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Improving Methods for Enantioselective Organophosphorus Synthesis by A Chiral Nucleophile-Metal Bifunctional Catalytic System

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Honors Thesis

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Abstract

The use of benzotetramisole (BTM) as a catalyst is a promising strategy for enantioselective organophosphorus synthesis since the reaction has been previously reported by Numan and Brichacek and has been tested in Dr. Erb's research laboratory. However, the yields are only moderate (46-58%) and the enantiomeric excess (ee) of the purified product are poor, with 62% being the highest reported ee. Preliminary computational data performed in the Erb lab has revealed that the cause of the lower ee (and possibly yield) could be the ability of the intermediate to adopt different conformations that are similar in energy and would therefore give a mixture of chirality in the product. The addition of a metal ion could result in the formation of a cyclic intermediate, providing a firm anchor that prevents rotation of the phosphorus-nitrogen bond, forming two possible intermediates and restricting conformational changes. Locking the rotation of the intermediate prevents the relief of steric strain between groups on the substrate and the organocatalyst in one intermediate, thus making it much higher in energy, less stable, and less likely to form. The other intermediate would also be locked in place in a similar way but has lower steric strain and thus would be more favorable. It may even be possible that the higher energy intermediate can isomerize to form the lower energy intermediate. Following this, bimolecular substitution by a nucleophile, such as an alcohol, would release of the catalyst and provide the product in improved enantioselectivity or yield. Several metals were tested to examine their effect on yield and enantioselectivity. Our results indicate that use of a bifunctional catalytic system with BTM and metal Lewis acids yields similar results to literature values obtained by use of BTM alone.

Acknowledgements

I would like to give my highest regards to Dr. Jeremy Erb for allowing me to collaborate on this project and also his great deal of effort and support for myself as a developing student. I would also like to thank the Department of Chemistry in its entirety for all of the support I have received as well as providing all of the financial assistance necessary to allow students, like myself, the opportunity to be involved in research.

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Introduction

Chiral molecules are sets of molecules that have the same atomic structure and connectivity but have differences in their three-dimensional arrangement. Consider how your hands are non-superimposable; lining them up on top of each other so that each palm faces upwards reveals that the thumbs point in different directions, and if you try to reorientate your hands such that your thumbs line up, you will find that your palms no longer face the same direction. Our hands are mirror images of each other, and in the same way chiral molecules can also be mirror images. Living things are often highly specific to chirality, and so in modern drug synthesis, it is important to consider biology's preference for certain chiral enantiomers molecules over others. Organophosphorus compounds have emerged as anti-viral drugs such as Sofosbuvir and potential treatments for tumors like the ProTide candidate Acelerin **(Figure 1)**.[1–3] Sofosbuvir imitates a uracil nucleotide with a modified deoxyribose sugar and a modified chiral phosphate group and Acelarin is a drug of similar structure. This sort of molecule mimics the function of nucleotides, such as in an enzyme-substrate complex, but due to its modified functional groups Sofosbuvir is less vulnerable to degradation in the body.[2] Studies found that the chirality of the modified phosphate group is crucial for successful binding to its target protein.[3]

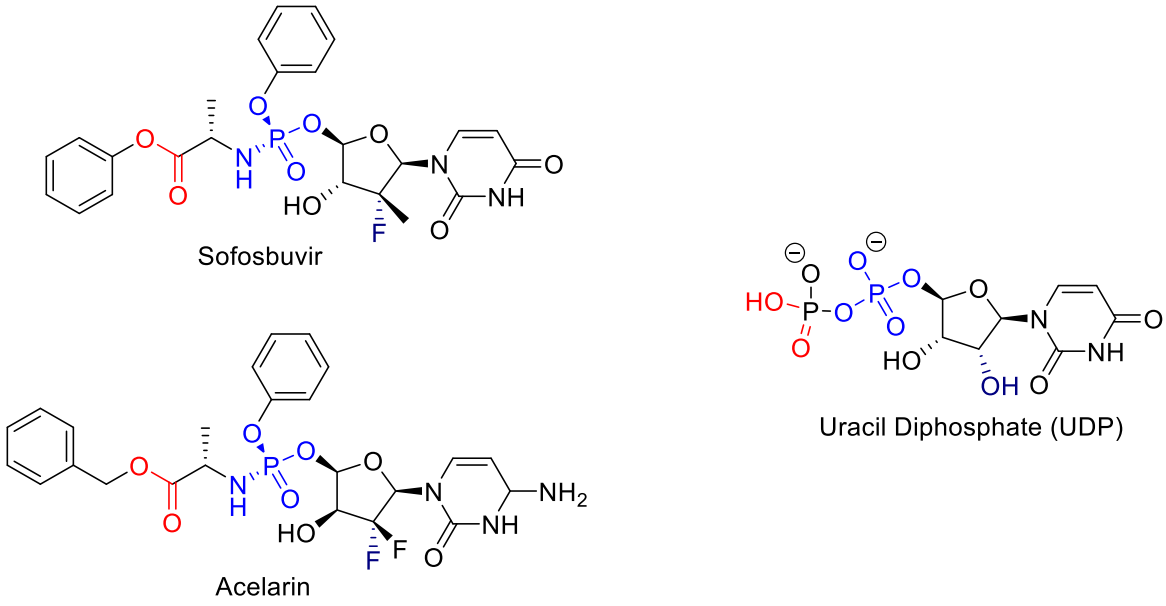


Figure 1: Analogous structures are highlighted in matching colors.

Much of the use of organophosphorous compounds comes from prodrug design and synthesis. Prodrugs are drugs that as administered are inactive and will not bind to their intended target, but once metabolized by the body they are broken down into the activated drug.[7] Phosphonates and the prodrugs they appear in play an important role in improving pharmaceutical properties such as bioavailability, the ability of a drug to reach the target macromolecule and produce a physiological difference, instability, and unwanted side effects. Phosphorus acids are characterized by a strongly negative charge which can be problematic when trying to cross a mostly nonpolar cellular membrane, but the use of protective groups, as in a prodrug, can remedy this complication by changing solubility and permeability characteristics of the inactive form of the drug. The phosphonate group itself can play a role in specific binding to a physiological target and are being utilized more and more frequently, but there remain synthetic limitations to their use, namely that synthesis of these compounds is generally racemic.[7] With biological systems being preferential to only one enantiomer and not the other, it means

that half of the synthetic product must be discarded, immediately cutting any yields already strained by difficult chemistry by 50%.

Methods that achieve this level of chiral control are relatively limited, especially when starting with achiral materials. Trichlorophosphane (PCl_3) and dichloro(phenyl)phosphane ($PhPCl_2$) can be substituted with alkoxyl groups stereospecifically with the use of a chiral auxiliary, which unfortunately is nonoptimal for synthesis of compounds in which an auxiliary group is undesirable **(Figure 2)**.[8] Other work has examined the use of a phosphine intermediate that is then oxidized into a P (V) chiral center **(Figure 3)**.[9] High optical purity was observed, however this synthesis requires that the starting compounds are already chiral, a property that is not always achievable in every phosphine. The use of catalytic molecules is the most common path used to generate these enantiomers, but recently research has utilized single-atom ions of transition metals. In the synthesis of ProTide drugs, such as the aforementioned Sofosbuvir, copper metal ions may also be used as a catalyst to stabilize certain conformations over others, influencing stereoselectivity.[2] The use of metal ions has also been applied to smaller organophosphate molecules like phosphoryl chloride when substituting chlorines for alkoxyl groups, though no control over chirality was observed.[10]

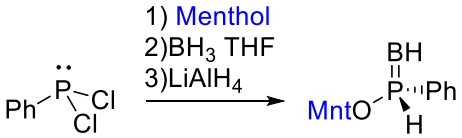


Figure 2: Reaction scheme in which achiral phosphine is combined with auxiliary menthol to create a chiral P (V) compound.

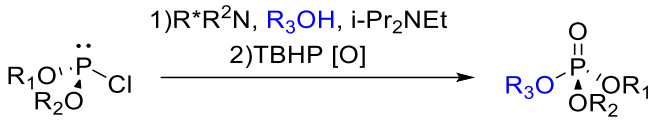


Figure 3: Reaction scheme in which a new alkoxyl group is added to a chiral phosphine and then oxidized to yield a chiral phosphate.

In fact, most current methods for generating chiral organophosphorous compounds through an enantioselective reaction act on P (III) compounds called phosphines or on carbon structures bonded to an achiral P (III) or P (V) atom. These sorts of compounds are synthesized through methods such as asymmetric hydrogenation, asymmetric reduction via complex metal hydrides or biocatalytic systems, and asymmetric oxidation.[8] One such example is an intermediate in the synthesis of mini-PHOS ligands **(Figure 4)**. The chirality in this instance is driven by steric hinderance of a bulky tert-butyl group, but while this method is able to generate a chiral center on a P (V) atom, there is no way to substitute the groups directly connected to phosphorus, rather the method uses groups already attached to phosphorous to influence chirality elsewhere in the molecule. In general, it is a continuing theme that the chirality is not usually centered on the phosphorous, but sits as a chiral substituent of a carbon chiral center.[8]

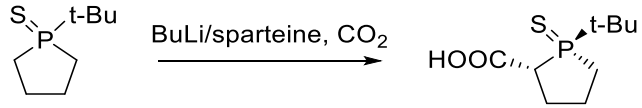


Figure 4: Intermediate step in the synthesis of mini-PHOS ligands.[8]

Previous attempts by Ahmed Numan and Matthew Brichacek showed that the use of BTM was able to yield a chiral phosphonate (58%) with an enantiomeric excess (ee) of 49% when used in 20% molar equivalences when reacted with an H- phosphinate and an alcohol. When BTM was used in smaller quantities (10% molar equivalence), the

reaction yielded less product (52%) and had lower ee (46%). An increased amount of BTM (50% molar equivalence) formed the product at only 46% yield but resulted in the highest amount of ee at 54%.[11]

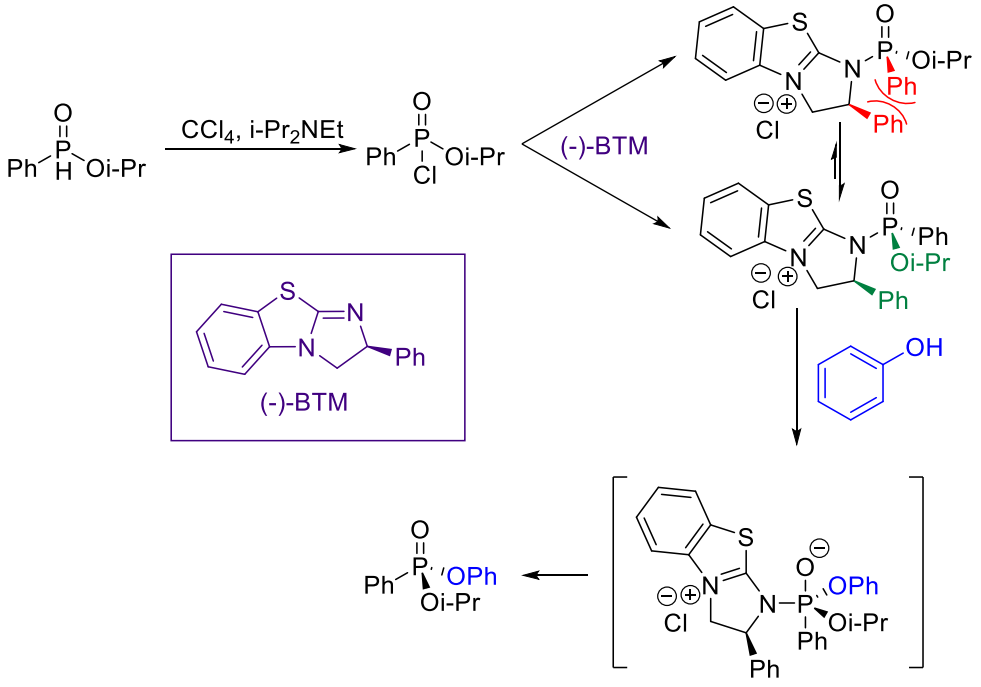


Figure 5: The mechanism of action proposed by Numan and Brichacek.[11] Isopropyl phenyl-H-phosphinate is deprotonated and chlorinated, then binds to the catalyst forming a salt. The steric bulk of the phenyl groups on BTM and the phosphinate prevent the formation of one enantiomer and favor the other enantiomer. An alcohol is then able to proceed through a biomolecular substitution reaction that yields a chiral product.

The mechanism for Numan and Brichacek's reaction **(Figure 5)** suggests that first, the phosphinic acid becomes chlorinated by carbon tetrachloride after being deprotonated by the base (here Hünig's base is used) in dichloromethane solution. The catalyst then replaces chlorine on the phosphorus center forming a salt. Due to steric hinderance between the phenyl groups on the phosphorus and BTM, the catalyst is favorably attached in the lower energy configuration. The alcohol can then be attached by an S_N2 mechanism and result in the *R* configuration of the phosphonate. However, yields and

selectivity in this type of reaction can be improved and bifunctional catalysis has been frequently invoked to address shortcomings of other stereoselective reactions.

The use of a bifunctional catalysis is exactly the approach explored in our research. We hypothesize that in Numan and Brichacek's model, the steric strain caused by the proximity of the phenyl rings can be relieved by the rotation of the single bond between phosphorus and nitrogen. Without the steric influence of the two phenyl groups, the otherwise less stable intermediate conformation can more easily be formed, which constitutes a loss of enantioselectivity. The addition of a metal-containing compound, such as copper (II) chloride, may be effective in preventing the rotation of the P-N bond. It does so by coordinating with the double-bonded oxygen of the phosphate and the sulfur atom of BTM **(Figure 7)**. Preliminary optimization and frequency calculations done using Gaussian 16 with a B3LYP/6-31+g(d) level of theory for optimizations on all atoms except for copper which used the SDD basis set suggested that without the presence of copper (II) chloride, the energy difference between the two enantiomers of the phosphate-BTM intermediate is 2.14 kcal per mole, and with copper (II) chloride, that difference increases to 2.49 kcal per mole **(Figure 6)**. The increased energy difference between the two enantiomers shows that exploring the bifunctional catalytic system may be fruitful in controlling the chirality of the synthesis.

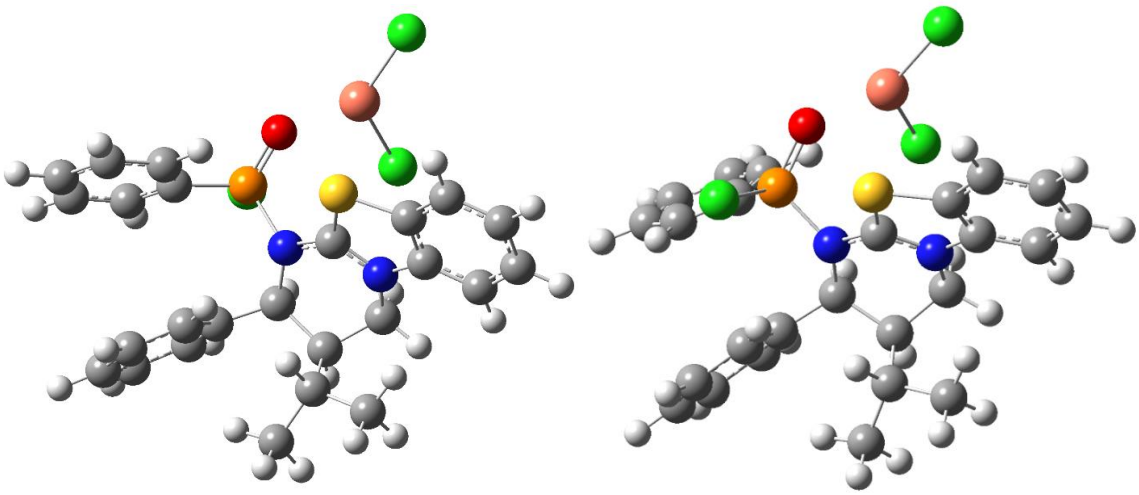


Figure 6: Results of preliminary calculations which revealed energy difference between *R* and *S* enantiomers in the presence of copper (II) chloride.

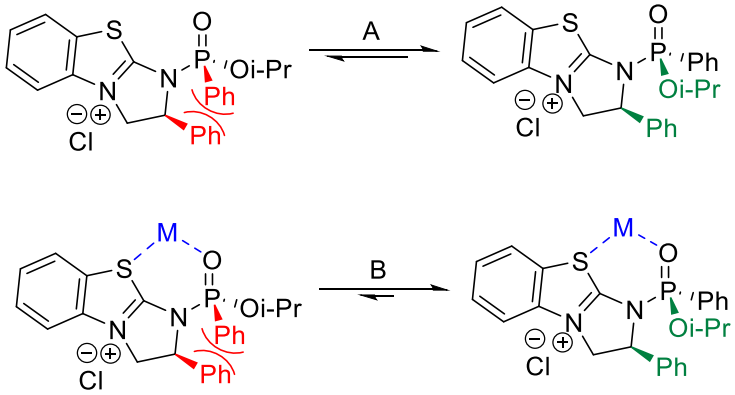


Figure 7: Addition of a metal catalyst in a bifunctional catalytic system possibly generates a new equilibrium (B) which more strongly favors one diastereomer intermediate than the other when compared to a standard catalytic system equilibrium (A).

Results and Discussion

Table 1: Isopropyl-phenyl-H-phosphinate with (-)-benzomtetramisole				
Alcohol	Product	Temperature	Yield (%)	Enatiomeric Excess (ee)
Methanol	Isopropyl-(methyl)-*(R)*-phenylphosphonate	0˚ C	10	44
Ethanol	Isopropyl-(ethyl)-*(R)*-phenylphosphonate	0˚ C	3	33
Phenol	Isopropyl-(phenyl)-*(R)*-phenylphosphonate	0˚ C	34	41
Benzyl	Isopropyl-(benzyl)-*(S)*-phenylphosphonate	0˚ C	6	44

The synthetic reaction demonstrated by Numan and Brichacek was found to be applicable to a variety of nucleophilic alcohols **(Table 1)**, although at varying yields and enantioselectivity that greatly differ from Numan and Brichacek's own results. For example, a yield of 56% and an enantiomeric excess of 51% for the synthesis of isopropyl-(methyl)- *(R)*-phenylphosphonate were reported,[11] however our reactions yielded far lower amounts of product and fell short of matching their enantioselectivity **(Table 1)**. Furthermore, our synthesis of isopropyl-(benzyl)-*(S)*-phosphonate exceeded the literature enantioselectivity when using Numan's conditions, exceeding it by a difference of around 9%, but again, yields were far lower than previously reported[11] **(Table 1)**. In addition to repeating experiments performed by Numan and Brichacek, we also included the synthesis of isopropyl-(ethyl)- *(R)*-phosphonate. Unfortunately, lower yields and enantioselectivity of this product were observed and so it was not included in later experiments in bifunctional catalysis. Instead we continued to focus mainly on benzyl alcohol and phenol as nucleophiles due to their high enantiomeric excesses and strong ultraviolet fluorescence which made isolating a pure product much easier.

Table 2: Isopropyl-phenyl-H-phosphinate with (-)-benzotetramisole and metal catalyst				
Metal Catalyst	Alcohol	Temperature	Yield (%)	Enantiomeric Excess (ee)
Control	Benzyl	0˚ C	6	44
	Phenol	0˚ C	34	41
Samarium (III) Triflate	Benzyl	rt	27	8
Indium (III) Triflate	Benzyl	rt	19	10
Zinc (II) Triflate	Benzyl	rt	33	11
		0˚ C	34	16
	Phenol	0˚ C	44	41
Zirconocene Dichloride	Benzyl	rt	17	15
		0˚ C	24	20
(R)-(+)-4-DMAP(C_5Ph_5)iron Chloride	Benzyl	rt	22	27
		0˚ C	13	30
	Phenol	0˚ C	29	51
Indium (III) Triflate/*(R)*-1,1'-Bi-2-napthol [a]	Benzyl	rt	38	4
Indium (III) Triflate/*(S)*-1,1'-Bi-2-napthol [a]	Benzyl	rt	51	11
	Phenol	0˚ C	30	39

[a] *in situ* combination of $In(OTF)_3$ and BINOL

Using our hypothesized bifunctional catalytic system, we observed variable results. When benzyl alcohol is used as a nucleophile, the addition of a metal catalyst usually greatly improved isolated yields, but decreased enantioselectivity was simultaneously observed **(Table 2)**. Considering phenol as the nucleophile of the reaction mechanism, different results were observed. The presence of zinc (II) triflate boosted isolated yield when compared to our control synthesis, but left enantioselectivity unchanged while indium (III) *(S)*-BINOL had comparable results to the control experiment **(Table 2)**. The most noteworthy entry in **Table 2** is the reaction performed with phenol and *(R)*-(+)-4-DMAP(C_5Ph_5)Fe chloride, which despite a slightly decreased isolated yield showed improved enantioselectivity, a difference of about 10% compared to our control synthesis. Although we observed improvements compared to the control

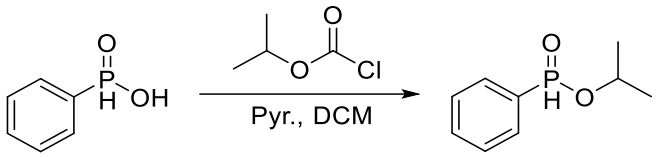
syntheses, it should be noted that literature yields and enantioselectivities for this reaction exceeded our own.

Conclusion and Future Directions

In general, the results serve as foundational experiments for future work to improve the stereoselectivity and yield. Future experiments will focus on the solubility of the transition metals as the copper (II) Lewis acid, as well as some of the other catalysts, had limited solubility in dichloromethane. The exception was *(R)*-(+)-4-DMAP(C_5Ph_5)Fe which was at least slightly soluble in dichloromethane due to the large organic ligands bonded to the central iron atom. The solubility of *(R)*-(+)-4-DMAP(C_5Ph_5)Fe in dichloromethane could be another contributing factor to its performance in our results. Previous literature demonstrates that the reaction can be done in acetonitrile, although heavily decreased enantioselectivity was observed.[11] Future work will also examine new catalysts or reagents that could be used to increase yield or selectivity in the reaction.

Experimental Procedures and Methods

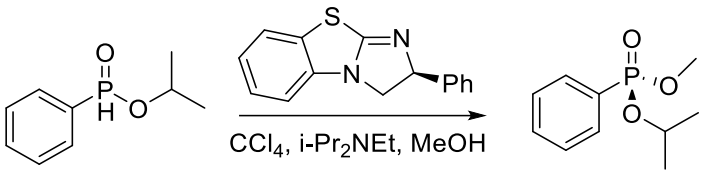
Synthesis of Isopropyl-(phenyl)-H-Phosphinate[12]



Scheme 1

1.00 g of phenylphosphinic acid (1.0 eq, 7.03 mmol) and 0.789 mL of isopropyl chloroformate (1.0 eq, 7.03 mmol) were dissolved in 14.69 mL of methylene chloride in a 50-mL round-bottom flask with a stir bar. With strong stirring, 0.567 mL of pyridine (1.0 eq, 7.03 mmol) was added dropwise to the round-bottom flask. Once effervescence ceased, the solution was refluxed for 15 minutes at 40 ºC. Once cooled to room temperature, the reaction was quenched with 5.3 mL of 0.1 M hydrochloric acid. The mixture was transferred to a separatory funnel where the organic layer was washed three times with deionized water before being dried over sodium sulfate. Methylene chloride was then vacuum evaporated to yield yellow oil. This yellow oil was then vacuum distilled in a kugelrohr apparatus at 110 ºC to yield isopropyl (phenyl)-H-phosphinate as a pure clear oil, which was verified by both ^{1}H NMR and ^{31}P CPD NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.85 (m, 2H) 7.62 (d, J = 559.6 Hz, 1H, PH), 7.46-7.63 (m, 3H), 4.62-4.80 (m, 1H, OCH), 1.39-1.46 (d, J = 6.0 Hz, 3H, CH_3), 1.32-1.39 (d, J = 6 Hz, 3H, CH_3) **(Supplement 1)**. ^{31}P CPD NMR (400 MHz, $CDCl_3$) δ 22.18 (s) **(Supplement 2)**.

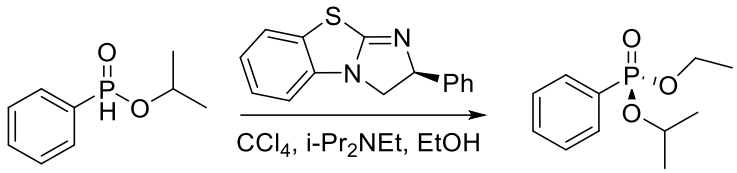
Procedure for Synthesis of Isopropyl-(Methyl)-(R)-Phenylphosphonate



Scheme 2

100 mg of isopropyl-(phenyl)-H-phosphinate (1.0 eq., 0.543 mmol) in 1.8 mL of dichloromethane was added to a 25 mL round bottom flask with a stir bar. The flask was then sealed and placed under a nitrogen atmosphere, then cooled to 0˚ C. 0.21 mL of carbon tetrachloride (4.0 eq, 2.172 mmol) was added once the solution had cooled. In a separate 5-mL vial, 27.4 mg of (-)-benzotetramisole (0.2 eq, 0.109 mmol), 0.189 mL of *N,N*-diisopropylethylamine (2.0 eq, 1.086 mmol), and 8.65 mg methanol (0.5 eq., 0.271 mmol) were dissolved in 0.3 mL of methylene chloride which was then transferred to the reaction flask. The reaction continued for approximately 8 hours at 0^{o} C. The reaction was then quenched with 1 mL of 1 M hydrochloric acid and the mixture was extracted three times with ethyl acetate before being dried over sodium sulfate. The product was isolated by flash silica gel chromatography using a gradient ratio of ethyl acetate and hexanes as an eluent **(Supplement 3)**. Products were verified for their purity by ^{1}H NMR and ^{31}P CPD NMR. Enantiomeric excess (ee) was determined by HPLC in a 5:95 ethyl acetate to hexanes mobile phase **(Supplement 6)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.87 (m, 2H), 7.52-7.60 (m, 1H), 7.42-7.51 (m, 2H), 4.67-4.83 (m, 1H, OCH), 3.68-3.77 (d, J = 11.3 Hz, 3H, OCH_3), 1.33-1.45 (d, J = 6.0 Hz, 3H, CH_3), 1.20-1.31 (d, J = 5.7 Hz, 3H, CH_3) **(Supplement 4)**. ^{31}P CPD NMR (400 MHz, $CDCl_3$) δ 19.20 (s) **(Supplement 5)**.

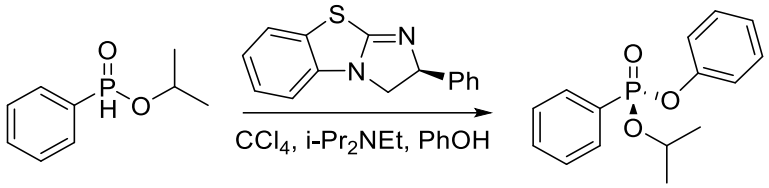
Procedure for Synthesis of Isopropyl-(Ethyl)-(R)-Phenylphosphonate



Scheme 3

100 mg of isopropyl-(phenyl)-H-phosphinate (1.0 eq., 0.543 mmol) in 1.8 mL of dichloromethane was added to a 25 mL round bottom flask with a stir bar. The flask was then sealed and placed under a nitrogen atmosphere, then cooled to 0˚ C. 0.21 mL of carbon tetrachloride (4.0 eq, 2.172 mmol) was added once the solution had cooled. In a separate 5-mL vial, 27.4 mg of (-)-benzotetramisole (0.2 eq, 0.109 mmol), 0.189 mL of *N,N*-diisopropylethylamine (2.0 eq, 1.086 mmol), and 12.5 mg ethanol (0.5 eq., 0.271 mmol) were dissolved in 0.3 mL of methylene chloride which was then transferred to the reaction flask. The reaction continued for approximately 8 hours at 0° C. The reaction was then quenched with 1 mL of 1 M hydrochloric acid and the mixture was extracted three times with ethyl acetate before being dried over sodium sulfate. The product was isolated by flash silica gel chromatography using a gradient ratio of ethyl acetate and hexanes as an eluent **(Supplement 7)**. Products were verified for their purity by ^{1}H NMR and ^{31}P CPD NMR. Enantiomeric excess (ee) was then determined by HPLC in a 5:95 ethyl acetate to hexanes mobile phase **(Supplement 10)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.87 (m, 2H), 7.50-7.58 (m, 1H), 7.40-7.50 (m, 2H), 4.65-4.78 (m, 1H, OCH), 3.97-4.18 (m, 2H, OCH_2), 1.36-1.40 (d, J = 6.0 Hz, 3H, CH_3), 1.28-1.34 (t, J = 7.1 Hz, 3H, CH_3), 1.22-1.27 (d, J = 6.1 Hz, 3H, CH_3) **(Supplement 8)**. ^{31}P CPD NMR (400 MHz, $CDCl_3$) δ 17.75 (s) **(Supplement 9)**.

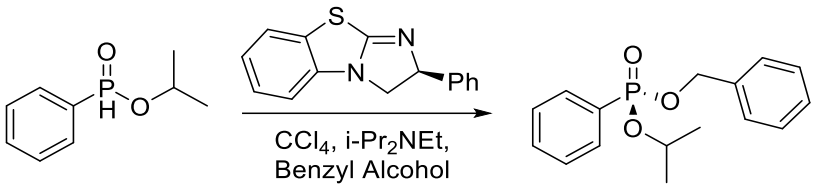
Procedure for Synthesis of Isopropyl-(Phenyl)-(R)-Phenylphosphonate



Scheme 4

100 mg of isopropyl-(phenyl)-H-phosphinate (1.0 eq., 0.543 mmol) in 1.8 mL of dichloromethane was added to a 25 mL round bottom flask with a stir bar. The flask was then sealed and placed under a nitrogen atmosphere, then cooled to 0˚ C. 0.21 mL of carbon tetrachloride (4.0 eq, 2.172 mmol) was added once the solution had cooled. In a separate 5-mL vial, 27.4 mg of (-)-benzotetramisole (0.2 eq, 0.109 mmol), 0.189 mL of *N,N*-diisopropylethylamine (2.0 eq, 1.086 mmol), and 25.5 mg phenol (0.5 eq., 0.271 mmol) were dissolved in 0.3 mL of methylene chloride which was then transferred to the reaction flask. The reaction continued for approximately 8 hours at 0° C. The reaction was then quenched with 1 mL of 1 M hydrochloric acid and the mixture was extracted three times with ethyl acetate before being dried over sodium sulfate. The product was isolated by flash silica gel chromatography using a gradient ratio of ethyl acetate and hexanes as an eluent **(Supplement 11)**. Products were verified for their purity by ^{1}H NMR and ^{31}P CPD NMR. Enantiomeric excess (ee) was then determined by HPLC in a 5:95 ethyl acetate to hexanes mobile phase **(Supplement 14)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.93 (m, 2H), 7.51-7.60 (m, 1H) 7.42-7.51 (m, 2H), 7.21-7.31 (m, 2H), 7.07-7.18 (m, 3H), 4.84-4.94 (m, 1H, OCH), 1.35-1.40 (d, J = 5.9 Hz, 3H, CH_3), 1.29-1.34 (d, J = 6.2 Hz, 3H, CH_3) **(Supplement 12)**. ^{31}P CPD NMR (400 MHz, $CDCl_3$) δ 14.39 (s) **(Supplement 13)**.

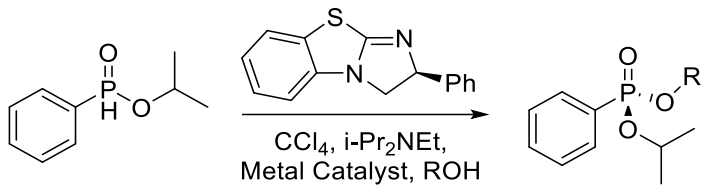
Procedure for Synthesis of Isopropyl-(Benzyl)-(S)-Phenylphosphonate



Scheme 5

100 mg of isopropyl-(phenyl)-H-phosphinate (1.0 eq., 0.543 mmol) in 1.8 mL of dichloromethane was added to a 25 mL round bottom flask with a stir bar. The flask was then sealed and placed under a nitrogen atmosphere, then cooled to 0˚ C. 0.21 mL of carbon tetrachloride (4.0 eq, 2.172 mmol) was added once the solution had cooled. In a separate 5-mL vial, 27.4 mg of (-)-benzotetramisole (0.2 eq, 0.109 mmol), 0.189 mL of *N,N*-diisopropylethylamine (2.0 eq, 1.086 mmol), and 29.3 mg benzyl alcohol (0.5 eq., 0.271 mmol) were dissolved in 0.3 mL of methylene chloride which was then transferred to the reaction flask. The reaction continued for approximately 8 hours at 0° C. The reaction was then quenched with 1 mL of 1 M hydrochloric acid and the mixture was extracted three times with ethyl acetate before being dried over sodium sulfate. The product was isolated by flash silica gel chromatography using a gradient ratio of ethyl acetate and hexanes as an eluent **(Supplement 15)**. Products were verified for their purity by ^{1}H NMR and ^{31}P CPD NMR. Enantiomeric excess (ee) was then determined by HPLC in a 5:95 ethyl acetate to hexanes mobile phase **(Supplement 18)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.80 (m, 2H), 7.42-7.51 (m, 1H), 7.32-7.42 (m, 2H), 7.16-7.27 (m, 5H), 4.88-5.10 (dm, 2H, OCH_2), 4.62-4.75 (m, 1H, OCH), 1.25-1.32 (d, J = 6.1 Hz, 3H, CH_3), 1.17-1.22 (d, J = 6.0 Hz, 3H, CH_3) **(Supplement 16)**. ^{31}P CPD NMR (400 MHz, $CDCl_3$) δ 18.15 (s) **(Supplemental 17)**.

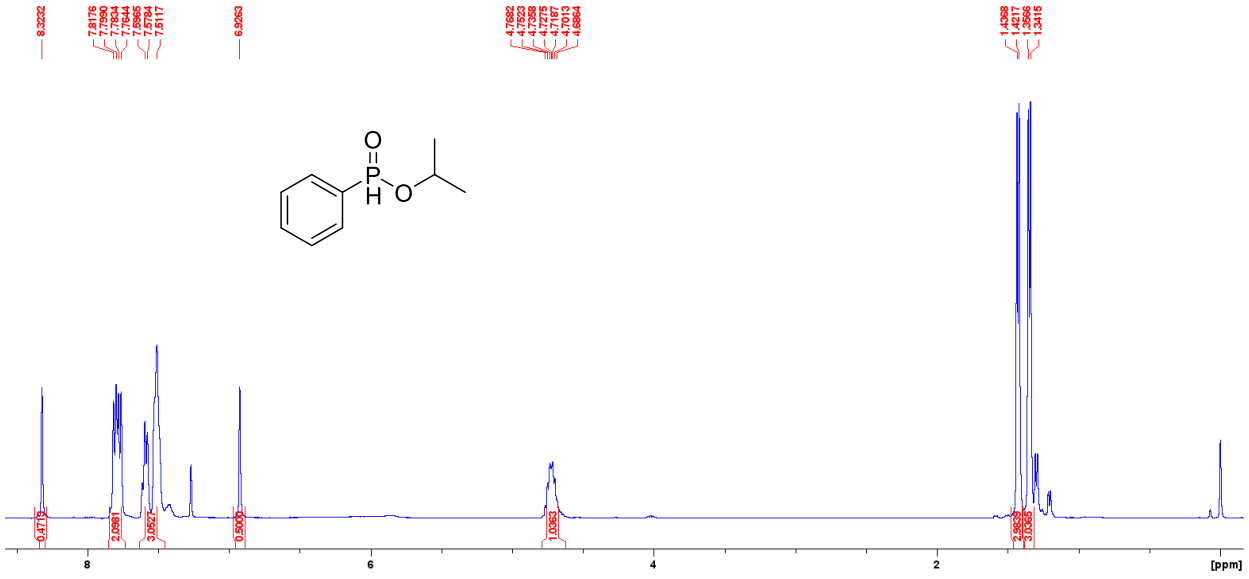
General Procedure for Bifunctional Catalytic Synthesis of Isopropyl-(Alkyl)-Phenylphosphonate



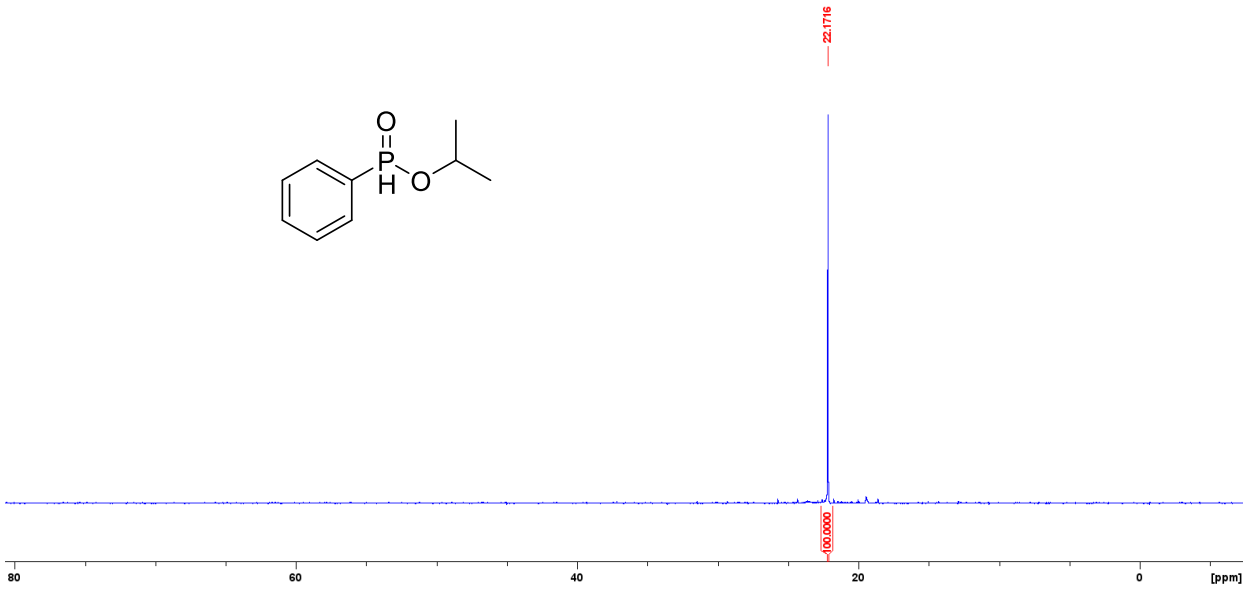
Scheme 6

100 mg of isopropyl-(phenyl)-H-phosphinate (1.0 eq., 0.543 mmol) in 1.8 mL of dichloromethane was added to a 25 mL round bottom flask with a stir bar. The flask was then sealed and placed under a nitrogen atmosphere, then cooled to 0˚ C. 0.21 mL of carbon tetrachloride (4.0 eq, 2.172 mmol) was added once the solution had cooled. In a separate 5-mL vial, 27.4 mg of (-)-benzotetramisole (0.2 eq, 0.109 mmol), 0.189 mL of *N,N*-diisopropylethylamine (2.0 eq, 1.086 mmol), and an alcohol (0.5 eq., 0.271 mmol) were dissolved in 0.3 mL of methylene chloride which was then transferred to the reaction flask. The reaction continued for approximately 8 hours at 0° C (alternatively 2 hours at rt). The reaction was then quenched with 1 mL of 1 M hydrochloric acid and the mixture was extracted three times with ethyl acetate before being dried over sodium sulfate. The product was isolated by flash silica gel chromatography using a gradient ratio of ethyl acetate and hexanes as an eluent. Products were verified for their purity by ^{1}H NMR and ^{31}P CPD NMR. Enantiomeric excess (ee) was then determined by HPLC in a 5:95 ethyl acetate to hexanes mobile phase.

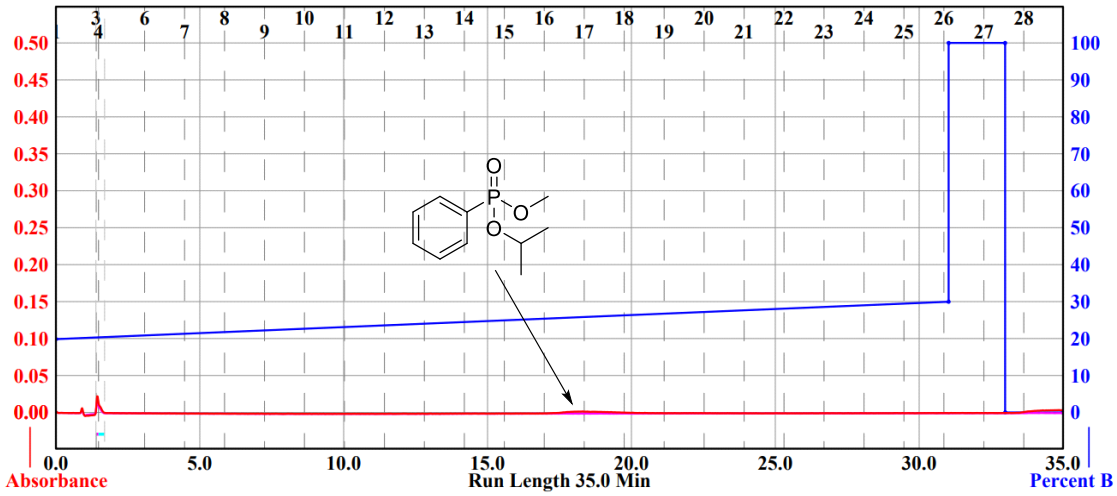
Supplementary Data



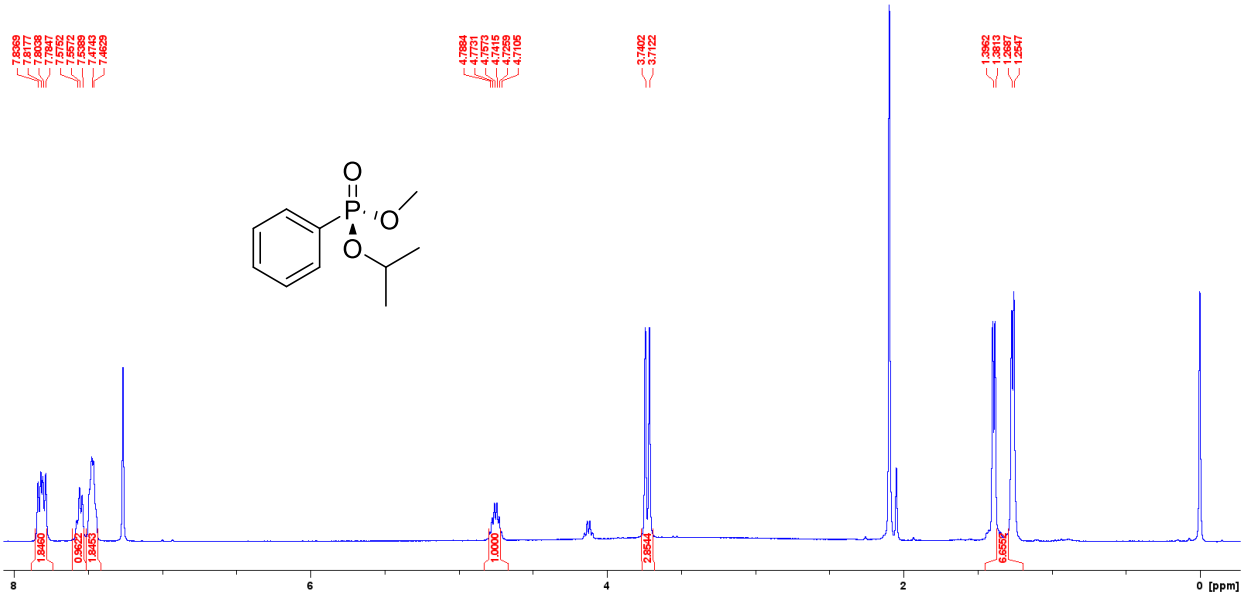
Supplement 1: ^{1}H NMR



Supplement 2: ^{31}P CPD NMR



Supplement 3: Flash Column Chromatography



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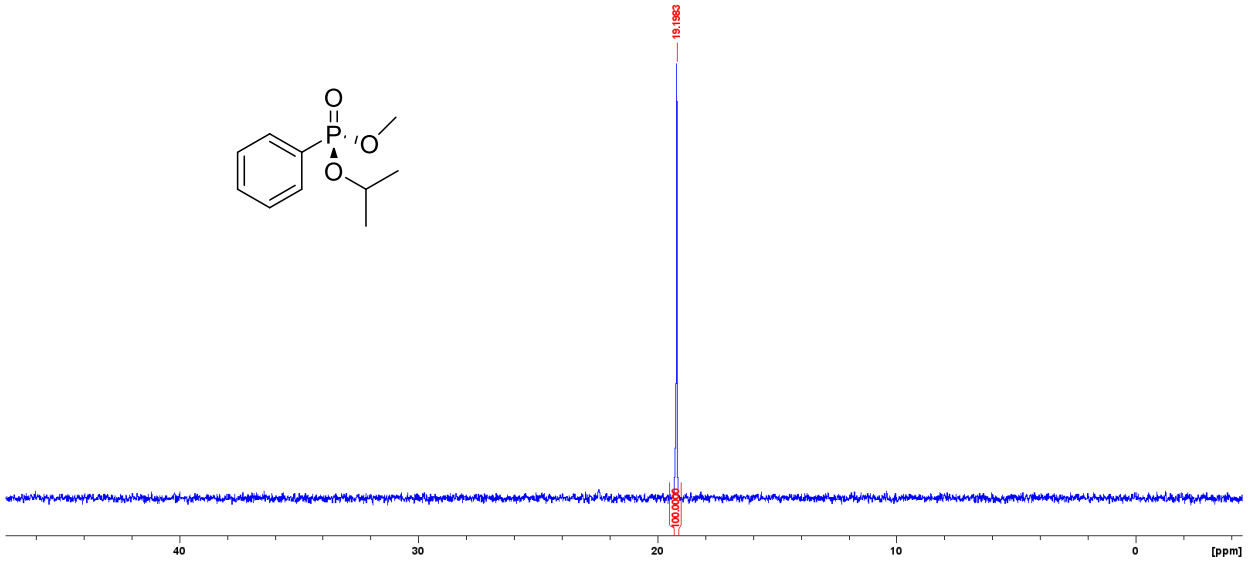
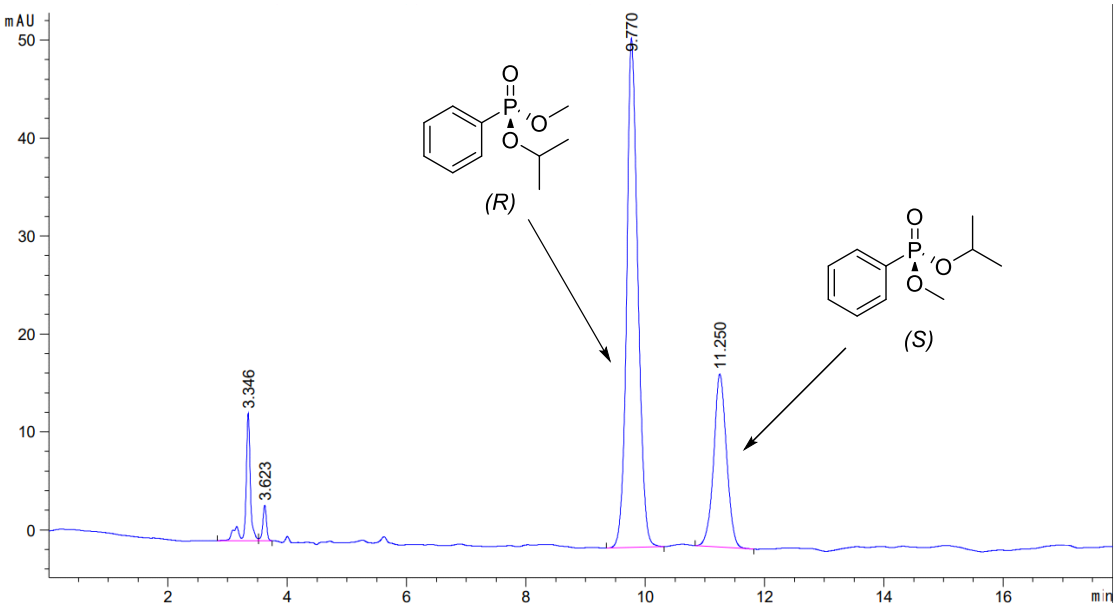
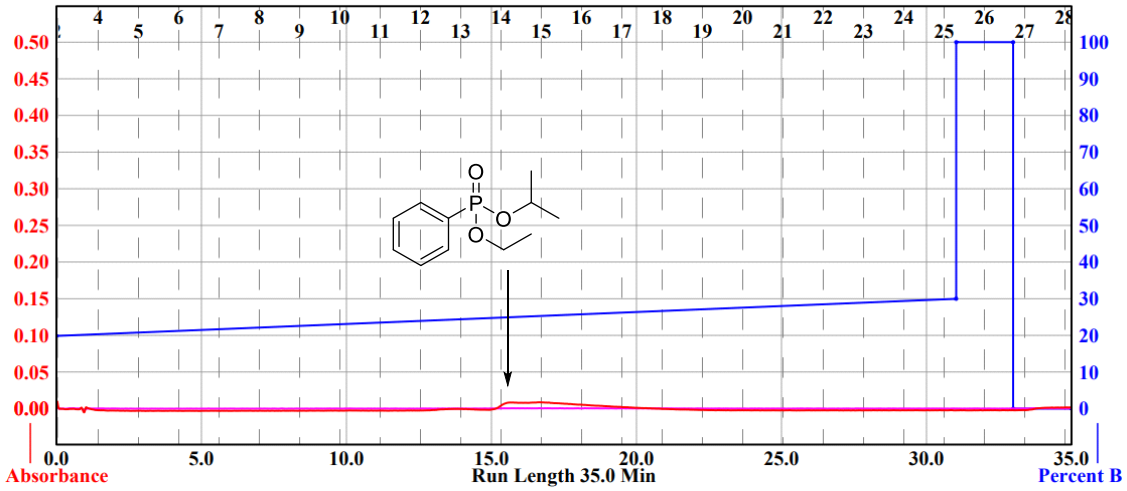


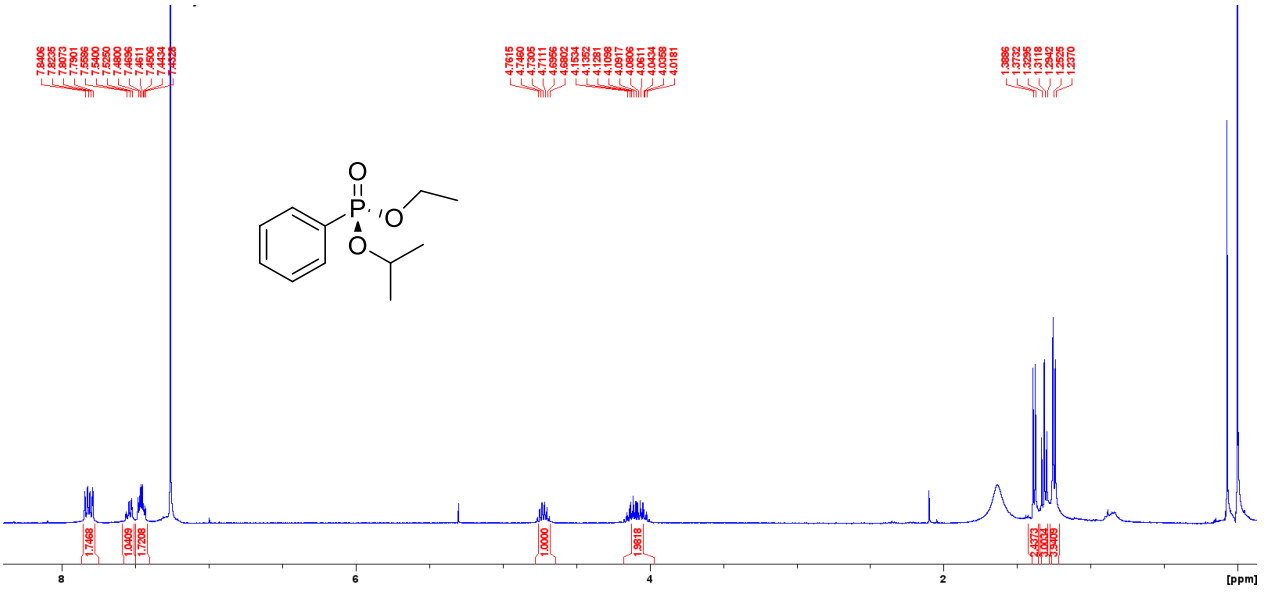
Supplement 5: ^{31}P CPD NMR



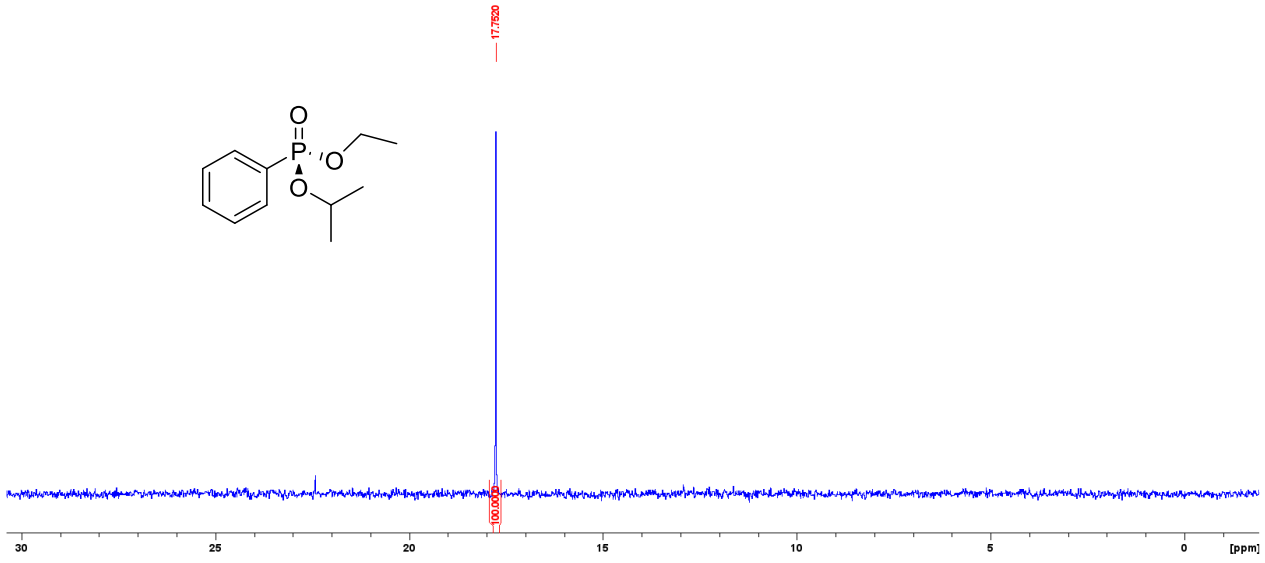
Supplement 6: HPLC



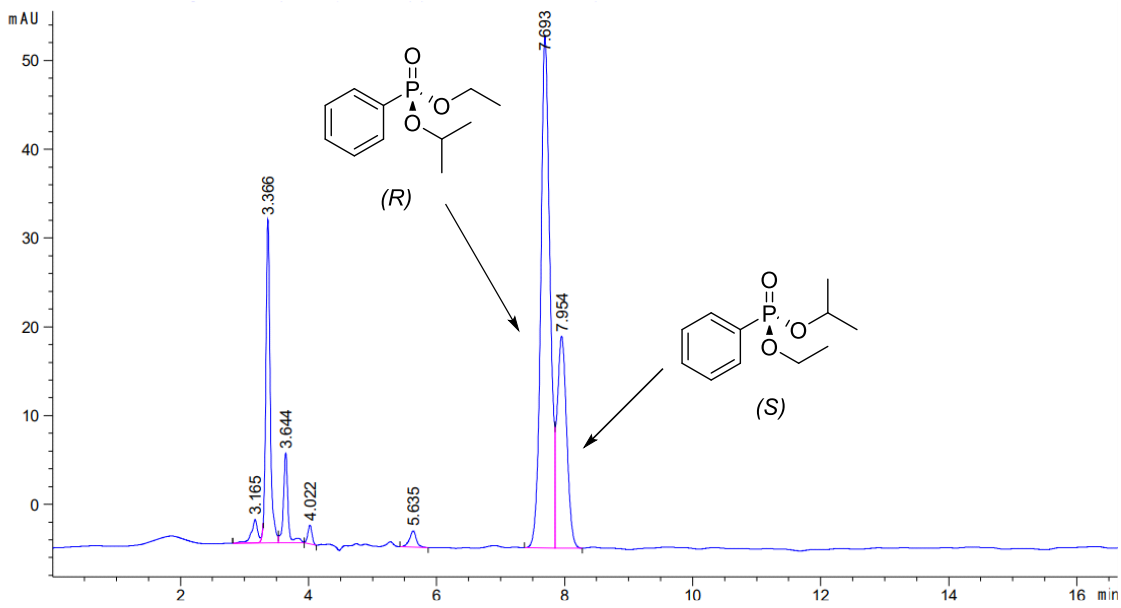
Supplement 7: Flash Column Chromatography



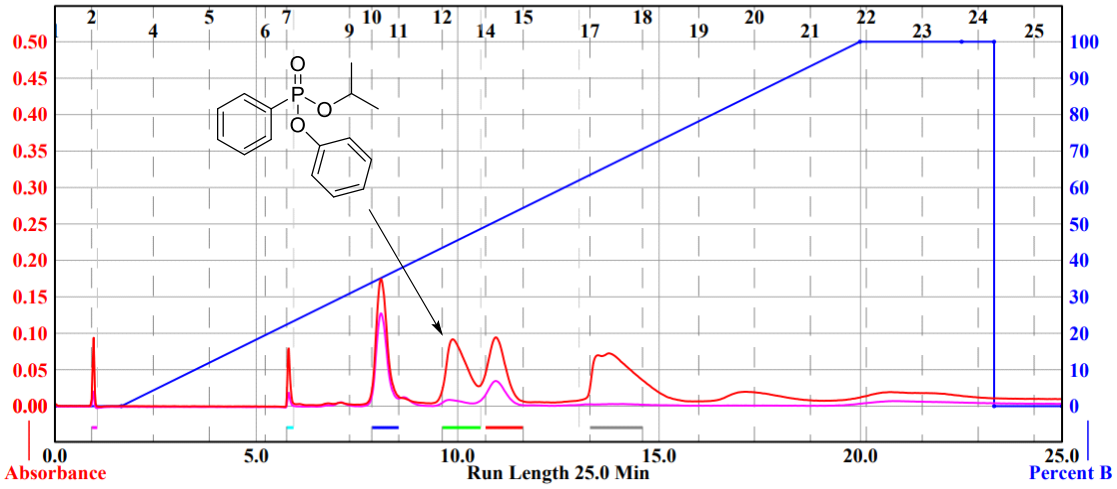
Supplement 8: ^{1}H NMR



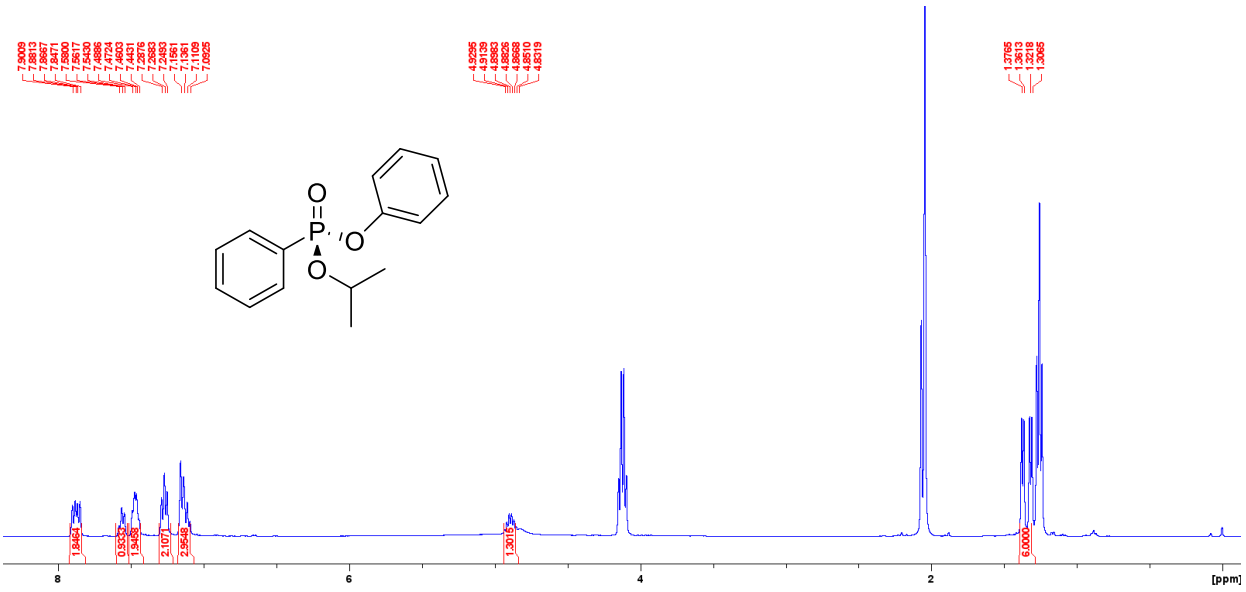
Supplement 9: ^{31}P CPD NMR



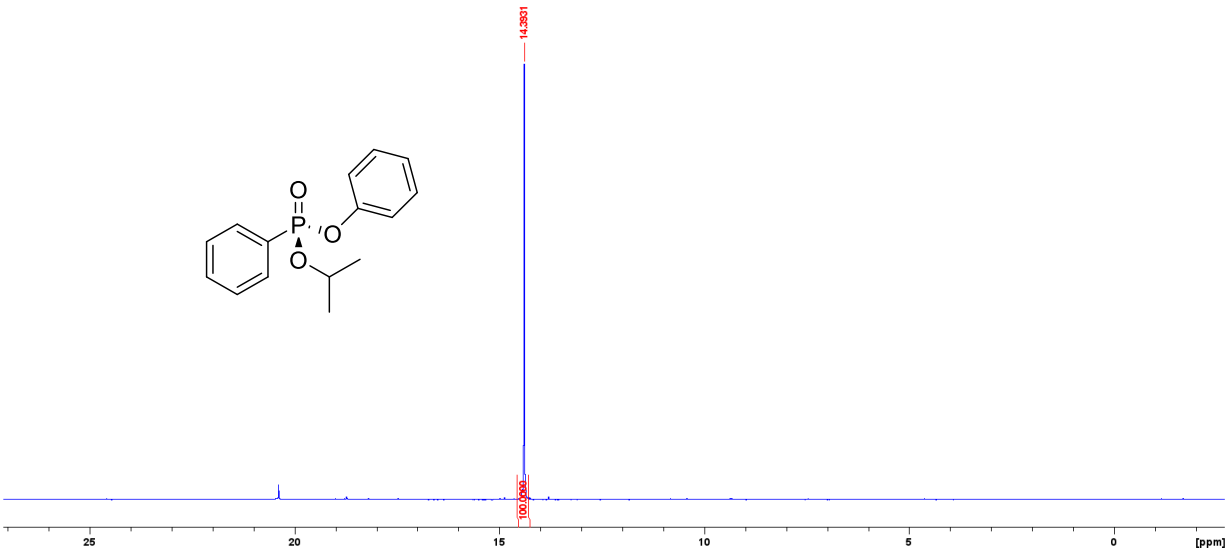
Supplement 10: HPLC



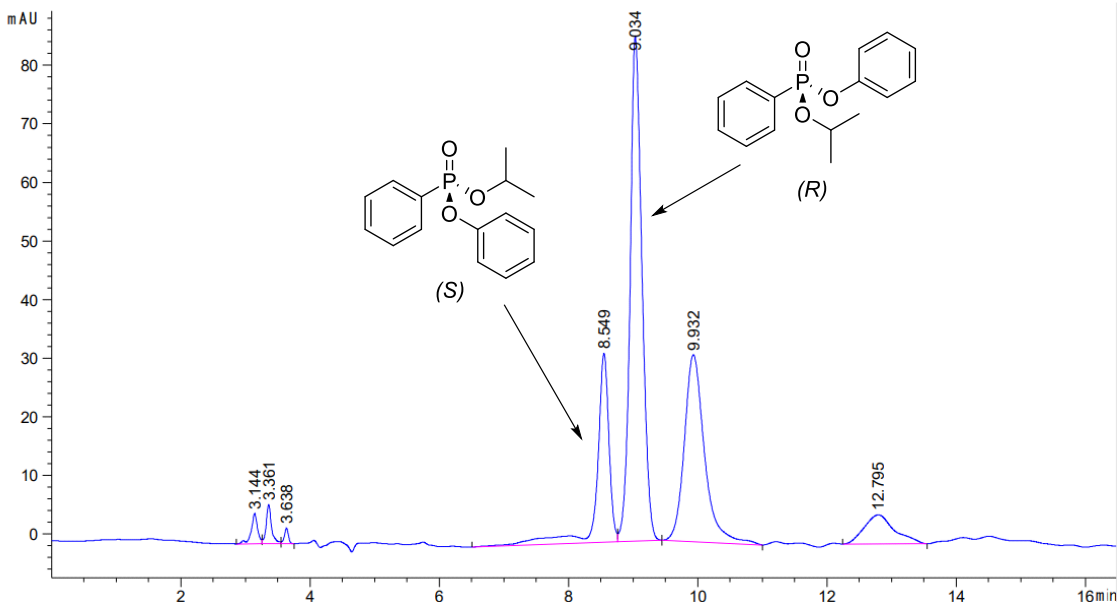
Supplement 11: Flash Column Chromatography



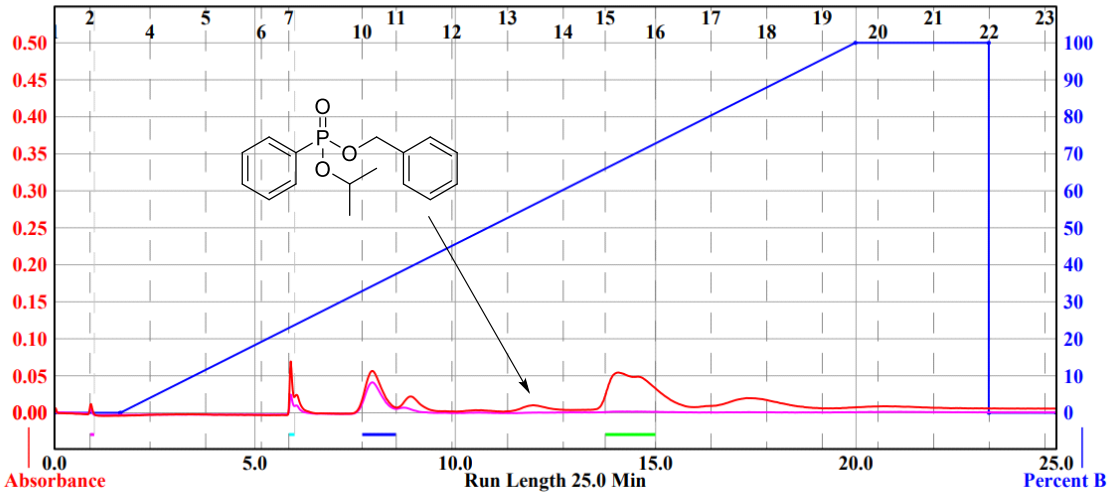
Supplement 12: ^{1}H NMR



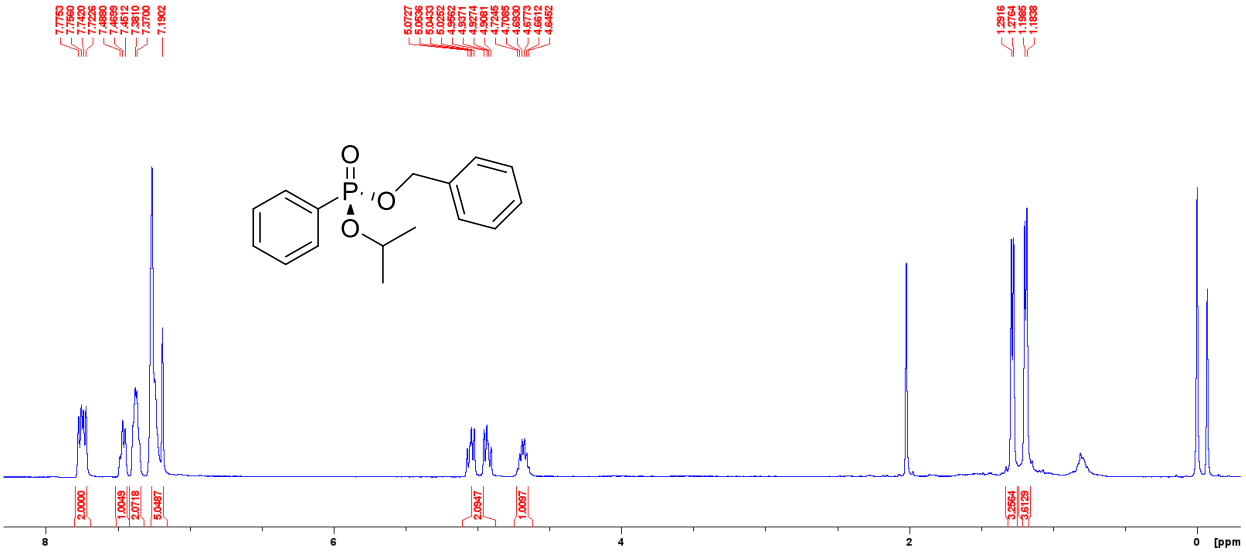
Supplement 13: ^{31}P CPD NMR



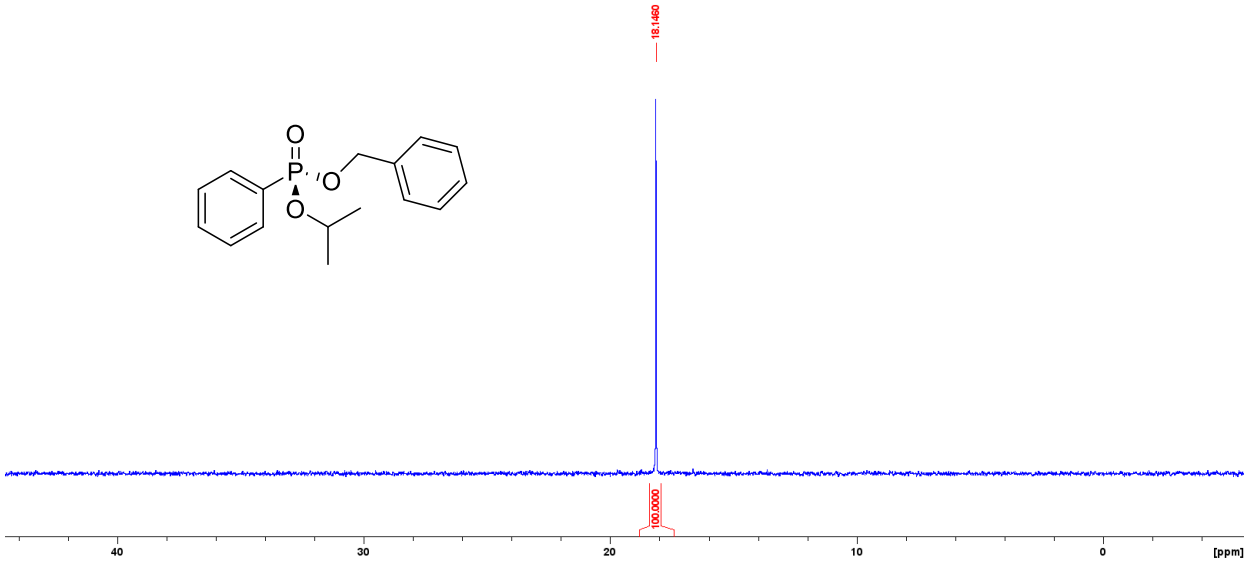
Supplement 14: HPLC



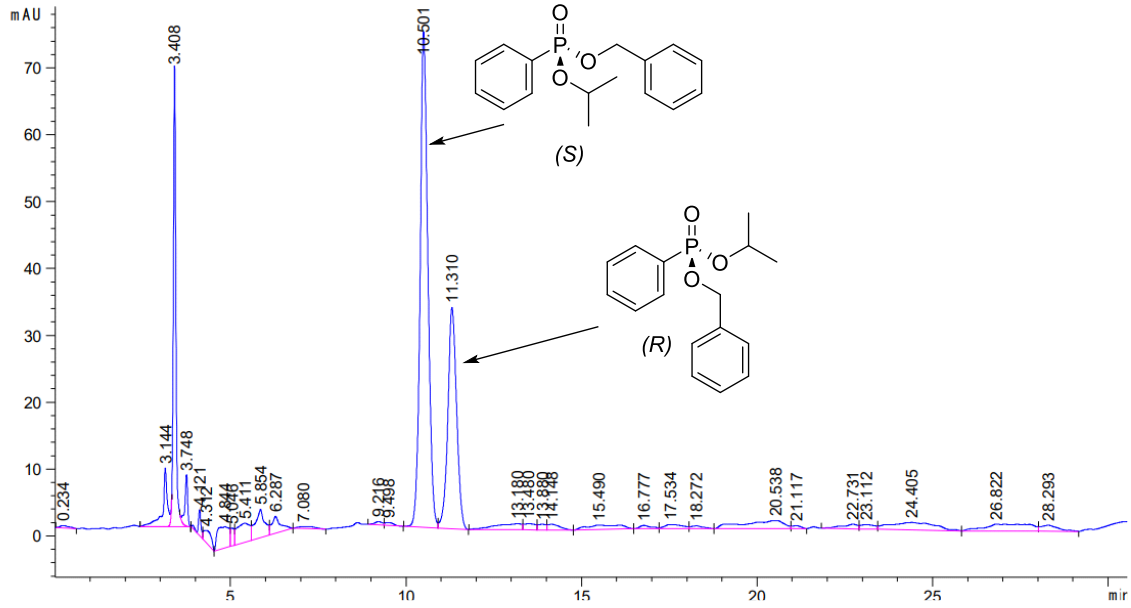
Supplement 15: Flash Column Chromatography



Supplement 16: ^{1}H NMR



Supplement 17: ^{31}P CPD NMR



Supplement 18: HPLC

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