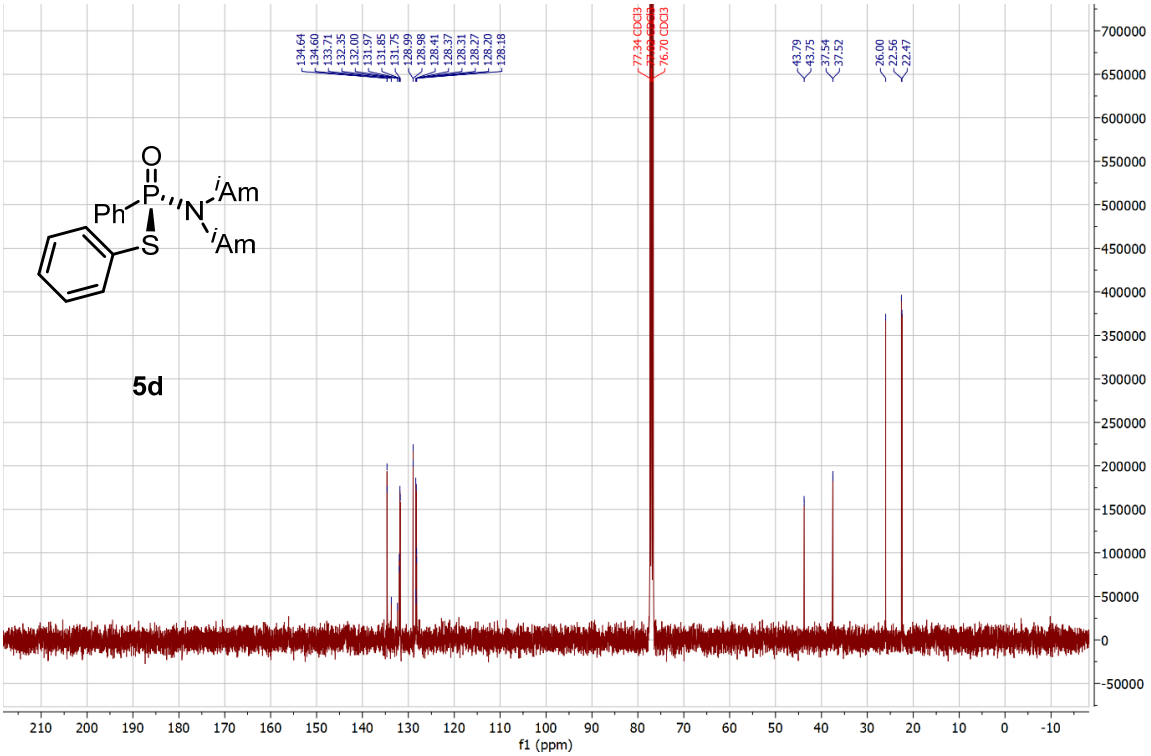
^{31}P NMR


21.20
O
P
Ph
N
iAm
iAm
O
5c
8000000
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

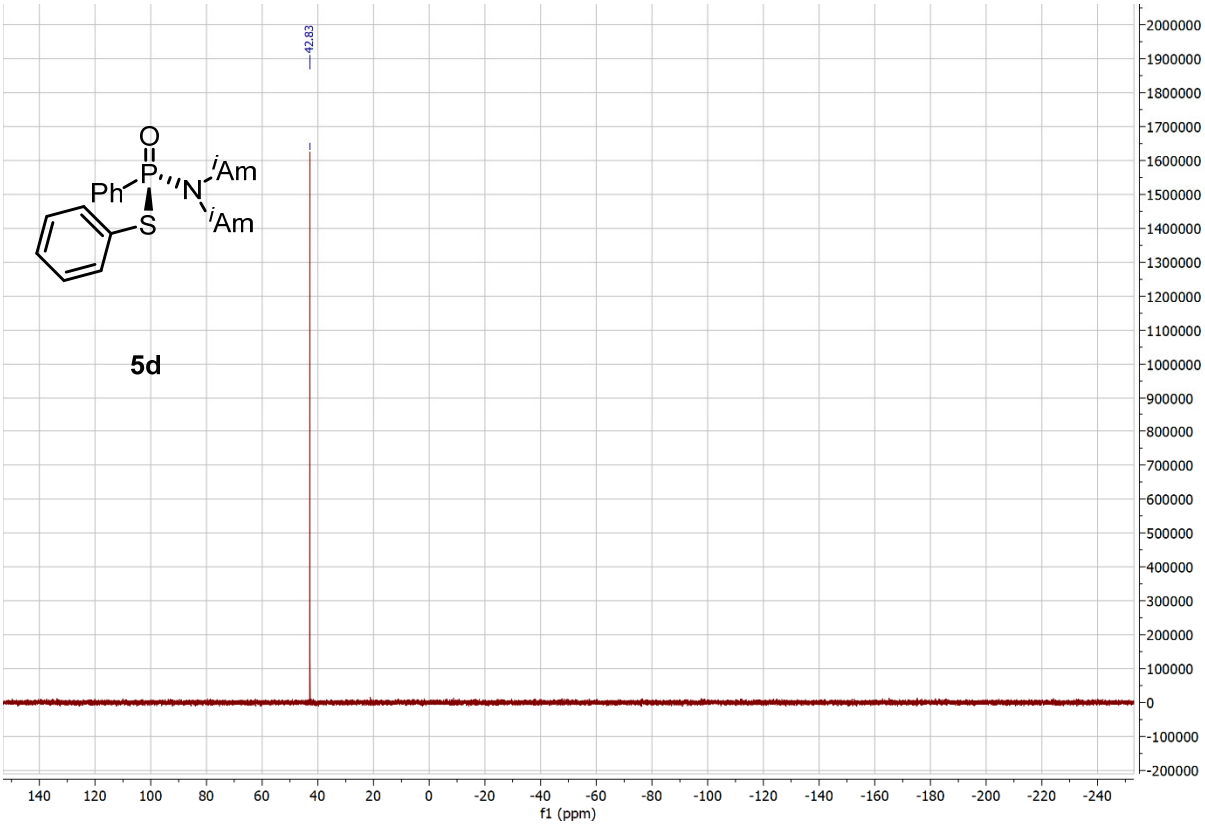
^{1}H NMR



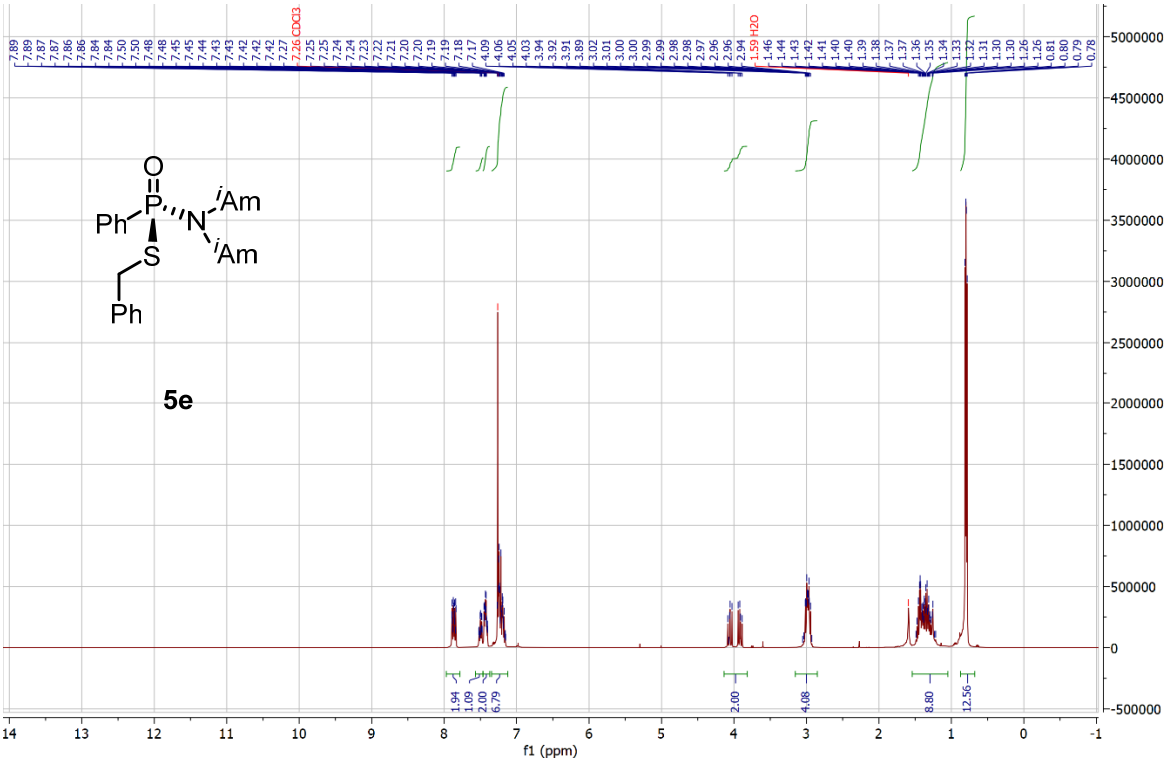
^{13}C NMR



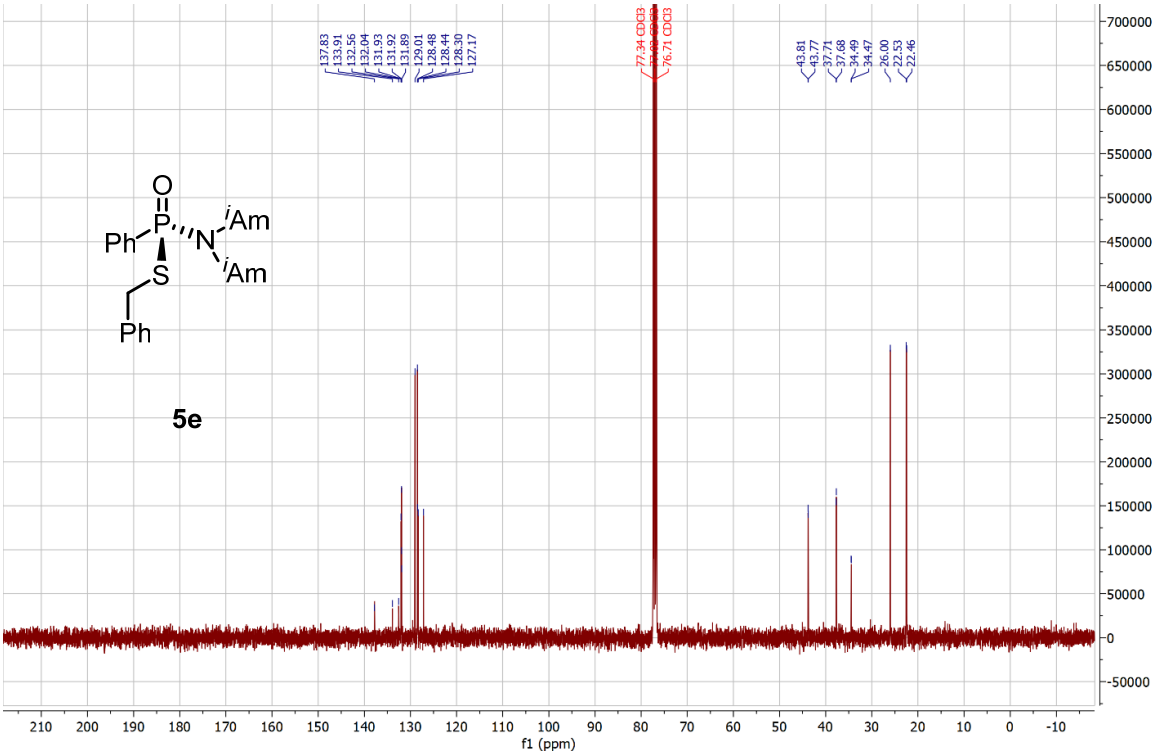
^{31}P NMR


42.83
O
P
Ph
S
N
iAm
iAm
5d
2000000
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

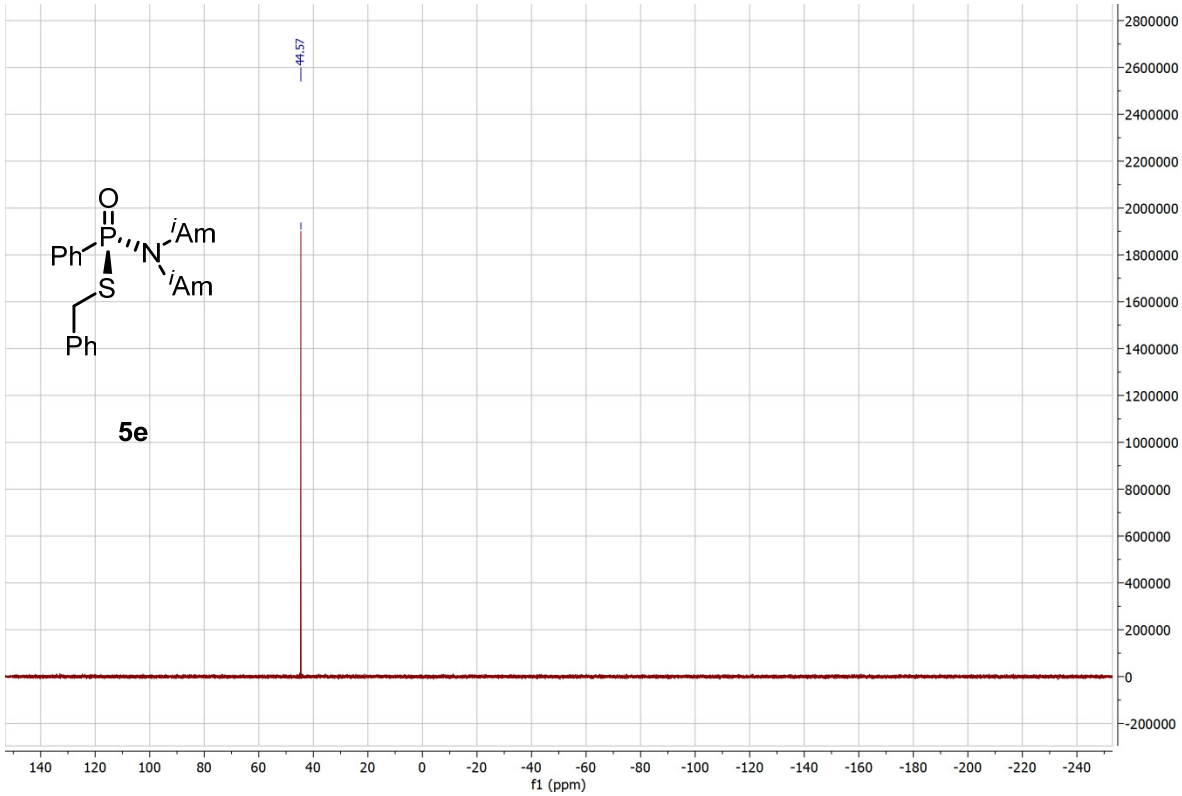
^{1}H NMR



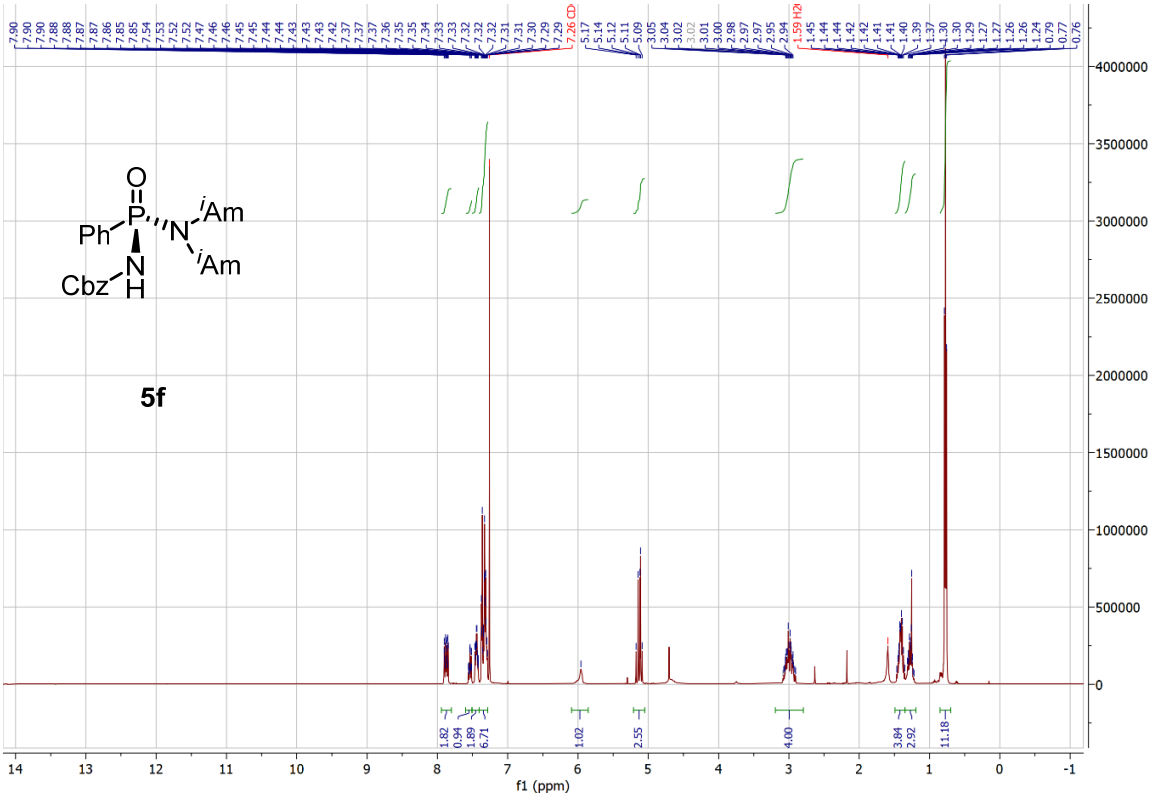
^{13}C NMR



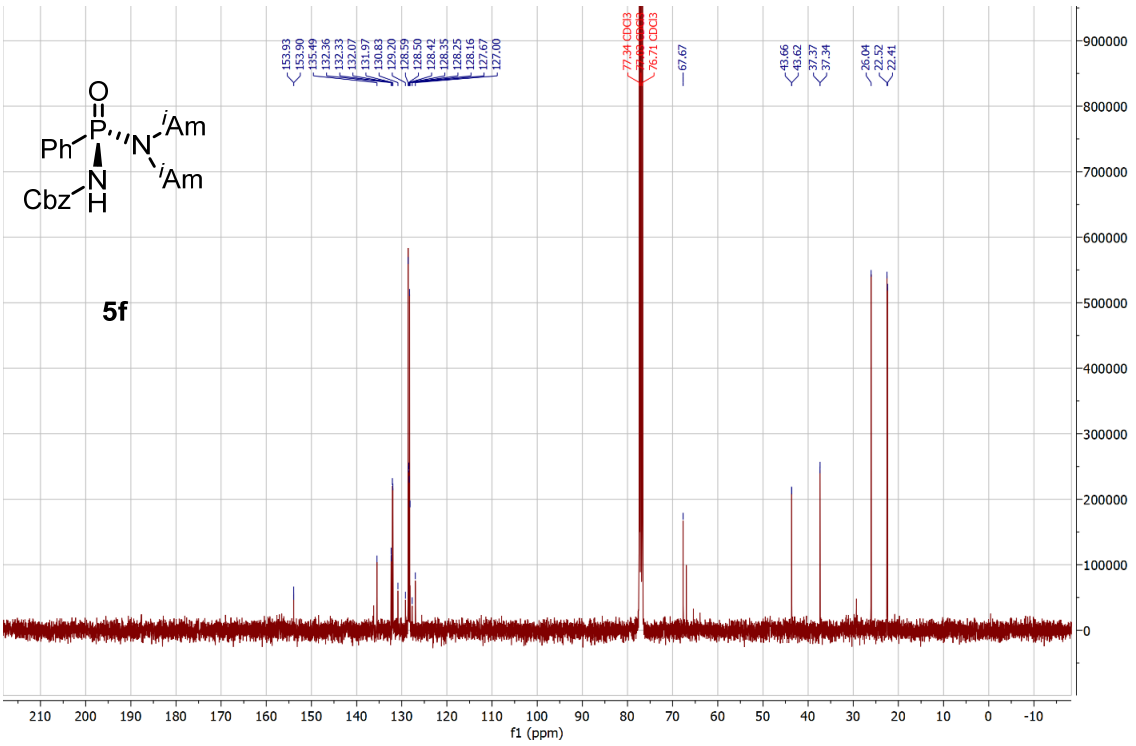
^{31}P NMR


44.57
O
P
N
Ph
S
Ph
iAm
iAm
5e
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

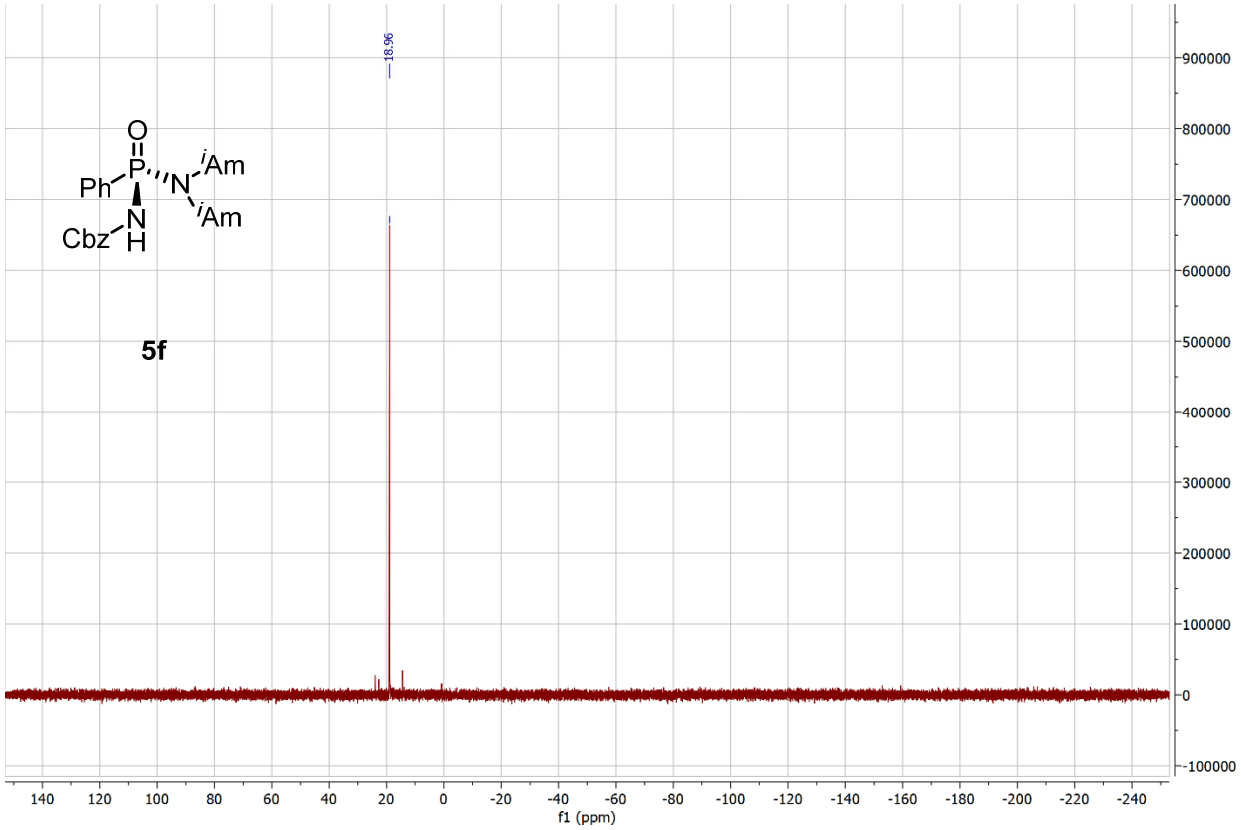
^{1}H NMR



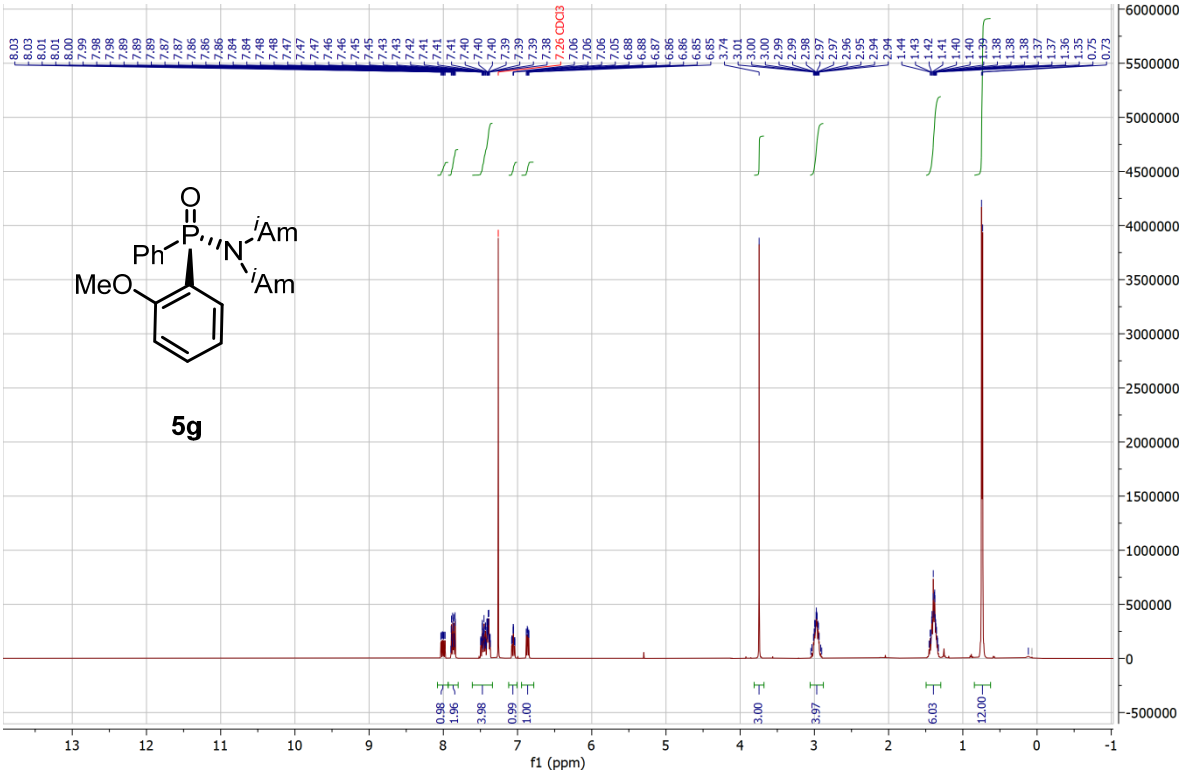
^{13}C NMR



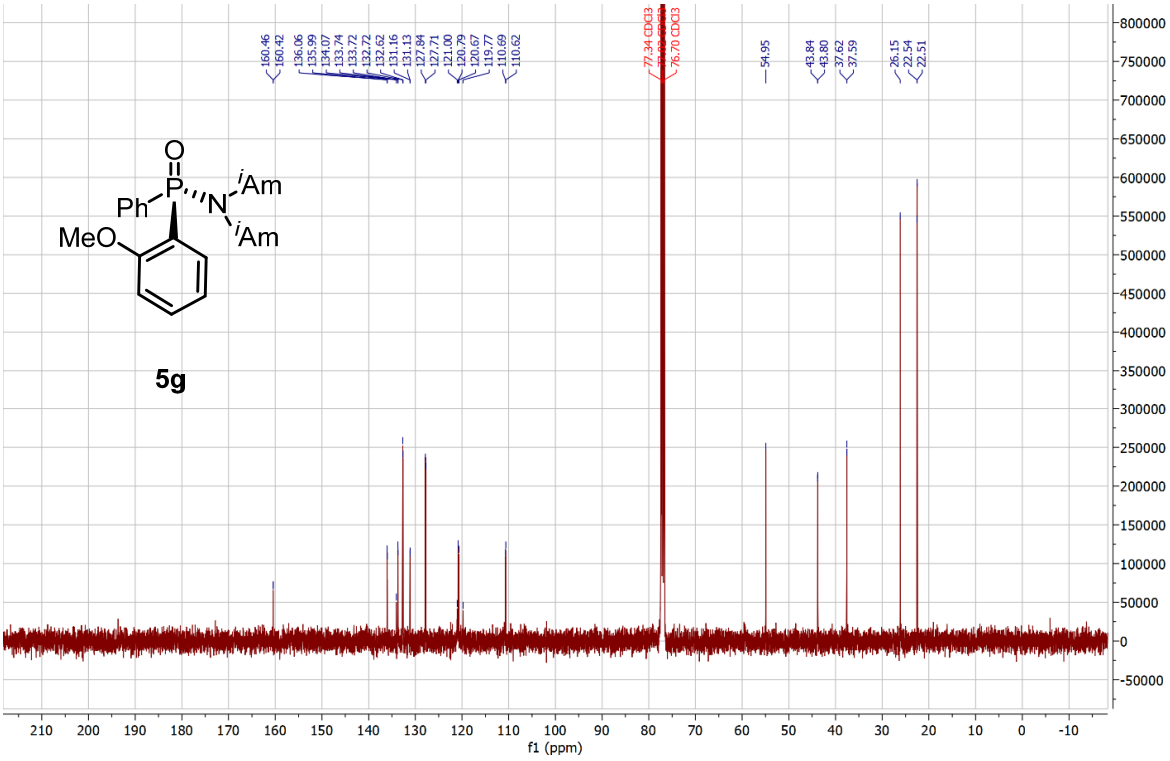
^{31}P NMR


18.96
O
P
Ph
N
iAm
N
H
Cbz
iAm
5f
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

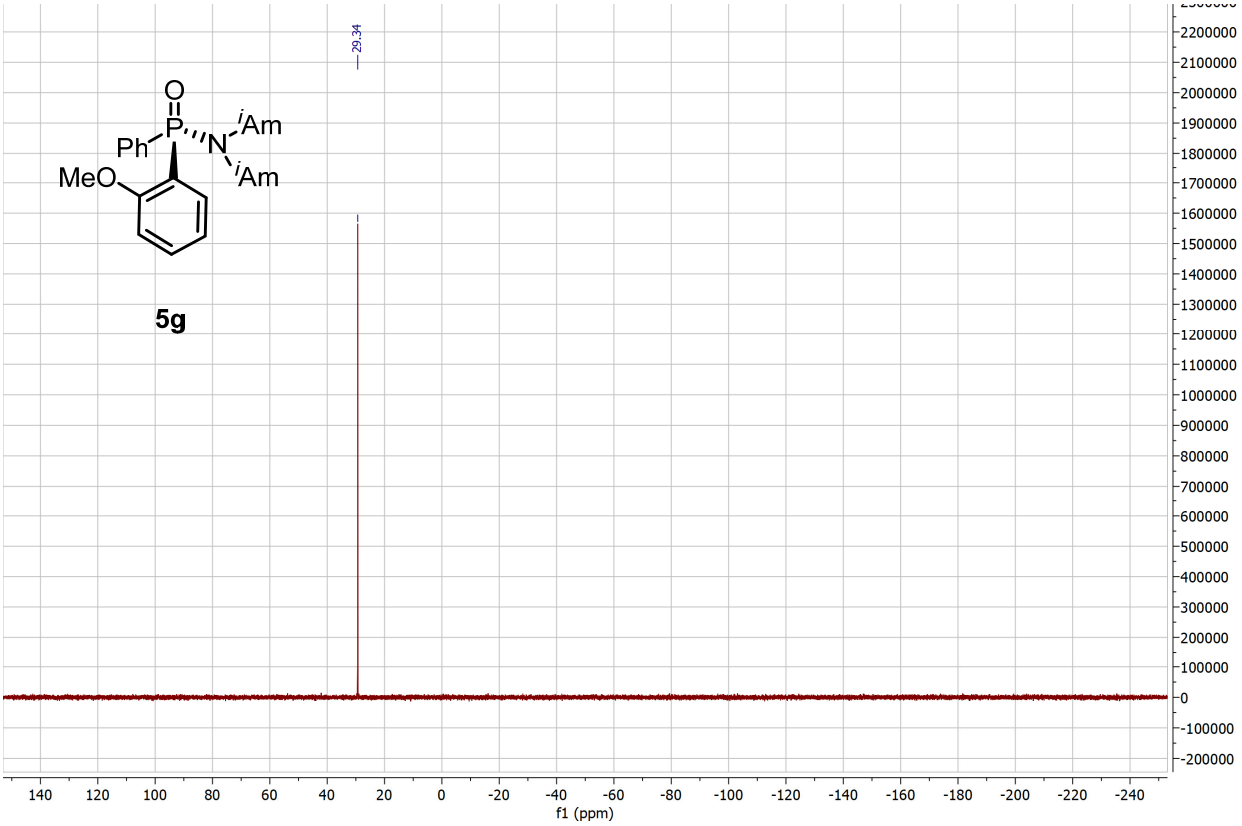
^{1}H NMR



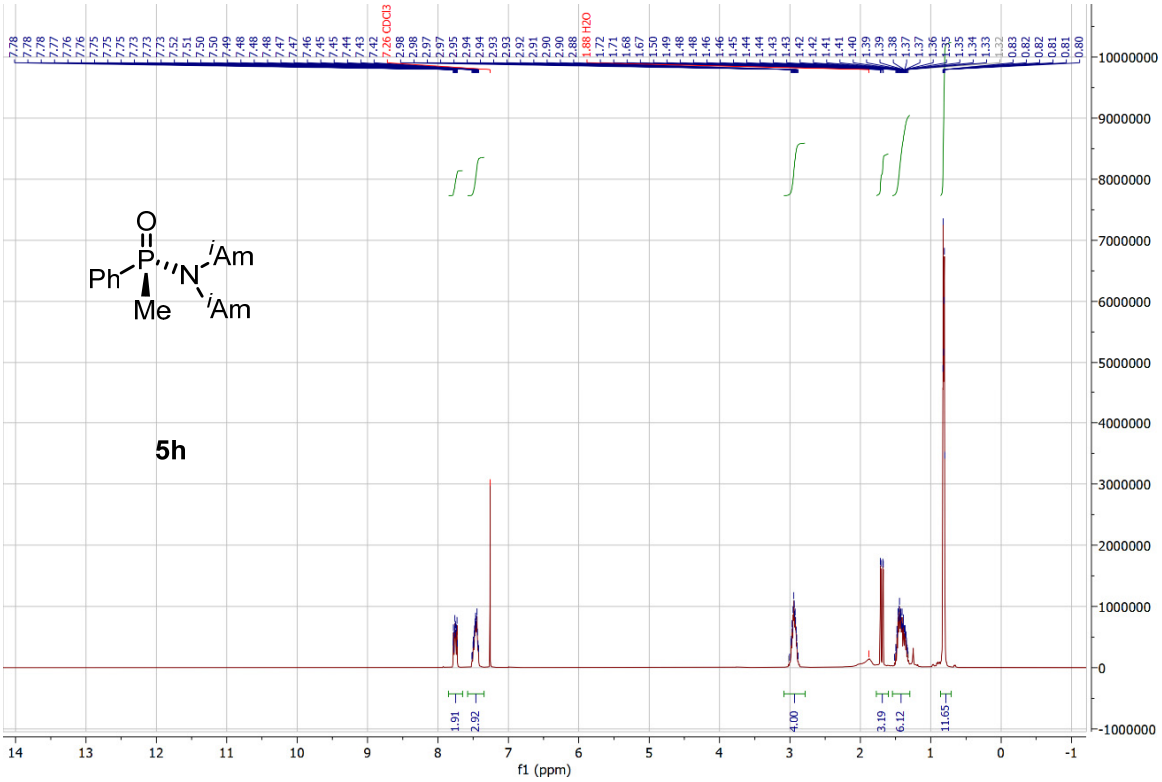
^{13}C NMR



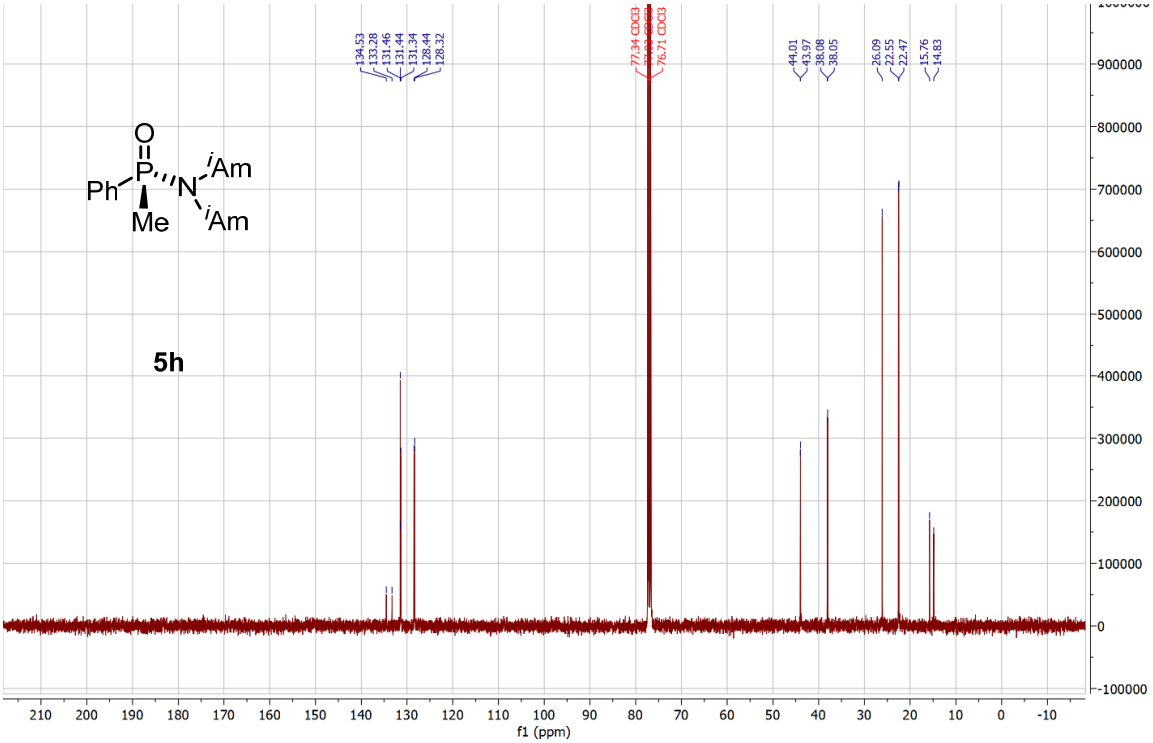
^{31}P NMR


29.34
O
P
Ph
MeO
N
iAm
iAm
5g
2200000
2100000
2000000
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

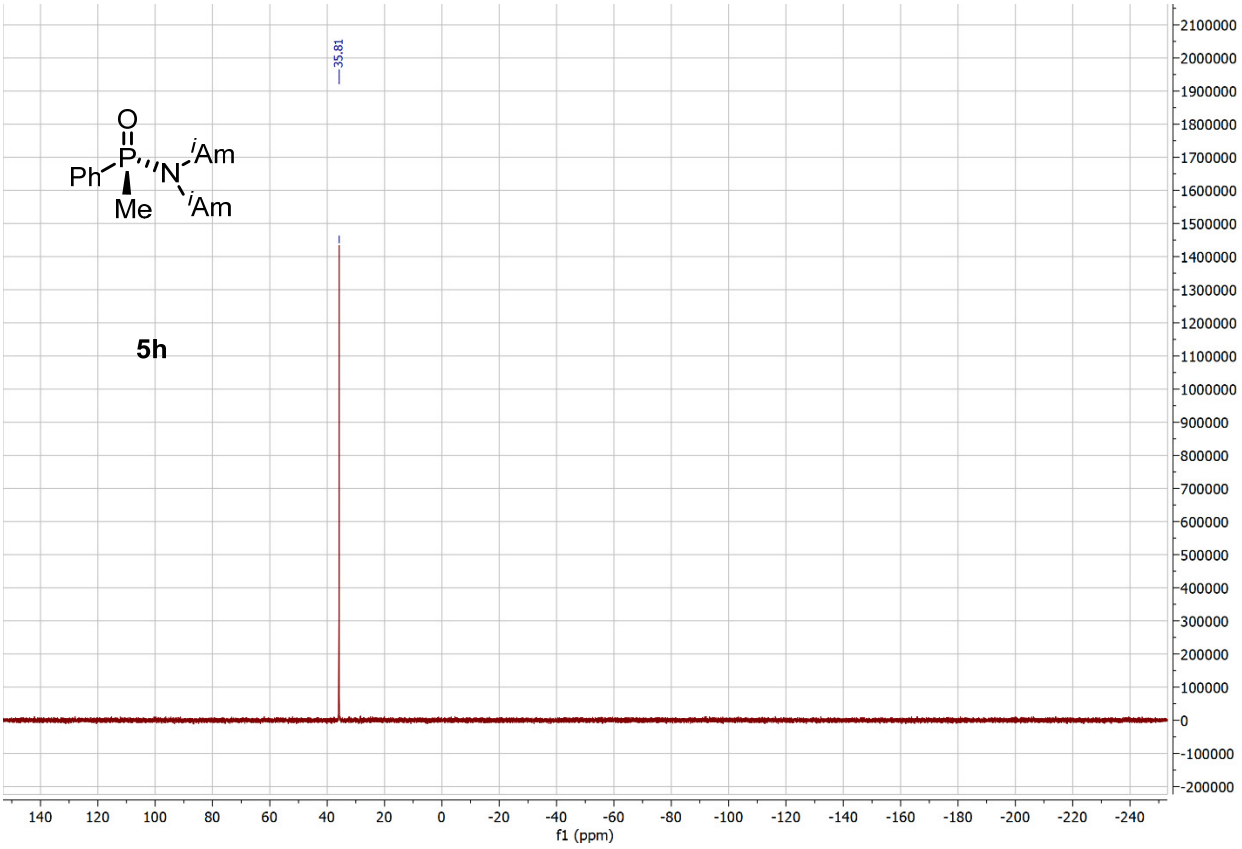
^{1}H NMR



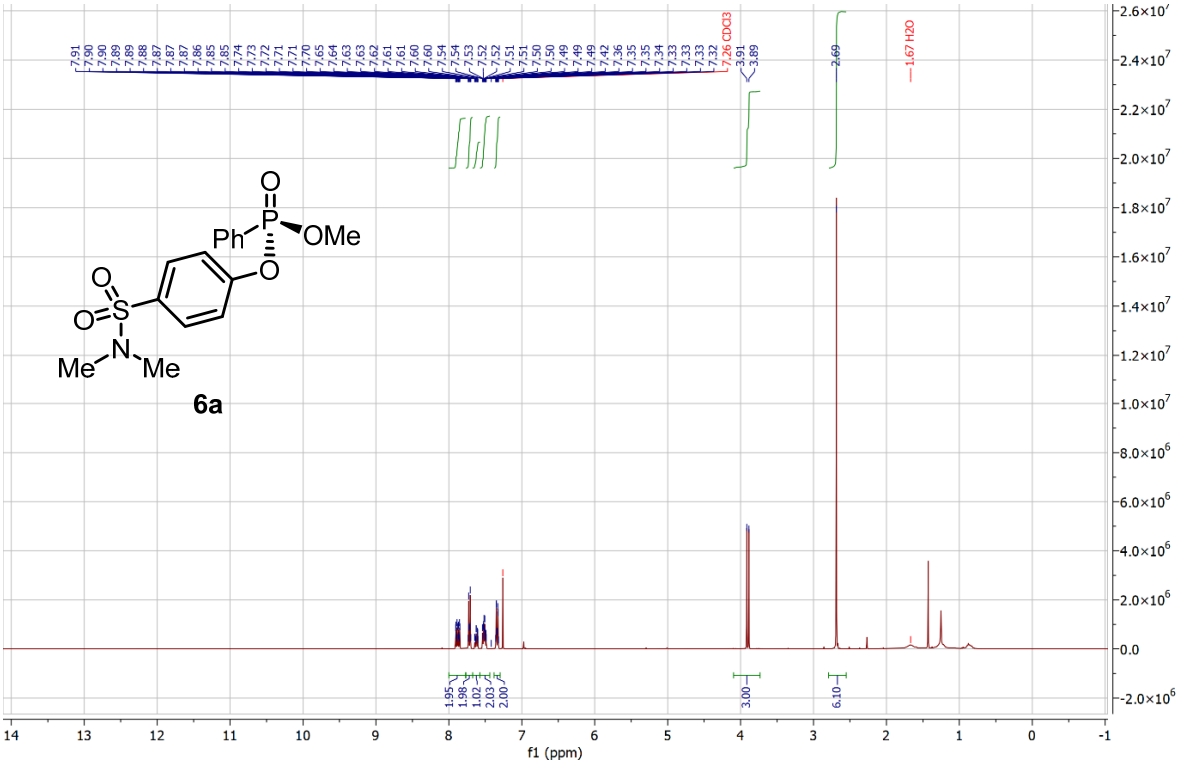
^{13}C NMR



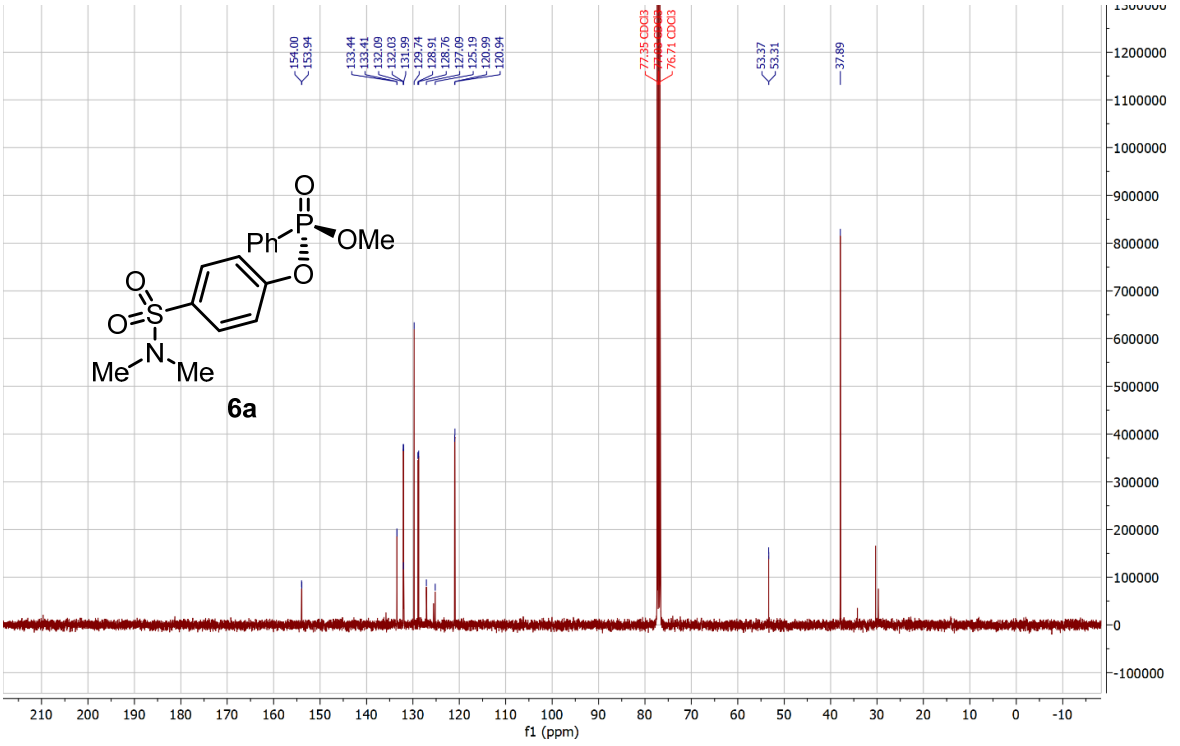
^{31}P NMR


35.81
O
P
Ph
Me
N
iAm
iAm
5h
2100000
2000000
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

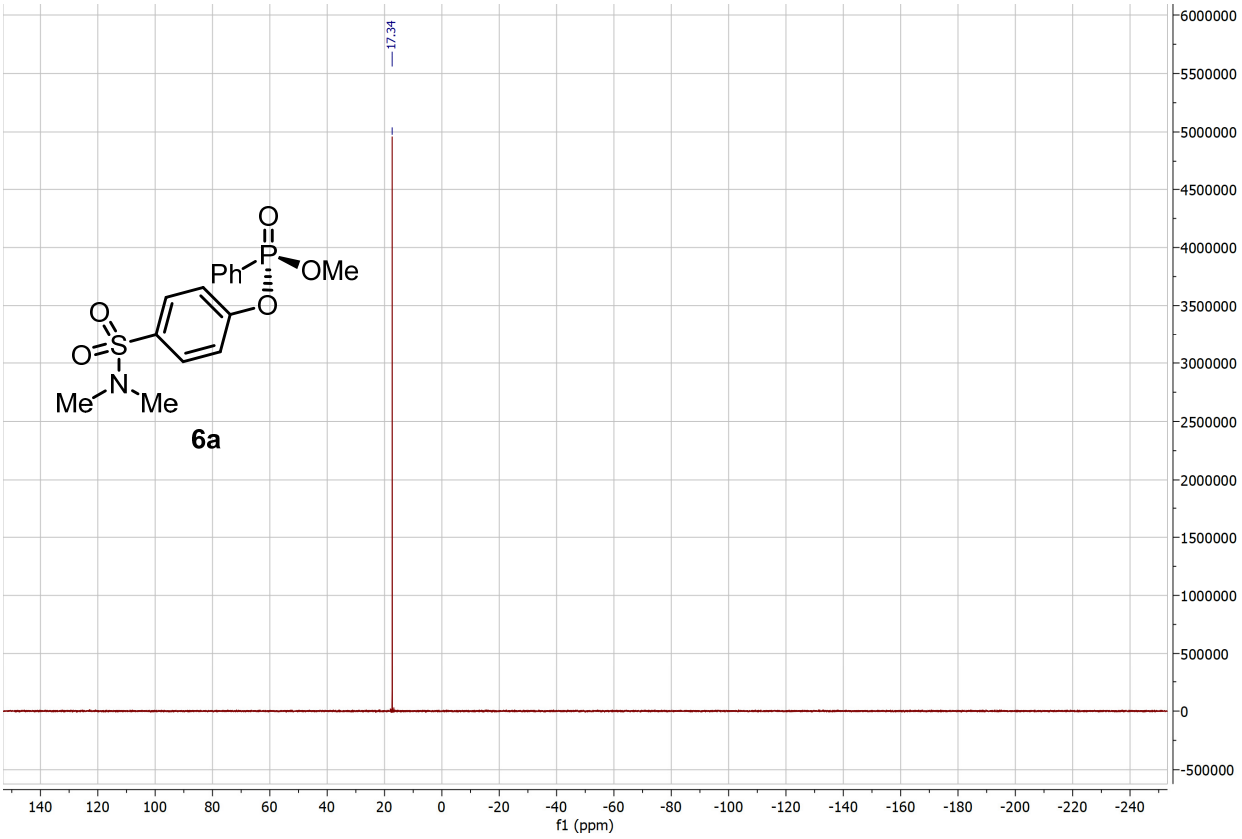
^{1}H NMR



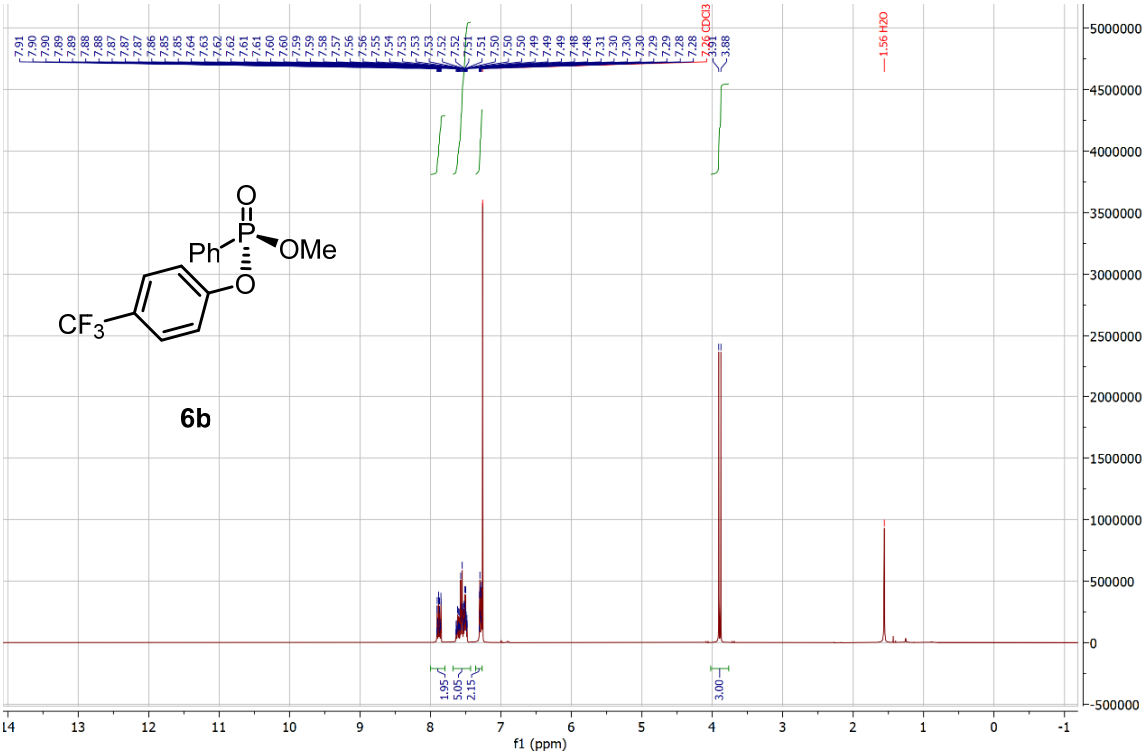
^{13}C NMR



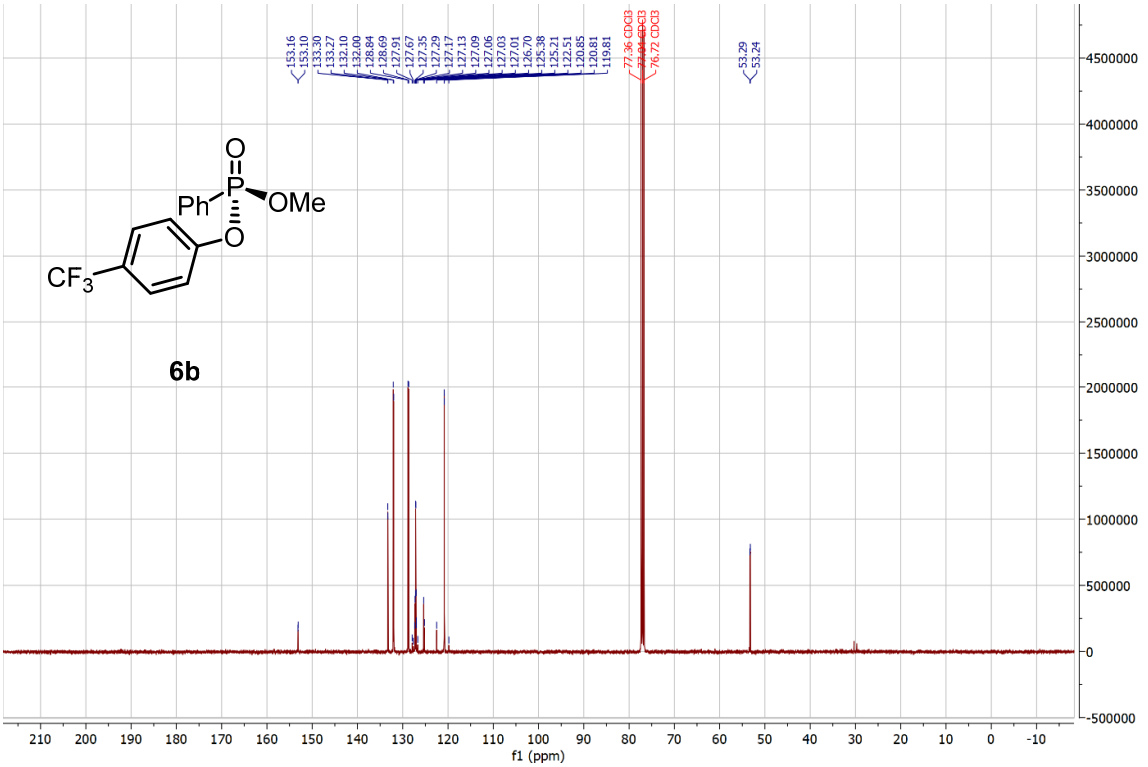
^{31}P NMR


17.34
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)
O
P
Ph
OMe
O
O
S
O
N
Me
Me
6a

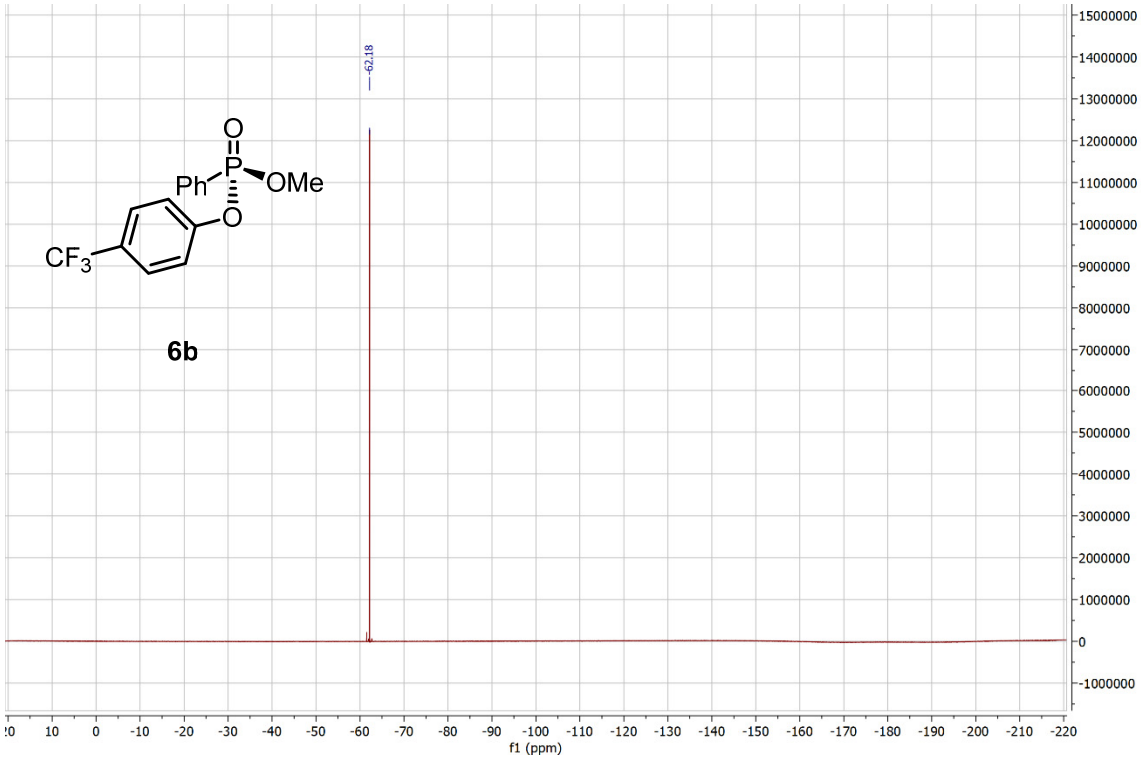
^{1}H NMR



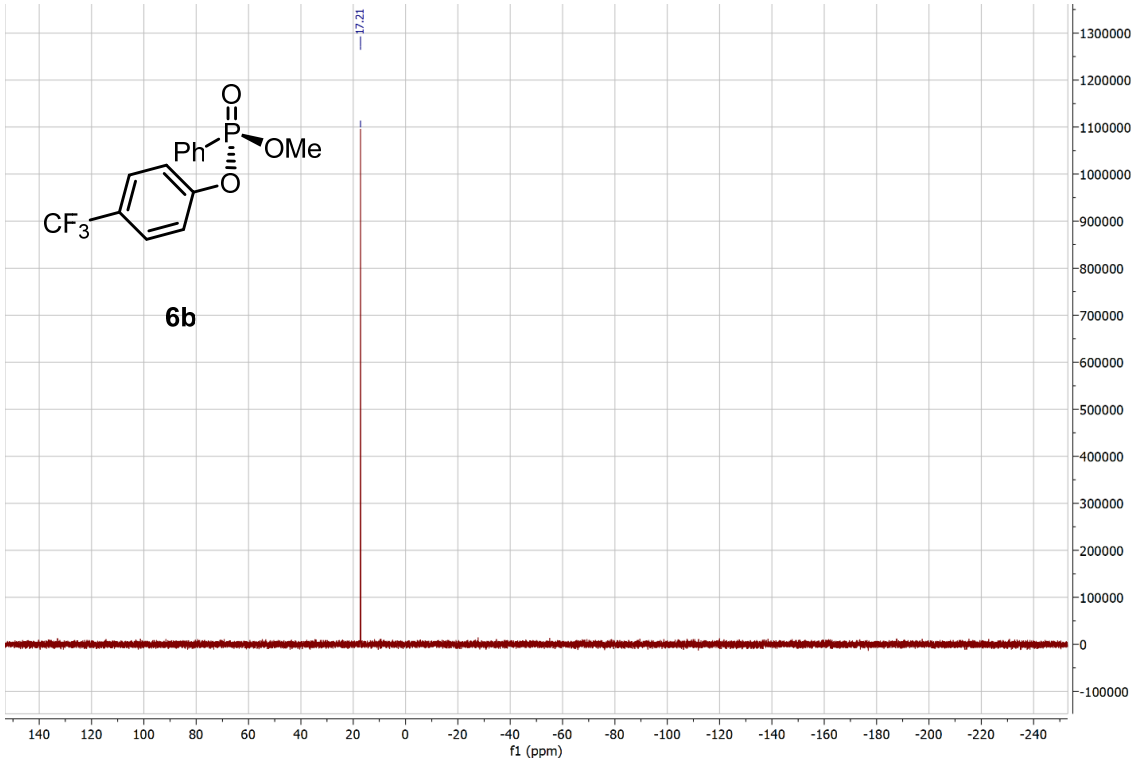
^{13}C NMR



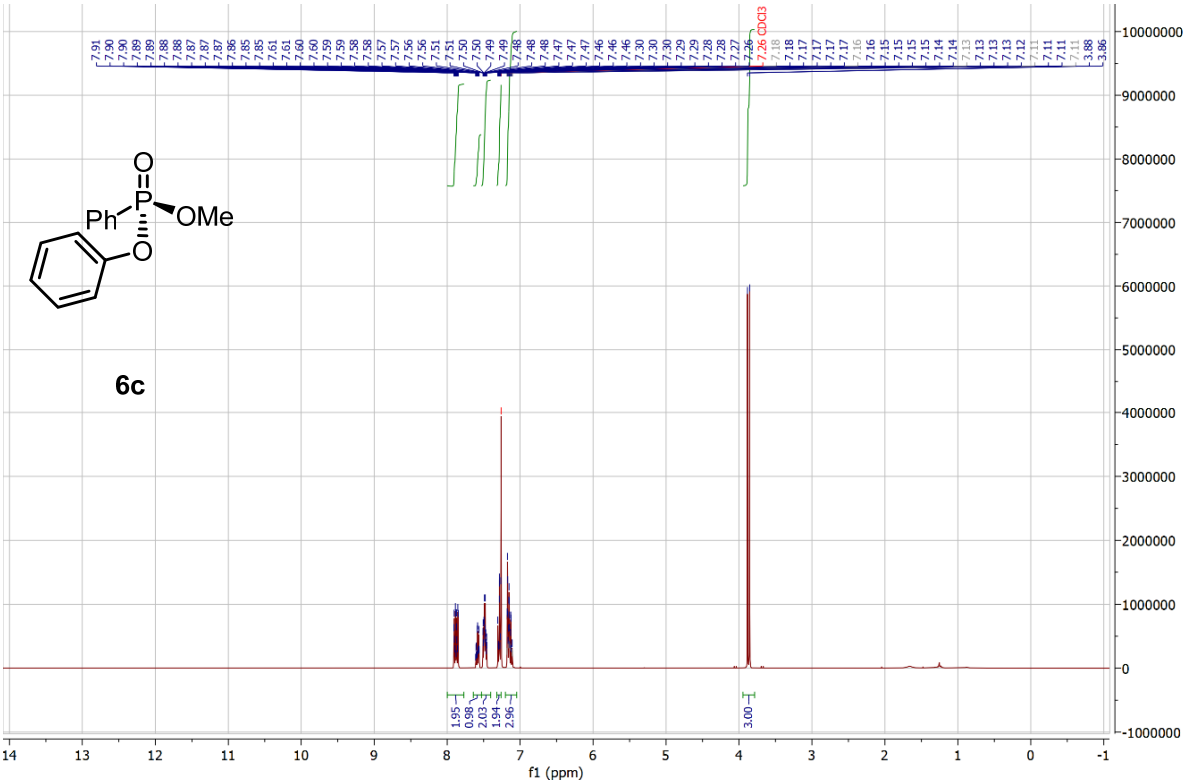
^{19}F NMR



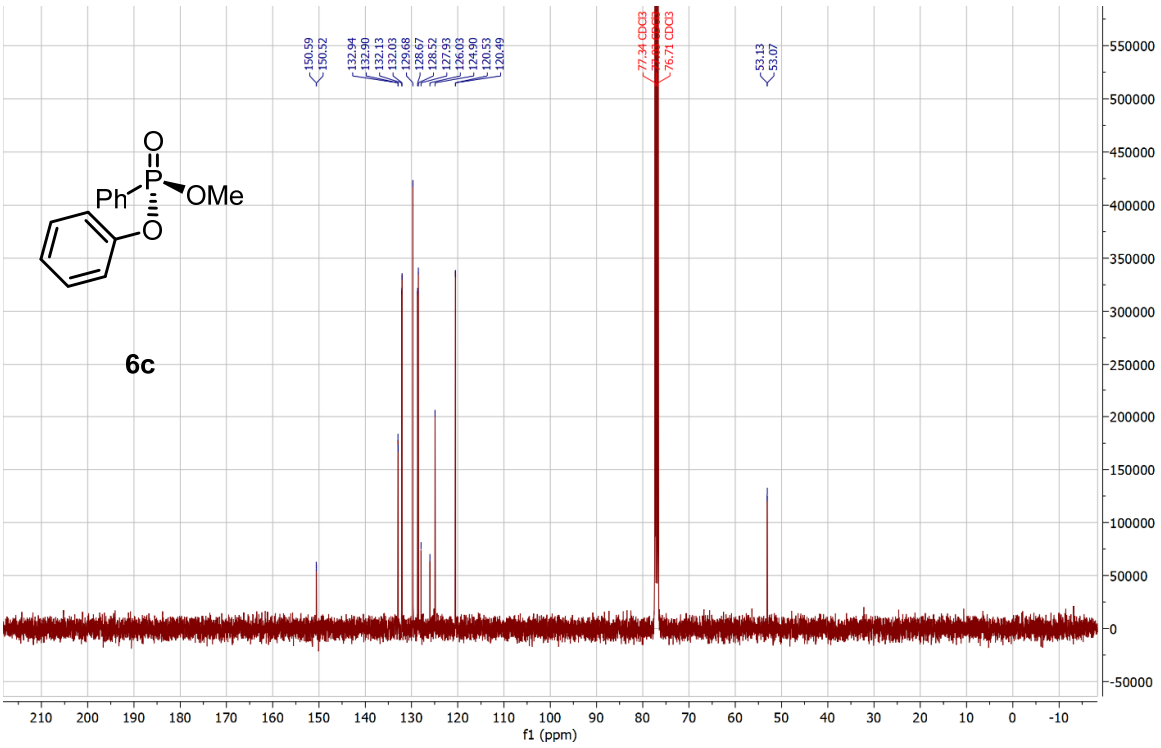
^{31}P NMR



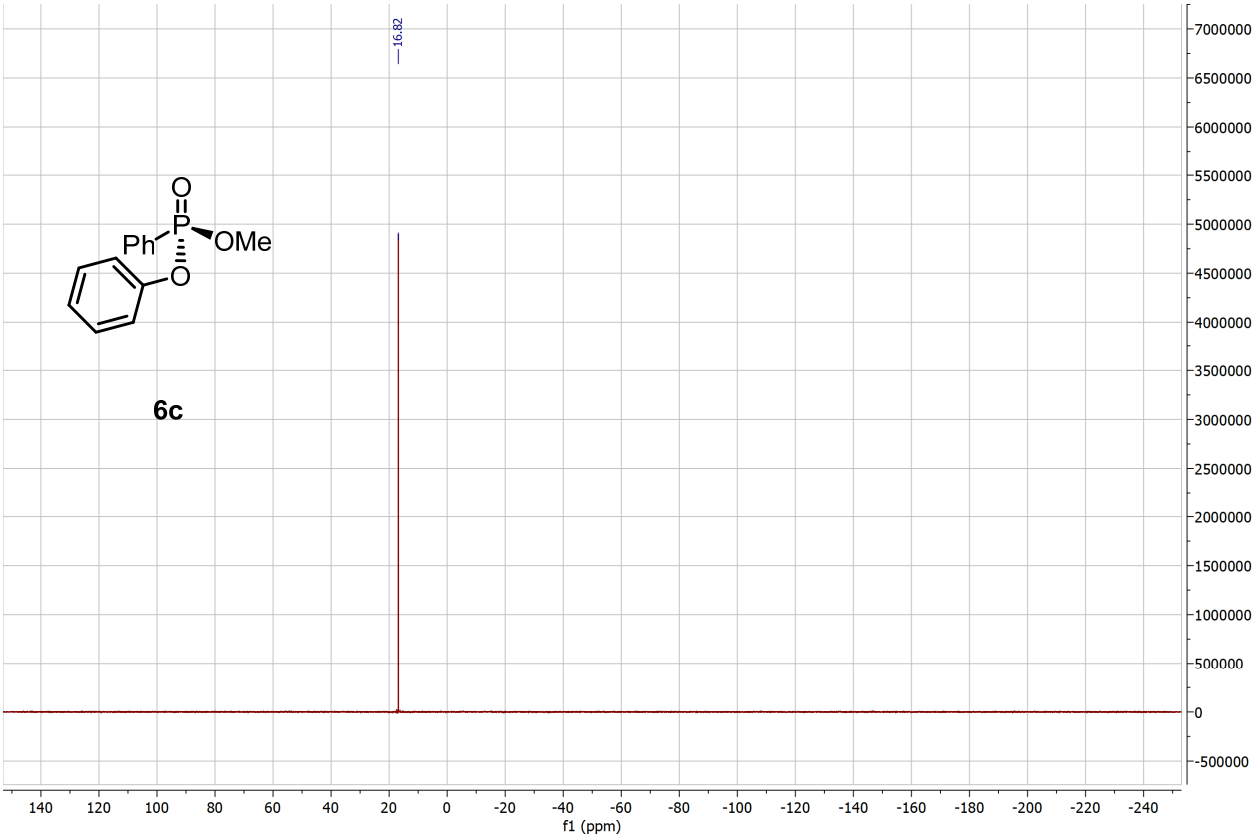
^{1}H NMR



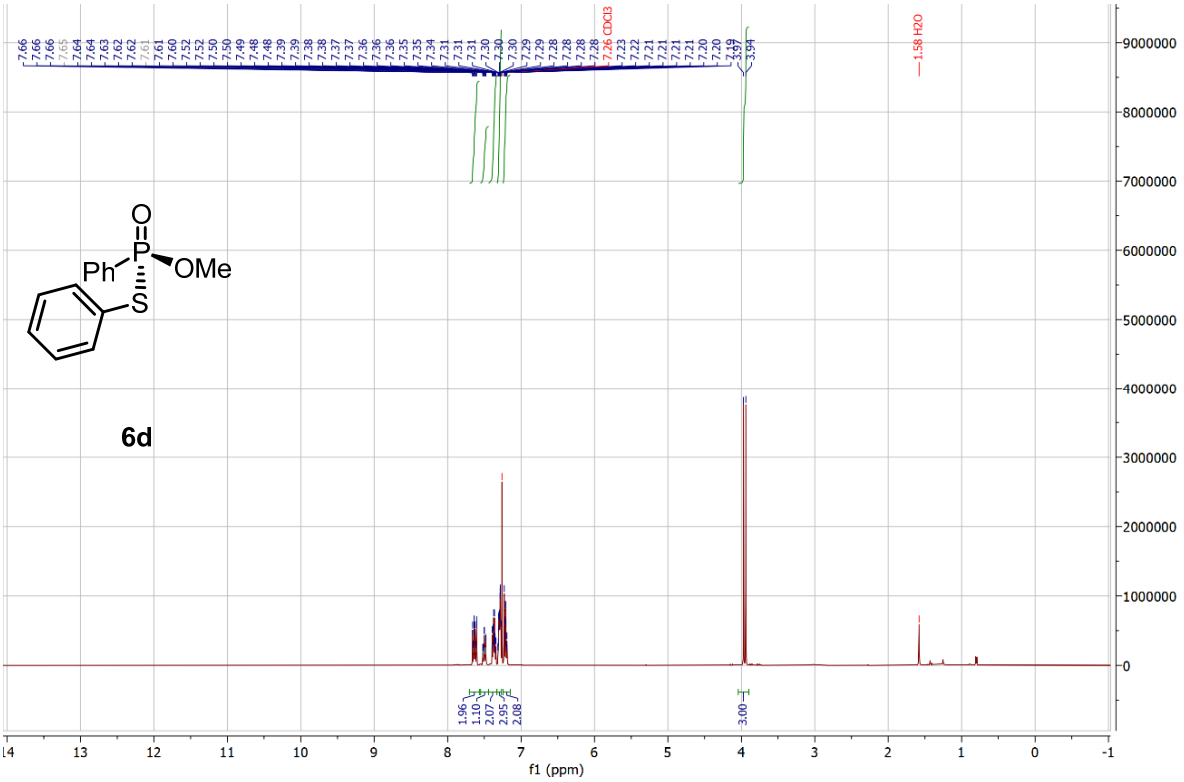
^{13}C NMR



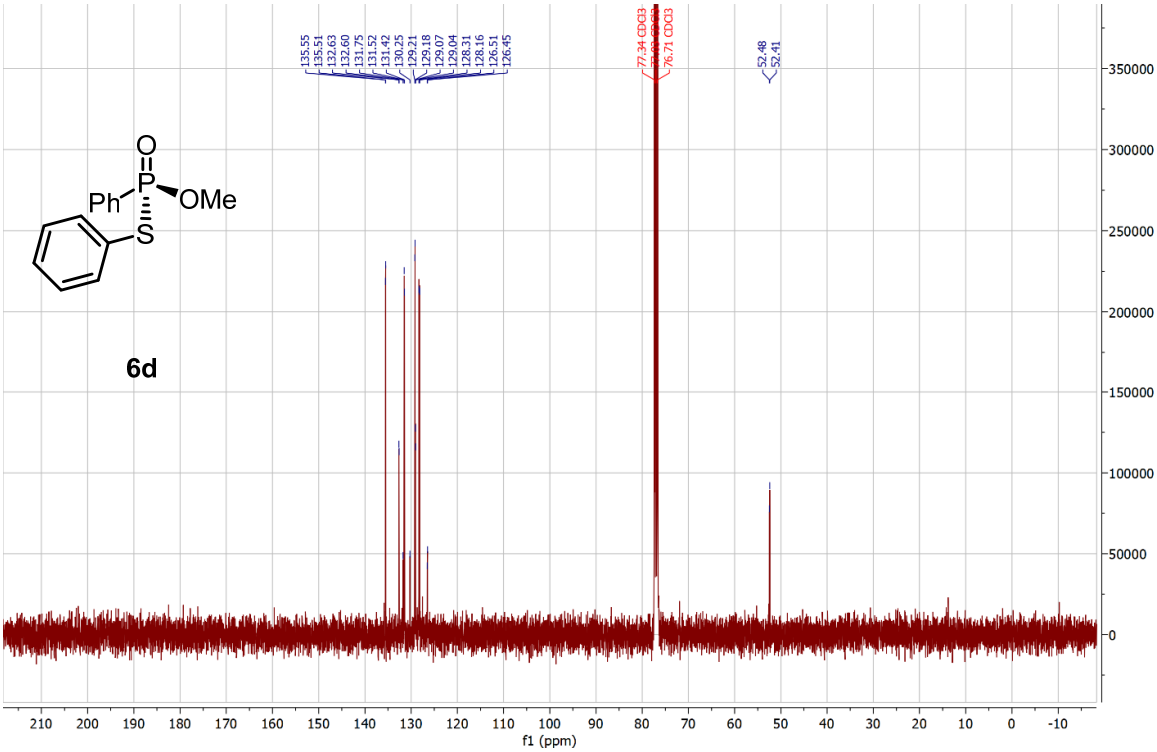
^{31}P NMR


16.82
Ph
OMe
O
O
O
6c
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

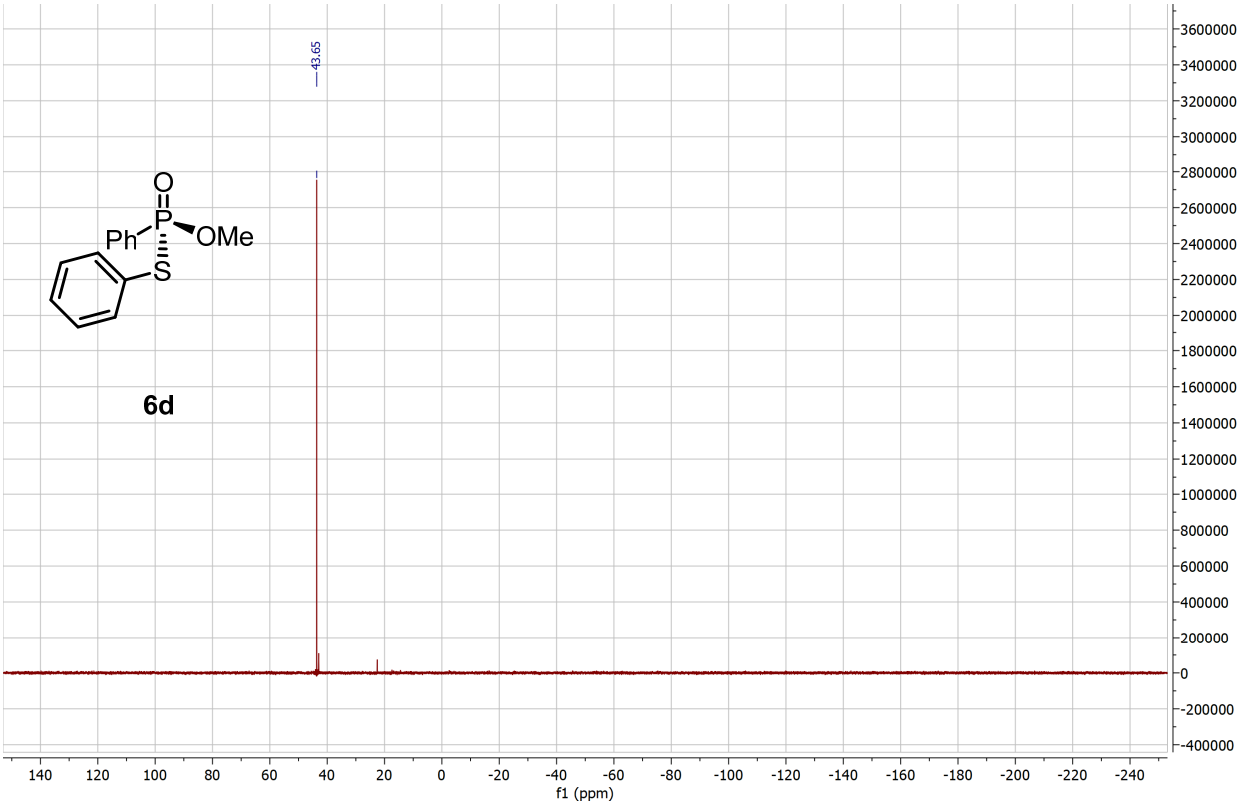
^{1}H NMR



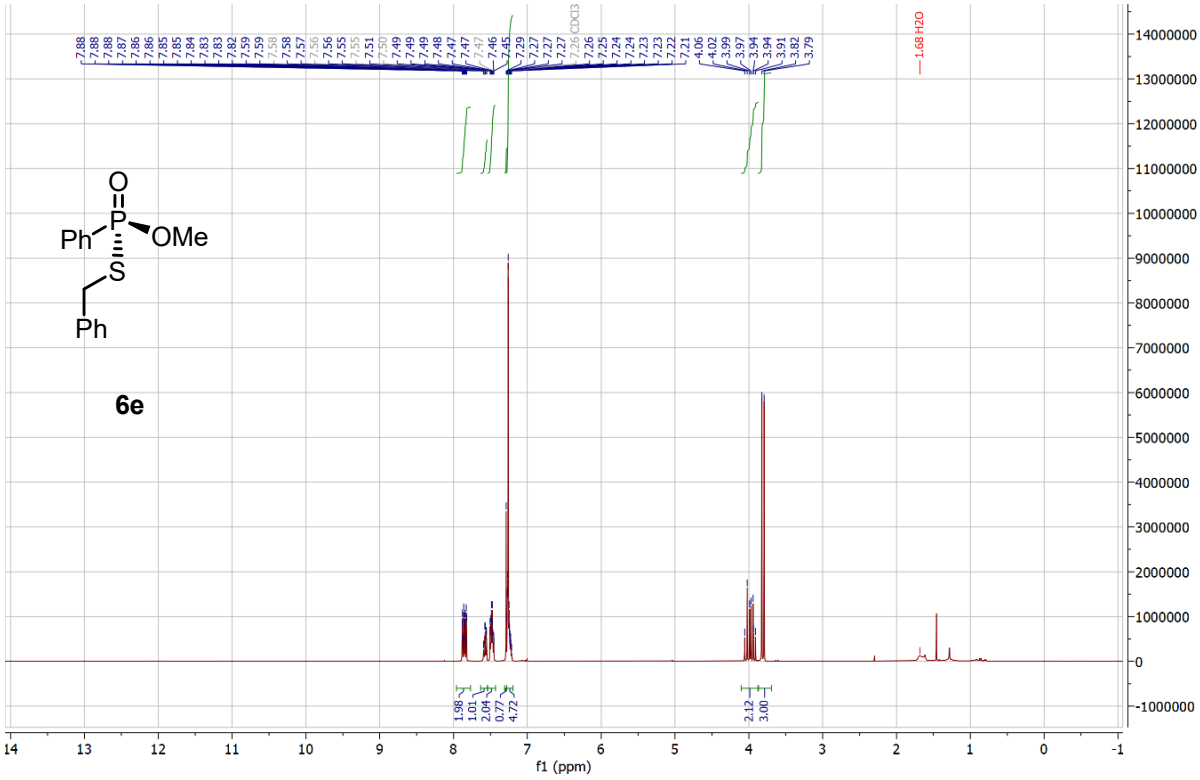
^{13}C NMR



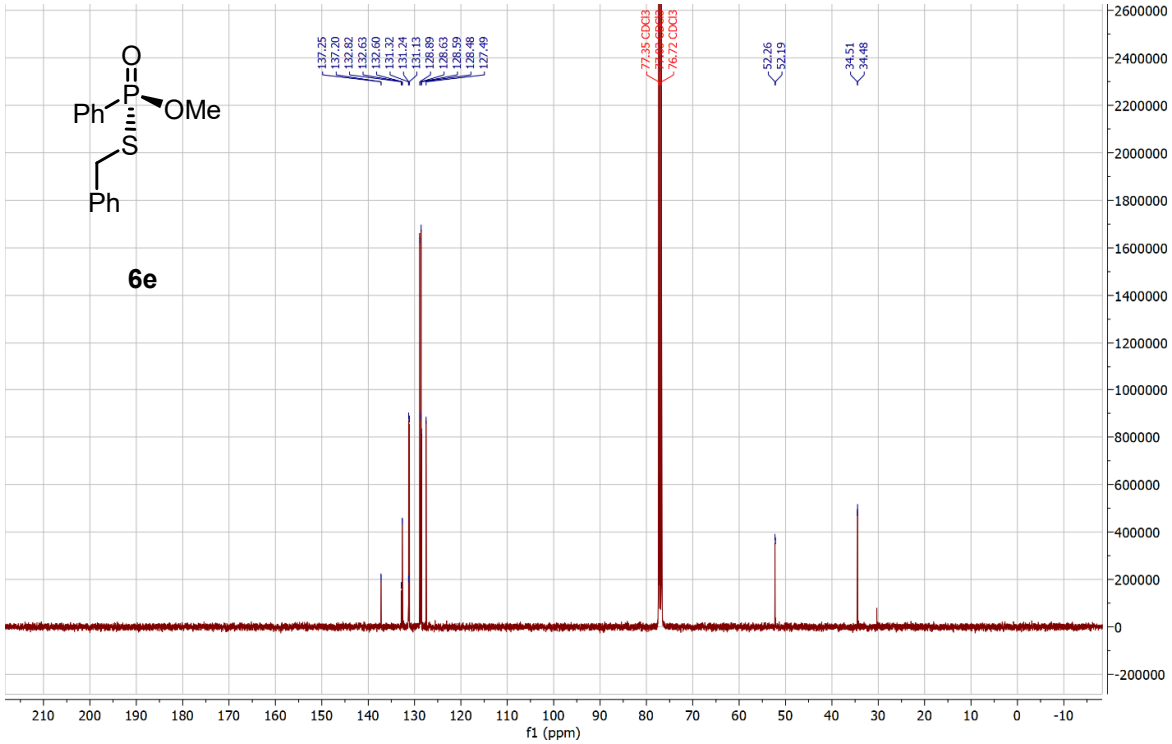
^{31}P NMR


43.65
O
P
Ph
OMe
S
6d
3600000
3400000
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
-400000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

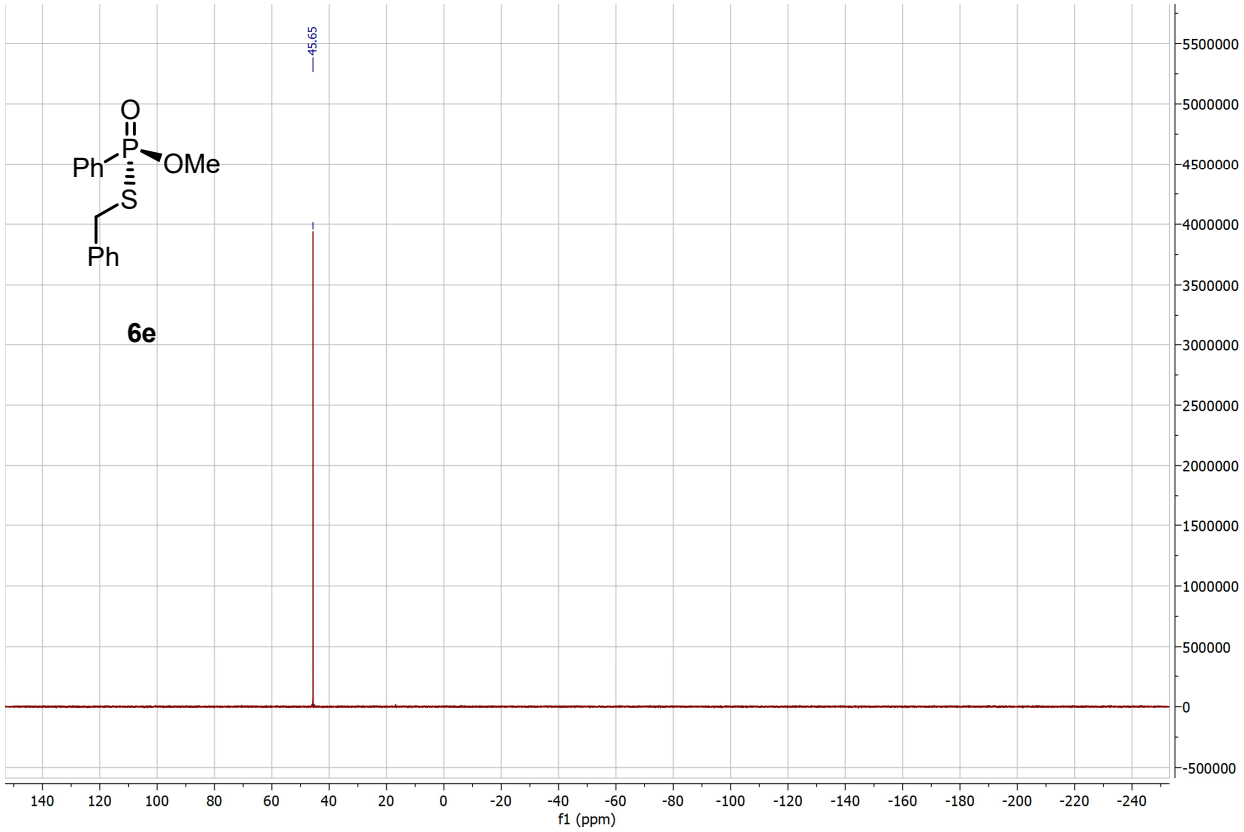
^{1}H NMR



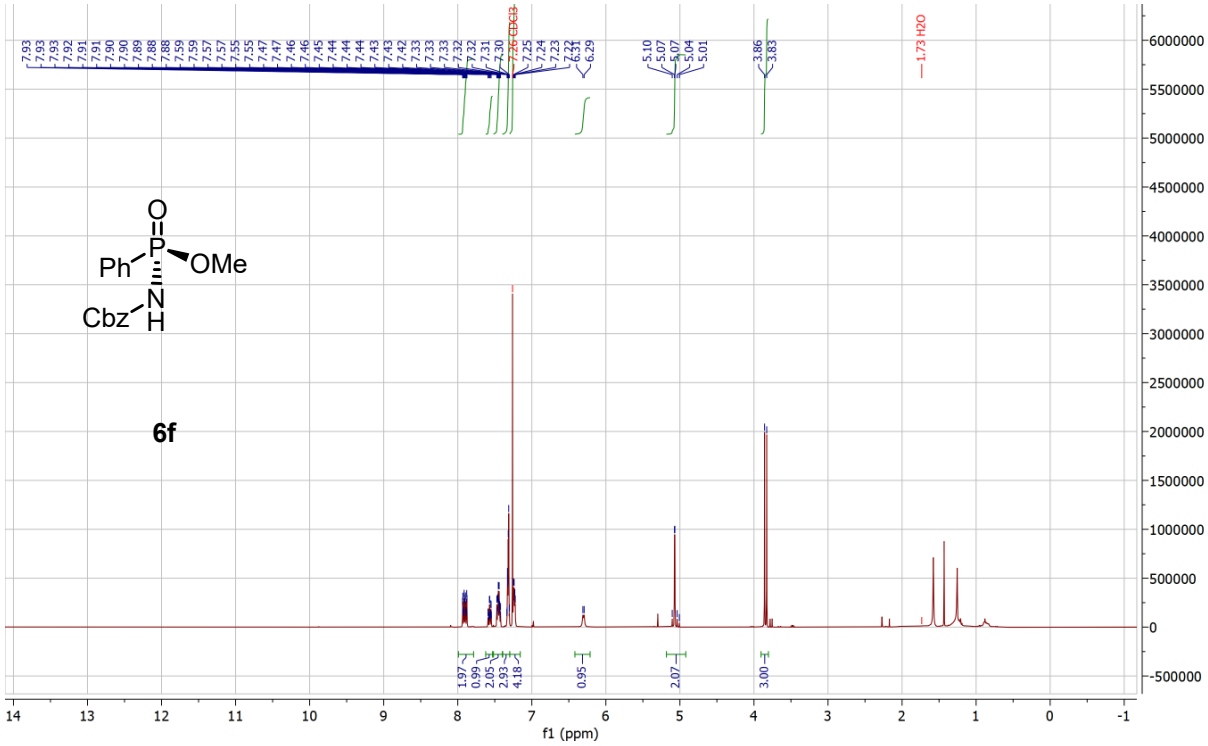
^{13}C NMR



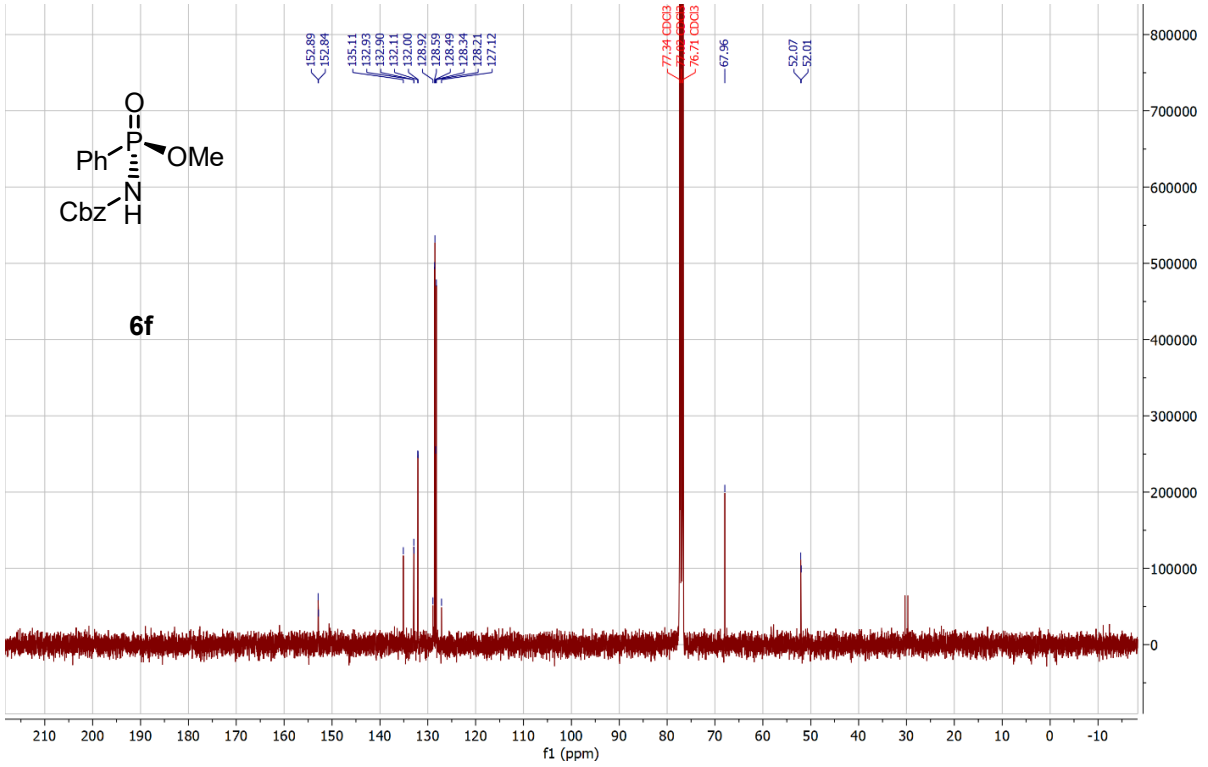
^{31}P NMR


45.65
O
P
Ph
OMe
S
Ph
6e
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

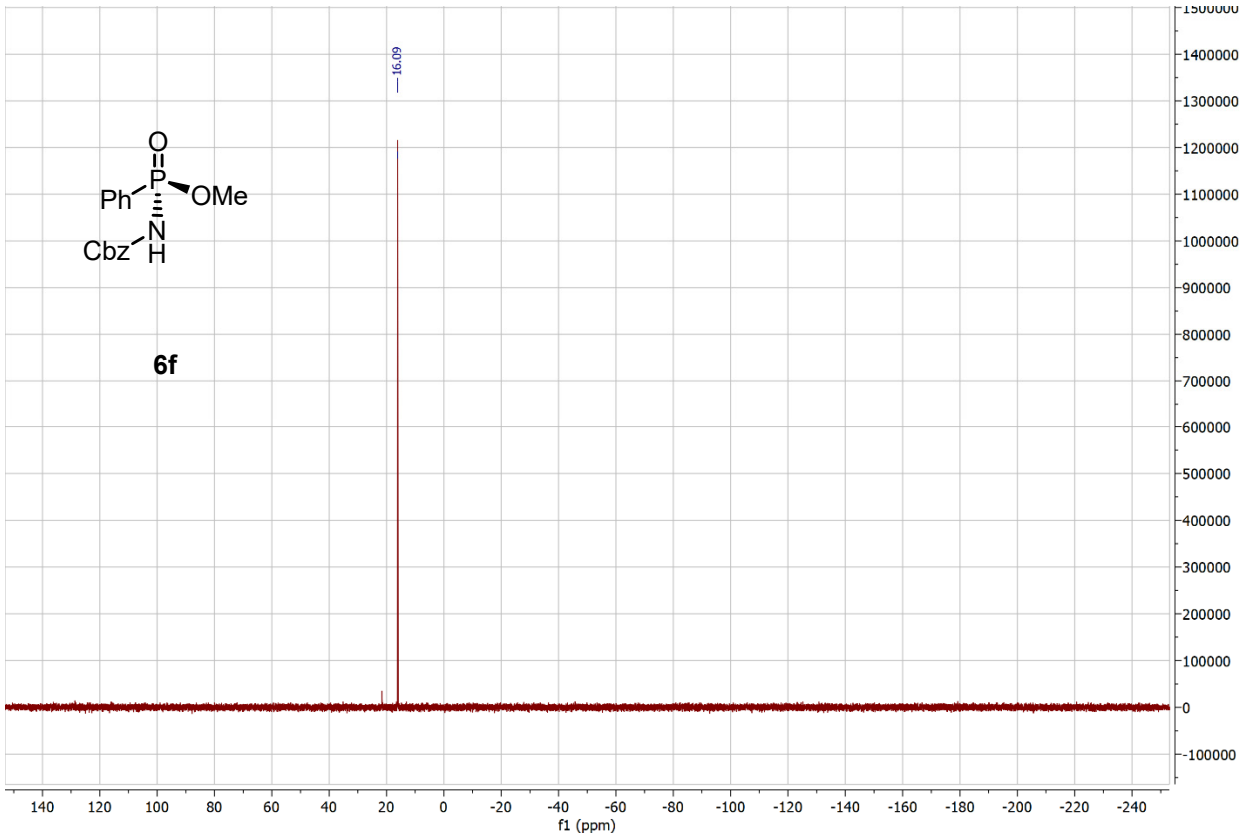
^{1}H NMR



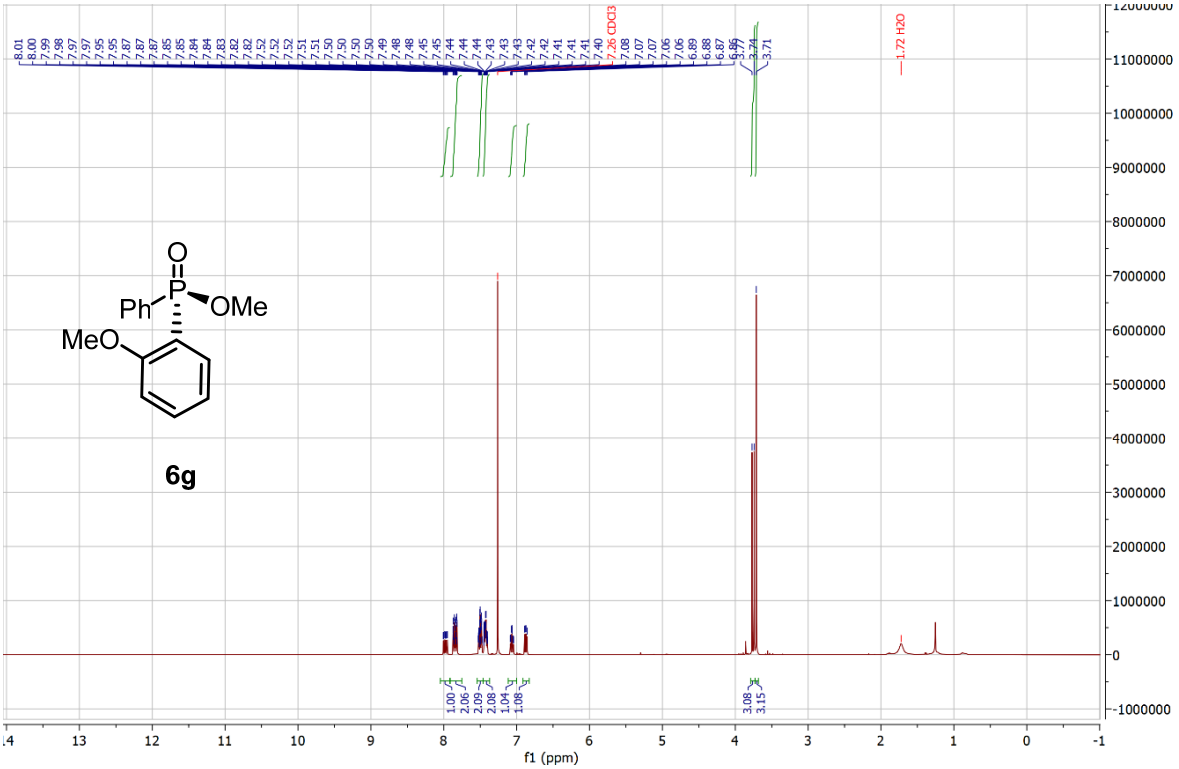
^{13}C NMR



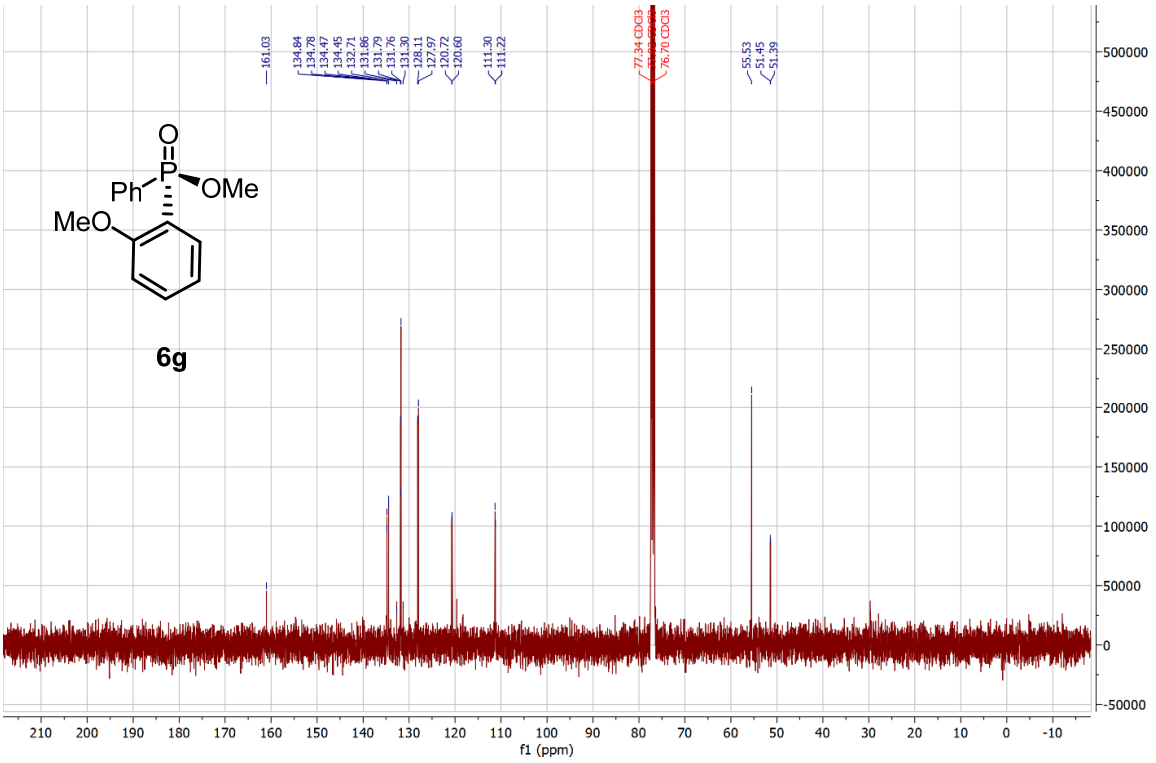
^{31}P NMR


16.09
O
P
Ph
OMe
N
H
Cbz
6f
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

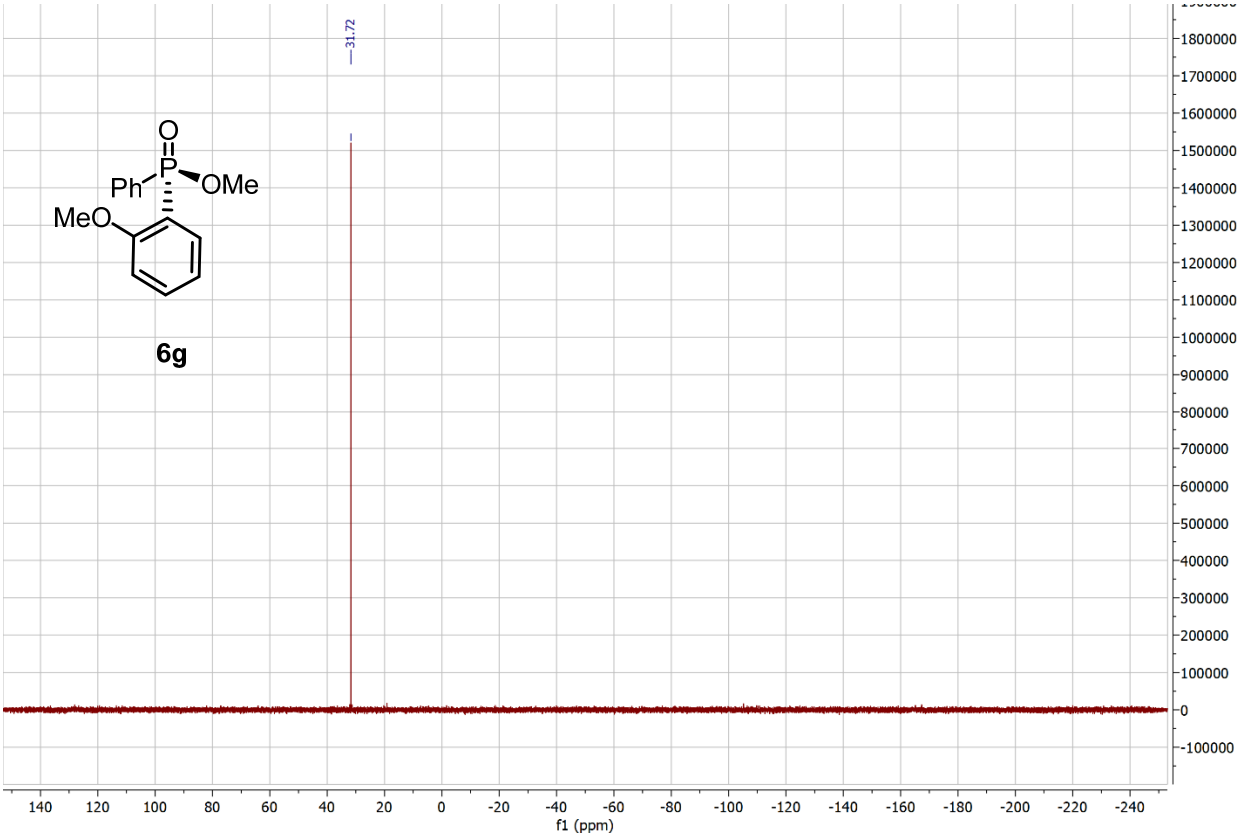
^{1}H NMR



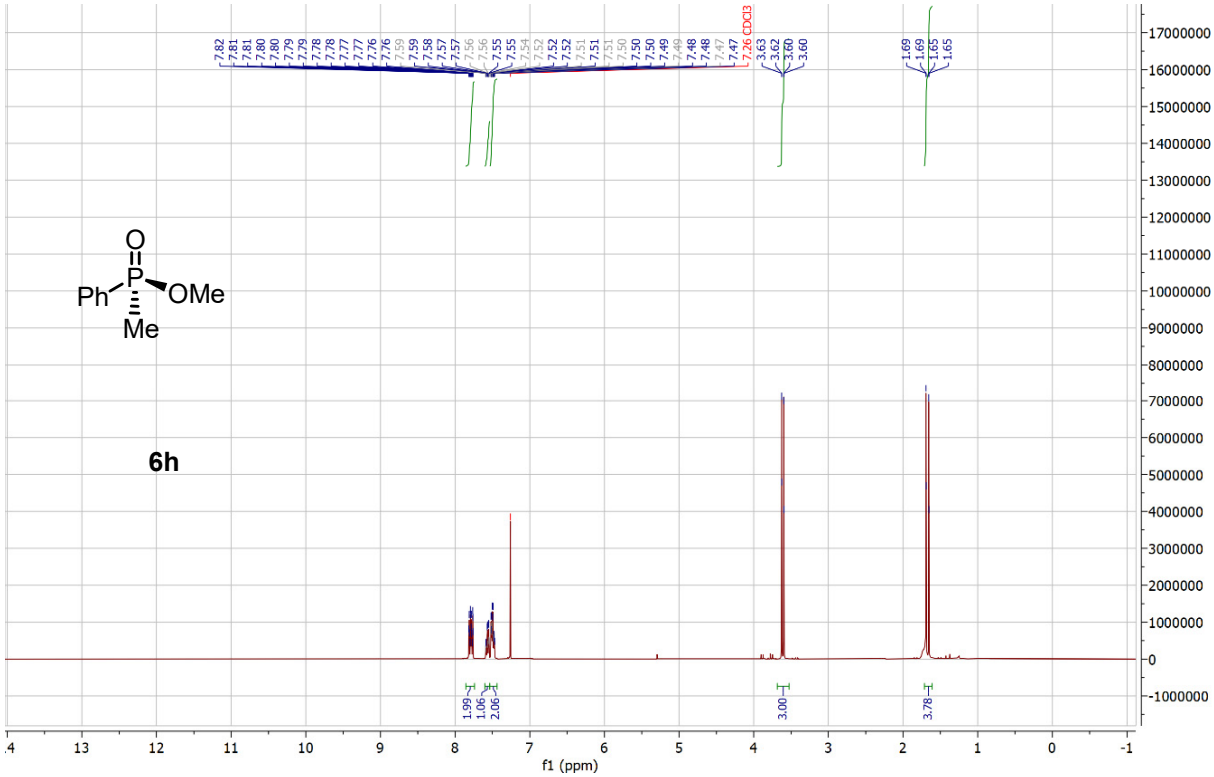
^{13}C NMR



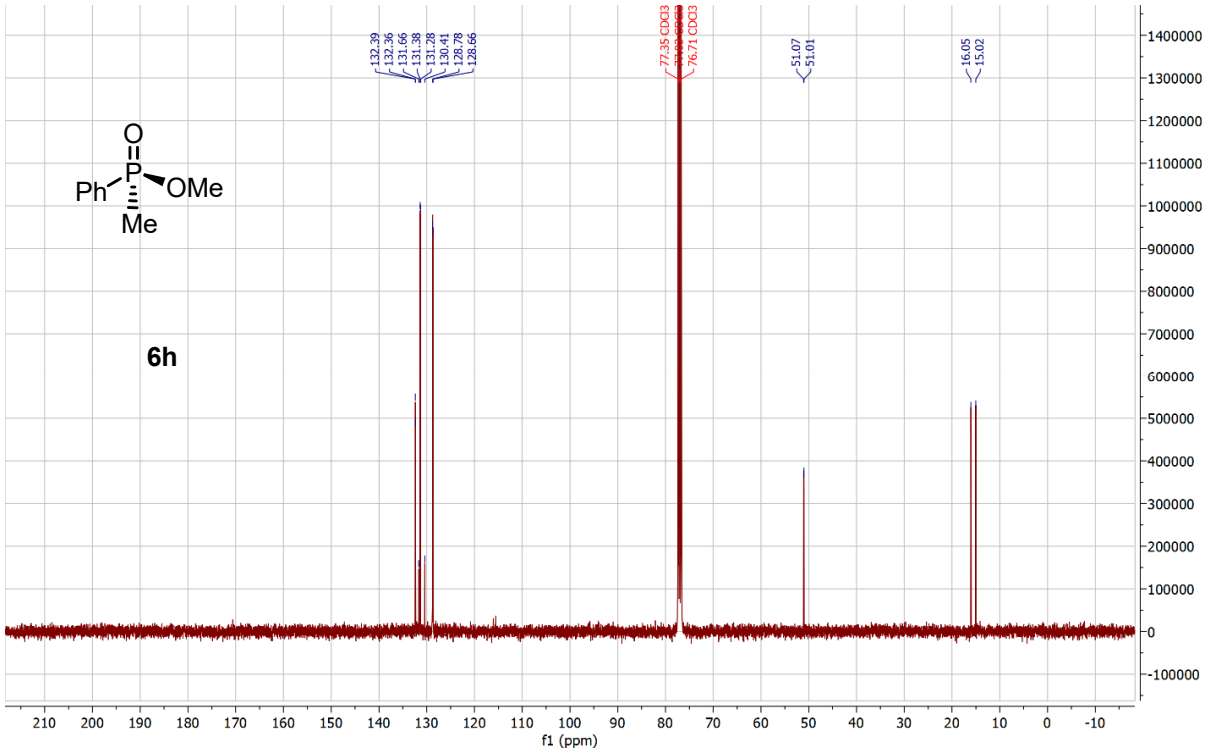
^{31}P NMR


31.72
O
P
Ph
OMe
MeO
6g
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

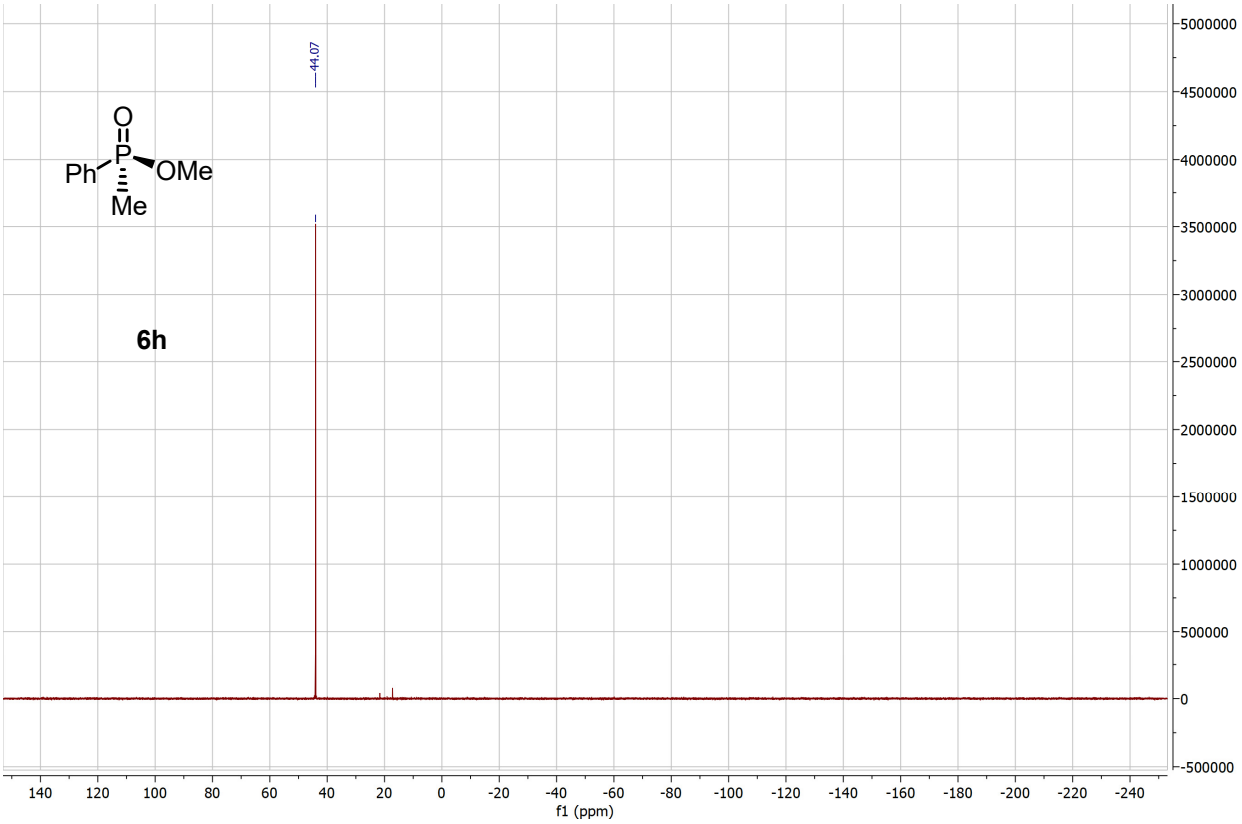
^{1}H NMR



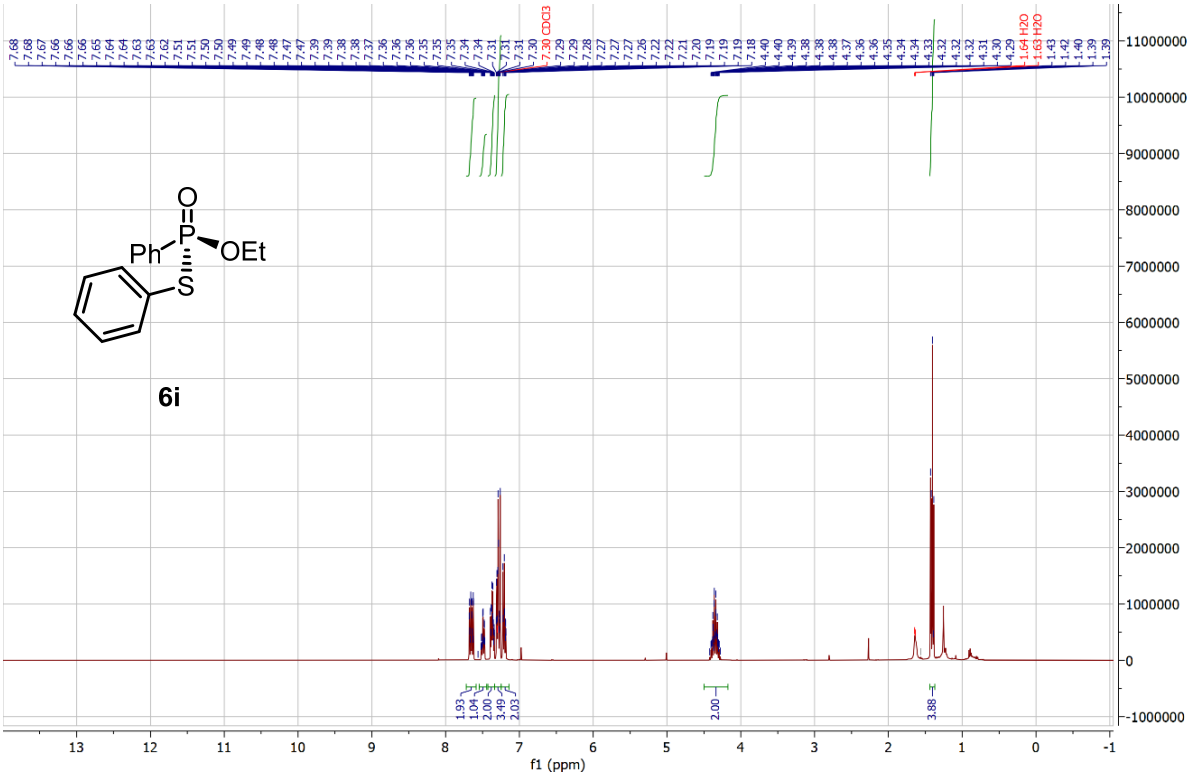
^{13}C NMR



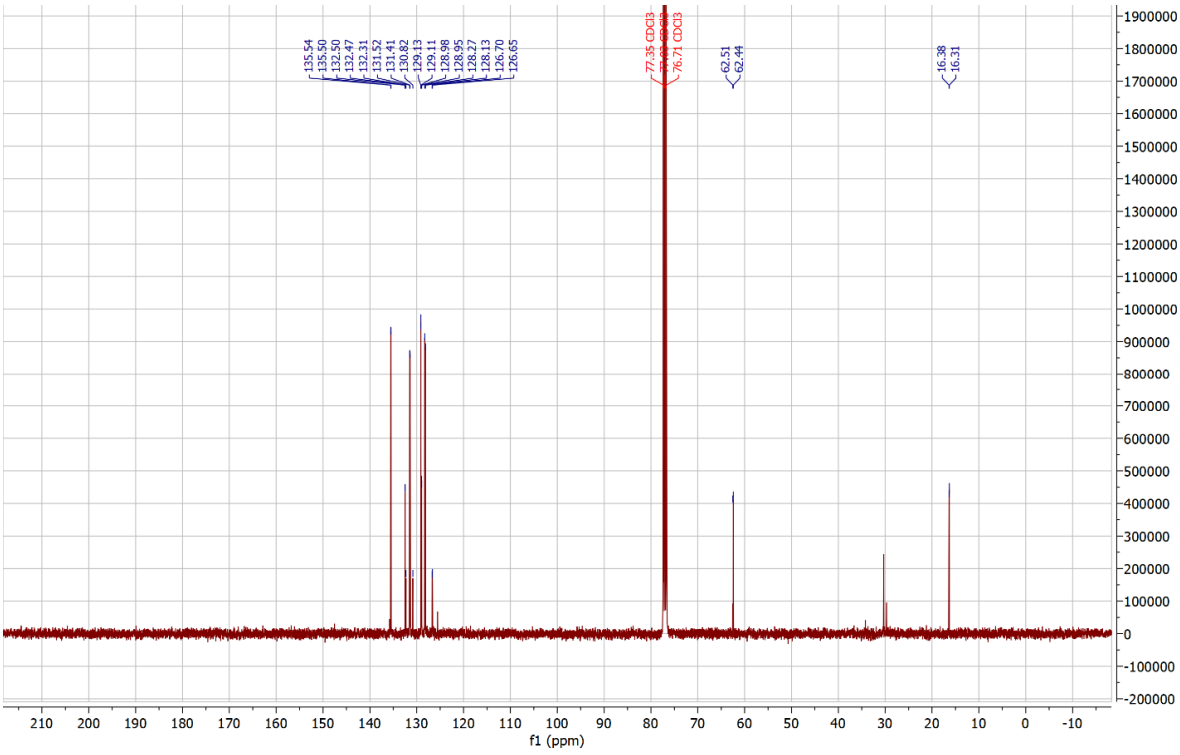
^{31}P NMR


44.07
O
P
Ph
OMe
Me
6h
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

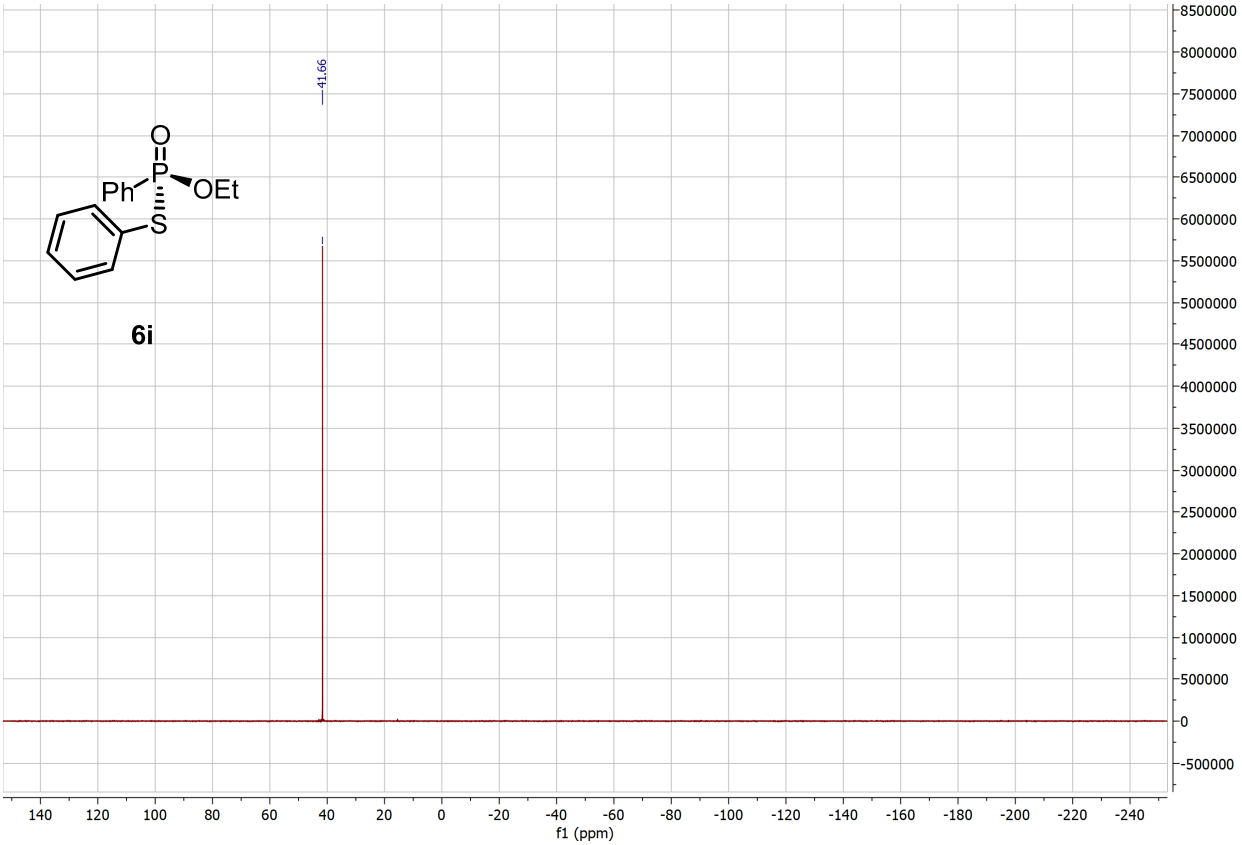
^{1}H NMR



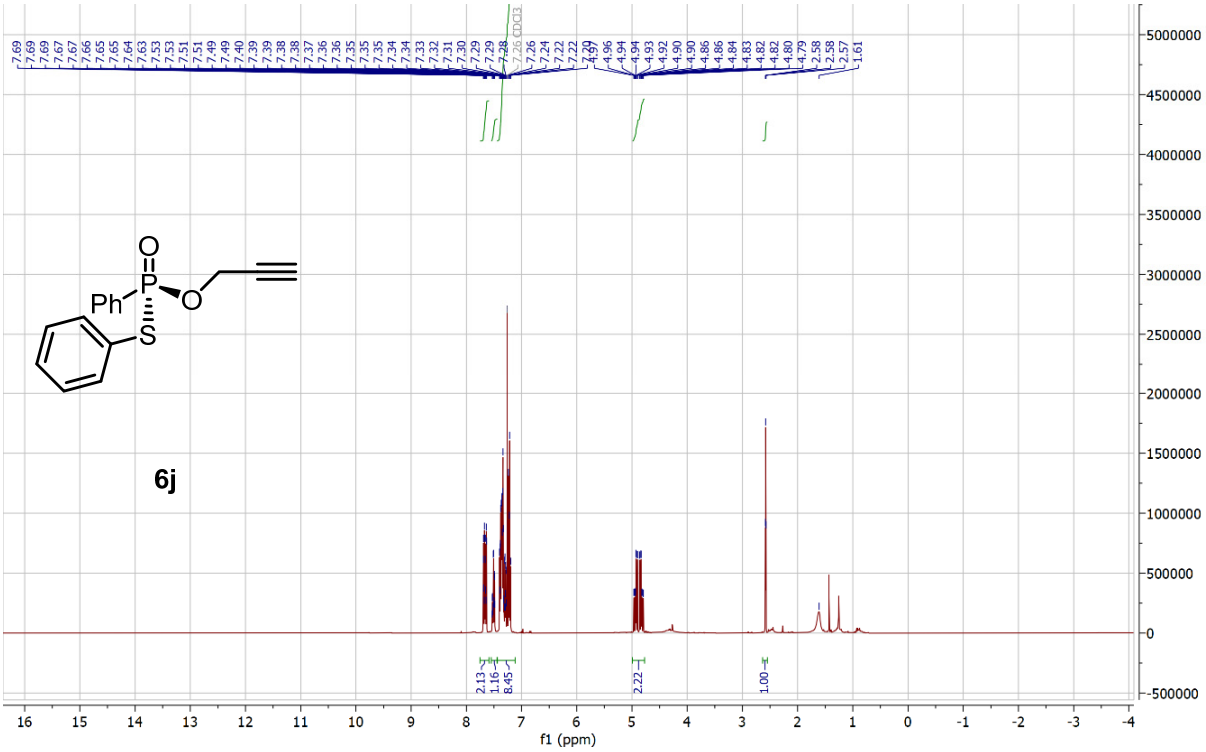
^{13}C NMR



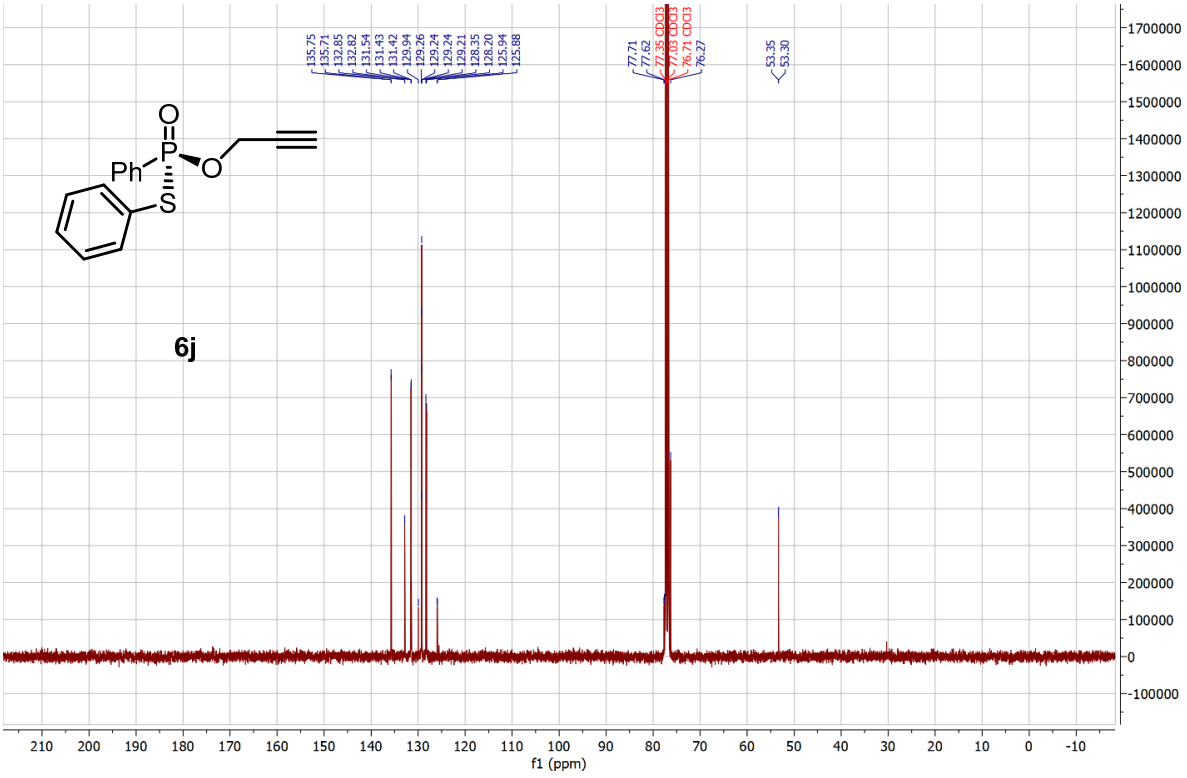
^{31}P NMR


41.66
O
P
Ph
OEt
S
6i
8500000
8000000
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

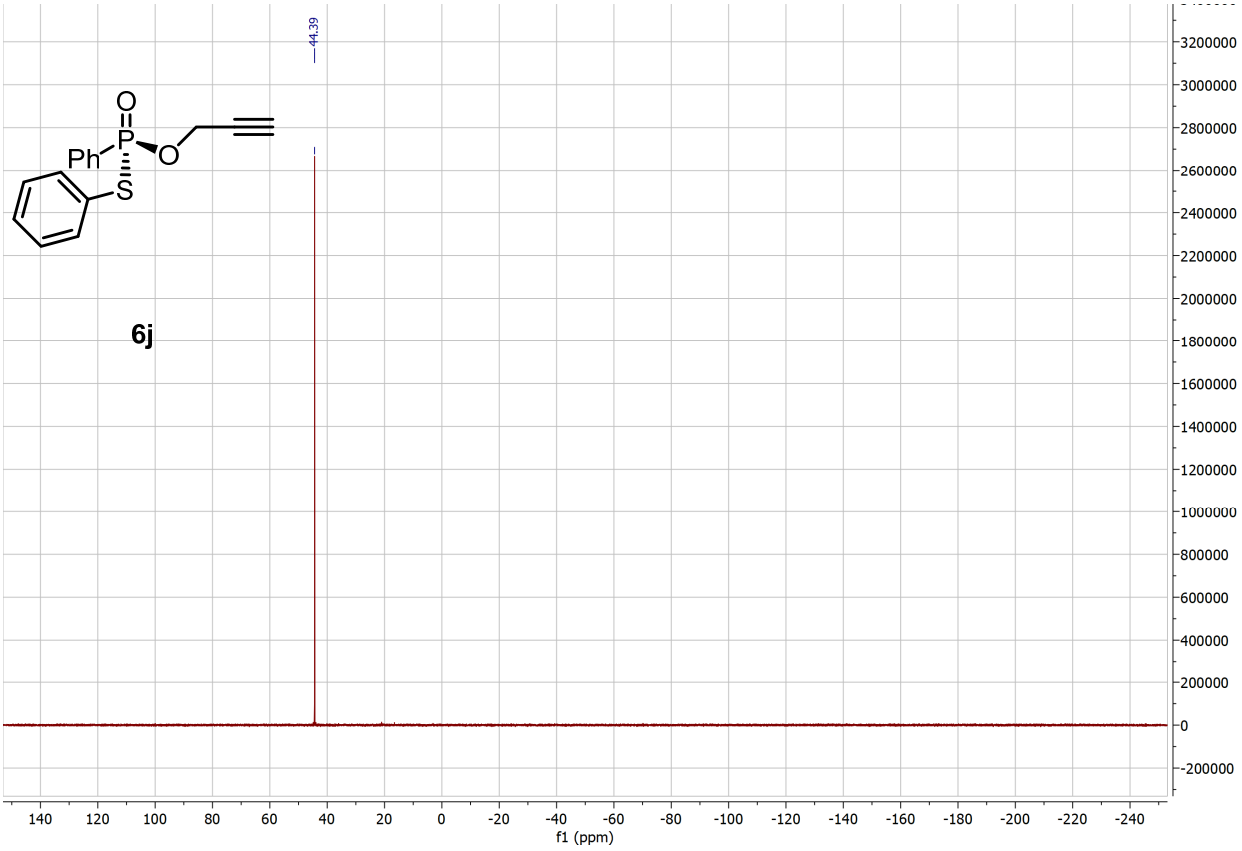
^{1}H NMR



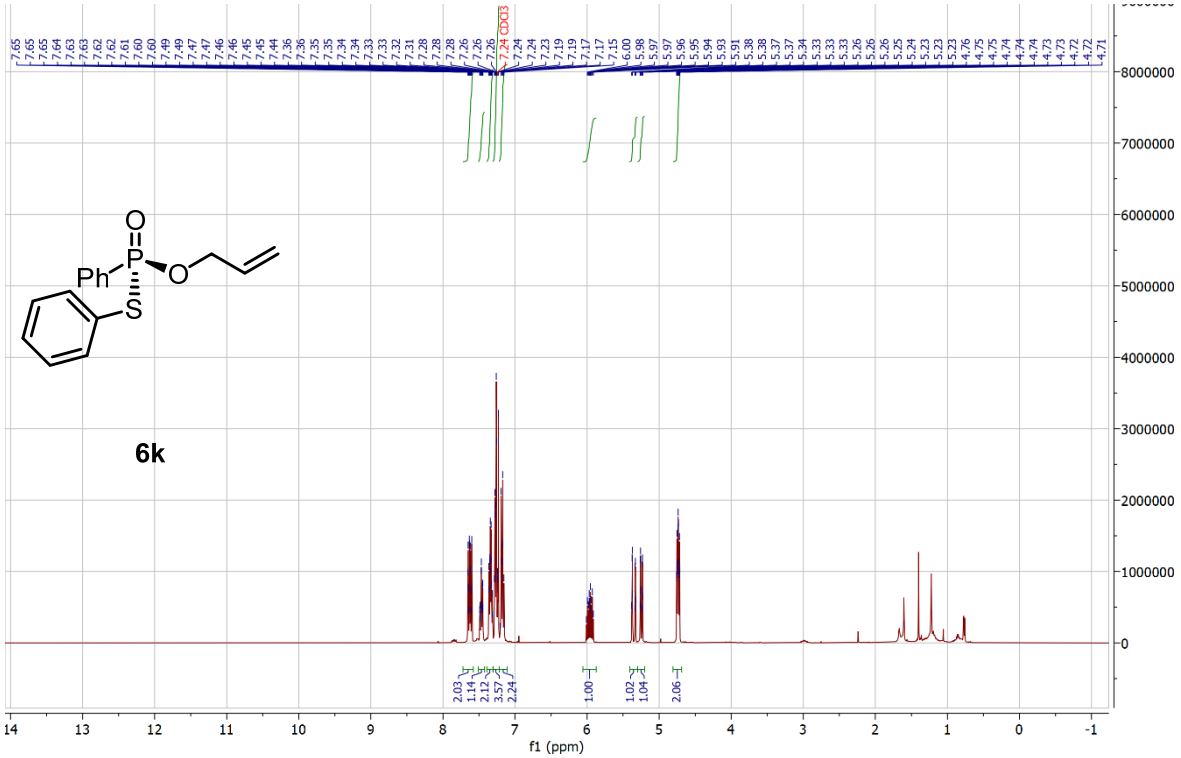
^{13}C NMR



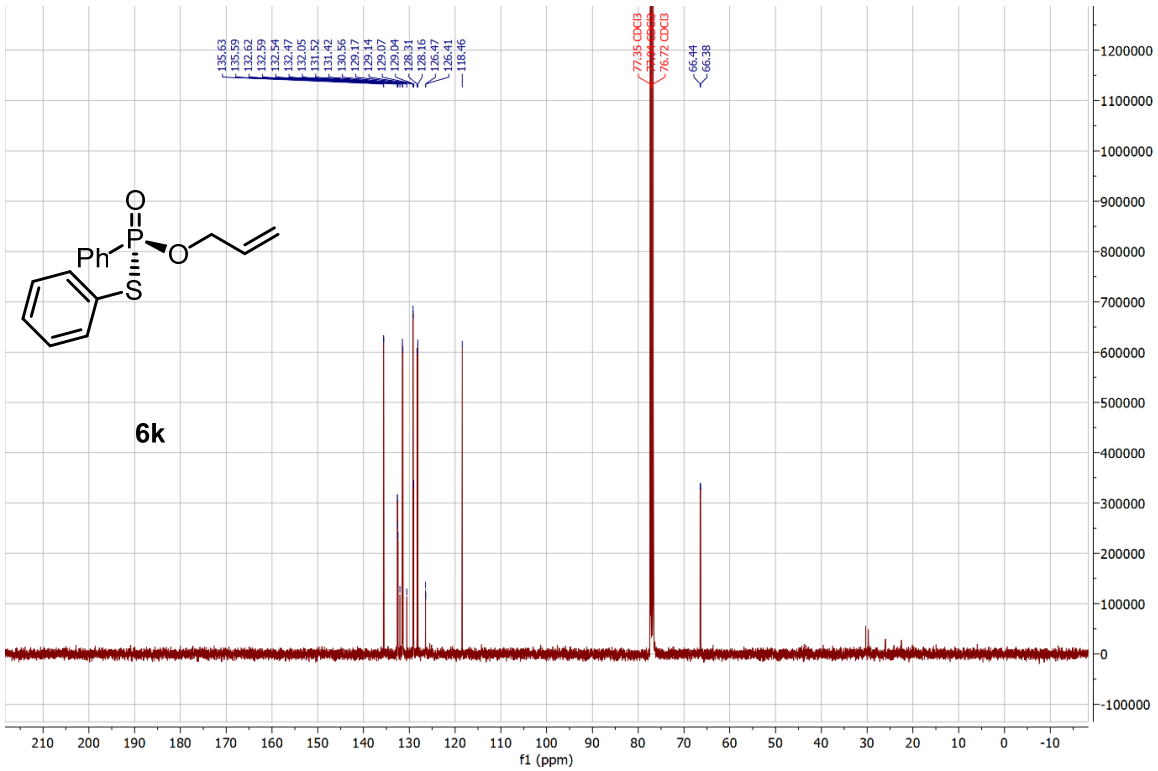
^{31}P NMR


44.39
O
P
Ph
O
S
6j
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

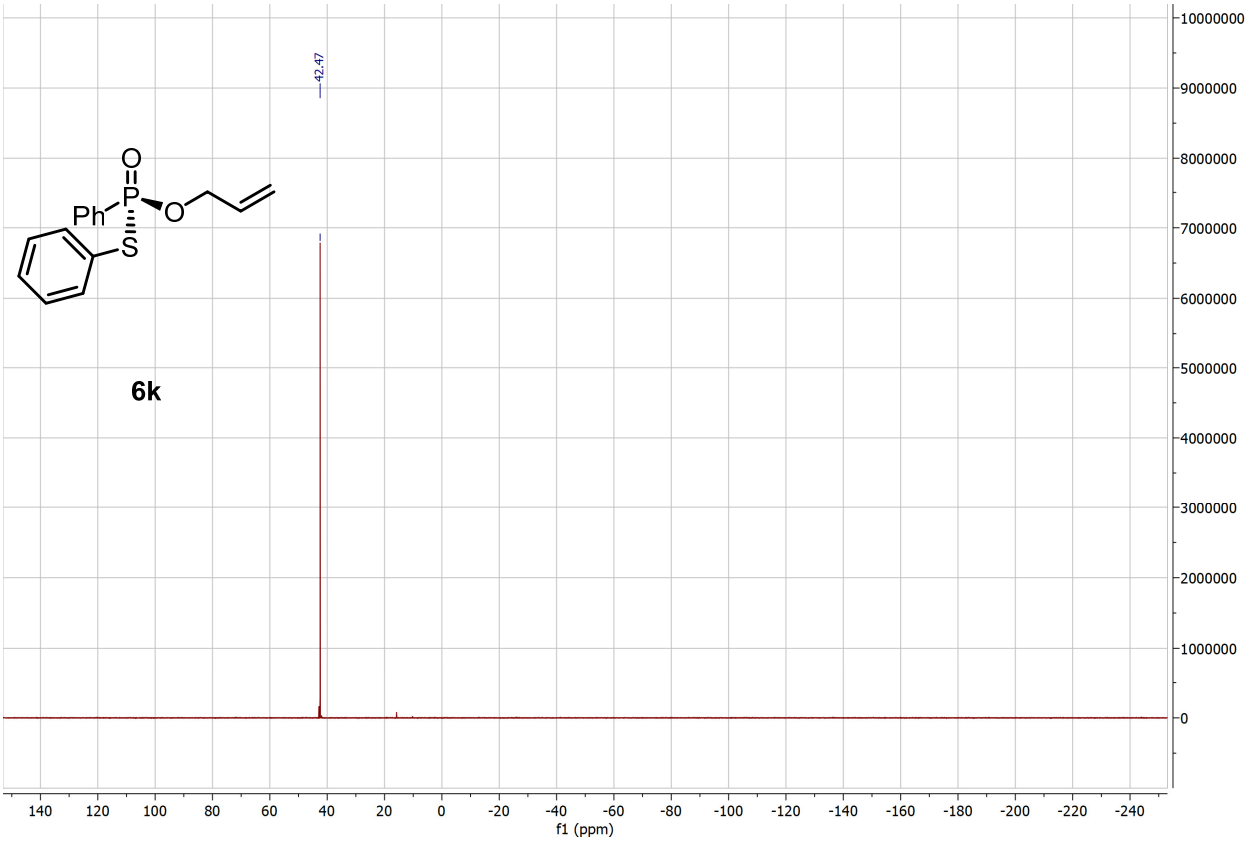
^{1}H NMR



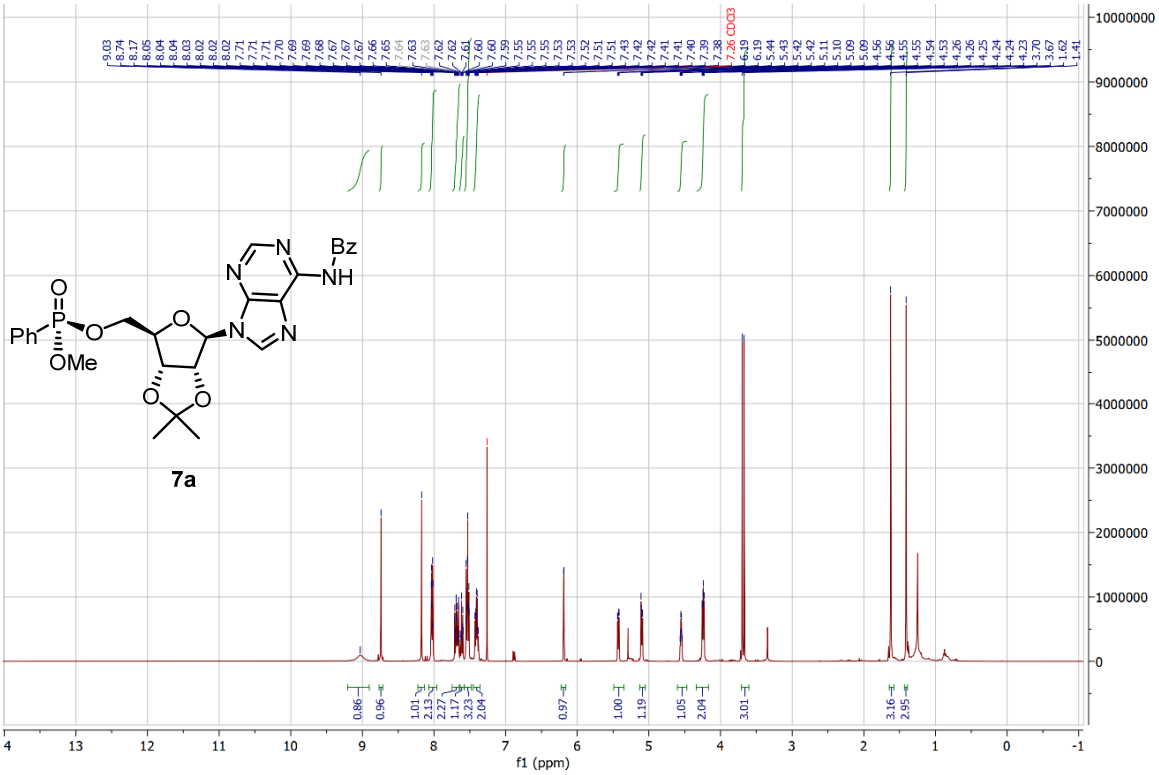
^{13}C NMR



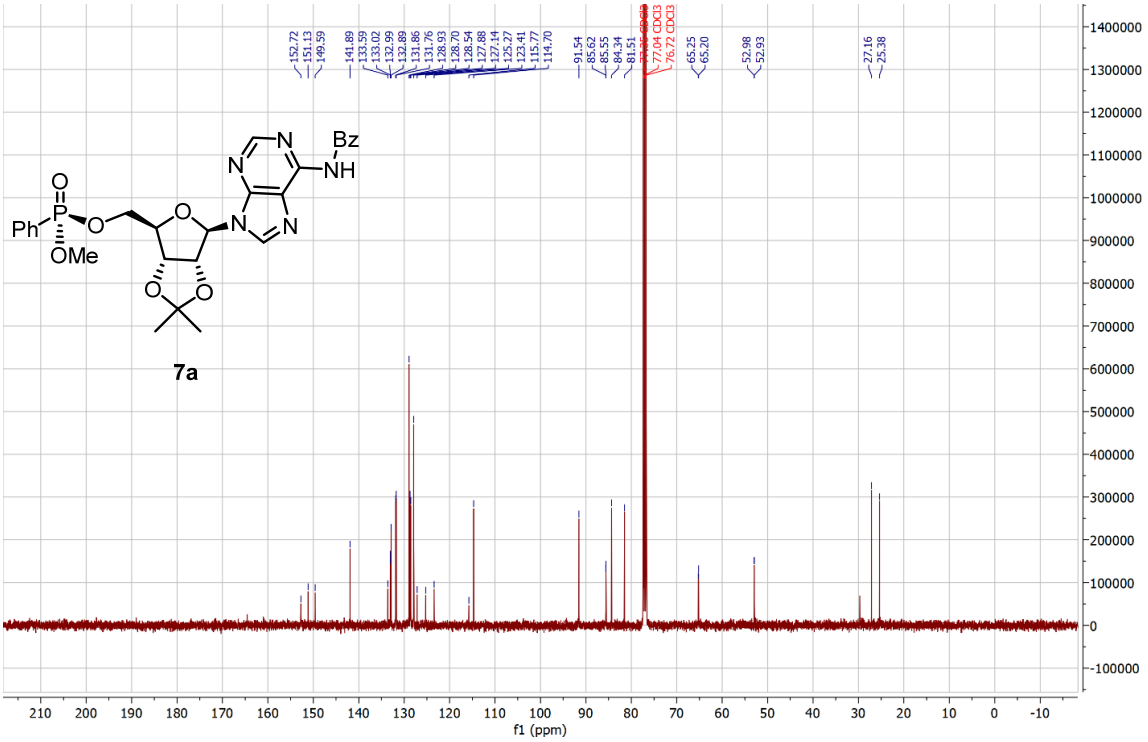
^{31}P NMR


42.47
O
P
Ph
O
S
6k
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

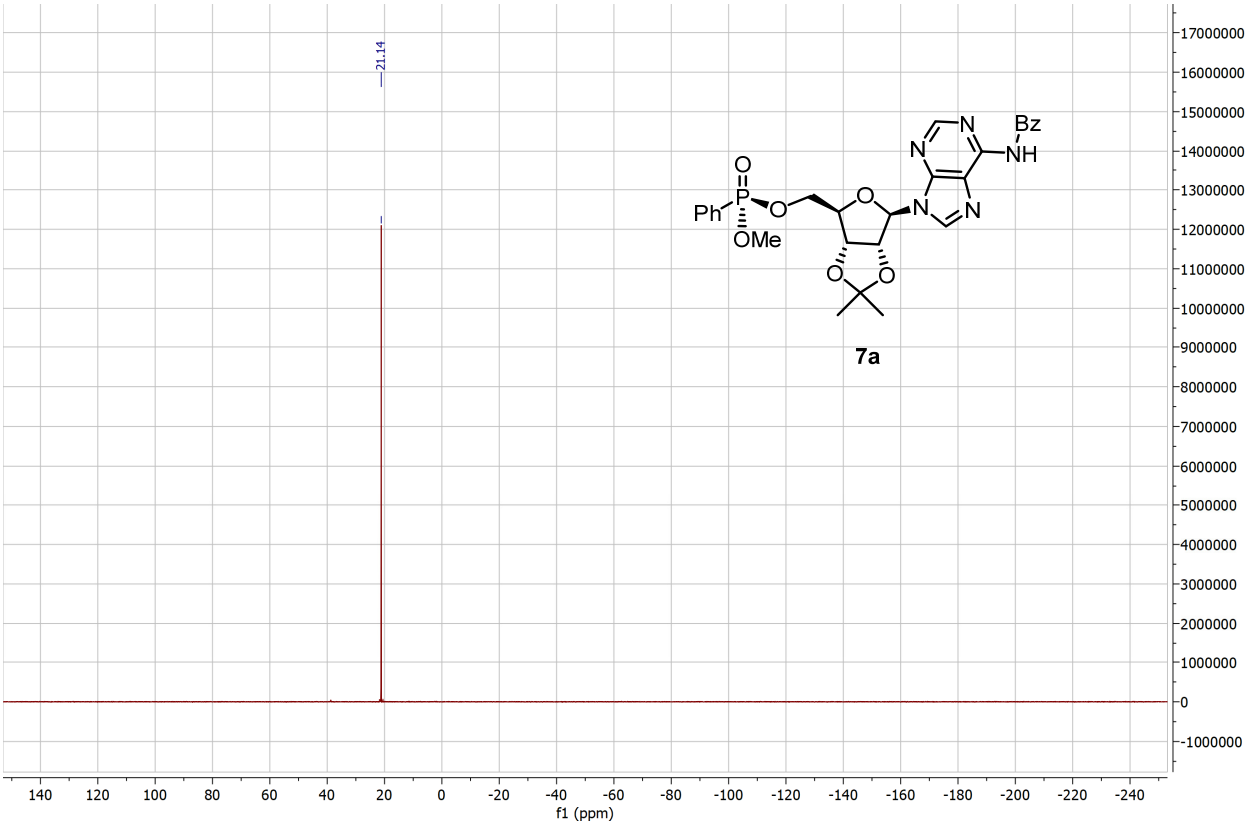
^{1}H NMR



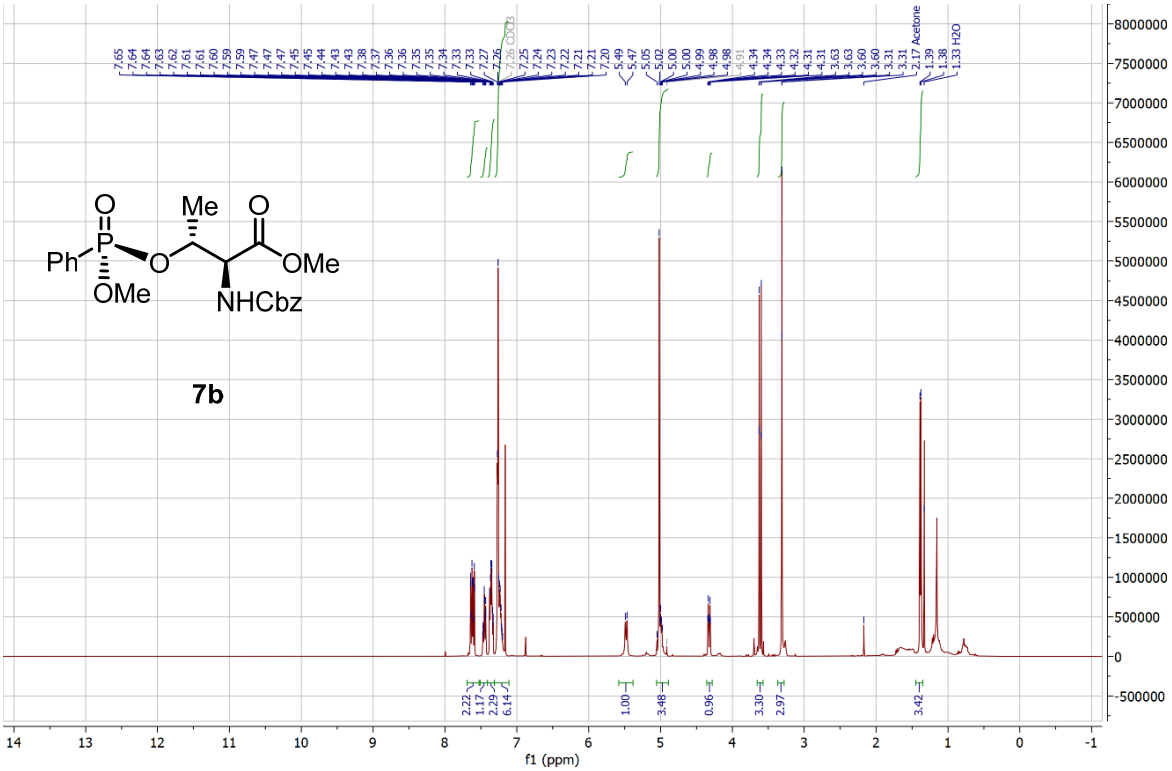
^{13}C NMR



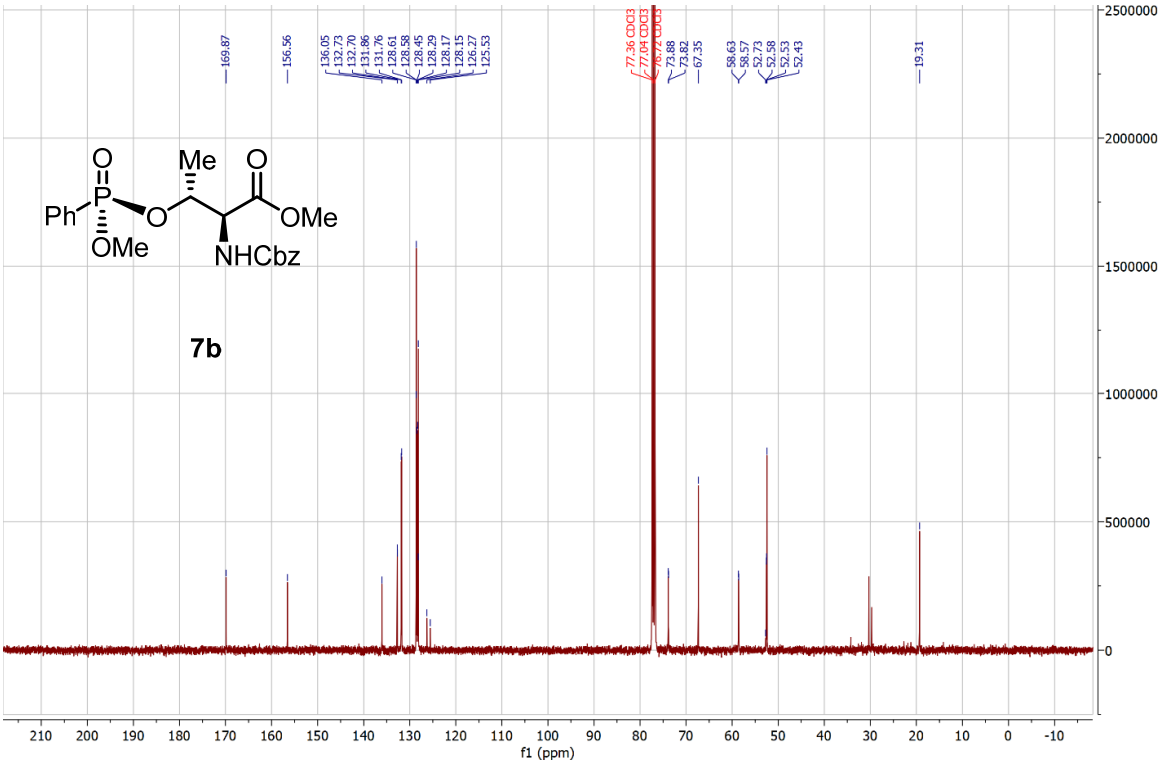
^{31}P NMR


21.14
Ph
O
P
OMe
O
O
O
N
N
N
N
Bz
NH
7a
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

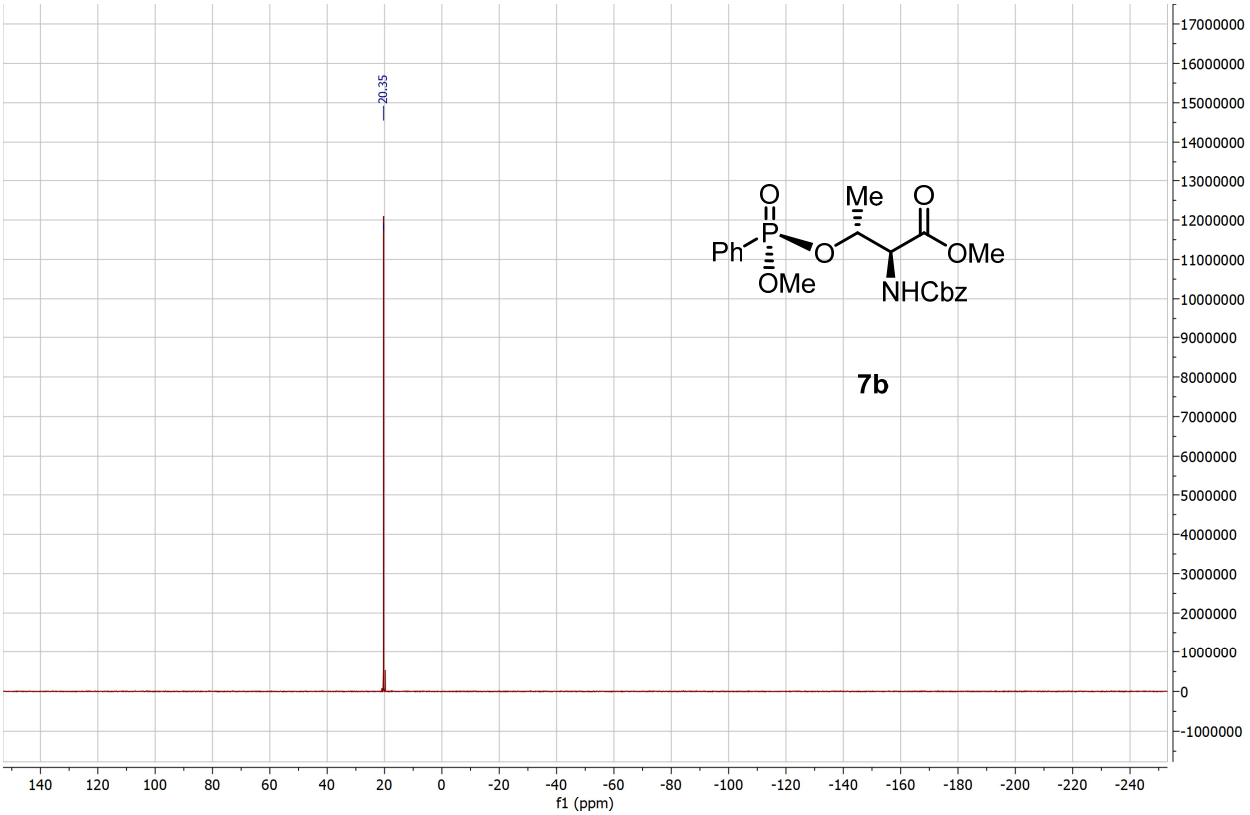
^{1}H NMR



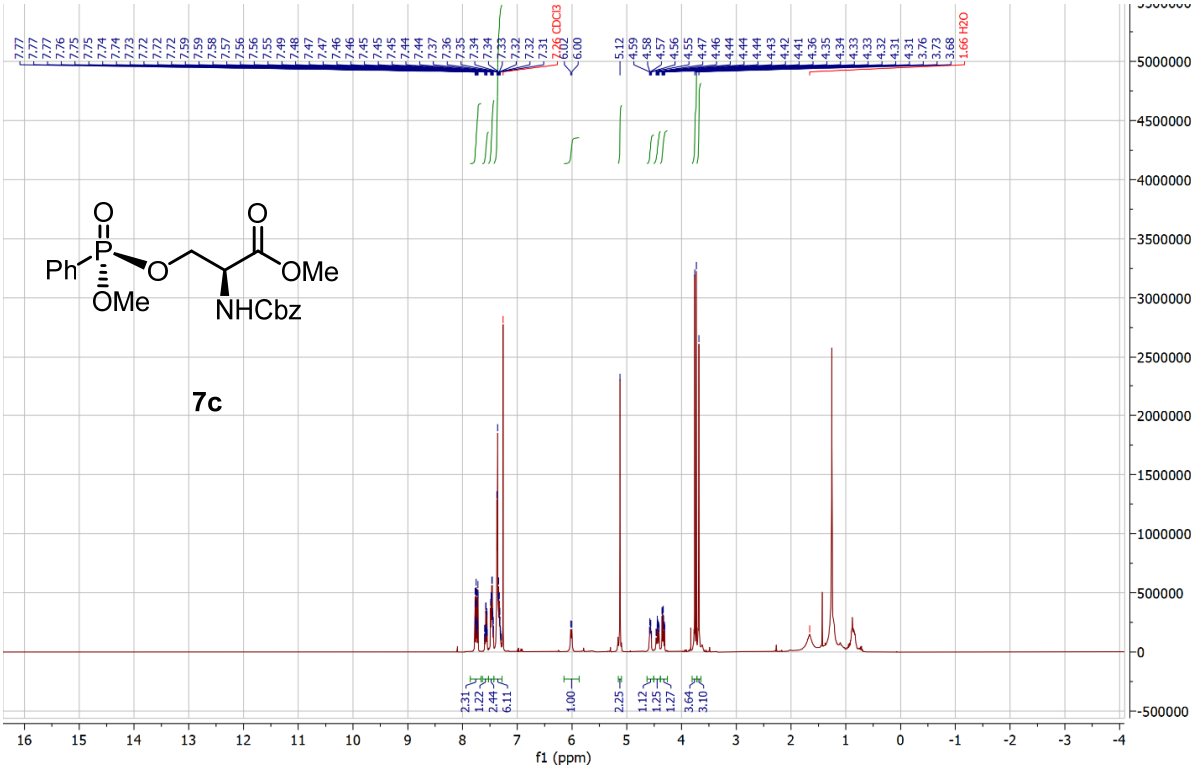
^{13}C NMR



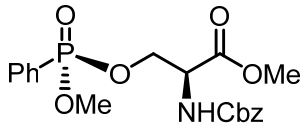
^{31}P NMR


20.35
O
Me
O
Ph
P
O
OMe
OMe
NHCbz
7b
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

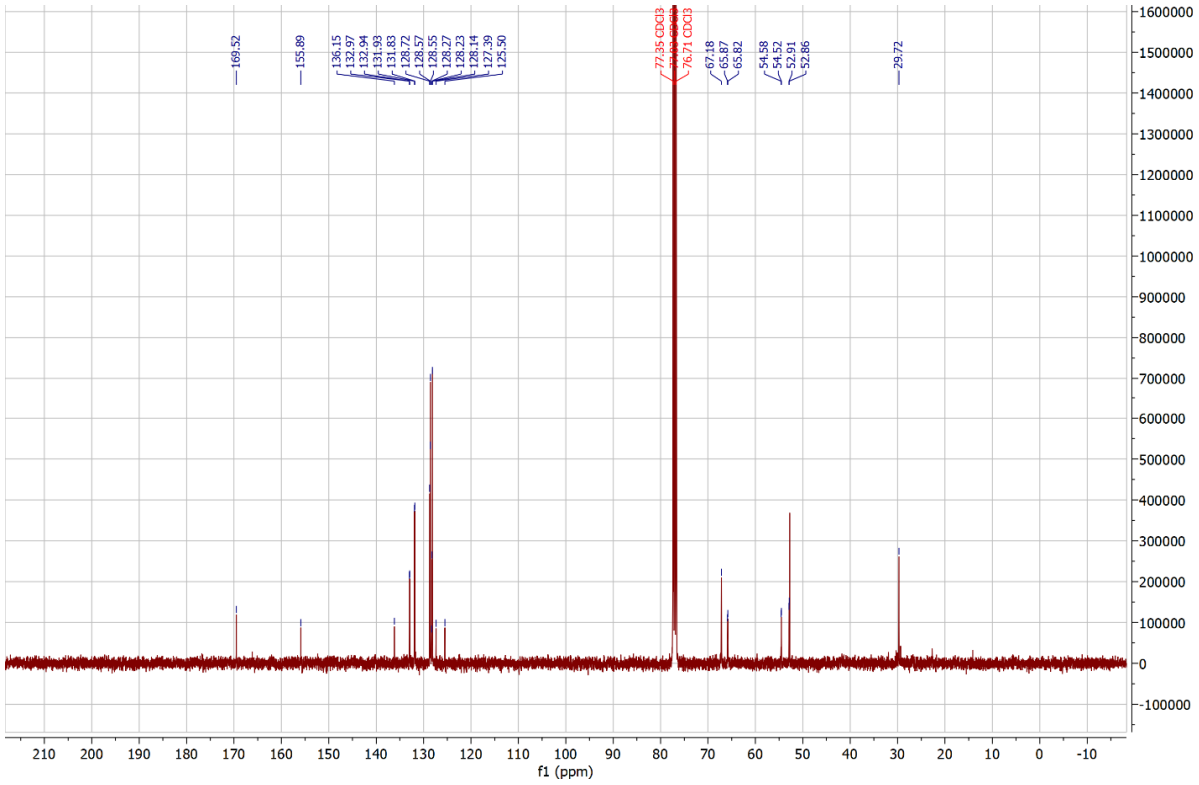
^{1}H NMR



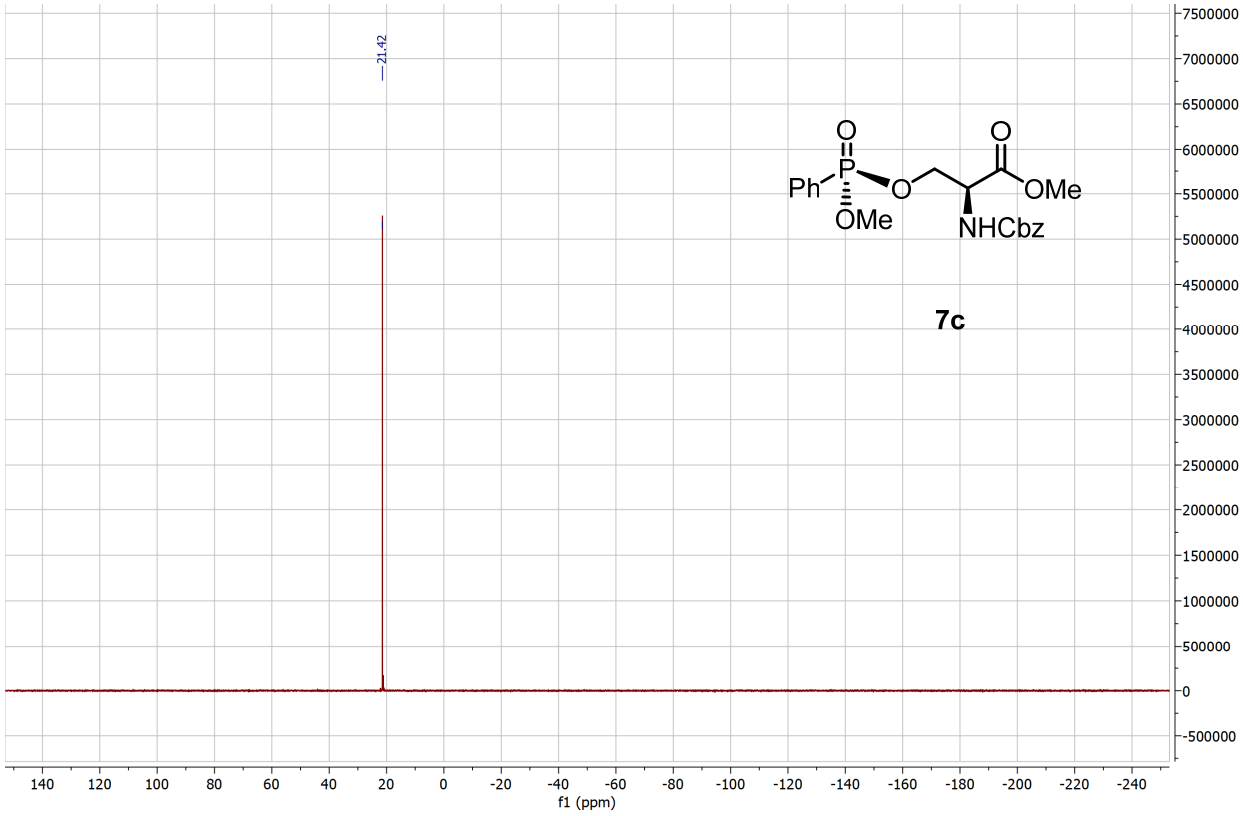
^{13}C NMR



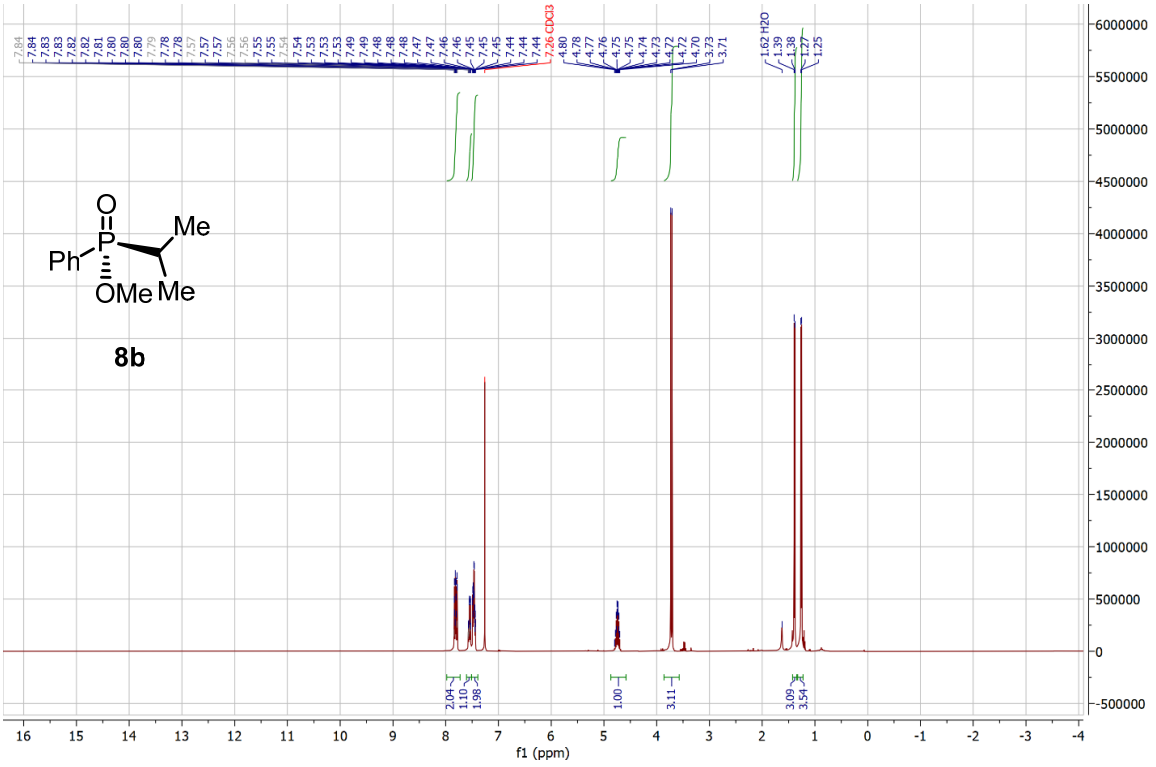
7c


169.52
155.89
136.15
132.97
132.94
131.93
131.83
128.72
128.57
128.55
128.27
128.23
128.14
127.39
125.50
77.35 CDCl3
76.71 CDCl3
67.18
65.87
65.82
54.58
54.52
52.91
52.86
29.72
f1 (ppm)

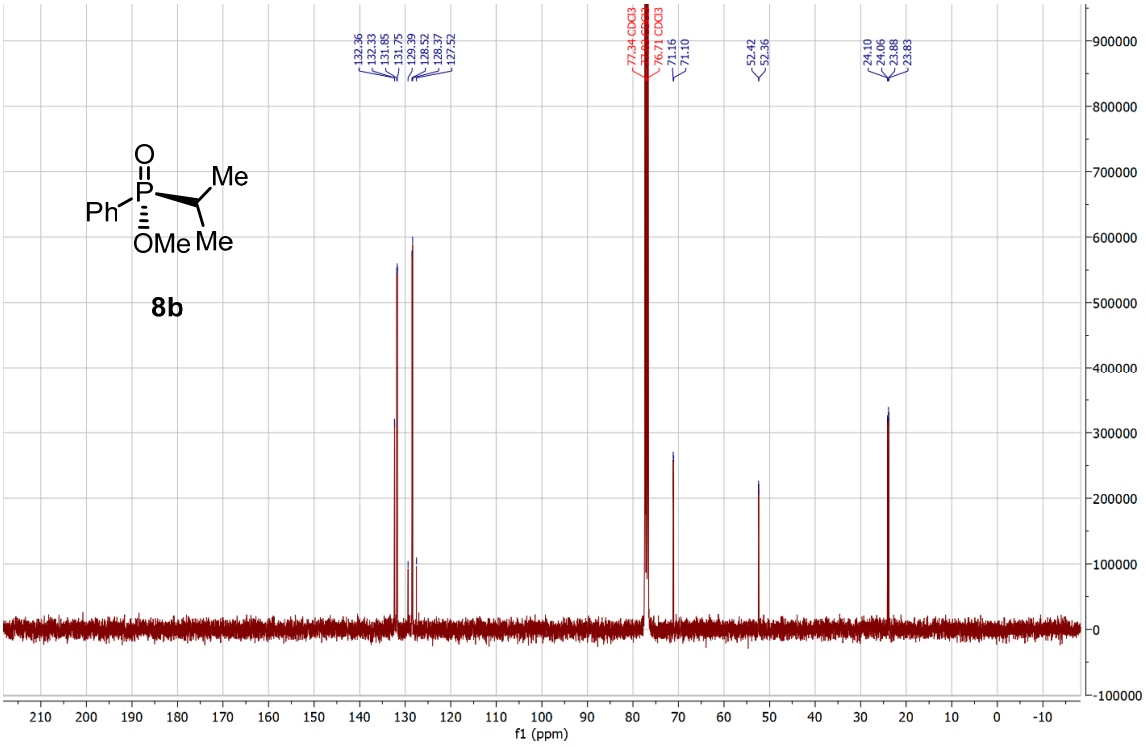
^{31}P NMR


21.42
Ph
O
P
O
OMe
OMe
O
NHCbz
7c
f1 (ppm)

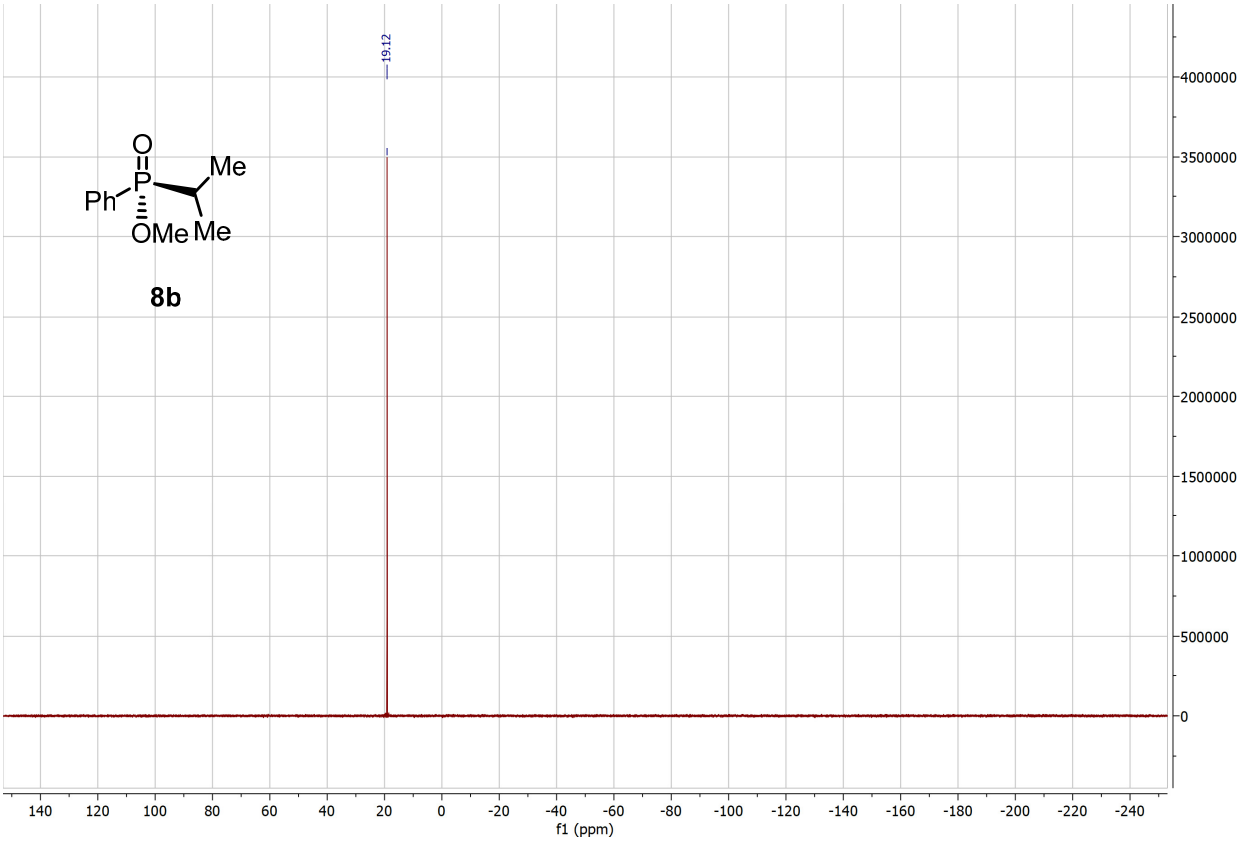
^{1}H NMR



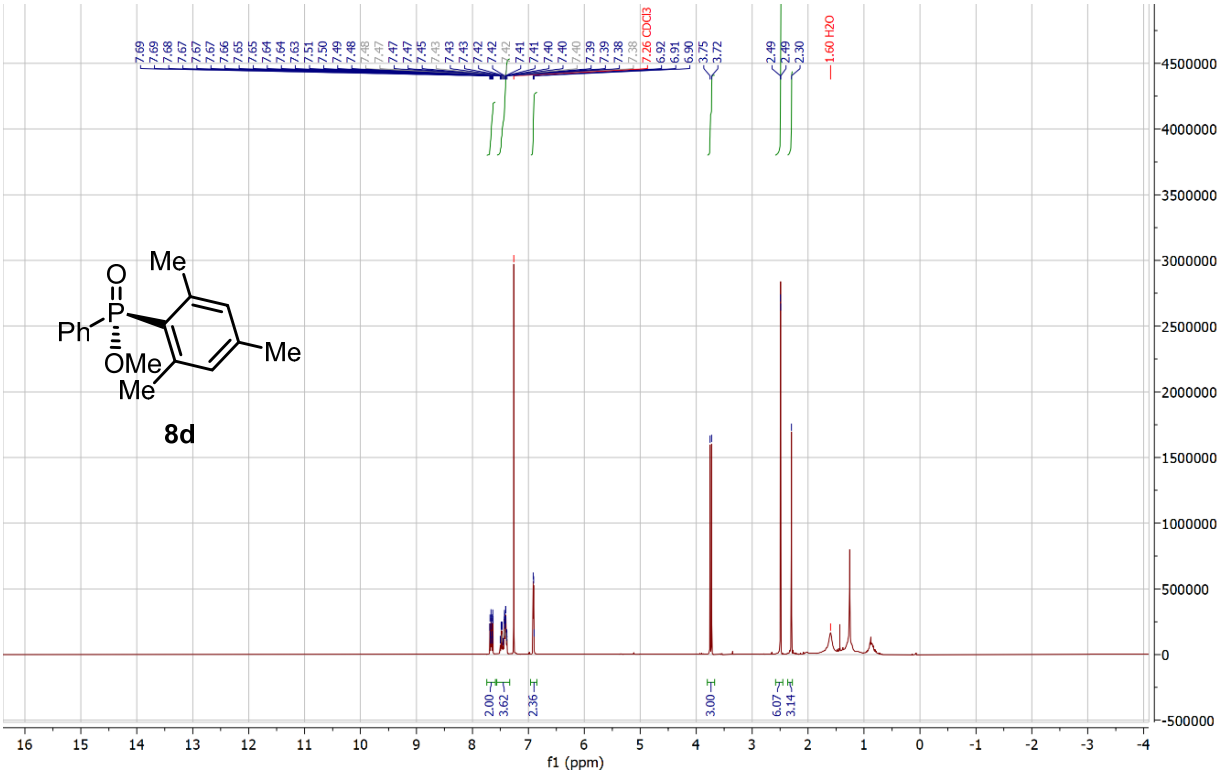
^{13}C NMR



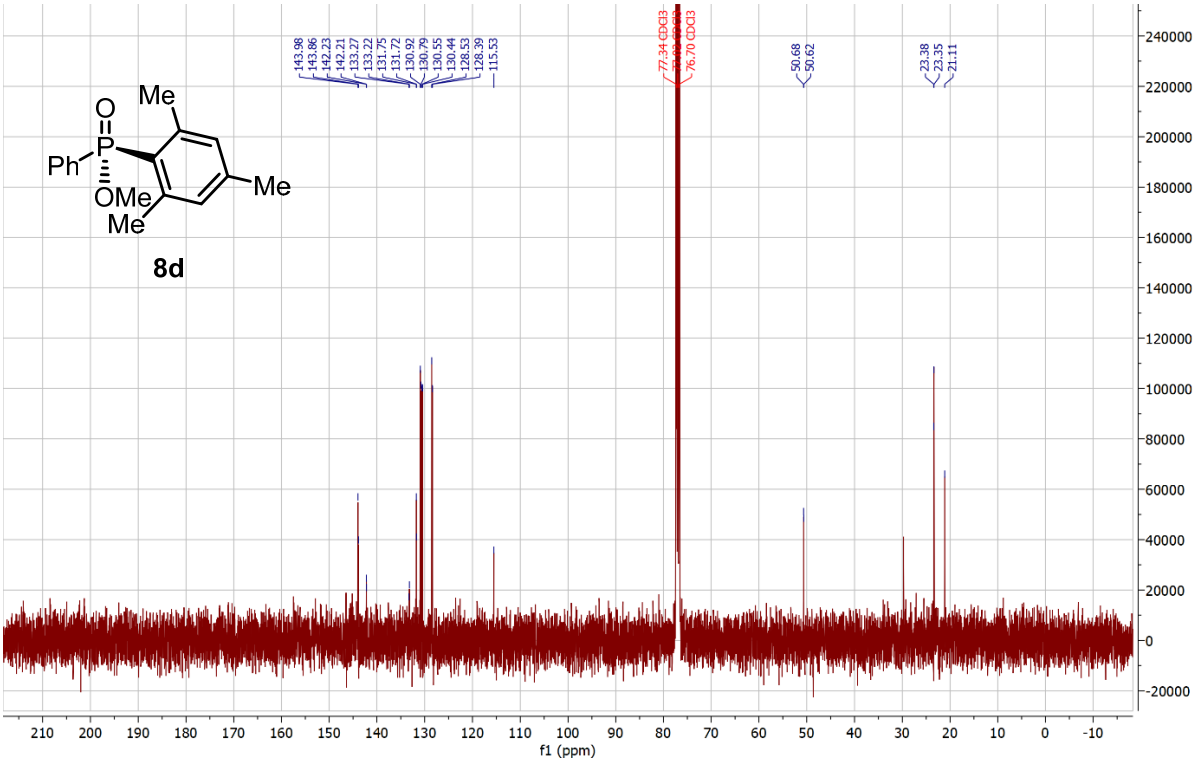
^{31}P NMR


19.12
O
P
Ph
Me
OMe
Me
8b
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

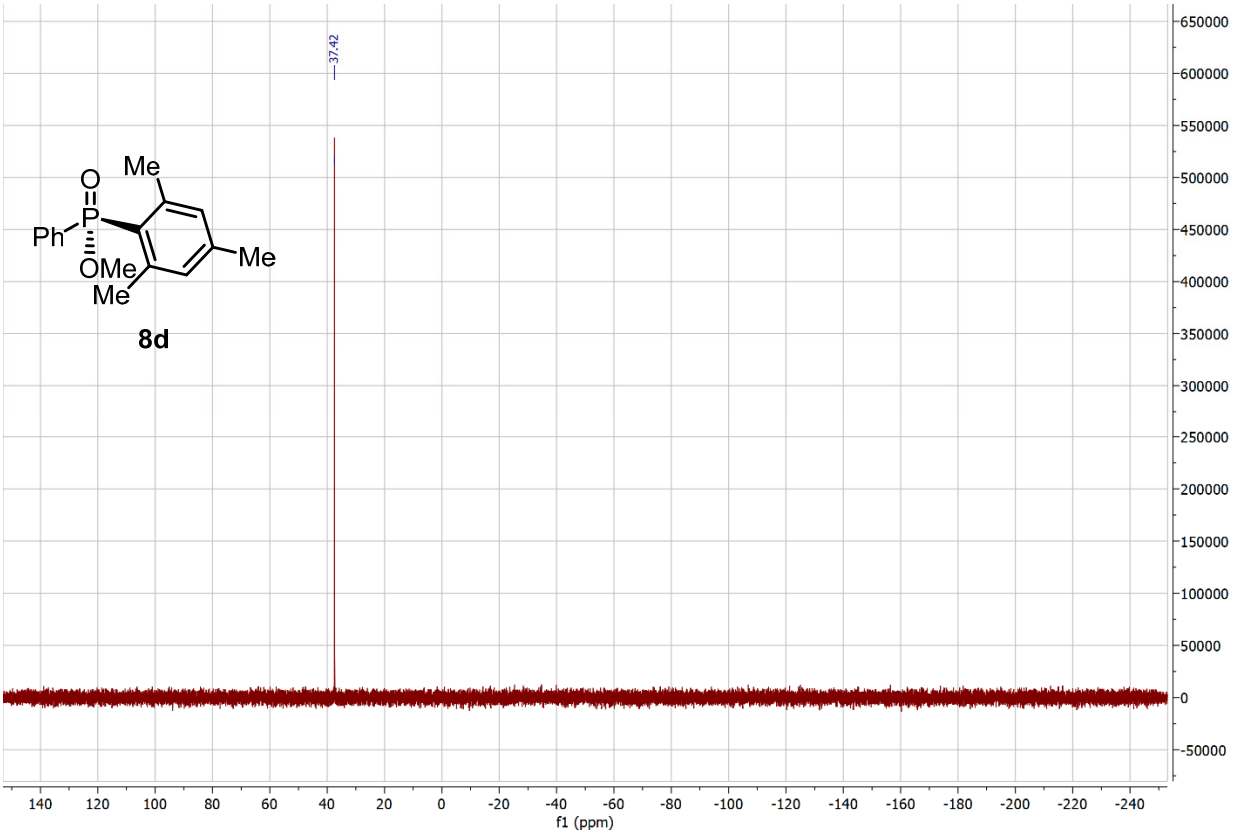
^{1}H NMR



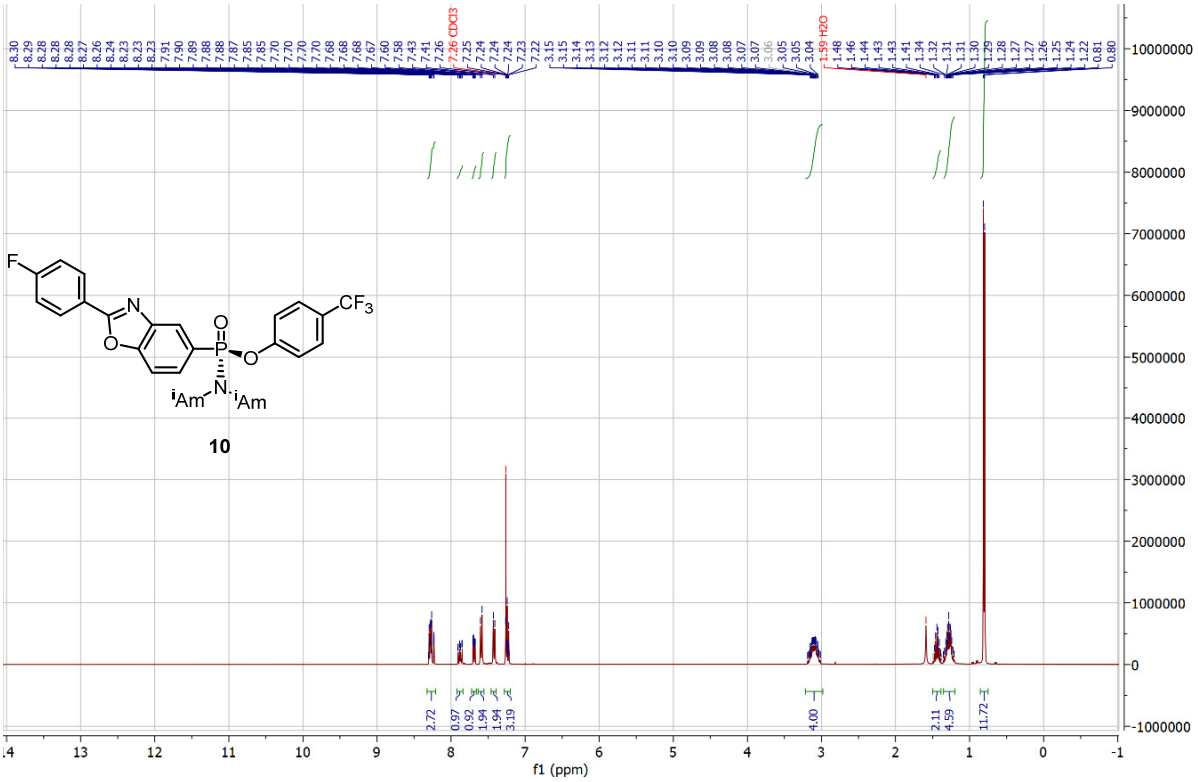
^{13}C NMR



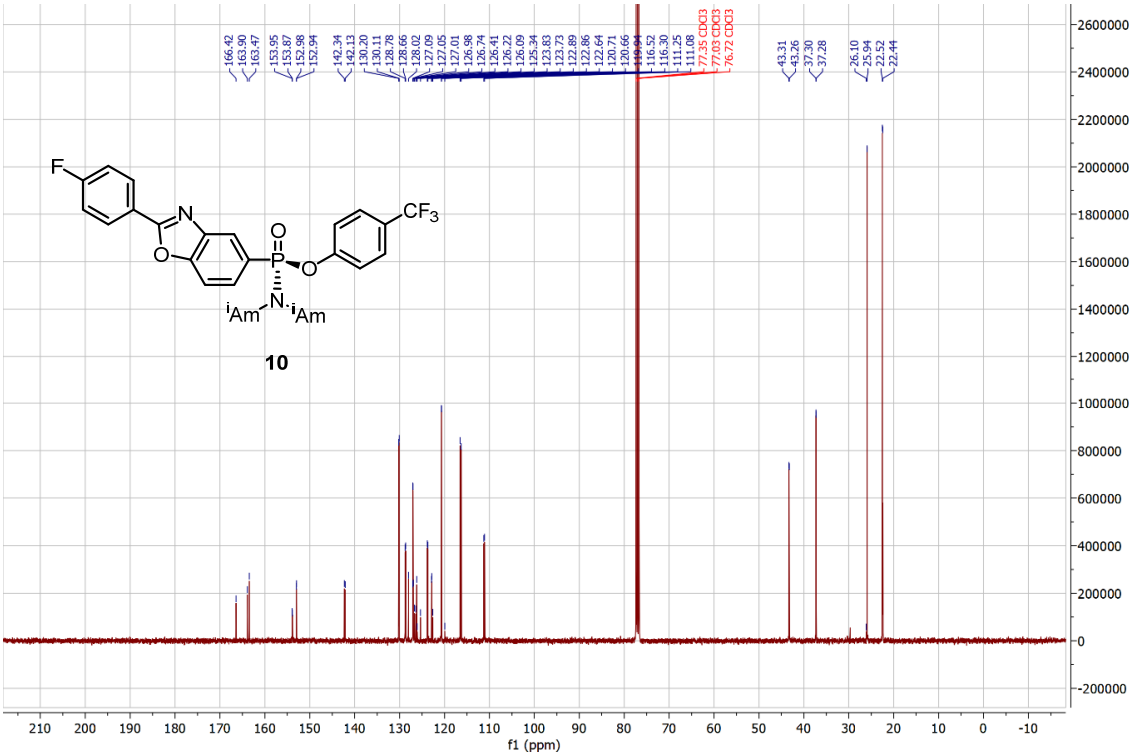
^{31}P NMR


37.42
Me
O
P
Ph
OMe
Me
Me
8d
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

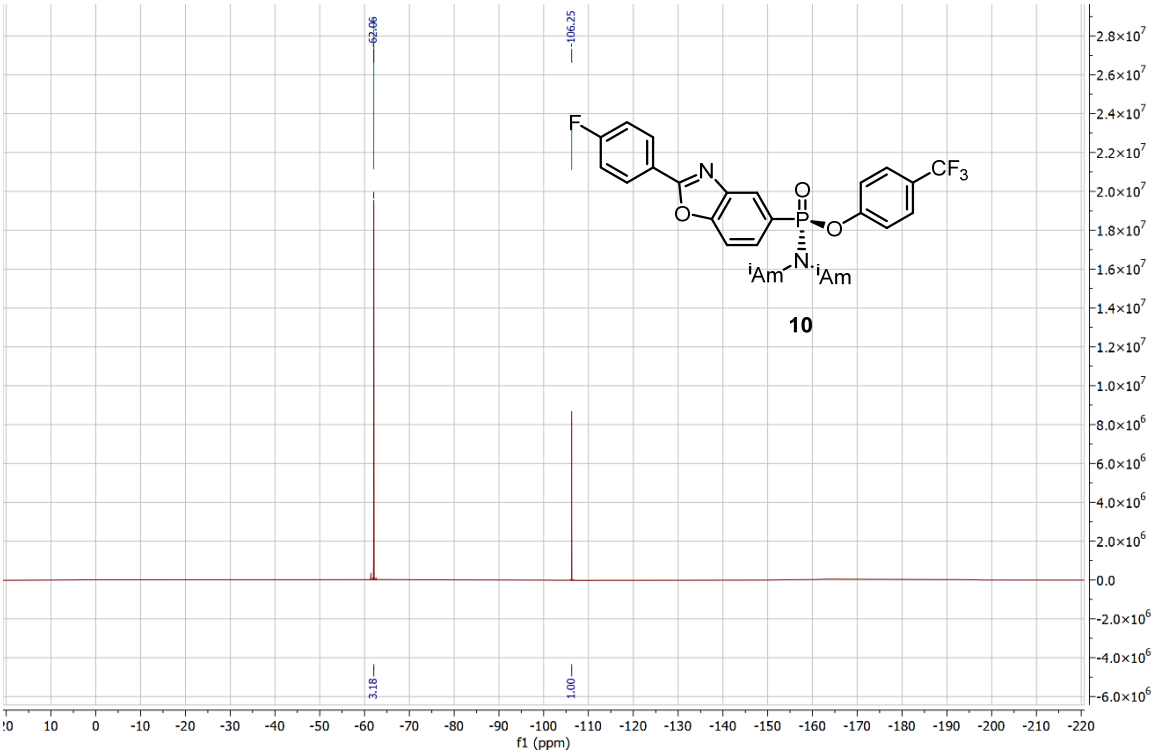
^{1}H NMR



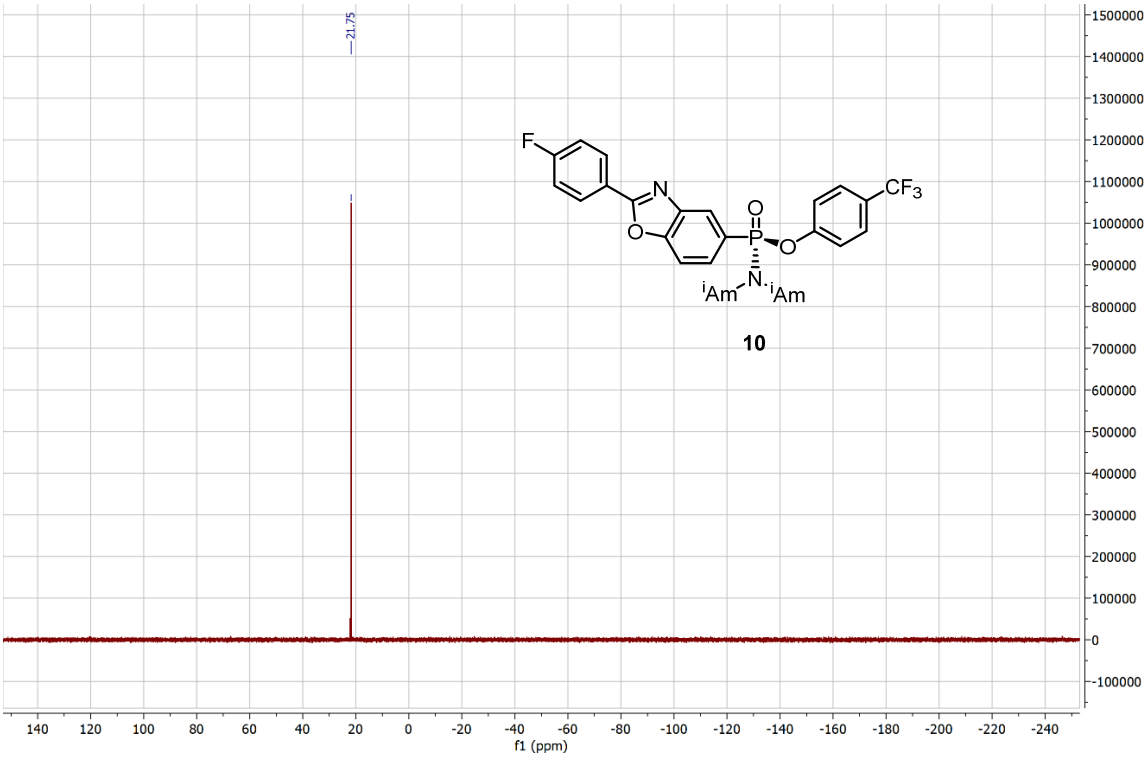
^{13}C NMR



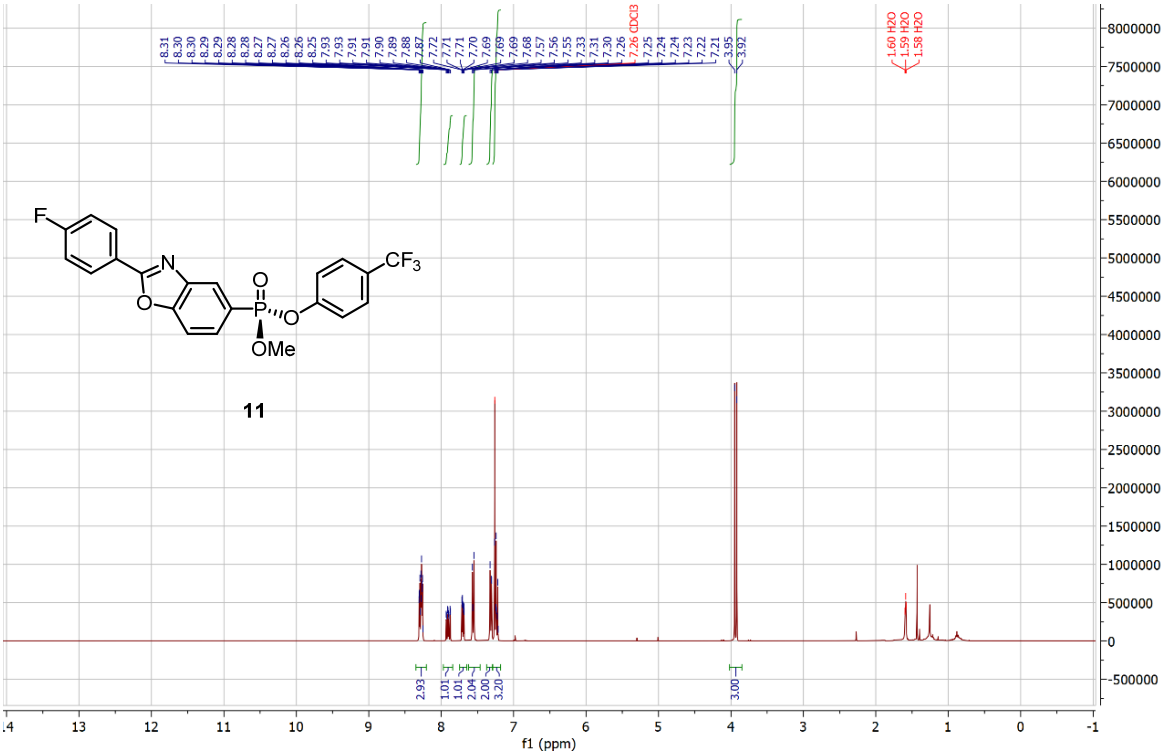
^{19}F NMR



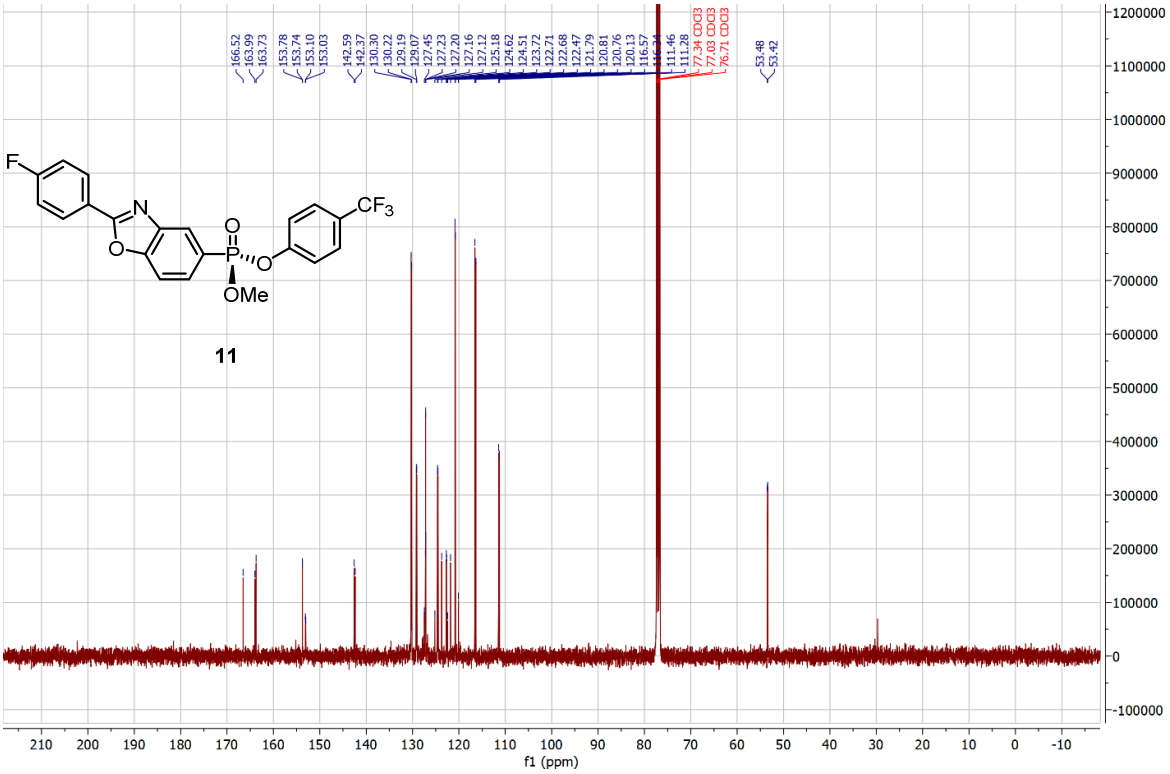
^{31}P NMR



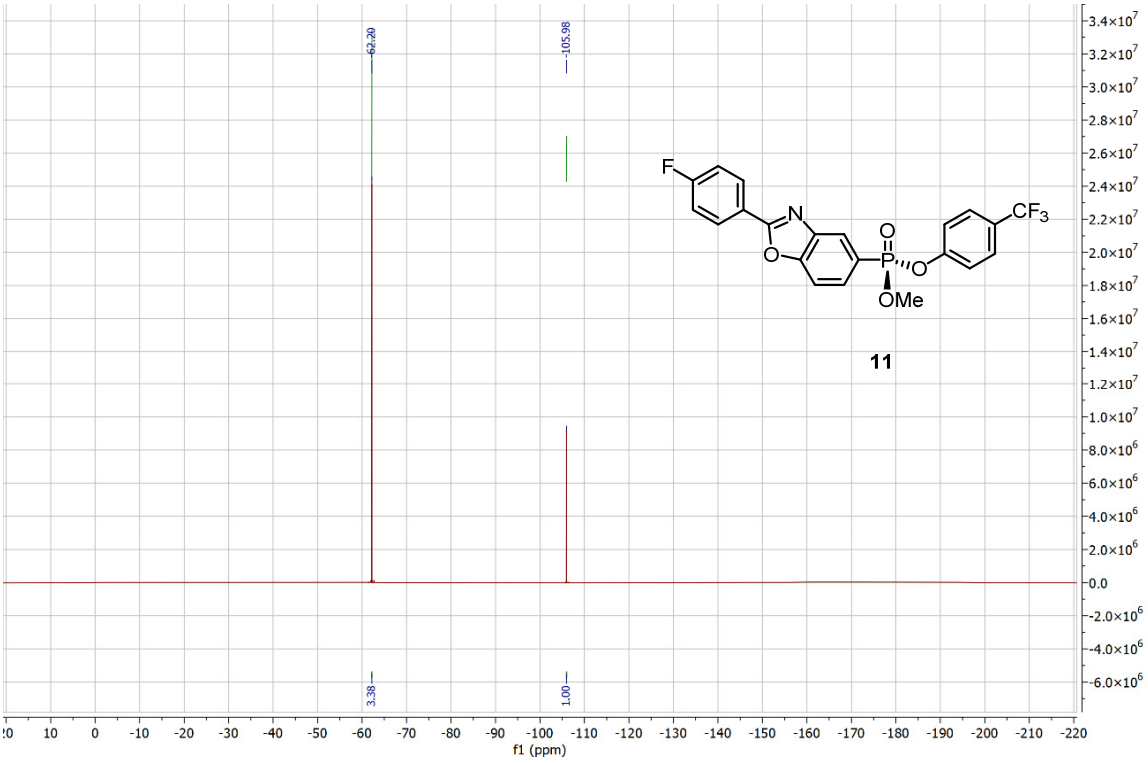
^{1}H NMR



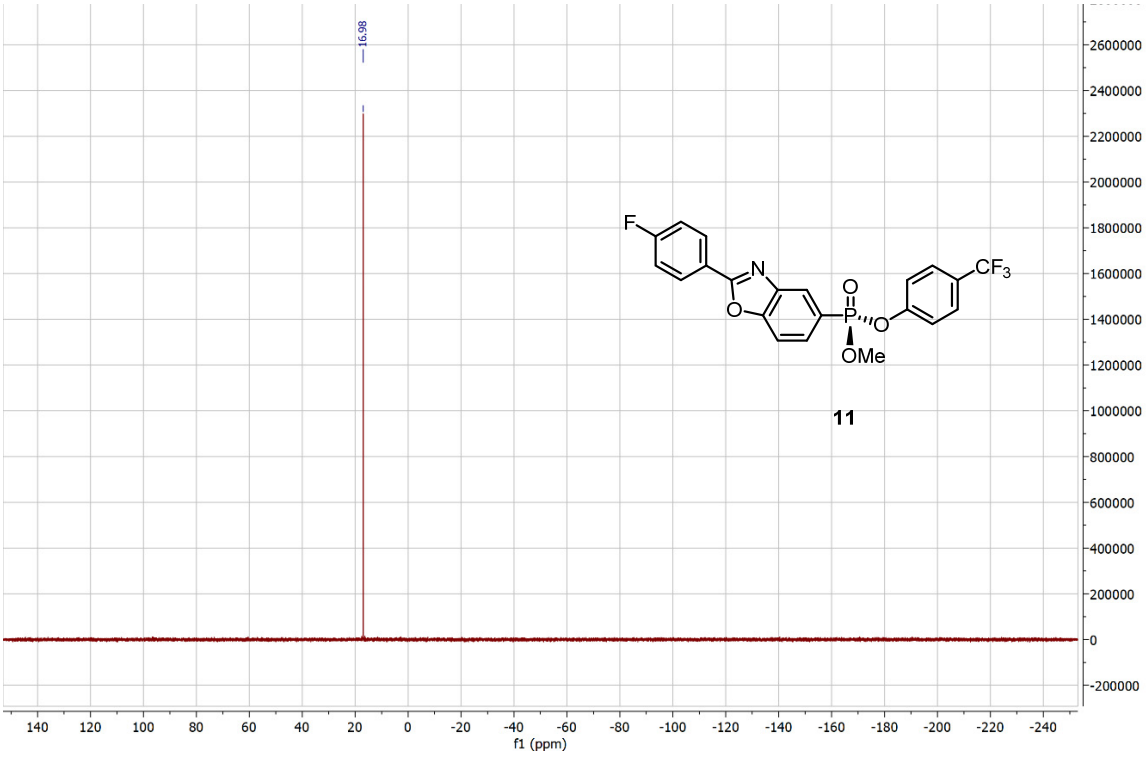
^{13}C NMR



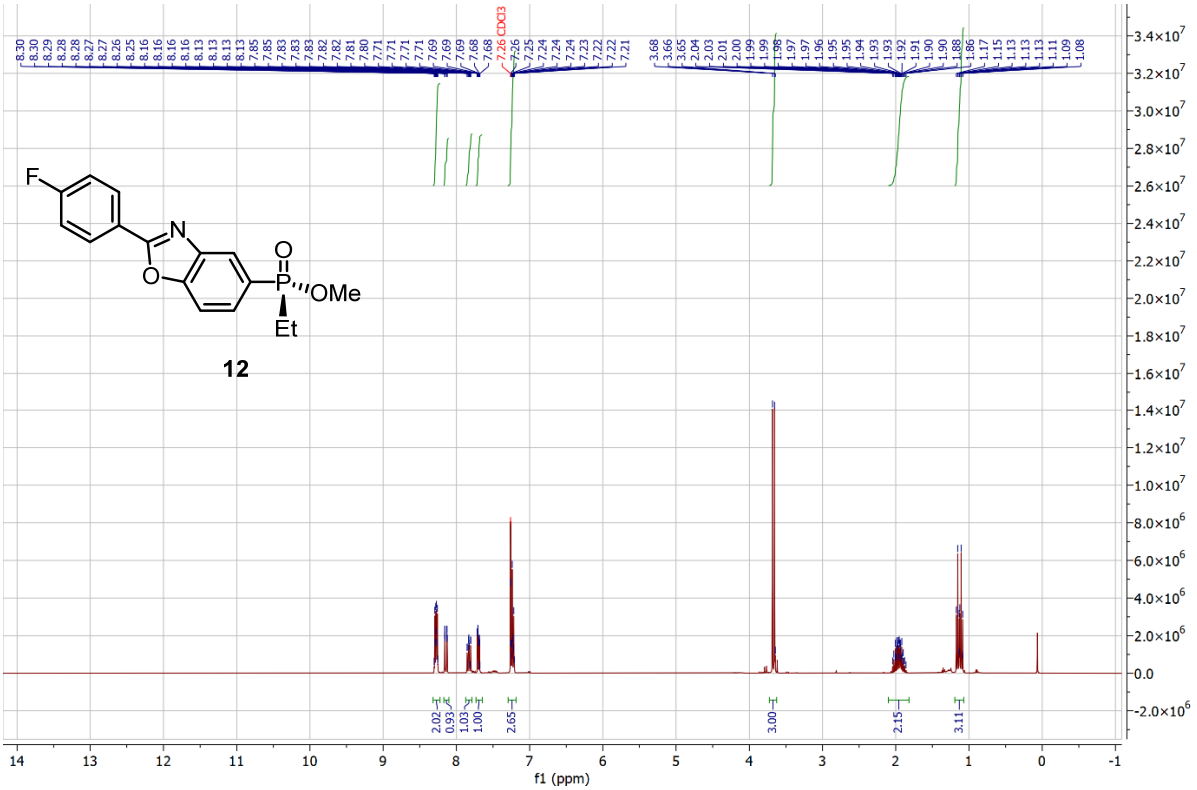
^{19}F NMR



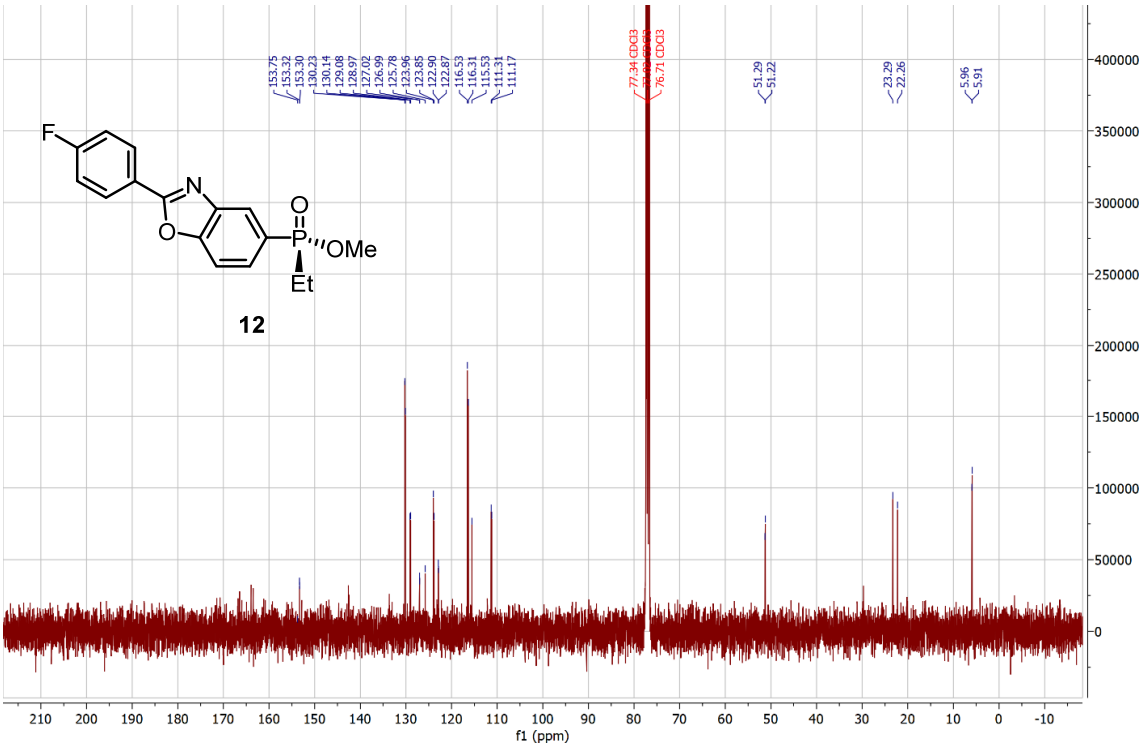
^{31}P NMR



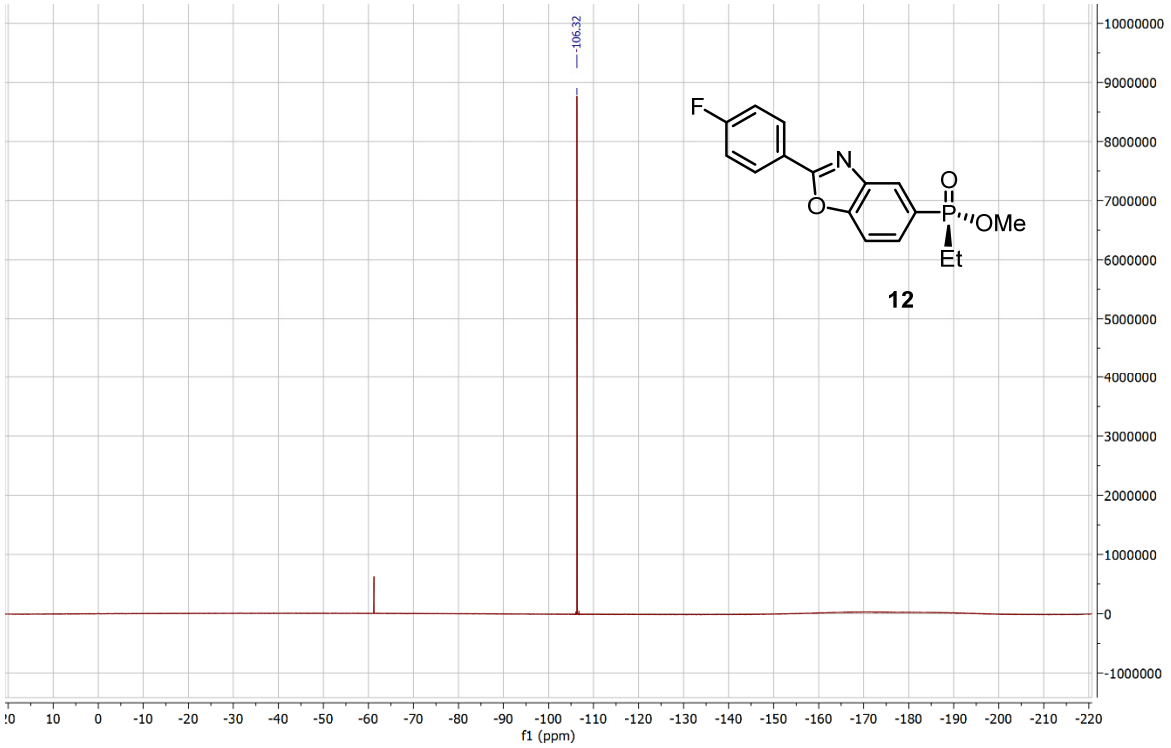
^{1}H NMR



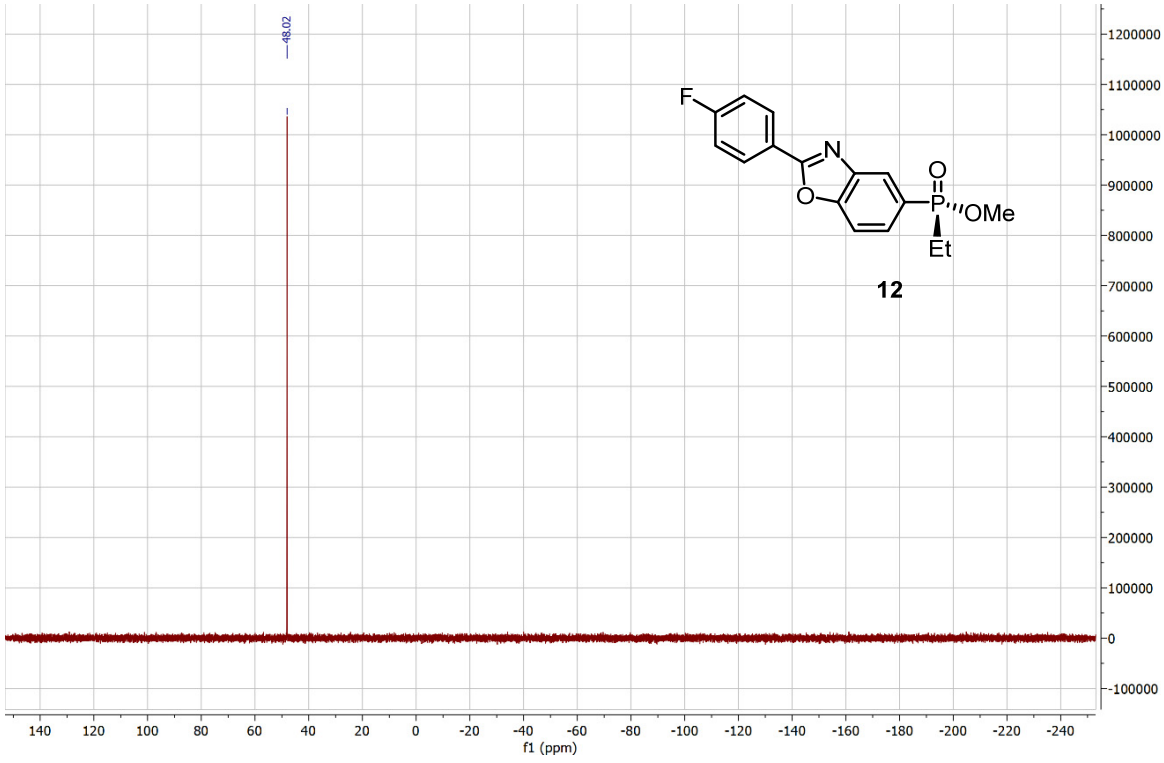
^{13}C NMR



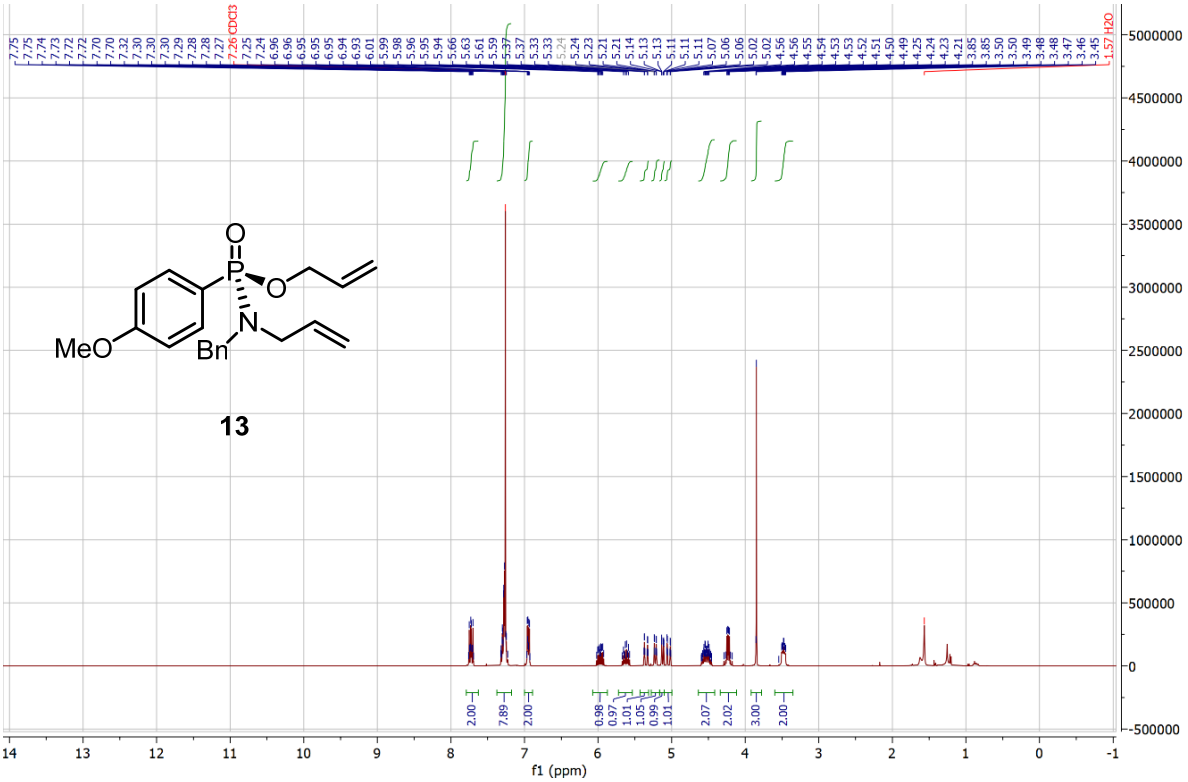
^{19}F NMR



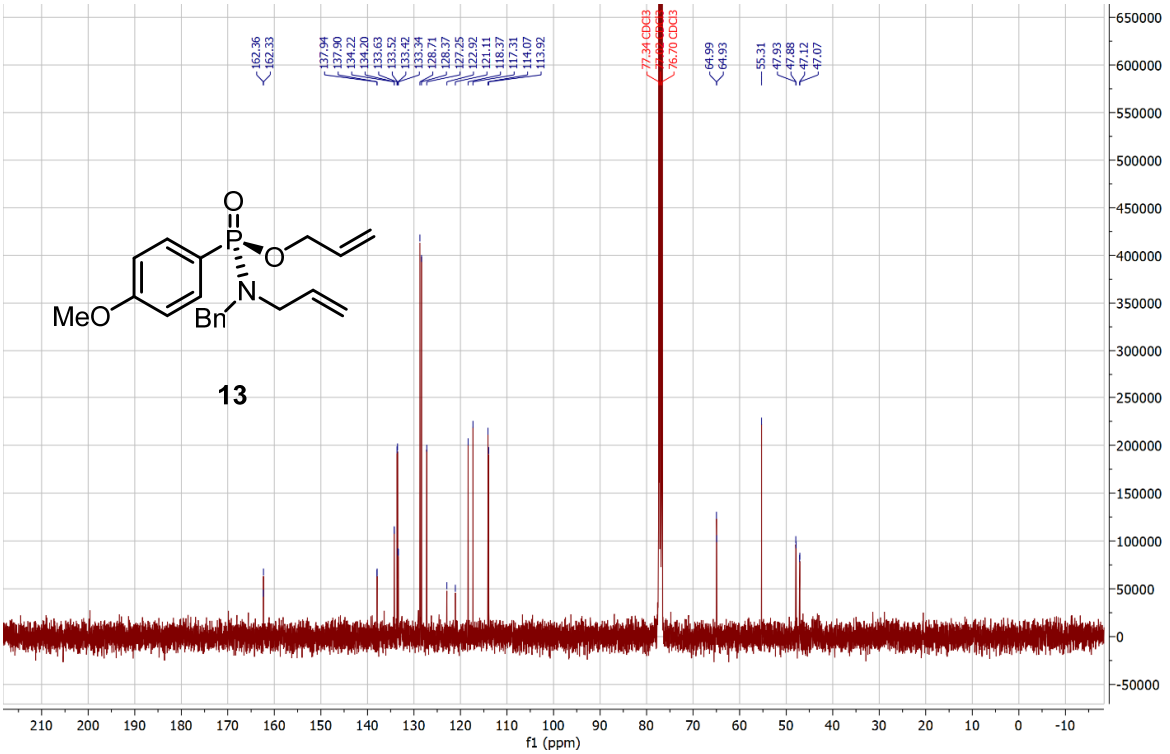
^{31}P NMR



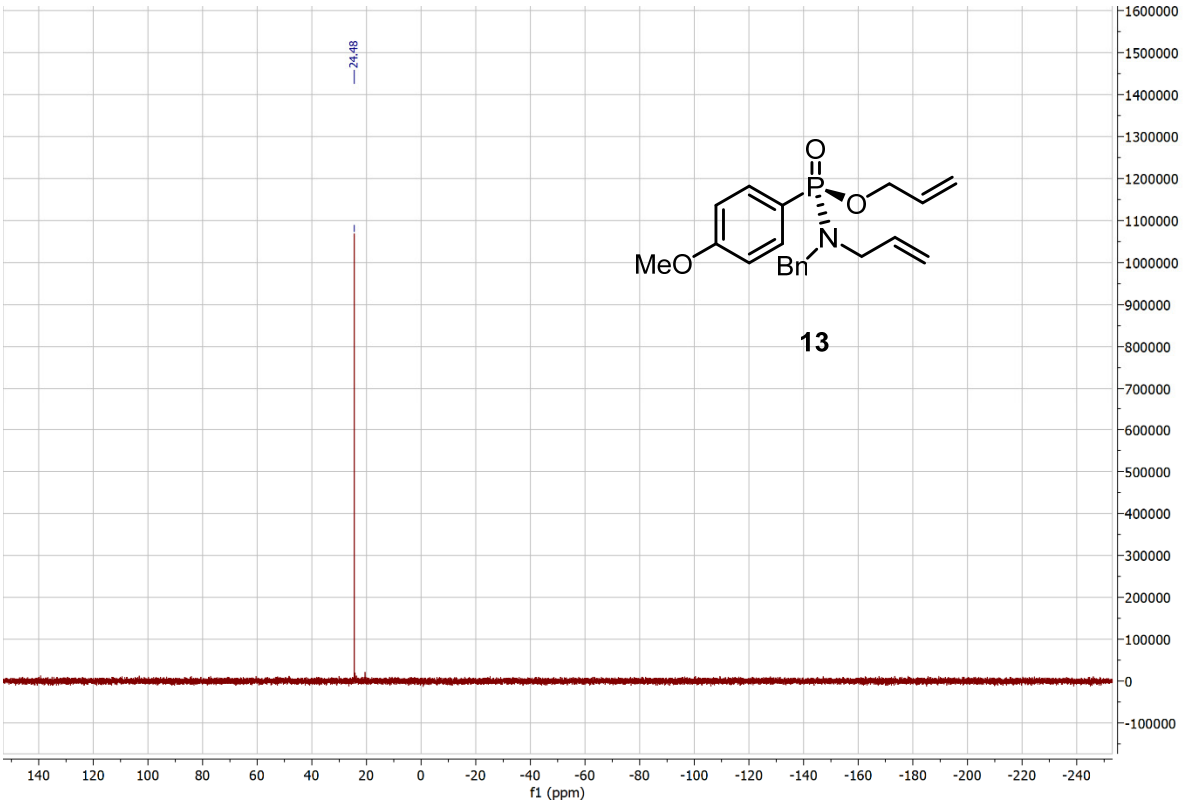
^{1}H NMR



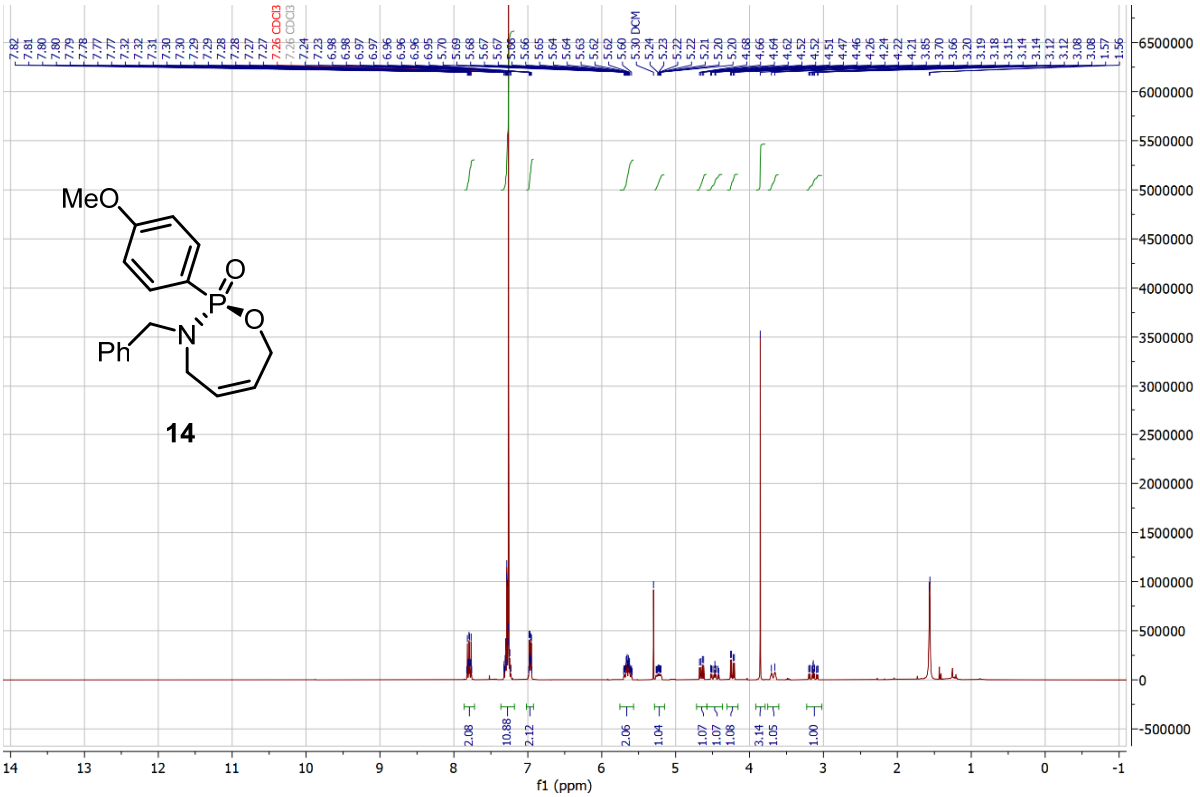
^{13}C NMR



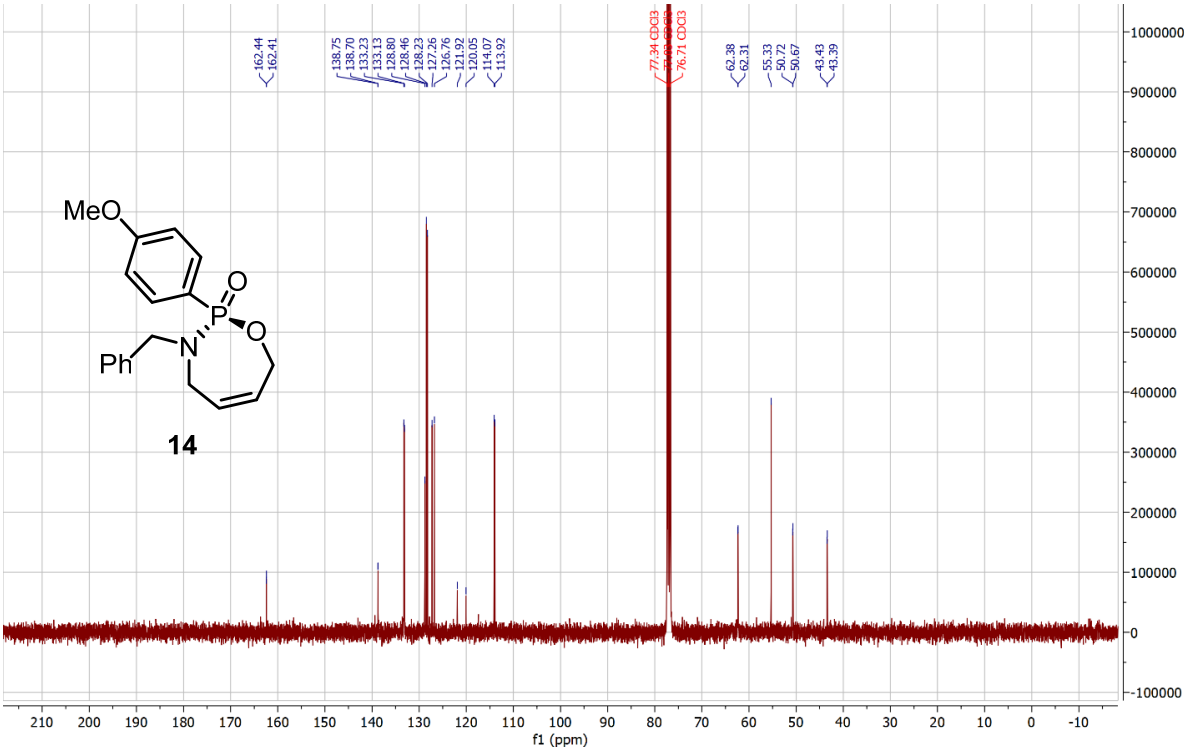
^{31}P NMR



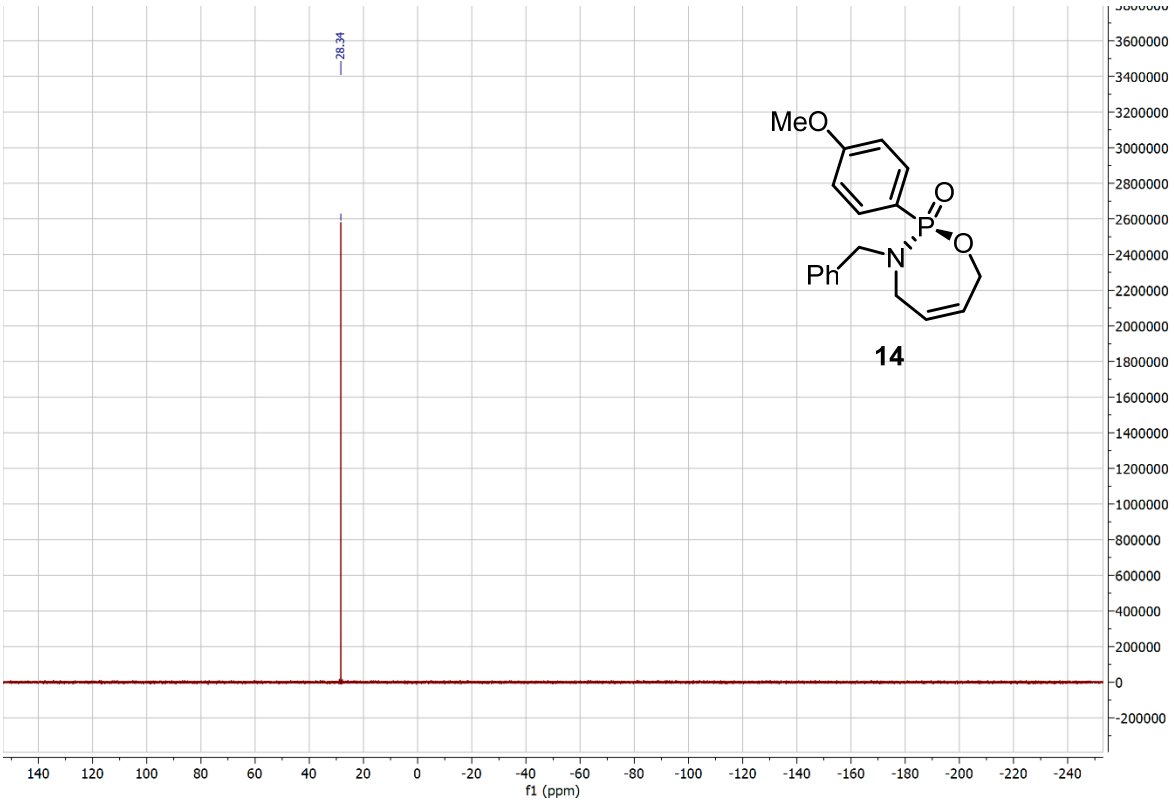
^{1}H NMR



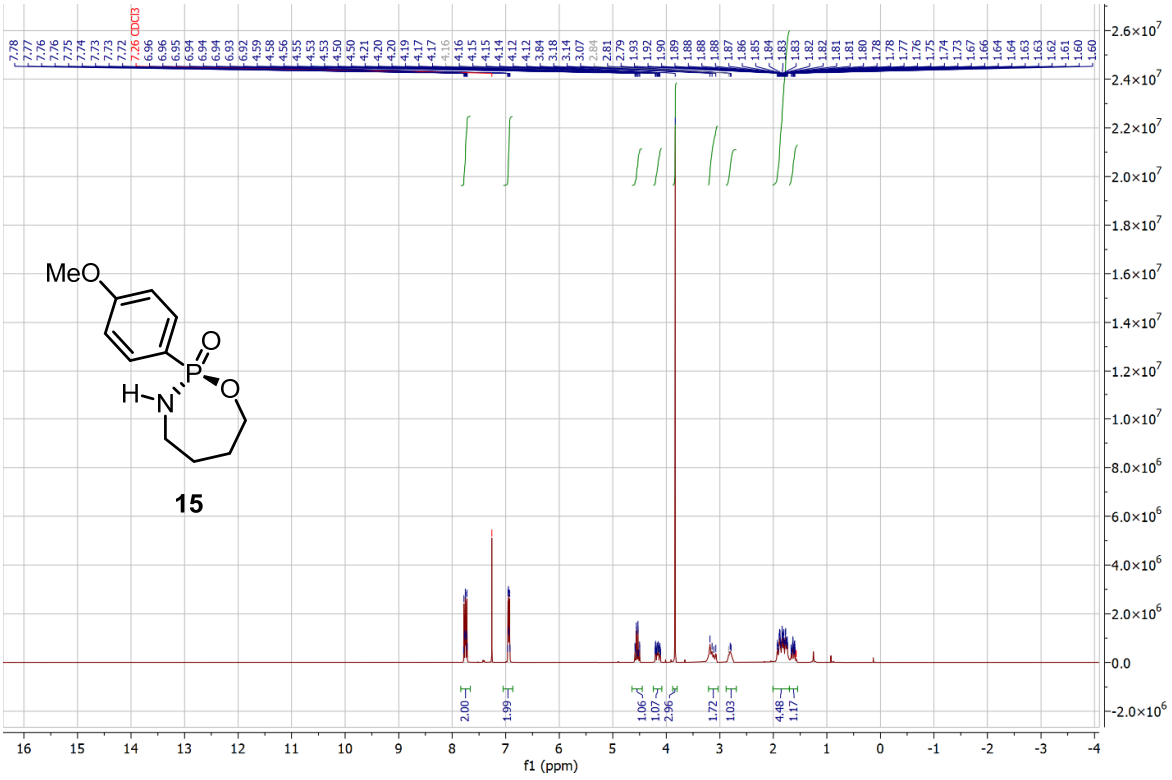
^{13}C NMR



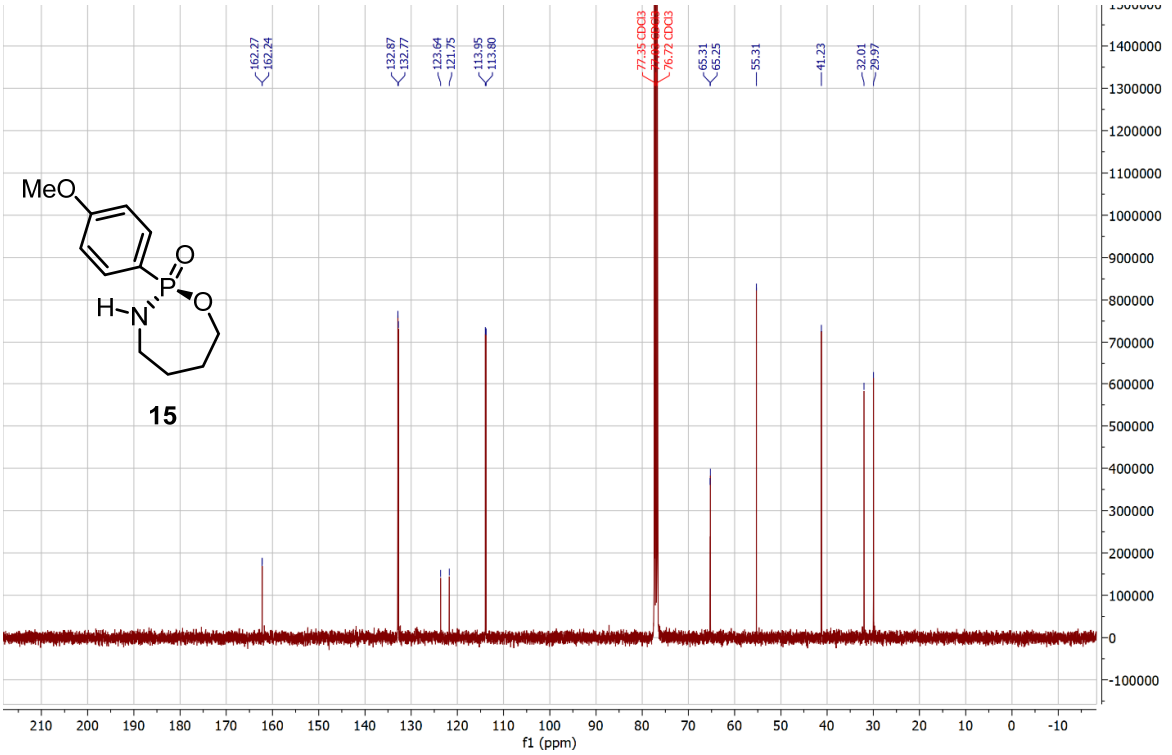
^{31}P NMR


28.34
MeO
O
P
O
N
Ph
14
3600000
3400000
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

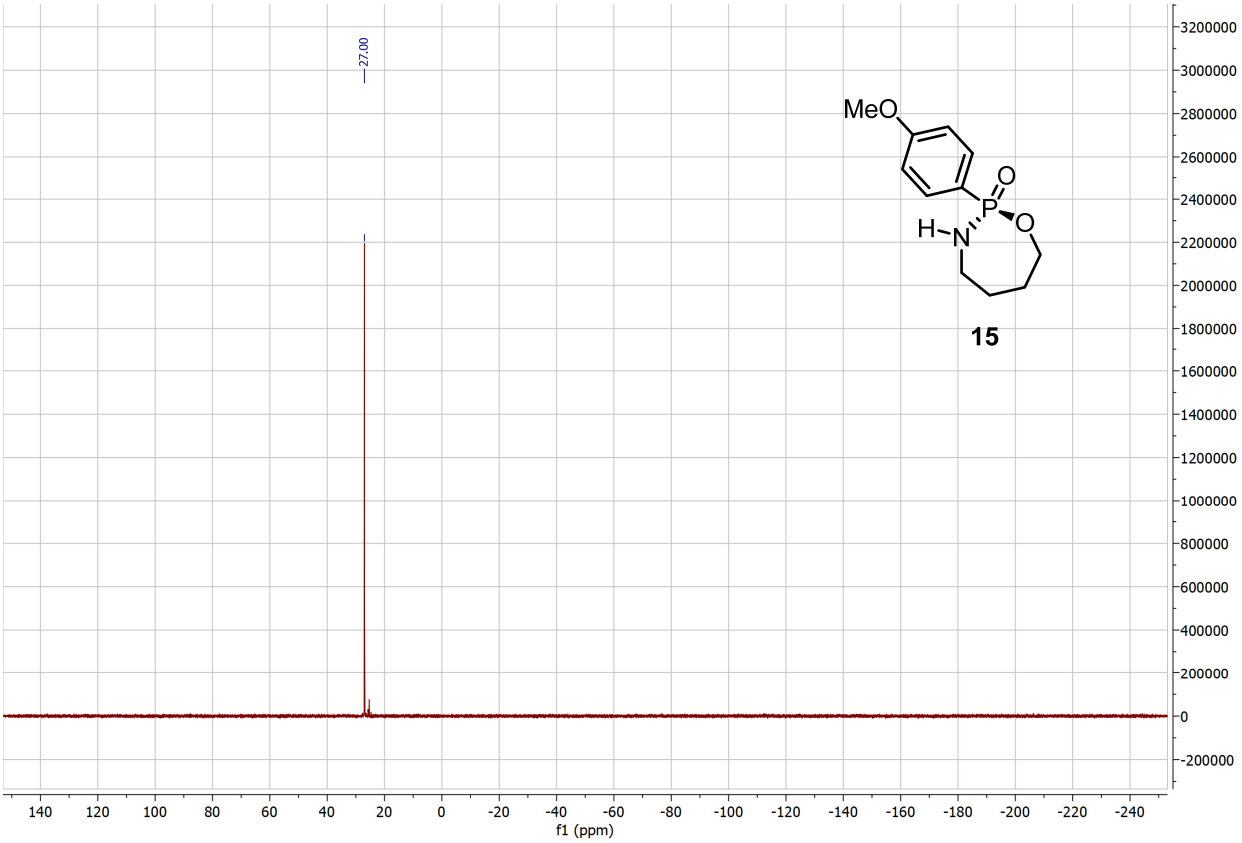
^{1}H NMR



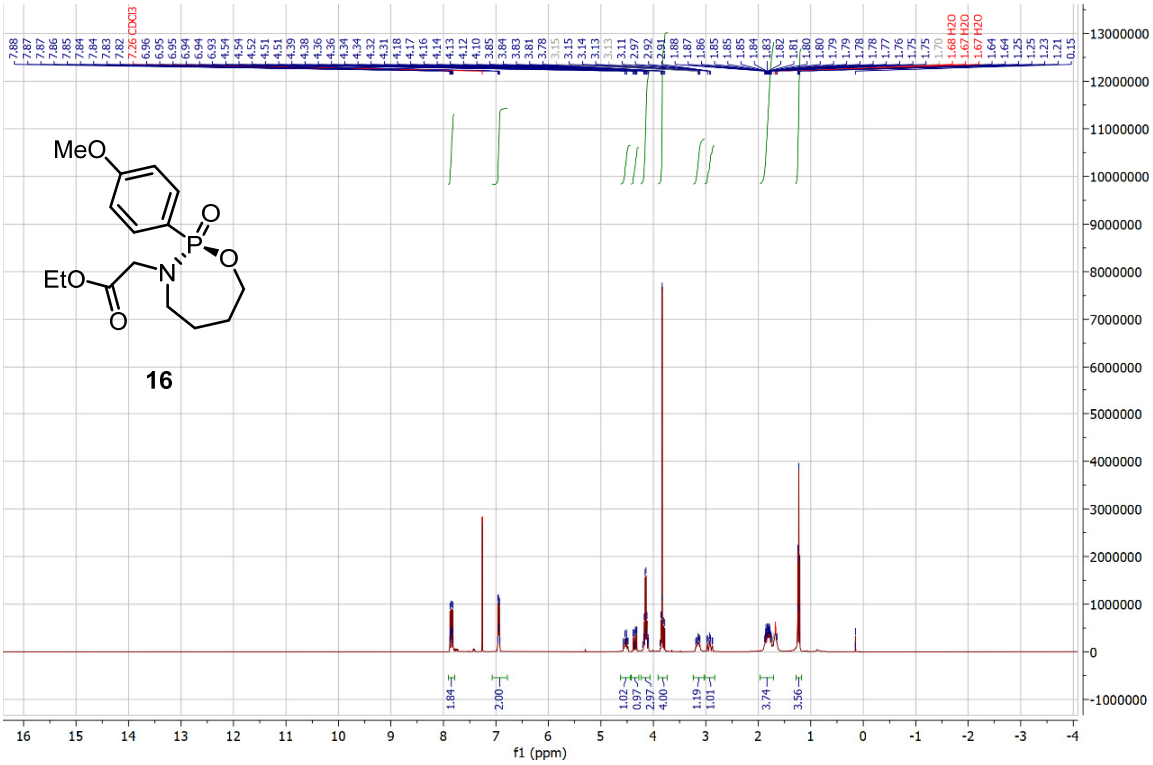
^{13}C NMR



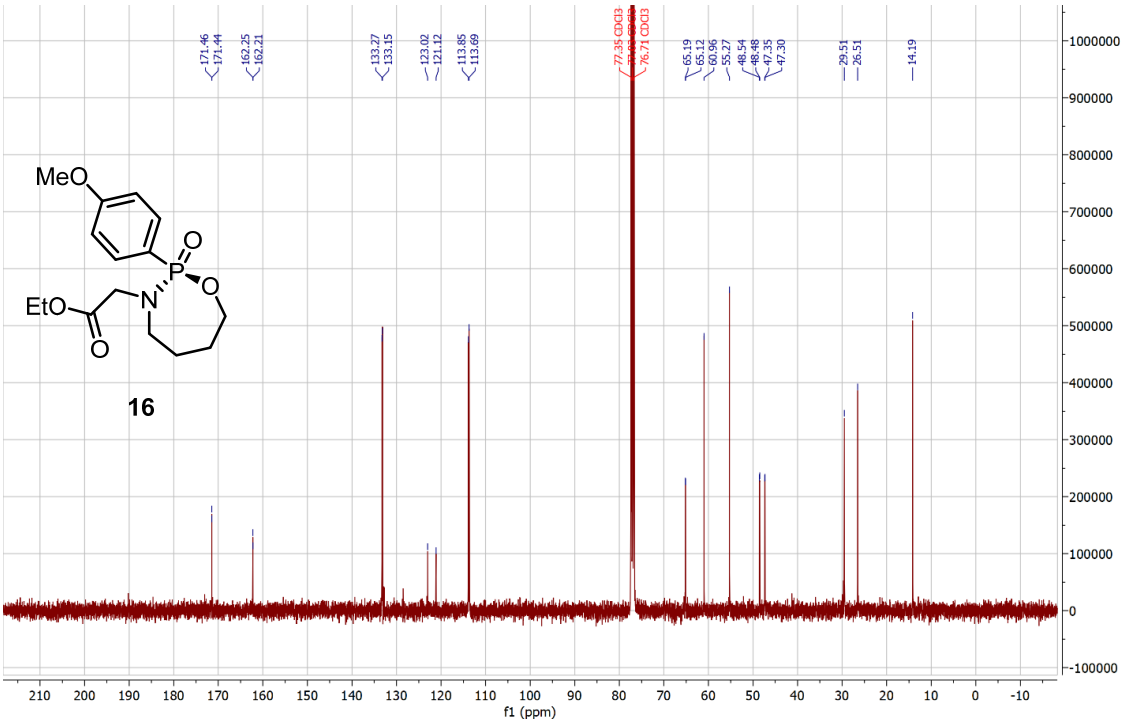
^{31}P NMR


27.00
MeO
O
P
O
H
N
15
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

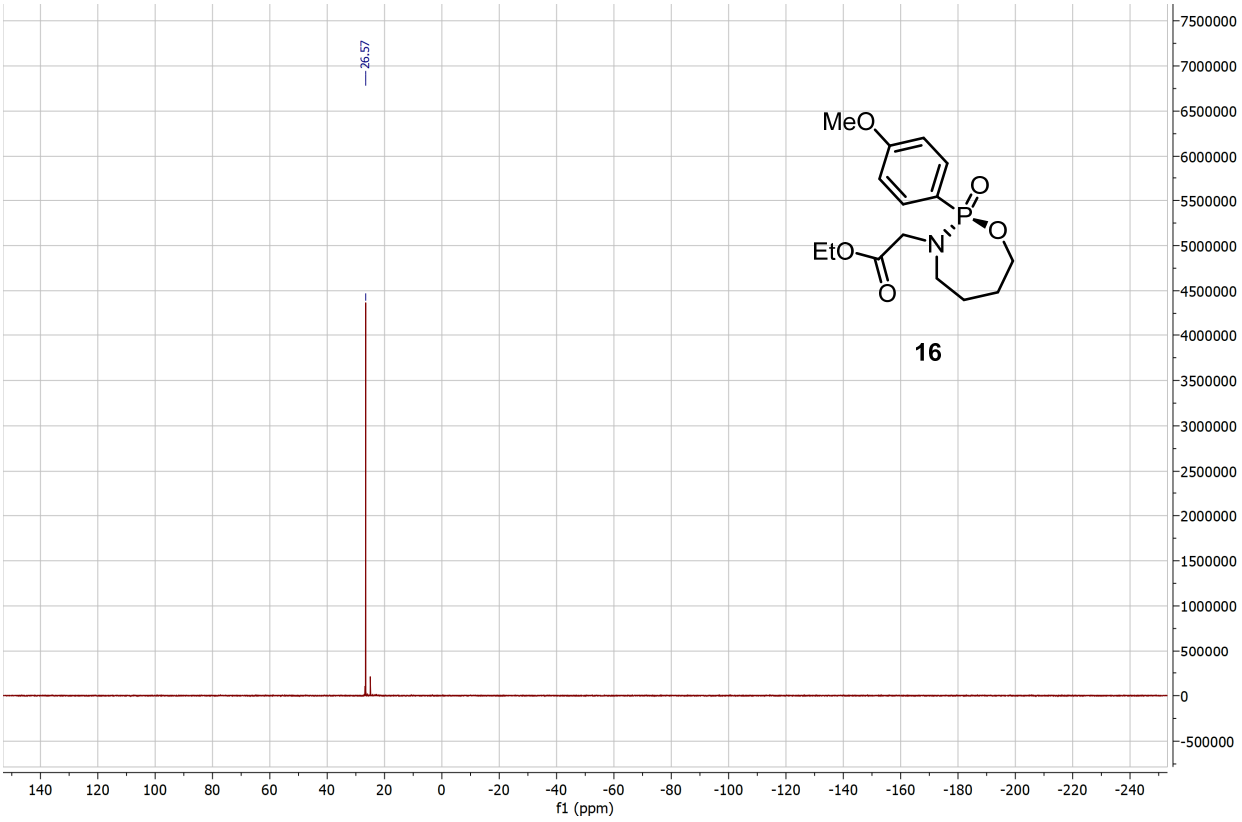
^{1}H NMR



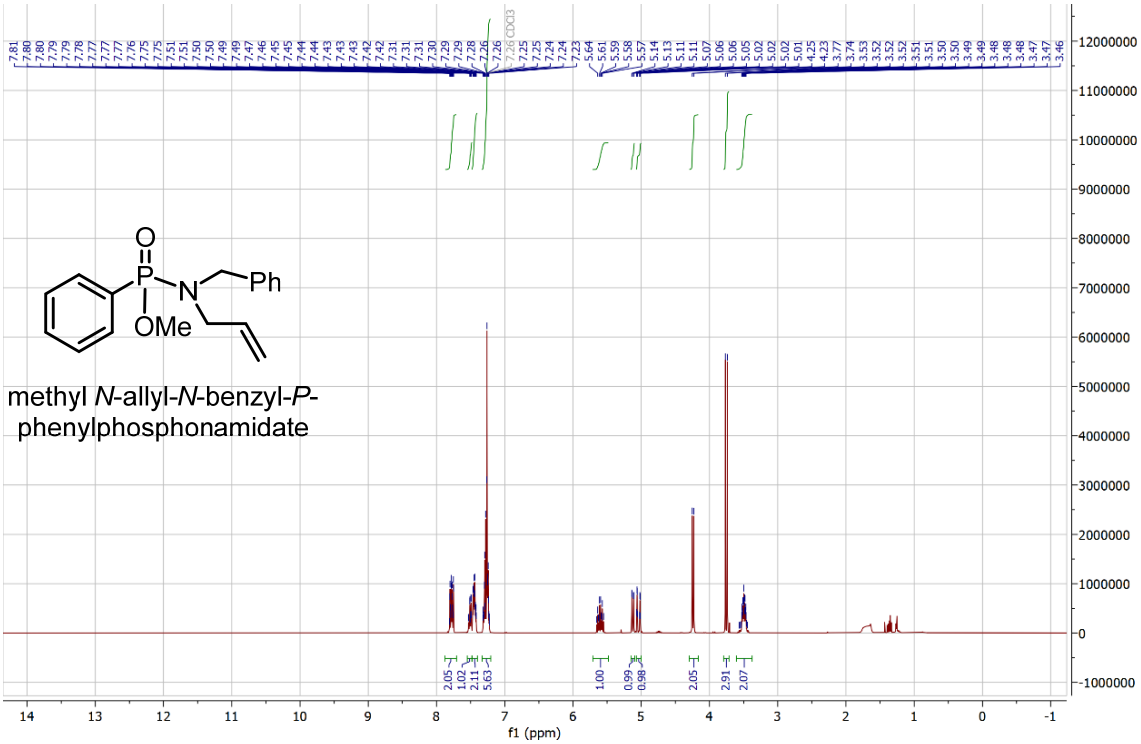
^{13}C NMR



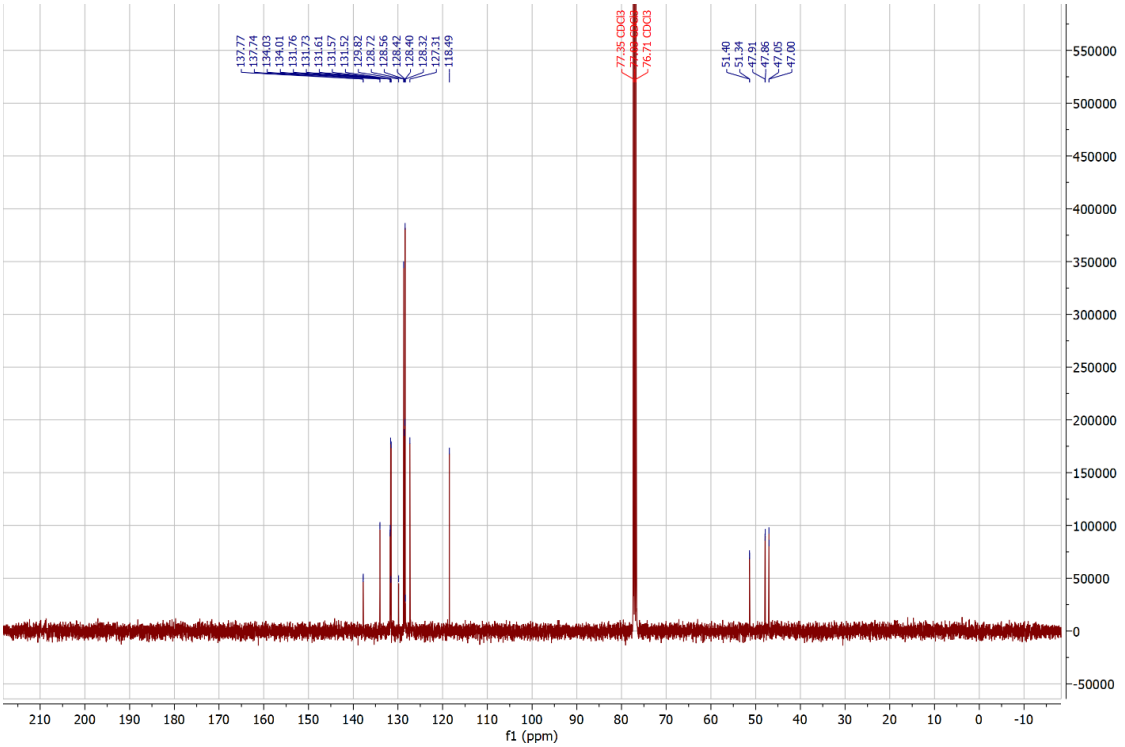
^{31}P NMR


26.57
MeO
O
P
O
N
EtO
O
16
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

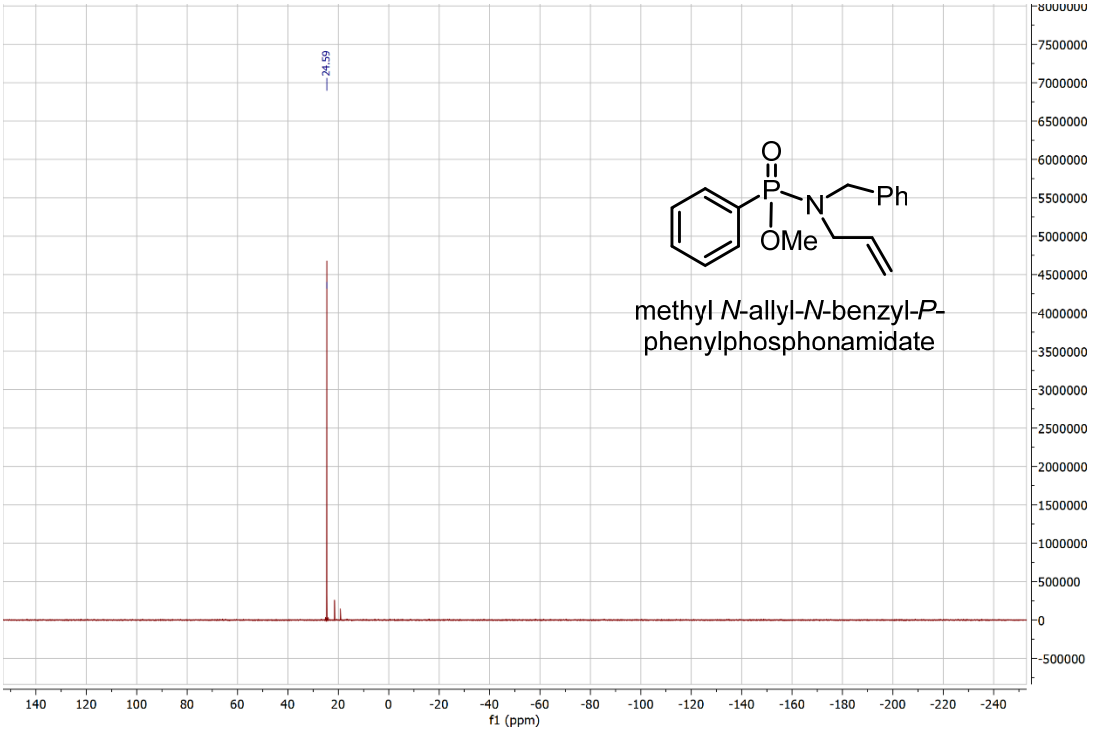
^{1}H NMR



^{13}C NMR



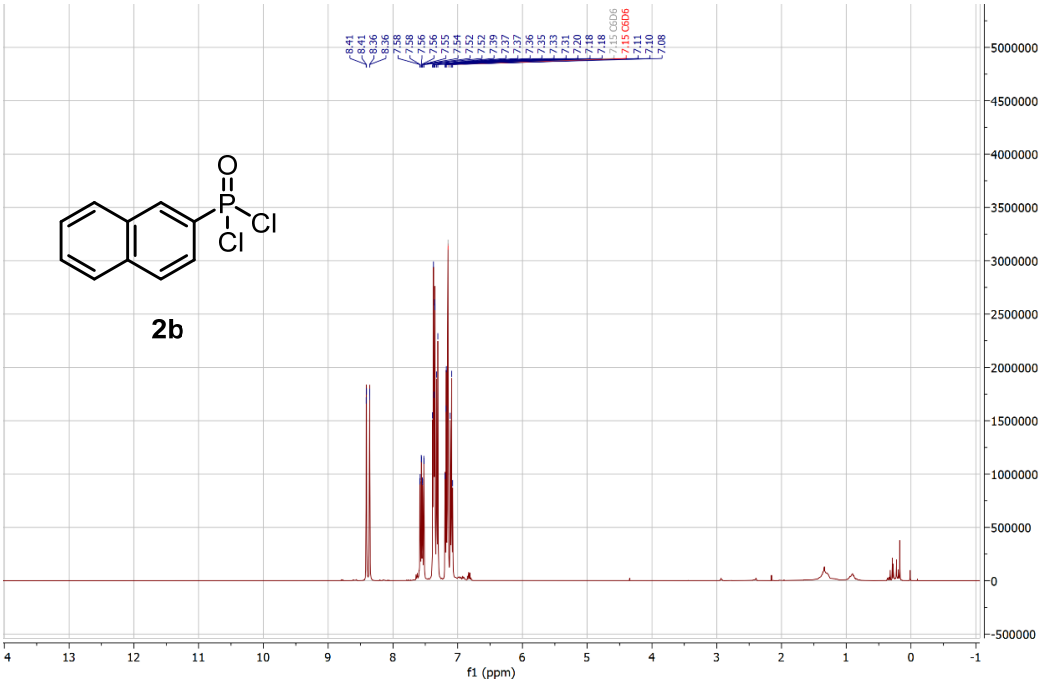
^{31}P NMR


24.59
O
P
N
Ph
OMe
methyl *N*-allyl-*N*-benzyl-*P*-phenylphosphonamidate
f1 (ppm)

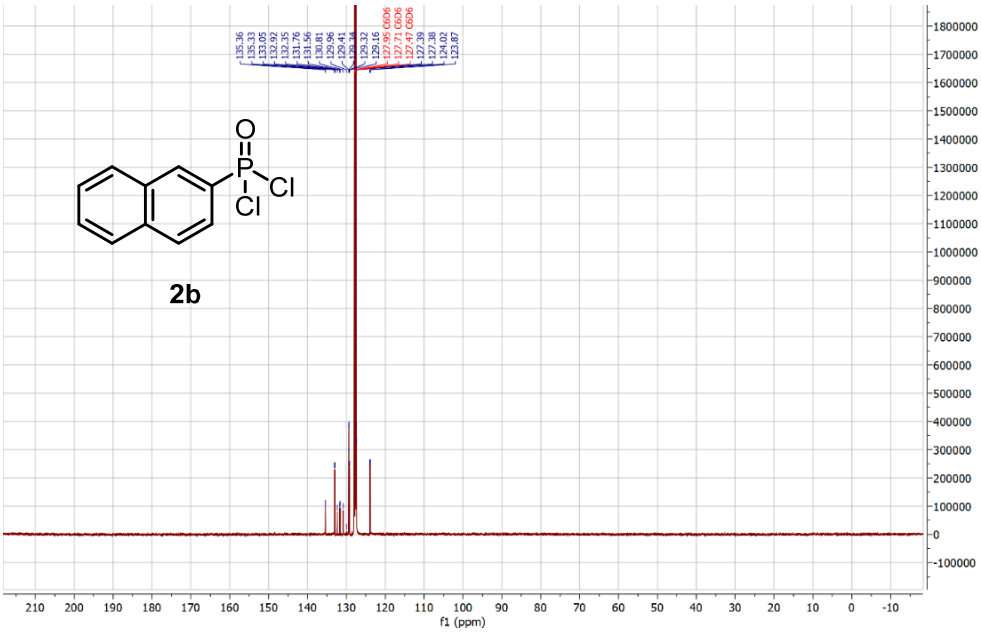
NMR spectra of crude non-commercial phosphonyl dichlorides (2b-f)

**Note: for the purpose of characterization, these compounds were prepared using N,N-dimethylformamide-d7.*

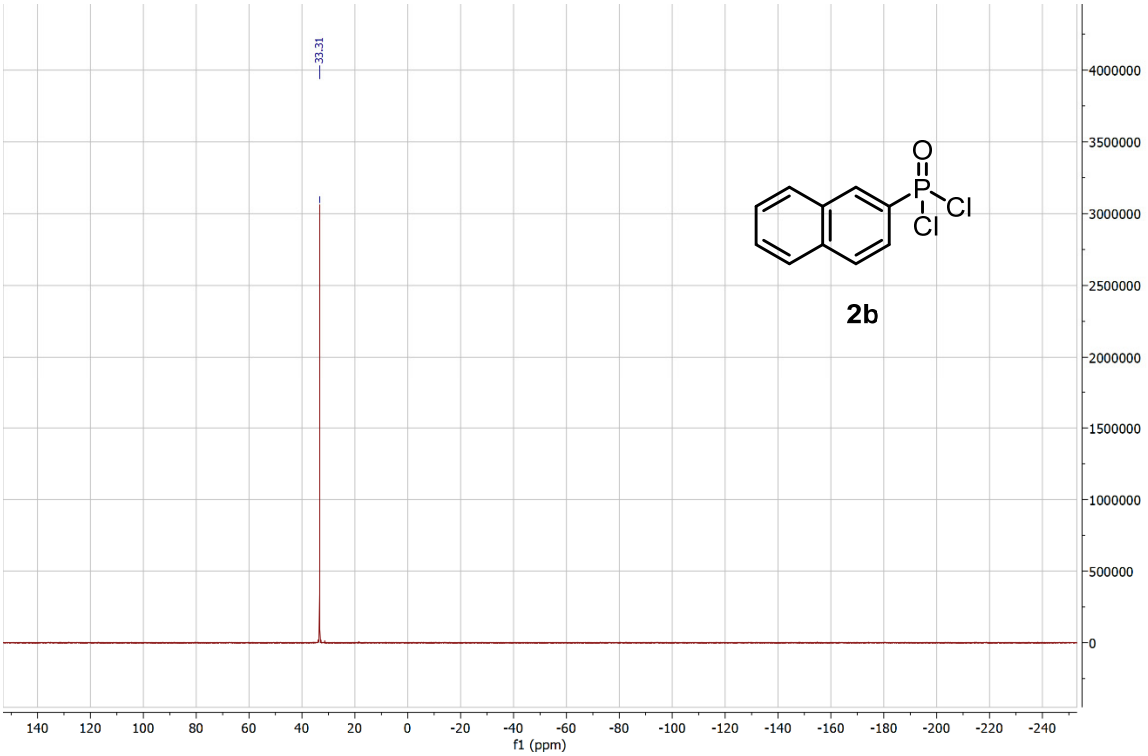
^{1}H NMR



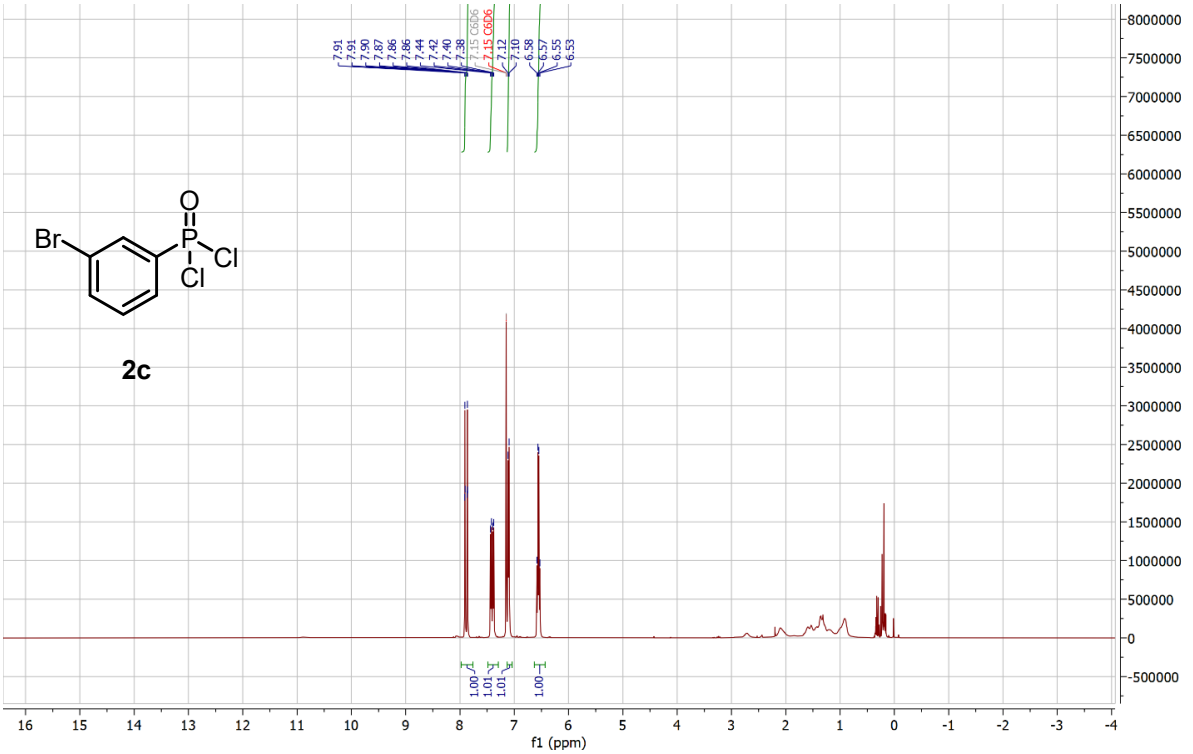
^{13}C NMR



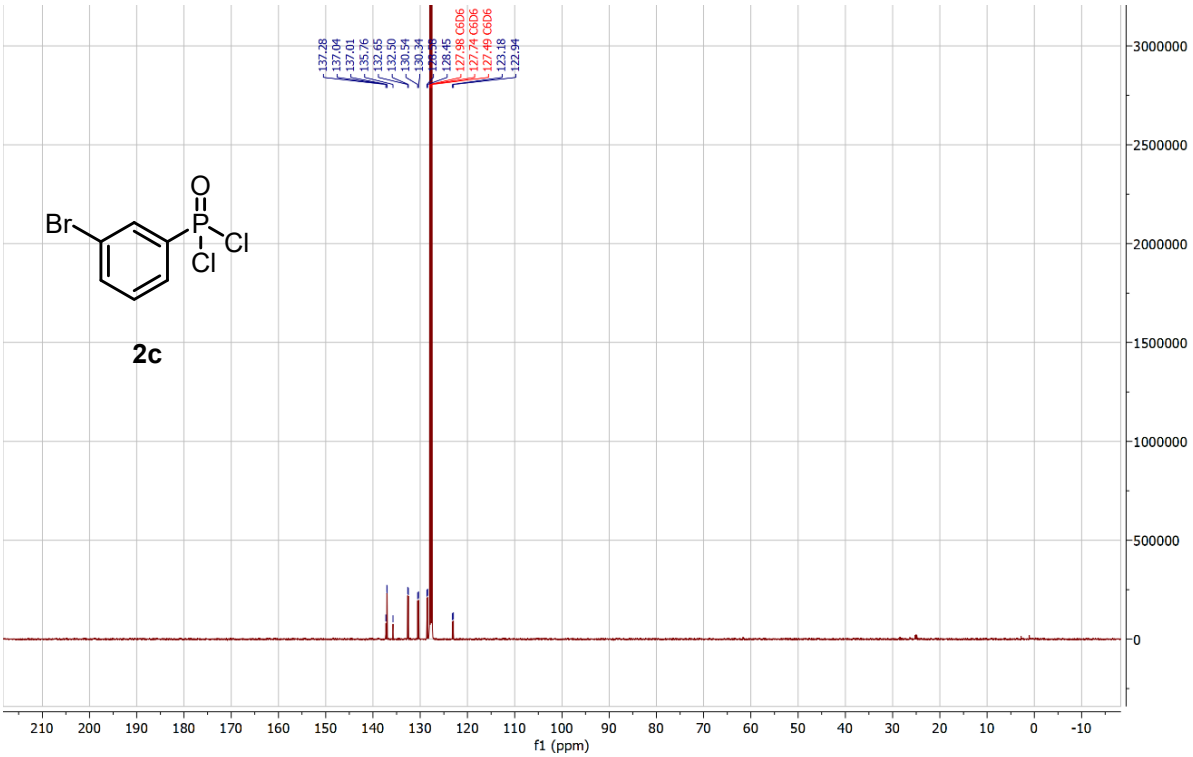
^{31}P NMR


33.31
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)
O
P
Cl
Cl
2b

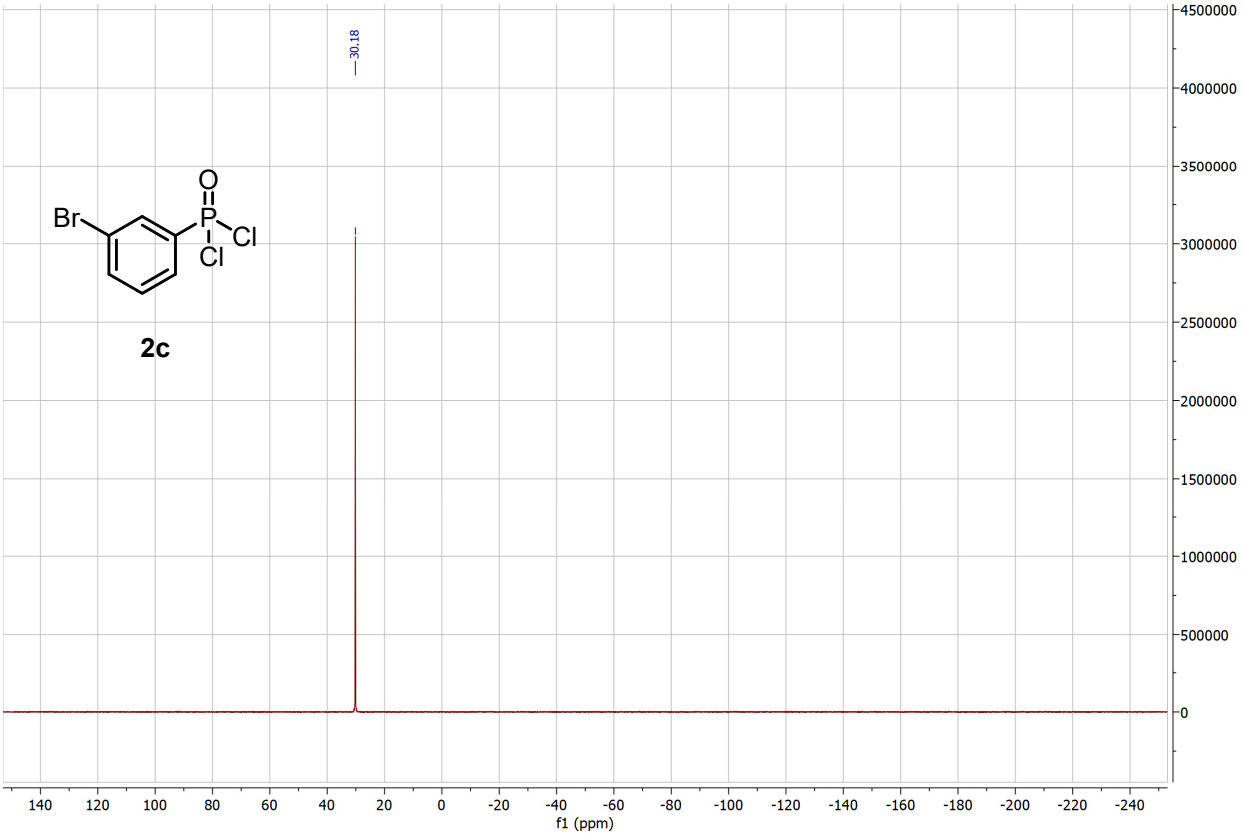
^{1}H NMR



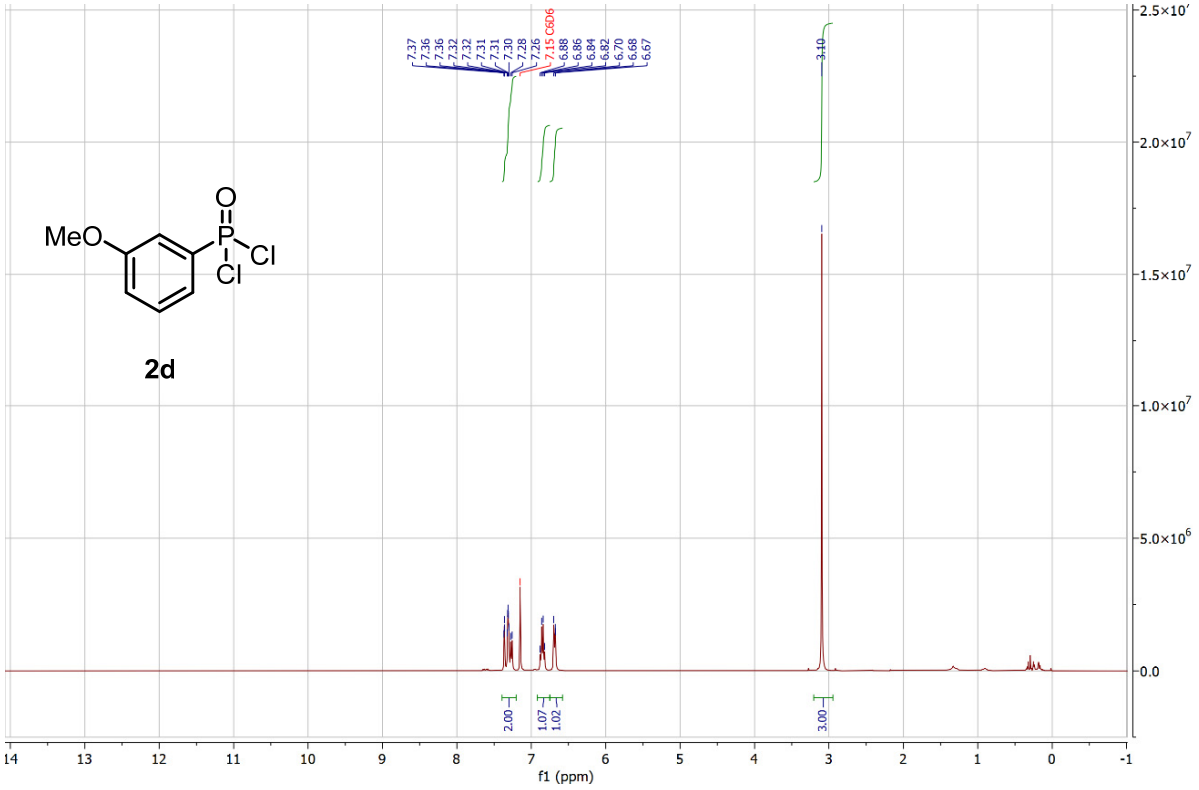
^{13}C NMR



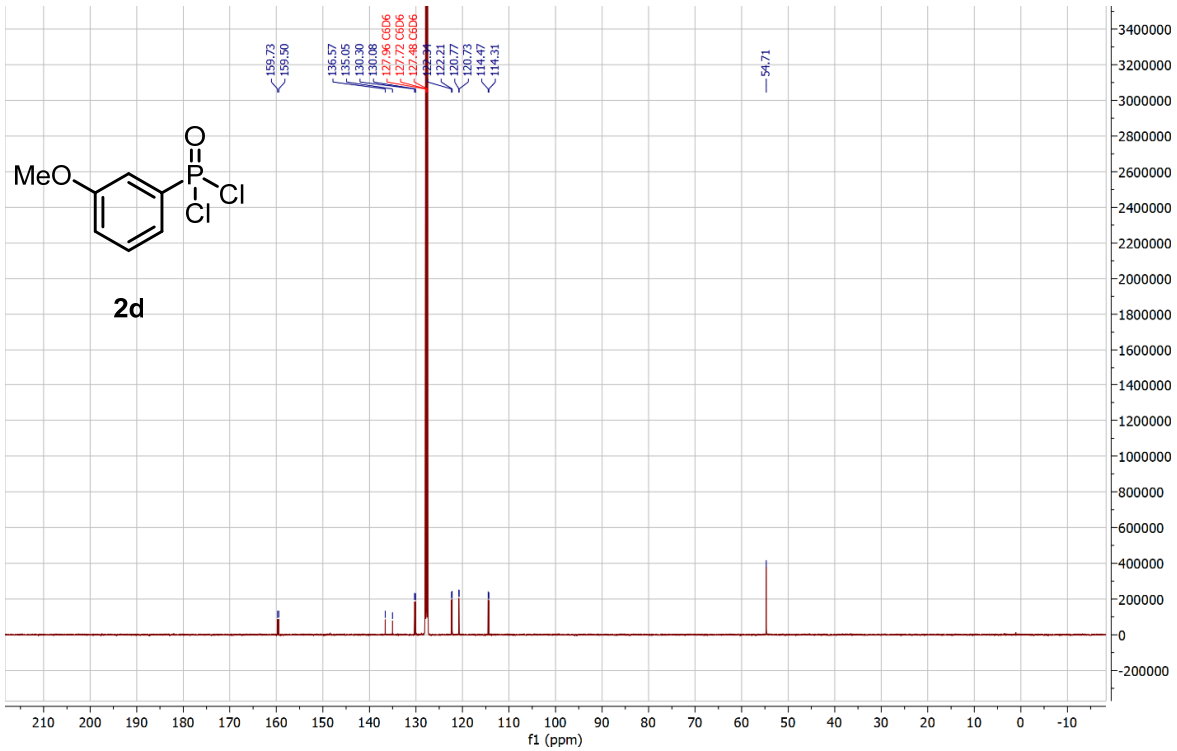
^{31}P NMR


30.18
Br
O
P
Cl
Cl
2c
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

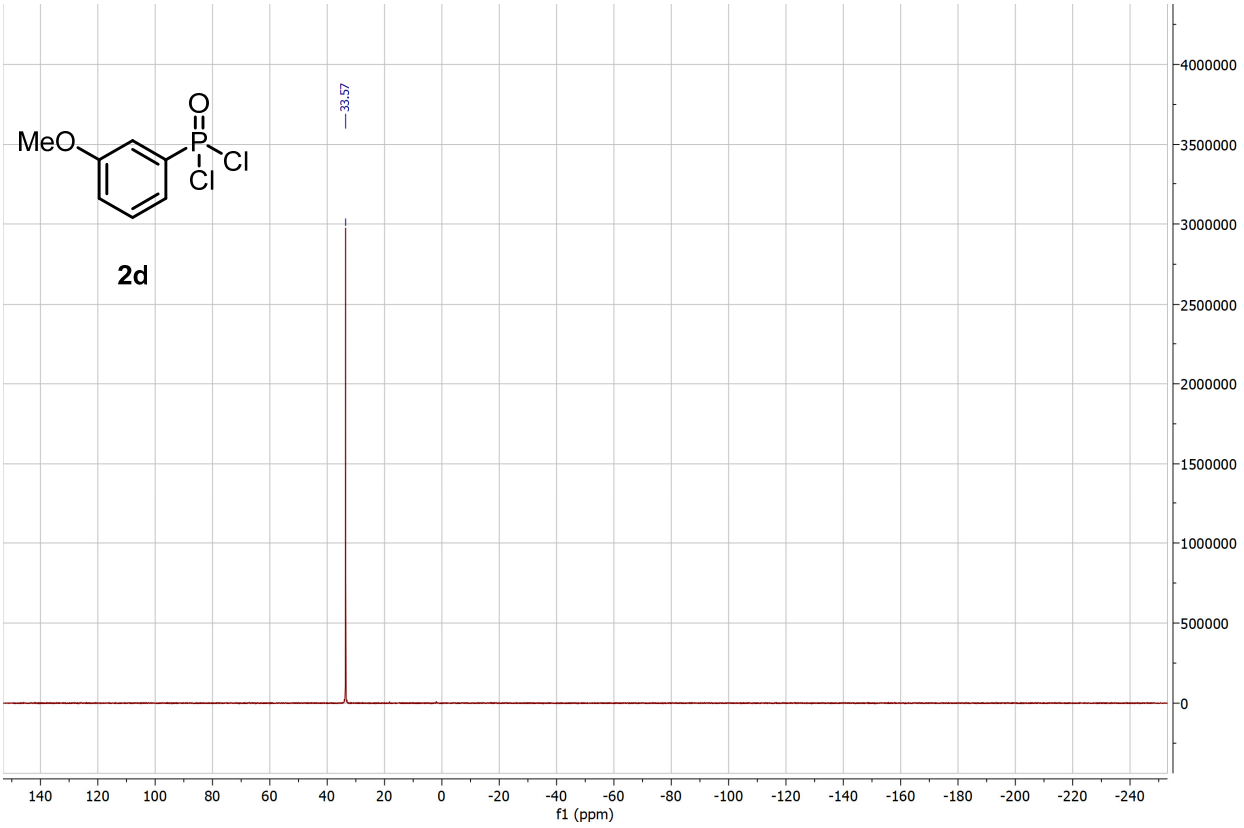
^{1}H NMR



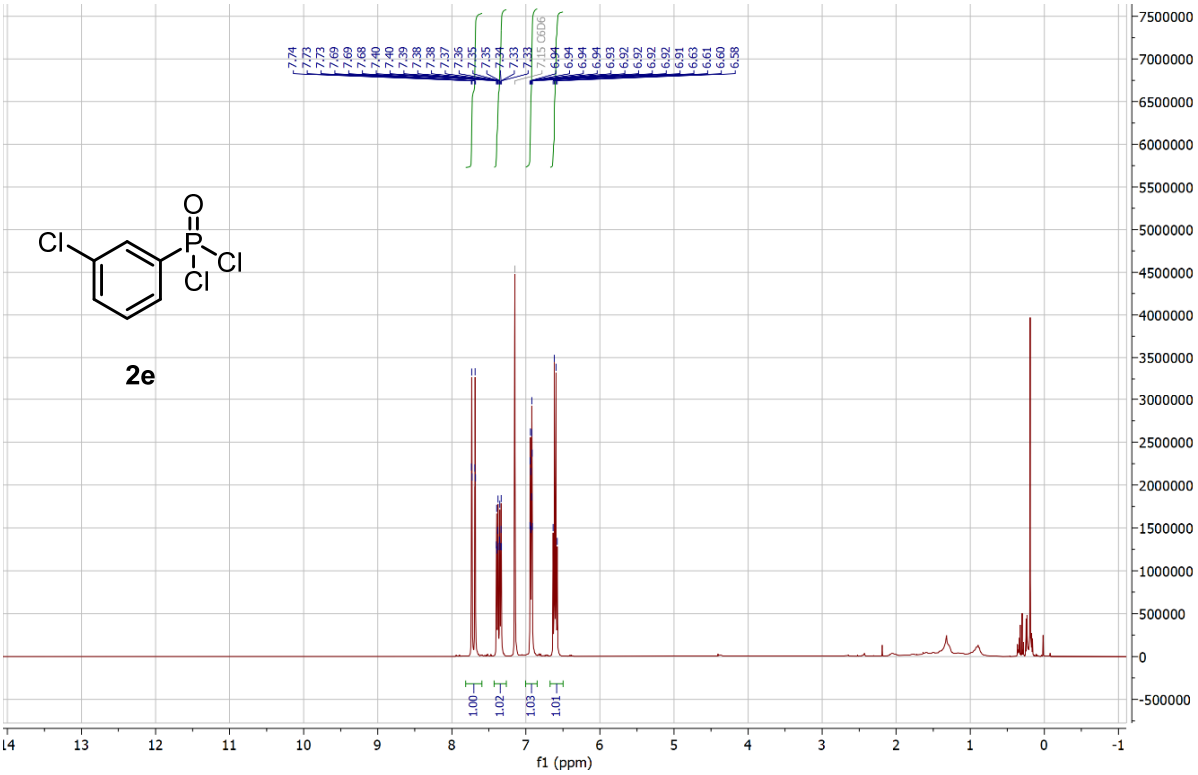
^{13}C NMR



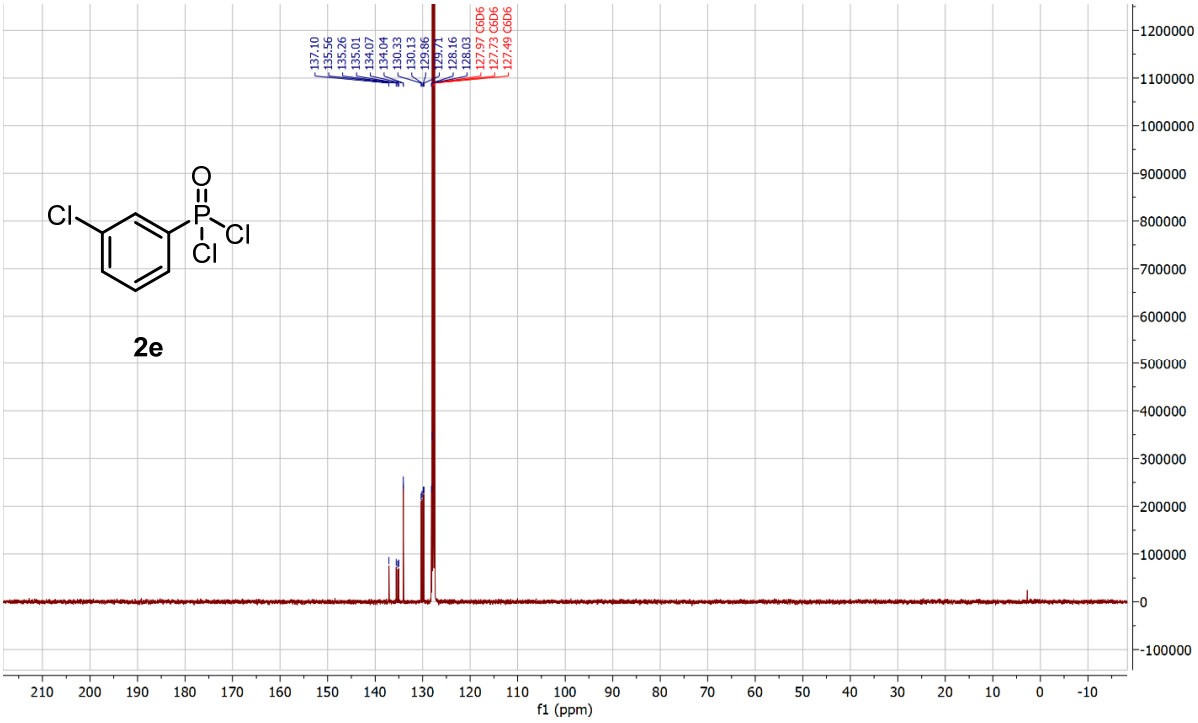
^{31}P NMR


MeO
O
P
Cl
Cl
2d
33.57
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

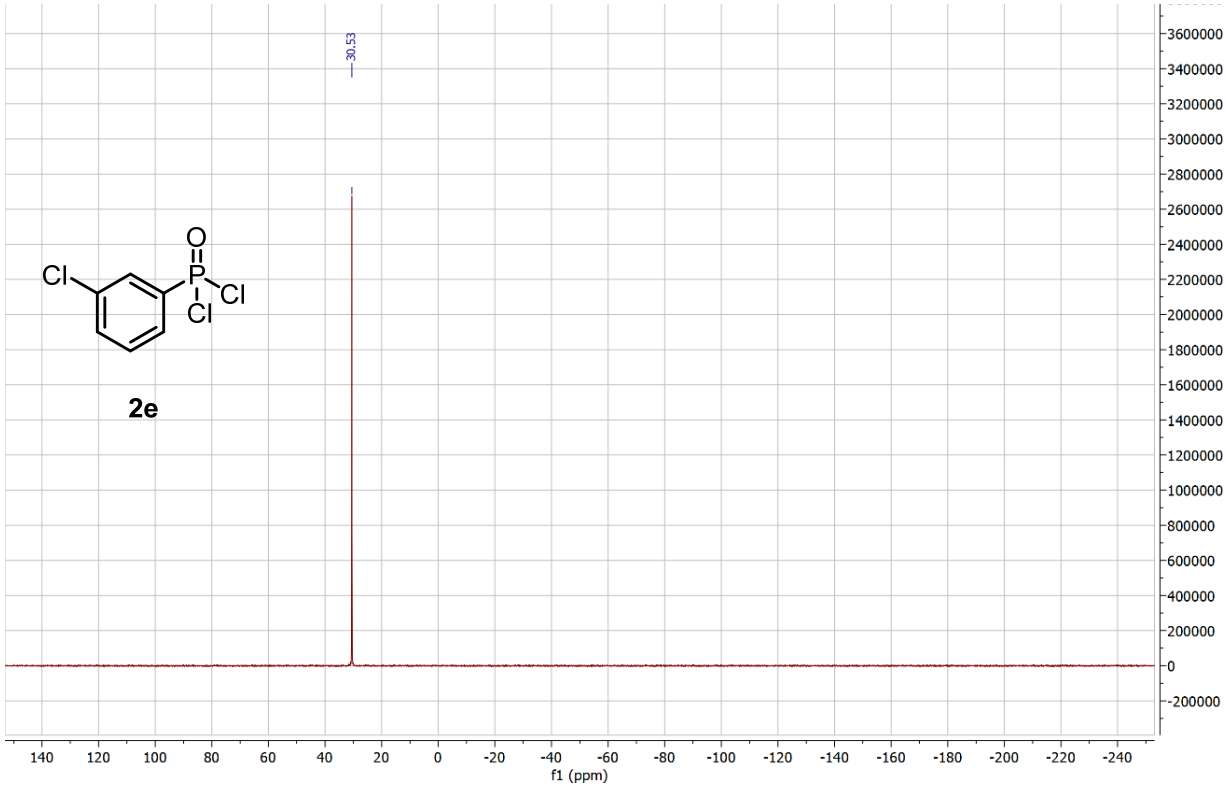
^{1}H NMR



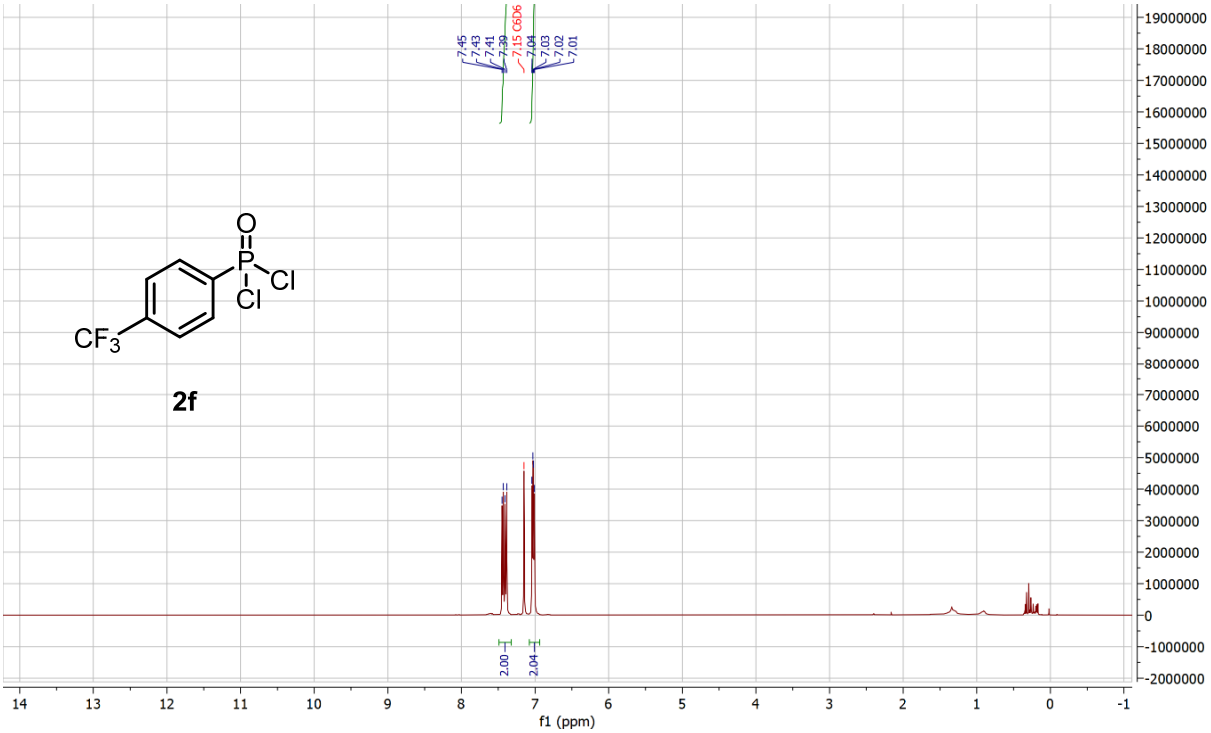
^{13}C NMR



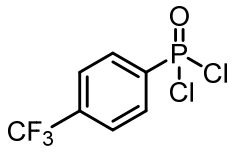
^{31}P NMR

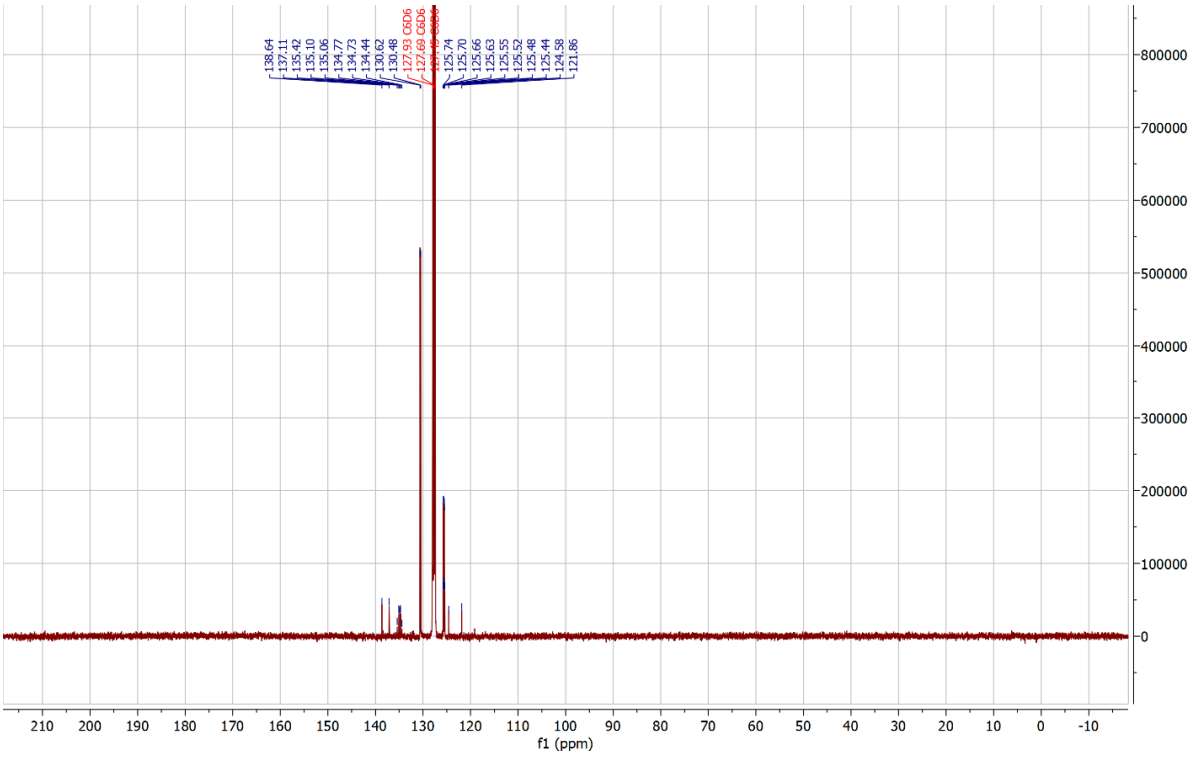

30.53
O
P
Cl
Cl
Cl
2e
3600000
3400000
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

^{1}H NMR

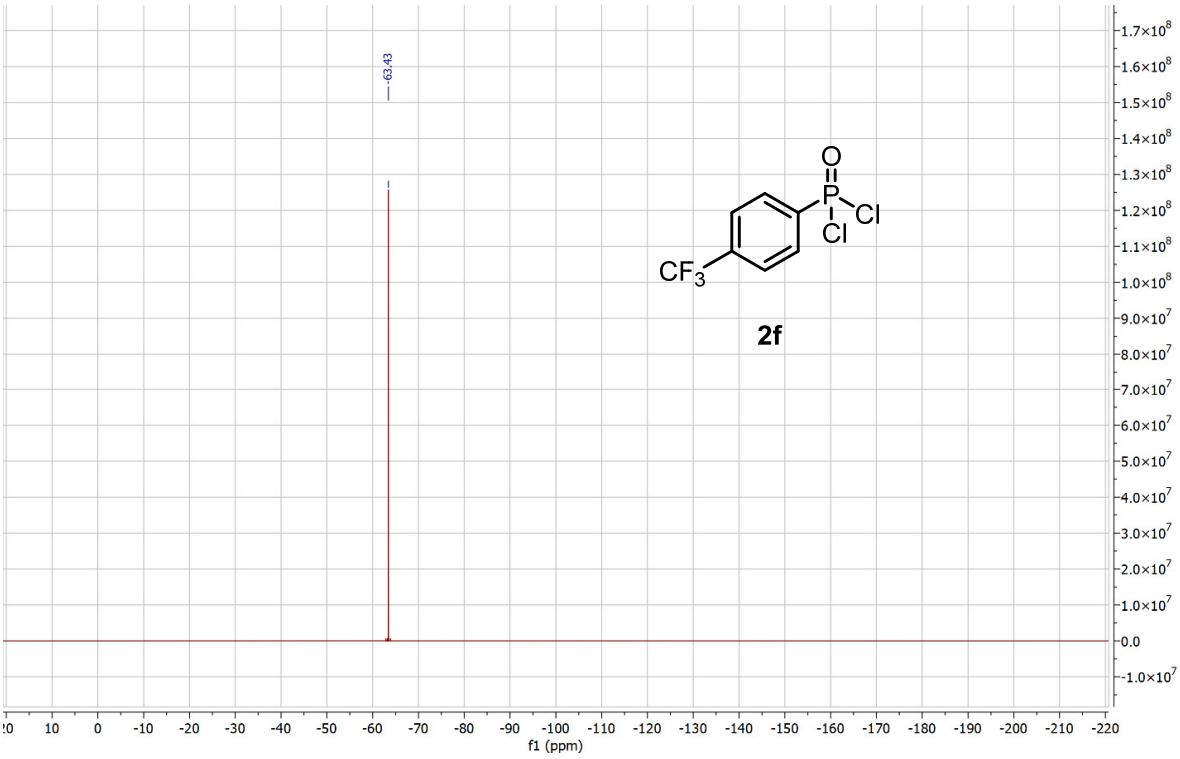


^{13}C NMR



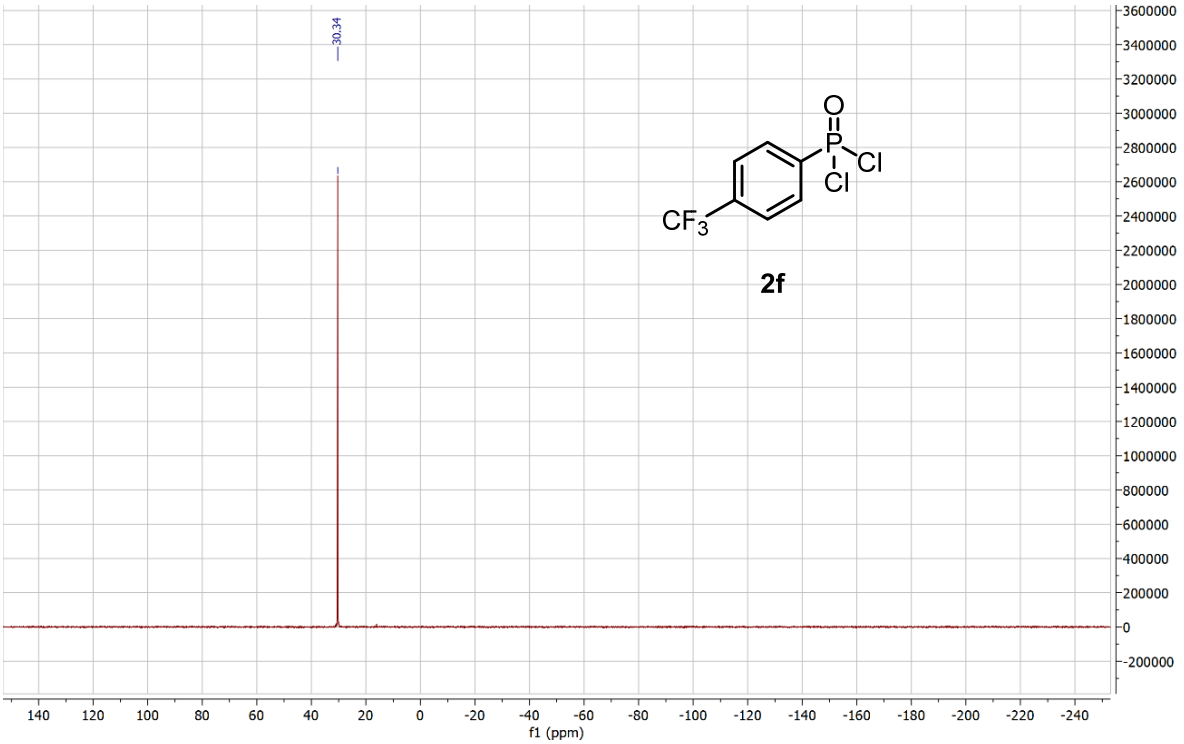


^{19}F NMR



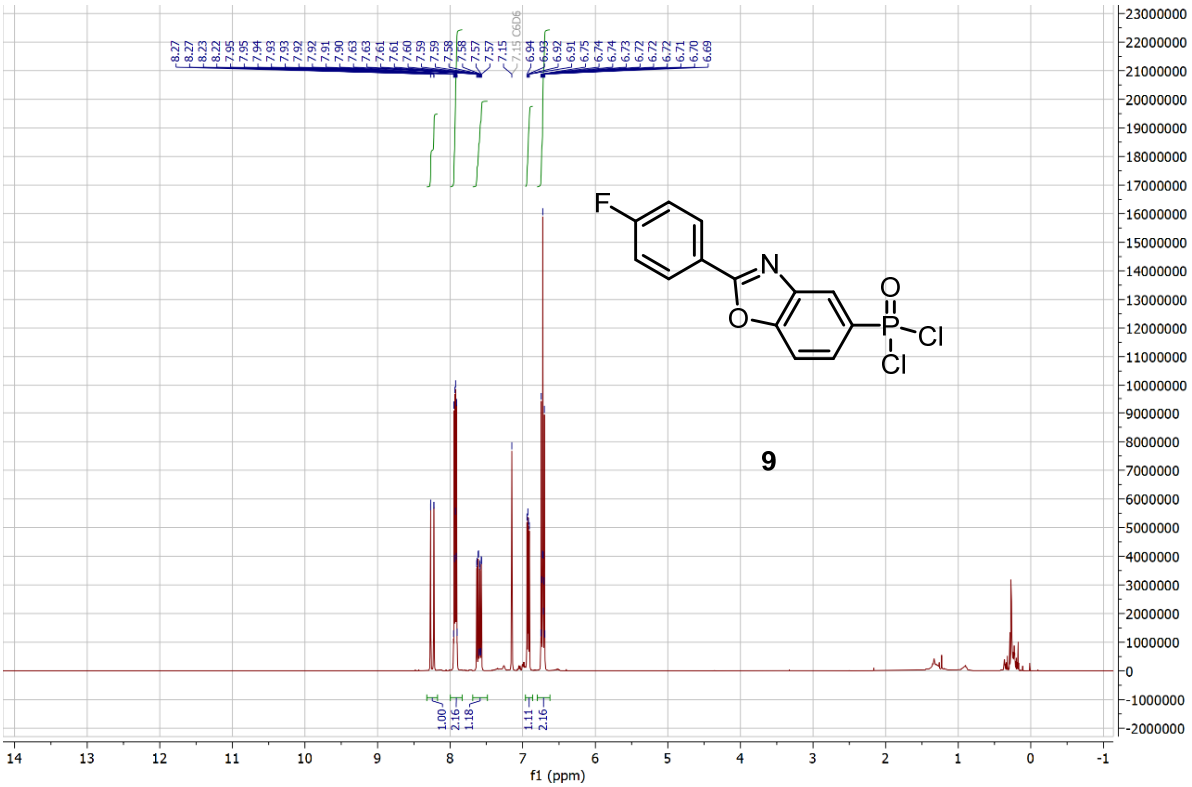
2f

^{31}P NMR



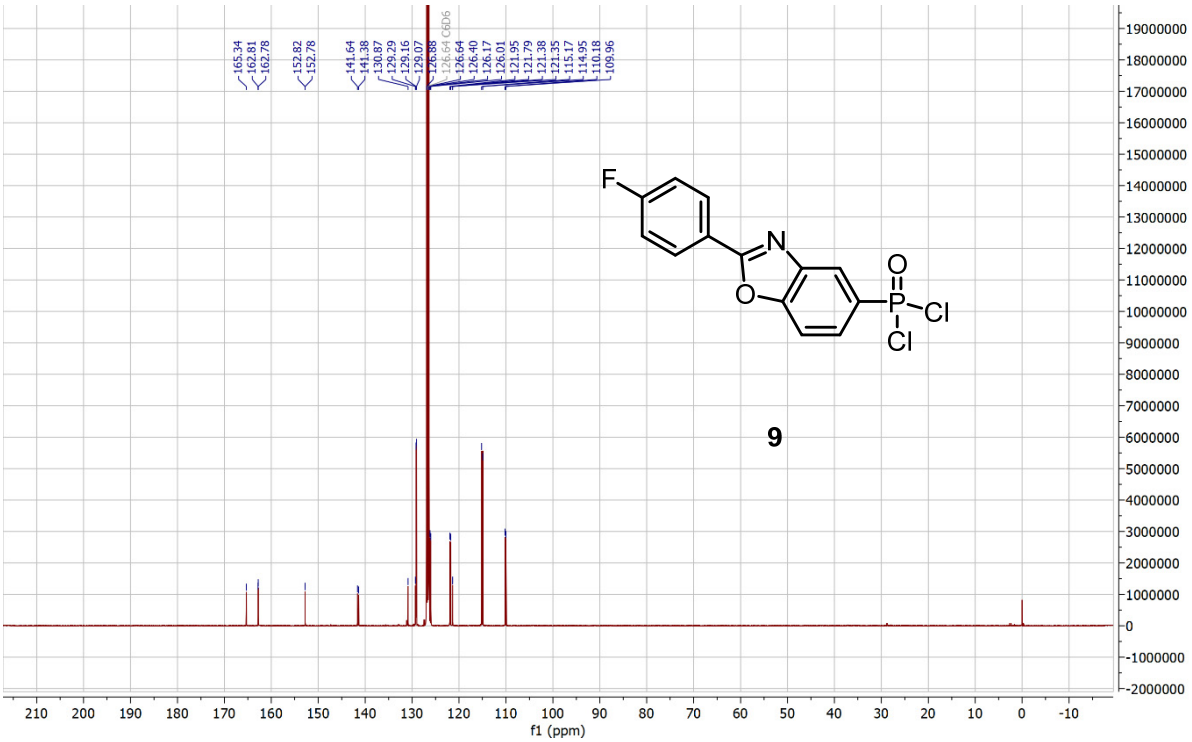
2f

^{1}H NMR

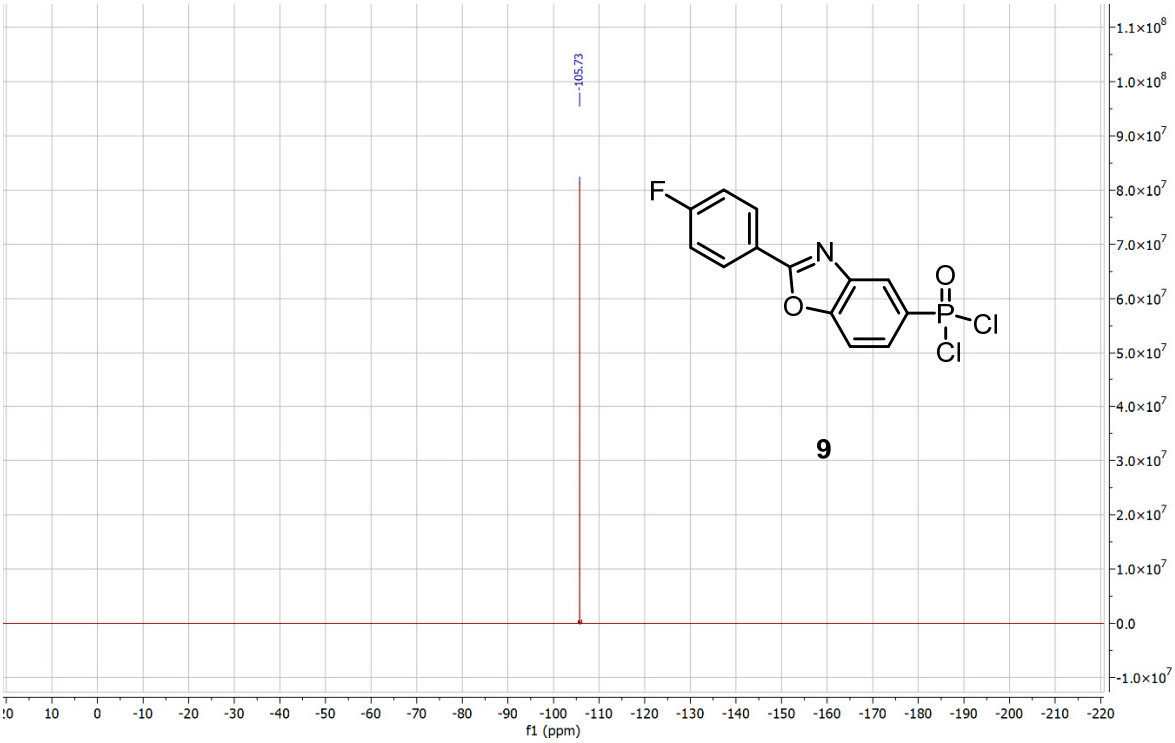


9

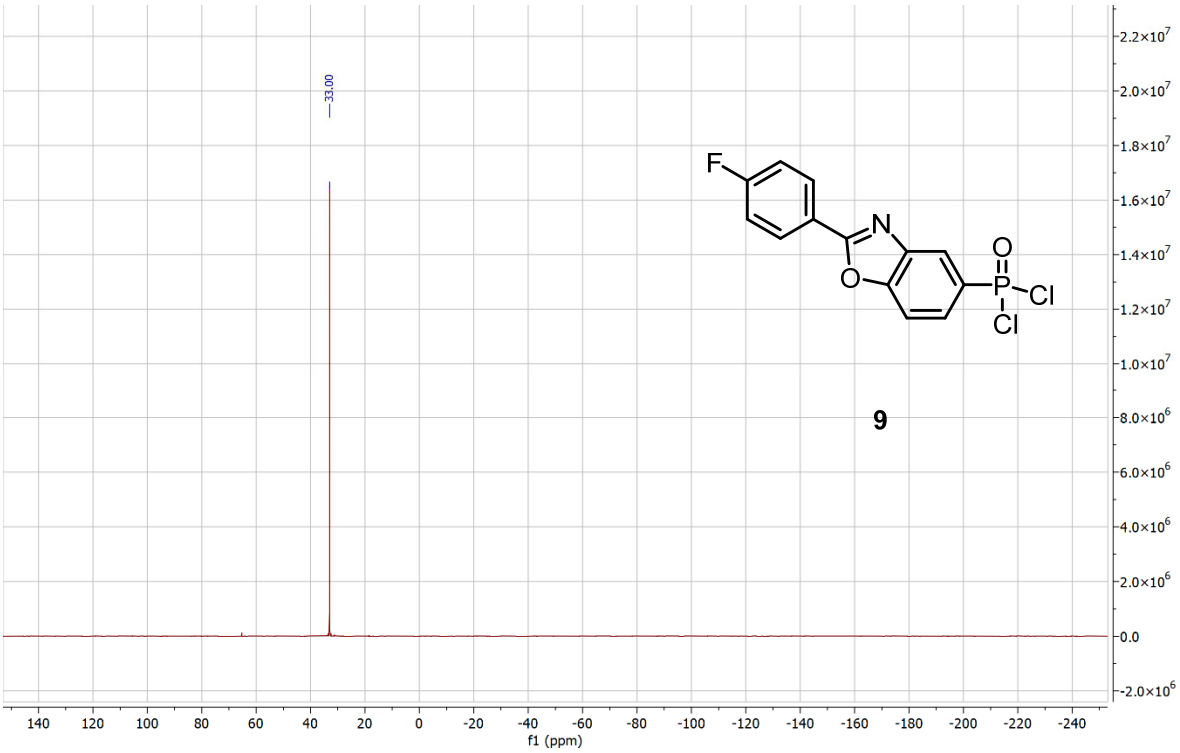
^{13}C NMR



^{19}F NMR



^{31}P NMR


33.00
F
N
O
O
P
Cl
Cl
9
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

References

1. U. Pradere, E. C. Garnier-Amblard, S. J. Coats, F. Amblard, R. F. Schinazi, Synthesis of Nucleoside Phosphate and Phosphonate Prodrugs. *Chem. Rev.* **114**, 9154–9218 (2014).

2. M. D. Sørensen, L. K. A. Blæhr, M. K. Christensen, T. Høyer, S. Latini, P.-J. V. Hjarnaa, F. Björkling, Cyclic phosphinamides and phosphonamides, novel series of potent matrix metalloproteinase inhibitors with antitumour activity. *Bioorg. Med. Chem.* **11**, 5461–5484 (2003).

3. M. Sawa, T. Kiyoi, K. Kurokawa, H. Kumihara, M. Yamamoto, T. Miyasaka, Y. Ito, R. Hirayama, T. Inoue, Y. Kirii, E. Nishiwaki, H. Ohmoto, Y. Maeda, E. Ishibushi, Y. Inoue, K. Yoshino, H. Kondo, New Type of Metalloproteinase Inhibitor: Design and Synthesis of New Phosphonamide-Based Hydroxamic Acids. *J. Med. Chem.* **45**, 919–929 (2002).

4. A. Babbs, A. Berg, M. Chatzopoulou, K. E. Davies, S. G. Davies, B. Edwards, D. J. Elsey, E. Emer, A. L. A. Figuccia, A. M. Fletcher, S. Guiraud, S. Harriman, L. Moir, N. Robinson, J. A. Rowley, A. J. Russell, S. E. Squire, J. E. Thomson, J. M. Tinsley, F. X. Wilson, G. M. Wynne, Synthesis of SMT022357 enantiomers and in vivo evaluation in a Duchenne muscular dystrophy mouse model. *Tetrahedron*. **76**, 130819 (2020).

5. A. Nocentini, V. Alterio, S. Bua, L. Micheli, D. Esposito, M. Buonanno, G. Bartolucci, S. M. Osman, Z. A. ALOthman, R. Cirilli, M. Pierini, S. M. Monti, L. Di Cesare Mannelli, P. Gratteri, C. Ghelardini, G. De Simone, C. T. Supuran, Phenyl(thio)phosphon(amid)ate Benzenesulfonamides as Potent and Selective Inhibitors of Human Carbonic Anhydrases II and VII Counteract Allodynia in a Mouse Model of Oxaliplatin-Induced Neuropathy. *J. Med. Chem.* **63**, 5185–5200 (2020).

6. A. Nocentini, P. Gratteri, C. T. Supuran, Phosphorus versus Sulfur: Discovery of Benzenephosphonamidates as Versatile Sulfonamide-Mimic Chemotypes Acting as Carbonic Anhydrase Inhibitors. *Chem. – Eur. J.* **25**, 1188–1192 (2019).

7. W. A. Lee, G.-X. He, E. Eisenberg, T. Cihlar, S. Swaminathan, A. Mulato, K. C. Cundy, Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. *Antimicrob. Agents Chemother.* **49**, 1898–1906 (2005).

8. T. Imamoto, Synthesis and applications of high-performance P-chiral phosphine ligands. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **97**, 520–542 (2021).

9. M. Dutartre, J. Bayardon, S. Jugé, Applications and stereoselective syntheses of P-chirogenic phosphorus compounds. *Chem. Soc. Rev.* **45**, 5771–5794 (2016).

10. O. I. Kolodiazhnyi, Phosphorus Compounds of Natural Origin: Prebiotic, Stereochemistry, Application. *Symmetry*. **13**, 889 (2021).

11. O. I. Kolodiazhnyi, A. Kolodiazhna, Nucleophilic substitution at phosphorus: stereochemistry and mechanisms. *Tetrahedron Asymmetry*. **28**, 1651–1674 (2017).

12. O. I. Kolodiazhnyi, Recent developments in the asymmetric synthesis of P-chiral phosphorus compounds. *Tetrahedron Asymmetry*. **23**, 1–46 (2012).

13. X. Ye, L. Peng, X. Bao, C.-H. Tan, H. Wang, Recent developments in highly efficient construction of P-stereogenic centers. *Green Synth. Catal.* **2**, 6–18 (2021).

14. S. Jugé, J. P. Genet, Asymmetric synthesis of phosphinates, phosphine oxides and phosphines by Michaelis Arbuzov rearrangement of chiral oxazaphospholidine. *Tetrahedron Lett.* **30**, 2783–2786 (1989).

15. S. Jugé, M. Stephan, J. A. Laffitte, J. P. Genet, Efficient asymmetric synthesis of optically pure tertiary mono and diphosphine ligands. *Tetrahedron Lett.* **31**, 6357–6360 (1990).

16. T. Koizumi, R. Yanada(nee Ishizaka), H. Takagi, H. Hirai, E. Yoshii, Grignard reaction of 2-phenyl-tetrahydropyrrolo-1,5,2-oxazaphospholes, observation of the stereospecific inversion of configuration. *Tetrahedron Lett.* **22**, 571–572 (1981).

17. Z. S. Han, N. Goyal, M. A. Herbage, J. D. Sieber, B. Qu, Y. Xu, Z. Li, J. T. Reeves, J.-N. Desrosiers, S. Ma, N. Grinberg, H. Lee, H. P. R. Mangunuru, Y. Zhang, D. Krishnamurthy, B. Z. Lu, J. J. Song, G. Wang, C. H. Senanayake, Efficient Asymmetric Synthesis of P-Chiral Phosphine Oxides via Properly Designed and Activated Benzoxazaphosphinine-2-oxide Agents. *J. Am. Chem. Soc.* **135**, 2474–2477 (2013).

18. E. J. Corey, Z. Chen, G. J. Tanoury, A new and highly enantioselective synthetic route to P-chiral phosphines and diphosphines. *J. Am. Chem. Soc.* **115**, 11000–11001 (1993).

19. K. W. Knouse, J. N. deGruyter, M. A. Schmidt, B. Zheng, J. C. Vantourout, C. Kingston, S. E. Mercer, I. M. Mcdonald, R. E. Olson, Y. Zhu, C. Hang, J. Zhu, C. Yuan, Q. Wang, P. Park, M. D. Eastgate, P. S. Baran, Unlocking P(V): Reagents for chiral phosphorothioate synthesis. *Science*. **361**, 1234–1238 (2018).

20. D. Xu, N. Rivas-Bascón, N. M. Padial, K. W. Knouse, B. Zheng, J. C. Vantourout, M. A. Schmidt, M. D. Eastgate, P. S. Baran, Enantiodivergent Formation of C–P Bonds: Synthesis of P-Chiral Phosphines and Methylphosphonate Oligonucleotides. *J. Am. Chem. Soc.* **142**, 5785–5792 (2020).

21. K. Kuwabara, Y. Maekawa, M. Minoura, T. Maruyama, T. Murai, Chemoselective and Stereoselective Alcoholysis of Binaphthyl Phosphonothioates: Straightforward Access to Both Stereoisomers of Biologically Relevant *P* -Stereogenic Phosphonothioates. *J. Org. Chem.* **85**, 14446–14455 (2020).

22. A. Mondal, N. O. Thiel, R. Dorel, B. L. Feringa, P-chirogenic phosphorus compounds by stereoselective Pd-catalysed arylation of phosphoramidites. *Nat. Catal.* **5**, 10–19 (2021).

23. D. A. DiRocco, Y. Ji, E. C. Sherer, A. Klapars, M. Reibarkh, J. Dropinski, R. Mathew, P. Maligres, A. M. Hyde, J. Limanto, A. Brunskill, R. T. Ruck, L.-C. Campeau, I. W. Davies, A multifunctional catalyst that stereoselectively assembles prodrugs. *Science*. **356**, 426–430 (2017).

24. A. L. Featherston, Y. Kwon, M. M. Pompeo, O. D. Engl, D. K. Leahy, S. J. Miller, Catalytic asymmetric and stereodivergent oligonucleotide synthesis. *Science*. **371**, 702–707 (2021).

25. M. Formica, T. Rogova, H. Shi, N. Sahara, A. J. M. Farley, K. E. Christensen, F. Duarte, D. J. Dixon, Catalytic Enantioselective Nucleophilic Desymmetrisation of Phosphonate Esters (2021), doi: 10.26434/chemrxiv-2021-5714s-v2.

26. C. Bauduin, D. Moulin, E. B. Kaloun, C. Darcel, S. Jugé, Highly Enantiomerically Enriched Chlorophosphine Boranes: Synthesis and Applications as P-Chirogenic Electrophilic Blocks. *J. Org. Chem.* **68**, 4293–4301 (2003).

27. T. Kimura, T. Murai, Enantiomerically pure P-chiral phosphinoselenoic chlorides: inversion of configuration at the P-chirogenic center in the synthesis and reaction of these substances. *Chem. Commun.*, 4077–4079 (2005).

28. T. Kimura, T. Murai, P-Chiral Phosphinoselenoic Chlorides and Optically Active P-Chiral Phosphinoselenoic Amides: Synthesis and Stereospecific Interconversion with Extrusion and Addition Reactions of the Selenium Atom. *Chem. Lett.* **33**, 878–879 (2004).

29. A. G. Doyle, E. N. Jacobsen, Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **107**, 5713–5743 (2007).

30. D. A. Kutateladze, D. A. Strassfeld, E. N. Jacobsen, Enantioselective Tail-to-Head Cyclizations Catalyzed by Dual-Hydrogen-Bond Donors. *J. Am. Chem. Soc.* **142**, 6951–6956 (2020).

31. A. J. Bendelsmith, S. C. Kim, M. Wasa, S. P. Roche, E. N. Jacobsen, Enantioselective Synthesis of α-Allyl Amino Esters via Hydrogen-Bond-Donor Catalysis. *J. Am. Chem. Soc.* **141**, 11414–11419 (2019).

32. D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen, Anion-Abstraction Catalysis: The Cooperative Mechanism of α-Chloroether Activation by Dual Hydrogen-Bond Donors. *ACS Catal.* **6**, 4616–4620 (2016).

33. K. L. Tan, E. N. Jacobsen, Indium-Mediated Asymmetric Allylation of Acylhydrazones Using a Chiral Urea Catalyst. *Angew. Chem. Int. Ed.* **46**, 1315–1317 (2007).

34. H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, Asymmetric Cooperative Catalysis of Strong Brønsted Acid–Promoted Reactions Using Chiral Ureas. *Science*. **327**, 986–990 (2010).

35. D. A. Strassfeld, E. N. Jacobsen "The Aryl-Pyrrolidine-tert-Leucine Motif as a New Privileged Chiral Scaffold: The Role of Noncovalent Stabilizing Interactions" in *Supramolecular Catalysis: New Directions and Developments*, P.W.N.M. van Leeuwen, M. Raynal, Eds. (Wiley, 2022), chap. 25, pp. 361-385.

36. I. V. L. Wilkinson, K. J. Perkins, H. Dugdale, L. Moir, A. Vuorinen, M. Chatzopoulou, S. E. Squire, S. Monecke, A. Lomow, M. Geese, P. D. Charles, P. Burch, J. M. Tinsley, G. M. Wynne, S. G. Davies, F. X. Wilson, F. Rastinejad, S. Mohammed, K. E. Davies, A. J. Russell, Chemical Proteomics and Phenotypic Profiling Identifies the Aryl Hydrocarbon Receptor as a Molecular Target of the Utrophin Modulator Ezutromid. *Angew. Chem. Int. Ed.* **59**, 2420–2428 (2020).

37. A. Babbs, A. Berg, M. Chatzopoulou, K. E. Davies, S. G. Davies, B. Edwards, D. J. Elsey, E. Emer, S. Guiraud, S. Harriman, C. Lecci, L. Moir, D. Peters, N. Robinson, J. A. Rowley, A. J. Russell, S. E. Squire, J. M. Tinsley, F. X. Wilson, G. M. Wynne, 2-Arylbenzo[d]oxazole Phosphinate Esters as Second-Generation Modulators of Utrophin for the Treatment of Duchenne Muscular Dystrophy. *J. Med. Chem.* **63**, 7880–7891 (2020).

38. M. Chatzopoulou, E. Emer, C. Lecci, J. A. Rowley, A.-S. Casagrande, L. Moir, S. E. Squire, S. G. Davies, S. Harriman, G. M. Wynne, F. X. Wilson, K. E. Davies, A. J. Russell, Decreasing HepG2 Cytotoxicity by Lowering the Lipophilicity of Benzo[d]oxazolephosphinate Ester Utrophin Modulators. *ACS Med. Chem. Lett.* **11**, 2421–2427 (2020).

39. M. V. Overtveldt, T. S. A. Heugebaert, I. Verstraeten, D. Geelen, C. V. Stevens, Phosphonamide pyrabactin analogues as abscisic acid agonists. *Org. Biomol. Chem.* **13**, 5260–5264 (2015).

40. M. Buti, M. Riveiro-Barciela, R. Esteban, Tenofovir Alafenamide Fumarate: A New Tenofovir Prodrug for the Treatment of Chronic Hepatitis B Infection. *J. Infect. Dis.* **216**, S792–S796 (2017).

41. M. Slusarczyk, M. Serpi, F. Pertusati, Phosphoramidates and phosphonamidates (ProTides) with antiviral activity. *Antivir. Chem. Chemother.* **26** (2018).

42. M.-A. Kasper, M. Glanz, A. Stengl, M. Penkert, S. Klenk, T. Sauer, D. Schumacher, J. Helma, E. Krause, M. C. Cardoso, H. Leonhardt, C. P. R. Hackenberger, Cysteine-Selective Phosphonamidate Electrophiles for Modular Protein Bioconjugations. *Angew. Chem. Int. Ed.* **58**, 11625–11630 (2019).

43. N. A. Lentini, B. J. Foust, C.-H. C. Hsiao, A. J. Wiemer, D. F. Wiemer, Phosphonamidate prodrugs of a butyrophilin ligand display plasma stability and potent Vγ9Vδ2 T cell stimulation. *J. Med. Chem.* **61**, 8658–8669 (2018).

44. Z. Zhao, Q. Zhu, S. Che, Z. Luo, Y. Lian, Palladium/nickel-mediated cross coupling reaction between phosphorylamides and alkenes toward enephosphorylamides. *Synth. Commun.* **50**, 2338–2346 (2020).

45. J. Xiao, P. Li, Y. Zhang, D. Xie, Z. Peng, D. An, W. Dong, Cobalt-catalyzed oxidative arylmethylation of phosphorylamides. *Tetrahedron*. **74**, 4558–4568 (2018).

46. Y. Xu, Q. Su, W. Dong, Z. Peng, D. An, The Chan-Evans-Lam N-arylation of phosphonic/phosphinic amides. *Tetrahedron*. **73**, 4602–4609 (2017).

47. L. Zhong, Q. Su, J. Xiao, Z. Peng, W. Dong, Y. Zhang, D. An, Ligand-Free Copper-Catalyzed Arylation of Phosphonamides and Phosphinamides with Aryl Siloxanes. *Asian J. Org. Chem.* **6**, 1072–1079 (2017).

48. Q. Zhu, S. Che, Z. Luo, Z. Zhao, Ligand-free copper-catalyzed denitrogenative arylation of phosphorylamides with arylhydrazines. *Synth. Commun.* **50**, 947–957 (2020).

49. T. L. Schull, S. L. Brandow, W. J. Dressick, Synthesis of symmetrical triarylphosphines from aryl fluorides and red phosphorus: scope and limitations. *Tetrahedron Lett.* **42**, 5373–5376 (2001).

50. N. Ohmura, A. Nakamura, A. Hamasaki, M. Tokunaga, Hydrolytic Deallylation of N-Allyl Amides Catalyzed by PdII Complexes. *Eur. J. Org. Chem.* **2008**, 5042–5045 (2008).

51. Bruker AXS APEX3 (2015).

52. L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *J. Appl. Crystallogr.* **48**, 3–10 (2015).

53. G. M. Sheldrick, SHELXT – Integrated space-group and crystal-structure determination. *Acta Crystallogr. Sect. A Found. Adv.* **71**, 3–8 (2015).

54. G. M. Sheldrick, Crystal structure refinement with SHELXL. *Acta Crystallogr. Sect. C Struct. Chem.* **71**, 3–8 (2015).

55. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. a. K. Howard, H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **42**, 339–341 (2009).

56. Accelrys Software Inc., Accelrys DS Visualizer v2.0.1 (2007).