1997

The Synthesis of Novel Phosphine-Modified Ligands for Use in Bimetallic Hydroformylation.

Howard Frederick Koch III

Louisiana State University and Agricultural & Mechanical College

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THE SYNTHESIS OF NOVEL PHOSPHINE MODIFIED LIGANDS FOR USE IN BIMETALLIC HYDROFORMYLLATION

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirement for the degree of Doctor of Philosophy in The Department of Chemistry

by

Frederick Koch III
B.S., Texas Lutheran College, 1989
December, 1997
The whole of science is nothing more than a refinement of everyday thinking.

—Albert Einstein
ACKNOWLEDGMENTS

I would like to thank the members of the Stanley group, past and present for their assistance and friendship through the years, especially the following; Dr. Scott Laneman for introducing me to organophosphorus chemistry, Dr. Wei-Jun Peng for his insight and instruction, Barry Misquitta for his giving me the chance to pass on some of my skills, and Dr. Spencer Train for all his help and his calming influence. I would also like to thank Dr. Bill Glover for all off his assistance and Dr. Roland Tittsworth for the numerous discussions on what "real chemistry" is. I am very grateful to the faculty of the LSU chemistry department, particularly the members of my committee: Dr. Andy Maverick, Dr. Randy Hall, Dr. Brian Hales, and Dr. Art Sterling. Most importantly, I would like to thank my advisor, Dr. George Stanley, for his tuition, guidance, and especially for putting up with me all these years and helping me to keep my perspectives straight.
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<tr>
<td>Cy</td>
<td>cyclohexyl, $-\text{C}<em>6\text{H}</em>{11}$</td>
</tr>
<tr>
<td>DCAM</td>
<td>bis(dichloroalumino)methane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DCPM</td>
<td>bis(dichlorophosphino)methane</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl, $-\text{CH}_2\text{CH}_3$</td>
</tr>
<tr>
<td>FT</td>
<td>fourier transform</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>M</td>
<td>a generic metal</td>
</tr>
<tr>
<td>Me</td>
<td>methyl, $-\text{CH}_3$</td>
</tr>
<tr>
<td>NBD</td>
<td>norbornadiene</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>$^{31}\text{P}$</td>
<td>phosphorus 31, the most abundant isotope of phosphorus</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl, $-\text{C}_6\text{H}_5$</td>
</tr>
<tr>
<td>R</td>
<td>a generic alkyl group</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilane, $-\text{Si(CH}_3)_3$</td>
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ABSTRACT

The tetraphosphine ligand, \( \text{Et}_2\text{P}(\text{CH}_2)_2\text{P(Ph)CH}_2\text{P(Ph)(CH}_2)_2\text{PEt}_2, \text{et,ph-P}_4 \), was designed to be a binucleating ligand for use in bimetallic hydroformylation catalysis. This ligand can be tailored for both electronic and steric factors at the internal and external phosphorus atoms. It is hoped that through careful tuning of this ligand, the rate and selectivity of our bimetallic catalyst can be optimized for various substrates. Modification of the original ligand may also lead us to a better understanding of the mechanism involved in the catalytic cycle. My goal has been to replace the phenyl substituents on the internal phosphorus atoms with various alkyl groups. These modifications have fallen into two broad categories: the \( \text{P(TMS)}_3 \) and the \( \text{Cl}_2\text{PCH}_2\text{PCl}_2 \) synthetic pathways. While investigating the chemistry of \( \text{Cl}_2\text{PCH}_2\text{PCl}_2 \), a new highly synthetic method for functionalizing halogenated phosphines based on \( \text{RZnCl} \) reagents was discovered. This has opened up new routes to previously unattainable compounds, and provided a far simpler path to existing organophosphines. It is this zinc based chemistry combined with the \( \text{Cl}_2\text{PCH}_2\text{PCl}_2 \) derivatives which holds the most promise, especially for future stereoselective synthesis.

x
CHAPTER 1. INTRODUCTION

Monometallic complexes have long been known as effective homogeneous catalysts and appear to be much more effective catalysts than dimer or cluster systems. Our research group has diverged from the mainstream of monometallic catalysis and developed a remarkable bimetallic hydroformylation catalyst. This catalyst makes use of two metal atoms working together to carry out its chemistry. The heart of our catalyst system is a novel binucleating tetraphosphine ligand that chelates and bridges two metal centers.

Phosphines have been extensively studied as ligands in coordination chemistry and homogeneous catalysis. Phosphines are quite remarkable and versatile ligands because of the presence of a relatively high energy lone pair of electrons and empty d-orbitals, which are both available to varying degrees for bonding with metal atoms. By changing the organic substituents on the phosphorus atoms, the donor/acceptor properties of a ligand can be tailored to bind well to almost any metal in most oxidation states. The steric properties of the ligand can also be altered to enforce particular three dimensional structures as dictated by the cone angles of the phosphorus' substituents. This allows for the customization of phosphine ligands for almost any environment and purpose.

A new polyphosphine ligand, exploiting these properties, was synthesized in our laboratories by Laneman in 1988. This ligand, Et₂P(CH₂)₂P(Ph)CH₂P(Ph)(CH₂)₂PEt₂ (previously reported as eLTTP and now renamed et,ph-P4), contains a central bridging bis(phosphino)methane moiety (-PCH₂P-), two chelating bis(phosphino)ethane linkages
(Et₂P(\text{CH}_2\text{P})_2\text{P}-), and two strongly binding electron-rich alkylphosphines (-PEt₂). This ligand was initially designed to coordinate two metal atoms and hold them in proximity allowing for metal-metal bond breakage and reformation, while inhibiting the dissociation and fragmentation of the overall catalyst system. In addition, the ethylene linked arms allow the ligand to form very stable five-membered chelate rings with a metal center, which also helps to reduce fragmentation of the catalyst. This ligand has been fully characterized by $^1\text{H}$ NMR, $^{31}\text{P}$ NMR, elemental analysis, and X-ray crystallography, and exists in two diastereomeric forms (Figure 1).

![Figure 1. Diastereomeric Forms of et,ph-P⁴](image)

The bulk of my research has been in the modification of this ligand system, primarily to replace the phenyl groups on the internal phosphorus atoms with various alkyl groups (particularly methyl and cyclohexyl), to increase the electron density on
the coordinated metal atom and control access to the metal's olefin binding site during hydroformylation catalysis. Attempts have also been made at synthesizing only one diastereomeric form, the racemic, of this ligand.

The synthesis of et,ph-P₄ involves the combination of two phosphines; the bridge, bis(phenylphosphino)methane (C₆H₅(PH)PCH₂P(H)C₆H₅), and the ethylene linked “arms”, diethylvinylphosphine,((CH₃CH₂)₂PCH=CH₂) as seen in Figure 2.

The reaction of these units is based upon the well known catalyzed addition of P-H bonds to C=C double bonds.⁵ We originally used AIBN (2,2'-azobis(isobutyronitrile)) as a free-radical catalyst for this reaction,⁶ but have now switched to the simpler and cleaner photolytically catalyzed addition. This photolysis reaction is quantitative and works quickest when the phosphines are reacted in the absence of solvent. Our approach to creating modified ligands was to start with various alkyl-substituted phosphine bridges of the type RP(H)CH₃(H)PR and combine them with the diethylvinylphosphine using this same technique. Unfortunately, Stelzer's⁷ method for synthesizing the methylene bridged bisphosphate from phenyl phosphine and

Figure 2. Synthetic Scheme for et,ph-P₄.
dichloromethane fails to work with alkyl phosphines, so two new synthetic pathways were explored, the tris(trimethylsilyl)phosphine, P(TMS)$_3$, and bis(dichlorophosphino)methane, Cl$_2$PCH$_2$PCl$_2$, reactions.
CHAPTER 2. HYDROFORMYLATION CATALYSIS

2.1 Introduction

The purpose of designing and synthesizing these new tetraphosphine ligands is to develop the optimal ligand for use in the bimetallic hydroformylation of various olefinic substrates. Hydroformylation is the catalytic process of converting olefins (alkenes) into aldehydes using synthesis gas (H\textsubscript{2} and CO), typically with soluble rhodium or cobalt based transition metal catalysts (Figure 3). This is the most widely employed catalytic process in the world today, with over 12 billion pounds of industrially important aldehydes and alcohols (from a subsequent hydrogenation of the aldehyde) being produced annually.\textsuperscript{8}

\[
\begin{align*}
\text{H}_2\text{C}=\text{CHR} & \xrightarrow{\text{H}_2/\text{CO}} \text{H-C-CH}_2\text{CH}_2\text{R} + \text{H}_3\text{C}-\text{CHR} \\
\text{Rh or Co catalyst} & \\
\end{align*}
\]

\textbf{linear} \hspace{2cm} \textbf{branched}

\textbf{Aldehydes}

\textbf{Figure 3. Generalized Scheme for Hydroformylation}

Cobalt hydroformylation was first discovered in 1938 by Otto Roelen,\textsuperscript{4} but it was not until 1961 that Heck and Breslow\textsuperscript{9} proposed the first reasonable monometallic mechanism for cobalt-catalyzed hydroformylation (Figure 4).
Figure 4. Heck-Breslow Hydroformylation Mechanism

The basic steps in this cycle are: coordination of the olefin to the metal (1), olefin insertion into the metal-hydrogen bond (2), CO coordination and insertion into the metal-alkyl bond to form the acyl complex (3), oxidative addition of molecular hydrogen (4), and reductive elimination of the aldehyde and regeneration of the active catalyst species (5). Depending on how the coordinated alkene inserts into the metal-hydride bond in step 2, the final aldehyde may be produced in either the linear or branched form. It is generally the linear aldehyde that is the desired product, and thus
the linear to branched ratio of the products is used to express the regio-selectivity of the hydroformylation process.

Heck also proposed an alternative mechanism, enclosed in dashes in figure 4, which represents one of the first examples of bimetallic cooperativity: that is, two metals working together in a homogeneous catalyst. He proposed that a second HCo(CO)₄ provides the hydride needed for the reductive elimination of the aldehyde through an intermolecular hydride transfer. The two metal centers then come together to form a cobalt dimer, which upon oxidative addition of molecular hydrogen breaks apart to reform the active monometallic catalytic species, HCo(CO)₄. This theory was considered quite attractive for many years, until in depth FT-IR studies proved that a monometallic cycle dominated the catalysis. Nonetheless, Bergman, Halpern, Norton, and Marko have found and reported evidence that intermolecular hydride transfers can occur in stoichiometric reactions between metal hydrides and metal acyl complexes. These reports provided the motivation for our study of the hydroformylation activity of bimetallic complexes based on our et,ph-P₄ ligand.

In the late 1960's, scientists started looking into hydroformylation processes based on rhodium instead of cobalt. Rhodium has several advantages over cobalt in homogeneous catalysis; it is almost 1000 times more reactive than cobalt, and it requires much milder reaction conditions: H₂/CO pressures of 5-25 atm and temperatures of 60-120°C, compared to 100-320 atm. and 200-250°C for cobalt. Rhodium/phosphine catalysts are also typically more stable and selective than their analogous cobalt catalysts. The mechanism for the Union Carbide Rh/PPh₃ catalyst
system is one of the most extensively studied examples of rhodium based hydroformylation, and is believed to follow the cycle shown below in Figure 5. The steps involved in this cycle are the same as those described in the monometallic Heck/Breslow mechanism.

![Figure 5. Union Carbide's Rh/PPh₃ Hydroformylation Mechanism](image)

2.2 Our Rh/et,ph-P4 Catalyst

Armed with this information, we began the hydroformylation studies of our bimetallic catalyst precursor [Rh₂(NBD)₂(et,ph-P4)](BF₄)₂ (NBD = norbornadiene)
with 1-hexene. Our results were remarkable, showing very high product selectivities (28:1 linear to branched aldehyde ratio) and an initial turnover rate of 639/hr for the racemic form of our catalyst (Figure 6).\textsuperscript{15}

These results can be compared to the Union Carbide Rh/PPh\textsubscript{3} catalyst system which gives a linear-to-branched product selectivity of 17:1 with an initial turnover rate of 540/hr for 1-hexene, but requires an 820 fold excess of PPh\textsubscript{3}, while our catalyst requires no excess phosphine ligand. This excess phosphine is required due to the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hydroformylation.png}
\caption{Uptake Curves for the Hydroformylation of 1-Hexene}
\end{figure}
lability of the phosphine and its ease of replacement by CO. When a phosphine
dissociates, the resulting di-, or even tri-, carbonyl species becomes much more active,
greatly enhancing the rate, but with an accompanying drop in selectivity, dramatically
lowering the linear-to-branched aldehyde ratio. Our chelating phosphine prevents this
ligand dissociation and thus negates the need for any excess phosphine to be added to
the reaction. These studies showed that our bimetallic system is only 30% slower
relative to the current best commercial system on a per rhodium basis, but has a higher
product selectivity ratio without requiring excess phosphine ligand. It is also
interesting to note that the racemic form of our catalyst is much more active than the
meso form, which yielded only 55 turnovers per hour with an accompanying drop in
selectivity to 14:1 and considerably higher side reactions.

These results were quite encouraging, but raised the question as to why our
system was so fast and selective. Industrial and academic studies have shown that
electron-rich chelating phosphine ligands (especially those that form 5-membered
chelate rings) almost always deactivate monometallic rhodium centers towards
hydroformylation, greatly reduce the selectivity to the linear aldehyde product, and
greatly increase alkene isomerization and hydrogenation side reactions. We believe that
the answer to the first part of this question, why we experience such high rates, is due
to homobimetallic cooperativity between the two rhodium metal centers, specifically,
an intramolecular hydride transfer. In order for this proposed intramolecular hydride
transfer to occur, the two metal centers must be able to closely approach each other.
Molecular modeling studies carried out using the SYBYL molecular
mechanics/graphics program package have shown that our catalyst can indeed access a closed-mode orientation in which the two rhodium centers approach one another. This transfer can be seen in our currently proposed bimetallic cycle shown below (Figure 7):
This mechanism incorporates the same fundamental steps as the Heck/Breslow and Union Carbide mechanisms along with some new steps. The oxidative addition of molecular hydrogen now moves to the beginning of the cycle (1) with both hydrogen atoms adding to the same rhodium center. Now we see the first example of bimetallic cooperativity in our catalyst system with the formation of a doubly bridged species in step 2. This enables the proposed intramolecular hydride transfer in step 3 to form the symmetric Rh-Rh bonded species which helps to stabilize the overall molecule. We then have olefin coordination (4) to one of the rhodium atoms and insertion (5) into the rhodium hydride bond. This same metal center then undergoes CO coordination and insertion (6) into the metal-alkyl bond to form the metal acyl species. Our catalyst again relies upon cooperation from the second rhodium to provide the hydride needed for the reductive elimination of the final aldehyde product (7). The addition of two carbonyls then regenerates our active catalytic species which is ready to begin the cycle again with another oxidative addition of hydrogen.

In order to provide additional experimental support for this bimetallic cooperativity effect that we believe we are seeing with our et,ph-P4 system, two model "spacer" ligands were prepared and tested. These two "spacer" ligand systems replace the methylene bridge between the two internal phosphorus atoms with a rigid para-xylyl and more flexible propyl group, respectively (Figure 8). These para-xylyl- and propyl-bridged analogues retain the same basic characteristics of our et,ph-P4 ligand except that the para-xylyl analogue will not allow the two rhodium centers close enough to carry out the proposed intramolecular transfer, and the propyl version will prefer the
splayed, open-mode conformation instead of the closed mode conformation required for the hydride transfer.

As expected, these two spacer systems proved to be very poor hydroformylation catalysts. They gave extremely low conversion to the aldehyde product (1/2 - 6 TO/hr), low linear-to-branched ratios (3:1), and large amounts (50-70%) of alkene isomerization and hydrogenation side reactions.

After explaining the high rates observed for our catalyst system, we undertook proposing an explanation for the accompanying high selectivity. Molecular modeling studies conducted on our et,ph-P4 based catalyst system show a sterically enforced conformation that favors olefin coordination and insertion in a terminal mode, which leads to formation of the linear aldehyde product. We believe that by changing the substituents on the internal phosphorus atoms, we can tailor the olefin binding site to allow specific olefin coordination modes while excluding or greatly hindering others. This olefin binding site and how it directs olefin coordination can be seen schematically (Figure 9) and in a space-filling model (Figure 10) below. These figures show how

Figure 8. Spaced Analogues of et,ph-P4

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access to the rhodium center is largely controlled by the organic substituents on the internal and, to a lesser extent, external phosphorus atoms.

Figure 9. Schematic of Olefin Binding Site
Figure 10. Space Filling Model of Olefin Binding Site
Substituents which occlude the space between the internal and external phosphorus atoms will force the alkyl “tail” of the olefin to the opposite, more open side of the catalyst. Hydride insertion then occurs to give the linear alkyl, which goes on to produce the linear aldehyde. For cases where the branched product is desirable (see next section), the size of the internal substituents can be reduced to allow the alkene “tail” to lie in the gap between the internal and external phosphines, which allows for hydride insertion to give the branched alkyl, leading to formation of the branched aldehyde.

2.3 Asymmetric Hydroformylation Catalysis

Chirality is a fundamental principle that has long been known to be of great importance, especially in the biological and pharmaceutical fields. In many cases only one enantiomeric form of a substance is responsible for its desired properties, or one form possesses properties which are detrimental to its desired use. Originally, the only route to optically active compounds was the resolution of racemates, with the undesired enantiomer often being discarded, greatly reducing the final yield of product. The transformation of prochiral natural products has provided another route to these compounds, but is limited in scope by the inherit specificity of these naturally occurring compounds. The ability to catalytically produce large amounts of chiral products from a small amount of a chiral man-made catalyst has been an incredible breakthrough in synthetic chemistry and has helped to strengthen its importance to the biological and medicinal sciences.19
The majority of our initial work was directed towards optimizing our ligand system towards regular hydroformylation catalysis, with the linear aldehyde being the desired product. Our ligand, however, has centers of chirality at both of the internal phosphorus atoms so we have the potential to carry out asymmetric hydroformylation, which involves the production of predominantly one enantiomeric form of the branched aldehyde product. In order to test our catalyst's ability for asymmetric hydroformylation we first separated the racemic form of our ligand into its separate enantiomers using a chiral HPLC column. The resolved ligand was then added to the rhodium precursor, [Rh(NBD)₂]BF₄, to form the chiral catalysts (+) and (−)-[Rh₂(NBD)₂(et,ph-P₄)](BF₄)₂ which was used for the asymmetric hydroformylation of vinyl acetate (Figure 11).

![Chemical structure](image)

**Figure 11. Synthetic Scheme for the Asymmetric Hydroformylation of Vinyl Acetate**

The results of this reaction show that our catalyst system is indeed capable of performing asymmetric hydroformylation. For vinyl acetate we see a regioselectivity of 4.3:1 (branched to linear) and an enantiomeric excess of 85% with almost 90% conversion of the olefin and less than 2% hydrogenation and decomposition side product.
reactions. The enantiomeric excess (ee), a ratio of one enantiomer to the other, is defined by the equation:

$$ee = \frac{|R-S|}{R+S} \times 100\%$$

The results for our system and the two leading catalyst systems, Takaya's and Babin's, are shown below in Figure 12.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>psig</th>
<th>°C</th>
<th>Hrs</th>
<th>TO</th>
<th>b:l</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babin's Rh/UC-P₂*</td>
<td>130</td>
<td>50</td>
<td>?</td>
<td>400</td>
<td>&gt;30</td>
<td>50</td>
</tr>
<tr>
<td>Takaya's Rh/binaphos</td>
<td>1400</td>
<td>60</td>
<td>36</td>
<td>400</td>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>Takaya's Rh/binaphos</td>
<td>1400</td>
<td>80</td>
<td>72</td>
<td>2000</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>Rh₂(et,ph-P₄)²⁺</td>
<td>90</td>
<td>85</td>
<td>4</td>
<td>500</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Rh₂(et,ph-P₄)²⁺</td>
<td>90</td>
<td>90</td>
<td>40</td>
<td>2000</td>
<td>4</td>
<td>83</td>
</tr>
</tbody>
</table>

Figure 12. Results of Asymmetric Hydroformylation of Vinyl Acetate.

These results, coupled with the results from our regular hydroformylation studies, show the extreme versatility of our ligand system. While our system is not the best catalyst system for either regular or asymmetric hydroformylation, it is the only system that can do both and be competitive with the leading commercial catalysts. And all of these results are with the same, unmodified form of our original et,ph-P₄ ligand. A recent absolute crystal structure of our ligand and continuing molecular modeling studies have given us unprecedented understanding into the nature of the binding site in our catalyst, a "window" into the heart of the hydroformylation mechanism. Now the
modification of our ligand to tailor this binding site becomes an even more valuable
tool both for increasing the performance of our catalyst and understanding the
mechanistic properties of hydroformylation catalysis.
CHAPTER 3 $^{31}$P NMR

The majority of our organophosphorus synthesis products are initially characterized by their $^{31}$P NMR spectra. The sensitivity of the phosphorus nucleus to shielding effects and its large resonance window, with shifts of $+250 \text{ ppm} - -250 \text{ ppm}$ being quite common, allow us to detect minute changes in a compound’s structure with $^{31}$P NMR. We can even easily differentiate the meso and racemic forms of our diastereomeric phosphines. The variability of $^{31}$P resonances, however, also makes it difficult to accurately predict where a certain phosphorus compound will appear. The general rule of thumb regarding $^{31}$P NMR is, "The only thing predictable about $^{31}$P chemical shifts is that they are unpredictable."\textsuperscript{20}

Our main guideline for estimating and predicting $^{31}$P NMR chemical shifts has been a table of known $^{31}$P NMR chemical shifts compiled by Mark et al in 1967.\textsuperscript{21} Using this data, we could usually "guesstimate" whether one of our new compounds would appear upfield or downfield of a similar known compound in the table. The problem with this method is that we could not get quantitative estimates, and not always a reasonably qualitative one either. When substituents have enough steric bulk around a phosphorus atom, they distort its geometry away from pyramidal, becoming more planar $sp^2$ like, thus increasing the $s$ character of the phosphorus atom and causing a downfield shift of its resonance. By studying some of the trends in the chart, I observed some general features in substituent contribution to the overall chemical shift, which held true for a majority of cases. Using a similar approach, Grim\textsuperscript{22} proposed a first order group contribution additivity scheme for predicting the $^{31}$P NMR
chemical shifts for trivalent phosphines, based largely on the cone angles of the various substituents. Grim's approach worked very well with alkyl and aryl substituted phosphines, but failed to work for substituents with quite different electronegativities, notably hydrogen and the halides. These more electron withdrawing groups give rise to large downfield shifts while the more electron donating organic groups provide an opposite, though not as large, upfield shift. This is not surprising considering that the shielding of a nucleus is affected by not only its steric, but also its electronic environment.

Payne and Stephan\textsuperscript{23} seized upon this idea and worked out a method to add an electronic consideration to Grim's scheme. Instead of using a first order method where each substituent's contribution is considered individually, they developed a second order additivity scheme where the substituents are considered as three pairs (for a three coordinate phosphorus atom). For example, a phosphine with substituents A, B, and C, (PABC) would have a chemical shift equal to the sum of the contributions from the three pairs A-B, A-C, and B-C. Payne \textit{et al} assigned values to these substituent pair contributions by "back-calculating" from tables of known $^{31}\text{P}$ NMR resonances.

Unfortunately, Payne and Stephan's table of substituent pairs included no data for bisphosphines similar to our ligand which contain a methylene bridge between two phosphorus atoms. Because there has not been enough $^{31}\text{P}$ NMR data published for substituted $-\text{P-CH}_2\text{-P-}$ linkages, I could not calculate a series of methylene-$\text{P}$ contributions in the same manner as Payne. Instead, realizing that our bridge is similar
to an ethyl group (–CH₂P₂), I manipulated the contribution values for various alkyl pairs containing ethyl groups obtained using Payne’s method, finally arriving at an approximation for our methylene bridge as 120% of an Et group. For example, Payne’s Et-Me group contribution is –14.2 ppm, so the –CH₂P-Me contribution would be (1.2)(–14.2) or –17 ppm. This approximation has proven accurate for all of the reported experimental ³¹P NMR data I have been able to find, as well as for new compounds synthesized in our laboratory.

Using the same “back-calculating” method as Payne and Stephan, I was also able to develop a series of contributions for substituent pairs incorporating chlorine atoms. These chlorine and methylene bridge (represented by PCP) pairs and their contributions are shown, highlighted, along with Payne’s alkyl and aryl pairings in Figure 13.

My extension of Payne’s method to include chlorine and methylene bridge contributions has provided an important accessory to our synthetic work. Especially after the discovery and development of the zinc modified chemistry, the ability to accurately predict ³¹P NMR resonances has saved immeasurable time in isolating and characterizing undesired products. To illustrate how well these new extensions work, several of our synthesis products are shown in Figure 14 along with the calculated and observed ³¹P NMR resonances for them.
<table>
<thead>
<tr>
<th>Substituent pair</th>
<th>Contribution</th>
<th>Substituent pair</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-H</td>
<td>-42.1</td>
<td>tBu-tBu</td>
<td>20.4</td>
</tr>
<tr>
<td>Me-Me</td>
<td>-20.5</td>
<td>tBu-Ph</td>
<td>9.6</td>
</tr>
<tr>
<td>Me-Et</td>
<td>-14.2</td>
<td>Cy-H</td>
<td>-17.7</td>
</tr>
<tr>
<td>Me-Pr</td>
<td>-17.4</td>
<td>Cy-Cy</td>
<td>2.3</td>
</tr>
<tr>
<td>Me-Cy</td>
<td>-11.3</td>
<td>Cy-Ph</td>
<td>-0.7</td>
</tr>
<tr>
<td>Me-Ph</td>
<td>-13.0</td>
<td>Ph-H</td>
<td>-21.3</td>
</tr>
<tr>
<td>Me-Bz</td>
<td>-13.2</td>
<td>Ph-Ph</td>
<td>-2.2</td>
</tr>
<tr>
<td>Et-H</td>
<td>-24.4</td>
<td>Ph-Bz</td>
<td>-4.1</td>
</tr>
<tr>
<td>Et-Et</td>
<td>-6.5</td>
<td>Bz-Bz</td>
<td>-4.3</td>
</tr>
<tr>
<td>Et-Cy</td>
<td>-1.8</td>
<td>H-H</td>
<td>-79.3</td>
</tr>
<tr>
<td>Et-Ph</td>
<td>-5.1</td>
<td>PCP-H</td>
<td>-29.3</td>
</tr>
<tr>
<td>Pr-Pr</td>
<td>-11.0</td>
<td>PCP-Me</td>
<td>-17.0</td>
</tr>
<tr>
<td>Pr-Cy</td>
<td>-5.0</td>
<td>PCP-Et</td>
<td>-7.8</td>
</tr>
<tr>
<td>Pr-Ph</td>
<td>-8.0</td>
<td>PCP-Cy</td>
<td>-2.2</td>
</tr>
<tr>
<td>iPr-iPr</td>
<td>6.6</td>
<td>PCP-Ph</td>
<td>-6.1</td>
</tr>
<tr>
<td>iPr-Ph</td>
<td>1.4</td>
<td>PCP-Cl</td>
<td>50.8</td>
</tr>
<tr>
<td>Bu-H</td>
<td>-29.4</td>
<td>Cl-Me</td>
<td>57.3</td>
</tr>
<tr>
<td>Bu-Bu</td>
<td>-10.8</td>
<td>Cl-Et</td>
<td>62.8</td>
</tr>
<tr>
<td>iBu-iBu</td>
<td>-15.1</td>
<td>Cl-Cy</td>
<td>65.4</td>
</tr>
<tr>
<td>iBu-Ph</td>
<td>-9.6</td>
<td>Cl-Ph</td>
<td>41.1</td>
</tr>
<tr>
<td>tBu-H</td>
<td>-0.2</td>
<td>Cl-Cl</td>
<td>73.3</td>
</tr>
</tbody>
</table>

Figure 13. Table of $^{31}$P NMR Shift Contributions
### Figure 14. Table of $^{31}$P NMR Shift Comparisons

<table>
<thead>
<tr>
<th>Compound</th>
<th>Calculated Shift</th>
<th>Observed Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>MePCl$_2$</td>
<td>188</td>
<td>190</td>
</tr>
<tr>
<td>Me$_2$PCl</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>EtPCl$_2$</td>
<td>199</td>
<td>197</td>
</tr>
<tr>
<td>Et$_2$PCl</td>
<td>119</td>
<td>118</td>
</tr>
<tr>
<td>Cl$_2$PCH$_2$PCl$_2$</td>
<td>175</td>
<td>174</td>
</tr>
<tr>
<td>Cy(H)PCH$_2$P(H)Cy</td>
<td>-49.2</td>
<td>-51, -52</td>
</tr>
<tr>
<td>Me(H)PCH$_2$P(H)Me</td>
<td>-88.4</td>
<td>-87, -88</td>
</tr>
<tr>
<td>Ph(H)PCH$_2$P(H)Ph</td>
<td>-56.7</td>
<td>-56, -57</td>
</tr>
</tbody>
</table>

As can be seen in Figure 14, this new method of predicting $^{31}$P NMR chemical shifts works quite well, with the predicted values being within a few ppm of the experimentally determined values. The fact that this method holds accurate for resonances far upfield and downfield shows that the pairwise consideration of phosphorus substituents quantitatively represents both the steric and electronic environments about the phosphorus atom.
CHAPTER 4 P(SiMe₃)₃ BASED CHEMISTRY

4.1 P(SiMe₃)₃

Tris(trimethylsilyl)phosphine, P(TMS)₃, was the basis for much of our early work at designing an alkylated version of our et,ph-P₄ ligand. P(TMS)₃ had been previously used as a starting material for the synthesis of the methylene bridged species, (TMS)₂PCH₂P(TMS)₂, used in the preparation of the hexaphosphine ligand (Et₂PCH₂CH₂)₂PCH₂P(CH₂CH₂PEt₂)₂, the “godfather” of our current tetraphosphine ligand. Although P(TMS)₃ can be purchased commercially, it is very expensive ($75/gm) and often out of stock at the supplier, so we began to synthesize it ourselves. This reaction seemed simple in theory, utilizing elemental phosphorus, reducing it with sodium/potassium alloy, and combining this with trimethylchlorosilane (Figure 15), but in practice turned out to be much more complicated.

\[
P \xrightarrow{1)} \Delta H \xrightarrow{2)} \text{Na/K} P^{3-} \xrightarrow{(\text{Me})₃\text{SiCl}} P(\text{TMS})₃
\]

Figure 15. Synthetic Scheme for P(TMS)₃.

This synthesis was first reported by Becker, but our early attempts at duplicating his results suffered from low yields and all too common catastrophes. We were losing about half of our reactions to fires and explosions resulting from the extremely pyrophoric nature of the elemental phosphorus and sodium/potassium alloy used as a reducing agent, coupled with the ethereal solvent used. The reactions that
succeeded then required extensive purification with an accompanying decrease in the final yield.

Through a complete redesign of the apparatus and my modified experimental technique, we have eliminated all mishaps, making the reaction much safer, and increasing the overall yield. The first problem to correct was leakage through the adapter that held the shaft of the mechanical stirrer. Stirring is not a trivial matter in this experiment, with the yields being severely reduced if a good rate of stirring is not maintained. The reaction mixture thickens with the formation of sodium and potassium salts, until it is almost solid, rendering magnetic stirrers ineffective. This necessitated the use of a high torque mechanical stirrer, which creates the problem of sealing between the shaft and the reaction vessel. This seal must be tight enough to prevent leakage, of either the reaction mixture out of the system or air into the system, but loose enough to allow the shaft to rotate. Several different types of adapters were tried, with one machined from Teflon and stainless steel found to be the best. The corrosive nature and high temperature of the reaction still eroded the Viton seals inside of this adapter, allowing leakage at the shaft. To prevent this, I had our glassblowers make an oversized condenser to fit over the stirring shaft and keep the refluxing reaction from reaching the adapter, allowing us to maintain a sealed system.

The second major problem involved the addition of the sodium/potassium alloy. Originally, a large bore cannula was used for the addition, but this clogged after several minutes. Addition funnels were tried, but the stopcocks clogged as well and the Na/K attacked the stopcock grease, locking the stopcock in place. These funnels also
trapped air in the space below the stopcock which entered the system when attaching to the reaction flask. These problems were solved by having the glassblowers make a new addition funnel with a large bore Teflon stopcock and tube with a 3-way stopcock going from the top of the funnel to just below the Teflon stopcock. This allowed us to have a flow of nitrogen blowing through the bottom of the funnel, keeping oxygen out of the system.

The final problem came when trying to remove the stirrer from the flask at the end of the reaction. The Teflon paddle at the end of the stirring shaft which normally hangs horizontally has to be rotated 90° in order to come up through the neck of the flask. This was done with long tweezers or a piece of stiff wire, but the nitrogen flow required to keep air out of the system pushed the flammable vapors through the neck, and when the shaft, coated with the pyrophoric product, touched the air it burst into flames and ignited the ethereal vapor.

In order to speed up the removal of the stirrer shaft, the flask was redesigned, enlarging the center neck and a different paddle was used. Thicker, and thus heavier Teflon paddles were purchased and a hole was cut in one end. With the hole cut into it, one end of the paddle is heavier than the other letting it swing the 90° on its own so that the stirrer assembly could simply be pulled quickly out and the flask capped without catching fire. The schematic for this new apparatus can be seen below in Figure 16.
The result of these modifications is a reaction that has become almost as simple in practice as in theory. This reaction of phosphorus, sodium/potassium alloy, and
ClSi(CH$_3$)$_3$ is currently done on as large a scale as possible (5 L), limited only by the size of reaction vessel we can transfer into the glove box. Yields for this reaction are fair, 69%, owing to oxidation products, the only other species visible in the $^{31}$P NMR of the crude reaction mixture.

4.2 (TMS)$_2$PCH$_2$P(TMS)$_2$

The P(TMS)$_3$ was used to synthesize the first methylene bridged bisphosphine I studied, (TMS)$_2$PCH$_2$P(TMS)$_2$ (Figure 17). This reaction itself is remarkable in that it is one of the few reactions in phosphorus chemistry which forms a methylene bridged bisphosphine cleanly and in quantitative yield. It was because we had this excellent route for synthesizing a methylene bridged species that we devoted extensive effort towards utilizing this chemistry to develop an alkylated bridging species.

![Figure 17. Synthetic Scheme for (TMS)$_2$PCH$_2$P(TMS)$_2$](image)

It was believed that this compound could be easily and selectively alkylated to give the bis(phosphonium)methane species [R(TMS)$_2$PCH$_2$P(TMS)$_2$R]$^{2+}$, which could then be converted to the desired alkyl bisphosphine, R(H)PCH$_2$P(H)R (Figure 18), through TMS cleavage.
This was attempted with numerous alkyl-halide reagents, primarily methyl iodide. Following nucleophilic attack to give the bisphosphonium it was hoped that we could exploit the nature of TMS as an excellent leaving group. Reaction with an alkyl-lithium reagent should produce the dialkylated form of our TMS bisphosphine. Reaction conditions including temperature, solvent, concentration, reaction time, and molar ratio were all investigated and varied, but the desired product could only rarely be detected in small quantities in a large mixture of products. The only species that could be consistently isolated and characterized was the tetra-alkylated form of the bridge, \( R_2PCH_2PR_2 \). The one reaction that does work well with the TMS-bridge is the addition of 4 equivalents of methanol to quantitatively form the tetrahydrido bridged bisphosphine \( H_2PCH_2PH_2 \). Even this reaction is limited in scope, as regardless of the stoichiometry, only the tetrahydrido species could be produced, the reaction would not stop at the disubstituted species, TMS(H)PCH_2P(H)TMS.

4.3  \( H_2PCH_2PH_2 \)

After exhausting all possibilities for substituting \((\text{TMS})_2PCH_2P(\text{TMS})_2\), I turned my attention to the tetrahydrido species, \( H_2PCH_2PH_2 \). It was hoped that this would be less reactive or more selective than the TMS species. Much of the same
chemistry was tried on this bridged species along with the variations in reaction conditions, and it was found to be less reactive than the TMS species. Unfortunately it was much too unreactive, often remaining untouched in the reaction vessel.

It was our hope to mono-deprotonate each phosphorus and substitute an alkyl group of our choice (Figure 19), however, it turned out that the protons on the central methylene bridge were more acidic than those on the phosphorus atoms. When a base strong enough to overcome the reduced reactivity of this species were employed, potassium hydride, it was the carbon that was deprotonated rather than the phosphorus.

\[
\text{H}_2\text{PCH}_2\text{PH}_2 + 2 \text{Base}^- \rightarrow [\text{HPCH}_2\text{PH}]^{-2} 2 \text{RX} \rightarrow \begin{array}{c}
\text{R} \\
\text{H} \\
\text{P} \\
\text{H}
\end{array} + 2 \text{X}^-
\]

Figure 19. Proposed Synthetic Scheme for R(H)PCH₂P(H)R.

Deprotonation at the carbon was deduced from the NMR spectra of the reaction mixture. The \(^{31}\text{P}\) NMR showed the expected doublet, but shifted downfield, rather than upfield as characteristic of alkyl phosphines, but more enlightening was the phosphorus-proton coupled spectra. This retained the triplet pattern, indicating two hydrogens on each phosphorus, instead of the expected doublet arising from a single hydrogen. While this reaction did not prove useful for generating an alkylated bisphosphine, it may provide the means for attaching our ligand system to a solid support.

In addition to the direct alkylations, another reaction attempted with this bisphosphine was addition to a C=C double bond. Two equivalents of our
diethylvinylphosphine were added to the tetrahydrido bridge in the hopes of attaching our ethylene linked arms first, and then deprotonating and alkylating the internal phosphorus atoms which could now only monoalkylate (Figure 20).

Figure 20. Proposed Synthetic Scheme for \( \text{Et}_2\text{PCH}_2\text{CH}_2(\text{R})\text{PCH}_2\text{P(\text{R})CH}_2\text{CH}_2\text{P}\text{Et}_2 \).

The addition to the P-H bond was also found to be uncontrollable, producing only the previously discussed hexaphosphine ligand, eHTP.

4.4 Supported Forms of Our Ligand

One of the persistent problems with homogeneous catalysis is the separation of the reaction product(s) from the catalyst. This is made even more difficult when dealing compounds with higher boiling points, such as aldehydes or alcohols. If the catalyst can be attached to a solid surface, effectively creating a "heterogeneous" homogeneous catalyst, the problems of product separation and catalyst recovery can be solved.

Supported homogeneous catalysts have been prepared from monophosphine ligated catalyst systems by attaching the phosphine to a silica support. This did not work as hoped, due to the lability of the monophosphines. As discussed previously,
this problem is characteristic of monophosphine complexes, giving rise to a decrease in selectivity for a catalyst system. In this case, when the phosphines dissociated, the metal was released from its moorings and allowed to drift into the solution.

The resistance of our P4 ligand system to dissociation again makes heterogenizing a homogeneous catalyst an attractive proposition. The carbon atom of our central bis(phosphino)methane unit of our ligand provides a handle for doing just this, and its preferential deprotonation provides a means for anchoring it down, as shown in Figure 21.

Figure 21. Solid Supported Form of et,ph-P4

The deprotonated methylene bridge should behave as any nucleophile and undergo a $S_N2$ reaction with a long-chain alkyl halide, allowing us to attach a tether.
onto our ligand (Figure 22). The free end of this alkyl chain can then be functionalized and attached to the solid support, presumably a silica surface.

The lack of success in synthesizing an alkylated bridge, \( R(H)PCH_2P(H)R \), through the chemistry of \( P(TMS)_3 \), forced us to look for a new route to a methylene bridged bisphosphine. The result of this search led us to our most successful bridging precursor, bis(dichlorophosphino)methane, \( Cl_2PCH_2PCl_2 \), described in chapter 5.

4.5 Tris(2-picoline)phosphine

An offshoot of the \( P(TMS)_3 \) chemistry was the discovery of the ability to synthesize novel tri-substituted monophosphines. The commonly used method for the synthesis of tri-substituted phosphines is to react three or more equivalents of a Grignard reagent with phosphorus(III) chloride. The drawback to this method is that it is limited by the available Grignard reagents. A modification of the \( P(TMS)_3 \) synthesis
can be employed which requires only a halogenated form of the desired organic
substituent rather than the rarer Grignard form (Figure 23).

\[
P \xrightarrow{1) \Delta H} \xrightarrow{2) \text{Na/K}} P^3- \xrightarrow{3: \text{Cl-2-picoline}} \text{P(o-2-picoline)3}
\]

**Figure 23.** Modified P(TMS)$_3$ Synthesis Tris(o-2-picoline)phosphine.

As a test for this reaction, I attempted to synthesize P(o-2-picoline)$_3$ from the
commercially available 6-chloro-2-picoline. This provides an excellent test for the
selectivity and versatility of this new route, for to produce the desired phosphine,
several obstacles must be overcome. Pyridines are much less reactive than benzene,
requiring harsher reaction conditions. The substituents in 6-chloro-2-picoline all favor
addition at undesired positions; the nitrogen itself favors the meta- position, while the
methyl and chloro groups both favor the ortho- and para- positions (relative to
themselves), the three of these combine to strongly favor addition at the undesired 3
and 5 positions. Upon reaction of the halogenated picoline with reduced elemental
phosphorus, only one compound was detected in the $^{31}$P NMR at $\delta$ 2.1 ppm. This
product was further characterized by mass spectroscopy and shown to be the desired
product, P(o-2-picoline)$_3$. 

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The selectivity of this method provides a simple and straightforward route to almost any homo-trisubstituted phosphine desired. This modification of the P(TMS)$_3$ route also allows for the incorporation of functional groups not available through the use of Grignard chemistry, such as carbonyls and amines.
CHAPTER 5. BIS(DICHLOROPHOSPHINO)METHANE

The synthesis of bis(dichlorophosphino)methane, DCPM, from readily available and inexpensive starting materials has been reported in the literature, but is often difficult to repeat. This reaction (Figure 24) is an all or nothing reaction. If the aluminum begins to react with the dichloromethane to form the DCAM, bis(dichloroalumino)methane, the reaction will proceed as shown, leading to the desired product in high yield (>95%). Unfortunately the reaction does not always, or even usually, start, even with continued refluxing of the aluminum for several days.

Through modification and combination of the reported syntheses I have developed my own method for this synthesis. Before beginning refluxing of the DCM, approximately 3% v/v dibromomethane is added to the reaction. After the solution begins to reflux, 2-3 ml. of diiodomethane is added and the solution is allowed to continue refluxing overnight. Neither the bromine nor the iodine is incorporated into the final product, but are used to generate the aluminum monohalide needed as an intermediate.
The use of other dihalomethanes is required since aluminum does not directly reduce dichloromethane. Dichloromethane will, however, react with with a bis(dihaloalumino)methane.\(^{28}\) Only a small amount of the dibromo- or diiodo- methane is required, as it is regenerated in the halogen exchange reaction with dichloromethane (Figure 25).

\[
\begin{align*}
\text{XY} & + \text{CH}_2\text{Cl}_2 \rightarrow \text{XY} + \text{CH}_2\text{ClX} \\
\text{X} & + \text{CH}_2\text{ClX} \rightarrow \text{X} + \text{CH}_2\text{X}_2
\end{align*}
\]

Figure 25. Halogen Exchange in DCAM Synthesis

A straightforward transmetallation with PCl\(_3\) produces our desired product, DCPM. The phosphorus oxychloride is required because of the strong lewis acid complex AlCl\(_3\) forms with the phosphine.\(^{28}\) The OPCl\(_3\) serves as a transfer reagent, preferentially binding to the aluminum, freeing the phosphine.\(^{29}\)

Now we have achieved reproducible success with the reaction starting in a matter of hours. Using DCPM as the basis for our methylene bridge negates the need to deprotonate the phosphorus atoms in H\(_2\)PC\(_2\)PH\(_2\) and it was believed it would allow the use of straightforward Grignard chemistry to form our alkylated bridge.

While Grignard reactions with monophosphines are quite common, although uncontrollable, analogous chemistry with the bisphosphine bridge Cl\(_2\)PCH\(_2\)PCl\(_2\) has
been extremely uncontrollable, only occasionally producing the desired alkylated bisphosphine, \( R(H)PCH_2P(H)R \), as a very minor product. Instead of the desired 1-3 di-alkylated product, standard Grignard reagents produced a mixture of 1-1 di-alkylated, 1-1-2 tri-alkylated, tetra-alkylated, and uncharacterized polymerization products. With the belief that the alkyl-magnesium Grignard reagents were too reactive for our system, similar reactions were tried with two different metals, copper (the Corey-House synthesis),\(^{30}\) and zinc (similar to the Reformatsky reaction). These two metals were chosen because they are both less reactive than magnesium.

The copper based system also proved to be difficult. The copper appeared too reactive, giving a wide range of alkylated products, and the iodine involved in the Corey-House synthesis was causing problems with separation and clean up. It was while working on modifying the copper synthesis that the zinc route was found to work, so the copper chemistry was set aside and my attention devoted to the zinc route (chapter 6). As well as providing a starting point for the alkylated forms of our ligand, \( \text{Cl}_2PCH_2PCl_2 \) was also used in attempts to synthesize just one enantiomer of our ligand, as described in chapter 7.
CHAPTER 6 ZINC CHEMISTRY

6.1 Introduction

The discovery of the alkyl zinc substitution chemistry represents a major breakthrough for preparing mono- or di-alkyl phosphine compounds, providing a simple and very controllable route for synthesizing these very useful starting materials. Grignard reactions with halogenated phosphines have long been known, but suffer from the inability to control addition to the phosphorus atom, requiring lengthy and often extremely difficult separations of the reaction products. Our zinc modified Grignard chemistry simplifies these reactions and requires little or no clean up of the product.

The use of Grignard chemistry in phosphorus synthesis is very attractive because of the wide range of available halogenated phosphines, and particularly the low cost of phosphorus(III) chloride, \( \text{PCl}_3 \). The selective substitution of \( \text{PCl}_3 \) provides the basis for any alkylated monophosphine of the type \( \text{RPCl}_2 \) or \( \text{R}_2\text{PCl} \). Grignard chemistry does have its drawbacks though; the aforementioned uncontrollability gives a range of substitution and by-products, and these are serious limitations as to which functional groups may be added.\(^{30}\) It was the need for a synthetic method that had the advantages of standard Grignard chemistry, but allowed more control over the alkylation of the phosphine that led to the discovery of the zinc route.

The reduced reactivity of zinc compared to magnesium provides the basis for this route. The idea for this chemistry came from teaching a general chemistry laboratory, particularly an experiment dealing with the comparative reactivities of several metals. The lab exercise had the students comparing the reactivities of Mg, Al,
Zn, and Cu. When I realized that the magnesium was just too reactive for our needs, I looked at the relative reactivities of these metals, Mg > Al > Zn > Cu, and decided to switch metals, starting at the bottom of the reactivity scale. As previously mentioned, copper was not working so I moved up the scale to zinc. It was here that we finally experienced our first success with controllable alkylation of a polyhalogenated phosphine.

A simple transmetallation reaction between zinc chloride and an alkylmagnesium chloride produces our alkylzinc reagent, RZnCl. This can then be added to PCl₃, and by controlling the stoichiometry, mono- or di-substitution is achieved easily, cleanly, and in virtually quantitative yields, eliminating the need for complicated separations (Figure 26). This reaction can be carried out one-pot, as the presence of the MgX₂ salts does not affect the reaction.

\[ \text{ZnCl}_2 + \text{RMgX} \rightarrow \text{RZnCl} \]

Figure 26. Generalized Scheme for Zinc Modified Reactions

This reaction is well illustrated in the synthesis of diethylchlorophosphine, Et₂PCl, the starting material used in the synthesis of diethylvinylphosphine, which we
use to prepare the ethylene-linked external phosphorus arms of our et,ph-P4 ligand (Figure 27).

\[ 2\text{ClZnEt} + \text{PCl}_3 \rightarrow \text{Et}_2\text{PCl} \]

Figure 27. Zinc Modified Synthesis of Et₂PCl

Et₂PCl is available commercially, and although somewhat expensive ($15/gm), it is often out of stock or available only in limited quantities due to the difficulty of separation and purification required by the current synthetic methods. Et₂PCl has been commercially synthesized from PCl₃ and two equivalents of the ethyl Grignard reagent, CH₃CH₂MgCl, which produces a mixture of the mono-, di-, and tri-substituted phosphines EtPCl₂, Et₂PCl, and PEt₃, other unidentified side products, and leaves unreacted PCl₃. The boiling points of these compounds are: 113°C (EtPCl₂), 131°C (Et₂PCl), 128°C (PEt₃), and 76°C (PCl₃). It is the closeness of the boiling points of the Et₂PCl and PEt₃ that complicates their separation. In contrast, the zinc modified route to Et₂PCl produces only one minor side product, the mono-substituted product, EtPCl₂, which can be removed from the desired product under reduced pressure (Figure 28).
Figure 28. Comparison of $^{31}$P NMR of Grignard and Zinc reactions.
These remarkable results have been made even better through optimization of this reaction. Because of the reduced reactivity of the alkyl zinc reagent, the reaction actually has to be forced to go to the tri-alkylated phosphine, PR$_3$, and I have used this feature in its optimization. By adding a 20% excess of the alkyl zinc reagent, all of the mono-alkylated phosphine, RPCI, is converted to the desired di-alkylated product, R$_2$PCl. An offshoot of this chemistry has been the use of dialkyl zinc reagents, R$_2$Zn, to perform the same alkylations. This chemistry is currently being developed by other members of our research group.

This alkylzinc chemistry is not the only route to alkylated phosphines however. Strem currently uses trialkylaluminum reagents for their commercial syntheses of alkylated phosphines (Figure 29). This chemistry relies on the chlorophilicity of aluminum to provide the driving force and the increasing difficulty of breaking subsequent aluminum-carbon bonds to provide the selectivity. This route provides access to the same mono- and di-alkylated phosphines, RPCl$_2$ and R$_2$PCl, but suffers from complications with the separation of the aluminum salts. Since aluminum halides are much stronger Lewis acids than zinc halides, they want to hold on to the phosphate products, requiring the addition of a stronger base, such as OPCI$_3$, to complex with the aluminum salts.

$$2R_3Al + 3PCl_3 \rightarrow 3R_2PCl + 2AlCl_3$$

Figure 29. Synthetic Scheme for Alkylphosphines via Aluminum Trialkyls.
Our research group is currently using this alkyl zinc chemistry to synthesize our long desired alkylated ligands, \( \text{R(H)PCH}_2\text{P(H)R} \), and the alkylated phosphines, \( \text{R}_2\text{PCl} \), we use as starting materials for our other synthesis. Presently, the methyl and cyclohexyl versions of our bridged intermediate, \( \text{R(H)PCH}_2\text{P(H)R} \), have been synthesized and characterized, and virtually any other alkyl substituted bisphosphine is now available to us.

### 6.2 R(H)PCH\(_2\)P(H)R

It was this zinc chemistry that produced the first acceptable route to a selectively alkylated bisphosphine bridge. By utilizing a transmetallation reaction to replace the magnesium in a Grignard reagent with the less reactive zinc we are now able to selectively alkylate our tetrachloro bisphosphine bridge and subsequently hydrolyze the remaining two chlorines to give us \( \text{R(H)PCH}_2\text{P(H)R} \) (Figure 30). This is accomplished by simply adding two equivalents of a commercial Grignard reagent containing the alkyl of choice to an equimolar solution of zinc chloride in THF. The intermediate alkyl zinc compound, \( \text{RZnCl} \), can then be separated from the magnesium halide salts by filtration, or reacted \textit{in situ} with one equivalent of \( \text{Cl}_2\text{PCH}_2\text{PCl} \), to give selective mono- alkylation of the phosphine.

The first alkylated form of our ligand synthesized was the methylated version, \text{et,me-P4}. For this ligand, \( \text{MeMgBr} \) is used as the initial alkyl source and added to an equimolar amount of zinc chloride.
The first alkylated form of our ligand synthesized was the methylated version, et,me-P₄. For this ligand, MeMgBr is used as the initial alkyl source and added to an equimolar amount of zinc chloride. This mixture of MeZnCl and MgCl₂ is cooled and Cl₂PCH₂PCl₂ is added in a 1:3 ratio. The excess alkyl zinc is required to make sure that all of the mono-alkylated species, MeClPCH₂PCl₂, is converted to the desired product. After the presence of only the desired dialkylated product, MeClPCH₂PClMe, is determined by ³¹P NMR (racemic and meso diastereomers at 91,92 ppm), the reaction mixture is added to a solution of 2 equivalents of LiAlH₄. The reaction is then quenched with aqueous NaOH, the organic layer removed and evaporation of solvent leaves pure product, Me(H)PCH₂P(H)Me, which has been characterized by ³¹P NMR (-84, -87 ppm). The cyclohexyl substituted ligand, et,cy-P₄, is synthesized in an identical manner except that only 2 equivalents of the cyclohexylzinc reagent is required.
CHAPTER 7. CHIRAL BRIDGES

7.1 Introduction

In order to synthesize only one specific enantiomer of our ligand, various attempts were made at imposing chirality on our bridging intermediate through the use of chiral protecting groups. Because P-chiral organophosphorus compounds cannot be found in the natural pool of chirality, their synthesis is of vital importance and has received considerable attention from the organometallic community. One of the pioneers in the field of chiral phosphine synthesis has been Juge, who developed the thermal condensation of bis(diethylamino)phenyl phosphine with (-)-ephedrine (Figure 31).

![Figure 31. Juge's (-)-Ephedrine Condensation.](image)

While this synthesis provided access to a wide range of chiral phosphines, it was not without its problems. The reaction suffered from low yields, 15 - 30%, and the formation of large amounts of polar by-products. A modification of Juge's synthesis was developed by Sheehan and coworkers which gives yields of 70 - 82%. Sheehan's approach was to use an "ionic" coupling reaction between the ephedrine and the...
phosphine to obtain the initial phosphorus-oxygen bond, and then follow up with thermolytic ring closure (Figure 32).

\[
\begin{align*}
R-\overset{\text{Cl}}{\text{P}} & \quad + \quad \overset{\text{Ph}}{\text{HO}} \quad \overset{\text{Ph}}{\text{Ph}} \\
\overset{\text{NMe}_2}{\text{N}} & \quad \overset{\text{CH}_3}{\text{CH}_3} & \quad n-\text{BuLi} & \quad \overset{\text{Me}_2\text{N}}{\text{R}} \quad \overset{\text{Ph}}{\text{O}} \\
\overset{\text{CH}_3}{\text{CH}_3} & \quad \overset{\Delta}{\text{Ph}} & \quad \overset{\text{H}_3\text{B}\cdot\text{SM}_3}{\text{Ph}} \\
\end{align*}
\]

**Figure 32.** Sheehan’s Modified (−)-Ephedrine Condensation.

This method provided a high yield route to chiral phosphines and expanded the range of available phosphines by being able to couple alkyl as well as aryl phosphines with the ephedrine. One common feature of both of these reactions is that the final phosphine product is a BH₃ adduct. The boron is used to tie up the lone electron pair of the phosphorus, thus making it more stable and allowing it to be stored for longer periods of time. I have not attempted to use boron hydrides in my research, but it may be helpful in our group’s future work with an ephedrine modified bisphosphine bridge.
7.2 Chiral Bridged Phosphines

With the discovery that it was only the racemic form of our catalyst system that was responsible for our observed high rates and selectivities, we became interested in synthesizing only one specific diastereomer of our ligand. This stereoselective synthesis would eliminate the need for repeated recrystallizations to separate the racemic and meso forms of our ligands, and increase the overall yield since none of the undesired diastereomer would be produced. This became even more desirable after it was found that our chiral bimetallic catalyst is also an effective asymmetric hydroformylation catalyst for vinyl esters.

In order to carry out this asymmetric synthesis we needed to impose a specific chirality upon our achiral tetrachloro bridging intermediate, $\text{Cl}_2\text{PCH}_2\text{PCl}_2$. This was attempted through the incorporation of commercially available chiral directing groups. The chiral directing group employed needs to have sufficient steric bulk to direct the incoming alkyl substituent to a specific face of our bisphosphine, and a functional group that would give us a handle for attaching it to our tetrachloro species. The functional groups of choice were the hydroxyl, $\text{-OH}$, and amino, $\text{-NH}_2$, groups. After a search of the available chiral auxiliaries, the various chiral agents chosen for these synthesis were quinidine, $(2S,3R)$-$(+)$-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (DMDB), $(1S,2R)$-$(+)$-ephedrine, $(1R,2S,5R)$-$(\text{-})$-menthol, and $(1S,2R,5S)$-$(+)$-menthol (Figure 33).
The hydroxyl group on each of these chiral compounds was deprotonated with triethylamine and attached to the bridging intermediate, $\text{Cl}_2\text{PCH}_2\text{PCl}_2$, replacing one chlorine on each phosphorus atom. The exception to this is the ephedrine, which also has the amine group deprotonated and forms a five-membered chelate ring around each phosphorus, removing both chlorine atoms from each phosphorus. It is hoped that the steric bulk of these chiral agents will favor the formation of the racemic form of our bridge and the reaction can then be further tailored to produce predominantly one enantiomer. Of these chiral agents, the DMDB and quinidine failed to coordinate to our chlorinated bridge and so the majority of work has been done with the menthols and ephedrine.
7.3 Menthol

The menthol groups can be added selectively to each side of our chlorinated bridge to produce the bis(menthoxy-chlorophosphino)methane, 

\[(\text{C}_{10}\text{H}_{19}\text{O})\text{ClPCH}_{2}\text{PCl}(\text{C}_{10}\text{H}_{19}\text{O})\], Figure 34, unfortunately with a racemic/meso ratio of 1:1.

![RACEMIC and MESO](image)

**Figure 34. Diastereomeric Forms of Menthoxy Phosphine.**

The ratio of the menthoxy diastereomers was determined from the 2D COSY \(^{31}\text{P}\) NMR spectrum of the mixture (Figure 35). This spectrum, which initially appears to be three doublets, is actually a doublet of doublets surrounding two singlets. The logic behind our interpretation of this spectra can be seen in the table we developed for the assignment of the resonances (Figure 36).
Figure 35. COSY $^{31}P$ NMR Spectra of Menthoxy Substituted Bisphosphine
Figure 36. Stanley Table for Assigning 2D NMR Resonances.

<table>
<thead>
<tr>
<th></th>
<th>Menthol</th>
<th>P&lt;sub&gt;A&lt;/sub&gt;</th>
<th>P&lt;sub&gt;B&lt;/sub&gt;</th>
<th>Menthol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meso</td>
<td></td>
<td>R</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Meso</td>
<td></td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Racemic</td>
<td></td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Racemic</td>
<td></td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
</tbody>
</table>

This table shows the possible chiralities for each phosphorus atom and the two attached menthol groups. Two notes need to be made concerning our table; first, the terms *meso* and *racemic* refer only to the phosphorus-carbon-phosphorus backbone and does not include the menthols, and second, only the (−) form of menthol was used for this experiment and so this is the only possible form for these groups.

Looking at the table, we can see that for the two *racemic* compounds the phosphorus’s are of the same chirality, and so would not cause splitting of one another in the 31P NMR spectra. This produces the pair of singlets at 193.2 and 193.6 ppm. For the two *meso* compounds the phosphorus’s do differ in their chirality and so will cause splitting of one another. This gives rise to the doublet of doublets patterns at 191.5 and 194.5 ppm.

While this reaction worked well, giving us the menthol substituted phosphine in quantitative yields, it failed to produce one diastereomer preferentially over the other.
Attempts to selectively alkylate or hydrolyze these species also proved unsuccessful. Rather than pursuing means to selectively substitute this menthoxyl bisphosphine, I turned my attention towards finding a bulkier directing group that would impart diastereo-, and hopefully enantio-selectivity.

7.4 Ephedrine

The ephedrine group can be added to our chlorinated bridge similarly to menthol, except that we deprotonate the amino as well as the alcohol group. The ephedrine adds easily to the bridging bisphosphine to give an orange solid in quantitative yield. We believe that this solid is the dicationic species shown below (Figure 37), but characterization has proven to be extremely difficult.

\[ CH_3 \quad \text{N} \quad \begin{array}{c} \text{P} \\ \text{O} \end{array} \quad \begin{array}{c} \text{P} \\ \text{O} \end{array} \quad \text{Ph} \quad 2^+ \]

Figure 37. Proposed Structure of Ephedrine Compound.

In addition to our normal $^{31}$P NMR, we also used 2D $^{31}$P NMR, mass spectrometry, and elemental analysis in an attempt to characterize this product. The 2D COSY experiment (Figure 38) shows that the two resonances seen in the $^{31}$P NMR spectra are two singlets. This indicates two symmetrical species, which we believe are the R,R and S,S enantiomers of the _racemic_ diastereomer of Figure 37.
Figure 38. COSY $^{31}$P NMR Spectra of Ephedrine Compound

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In order to explain why these resonances appear so far downfield, -66.2 and -69.2 ppm, we proposed a cationic phosphonium complex, examples of which are known to appear downfield, and since we needed a symmetrical species, it must be dicationic rather than monocationic. The mass spectra for this compound were useless in aiding in the characterization, with five different runs giving five different parent peaks. A sample of the product was also sent off for elemental analysis, and the following composition was reported: C 57.53%, H 6.65%, N 6.05%, and P 19.49%. The percent compositions for our proposed product, assuming two chlorine counter anions, is: C 53.05%, H 6.32%, N 5.89%, and P 13.05%. Only the nitrogen and hydrogen compositions were found to be close (± .5%) to their predicted values. Another sample has been sent off for elemental analysis to check the validity of the original results.

Attempts to proceed with the alkylation of the product from the ephedrine reaction also failed. The breaking of the phosphorus-oxygen bond and alkylation of the phosphorus via alkyl lithium reagents is well known, but their reaction with the ephedrine compound does not take place, leaving only the initial complex. Reports in recent literature suggest that we may need to look into using boranes to tie up the phosphorus lone pair before addition of the ephedrine in order to prevent formation of this proposed dicationic species and allow isolation characterization of the reaction products.
CHAPTER 8. METHYLENE BRIDGE MODIFICATIONS

The heart of our et.ph-P4 ligand system and any of its analogues is the central methylene bridge. Modifications of our original phenylated ligand depend upon our ability to synthesize variants of bis(phenylphosphino)methane. Whether we are trying to selectively alkylate the internal phosphorus atoms or functionalize the central methylene carbon to provide an attachment point for a supported form of our catalyst system, a detailed understanding of its chemistry is essential. Prior to the discovery of the zinc modified route for synthesizing alkylated forms of this bridge, we relied on Stelzer’s synthesis to produce our phenylated bridge.

One aspect of this reaction that has always bothered us is that we have never been able to approach Stelzer’s reported yield of 70%. Every member of our research group (graduate students, postdocs, and undergraduates) has performed this reaction and never obtained much higher than a 50% yield, no matter how careful or talented the chemist. It was in an attempt to more fully understand this lack of reproducibility that some recent experiments were carried out in order to probe the mechanism of this reaction.

This reaction appears to be similar to a standard organic $S_N2$ reaction, first involving deprotonation of the phenyl phosphine to produce the phosphide anion, followed by its bimolecular nucleophilic attack on the dichloromethane as shown below in Figure 39.
As the base is added to the mixture of phosphine and DCM, the solution turns increasingly yellow (due to the formation of the phosphide anion), and after the addition is complete and the reaction mixture stirs, the color gradually fades (due to formation of the bridged species). One of the first variations of this reaction attempted was the use of an alkyl phosphine (methyl phosphine) instead of phenyl phosphine to produce an alkylated phosphine bridge. This reaction started off similarly, turning yellow to indicate the formation of the corresponding phosphide, but upon workup, only unreacted starting material was present in the $^{31}$P NMR spectra. Since an $S_{N2}$ mechanism is dominated primarily by steric factors, the less bulky methyl phosphine should have reacted at least as quickly as the phenyl phosphine. The methyl substituents are also more electron donating than the phenyl groups, giving a more
electron rich phosphorus center and thus increasing its nucleophilicity. This reaction was repeated with other alkylated phosphines giving the same result. These discrepancies were originally considered curiosities and this area of research was shelved in favor of the P(TMS)$_3$ chemistry.

Stelzer's chemistry was examined again recently, except this time it was not the phosphine that was varied but rather the alkyl halide. We were hoping to achieve two things through these experiments: 1) probe the mechanism of this reaction, providing some understanding of its limitations, and 2) alter the central methylene bridge in preparation for attachment to a support and to vary the geometry about the bridge, perhaps obtaining a more favorable relationship between the two metal centers.

Instead of using dichloromethane, three other geminal dihalides were used as a basis for the methylene bridge; 1,1-dichloro-2,3-dimethylcyclopropane, 1,1-dichloropropane, and 2,2-dichloropropane (Figure 40). These three compounds were chosen from a search of the Aldrich Structure Index, and were the only geminal dichloroalkanes available.

![Figure 40. Test Compounds for Stelzer's Reaction](image-url)
The reactions were carried out following Stelzer's procedure but substituting the test compound for dichloromethane. The reactions started out as expected, with the solution turning yellow to indicate the formation of the phosphide anion, but after hydrolysis the only phosphorus species detected in the $^{31}$P NMR was the starting material, phenyl phosphine. Reaction conditions including time, temperature, and concentration were varied to no avail.

Assuming that a $S_N2$ mechanism was involved, the negative results for the cyclopropyl and 2,2-dichloropropyl groups were believed to be due to the steric bulk of these compounds inhibiting backside attack by the phosphonium anion. The 1,1-dichloropropane, however, should not be so encumbered and so another explanation was needed for its behavior.

The common competing reaction for a $S_N2$ mechanism is elimination, E2. This was a strong possibility since dichloromethane has no $\beta$-hydrogens which can eliminate, while each of our test compounds does. In the case of 1,1- and 2,2-dichloropropane, the elimination product would be propene, a gas at reaction conditions. No precautions were taken to trap an evolved gas, but in each experiment the starting alkyl dihalides were still present in the proton NMR at the end of the reaction.

In an effort to determine if our lack of success with these reactions was due to domination by the competing E2 elimination pathway, a final experiment was performed using carbon tetrachloride, CCl$_4$, as the basis for the methylene bridge. With no $\beta$-hydrogens, elimination would be impossible and the extra two electron withdrawing chloride groups should make the carbon even more electropositive, and
thus more susceptible to nucleophilic attack. The proposed product, \((\text{PhP(H)})_4\text{C}\),
would not provide an attachment point on the methylene bridge, but should close the
phosphorus-carbon-phosphorus angle from the 120° observed for the \(\text{et,ph-P}_4\)
complexes to 109.5° for a tetrahedral geometry, bringing the metal centers closer
together.

As the addition of base proceeded, the solution gradually turned yellow, again
indicating phosphide formation. After quenching with water and extraction and
concentration of the organic layer, a clear liquid was obtained. \(^{31}\text{P}\) NMR showed three
species: unreacted \(\text{PhPH}_2\), (s) –125 ppm, \(\text{PhP(H)Me}\), (s) –72 ppm, and a bridged chiral
polyphosphine, (d) –56.5 ppm (Figure 41). The proton coupled \(^{31}\text{P}\) NMR showed the
expected splitting of the \(\text{PhPH}_2\) and \(\text{PhP(H)Me}\) resonances into a triplet and doublet
respectively, and the bridged species split into two doublets of doublets (Figure 42).
The splitting of the doublet observed in the decoupled spectra into a doublet of
doublets is expected for a phosphine with one attached hydrogen, and the further
splitting of this pattern is explained by the fact that the phosphorus is chiral, appearing
in both racemic and meso forms.

In order to support the formation of the bridged tetraphosphino species
\(\text{C(PhPH)}_4\), samples were submitted for mass spectrometry. At the time of these
experiments, the mass spectrometry facility was inoperative and by the time it had
resumed operations the samples had decomposed.
Figure 41. $^3$P NMR Spectra of CCl$_4$ + NaOH + PhPH$_2$. 
CHAPTER 9. CONCLUSION

The chelating tetraphosphine ligand system, et.ph-P4, has been shown to form bimetallic complexes that are effective catalysts for hydroformylation. This catalyst system is unprecedented in its ability to act as an effective catalyst for both regular and asymmetric hydroformylation. In situ studies and monometallic model systems have been used to show that the performance of this catalyst system is due to bimetallic cooperativity between the two metal centers. The desire to modify this ligand to optimize its performance has led to several refinements and a major breakthrough in synthetic phosphorus chemistry.

The synthesis of tris(trimethylsilyl)phosphine has been re-engineered and optimized. P(TMS)_3 has been used to synthesize two bisphosphinomethane compounds as precursors for attaching our ligand system to a solid support. A modification of the P(TMS)_3 synthesis provides a route to previously unattainable trisubstituted phosphines.

The synthesis of bis(dichlorophosphino)methane, DCPM, has been improved and has become a valuable precursor for making modified forms of our et.ph-P4 ligand. This DCPM has also been functionalized with chiral auxiliaries and used in attempts to synthesize predominantly one diastereomeric form of our ligand.

The greatest addition to our synthetic toolbox has been the discovery and development of the zinc chemistry. The use of a “zinc modified” Grignard reagent, RZnX, has given us the ability to selectively and controllably alkylate phosphorus halides. This chemistry has been used with monophosphines to allow us to synthesize...
our own starting materials, and with DCPM to synthesize our long desired alkylated
forms of our et,ph-P4 ligand.

All of synthetic phosphorus work has been aided by the refinement and use of a
method for predicting $^{31}$P NMR resonances. A group additivity scheme has been
shown to be accurate for predicting $^{31}$P chemical shifts for trivalent mono- and di-
phosphines over a wide range.
CHAPTER 10. EXPERIMENTAL

10.1 General Procedures

NMR spectra were collected on Bruker AC-100, AC-200, AC-300 and AC-400 spectrometers in 5mm glass tubes at room temperature (25°C). $^1$H NMR resonances are reported in ppm, using TMS as an external reference. $^{31}$P NMR resonances are reported in ppm, using 85% $\text{H}_3\text{PO}_4$ as an external reference. Elemental analysis was performed by Oneida Research Services, Inc., Whitesboro, New York.

All experiments were carried out under inert atmosphere (nitrogen) using standard Schlenk line and glove box techniques. Glove boxes used were of the double workstation type purchased from Vacuum Atmospheres and Innovative Technologies. Schlenk lines were of a standard double manifold design and manufactured in house by the LSU glass shop. The nitrogen used was generated from the boil off from liquid nitrogen tanks and used without further purification. All solvents were redistilled under inert atmosphere from the appropriate drying agents as follows: toluene and tetrahydrofuran from sodium/potassium alloy; hexane and pentane from potassium; methanol and ethanol from magnesium turnings; and dichloromethane from calcium hydride.

Reagents were purchased at the highest purity available and used without further purification. All reagents and deuterated NMR solvents were purchased from Aldrich except; $\text{PhPH}_2$ and $\text{Et}_2\text{PCl}$ from Strem, $\text{ClSi(CH}_3)_3$ and K from Janssen, and aluminum foil from Wal-Mart.
10.2 P(TMS)$_3$

We have improved on this reaction originally reported by Becker,\textsuperscript{25} completely redeveloping the apparatus and technique while maintaining the same chemistry. 60 gm of white phosphorus is cut and scraped, to remove the surface oxide coating, under water and transferred to a 5-L three-neck flask equipped with two reflux condensers under nitrogen (Figure 43) and dried via vacuum. The center condenser, which will surround the stirring shaft, is attached with a Rotavis joint. The system is filled with nitrogen, a mechanical stirrer inserted, and dimethoxyethane (3.5 L) is added via cannula and allowed to reflux until all of the phosphorus has dissolved, 3-4 hr. The solution is allowed to cool to room temperature and 205 gm of sodium/potassium alloy (64.2 gm Na/145 gm K) is added dropwise through a large bore addition funnel. The rate of addition is controlled to prevent the solvent from boiling. The solution warms spontaneously and darkens as the phosphorus is reduced. After the addition is complete, the addition funnel is removed and the solution is refluxed for 24 hr. to allow complete reaction of the Na/K. The reaction mixture progressively darkens until it takes on the appearance of strong coffee.

To the refluxing solution, degassed chlorotrimethylsilane (894 ml.) is added via cannula, causing the mixture to thicken and lighten in color. The motor speed must be occasionally adjusted to maintain good stirring and the solution is allowed to reflux for 72 hr. Good mixing is essential or the final yield will be greatly reduced. As the reaction nears completion, it has the appearance and consistency of a mint-chocolate-chip milkshake.
After cooling, the reaction flask is taken into a glove box and the mixture is filtered through a 2-L fritted filter flask and the salts washed with several portions of hexane. Care should be taken in disposing of the salts, since they are highly pyrophoric. The filtrate and washings are combined and roto-vapped to remove all of the ether and hexane, and the residue is vacuum distilled at 2 mm Hg. 332 gm (69% yield) of P(TMS)$_3$ (bp 77-79°C @ 2mm Hg), a clear, thick liquid, is collected. $^{31}$P NMR (C$_6$D$_6$): $-251$ (s).

Figure 43. Apparatus for P(TMS)$_3$ Synthesis
10.3 $\text{H}_2\text{PCH}_2\text{PH}_2$

MeOH (4.03 gm, $1.26 \times 10^{-1}$ mol) is added dropwise via cannula to a stirring solution of $(\text{TMS})_2\text{PCH}_2\text{P(TMS)}_2$ $^{36}$ (11.61 gm, $3.15 \times 10^{-2}$ mol) in 20 ml of hexane, and allowed to stir for 1 hr. The hexane and any excess methanol is then removed under reduced pressure leaving 2.5 gm of $\text{H}_2\text{PCH}_2\text{PH}_2$ (99% yield) as a viscous, colorless liquid. $^{31}\text{P NMR}(\text{C}_6\text{D}_6)$: $-121$ (s).

10.4 *Racemic, Meso-*$\text{Et}_2\text{PCH}_2\text{CH}_2(\text{Ph})\text{PCH}_2(\text{p-C}_6\text{H}_4)\text{CH}_2\text{P(Ph)CH}_2\text{CH}_2\text{PEt}_2$

$\text{K}[\text{(Ph)PH}]^{37}$ (3.25 gm, $2.19 \times 10^{-2}$ mol) in 50 ml of THF is added dropwise to a solution of $\alpha,\alpha'$-dibromo-$p$-xylene (2.90 gm, $1.10 \times 10^{-2}$ mol) in 50 ml of THF. As the addition proceeds the solution becomes opaque orange and then lightens to an opaque yellow with the formation of a white precipitate clinging to the sides of the flask. The reaction is allowed to stir for 1 hr. and then the solvent is removed under reduced pressure, leaving a white solid, $\text{Ph(H)PCH}_2(\text{p-C}_6\text{H}_4)\text{CH}_2\text{P(Ph)CH}_2\text{CH}_2\text{P}$. To the solid is added $\text{Et}_2\text{PCH}=$CH$_2$ (1.40 gm, $1.20 \times 10^{-2}$ mol) in the absence of any solvent and the mixture is photolyzed for 12 hr. using a xenon lamp. The excess $\text{Et}_2\text{PCH}=$CH$_2$ is removed under reduced pressure leaving 4.90 gm of the product (a 1:1 mixture of the *racemic* and *meso* diastereomers) as a white solid (80% yield). $^{31}\text{P NMR}(\text{C}_6\text{D}_6)$: $-14.7$, $-15.3$ (dd) internal phosphorus atoms; $-18.2$, $-18.7$ (dd) external phosphorus atoms (Figure 44).
Figure 4. 31P NMR Spectra of Et$_3$PCH$_2$CH$_2$P(Ph)(p-xyl)CH$_2$P(Ph)CH$_2$PCH$_2$Et.
10.5 $\text{Cl}_2\text{AlCH}_2\text{AlCl}_2$

Bis(dichloroalumino)methane, $\text{Cl}_2\text{AlCH}_2\text{AlCl}_2$, is prepared via a halogen exchange reaction. Commercial grade aluminum foil (48.57 gm) is cut into approximately 1 inch squares and added to a 2-L two necked flask fitted with a reflux condenser, and evacuated while warming for several hours to dry. Note: brand of foil seems to make no difference, but aluminum powder, even of fine mesh and high purity, will not work, presumably due to the decrease in surface area. The flask is cooled and filled with nitrogen, and 1.5 L of dichloromethane followed by 35 ml. of dibromomethane are added via cannula. The mixture is heated and allowed to reflux until all of the aluminum has reacted, forming a dark gray solution with suspended black particles (about 24 hr.). If the reaction has not started after 2 hr. of refluxing, as witnessed by a darkening of the solution and dissolving of the foil, a few ml. (2-3 ml.) of diiodomethane can be injected into the refluxing solution to help catalyze the reaction.

After all of the aluminum foil has reacted, the condenser is removed and the reaction flask is quickly taken into the glove box while still warm to prevent the product from precipitating out of solution. The solution is filtered through a medium frit, removing an insoluble gray precipitate, presumably impurities from the aluminum foil. The solid is washed with several portions of DCM and the filtrate and washings are combined and vacuum evaporated down to leave 188.54 gm of the product, DCAM, as a fine light orange powder (99% yield based on aluminum). The DCAM
is air sensitive, reacting violently with water, but can be stored indefinitely under an inert atmosphere.

10.6 \( \text{Cl}_2\text{PCH}_2\text{PCl}_2 \)

\( \text{Cl}_2\text{AlCH}_2\text{AlCl}_2 \) (110 gm, 5.2 x 10^{-1} mol) is dissolved in 1 L of DCM and added slowly via cannula to a 2-L two neck flask equipped with a condenser and containing a stirring solution of \( \text{PCl}_3 \) (144.2 gm, 1.05 mol) in 300 ml DCM.\(^{39}\) After the addition is complete, the mixture is heated and allowed to reflux for 6 hr. The reaction is allowed to cool to room temperature and \( \text{POCl}_3 \) (161 gm, 1.05 mol) is added via cannula to the cooled reaction mixture, to scavenge the \( \text{AlCl}_3 \) produced from the first step. The mixture is then heated to boiling and allowed to reflux for an additional 4 hr. The reaction mixture is allowed to cool, the condenser removed, and the flask is taken into the glove box.

The mixture is filtered through a medium frit to remove any unreacted DCAM and aluminum salts and the solid is washed with several portions of DCM. The filtrate and washings are combined and concentrated down to a paste under reduced pressure. The paste is distilled under vacuum at 2 mm Hg to give 54 gm (48% yield) of the product, \( \text{Cl}_2\text{PCH}_2\text{PCl}_2 \) (bp 67-71°C @ 2mm Hg). Note: Any remaining \( \text{AlCl}_3 \) may begin to sublime on the walls of the distillation apparatus if the distillation is continued too long or over heated. \(^{31}\text{P} \) NMR (\( \text{C}_6\text{D}_6 \)): 175 (s). \(^1\text{H} \) \(^{31}\text{P} \) NMR (\( \text{C}_6\text{D}_6 \)): 2.49 (t) (Figure 45).
Figure 45. $^1$H $^{31}$P NMR Spectra of Cl$_2$PCH$_2$PCl$_2$. 
10.7 Menthoxy(Cl)PCH₂P(Cl)Menthoxy

Two equivalents of (+) or (−) menthol is dissolved in slightly over 2 equivalents of (CH₃CH₂)₂N to deprotonate the hydroxyl group. This mixture is then added dropwise via cannula to 1.05 equivalent of Cl₂PCH₂PCl₂ in THF (approximately 10 ml. THF/1 gm phosphine), immediately producing a large amount of a white precipitate, the amine salt. The salt is filtered off with a fine frit and washed with several portions of THF. The filtrate and washings are combined and concentrated under reduced pressure, removing solvent and remaining excess amine and Cl₂PCH₂PCl₂, leaving a clear, viscous liquid.

The product was characterized by ¹H NMR, ³¹P NMR, and ³¹P COSY NMR experiments. The ³¹P NMR showed a confusing 6 peak pattern at 194-190 ppm with no proton coupling appearing in the proton coupled spectra. The ³¹P COSY experiment (Figure 46) showed this pattern to be two doublets flanking a pair of singlets, with the doublets coupling to one another, but not themselves. The doublets were determined to be the two phosphorus atoms in the “meso” form of the menthoxy substituted bridge, while the singlets are the phosphorus atoms in the “racemic” form (Figure 47). Integration shows that both the “meso” and “racemic” forms are produced in equal amounts. In this case the terms “meso” and “racemic” refer only to the stereochemistry about the phosphorus atoms and not the attached menthoxy moieties.
Figure 46. COSY $^{31}$P NMR Spectra of Menthoxyl Phosphine
10.8 Ephedrine Compound

(+)-Ephedrine hydrochloride (1.85 gm) and triethylamine (2.79 gm) are mixed in 100 ml. of THF and cooled to -78°C. \( \text{Cl}_2\text{PCH}_2\text{PCl}_2 \) (1.00 gm) is added dropwise via cannula over 1 hr. The solution turns orange and a precipitate forms upon addition of the first drop, and the color deepens to a rich brown as the solution is allowed to warm to room temperature and stir overnight. The reaction mixture is taken into the box and filtered through a fine frit. A pale orange solid is filtered off and washed with several portions of THF. The filtrate and washings are combined and concentrated down to dryness under reduced pressure, leaving an orange solid believed to be the compound shown below (Figure 48).

This structure is supported by \(^1\text{H} \text{NMR}\) and \(^{31}\text{P} \text{NMR}\), but elemental analysis, mass spectrometry, and further chemistry fail to support this proposed structure. The \(^1\text{H} \text{NMR}\) of this product shows the expected ephedrine resonances, shifted slightly...
upfield as would be expected upon coordination to the phosphine. The $^{31}\text{P}$ NMR
(Figure 49) shows two uncoupled singlets of equal intensity at $-66.2$ and $-69.2$ ppm,
corresponding to the two diastereomers, meso and racemic. Mass spectroscopy
proved inconclusive and unreliable for structural determination, giving 5 different
parent peaks for five runs of the same sample. Elemental analysis also proved puzzling,
reporting the following composition which we are presently unable to provide an
explanation for: C, 57.53; H, 6.65; N, 6.05; P, 19.49.

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} \quad \text{P} \quad \text{P} \quad \text{O} \quad \text{Ph} \quad 2^+ \\
\text{Ph} & \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{N} \quad \text{CH}_3
\end{align*}
\]

**Figure 48. Proposed Structure of Ephedrine Compound**
Figure 49. COSY $^{31}$P NMR Spectra of Ephedrine Compound
10.9 \( \text{CH}_3(\text{H})\text{PCH}_2\text{P(\text{H})CH}_3 \)

Methylmagnesium bromide (2 eq.) is added to zinc chloride (2 eq.) in THF and stirred for 30 minutes. This stirring mixture is then cooled to \(-10^\circ\text{C}\) and \(\text{Cl}_2\text{PCH}_2\text{PCl}_2\) (1 eq.) also at \(-10^\circ\text{C}\) is added dropwise via cannula. After the addition is complete, the reaction is allowed to warm to room temperature and stirring is continued overnight. The solution is taken into the glove box and filtered through a medium frit, removing a white precipitate. The precipitate is washed with several portions of THF and the filtrate and washings combined, removed from the box and then recooled to \(-10^\circ\text{C}\). The cooled solution is treated with \(\text{LiAlH}_4\) (2 eq.) in diethyl ether and allowed to stir overnight while gradually warming. The mixture is quenched with degassed aqueous \(\text{NaOH}\) (5M, 2 eq.), the THF layer is removed, and the salts washed with ether. The combined organic extracts are vacuum concentrated leaving a mixture of products: \(\text{H}_2\text{PCH}_2\text{P(\text{H})CH}_3\); \(^{31}\text{P NMR (C}_6\text{D}_6\): (d) \(-69.7\), (d) \(-142.6\), and \(\text{CH}_3(\text{H})\text{PCH}_2\text{P(\text{H})CH}_3\); \(^{31}\text{P NMR (C}_6\text{D}_6\): \(-84.4\), \(-87.6\) (Figure 50). Proton coupled \(^{31}\text{P NMR of the mixture showed the \(-69.7\) and \(-142.6\) resonances of the unsymmetrical species split into a doublet of doublets and a triplet of doublets, respectively. The resonances for the desired symmetrical product split into doublets upon proton coupling. The \(^{31}\text{P COSY spectra was as expected, showing phosphorus-phosphorus coupling between the \(-69.7\) and \(-142.6\) peaks, and none between the others.}}\)
Figure 50. $^{31}$P NMR Spectra of Me(H)PCH$_2$P(H)Me
10.10 C₆H₁₁(H)PCH₂P(H)C₆H₁₁

Two equivalents of cyclohexylmagnesium chloride in THF is added to a solution of zinc chloride (2 eq.) in THF and stirred for 30 minutes. This stirring solution is then removed from the glove box and cooled to -10°C and one equivalent of Cl₂PCH₂PCl₂ also at -10°C is added dropwise via cannula. After the addition is complete, the reaction mixture is allowed to warm to room temperature while stirring is continued overnight. The reaction flask is taken into the glove box and filtered through a medium frit, removing a coarse white precipitate. The precipitate is washed with several portions of THF and the filtrate and washings combined, removed from the box and then recooled to -10°C.

The cooled phosphine solution is slowly treated with two equivalents of a LiAlH₄ solution in diethyl ether and allowed to stir overnight while gradually warming. The mixture is quenched with degassed aqueous NaOH (5M, 2 eq.) until evolution of a gas ceases. The THF layer is transferred to an empty flask via cannula, and the salts are washed with several portions of diethyl ether. The ether is also removed via cannula after each washing and combined with the THF layer. These organic extracts are concentrated under vacuum, leaving the product as a clear liquid in quantitative yields. ³¹P NMR (C₆D₆): -51.1, -52.5 ppm (Figure 51). The proton coupled ³¹P NMR showed each resonance split into the expected doublet due to the attached hydrogen atom.
Figure 5. $^{31}P$ NMR Spectra of $C_6H_5(CH_2P)(H)C_6H_5$.
10.11 (CH₃CH₂)₂PCl

Zinc chloride and ethylmagnesium chloride (2.4 equivalents each) are mixed in THF for thirty minutes and then added dropwise to one equivalent of phosphorus trichloride in THF at −10°C. The solution is allowed to stir overnight, forming copious amounts of a white precipitate. The salts are filtered off and washed with THF, and the washes combined and concentrated. ³¹P NMR shows only one product, Et₂PCl (s, 117 ppm). Vacuum removal of the solvent yields pure Et₂PCl, a clear liquid, in 99+% yield.

10.12 (C₆H₁₁)₂PCH₂PH₂

Cl₂PCH₂PCl₂ (2.48 gm, 22.8 mmol) is diluted with 40 ml. of THF and cooled to −78°C. i-PrOLi (7.34 ml., 22.8 mmol) is added slowly via cannula and the mixture allowed to stir for 1 hr. The flask is allowed to warm to room temperature and then CyMgCl (9.91 gm, 22.8 mmol) is added via cannula and stirred for 2 hr. As the reaction proceeds the mixture turns a yellowish/orange color. The flask is cooled to 0°C and LiAlH₄ is added slowly and allowed to stir for 4 hr. while gradually being allowed to warm to room temperature after the second hour. The solution begins to fade to a pale yellow and thickens with the formation of a white solid. To the reaction mixture 15.6 ml. of acetic acid (2.6 ml. of acetic acid in 13 ml. of degassed H₂O) is added, turning the solution cloudy white. The mixture is extracted with hexane, the organic layers combined, concentrated, and distilled to give (C₆H₁₁)₂PCH₂PH₂. ³¹P NMR (C₆H₆): (d) −36, (d) −139.6 (Figure 52). Proton coupled ³¹P NMR shows the expected splitting of the doublet at −139.6 into a triplet of doublets (Figure 53).
Figure 5. 31P NMR Spectra of (C₆H₅)₂PCH₂PH₂
Figure 53. \(^1\text{H}^{(31\text{P})}\) NMR Spectra of \((\text{C}_6\text{H}_{11})_2\text{PCH}_2\text{PH}_2\)
REFERENCES


86
Rates for bimetallic systems are divided by 2 to give normalized rates on a per rhodium basis. This allows for direct comparison between monometallic and bimetallic catalysts.


George Stanley in numerous discussions.


(f) Kubiak, C. P. Private communication.


39 Kubiak, C.P.; Private communication.

VITA

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DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Frederick Koch III

Major Field: Chemistry

Title of Dissertation: The Synthesis of Novel Phosphine Modified Ligands for Use in Bimetallic Hydroformylation

Approved:

[Signatures]

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Date of Examination:

April 9, 1997