Synthesis and Characterization of Novel Ligand for Use on Rhodium Paddlewheel Complexes

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ABSTRACT

Dirhodium (II) paddlewheel complexes have proven to be useful catalysts in many transformations including C-H insertions, cyclopropanation, and silane insertion reactions. One deficiency of these catalysts is the inability to modulate the enantioselectivity with reactive diazo compounds. One avenue for potential improvement of paddlewheel complexes is coordinating ligands in the axial site to increase enantioselectivity. The axial site has been occupied by various ligands including N-heterocyclic carbenes, nitrogen compounds, and phosphorous compounds. This work examines compounds that can be used as ligands on dirhodium complexes that have a pendant chain containing a dibenzyl phosphite and dibenzyl phosphate, both of which are unpublished compounds. By having these pendant chains tethered to the oxazolidinone backbone, control is built-in due to the proximity effect and hemilability of the ligand being synthesized. This study also optimized the process for making oxazolidinones after cyclization resulted in some six-membered ring when the five-membered ring was desired. Purification of the phosphite ligand proved to be difficult due to the contamination of side products formed during the process, but was solved by using triethylamine in the eluent of the chromatography process. The ligands obtained can replace bridging ligands on dirhodium (II) complexes and can be used for diazo-mediated reactions.

TABLE OF CONTENTS

CHAPTER ONE INTRODUCTION AND GENERAL INFORMATION..... 1
CHAPTER TWO RESULTS AND DISCUSSION..... 10
CHAPTER THREE EXPERIMENTAL SECTION..... 18
CHAPTER FOUR CONCLUSIONS AND RECOMMENDATIONS 22
LIST OF REFERENCES..... 24
APPENDIX…….…… 27
VITA…… 35

LIST OF FIGURES

Figure 1.1. Rhodium Paddlewheel Complexes……1
Figure 1.2. Catalytic Cycle for Rhodium Paddlewheel Complexes…….....1
Figure 1.3. Diazo Compounds…….2
Figure 1.4. C-H Insertion vs. Cyclopropanation…….3
Figure 1.5. C-H Insertion Transition State……..4
Figure 1.6. Lactam Ring Formation with NHC's in Axial Site……...5
Figure 1.7. Cyclopropanation with On-bead catalysts……6
Figure 1.7. Turro's Rhodium Complex with Nitrogen Tether…….7
Figure 1.9. Representation of Cone Angle……..8
Figure 2.1. Optimization of Oxazolidinone……12
Figure 2.2. HPLC trace of isolated material……...16

LIST OF SCHEMES

Scheme 2.1. Synthesis of Oxazolididnone……10
Scheme 2.2. Baldwin's Rules Reaction……..12
Scheme 2.3. Synthesis of Phosphite and Phosphate……...12
Scheme 2.4. Mechanism to make Tetrazole Salt……13
Scheme 2.5. Synthetic Pathways to Phosphines…….14
Scheme 2.6. Alternative Routes to Catalyst Synthesis……...17
Scheme 4.1. Synthesis of Phosphines …….20

CHAPTER ONE
INTRODUCTION AND GENERAL INFORMATION

Dirhodium (II) paddlewheel complexes (Figure 1.1) have been used as catalysts for C-H insertion[1-4], cyclopropanation[5-9], and silane insertion reactions.[10-11] The equatorial groups, shown as acetate groups in Figure 1, can influence enantioselectivity with reactive diazo compounds based on the ligand symmetry, chirality, and donor ability. The axial sites, designated as L groups in Figure 1, are the reactive sites of the complexes. A lot of research has been performed using $Rh_2(OAc)_4$, yet since $Rh_2(OAc)_4$ is achiral, much of the research into increasing enantioselectivity has looked into varying the ligands to create more enantioselective products.

Rhodium paddlewheel complexes use diazo compounds to generate intermediate rhodium carbenoid species, which are able to undergo a variety of addition reactions. The proposed catalytic cycle (Figure 1.2) starts with the diazo compound reacting with one of the rhodium atoms, losing dinitrogen to form a metal-carbene species. This step was confirmed that a carbanion must be formed since, spatially, there is not enough room for a box-like intermediate to be

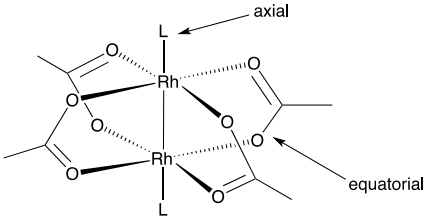


Figure 1.1 (left) A rhodium paddlewheel complex where the L represents a ligand in the axial site and the acetates are the equatorial, or bridging ligands.

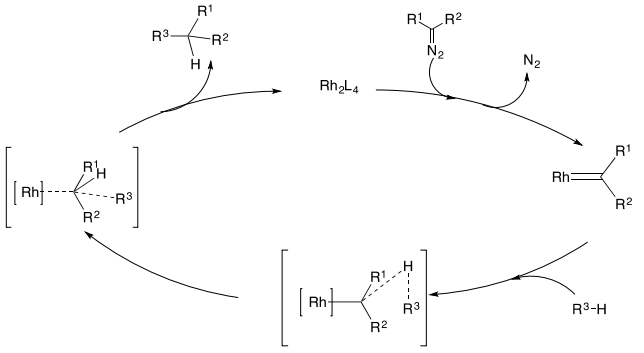


Figure 1.2 (right) Catalytic cycle of rhodium paddlewheel complexes.

formed. Once this step takes place, a step-wise reaction occurs to abstract a hydrogen from the substrate. The electrons that form the bond to the hydrogen come from the carbenoid, resulting in a carbocation. The catalytic cavity is used to position the substrate in the most favorable conformation, but is a quick concerted step to form the new C-C bond and regenerate the rhodium paddlewheel catalyst.

Diazo compounds most commonly used in dirhodium catalysis are categorized into three general groups, depending on what is attached to the carbon bound to the diazo group: donor-acceptor, acceptor, and acceptor-acceptor. A donor refers to electron-donating groups, while an acceptor denotes an electron-withdrawing group. The electronic nature of the diazo substrate has a large effect on the regio- and diastereoselectivity of the rhodium-catalyzed reaction. As seen in Figure 1.3, as the substituents on the diazo carbon are less electron-donating, these species become more reactive; however, the trend for selectivity goes in the inverse direction. More electron-rich diazo compounds are less reactive because they are able to help donate more electron density to the rhodium center, making the rhodium center less electrophilic. Due to this tight bind, donor-donor substrates are not typically used in catalytic activity. Many have

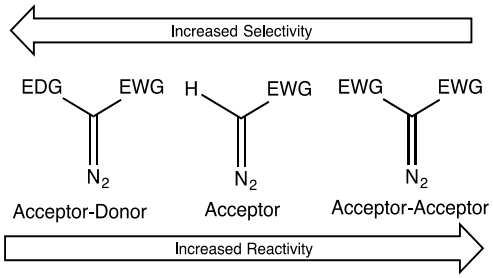
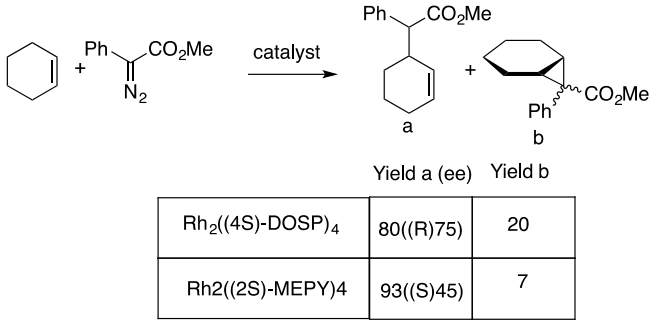


Figure 1.3 Influence of diazo electronic structure on reactivity and selectivity in Rh-catalyzed reactions (where EDG is an electron-donation group, and EWG is an electron-withdrawing group).

taken advantage of replacement of the achiral acetate ligands with chiral equatorial ligands as a means to improve the stereoselectivity of the rhodium catalyst.

One way that these complexes can be tuned to improve selectivity is to exchange the equatorial ligands on the complex. These equatorial ligands can vary from carboxylic acid, amide, and many other derivatives. By increasing the electron donation, the stability of the dirhodium complex may be increased, inducing the substrates to linger in a later transition state, allowing the ligands to have a greater influence over stereoselectivity. By modulating the ligands that are bound to the rhodium, reactivity and selectivity can be adjusted to fit the needs of the process at hand. One complex that has undergone a lot of research is the $Rh_2(DOSP)_4$, where DOSP= [(R)-(+)-N-(p-dodecylphenylsulfonyl)prolinato], developed by Huw Davies' group.[1] $Rh_2(DOSP)_4$ is a



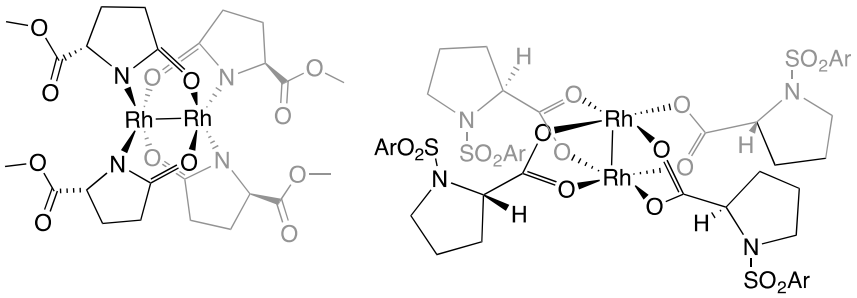


Figure 1.4 Shown is Muller and Tohill's experiment with rhodium catalysts. In parenthesis are the enantiomeric selectivity and the enantiomeric excess. (bottom left) $Rh_2(MEPY)_4$ (bottom right) $Rh_2(DOSP)_4$ (Ar=p-$C_{12}H_{25}C_6H_4$).

prolinate derivative that uses the D_{2h} symmetry (Figure 1.4) to induce stereochemistry in C-H insertions. The influence of the ligand on stereoselectivity is highlighted in a study by Muller and Tohill (Figure 1.4): In a reaction comparing the ratios of C-H insertion vs. cyclopropanation, $Rh_2(DOSP)_4$ was able to give a 4:1 ratio in favor of C-H insertion, while $Rh_2(MEPY)_4$ was able to favor the C-H insertion in about a 9:1 ratio.[12] By modulating the ligands, it would stand to reason that we would be able to produce more chemoselectivity (C-H insertion vs. cyclopropanation), yet create better enantioselectivity (R vs. S-enantiomer). C-H insertions reactions can change the direction of synthetic chemistry. By allowing for addition at specific carbons, C-H insertion chemistry could revolutionize C-C bond formation. With chiral rhodium catalysts, inducing stereochemistry to molecules can be easier than many of the processes set in place now.

One area of study that has been overlooked in dirhodium paddlewheel complexes is the use of the axial site coordination because it is difficult to know the number of ligands that are bound to the axial sites. The axial sites of dirhodium complexes are where the catalytic reactions occur, but while one of these sites is being used to react with the diazo substrate, the other is being used as an electrophilic sink. There is evidence (Figure 1.5) that when reacting with the dirhodium complex, the reactive site becomes a

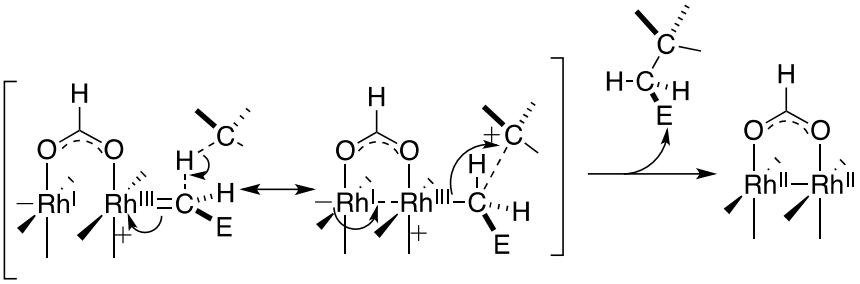
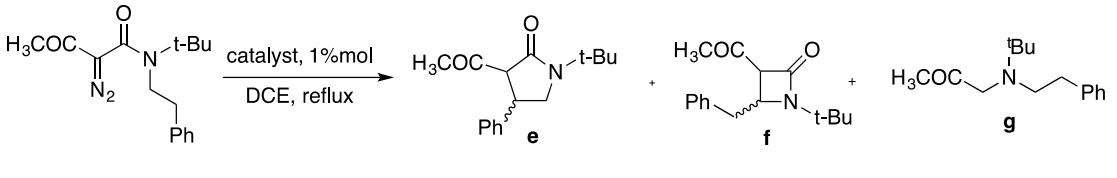
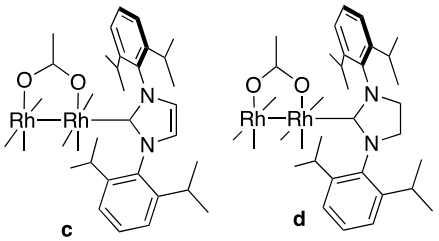


Figure 1.5 Nakamura's model for C-H insertion.

Rh^{III} after the carbenoid has been made and the extra electrons flow to the other rhodium.[13] Therefore, with the appropriate choice of axially-coordinating ligand, the rhodium carbenoid species may be stabilized allowing for greater selectivity. This research uses a novel ligand to bind to one of the axial sites via a tether, which will donate into the electrophilic sink rhodium. By tethering the donating ligand to the complex, if the bond is broken between the metal and heteroatom, the tether will allow for re-association to the metal. The bond between the ligand and the rhodium is difficult to break supporting that the complex would remain in a later transition state, or more like the product.

Several studies have looked into how the occupying the axial site affects the reactivity of the rhodium paddlewheel complexes. One of the earliest instances where the axial site was modulated for reactivity on the rhodium paddlewheel complexes was coordinating a N-heterocyclic carbene (NHC).[14] The NHC afforded the ability to strongly bind to the rhodium (Figure 1.6). The strong sigma donation should make the Rh-Rh bond breakage more facile. The Rh-L bond, being much stronger, is favored over the Rh-



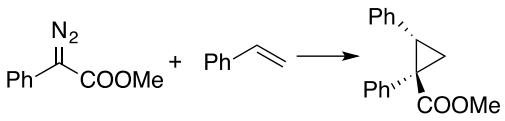


	e	f	g
$Rh_2(OAc)_4$	65	34	-
c	18	46	36
d	32	39	29

Figure 1.6 Bonding NHC's in the axial site in lactam ring formations also leads to the producing the undesired product **g**.

Rh bond, thus lengthening Rh-Rh bond to the point of breakage in the case of the NHC. It was observed that the extra electron-density provided by the NHC ligand resulted in a Wolf-Kishner rearrangement, due to the stability of the rhodium the diazo bound to, which expels carbon monoxide instead of cyclizing lactams. This study demonstrated that donation of electron density into the axial position is able to influence the reactivity of the rhodium center: introducing too much electron donation into the axial site may also result in undesired, but interesting, products.

Knowing that NHC ligands were too strong in σ-donation, research into other ligands was conducted. One such donor is nitrogen, which allows for a strong bond to the metal center and is also purely a σ-donor into metal centers. One study[15] used peptides as a support for the rhodium catalyst (Figure 1.7). By using aspartic acid residues as the bridging ligands, the next amino acid in the sequence could coordinate to the rhodium center. Compared to when the reaction had nothing in the axial site it was found that enantioselectivity was improved when histidine was added to the ligand sequence next to an aspartic acid, used as an equatorial ligand. Other amino acids, such as phenylalanine, where the nitrogen is coordinating, proved to give higher enantioselectivity in



	ee
Phe	51
[Rh]-His	97

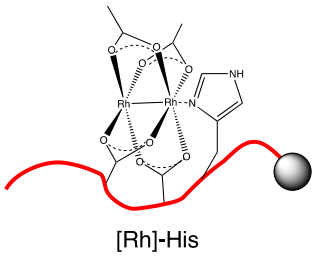


Figure 1.7 Quantitative reaction using on-bead rhodium catalyst.

cyclopropanation reactions (59% ee), but did not give ee's as high as that of histidine derivatives (97% ee).

Pyridines have been put in the axial site (Figure 1.8) to test the effectiveness of binding to DNA. By using naphthyridines with a pyridine as a pendant chain (Figure 1.7), it was found that when more than one axial site was bound to a nitrogen binding properties to DNA were nearly nonexistent nor did it help in the inhibition of transcription.[16] However, when one or both axial sites were open, the complex shows promise toward site on reactivity with biomolecules. One of the main points that came out of this study was that the ability for ligands to be attached to the equatorial ligand, yet still occupy an axial site. Another obstacle that this paper was able to overcome was making a heteroleptic catalyst with only one axial site being occupied. Both rhodium centers are susceptible to bonding to ligands donating electrons, so when pendant chains are introduced it is often difficult to obtain singly substituted catalysts. They were able to capitalize on nitrogen's donation into the rhodium center and, by only controlling stoichiometry of the pendant ligand, they were able to get substitution of only one ligand.

Phosphines have been bound to rhodium in many catalysts including the

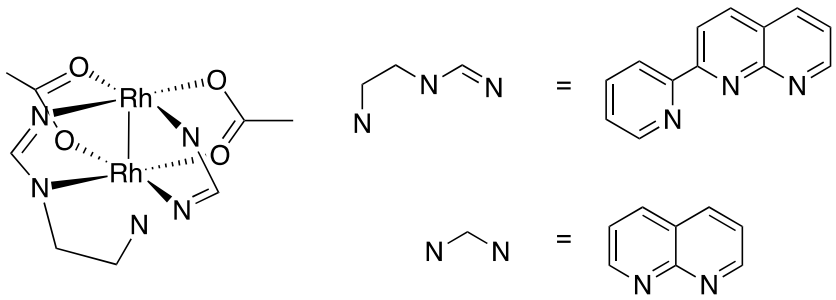
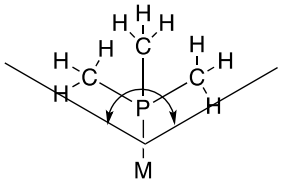


Figure 1.8 The dirhodium catalyst used by Turro's group to put pyridines in the axial site.

Wilkinson's catalyst, the oxo process, and on dirhodium paddlewheels.[17] Phosphines are particularly good ligands in organometallic chemistry because they are able to donate electron density into a metal and they are easily tunable. Being an L-type donor, the phosphines do not change the charge of the metal they bind to, but add to the electron count. Phosphites present a new challenge in being able to pi-backbond with metals. Back-bonding allows for the metal center to donate electrons back into the ligand, which can affect the electron density in the metal-metal bond. Using sterically bulky groups to surround the phosphorus to make the metal-phosphorus bond long enough can offset this back-bonding. By simply replacing the groups bound to the phosphorus, donation can be modulated as well. When donating into a metal center, phosphines with alkyl chains have the most donation, followed by aryl phosphines.[18] Much of this donation is due to the cone angle (Figure 1.8) that each phosphine has. Phosphites donate less than the phosphines and phosphates donate less than the phosphites (donation is through the oxygen in phosphates not through the phosphorus group, Figure 1.9).

Phosphorus ligands have been used in creating enantioselective reactions. Rhodium being bound to a peptide chain was tested with various phosphorus compounds including phosphines, alkyl and aromatic, and phosphites. It was found that when in the



$$PR_3 > P(OR)_3 > P(=O)(OR)_3$$

Figure 1.9. (left) A representation of cone angle that helps estimate donation into a metal center. (right) A list of donation capabilities for phosphorus containing groups to metal centers.

presence of triphenyl phosphite, enantioselectivity for silane additions went up to 66% ee compared to the 50% ee that was achieved with no additives.[10] This is one of the few cases where enantioselectivity is increased by an axial ligand. From this study, it can be concluded that phosphorus ligands as pendant chains on equatorial backbones would be a good way to control the axial ligands. By doing this, one can control the amount of "additives" that bind to the rhodium complex and they would be able to control the amount of donation by replacing more electron donating groups with less electron donating group (or electron withdrawing groups) on the phosphorus.

This research seeks to examine the donation into the rhodium metal center through the axial site with various phosphorus groups such as substituted aryl groups, alkyl groups, phosphites, and phosphates. By replacing these groups, the goal is to modulate the donation into the axial site with the enantioselectivity of products. This research will be using oxazolidinones as a backbone for the tethered phosphorus groups. Oxazolidinones are N, O donors, the atoms bind to the rhodium, and can be synthesized through known procedures.[19]

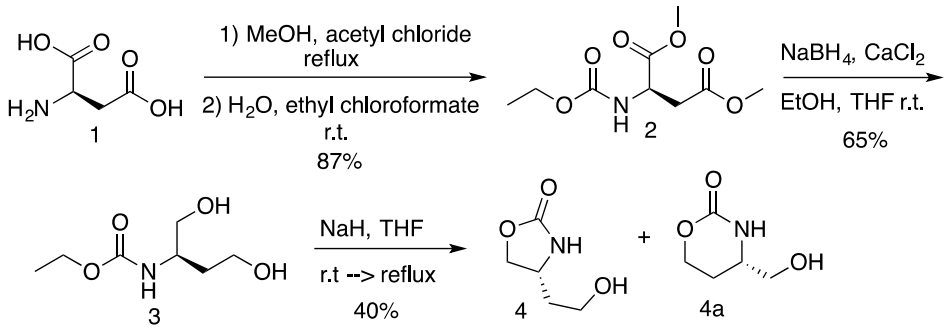
CHAPTER TWO
RESULTS AND DISCUSSION

In order to make ligands that would be analogous to the N, O donors (MEPY and MEOX), we started with amino acids to make the oxazolidinones. These oxazolidinones are capable of enhanced electron donation into the rhodium (II) paddlewheel complex compared to those with carboxylic acid residues, and can be synthesized starting from low-cost, enantio-enriched starting materials via established procedures.[19]

SYNTHESIS OF OXAZOLIDINONE BACKBONE

Following a published synthetic route[19] (Scheme 2.1), L-aspartic acid **1** underwent a Fischer esterification using methanol and acetyl chloride. The amine group of the resultant methyl ester was then protected with ethyl chloroformate to form the carbamate **2**. Combining these steps afforded **2** in good yields (87% over two steps) and did not require purification by column chromatography.

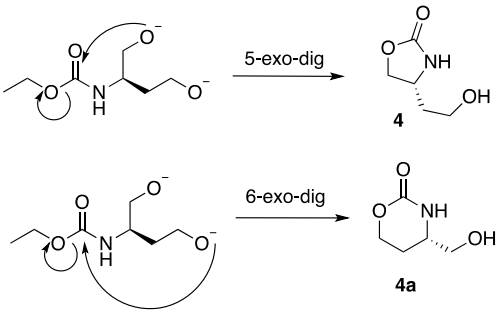
From the carbamate protected product, sodium borohydride and calcium chloride were used to reduce the methyl ester groups to alcohols. The calcium chloride was required in order to make the sodium borohydride a better reducing agent; procedures



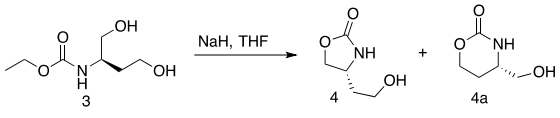
Scheme 2.1 Synthesis of oxazolidinone **4.**

using sodium borohydride or lithium chloride were performed, but did not give satisfactory results. Our results showed partial reduction even with the same equivalents as the procedure by Burgess's group.[19] Purification of the diol product was also troublesome. The diol is relatively soluble in water, making extraction of **3** from the aqueous phase difficult, requiring numerous extractions with ethyl acetate. By acidifying the solution, it was hypothesized that more of the diol product would be extracted because the diol product would be more soluble in the organic layer resulting in more product being obtained, but did not prove to give better results (50% yield).

As these reactions did not give high yields, we turned to a more straightforward approach to the reaction. A study by James O'Malley's group[20] reported the successful reduction of pyrrolidinone esters using sodium borohydride in methanol, and small-scale reactions following this procedure afforded diol **3** in good yields (65% yield). Unfortunately, when the reaction was scaled up, too much heat was produced with the addition of the sodium borohydride at 0°C. A possible solution to this would be to try the reaction at lower temperatures for a longer period of time or adding the $NaBH_4$ at a slower rate.



Scheme 2.2 Mechanism of Baldwin's Rules between 5-exo-dig **4** and 6-exo-dig **4a.**



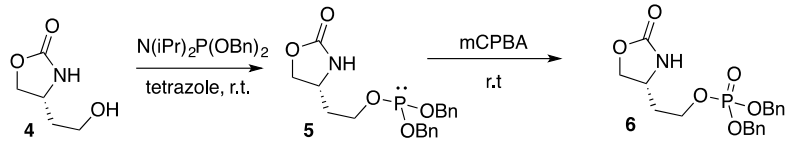
Time (hrs)	Temp (°C)	Yield (%)	4/4a
5	r.t → reflux	78%	5/1
18	reflux	60%	2/1
18	r.t.	40%	100/0

Figure 2.1 Optimization of oxazolidinone **4.**

Cyclization of diol **3** using sodium hydride completed the oxazolidinone synthesis. However, an issue with this reaction was competition between the formation of the desired five-membered ring **4** over the six-membered ring (**4a**). According to Baldwin's rules[21], the five-membered ring should be favored as the kinetic product via 5-exo-dig versus the six-membered ring through 6-exo-dig. When the reaction was performed at reflux for two hours, a 5:1 ratio favoring the 5-membered ring **4** was obtained (Figure 2.1). We found that the compounds were also not separable by column chromatography or by recrystallization. When refluxed overnight (18 hours), the reaction gave a 2:1 in favor of the five-membered ring **4** and when performed at room temperature (18 hours), the reaction was without the six-membered ring **4a**.

SYNTHESIS OF PHOSPHITE AND PHOSPHATE LIGAND

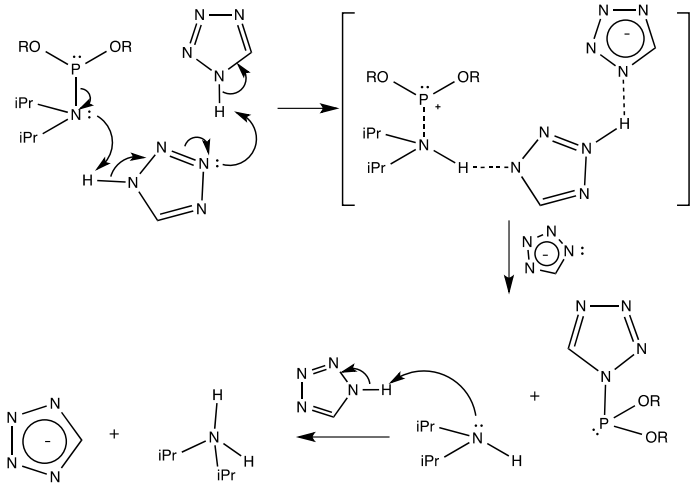
Phosphite ligand **5** was produced by performing a tetrazole-catalyzed phosphoramidite alcoholysis with diisopropyl N,N dibenzylphosphoramidite (Scheme 2.3).[22] This method enabled the direct use of oxazolidinone **4**, circumventing the need or the modification of the hydroxyl moiety into a leaving group. While this was beneficial for efficiency, the resulting phosphite was difficult to purify. To form the phosphite, the tetrazole is used to help activate the phosphoramidite. After losing the amine, the phosphorus attacks a tetrazole molecule to form the active compound for the reaction. The protonated amine portion and the now charged, aromatic tetrazole creates a salt. A



Scheme 2.3 (bottom) Synthesis of phosphite **5** and phosphate **6.**

large portion of the salt (protonated amine and aromatic tetrazole) was filtered out, but, upon column chromatography, the salt still persisted in the product (Scheme 2.4). Purification of the phosphite was attempted on flash alumina, and the phosphite did not elute from the column even with 100% EtOAc as the eluent. The phosphite was very easy to oxidize when exposed to air in the solid phase, but trace amounts of the oxidized product started to form after 4 hours when in EtOAc. Purification issues were finally solved by filtration of the salt, followed by chromatography with flash silica using mixtures of ethyl acetate, hexanes, and triethylamine as the eluent. By adding triethylamine into the mixture, the silica gel was deactivated and allowed for the phosphite (34% yield) to elute through the column without oxidation.

Due to all of the problems with the phosphite, the phosphate ligand **6** was obtained to prove that the phosphite **5** was being made and would provide another variation of donation into the complex.[23] The phosphate was isolated in an 85% yield, proving that the tetrazole-catalyzed reaction was working to make phosphite **5**.



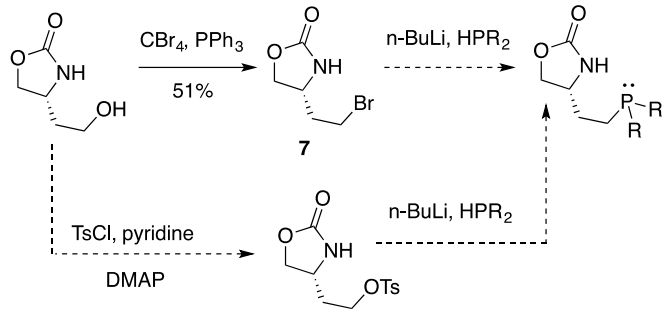
Scheme 2.4. Mechanism to activate phosphoramidite.

PATHWAY TO SYNTHESIS OF PHOSPHINES

Phosphine functionalized oxazolidinones can be synthesized from the displacement of alkyl bromides with n-butyl lithium and disubstituted phophines. Typical Appel conditions were used to produce the bromide-substituted material (Scheme 2.5).[24] The reaction enabled the separation of the 5-membered oxazolidinone from the undesired 6-membered compound via column chromatography despite low yields (51% yield). This technique was used as an option to separate out the ring sizes before the ring control experiments were conducted.

Another direction that this pathway could go is through the tosylation of the oxazolidinone (Figure 2.5). The tosyl product has been made before in a 40% yield by the Burgess group.[19] Once the tosyl product or brominated products are obtained, literature also provides a way to making oxazolidinones with phosphine tethers.[19] Once the phosphine residues are obtained, metalation onto the rhodium complex can be tested.

Once the phosphite ligand had been synthesized, coordination to the rhodium complex was attempted (refer to table 2.1 in Appendix). Doyle had proposed a synthesis for tetrakis rhodium paddlewheels with the use of chlorobenzene and a soxhlet adapter



Scheme 2.5 Synthetic pathways to phosphine ligands.

filled with a sand and sodium carbonate mixture.[25] We hypothesized that the carbonyl or phosphorus of ligand **5** would be able to coordinate to the axial site, and then displace an acetate group. When the carbonyl is coordinated in the axial site, the proton on the amide becomes more acidic during or after the displacement of the acetic acid ligand. If the phosphorus coordinates to the axial site, there is a risk that no substitution will occur. The reaction being refluxed would go through the soxhlet adapter and be neutralized with the sodium bicarbonate. When experimenting with various oxazolidinone products, isolated products were not attained. With the alcohol oxazolidinone, the problem was with the solubility of the oxazolidinone into the chlorobenzene. Upon addition of the phosphite to the chlorobenzene and rhodium (II) acetate mixture, there was an immediate formation of orange color produced likely due to the coordination of the phosphite into the axial site of the rhodium (II) acetate. The phosphite oxazolidinone might have been producing some useful catalyst, but I am under the impression that I was making both the mono-subsituted and bis-substituted catalysts and was not able to separate the two from one another. Another theory for the phosphite is that the conditions we were exposing the phosphite to could have oxidized it, making the phosphate. With the phosphate, there lies the possibility that the phosphate was exchanging into the axial site.

Another attempt at making the catalyst was by using solubility to help the reaction occur. In this attempt, the phosphite ligand was dissolved in DCM and rhodium acetate was added to the solution. I ran the reaction at both room temperature and reflux. I found that when the reaction was refluxed, I produced a purple color solution as opposed to the orange solution that was observed at room temperature. I was able to run silica columns

on the products and was able to isolate a single spot in 2.5% MeOH/DCM, but, when looking at a HPLC trace (Figure 2.2), the product was not fully isolated having three peaks overlap one another. Due to the fact that I ran these reactions on such a small scale (5mg $Rh_2(OAc)_4$), the NMR was very dilute, but it did not show a proton peak in the area of the proton on the nitrogen, which could be an indication that the nitrogen has bound to the rhodium complex.

Continued efforts for ligation may look towards the efforts by the Turro group[26] in which they used acetonitrile in the axial site to help the solubility of the rhodium (II) acetate into less polar solvents (Scheme 2.6). With the rhodium (II) acetate readily dissolving in the solvent, replacement of only one equatorial site is more likely. By having both axial sites pre-occupied, there is a competition between our ligand and the acetonitrile that we expect our ligands to outcompete. If the rhodium acetate is going into solution due to our ligand occupying the axial site, then there rises the opportunity for ligand to occupy the second axial site, substitute for two acetate groups, and create the bis-substituted complex. Another approach would be using trifluoroacetic acid to substitute for the equatorial acetate groups. By adding the trifluoroacetate groups to the rhodium complex, these groups are easier to displace than the acetate groups, due to the electron-withdrawing of the fluorines, and our ligand will prefer to occupy those

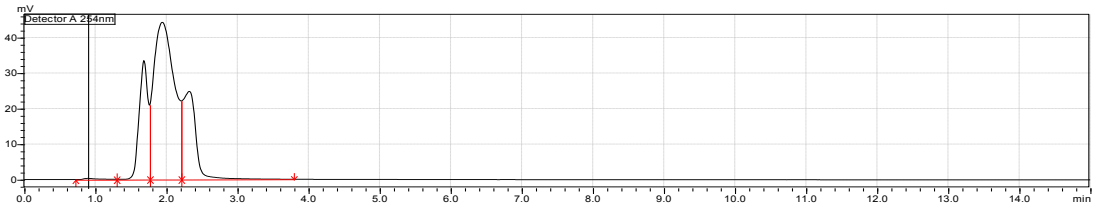
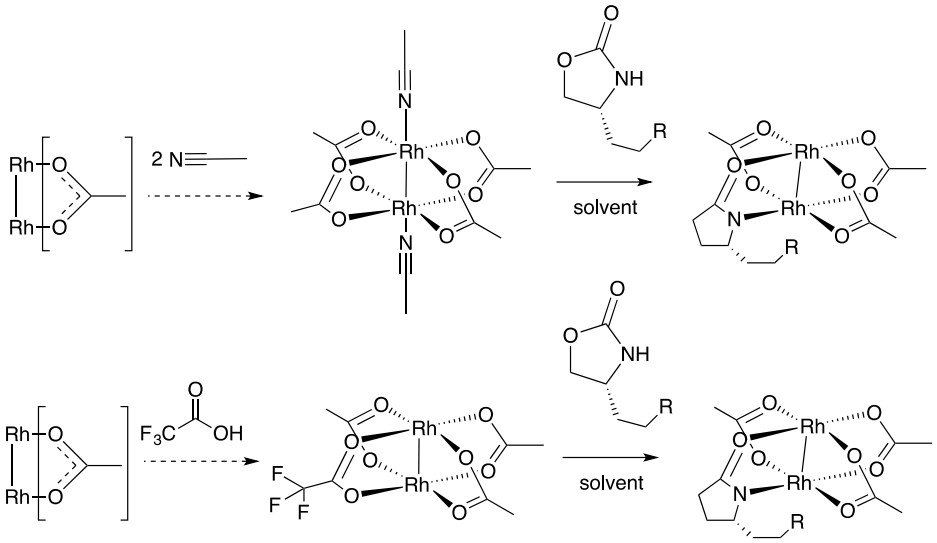


Figure 2.2. HPLC trace of isolated material.

equatorial sites. This will allow us to control how many ligands are exchanged.



Scheme 2.6. Alternative routes to catalyst synthesis.

CHAPTER THREE
EXPERIMENTAL SECTION

GENERAL PROCEDURES

NMR spectra were recorded on Varian Mercury Vx 300 MHz or Varian VNMRS 500MHz. Chemical shifts of ^{1}H and ^{13}C for NMR spectra were referenced by NMR solvents. Flash chromatography was performed using Sorbtech silica gel (40-60 μm) and Fisher alumina (60-325 mesh). Thin-layer chromatography was performed on Sorbtech aluminum backed plates coated with silica gel (200μm). Solvents were purchased from commercial suppliers. When noted, solvents were dried through alumina columns on an Inert Pure Solv Micro™ solvent purification system. High Pressure Liquid Chromatograph was a Shimadzu Prominence-I LC-2030. Unless otherwise stated, compounds were purchased from commercial suppliers and were used without further purification. All reactions were performed under nitrogen atmosphere.

OXAZOLIDINONE SYNTHESIS

Dimethyl (ethoxycarbonyl)-*D*-aspartate (1)

Compound **1** was prepared using the modification of known literature procedures[19]. Acetyl chloride (18 mL, 0.24 mol) was added dropwise to methanol (94 mL) at 0°C. The reaction stirred for 15 minutes. L-aspartic acid (10 g, 0.751 mmol) was added portionwise to the reaction at 0°C and refluxed for 3 hours. The reaction was cooled to room temperature, concentrated, and diluted with deionized water (267 mL). Sodium bicarbonate (33 g, 0.91 mol) then ethyl chloroformate (8 mL, 0.751 mmol) were each added to the reaction mixture at 0°C. The reaction mixture was stirred at room temperature for 8 hours. The reaction was then extracted with ethyl acetate (4x70 mL)

and washed with DI water and saturated NaCl. The solution was dried over Na_2SO_4 and then concentrated. Diester **2** was obtained as viscous oil (15.20 g, 0.65 mol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (s, 1H), δ 4.61 (m, 1H), δ 4.11 (q, 2H), δ 3.75 (s, 3H), δ 3.68 (s, 3H), δ 2.99 (dd, 1H), δ 2.85 (dd, 1H), δ 1.24 (t, 3H).

Ethyl (*R*)-(1,4-dihydroxybutan-2-yl)carbamate (3)

Diester **2** (25.26 g, 0.108 mol) was dissolved in THF (143 mL) and EtOH (286 mL). Calcium chloride (66.65 g, 0.601 mol) was added and stirred until the calcium chloride dissolved. Sodium borohydride (27.41 g, 0.735 mol) was added to the reaction at 0°C and stirred for 18 hours. Citric acid was used to quench the reaction and dissolved the solution. The reaction was extracted with ethyl acetate (6x100 mL) and washed with brine. A silica gel column was used to purify the compound (10% MeOH/DCM, R_f= 0.33). Diol **3** was produced as white crystals. (12.43 g, 0.07 mol, 65%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (s, 1H), δ 4.58 (t, 1H), δ4.35 (t, 1H), δ 3.94 (q, 2H), δ 3.40 (m, 2H), δ 3.23 (m, 1H), δ 1.63 (m, 1H), 1.44 (m, 1H), δ 1.14 (t, 3H).

(*R*)-4-(2-hydroxyethyl)oxazolidin-2-one (4)

Diol **3** (5.21 g, 2.94 mmol) was dissolved in anhydrous THF (73 mL). Sodium hydride (2.41 g, 6.03 mmol) was added to the reaction at 0°C and stirred for 2 hours. The mixture then refluxed for 3 hours, then cooled to room temperature. The reaction was quenched with 2M HCl, concentrated, and then re-dissolved in methanol. The reaction was dried over Na_2SO_4 and concentrated. A silica gel column (10% MeOH/DCM; R_f= 0.33) was used to purify the product. Oxazolidinone **4** was obtained as pale yellow crystals (1.56 g,

1.176 mmol, 40%). ^{1}H NMR: (300 MHz, DMSO-d_6) δ 7.64 (s, 1H), δ 4.51 (t, 1H), δ 4.36 (t, 1H), δ 3.91 (t, 1H), δ 3.82 (q, 1H), δ 3.42 (m, 2H), δ 1.59 (q, 2H).

SYNTHESIS OF PHOSPHITE AND PHOSPHATE LIGANDS

(*R*)-dibenzyl (2-(2-oxooxazolidin-4-yl)ethyl) phosphite (5)

A mixture of oxazolidinone **4** (200 mg, 1.53 mmol) and N,N dibenzyl phosphoramidite (0.855 mL, 2.29 mmol) were stirred in a flask. Tetrazole (10.7 mL, 4.58 mmol) in acetonitrile (3 to 4% w/v) was added to the flask dropwise at room temperature and a white precipitate formed. The reaction stirred for 4 hours. The reaction was filtered and concentrated. A deactivated silica gel column (1:9:10 triethylamine: hexanes: ethyl acetate) was used to purify phosphite **5** as a viscous oil (197 mg, 0.52 mmol, 34%). ^{1}H NMR: (300 MHz, acetone-d_6) δ 7.38 (m, 10H), δ 4.94 (s, 2H), δ 4.91 (s, 2H), δ 4.41 (m, 1H), δ 4.01 (m, 4H), δ 1.88 (q, 2H). ^{31}P NMR (121 MHz, acetone-d_6) δ +138.89ppm.

(*R*)-dibenzyl (2-(2-oxooxazolidin-4-yl)ethyl) phosphate (6)

Synthesis of phosphate **6** was performed on a 500 mg (3.82 mmol) scale following the procedure for phosphite **5** as seen above. Prior to filtration and isolation, meta-chloroperobenzoic acid (2.82 g, 11.46 mmol) was added to the solution at 0°C and stirred for 15 minutes. The solution was diluted with EtOAc and washed with $NaHSO_3$ (3x60 mL). The organic layer was dried over Na_2SO_4. The solution was purified on a silica gel column (100% EtOAc to 5% MeOH/EtOAc; R_f= 0.31). The resulting phosphate **6** was obtained as white crystals (1.27 g, 3.25 mmol, 85%) ^{1}H NMR (300 MHz, acetone-d_6) δ 7.41 (m,10H), 6.72 (bs, 1H), 5.10 (q, 4H), 4.42 (m, 1H), 4.15 (m, 2H), 3.99 (m, 2H) , 1.90 (m, 2H).

SYNTHESIS OF BROMINATED SPECIES

(*R*)-4-(2-bromoethyl)oxazolidin-2-one (7)

Triphenyl phosphine (801 mg, 3.05 mmol) was added to oxazolidinone **4** (100 mg, 7.63 mmol) in DCM. Carbon tetrabromide (506 mg, 1.53 mmol) was added to the mixture at 0°C. Upon addition, the solution turned orange and was stirred at 0°C for 40 minutes. The solution was concentrated. The solution was purified via silia gel (100% EtOAc; R_f=0.64). The brominated species **5** was obtained as a white solid (75 mg, 1.56 mmol, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), δ 4.56 (m, 1H), δ 4.09 (m, 2H), δ 3.43 (m, 2H), δ 2.15 (m, 2H).

CHAPTER FOUR
CONCLUSIONS AND RECOMMENDATIONS

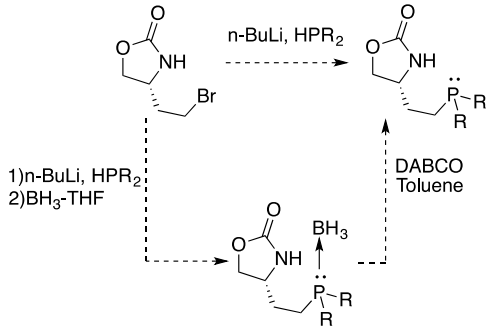
Much of the work shown in this thesis is a foundation for the development of a tethered phosphorus on an oxazolidinone backbone. Such tethered compounds may improve reactivity and selectivity. The possibilities of varying the donating properties into the axial site are very open to whoever continues this project.

One direction that this research could continue is by adding the phosphite and phosphate ligands onto a dirhodium catalyst. Several attempts by our group have been made to replace bridging ligands with the phosphite ligand, but there haven't been any successful attempts to date. One issue that may arise from this process is if the phosphite oxidizes, replacement of the equatorial ligands may not occur due to the phosphate replacing the equatorial ligands.[27] Phosphates have been used as a synergistic way to transfer protons in calculations.[28] Phosphites have shown promise for inducing enantioselectivity in previous studies[29] and more stable (more electron withdrawing) phosphites could be synthesized and used as possible pendants to vary the electron density of the rhodium paddlewheel.

Another direction that this research could go involves the synthesis of the phosphine groups. This thesis demonstrated steps towards synthesizing phosphines. Once the bromide species has been made, n-butyl lithium and a disubstituted phosphine can be used to add a plethora of phosphines with different donation capabilities into the rhodium center. Many phosphines need to be protected[19] with a boron species for handling purposes. Protection of these is fairly easy and deprotection of these compounds can be completed with amine groups.[30] These experiments have given quantitative yields in

literature and would allow for the deprotected phosphorus ligands to be free for coordination to the axial site.

Once these complexes have been made, there are a number of diazo- mediated reactions that can be performed. With the pendant phosphorus donor groups donating a variable amount of electron density into the complex, the stability of the complex should be improved, so enantioselective reactions with acceptor diazo compounds could be a possible route for this research to continue towards.



Scheme 4.1 Synthesis of phosphine ligands with and without the use of protection step.

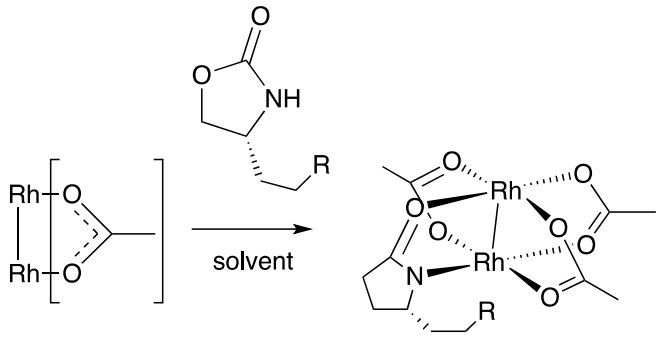
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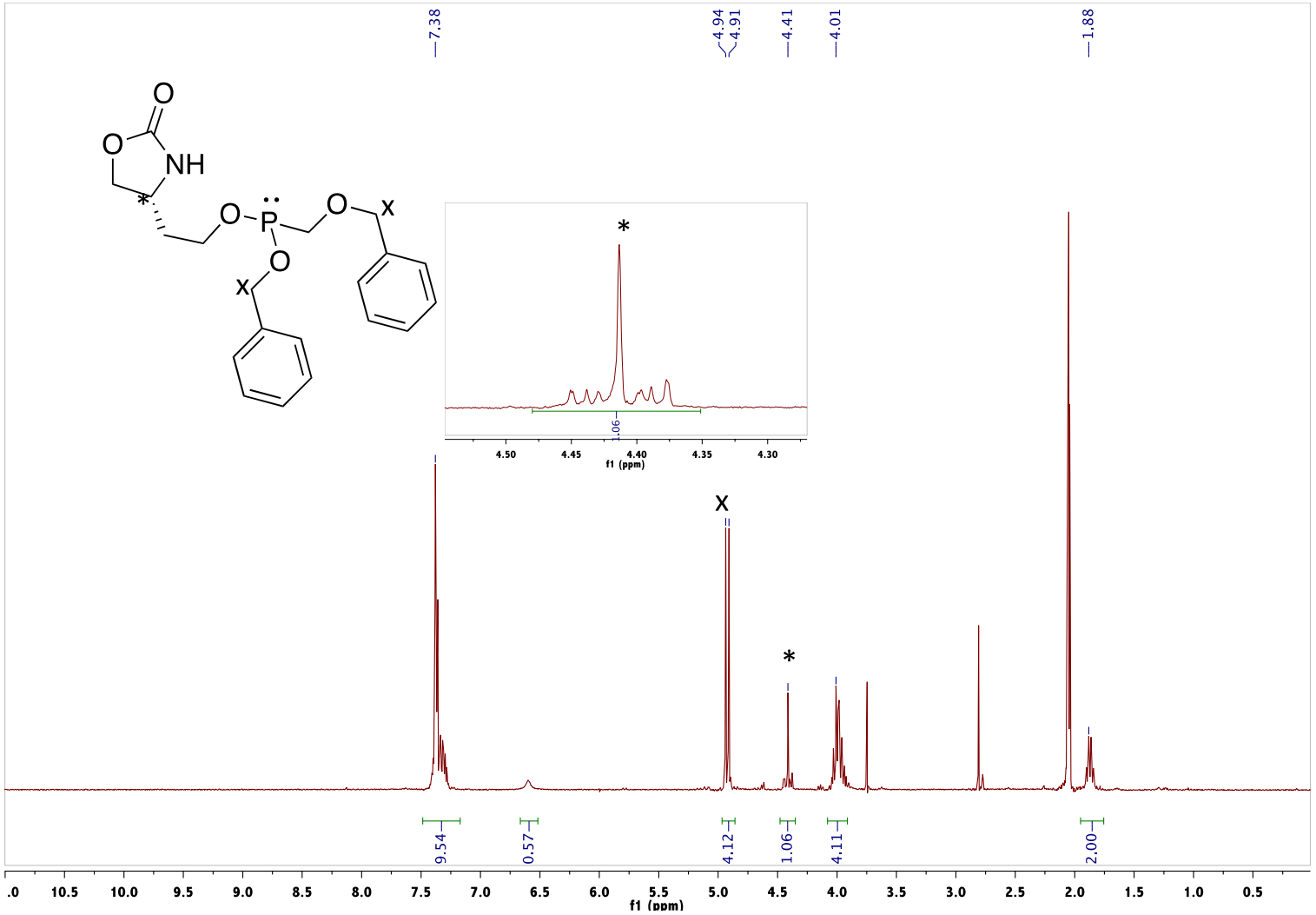
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APPENDIX

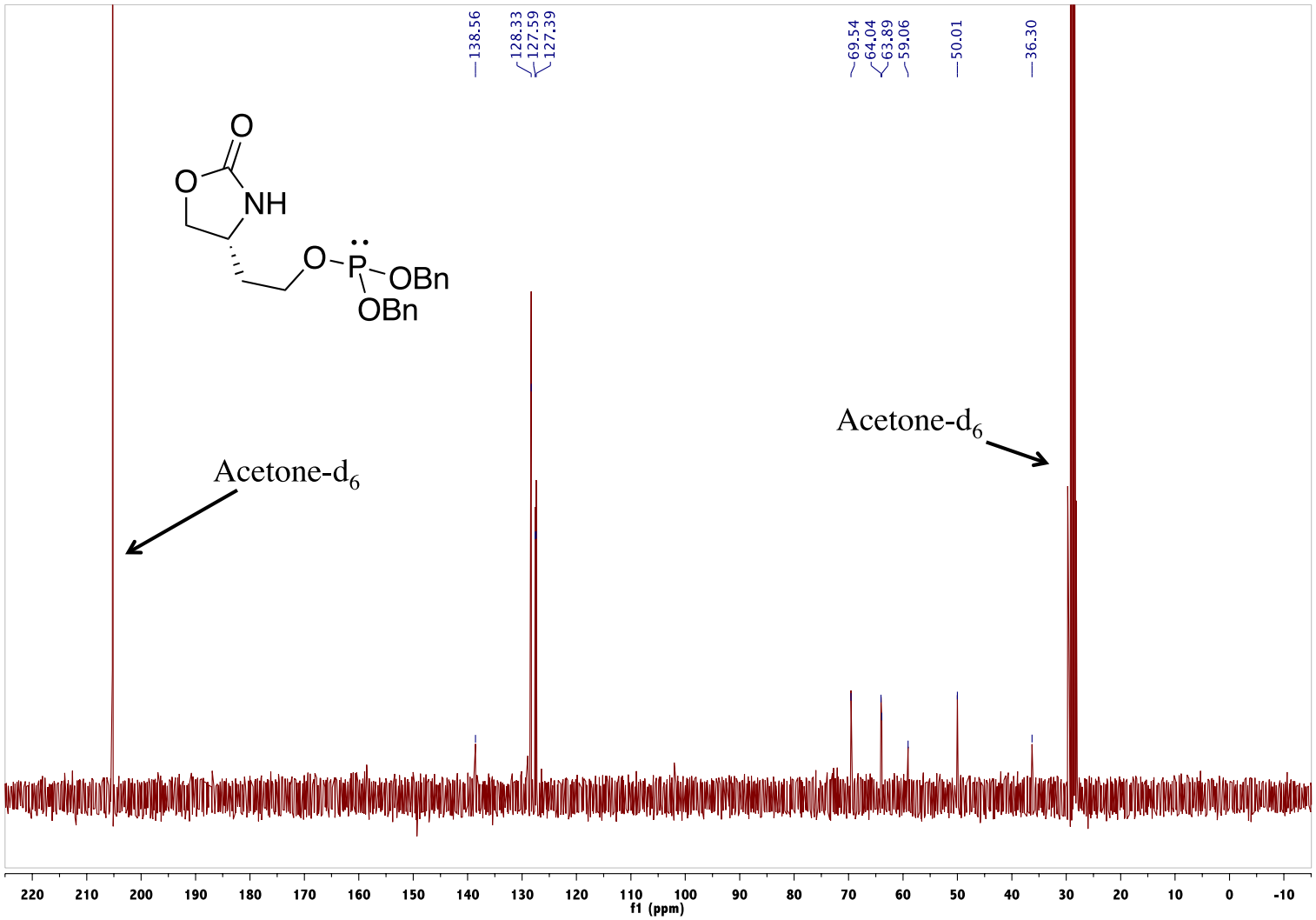
Table 2.1. Attempts of ligation to rhodium acetate complex.



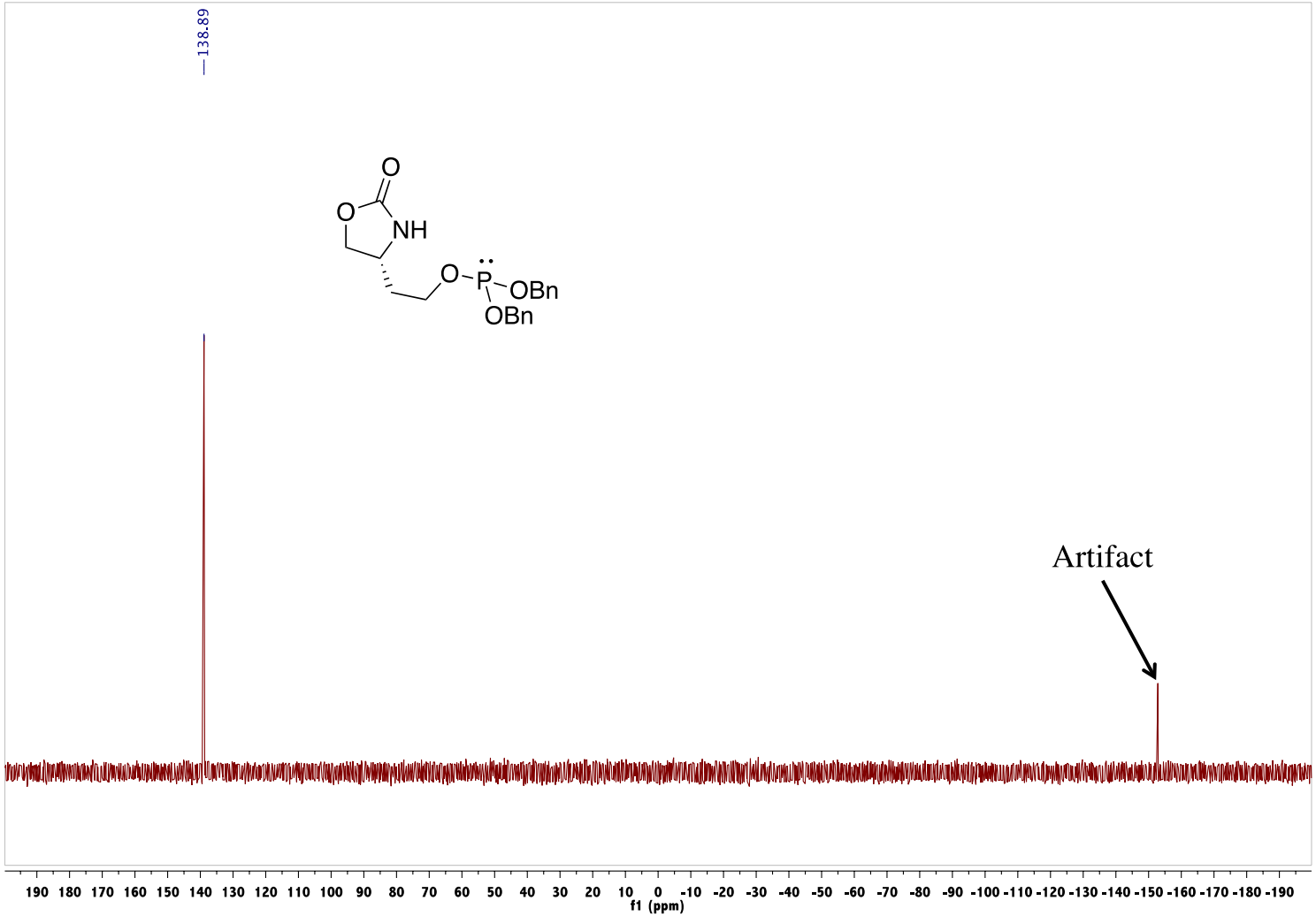
Ligand	Equivalent Ligand	Solvent	Temperature (°C)	Notes
OH	1.5	Chlorobenzene	165	
OH	2.5	Chlorobenzene	165->175	
OH	1.1	Chlorobenzene	165	10% MeOH/DCM
OH	2.5	Chlorobenzene	165	100% Acetone and 10% ACN/DCM
OH	1.1	Chlorobenzene	170	10% MeOH/DCM
$OP(OBn)_2$	2.5	Chlorobenzene	165->175	
$P(OBn)_2$	1.1	Chlorobenzene	reflux	Orange color product
$P(OBn)_2$	1	DCM	reflux	Purple product after 3 hours
$P(OBn)_2$	1	DCM	r.t	



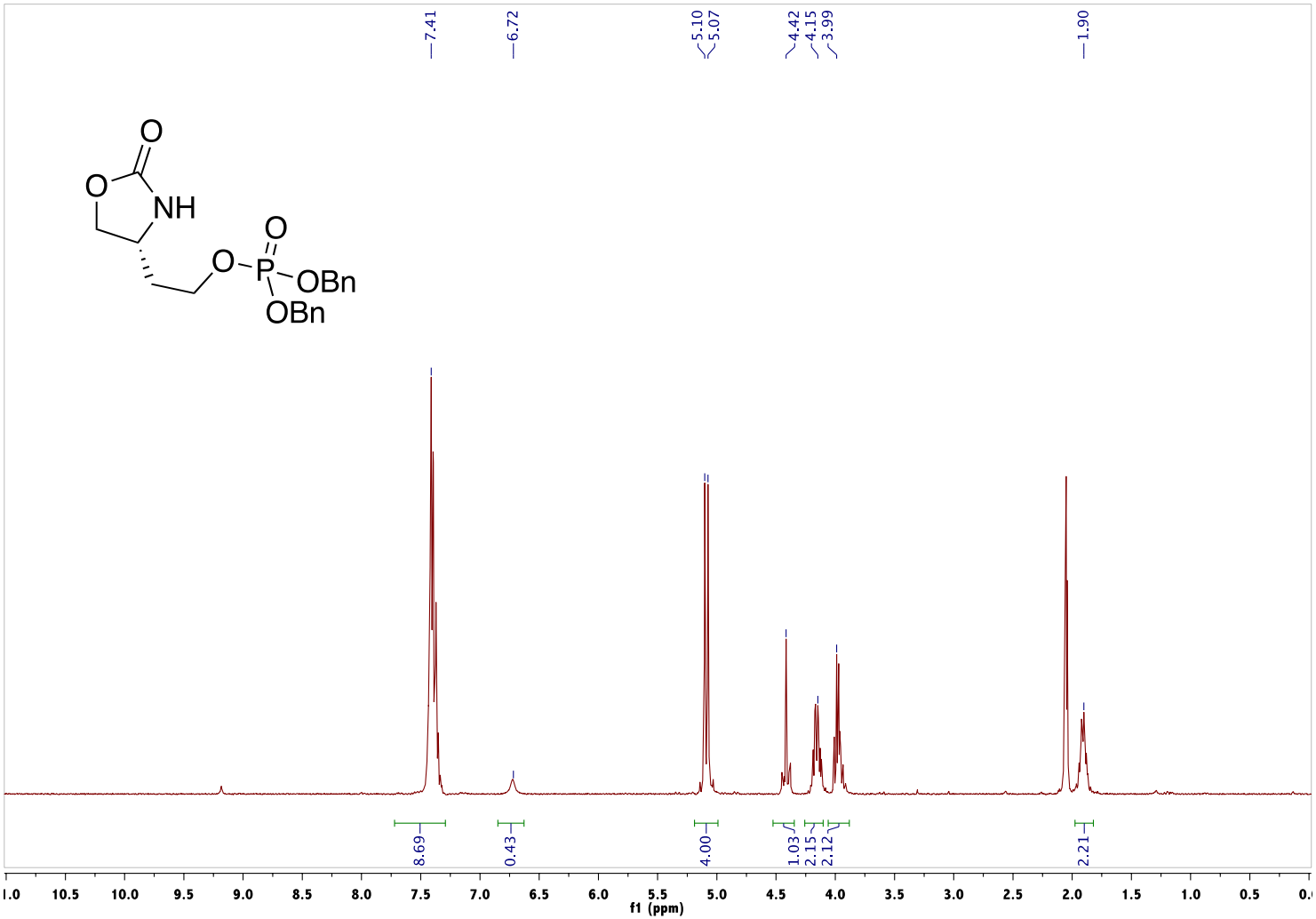
^{1}H NMR of Phosphite **5** in Acetone-d_6



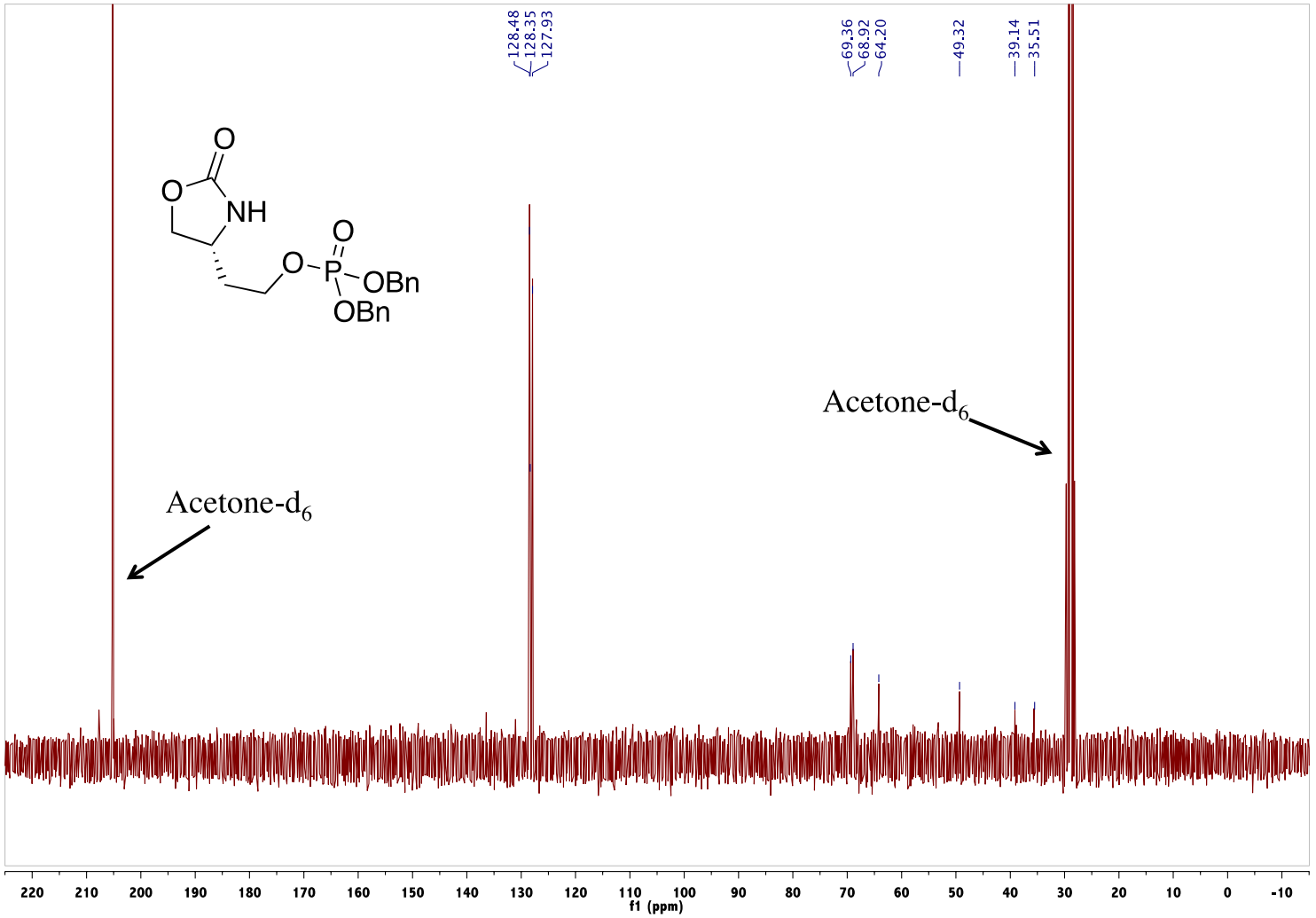
^{13}C of Phosphite **5** in Acetone-d$_6$



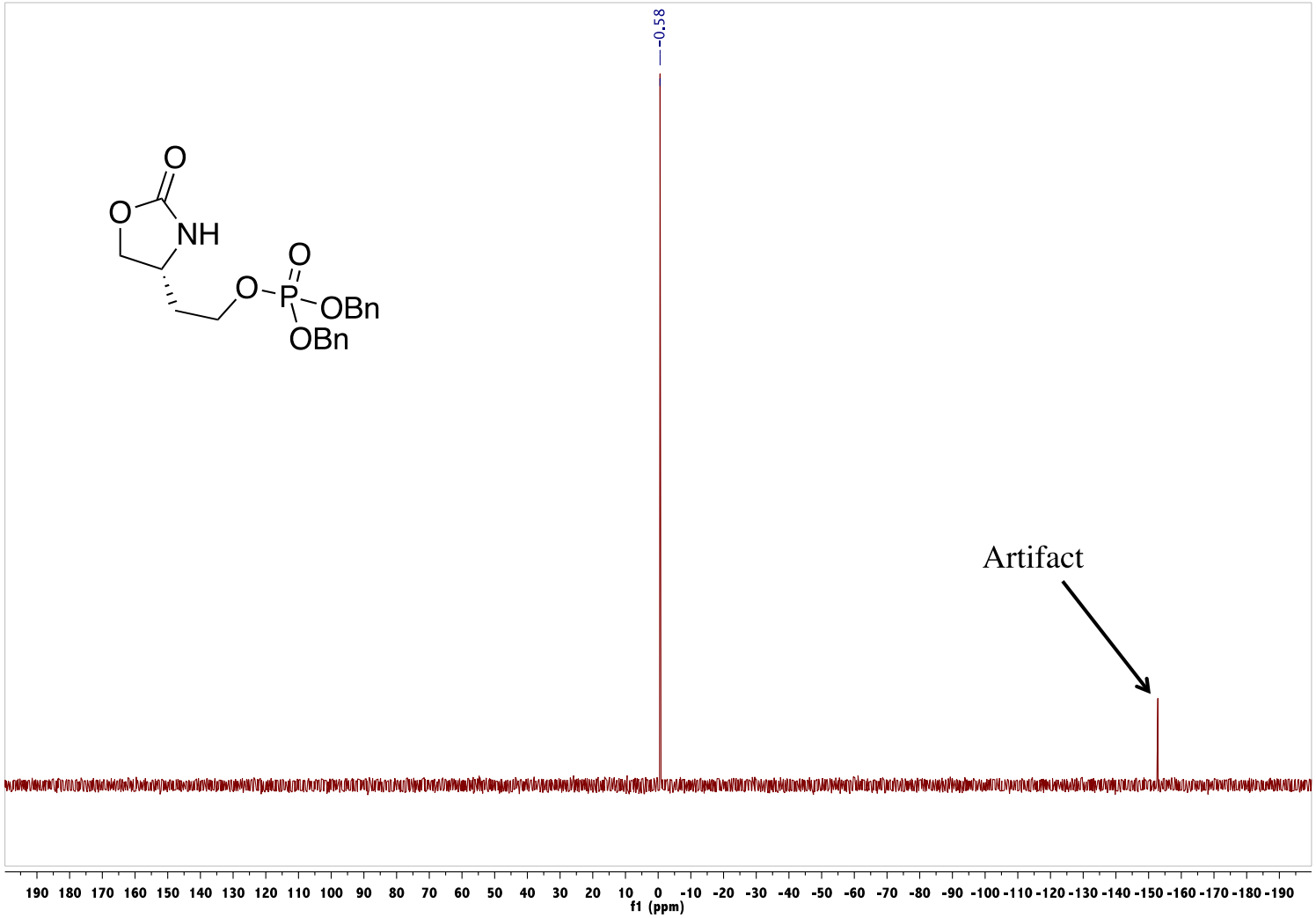
^{31}P NMR of Phosphite **5** in Acetone-d_6



^{1}H NMR of Phosphate **6** in Acetone-d_6



^{13}C NMR of Phosphate 6 in Acetone-d$_6$



^{31}P NMR of Phosphate **6** in Acetone-d_6

VITA

Gavin J. Rustin was born in Flint, MI on May 18th, 1992. His family moved to Tennessee where he graduated from Greeneville High School in 2010. Gavin graduated from East Tennessee State University with a Bachelor's of Science in Biochemistry with a concentration on Chemistry and graduated with Honors-In-Discipline in Chemistry in 2014. Gavin then started his graduate studies at the University of Tennessee Knoxville in August 2014.