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Toward the advancement of tetraphosphine ligand synthesis for homogeneous bimetallic catalysis

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TOWARD THE ADVANCEMENT OF TETRAPHOSPHINE LIGAND SYNTHESIS FOR HOMOGENEOUS BIMETALLIC CATALYSIS

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ABSTRACT

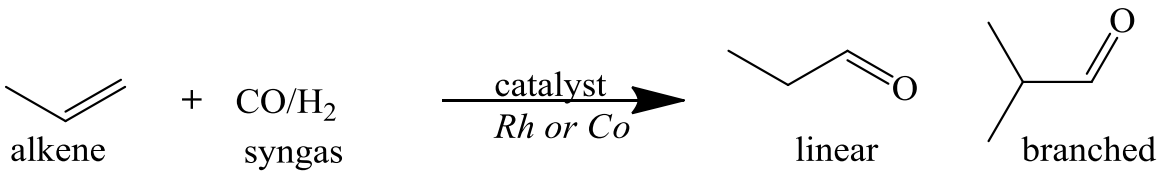
A tetraphosphine ligand *rac*-et,ph-P4 ($Et_2PCH_2CH_2(Ph)PCH_2P(Ph)CH_2CH_2PEt_2$) is used for the formation of a highly active and regioselective bimetallic hydroformylation catalyst. The proposed active catalytic species in acetone, $[Rh_2H_2(\mu\text{-}CO)_2(rac\text{-et,ph- P4})]^{2+}$, is formed *in situ* under H_2/CO pressure. This is one of the most impressive examples of cooperativity in homogeneous catalysis. The fragmentation of this catalyst by CO has been investigated and confirmed by *in situ* NMR spectroscopic studies. A new tetraphosphine ligand *rac*-et,ph-P4-Ph (et,ph-P4-Ph = $Et_2P(o\text{-}C_6H_4)P(Ph)CH_2(Ph)P(o\text{-}C_6H_4)PEt_2$) has been synthesized to combat this fragmentation problem. However, the inability to successfully separate the *meso* and *racemic* diastereomers led to the attempted alteration of the et,ph-P4 tetraphosphine ligand. Where the et,ph-P4-Ph ligand attempts to change the traditional ligand via altering the carbon system between internal and external phosphines, these systems attempt to replace the methylene linker between the internal phosphines with an amine linker.

Experimentation has been conducted on the basis of a retrosynthetic analysis with the possibility of two pathways for formation of these aza-bridged ligands. The first synthetic route involves a simple Grignard-mediated phosphorus-carbon coupling reaction between an amine bridge of the type $RN(PhPCl)_2$ with the "small arm" phosphine moiety $Et_2P(o\text{-}C_6H_4)I$. Impurities in the starting material and decreased reactivity of the amine bridge led to results that were undesirable. The second synthetic route relies upon coupling of the "large arm" phosphine moiety $Et_2P(o\text{-}C_6H_4)PPhCl$ with a primary amine to afford the desired ligand. This route was also unsuccessful due to the inability to obtain the pure phosphorus compound due to the "large arm" reaction not consistently going to completion.

CHAPTER 1: INTRODUCTION TO HYDROFORMYLATION

1.1 History

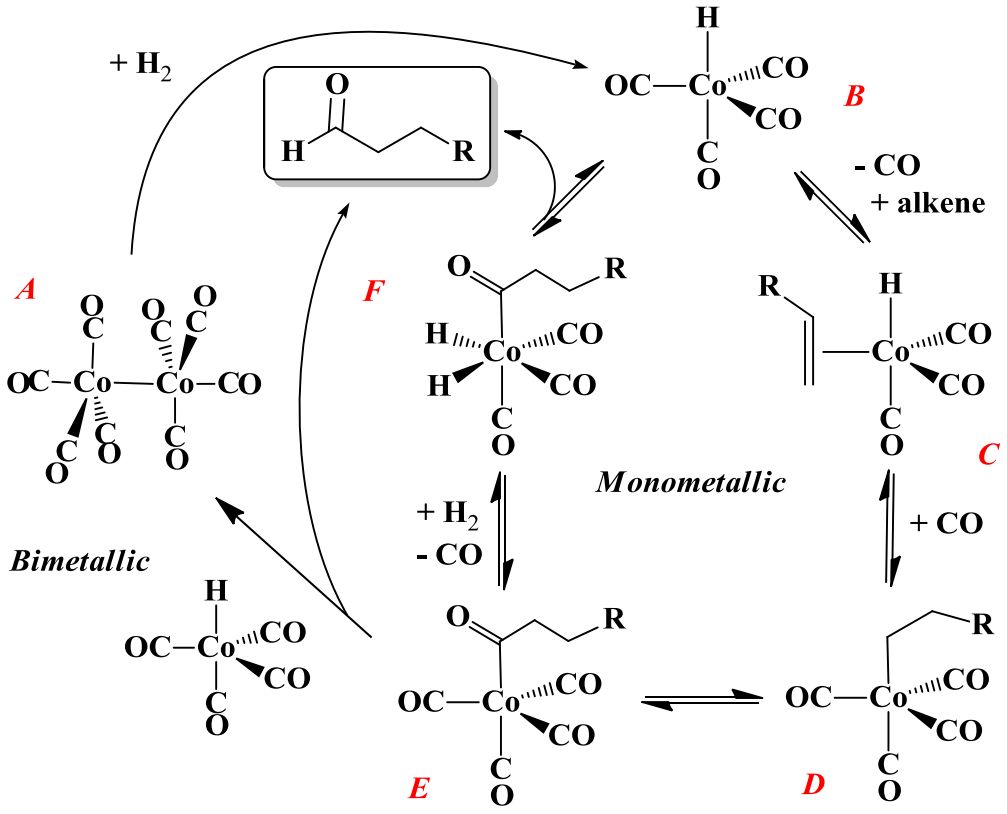
Otto Roelen's transition from the Kaiser-Wilhelm Institute to Rurchemie in 1934 was a significant milestone for aldehyde synthesis. While working there he was given the task of recycling "gasol", short chain alkenes (C_2-C_4), by their incorporation with ammonia into higher order hydrocarbons used in the Fischer-Tropsch process.[1] Near the end of 1937 while working on this project he discovered a white propionaldehyde-ammonia product coating the walls of the reactor; experiments were performed to optimize reaction conditions for the synthesis of propionaldehyde and on September 20, 1938 the first patent for the "oxo process" was filed.[1] The oxo proces, also known as hydroformylation, synthesizes a mixture of linear and branched aldehydes by reacting alkenes, carbon monoxide (CO), and hydrogen in the presence of a catalyst under pressure as depicted in Scheme 1.1.



Scheme 1.1. General depiction of the hydroformylation reaction.

1.2 Cobalt Catalyzed Hydroformylation

The first industrial scale hydroformylation reactions were begun by Ruchemie in 1942 utilizing the catalyst precursor $Co_2(CO)_8$ as seen in Heck's accepted catalytic cycle for this process in scheme 1.2. The dicobalt species ***A*** is hydrogenated to the key active catalytic intermediate $HCo(CO)_4$, ***B***. Dissociative substitution occurs between a CO ligand and an alkene, yielding ***C***. The alkene then inserts into the Co-H bond forming an alkyl carbonyl complex ***D***.



Scheme 1.2. Heck and Breslow's proposed Co hydroformylation mechanism.

The alkyl ligand of complex ***D*** undergoes a migratory insertion with a cis-CO ligand. A carbonyl ligand adds to the newly formed 16 e- complex to give the 18 e- acyl species ***E***. Heck proposed two ways to complete his catalytic cycle. Via the monometallic pathway, CO dissociates from the saturated complex to allow oxidative addition of H_2 ***F***. This is then followed by the reductive elimination of the acyl group with a hydride yielding the aldehyde product and returning to species ***B***. For his intermolecular bimetallic ending, ***E*** and ***B*** perform an intermolecular reductive elimination, yielding the aldehyde product and returning to the dicobalt cluster ***A.*** Species ***A*** is again hydrogenated to yield the key catalytic intermediate. The bimetallic pathway is only possible in high CO concentrations which would be needed to sustain

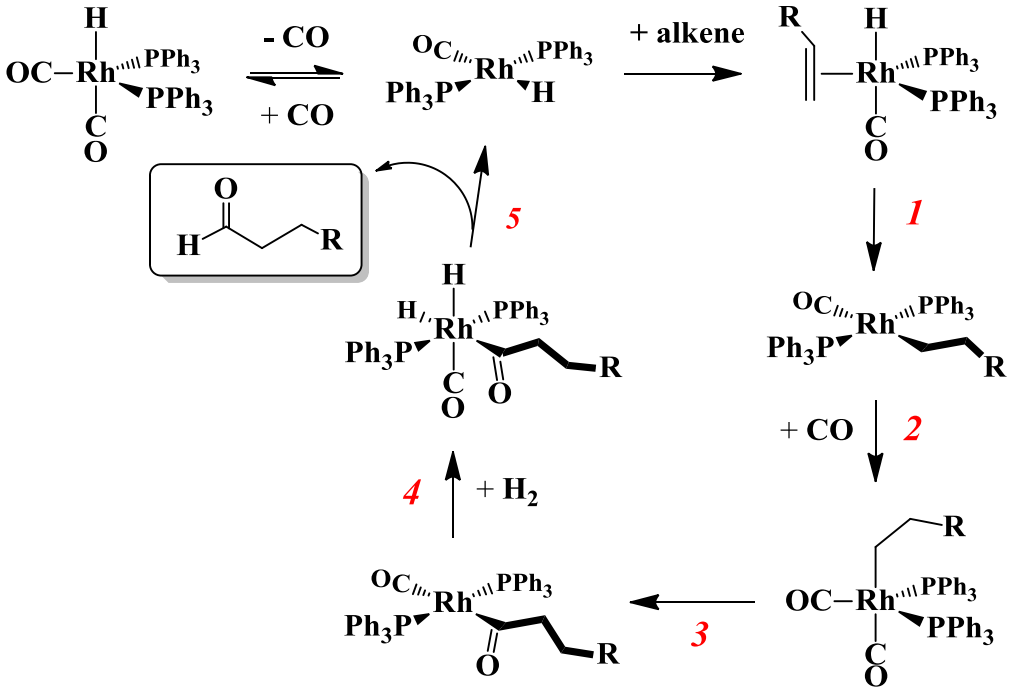
these species. With standard conditions ranging from 160-200 ^{o}C and pressures from 100-300 atm being unable to provide sufficient CO for its stability, its likelihood was abandoned.

Around the same time Heck proposed the Co hydroformylation mechanism, Shell researchers Slaugh and Millineaux found that alkyl phosphines increased catalyst regio-selectivities for linear product.[2-4] Though their findings did increase l:b ratios from 3-4:1 to 8-9:1 they also significantly increased the amount of undesirable hydrocarbon side products.[2,5] Co catalysts also tend to reduce aldehydes to alcohols which were often the end destination of the aldehydes. But due to Co's relatively poor chemoselectivity to the aldehyde itself, the other metals of group 9 as well as the surrounding metals on the periodic table were investigated to determine their viability for hydroformylation catalysis.

1.3 Rhodium Catalyzed Hydroformylation

It took nearly two decades from the inception of hydroformylation to make its way to the exploration of rhodium as a potential metal for catalysis.[6] In the early 1950's it was known that rhodium was more active than cobalt for hydroformylation under significantly less harsh conditions, which would balance out the cost difference between Co and Rh. The earliest investigations into Rh hydroformylation were performed with alkyl phosphines and halogenated Rh precursors. At the time it was unknown that both of these reactants impede hydroformylation due to alkyl ligands making stable complexes due to increased π-backbonding of CO and halogens essentially poisoning the active catalyst.[6-8] It was not until the research of Wilkinson in 1968 and Pruett in 1969 that we gained a true sense of rhodium's potential.[5,7] They discovered that combining Rh and aryl phosphines would not only yield better chemo- and regioselectivities, but would also be capable of operating under milder conditions:[7] 70-120 ^{o}C

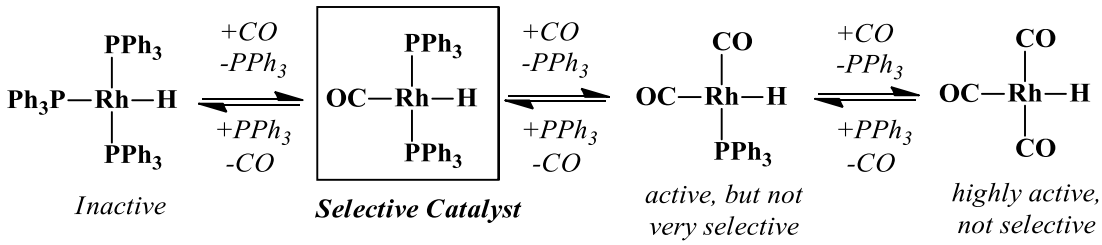
and H_2/CO (syngas) pressures ranging from 5-25 atm; today's standard conditions. These findings made possible the first industrial process using ligand modified rhodium catalysts by Celanese in 1974.[6] Today hydroformylation is one of industry's largest homogenous processes, yielding 10^6 tons of aldehyde per year.[2,6,9,10] Today most reactions are performed by rhodium-modified catalysts for C_8 and lower olefins but for longer chain alkenes cobalt is still the metal of choice due to larger alkanes usually being in mixtures of isomers rather than pure and the ability of Co to isomerize internal alkenes to their terminal analogues.[2]



Scheme 1.3. Proposed and accepted mechanism for Rh catalyzed hydroformylation.

Scheme 1.3 depicts Wilkinson's mechanism for hydroformylation using a PPh_3 modified rhodium catalyst which is nearly identical to the mechanism proposed by Heck.[7] Starting with an active 5-coordinate complex, a carbonyl ligand dissociates to yield a 16 e- species and initiates the catalytic cycle. From this point on, the catalyst runs through the following sequence

of steps: **1)** the coordination of an alkene to the catalyst, **2)** insertion of the alkene into the metal-hydride bond producing the metal alkyl complex, **3)** formation of an acyl complex via migratory insertion of CO into the metal-alkyl bond, **4)** oxidative addition of molecular hydrogen to the meal complex, and **5)** reductive elimination of the aldehyde and bringing us back to our 4-coordinate species ready for association of an alkene to continue the cycle. Throughout the intermediates of the catalytic cycle one thing that remains constant is the attachment of two phosphines, the importance of which can be seen in Scheme 1.4.



Scheme 1.4. Relationship between Rh-PPh_3 dissociation and selectivity.

At greater carbonyl concentrations with little to no phosphine we get a very active but not selective catalyst. On the other extreme, if we have only phosphine ligands attached we get no catalysis at all due to the bulk around the metal center not allowing an alkene to coordinate. With selectivity being of the upmost importance, there must be a balance between the steric and electronic properties of the ligand to obtain the highest *l:b* ratios. The most common ligands traditionally used for commercial rhodium catalyzed hydroformylation are monodentate phosphines, especially PPh_3. Because of the ease at which these ligands dissociate from the metal complex large excesses upwards of 400 equivalents per mmol Rh are required to maintain this balance.[6] For inexpensive and easily synthesized tertiary ligands such as PPh_3 this is not a major concern.

With the realization of the importance of coordination of two phosphorous species on the 4-coordinate active complex, researchers began investigating diphosphines and diphosphites as possible ligands. As early as 1966 bidentate ligands were used for catalysis with promising results with the use of $Ph_2PCH_2CH_2CH_2PPh_2$ (dppp). In 1975 Weinkauff and associates reported promising results using diphosphines for hydrogenation.[11] The earliest bidentate ligands used to study hydroformylation were similar in structure to dppp; but none of these ligands showed any improvement over PPh_3. It wasn't until the efforts of Devon in 1987 at Eastman Chemicals that diphosphines became applicable to large scale hydroformylation.[12,13]

To understand the delay of implementing bidenate ligands productively to hydroformylation we must consider the trigonal bipyramidal structure of the 5-coordinate complex; consisting of

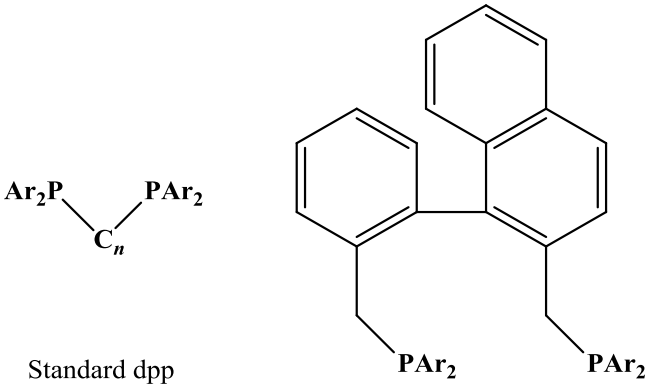


Figure 1.1. Basic diphenylphosphino- backbone and Devon's BISBI ligand

three ligands in an equatorial plane and two axial ligands dissecting that plane at 90^o. For species similar to dppp, the angle formed between the metal and the two phosphines is roughly 90^o. These ligands were only able to bind in an axial-equatorial (*ae*) fashion whereas Devon's BISBI ligand with a 124^o bite angle coordinates bis-equatorially (*ee*) which has been found to

increase *l:b* selectivity.[13,14] Since this discovery there has been enough research to support this general rule; whether it be a phosphine or phosphite, bidentate ligands with a bite angle closer to 120° yield higher *l:b* ratios than those with angles near 90°.

1.4 Polymetallic Catalysis

When changes to a catalyst for a desired product are needed or researched, these adjustments are often done by either modifying the ligand or using a different ligand all together. In hydroformylation these changes do not necessarily change how the metal behaves in the reaction; but the rates at which ligands and olefin associate/dissociate, as well as the position of the olefin R-group in respect to other ligands through steric effects. But there have been investigations into the performance of metal clusters as catalysts. Heck himself proposed bimetallic cooperativity between $HCo(CO)_4$ and $Co(acyl)(CO)_4$ complexes to perform an intermolecular hydride transfer and subsequent reductive elimination of the aldehyde and formation of $Co_2(CO)_8$.[4] In the mid 1970's the idea of metal cluster catalysis was enhanced through the efforts of Muetterties through his cluster-surface analogies and his catalysis with $Ni_4[CNC(CH_3)_3]_7$.[15-19] Soon after, there were reports of Rh cluster catalyzed oxidation and Co and Rh Carbonyl clusters being viable catalyst precursors for hydroformylation.

In 1977 Pittman and reported the use of cobalt clusters performing hydroformylation with indications that no fragmenting was taking place.[20] Subsequent spectroscopic studies provided further evidence that little or no cluster fragmentation was taking place in these systems.[21] There have been studies of $[HRu_3(CO)_{11}]^-$ performing hydroformylation with *l:b* ratios as high as 98.6:1.4.[22] This system's rates, however, are very poor and average less than 50 turnovers over

66 hrs, which isn't surprising considering the activity of transition metals for hydroformylation; Rh >> Co >> Ir, Ru > Os > Pt > Pd > Fe >Ni.

Though there have been a few studies of metal cluster catalysis without fragmenting taking place, none of these studies have clear proof of metal cooperativity taking place. For the cases where Rh clusters were used for hydroformylation, most rates and selectivities are similar to, and did not rule out the possibility of fragmenting to their monometallic analogues.

1.5 Rhodium Bimetallic Catalysis with et,ph-P4

To minimize fragmentation and to enhance the likelihood of bimetallic cooperativity, Stanley tethered two rhodium centers together with the tetraphosphine ligand $Et_2PCH_2CH_2(Ph)PCH_2P(Ph)CH_2CH_2PEt_2$ (et,ph-P4**)**.[23-28] This system remains the only known example of hydroformylation with extremely strong evidence for bimetallic cooperativity. This system rivals the best monometallic systems for a combination of rate and selectivity as seen in Table 1.1.

Because of the chiral centers of the two internal phosphines, et,ph-P4 exists as *meso*- and *racemic* diastereomers. Reacting *rac*- or *meso*-et,ph-P4 with 2 equivalents of $[Rh(nbd)_2]BF_4$ produces the catalyst precursor [*rac*- o*r meso*-$Rh_2(nbd)_2$(et,ph-P4)]$^{2+}$ seen in Figure 1.2. In addition to the *racemic* closed-mode species [*rac*-$Rh_2H_2(\mu\text{-}CO)_2(CO)_2$(et,ph-P4)]$^{2+}$, **2**, being more than 20 times faster than the *meso*-complex for hydroformylation, it also has far fewer alkene isomerization and hydrogenation side reactions. This species prefers bimetallic cooperativity via an *intra*molecular hydride transfer that allows the reductive elimination of the aldehyde with a *l:b* ratio of 25:1. The [*rac*-$Rh_2H_2(\mu\text{-}CO)_2(CO)_2$(et,ph-P4)]$^{2+}$ catalyst is far superior to the *meso* complex and equal or better than most of the best monometallic systems.

Table 1.1 Comparison of Stanley's catalyst with some of the best known monometallic catalysts in pure acetone solvent and a 30% water acetone mixture. Conditions: 90°C; 90 psig 1:1 H_2/CO; 1 M 1-hexene; 1 mM catalyst).[29]

Catalyst	% H_2O	Initial TOF* (min^{-1})	Aldehyde l:b	% iso
rac-et,ph-P4	0	20	25:1	2.5
rac-et,ph-P4	30	73	33:1	<0.5
Rh/PPh_3	0	13	9:1	<0.5
Rh/PPh_3	30	17	14:1	1.0
Rh/BISBI	0	25	70:1	<0.5
Rh/BISBI	30	37	80:1	2.0
Rh/Naphos	0	27	120:1	1.5
Rh/Naphos	30	35	100:1	2.2
Rh/Xantphos	0	13	80:1	5.0
Rh/Xantphos	30	28	60:1	<0.5

* TOF = turnover frequency

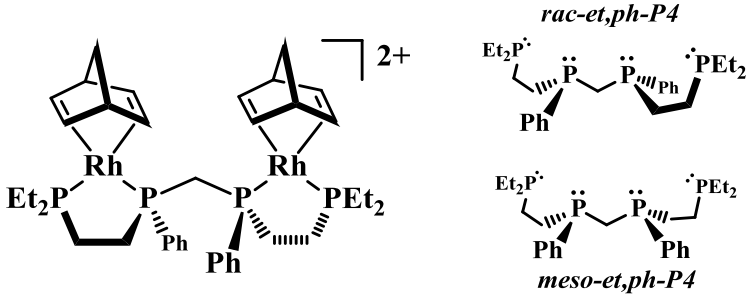
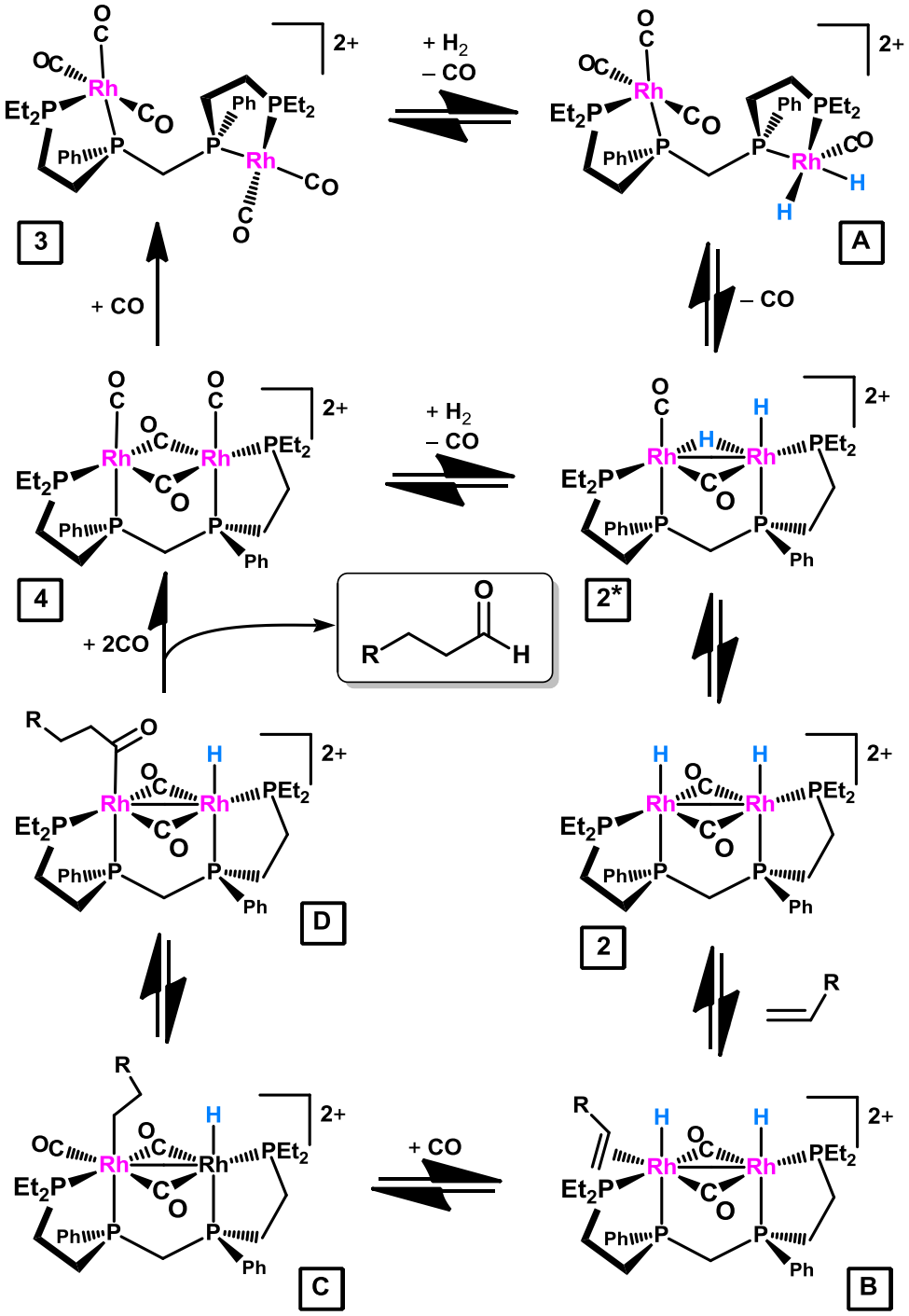


Figure 1.2. [*rac*-$Rh_2(nbd)_2$(et,ph-P4)]$^{2+}$ and the free *racemic* and *meso* ligands.

One notable difference is that it does not require excess ligand unlike virtually all monometallic phosphine catalysts. It should be noted the *meso*-catalyst can do an intramolecular hydride transfer, but it is far more difficult for it to form the lower energy doubly-bridged edge-sharing bioctahedral closed-mode intermediates.



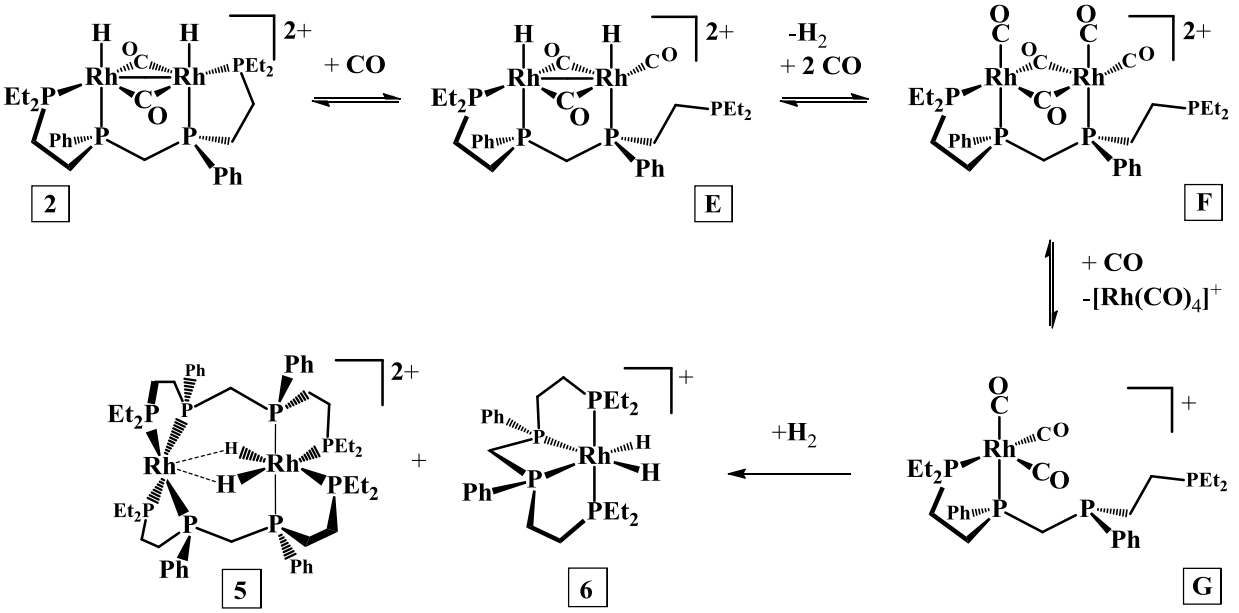
Scheme 1.5 Proposed mechanism for the bimetallic catalyst *rac*-et,ph-P4.

Stanley's proposed mechanism begins with the oxidative addition of H_2 giving species **A** of Scheme 1.5. This complex then performs an intramolecular hydride transfer between the two

rhodium centers giving the first bimetallic cooperativity step, generating the key catalytic species **2** through the intermediate **2***. Complex **2** undergoes a dissociative substitution between CO and an alkene to generate species **B**. Migratory insertion of the alkene into the rhodium-hydride bond followed by the association of CO produces the alkyl species **C**. Another migratory insertion occurs, with CO entering the alkyl-rhodium bond forming the acyl complex **D**. The second key cooperative step occurs with the intramolecular hydride transfer to reductively eliminate the final aldehyde product. Addition of two CO ligands produces the bridged complex [*rac*-$Rh_2(\mu\text{-}CO)_2(CO)_2$(et,ph-P4)]$^{2+}$, **4***, which can also react with another CO to reform **3** or directly react with H_2 to form **2***.

Evidence for the proposed bimetallic mechanism was provided partly through the synthesis of the following P_2 ligand based catalysts where bimetallic cooperativity would be highly unlikely: [Rh(nbd)(P_2)](BF_4) where P_2 = $Et_2PCH_2CH_2PEt_2$, $Et_2PCH_2CH_2PMePh$, $Et_2PCH_2CH_2PPh_2$, or $Ph_2PCH_2CH_2PPh_2$). Using these species for hydroformylation resulted in only very small amounts of hydroformylation with very poor *l:b* ratios and 50 to 70% alkene isomerization and hydrogenation side reactions.

One shortcoming of this catalyst system is that CO promotes fragmentation of the dirhodium catalyst generating complexes that are very poor at hydroformylation. The fragmentation of this catalyst is different than that experienced by monometallic Rh-phosphine catalysts where an unsaturated Rh- center can add P-Ph, P-OR, or even P-CH_2Ph bonds through oxidative addition, ultimately leading to phosphine and catalyst degradation. We believe that our dirhodium catalyst fragments by losing one of the Rhodium atoms to product the inactive 18e-saturated monometallic complex **5**, and the double-P4 coordinated dirhodium complex **6** seen in scheme 1.6.



Scheme 1.6. Proposed fragmentation equilibria for the dirhodium *rac*-et,ph-P4 catalyst

The root of the problem appears to be the facile dissociation of the chelating arms from Rh. The flexibility of the ethylene-bridged chelate combined with the higher oxidation state of the Rh(II) centers appears to be working against the effectiveness of the chelate effect. David Aubry found that using a 30% water/acetone solvent system inhibits the loss of Rh keeping the equilibrium between **2**, **E**, and **B**. Darina Polakova showed that water also promotes the loss of H^+ from the dicationic dihydride **2** to produce the more stable and less reactive monocationic dirhodium catalyst [*rac*-$Rh_2H(\mu\text{-}CO)_2(CO)$(et,ph-P4)]$^+$.[30] This monocationic species is far less susceptible to loss of Rh. Although it is less active than the dicationic system, there is more present with higher resistance to deactivation leading to the improved rates and selectivity in aceton-water solutions.

This equilibrium is strongly influenced by both H_2 and CO and nicely explains H_2/CO pressure and ratio results from Bobby Barker.[31] Species **E** should be less regioselective than **2**

due to the dissociation of the sterically directing PEt_2 group. The observed aldehyde regioselectivity observed reflects the relative amounts of **2** and **E** present. At low CO and high H_2 pressures the highly selective dirhodium catalyst **2** is most abundant, but under normal conditions selectivity is diminished by the less selective but more active catalyst **E.**

The primary focus of this dissertation is the investigation of impeding the fragmentation of the dirhodium catalyst. Chapter 2 will address this by describing the reason, methods and results of experiments related to synthesizing a stronger chelating ligand by modifying the bridge between the internal and external phosphine. Attempts to modify the traditional et,ph-P4 by augmenting the phenylene linker of the internal phosphine will also be discussed. These experiments will be aimed toward product-catalyst separation by changing the solubility of the traditional tetraphosphine catalyst and reducing leaching into the product liquor. Chapter 3 will discuss attempts at synthesizing aza-bridged tetraphosphine ligands. It is believed that the amine bridge would afford an increased diastereoselectivity for the *racemic* rather than *meso*-diastereomer.

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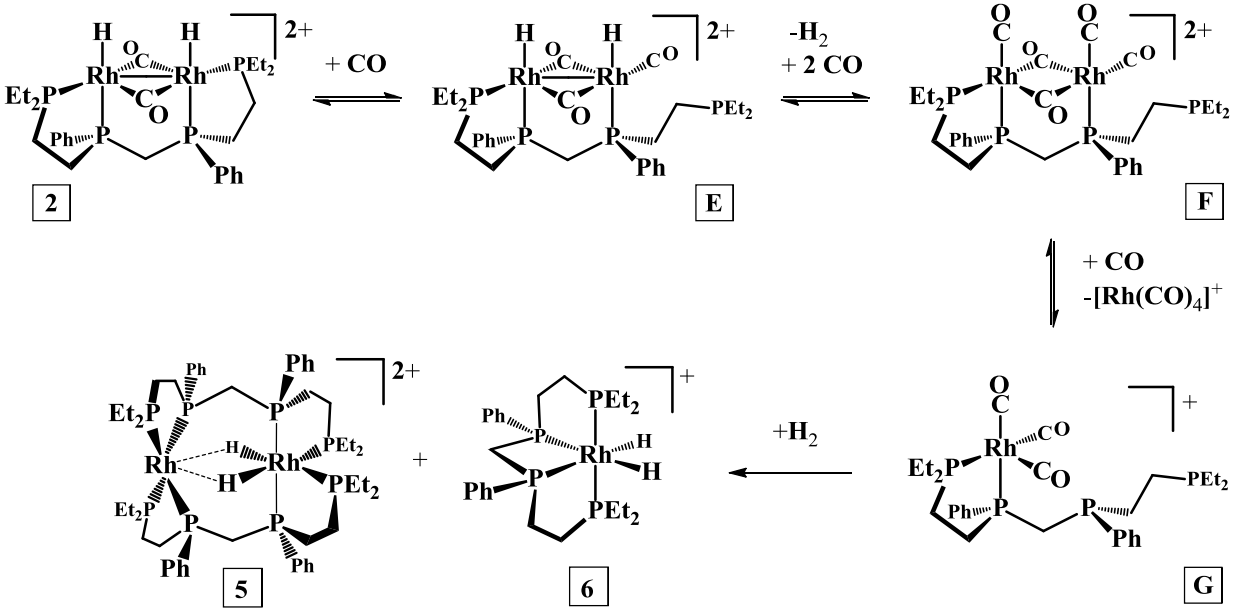
CHAPTER 2: SYNTHESIS OF A STRONGER CHELATING TETRAPHOSPHINE LIGAND

2.1 Introduction

One shortcoming of our catalyst system is that under higher CO concentrations, the catalyst undergoes fragmentation. The fragmentation of this catalyst is different than that experienced by monometallic Rh-phosphine catalysts. Usually, Rh-center can add P-Ph, P-OR, or even P-CH_2Ph bonds through oxidative addition, ultimately leading to phosphine and catalyst degradation. We believe that our dirhodium catalyst fragments by losing one of the rhodium centers to produce the inactive 18e- saturated monometallic complex **5,** and the double-P4 coordinated dirhodium complex **6** seen in scheme 2.1.



Scheme 2.1. Proposed fragmentation equilibria for the dirhodium *rac*-et,ph-P4 catalyst.

The root problem appears to be the facile dissociation of the chelating arms from Rh leading to loss of one of the rhodium centers and loss of bimetallic cooperativity. The flexibility of the

ethylene-bridged chelate combined with the cationic charge on the Rh(II) centers appears weaken the Rh-P bonding and the effectiveness of the chelate effect.

The primary focus of this chapter is the synthesis and attempted isolation of the stronger chelating tetraphosphine ligand et,ph-P4-Ph. The intent of this stronger chelate between the internal and external phosphines is simply to reduce the likelihood of a reductive elimination of H_2 and subsequent formation of the electron deficient Rh metal center **F** of scheme 2.1.

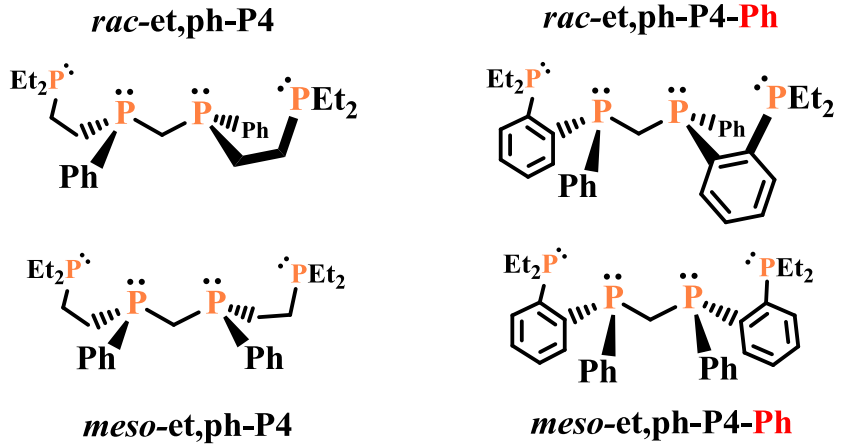
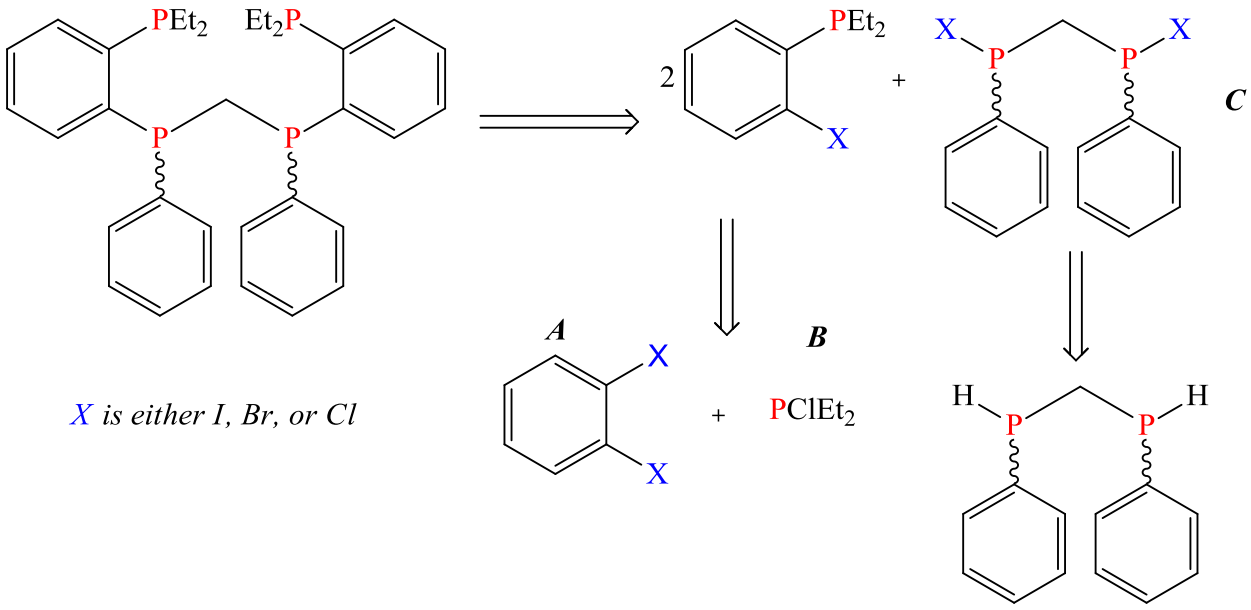


Figure 2.1. Depiction of the et,ph-P4-Ph and traditional et,ph-P4 tetraphosphine ligands

2.2 Synthetic Strategies

The synthesis of et,ph-P4-Ph was challenging and required the development of different strategies encompassing a variety of organic transformations pioneered by Alex Monteil.[1] Our synthesis of the original et,ph-P4 ligand required a simple and neat photochemical reaction to couple the easily synthesized (Ph)(H)PCH_2P(H)(Ph) building block with 2.0 equiv. of the readily prepared $Et_2P(CH{=}CH_2)$. In marked contrast, the difficulties in the synthesis of et,ph-P4-Ph lie in preparing two 1-(Et_2P)-2- phenylphosphinobenzene moieties tethered via a methylene bridge. Although there arze many 1,2-bisphopshinobenzene ligands reported in the literature, in every case in which the phosphines are *ortho* to one another we also found the ligand to be comprised

of phosphines that were identical.[2-9] With this in mind, we had to create a rather different approach to synthesizing this novel species. The approaches taken are based on the retrosynthesis of the desired et,ph-P4-Ph complex with the route receiving zthe most focus being directly related to the three starting components ***A***, ***B***, and ***C*** of Scheme 2.2. The logical approach for us is based on using the easily synthesized bis(phenylphosphino)methane. Multiple approaches have been taken based upon these 3 components with varying degrees of success. The results of those being discussed in the following sections will be based on organomagnesium and organolithium chemistry.

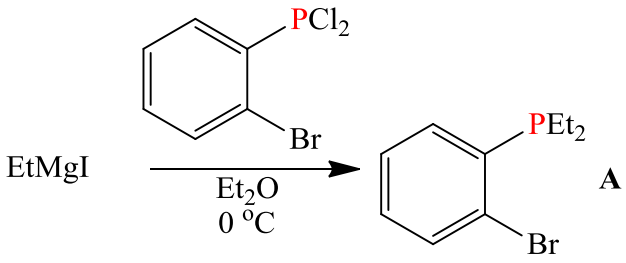


Scheme 2.2 Retrosynthesis of et,ph-P4-Ph to three reagent components.

2.3 Development of 1-Dialkylphosphino-2-halobenzene Moieties

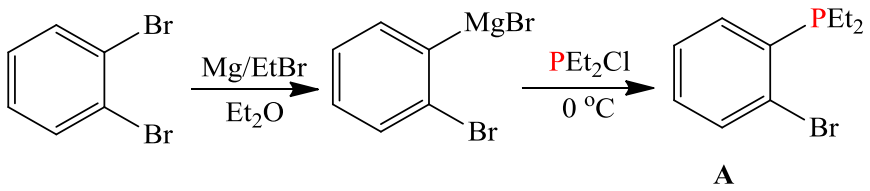
The basis of our work stems from the work of Hart in the synthesis of 1-(diethylphosphino)-2-chlorobenzene from o-dichlorobenzene. His monophosphine product is prepared by treating dichlorobenzene with nBuLi. While he reported yields as high as 50% with dichlorobenzene and

66% with dibromobenzene, attempts to reproduce his works with o-dibromobenzene have only given maximum yields of 22%. An explanation for the low yield was provided by Chen *et al.*[10] in their study of the thermal decomposition of *o*-bromophenyllithium. They found that the metallated intermediate was stable at −110 °C in ether:THF (1:1) for only 2 h. Allowing the reaction mixture to warm up to −90 °C resulted decomposition to benzyne and a multitude of other compounds. More recently, Bennett *et al.*[11] have developed a route to synthesize ***A*** in much larger yields (70%) by reaction of EtMgI with 1-(dichlorophosphino)-2-bromobenzene in diethyl ether (Scheme 2.3).



Scheme 2.3. Bennet's Synthesis of 1-diethylphopshino-2-bromobenzene(A)

This route requires the multistep synthesis of 1-(dichlorophosphino)-2-bromobenzene from *o*-bromoaniline with yields of only 24%. A viable and possibly easier route involving a Grignard reagent intermediate was also reported by Hart[9] for the synthesis of 1-(diethylphosphino)-2-chlorobenzene from *o*-dichlorobenzene in 50% yield. In this method he treated magnesium with 1,2-dichlorobenzene while refluxing. Unreacted Mg was separated and the resulting Grignard intermediate was treated with PEt_2Cl at 0 °C. We have attempted this route for the preparation of compound ***A*** using the starting material *o*-dibromobenzene. Again we were unable to attain Hart's yields: our isolated yields being less than 10% using Mg turnings and a slightly better 20% with Mg powder.



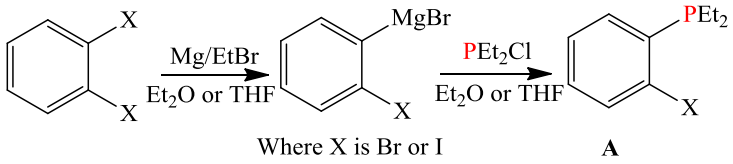
A

Scheme 2.4. *In situ* Grignard synthesis of 1-diethylphopshino-2-bromobenzene(A).

We discovered an interesting alternative in the work of Boymond *et al*[13] *w*ho applied an iodine-magnesium exchange mechanism for the preparation of highly functionalized aryl Grignard reagents. In particular, they reported the preparation of the Grignard reagent Br(*o*-C_6H_4)MgBr in high yield (95%) via this powerful method, which has been utilized in the preparation of aromatic aldehydes and allylic compounds[13], as well as polyfunctional unsaturated amines.[14] But its utilization in the synthesis of aryl phosphines has not been reported.

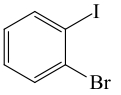
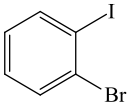
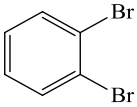
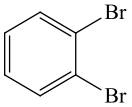
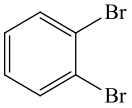
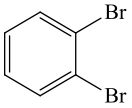
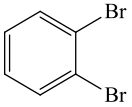
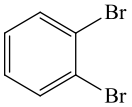
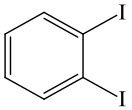
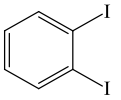
We believed that this synthetic route would be suitable for the synthesis of compounds similar to **A** by reaction of *i*PrMgBr with the appropriate *o*-dihalobenzene reagent, followed by addition of the PEt_2Cl. Various reaction conditions have been investigated in the preparation of compound **A**, and the results of this study are summarized in Table 2.1. We decided upon the use of *i*PrMgBr as a source of Mg as opposed to the reportedly more reactive *i*Pr_2Mg due to the easier preparation of the former reagent.[14,15] The synthesis of **A** was performed with 1-bromo-2-iodobenzene (entries 1 and 2), *o*-dibromobenzene (entries 3-8), and *o*-diiodobenzene (entries 9 and 10) on the reaction. When 1-bromo-2-iodobenzene was used, the yield appeared highly dependent on the addition temperature. Thus, the yield went from 60% when reaction additions were performed at –40°C and –78°C to only 40% when both additions were performed at –25 °C and the aryl Grignard intermediate was allowed to warm up to room temperature (entries 1 and 2).

Table 2.1. Dependence of the halide-magnesium exchange reaction on starting reagent and the reaction conditions for the preparation of arylphosphines.



Where X is Br or I

A

Entry	Substrate	Reaction Conditions	Product	% Yield
1		1.1 eq. *i*PrMgBr , –40 °C, 1h 1.1 equiv. PEt_2Cl, –78 °C	**A**	60
2		1.1 eq. *i*PrMgBr, –25 °C, 2h; 25 °C, 1h 1.1 equiv. PEt_2Cl, –78 °C	**A**	40
3		1.1 eq. *i*PrMgBr, –40 °C, 1h 1.1 equiv. PEt_2Cl, –78 °C	**A**	9
4		1.1 eq. iPrMgBr, 0 °C, 16h 1.1 equiv. PEt_2Cl, 27 °C	None	None
5		1.1 eq. iPrMgBr, 0 °C, 2h 1.1 equiv. PEt_2Cl, 0 °C	**A**	43
6		1.1 eq. iPrMgBr, 0 °C, 2h 1.1 equiv. PEt_2Cl, –25 °C	**A**	64
7		1.1 eq. iPrMgBr, 0 °C, 4h 1.1 equiv. PEt_2Cl, –25 °C	**A**	66
8		1.1 eq. iPrMgBr, 0 °C, 6h 1.1 equiv. PEt_2Cl, –25 °C	**A**	77
9		1.1 eq. iPrMgBr, 0 °C, 2h 1.1 equiv. PEt_2Cl, –25 °C	**A**	68
10		1.1 eq. iPrMgBr, 0 °C, 6h 1.1 equiv. PEt_2Cl, –25 °C	**A**	81

The lack of reactivity of *o*-dibromobenzene at low temperature led us to investigate higher reaction temperatures. Performing the additions at 25 ^{o}C and 0 ^{o}C did not generate any product (entry 4), but performing the additions at 0^{o}C and –25^{o}C gave much better results (entries 5-8). It is important to note that the temperature of the second addition appears to be more important as yields are more affected when this part of the reaction is allowed to occur at temperatures at or above 0 ^{o}C (entries 4-6). No product is observed when it is performed at room temperature (entry 4) and yields begin to increase as this addition occurs between 0 ^{o}C and –25 ^{o}C with yields being slightly higher as this temperature was closer to –25 ^{o}C. In contrast, the best results are obtained when the addition of *i*PrMgBr is performed at 0 ^{o}C, which avoids crystallization of the Grignard intermediate, followed by stirring at 0 ^{o}C for 6 h to allow the reaction to proceed to completion, and finally, addition of Et_2PCl at –25 ^{o}C (entries 7 and 10). In addition to giving the best results, this method also has the advantage of generating a very clean reaction mixture by ^{31}P NMR seen in figures 2.2 and 2.3.

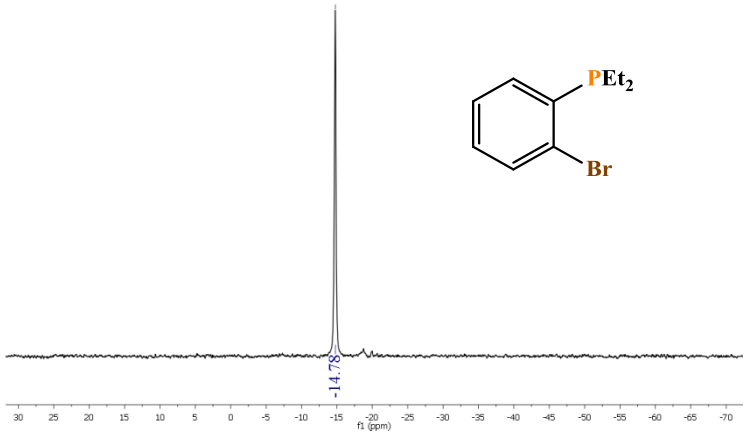


Figure 2.2. Crude ^{31}P NMR of 1-diethylphosphino-2-bromobenzene synthesized from *o*-dibromobenzene.

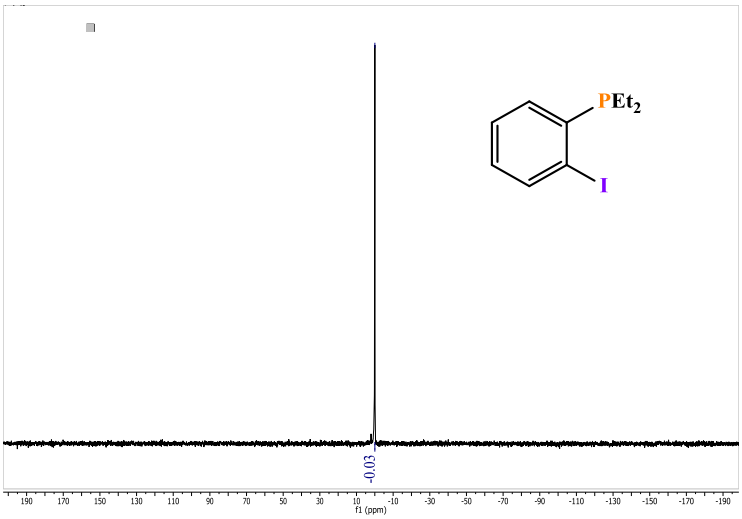
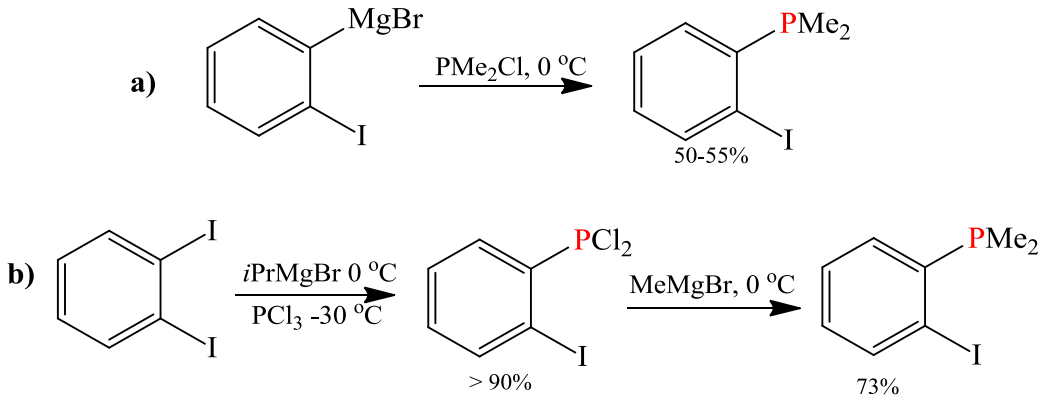


Figure 2.3. Crude ^{31}P NMR of 1-diethylphosphino-2-iodobenzene synthesized from *o*-diiodobenzene.

Equipped with this knowledge we undertook the task of changing the alkyl groups directly attached to the phosphorus atom. With alkyl groups consisting of 2 carbons or greater, we made the R_2PCl precursor and simply attached them to the (2-iodophenyl)magnesium bromide intermediate as was done to synthesize 1-diethylphosphino-2-bromobenzene. This synthesis worked for dicyclohexyl-, ditertbutyl-, disecbutyl-, and dineopentyl(2-iodophenyl)phosphine.

Attempts using this same method to synthesize (2-iodophenyl)dimethylphosphine were successful but only gave 50% yields (Scheme 2.5b). This was mainly a consequence of not being able to separate Me_2PCl from its THF reaction solvent. Uncertainties about the exact amount of Me_2PCl being used is the reason isolated yields are low for this phosphine. The ^{31}P NMR of the crude reaction mixture, however, is fairly clean so qualitatively this reaction is proceeding in high yield. Using the synthesis of the dichloro(2-iodophenyl)phosphine complex, which could be isolated, and substituting chloro-groups for methyl groups on the phosphine resulted in a 20% increased yield for this compound. The crude NMR for dimethyl(2-

iodophenyl)phosphine can be seen in figure 2.4. The product peak can be seen at δ = –43.1 ppm with a minor volatile impurity at –22.9 ppm.



Scheme 2.5. a) Initial synthesis for (2-iodophenyl)dimethylphosphine and b) the modified preparation.

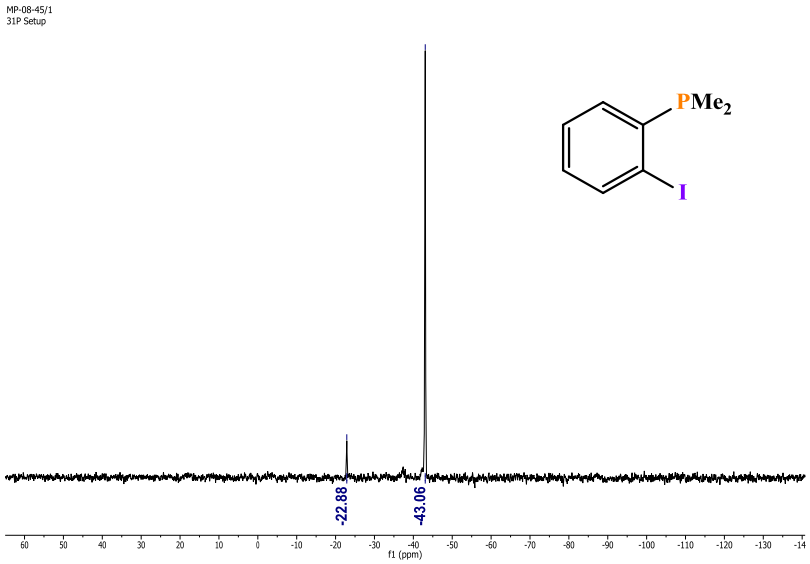
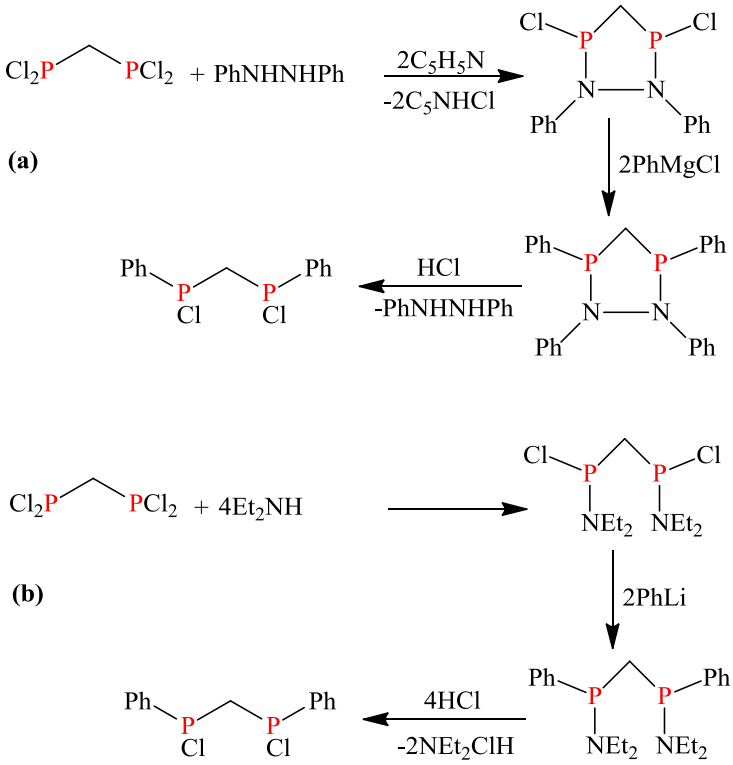


Figure 2.4. Crude ^{31}P NMR of dimethyl(2-iodophenyl)phosphine

2.4. Synthesis of Methylenebis(chlorophenylphosphine)

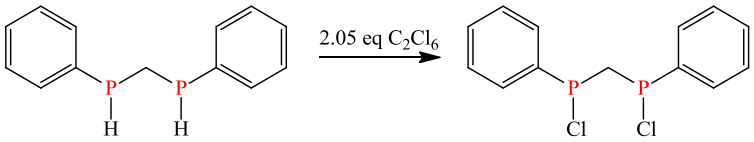
The preparation of methylenebis(chlorophenylphosphine), **C**, has been accomplished in two different ways via the methodologies developed by Stelzer *et al*,[16] (Scheme 2.6a), and

Schmidbaur and Schnatterer[17] (Scheme 2.6b). While these methods give acceptable yields, they are lengthy and necessitate the preparation of too many intermediates.



Scheme 2.6. Synthesis of methylenebis(chlorophenylphosphine) by (a) Stelzer and (b)Schnatterer.

We have opted for an easier and efficient method, namely the chlorination with C_2Cl_6 which was developed by Weferling,[17] which Alex Monteil[1] has applied, with success, to the preparation of chlorinated bisphosphine compounds in our group (Scheme 2.7).



Scheme 2.7. Synthesis of methylenebis(chlorophenylphosphine) utilizing C_2Cl_6 Reflux

The reaction was attempted under different conditions as reported in table 2.2. We first utilized toluene (entry 1) as the reaction solvent in an identical manner as previously described. A solution of the methylenebis(phenylphosphine) in toluene was added at to a concentrated (1.0 M) solution of C_2Cl_6 also in toluene, which resulted in a yellow mixture. Upon heating at 140 ^oC for 18 h, the reaction medium became black, and its content was then analyzed by ^{31}P NMR spectroscopy. The desired chlorinated product is present with a major resonance at δ = 81.7 ppm (s) (lit. = 81.8 ppm, s), but we also observe two resonances at δ = 161.8 ppm (s) and δ = 86.8 ppm (s) representing 40% of the phosphorus nuclei as determined upon integration of the signals. Schmidbaur and Schnatterer[18] have reported that compound **C** is subject to thermolability which results in its decomposition, at temperatures above 100 ^oC, into volatile $PhPCl_2$ and a polymer residue, thus preventing its distillation *in vacuo*.

Table 2.2. Conditions for the synthesis of methylenebis(chlorophenylphosphine) via Werferling's procedure.

Entry	Solvent	Conditions	% Yield
1	Toluene	140 ^oC for 18h	None isolated
2	THF	80 ^oC for 18h	None isolated
3	Et_2O	45 ^oC for 18 h	80-90 %

The formation of by-products in toluene at high temperatures prompted us to utilize a low-boiling point solvent that would allow us to purify the product, provided the reaction was cleanly conducted, by simple removal of the solvent *in vacuo* with the minimal heat applied (i.e., lower than 80 ^oC). Hexachloroethane is soluble in THF and diethyl ether and thus these solvents appeared attractive as they would allow its facile removal *in vacuo*. THF was subsequently (entry 2) used, yielding a ^{31}P NMR similar to that of reactions conducted in

toluene. The reaction in (entry 3) was performed by mixing the reagents at 25 ^{o}C prior to applying heat (45 ^{o}C) for 24 h. The completion of the reaction was indicated by the appearance of a pink coloration, and $^{31}P\{^{1}H\}$ NMR spectroscopy of the crude reaction medium showed the product **C** as the primary phosphorus-containing product (Figure 2.5). However, upon cooling to ambient temperature, a white solid deposited on the walls of the Schlenk flask, but its nature could not be determined, although it does not contain phosphorus nuclei by ^{31}P NMR spectroscopy, leading us to speculate that it is unreacted C_2Cl_6.

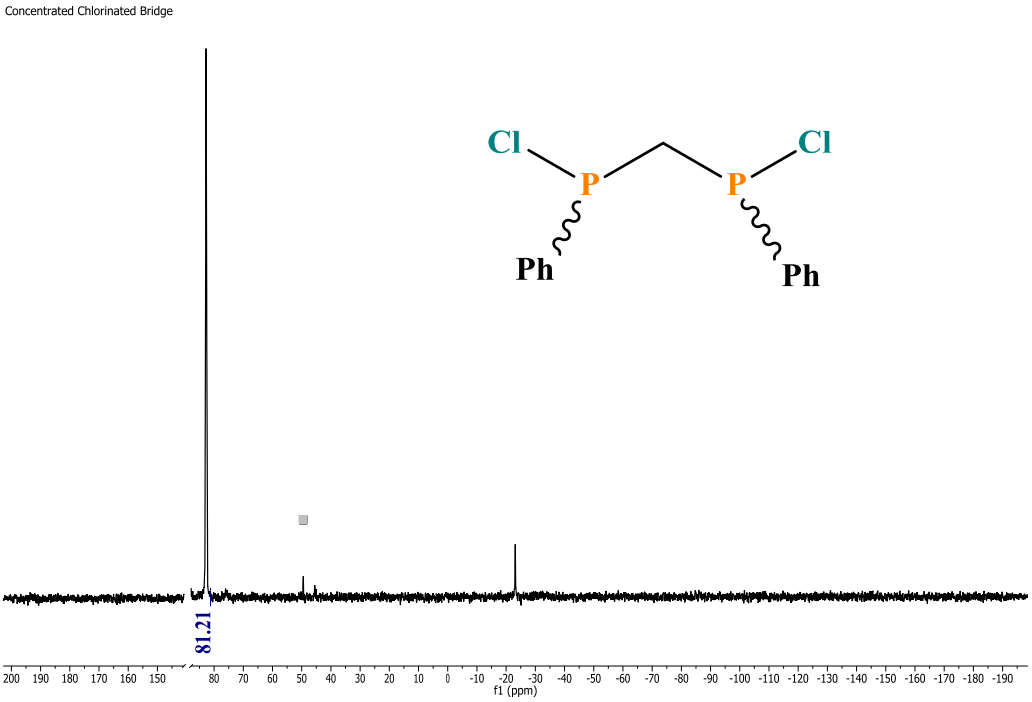


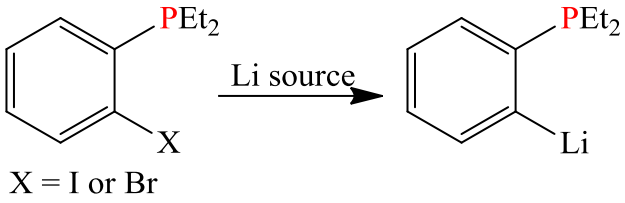
Figure 2.5. Crude ^{31}P NMR of methylenebis(chlorophenylphosphine).

Purification of the product was attained through filtration of the reaction medium through a plug of Celite to remove the solid by-product(s), and concentration *in vacuo* at 65-70 ^{o}C gave a pink oil which was pure compound **C** as confirmed by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopies.

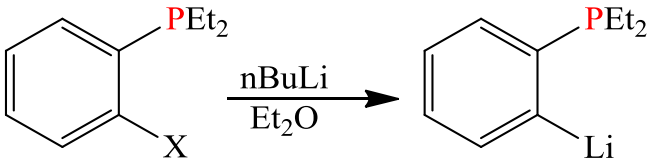
2.5. Synthesis of bis((2-(diethylphosphino)phenyl)(phenyl)phosphine)methane

2.5.1. Organolithium P-C Coupling Reactions

The metallation of phosphine **B** to the lithium phosphine is the logical next step in the preparation of ***rac,meso***-et,ph-P4-Ph (Scheme 2.8). The preparation of *o*-lithiophenyldiphenyl-phosphine, *o*-$LiC_6H_4PPh_2$, has been reported on different occasions. It was first reported by Hartley *et al.*[19] via the lithium- bromide exchange reaction between *n*BuLi and 1-bromo-2-(diphenylphosphino)benzene in diethyl ether (Scheme 2.9).



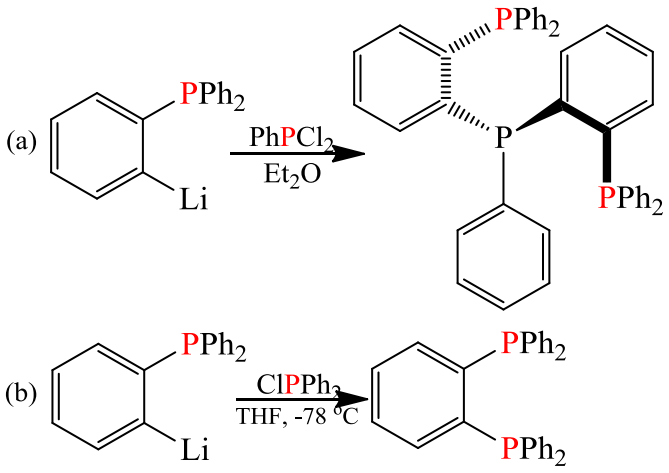
Scheme 2.8. Lithiation of diethylphosphino-2-*halo*benzene



Scheme 2.9. Preparation of *o*-$LiC_6H_4PPh_2$ via Li-Br exchange reaction

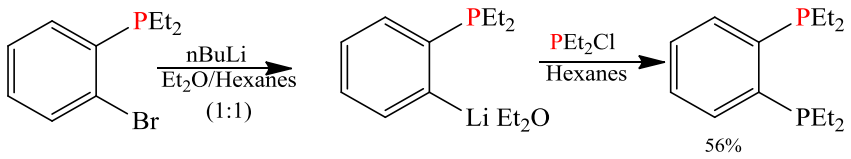
Tunney and Stille[20], on the other hand, have reported its preparation in THF at –78 ^oC. Finally, Bennett *et al.*[11] have also prepared this lithium complex in diethyl ether in 87% yield. Harder and co-workers[21] have isolated the lithium complex and have been able to determine its structure by single crystal X-ray diffraction. Thus, they found that the compound consists of dimeric aggregates in which the Li ions are solvated by an additional diethyl ether molecule. They also reported its slow decomposition in THF at –20 ^oC.

The *o*-lithium-phenylenediphenylphosphine compound has been utilized in conjunction with $PhPCl_2$ to produce $(o\text{-}C_6H_4PPh_2)_2PPh$ (Scheme 2.10a),[18] as well as with Ph_2PCl to generate $o\text{-}C_6H_4(PPh_2)_2$ (Scheme 2.10b),[19] and it was also utilized as a bridging ligand in the preparation of digold(I) complexes.[17]



Scheme 2.10. Preparation of (a) bis-(*o*-diphenylphosphinophenyl)phosphine, and (b) *o*-bis(diphenylphosphino)benzene.

Hart[9] demonstrated that **B** readily undergoes facile lithium-bromide exchange with *n*-BuLi in diethyl ether at room temperature to give the etherate precipitate. He also used this lithiated arylphosphine in the preparation of *o*-phenylenebis(diethylphosphine) in moderate yields (Scheme 2.11).

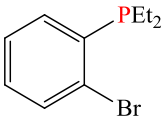
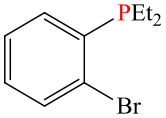
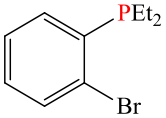
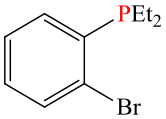
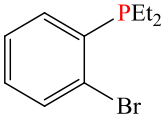


Scheme 2.11. Preparation of Li etherate and conversion to *o*- phenylenebis(PEt_2).

Additionally, Bennett *et al.*[11] have prepared this lithium complex in diethyl ether with *n*BuLi, and utilized it as bridging ligand in the preparation of digold(I) complexes. We have

attempted the preparation of the Li-etherate via the lithiation of **B**, and its use *in situ* in conjunction with chlorinated bisphosphine **C** for the preparation of the tetraphosphine ligands ***rac,meso***-et,ph-P4-Ph (Table 2.3).

Table 2.3. Attempted preparation of *rac*- and *meso*-et,ph-P4-Ph via Li mediated P-C coupling.

Entry		Solvent	Temperature		Results
			Step 1	Step 2	
1		THF	–78 °C/1h		Decomposition
2		THF	–35 °C/1.5h		Decomposition
3		Et_2O	0 °C/1h	0°C/1h 25 °C/1h 80 °C/24h	Decomposition
4		Et_2O	25 °C/30 min	25 °C	Decomposition
5		THF	–78 °C/6h	–78 °C/6h	Decomposition

The addition of an *n*-hexane *n*BuLi solution to **B** in THF (entries 1 and 2) or diethyl ether (entries 3 and 4) led to the formation of a yellow/orange to red coloration. The subsequent addition of a solution of **C** in the same solvent gave rise to a brown (entries 1 and 2) or mustard (entries 3 and 4) precipitate. Isolation of the lithiated intermediate was attempted, but without success, and ^{31}P NMR spectroscopy of the solution did not yield a clean enough spectrum for interpretation.

In entries 1, 3, and 4, we observe the decomposition of **B** to Et_2PPh. The reaction performed in THF at –78 ^oC (entry 1) generates an undetermined resonance at δ = –19.8 ppm (s), while the reactions in diethyl ether (entries 3 and 4), with or without heating, gives rise to resonances in the region δ = –25.0 to –32.0 ppm, which have not been assigned due to the poor resolution of the spectra. When the formation of the Li-etherate is conducted at –35 ^oC in THF followed by the addition of **C** at 0 ^oC (entry 2), we obtain a clean spectrum with only two resonances at δ= –22.6 ppm (s) and δ = –31.8 ppm (s), but the simplicity of these signals does not support the presence of *rac*- or *meso*-et,ph-P4-Ph, as this species has a complex second order coupling pattern.[1] Performing the reaction with **B** in THF (entry 5) did not yield the desired tetraphosphine ligands, but generated instead a sharp resonance at δ = –20.4 ppm (s) and broad resonances in the regions δ = –13.0 to –16.0 ppm and –28.0 to –33.0 ppm (Figure 2.6).

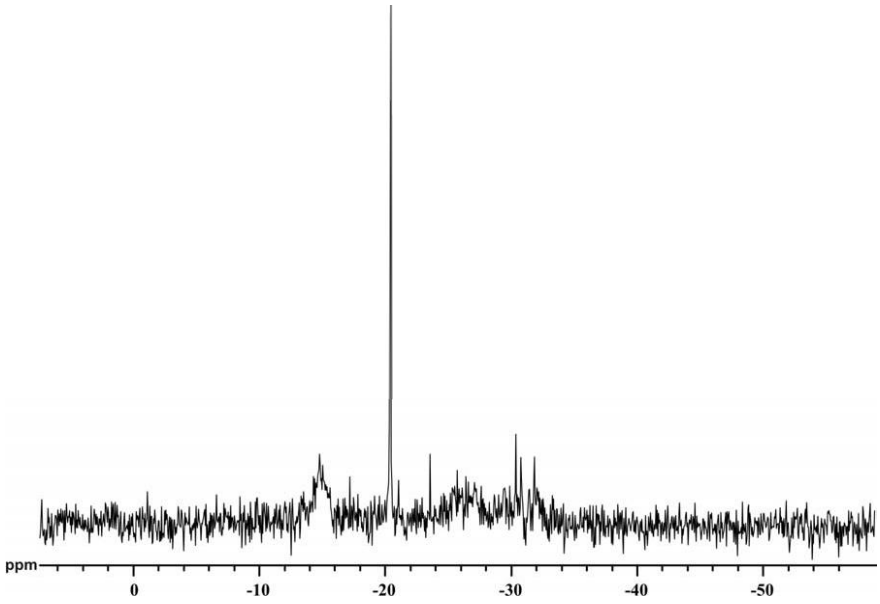


Figure 2.6. ^{31}P NMR spectrum from the lithium-mediated P-C coupling reaction of **B** with **C**.

2.5.2. Grignard-Mediated P-C Coupling Reaction

The last strategy we have devised for the synthesis of ***rac,meso***-et,ph-P4-Ph employs Grignard-mediated phosphorus-carbon coupling reactions. The first step is a halide-magnesium exchange reaction and is essentially identical to that proposed previously in this work, followed by the phosphorus-carbon coupling reaction between the arylphosphine Grignard intermediate and the dichlorobisphosphine **C**. This reaction was attempted with **B**, and the results are summarized in table 2.4.

Table 2.4. Results of the Grignard-mediated P-C coupling reaction of **B** and **C**.

Entry	Substrate	Conditions	Results
1	**B**	1.0 eq. *i*PrMgBr, 0 ^{o}C/5 h 0.5 eq. C, –25 ^{o}C, 25 ^{o}C/18h	Unreacted **B** and Et_2PH
2	**B**	2.0 eq. *i*PrMgBr, 0 ^{o}C/5 h 0.5 eq. C, –25 ^{o}C, 25 ^{o}C/18h	*rac,meso*-et,ph-P4-Ph

The addition of 1.0 equiv. of a THF solution of *i*PrMgBr to a solution of **B** (entry 1) in THF at 0 ^{o}C generated an orange reaction mixture, which, **C** in THF, became yellow as it was allowed to warm to ambient temperature. The $^{31}P\{^{1}H\}$ NMR spectrum of the products shows the presence of a main resonance at δ = –13.8 ppm (s), which could correspond to either unreacted **B** or the product resulting from the decomposition of **B** (i.e., Et_2PH).

Two additional resonances are also observed at δ = –11.7 ppm (s) and δ = –12.1 ppm (s). The nature of these resonances was ascertained through a simple reaction conducted in an NMR tube which consisted in the treatment of a solution of **C** in THF with a few drops of the *i*PrMgBr solution to produce the bisphosphine methylenebis(isopropylphenylphosphine), **C'**. Analysis of

the mixture by $^{31}P\{^{1}H\}$ NMR spectroscopy revealed two resonances at δ = –11.6 ppm (s) and δ = –12.0 ppm (s), thus confirming the nature of one of the products as being the two diastereomeric forms of **C'**. The Grignard reagent *i*PrMgBr appears to react preferentially with **C**, and we can conclude that **B** is not reactive enough and will remain unchanged in the reaction medium.

The addition of 1.0 equiv. of a THF solution of *i*PrMgBr to a solution of **B** in THF at 0 ^{o}C produced a beige solution. The reaction mixture was stirred at 0 ^{o}C for 8 h in order to allow the iodide-magnesium exchange reaction to complete, and a solution of **C** in THF was subsequently added at –25 ^{o}C, which generated a light green mixture.

Upon allowing the reaction medium to slowly warm to room temperature, the solution turned beige and was stirred an additional 18 h at room temperature until completion. The ^{31}P NMR spectroscopic analysis of the intermediate arylphosphine Grignard **p** (Figure 2.7) exhibits one major resonance at δ = –10.3 ppm (s), which is likely compound **p**, and two minor resonances at δ = –13.4 ppm (s) and δ = –15.3 ppm (s), which appeared to be impurities.

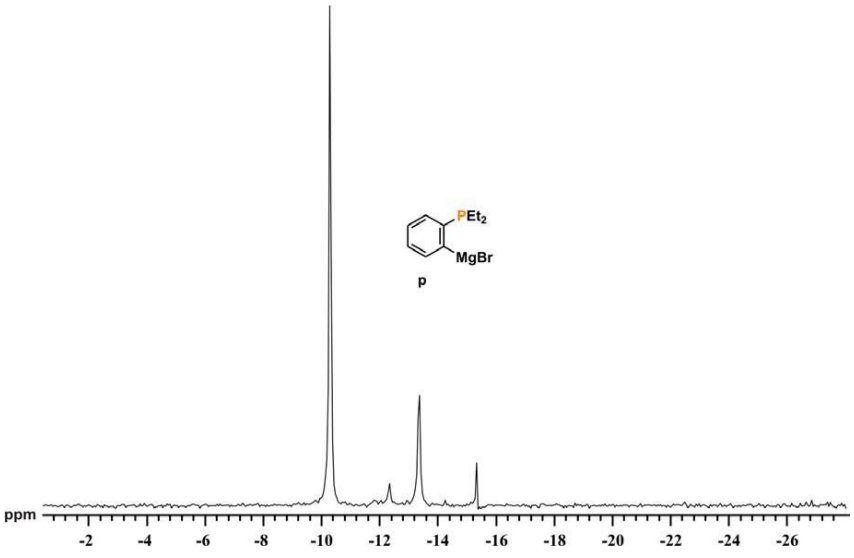


Figure 2.7. $^{31}P\{^{1}H\}$ NMR spectrum of the reaction of **B** with *i*PrMgBr.

The NMR spectrum obtained in THF upon reaction of **p** with $Cl(Ph)PCH_2P(Ph)Cl$ exhibits a second order pattern, which indicates the presence of *rac*- and *meso*-et,ph-P4-Ph (Figure 2.8, expansion). Indeed, the resonances at δ = –23.0 to –33.0 ppm shows a second order coupling pattern which is consistent with an AA′BB′ spin system for *rac*- and *meso*-et,ph-P4-Ph. The spectrum shows the presence of unreacted **B** at δ = 0.5 ppm (s), as well as the decomposition product **B′** at δ = –15.0 ppm (s).

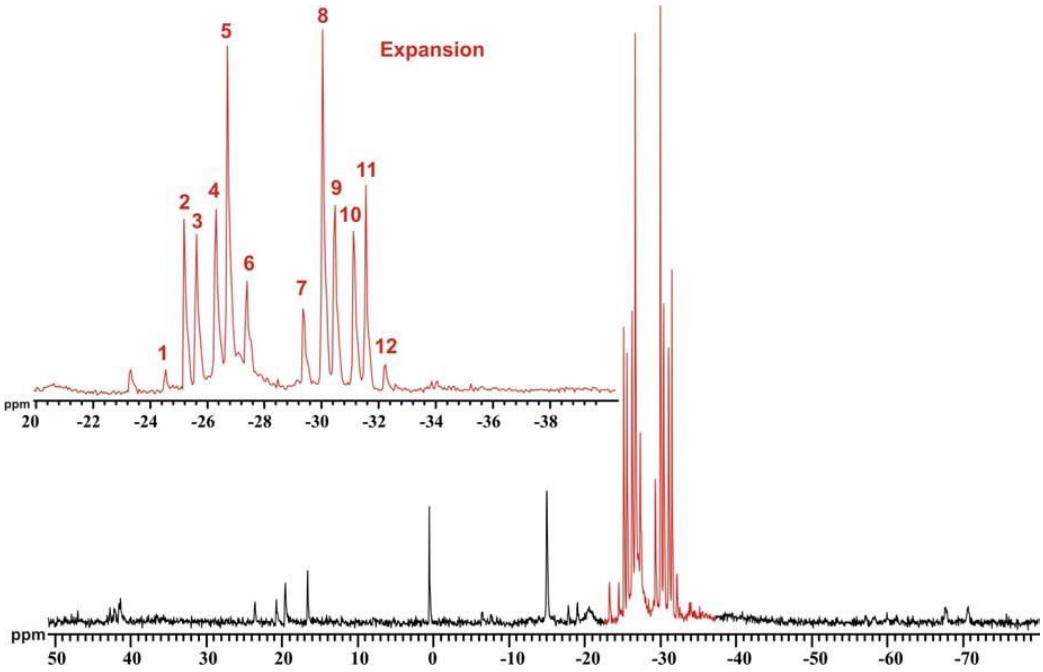


Figure 2.8. $^{31}P\{^1H\}$ NMR spectrum of the crude reaction mixture of *o*-$(PEt_2)(MgBr)C_6H_4$ (**p**) and $Cl(Ph)PCH_2P(Ph)Cl$.

Purification of the product mixture was performed by distillation *in vacuo* removed unreacted **B** and Et_2PH byproduct. The distillation residue was obtained as a highly viscous and thick white paste, which was then dissolved in EtOH and cooled to –70 ^oC for purification by precipitation. A white powder which dissolved in EtOH at room temperature was obtained, and its separation from the EtOH solvent was attempted via cold filtration via a cannula equipped

with a glass tube that had filter paper on one end and a small septum on the other, but with little success. Centrifugation of the solution led to partial isolation of the solid prior to it melting. The ^{31}P NMR spectrum of the solid is shown in Figure 2.9. The spectrum exhibits resonances 1-12 (shown in the expansion in Figure 2.7), but these appear with a slightly different coupling pattern than that observed in the crude reaction mixture. But the position and pattern is consistent with *rac,meso*-et,ph-P4-Ph.[1]

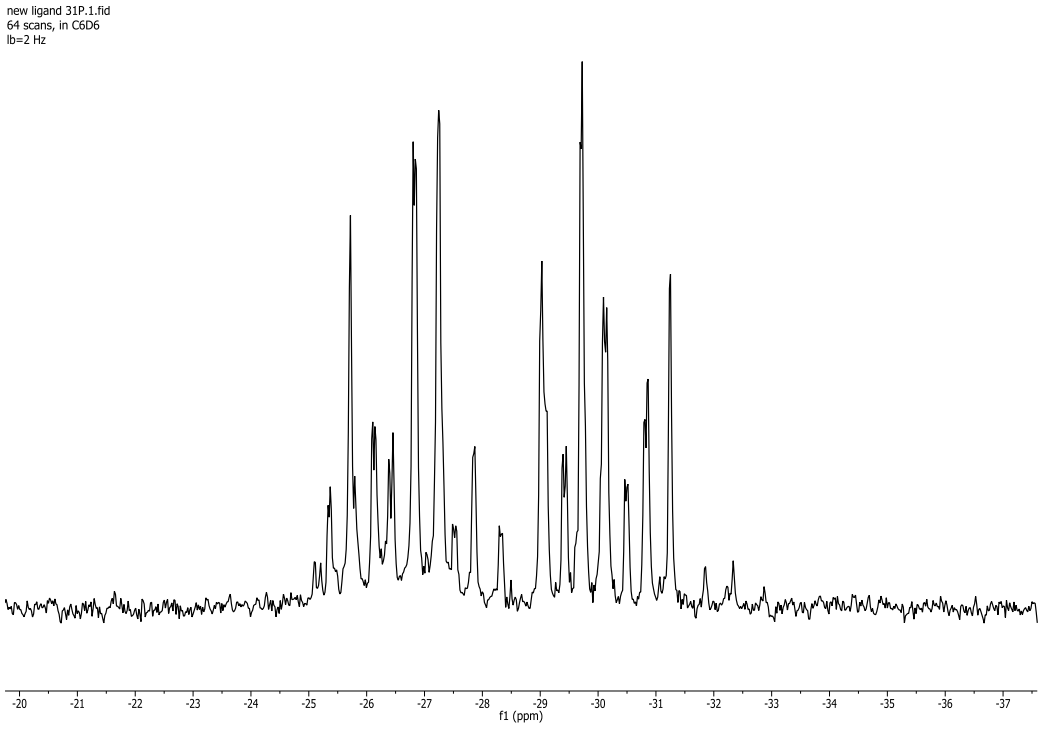


Figure 2.9. $^{31}P\{^{1}H\}$ NMR spectrum of the distillation residue upon crystallization from EtOH.

The solubility of the solid residue in various solvents was tested in order to select an adequate recrystallization solvent. The solubility was found to be in the following decreasing order: CH_2Cl_2 ~ EtOH ~ DMF > THF > benzene ~ hexanes > H_2O. Further purification was attempted by recrystallization using two well-known techniques: (*i*) recrystallization at low temperatures (i.e. –25 ^{o}C or 0 ^{o}C, depending on the solvent employed); and (*ii*) recrystallization

by slow evaporation of the solvent. Both techniques were attempted with CH_2Cl_2, EtOH, DMF, THF, and benzene, as well as with THF/hexanes and EtOH/H_2O solvent mixtures with no success.

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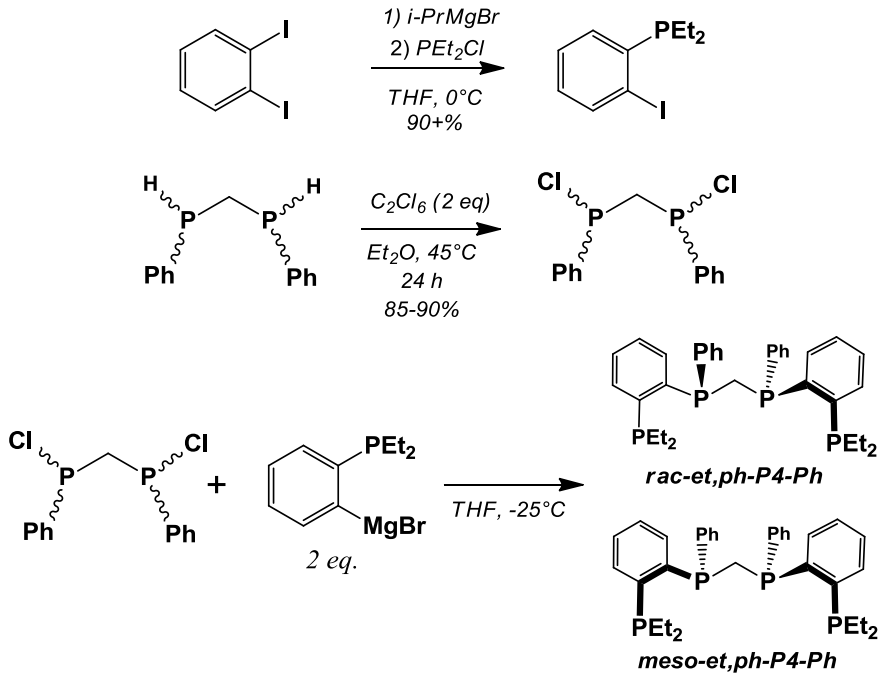
CHAPTER 3. SYNTHESIS OF AMINE BRIDGED TETRAPHOSPHINE LIGANDS

3.1. Introduction

As mentioned in the previous chapter the fragmentation problem motivated Prof. Stanley to design a new ligand that would have a more rigid framework using *o*-phenylene linked arms to hold the external phosphines in closer proximity to the metal center. We call this ligand et,ph-P4-Ph, or P4-Ph. Using a 1,2-disubstituted phenylene bridge instead of the rotationally more flexible ethylene groups in the P4 framework generates an extremely strong chelating bisphosphine compound. The synthetic scheme to build this ligand was designed by Dr. Alex Monteil and features Mg-I exchange reactions (Scheme 3.1).[1]



Scheme 3.1. Synthetic scheme for the et,ph-P4-Ph ligand**.**

We worked out an improvement in which 1,2-diiodobenzene has been replaced by 1-bromo-2-iodobenzene to ensure that the first reaction of *i*PrMgBr and the aryl halide only occurs at one site on the benzene ring to decrease the chance of byproducts. Personal attempts to separate the

meso- and *racemic* diastereomers of the P4-Ph ligand have been unsuccessful. Attempts were made to make derivatives of the P4-Ph ligand by adding different groups onto the *para* position on the internal phenyl rings (Fig. 3.1). This was done in hopes of achieving the desired separation of the *racemic* and *meso*- isomers of the ligand by recrystallization. We have been successful in forming the $-NMe_2$ and *–t*-Bu *para*-substituted primary halophosphines (83% yield).

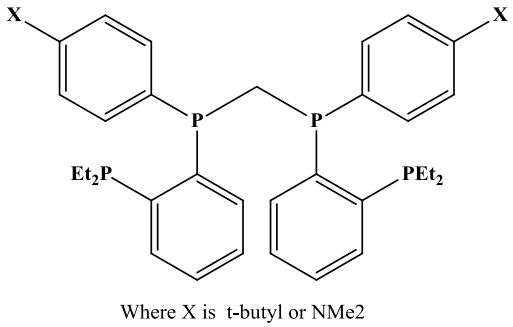
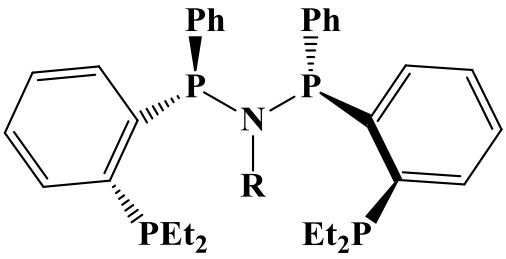


Figure 3.1. et,ph-P4-Ph with *para*-substituted internal phenyl rings.

Reduction of these compounds to the primary phosphines was attempted with lithium aluminum hydride, but only the phenylphosphine ring with the *t*-Bu moiety could be reduced. Having accomplished this, the next step was to form the bisphosphine bridge. The overall yield for the synthetic scheme was extremely low (9%) so higher yield routes to this general ligand framework are still needed.

The next step of ligand evolution came in the form of "PNP" type ligands. By replacing the methylene bridge with a tertiary amine bridge might allow an easier isomer separation (Fig. 3.2). It could also simplify the synthesis due to higher yielding routes to P-N(R)-P bridges.



R = Cy, Et, t-Bu

Figure 3.2. The new aza-bridged et,ph-P4-Ph ligand.

3.2. Changes in the Catalyst by Ligand Variation

3.2.1. The et,ph-P4 Ligand

The original tetraphosphine ligand, et,ph-P4, is a coordinating ligand that strongly binds to the metal centers. Normally, an alkylated phosphine ligand is too strong a σ donor to use successfully in rhodium-catalyzed hydroformylation. It causes the CO ligands to bond too strongly to the rhodium centers because of the increased electron density on the metal center and increased π-backdonation to the CO ligands. Dissociation of a CO ligand is vital to allow a saturated 18-electron complex to form a reactive 16-electron complex allowing coordination of the alkene or H_2. To allow facile dissociation of a CO ligand, the strong donor ability of the P4 ligand is compensated by having a dicationic (or monocationic when water is present) dirhodium catalyst.[3]

3.2.2. The et,ph-P4-Ph Ligand

The new et,ph-P4-Ph is a weaker σ-donor/better π-acceptor due to the ethylene linkages being replaced by mildly electron-withdrawing *ortho*-phenylene linkages. This should decrease the electron density on the rhodium centers allowing for faster dissociation of CO ligands. More electron deficient metal centers typically lead to a more active hydroformylation catalyst.

Regioselectivity of the product should not be a major concern with the P4-Ph ligand because our catalyst containing the et,ph-P4 is not subjective to the normal distortion of monometallic catalysts upon alkene addition due to the rigid structure enforced by the ligand, Rh-Rh bonding, and bridging CO ligands. The closer proximity of the external phosphorus atoms to the metal centers caused by the *ortho*-phenylene linkages may not completely inhibit dissociation of the arms due to the decreased donor ability of all the phosphorus atoms of the ligand, but it should coordinate orders of magnitude more strongly than our first generation et,ph-P4 ligand.

3.2.3. The RN-P4-Ph Ligands

Replacing the methylene bridge with an amine bridge can have interesting electronic and steric effects on the catalyst. The flexibility of the bridge should change a little due to the amine's ability to adopt a trigonal planar geometry. Peterson and coworkers[2] performed an *ab initio* study comparing diphosphinomethane (dpm) and diphosphinoamine (dpa). It showed that the optimal central angle for dpm is 113° while the optimal angle for dpa is 122° as it adopts a trigonal planar geometry (sp^2 hybridized N atom). These calculations are in agreement with solid state structures of bis(diphenylphosphino)amine (dppa) and bis(diphenylphosphino)methane (dppm).

The tension placed on the ligand when chelating a single metal due to the larger natural central angle of the PNP-ligand may explain why these ligands have a stronger tendency to bridge two metal centers rather than chelate a single metal center. The central angle for dpa, 122°, is closer to the angle needed to bridge two metal centers, 125°-130°. Conforming to this ideal bridging geometry only requires a 1.3 kcal mol^{-1} distortion for dpa, while 5.6 kcal mol^{-1} is required for dpm. Favoring binuclear coordination is exactly what we want for our catalyst,

since one of the fragmentation pathways leads to a chelated and thermodynamically very stable mononuclear complex (see Scheme 1.6). The ability to easily add a wide variety of central R groups to the N-atom of the PNP ligand is also a big advantage that we do not have with the P-CH_2-P-based ligands. Adding a bulkier group to the central N-atom could favor closed-mode bimetallic structures that we believe are important in catalysis.

These PNP ligands can also be tuned to favor chelation. Recently, Butcher and coworkers[5] have reported diphosphazanes with bulky groups attached to the phosphorus atoms, $EtN[P(OR)_2]_2$ (R = bulky $C_6H_3{}^iPr_2$-2,6 and $C_6H_3Me_2$-2,6). These groups cause a decrease in the central PNP bond angles to bring them closer to the angles needed to chelate one metal center, 109.5° and 113.1° respectively. The phenyl rings on the internal phosphorus atoms can be substituted in the ortho positions with methyl, ethyl, or isopropyl substituents to possibly decrease the PNP angle. Adding the amine bridge will cause the internal phosphines to be better electron donors than the methylene bridged phosphines, and the alkyl group attached to the amine can be altered to tailor the donation of the internal phosphines. This added donor tunability could be used, if necessary, to combat some of the decrease in the donation caused by the *ortho*-phenylene linkages.

As stated previously, the *rac*-ligand is the desired form and makes the active catalytic species. Norman and coworkers reported 9-12:1 *meso*:*rac* ratio for the synthesis of $iPrN[PhP(iPrNH)]_2$.[6] Our normal et,ph-P4 ligand *racemizes* at 120°C to give a 48%/52% *meso*/*rac* mixture after approximately 12 hours. The new PNP ligands may not be able to withstand these temperatures which could lead to decomposition of the ligand. This might pose a serious problem in ligand synthesis if we cannot obtain a good quantity of the *racemic* ligand.

Replacement of the methylene bridge with an amine bridge can cause significant changes in the coordination and structural features of the formed complexes. With suitable substituents on the P and N atoms, these ligands can stabilize metal-metal bonds, which we believe is important in our hydroformylation catalysis. A review by Balakrishna *et al.* highlights a large variety of PNP-M_X complexes.[7] As seen in Figure 3.3, PNP ligands can cause formation of clusters, bridged species without M-M bonds, bridged species with multiple metal-metal bonds, and metal centers containing bidentate and monodentate ligands.

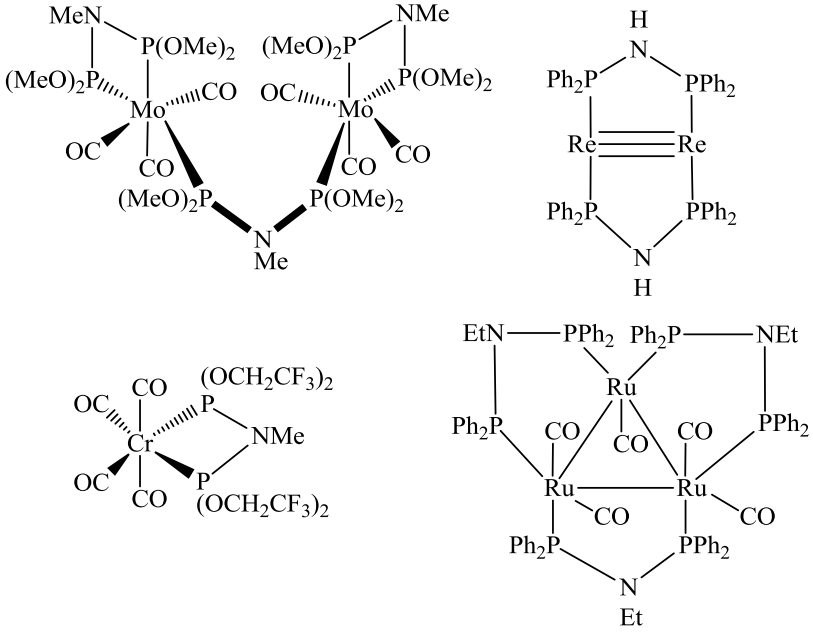


Figure 3.3. Some examples of PNP-metal complexes.

3.3. Fragmentation and Side Reactions of PNP Ligands

Several problems may arise with the use of PNP ligands. These ligands are susceptible to metal assisted cleavage when complexed with transition metals to give undesired products (Fig. 3.4).[8] Cleavage of a P-N bond can lead to iminophosphane type bridging ligands that donate to the metal centers through the phosphorus and nitrogen of the fragmented ligand and a separate

bridging phosphide ligand. It has recently been reported that the reaction of P(III)-N bonds of PNP compounds with aldehydes can lead to phosphine oxidation accompanied by C-insertion into the P-N bond or formation of a-hydroxy phosphine oxides.[9]

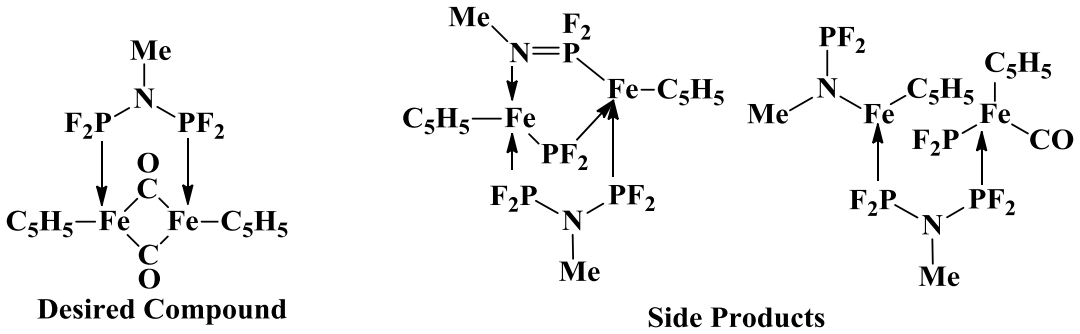
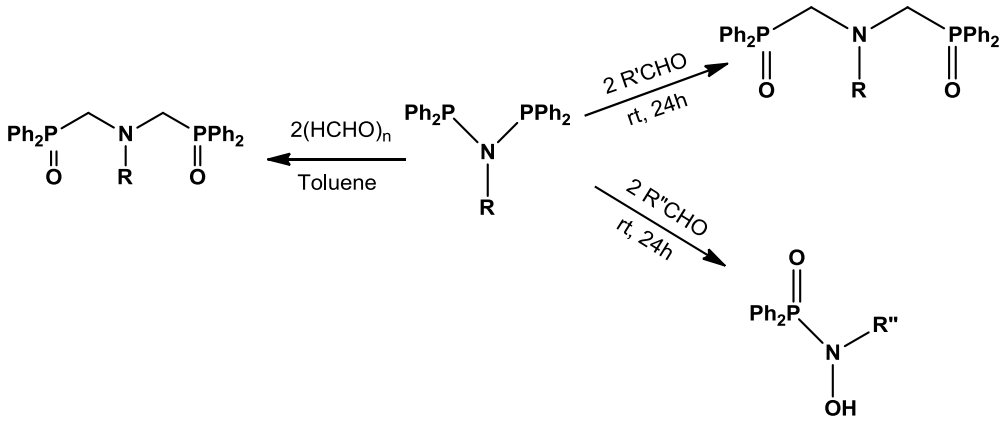


Figure 3.4. Some examples of metal assisted cleavage of PNP ligands.

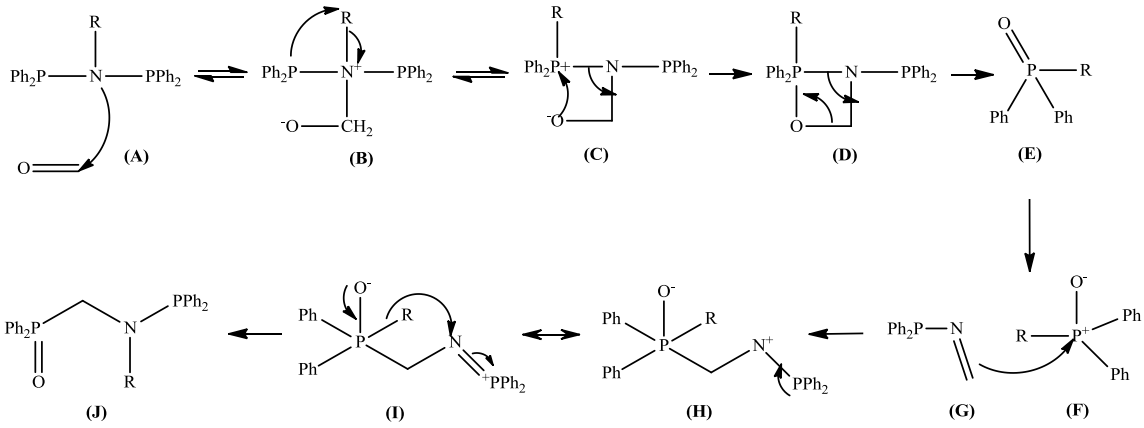
As seen in Scheme 3.2, when bis(diphenyl- phosphino)alkylamines were treated with 2 equivalents of furfural, benzaldehyde or paraformaldehyde, C-insertion of the carbonyl carbon occurred in the P-N bond with oxidation of phosphorus from P(III) to P(V).



Scheme 3.2. Fragmentation of PNP ligands via reaction with aldehydes.

This is similar to the Pudovik reaction (Scheme 3.4a). The proposed mechanism for this reaction is illustrated in Scheme 3.3. It begins with nucleophilic attack on the carbon by the

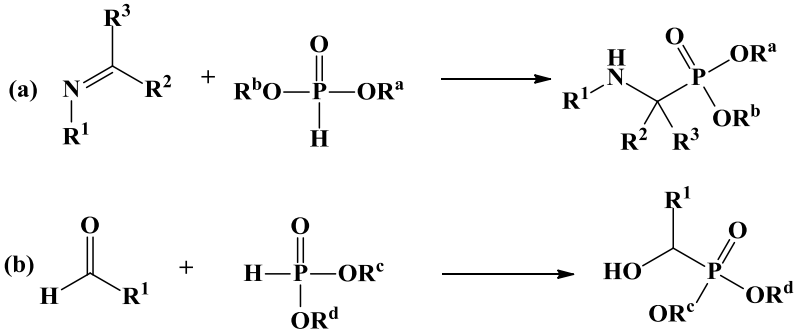
nitrogen atom to form species **B**. The lone pair of electrons on the phosphorus atom attacks the R group on the positively charged ammonium ion, which forms species **C**. The negatively charged oxygen attacks the positive phosphorus center to form a 1,3,2- oxazaphosphorine compound (**D**). The oxazaphosphorine then forms a phosphine oxide (**E**) and an imine (**G**). Electrophilic addition of **F** onto the N-C double bond leads to the formation of complex H which has electron deficient nitrogen. The positive charge on the nitrogen can be stabilized by the adjacent phosphorus atom (**I**) to allow carbonyl migration of the R group and give the final product (J).



Scheme 3.3. Proposed Mechanism for C-insertion into a P-N bond

Another possible reaction that can occur with aldehydes is the formation of a- hydroxy phosphine oxides, similar to the Abramov reaction (Scheme 3.4b). This reaction occurs from an initial P-N bond similar to the cleavage to form cleavage to form $Ph_2P(O)H$, which reacts with the aldehyde to form the a-hydroxy phosphine oxide. These reactions (Scheme 3.2) have not yet been shown to occur while the ligand is bound to a metal center, which we find encouraging. But, if our catalyst does lose a rhodium center as proposed in Scheme 2.6, formation of the α-

hydroxy phosphine oxide or C-insertion could occur when complex **G** is in solution with the aldehyde product of the hydroformylation reaction.



Scheme 3.4. (a) Pudovik and (b) Abramov reactions.

3.4. Applications

After extensive searching, no literature results were obtained in which PNP ligands were effectively used in hydroformylation catalysts. This is most likely due to the fact that simple PNP bridging or chelating ligands make poor hydroformylation catalysts. They are however used in several other reactions. In 1999, Gimbert and coworkers used a dicobalt compound containing a bridging PNP ligand with various substituents on the N and P atoms for use in asymmetric Pauson-Khand reactions.[10] These ligands were very effective in the reaction with yields >98% with the bimetallic complex shown in Figure 3.5.

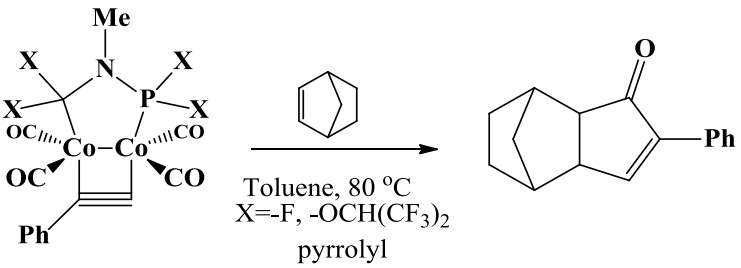


Figure 3.5. Bimetallic cobalt catalyst for asymmetric Pauson-Khand reactions.

These catalysts were also useful in providing the expected adduct from the less reactive indene in 72% yield, which is much higher than the best literature describing a 52% yield for this reaction.

PNP ligands have been utilized as polymerization/oligomerization catalysts. In 2001, Wass and coworkers reported a nickel(II) complex containing a bis(diarylphosphino)-methylamine ligand that was highly active toward the polymerization of ethylene yielding high molecular weight polymers (Fig. 3.6a).[11] Its performance was near that of the best nickel-based systems.[12] Another feature of this catalyst was that it was poison tolerant exhibiting activity with up to 10% (by volume) water content. In 2007, they also reported up to 95% isoprene trimerisation with PNP-chromium catalysts (Fig. 3.6b).[13] The activity, 660 h^{-1}, was more than two orders of magnitude higher than all previously reported isoprene trimerization catalysts.

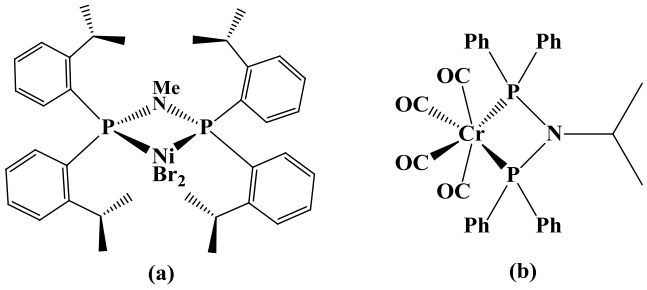
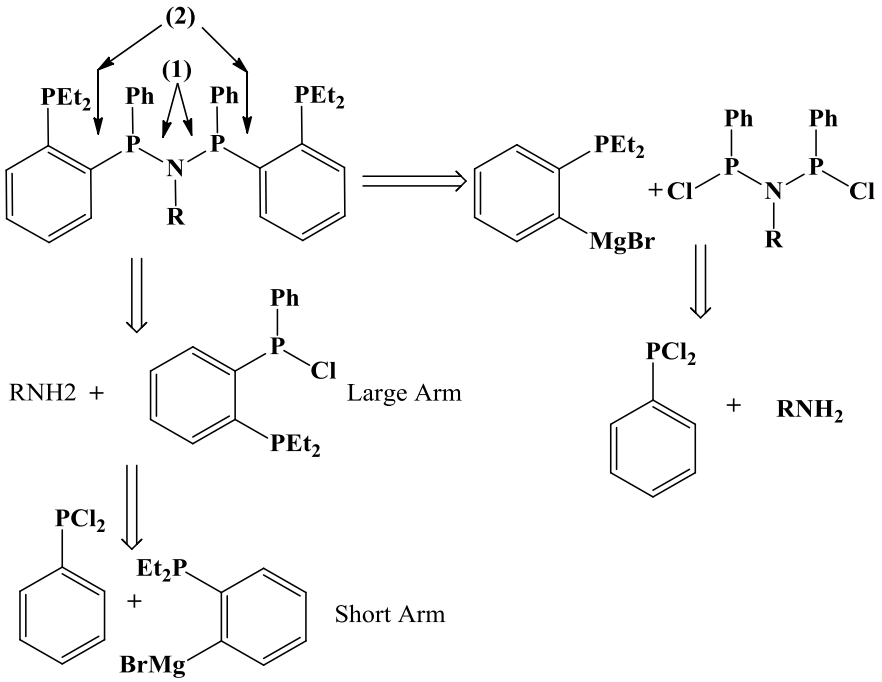


Figure 3.6. (a) Isoprene trimerization catalyst; (b) Ethylene polymerization catalyst.

3.5. Retrosynthesis of the Aza-Bridged Ligand

To form the aza-bridged ligands, there are two possible disconnection points that would allow the ligand to be synthesized (Scheme 3.5). Most of the synthesis relies on the work performed by Alex Monteil.[1] His work, based on that of Boymond *et al.*,[14] employed a simple iodine-magnesium exchange that was very effective in the synthesis of the arms of P4-Ph and produced yields in excess of 90%. This technique was used to build both the "large arm" and

"short arm." At disconnection point 1 in Scheme 3.5, the large arm and a primary amine are coupled by a Sn2 reaction to form the aza-bridged ligand. At disconnection point 2, the short arm is coupled with an "amine bridge" through a Grignard-mediated reaction to form the aza-bridged ligand.

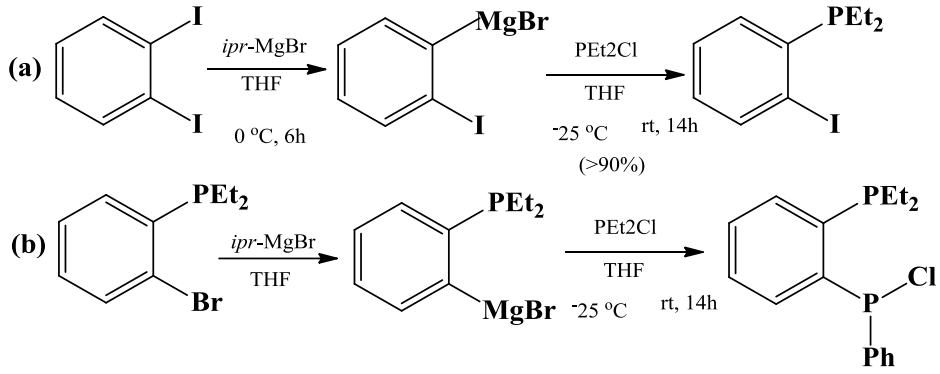


Scheme 3.5 Retrosynthetic analysis of RN-P4-Ph ligands.

3.5.1. Synthesis of RN-P4-Ph by "Large Arm" Amine Coupling

The short arm, (2-bromophenyl)diethylphosphine, is easily synthesized from 1-bromo-2-iodobenzene, *i*PrMgBr, and Et_2PCl in excellent yield (>85%) and is isolated by distillation under reduced pressure (Scheme 3.6a). To form the large arm chloro(2-(diethylphosphino)phenyl)-phenylphosphine, the same basic procedure is followed and Et_2PCl is reacted with the Grignard species (Scheme 3.6b). Attempts were made with several solvents (heptane, hexane, pentane, benzene, petroleum ether, CH_2Cl_2, and THF) to isolate the desired large arm from the crude

reaction mixture (white paste-like substance) but all were unsuccessful in giving a pure compound.



Scheme 3.6 Preparation of (a) (2-bromophenyl)diethylphosphine and (b) chloro(2-(diethylphosphino)phenyl)phenylphosphine utilizing halide-magnesium exchange reactions.

Distillation of the compound under an inert atmosphere at reduced pressure (0.25 Torr) was unsuccessful and caused the product to decompose in the distilling flask due to the excessive heating (up to 280 °C). One way to combat the isolation problem is to replace $PhPCl_2$ with the mono protected species, (N,N-diethylamino)-chlorophenylphosphine. A problem faced when trying to extract the large arm is that it cannot be treated with water to remove magnesium salts and quench unreacted Grignard reagent due to the reactive halophosphine, making solvent extractions difficult. Professor Stanley suggested quenching with an organic soluble anhydrous $[HNR_3][anion]$ salt followed by an organic extraction. This has not been performed, but may be worth researching.

If the large arm is made in which the P-Cl bond is replaced with $P\text{-}NEt_2$, a successful extraction could be performed and a pure compound isolated. The protected phosphine is then treated with 4 equivalents of ethereal HCl to obtain the large arm.

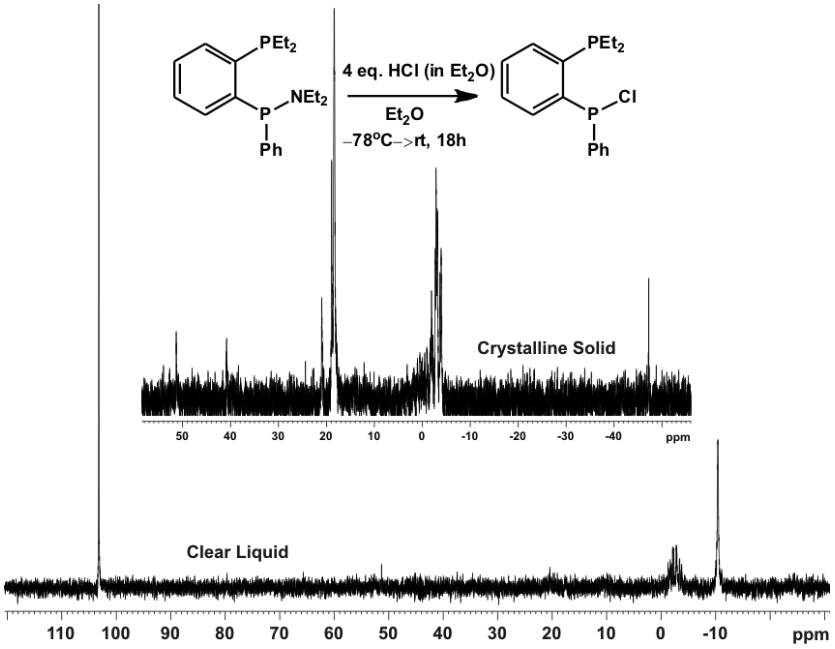


Figure 3.7. $^{31}P\{^{1}H\}$ NMR spectra of products obtained from the deprotection of the mono-protected large arm.

Initial results seemed impressive for the synthesis of the mono-protected large arm. When the compound was deprotected with HCl, two products formed, a clear liquid and translucent crystals, both of which showed resonances in $^{31}P\{^{1}H\}$ NMR (Fig. 3.7). The crystalline solid has been recrystallized by vapor diffusion, but has not been analyzed by x-ray crystallography. It is likely that the solid is the same species as the liquid product that has been protonated by the large excess of HCl to make a phosphonium complex. This reaction was performed again with a stoichiometric amount of ethereal HCl so that a protonated phosphorus species will be avoided. This reaction produced the same results.

The Grignard reaction was performed a second time and it was confirmed by ^{31}P NMR that the reaction did go to completion. (N,N-diethylamino)chlorophenylphosphine was added dropwise at –25 °C and the solution was stirred overnight. Upon quenching with water, a thick white precipitate formed in the aqueous layer. The organic layer was removed and the aqueous

layer was extracted with diethyl ether. The $^{31}P\{^{1}H\}$ NMR spectra (Fig. 3.8) of the crude organic extraction is somewhat different from the spectra obtained when it was first performed. Though the peaks are in the same positions the intensities of those peaks have changed. The aqueous quench layer needs to be analyzed to determine what species makes up the white precipitate. This may give some insight on whether the peak at −14 ppm is really the starting material that reformed during quenching or if it's just a coincidence that the peak has the same chemical shift as the starting material. Once this arm is attained coupling with a primary amine should afford the desired ligand, RN-P4-Ph.

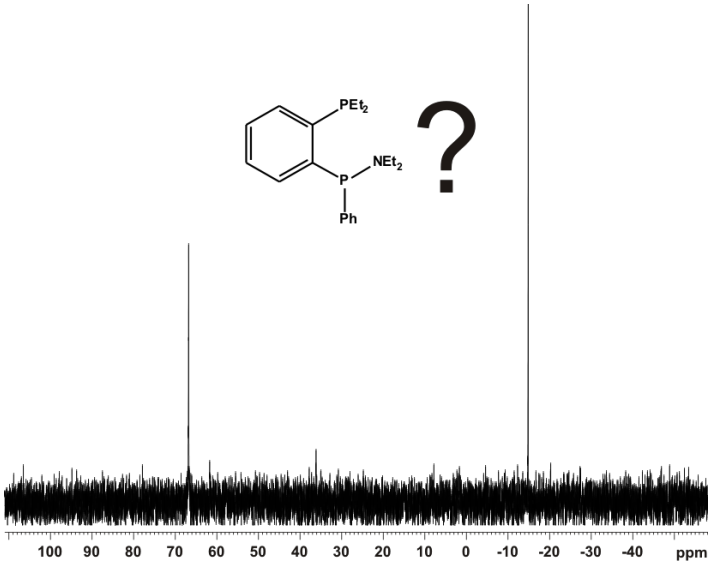
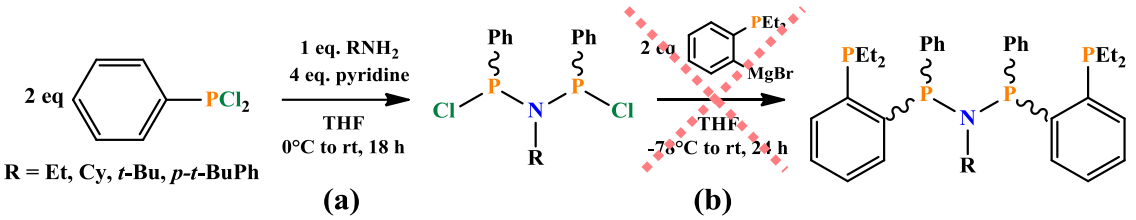


Figure 3.8. $^{31}P\{^{1}H\}$ NMR of what might be (N,N- diethylamino) [2(diethylphosphino)phenyl]phenylphosphine.

3.5.2 Synthesis of RN-P4-Ph by Grignard-mediated "Small Arm" Amine Bridge Coupling

The second synthetic approach to the aza-bridged ligands is using a Grignard-mediated coupling of the small arm and an amine bridge. The amine bridge is synthesized from a primary amine slowly treated with 2 equivalents of $PhPCl_2$ at 0°C while trapping liberated HCl with excess pyridine or NEt_3 (Scheme 3.7a). Filtration of the ammonium salts and removal of the

solvent *in vacuo* affords the amine bridge in 30-40% yield. It was then discovered that the reaction to synthesize the amine-bridges never went to completion. Some $PhPCl_2$ was always present in the final solution.



Scheme 3.7. PNP bridge synthesis and attempted Grignard-mediated coupling.

To correct this, the final mixture was treated again with 1 equivalent of the primary amine and excess pyridine or triethylamine. This additional reaction was used to synthesize the tert-butyl amine bridge and Figure 3.9 shows a large increase in the product peak (~120 ppm) and

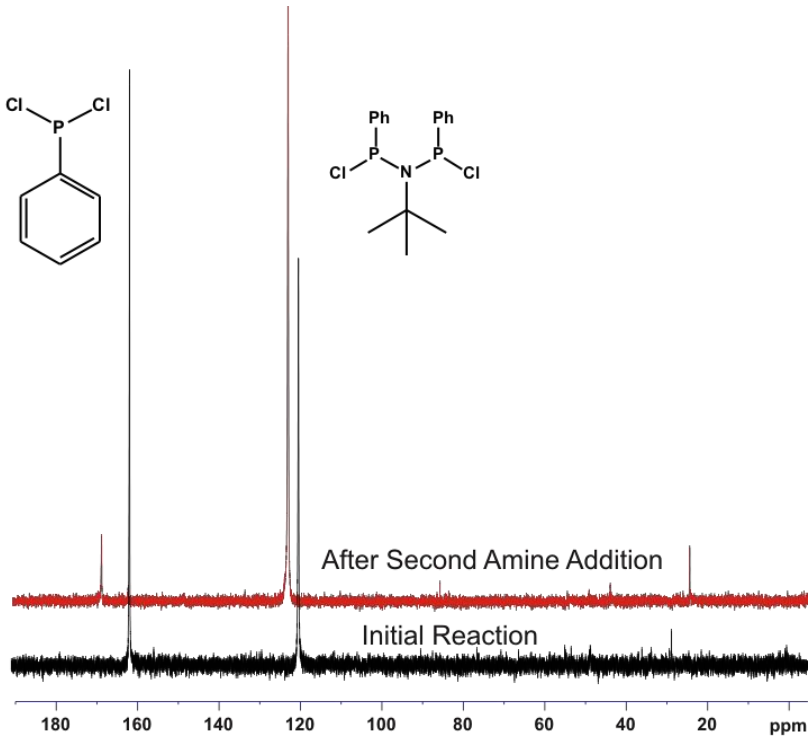


Figure 3.9. $^{31}P\{^{1}H\}$ NMR of *t*-butyl amine bridge after the initial reaction and second amine addition.

decrease in the the $PhPCl_2$ peak (~162 ppm).

The ethyl and cyclohexyl amine bridges need to be resynthesized according to this procedure in order to obtain pure compounds. The most recent amine bridge to be attempted is *para*-tert-butyl aniline as the primary amine used. The crude $^{31}P\{^{1}H\}$ NMR for this bridge (Fig. 3.10) shows two possible product peaks (112 ppm, 126 ppm) and a $PhPCl_2$ peak (~162 ppm).

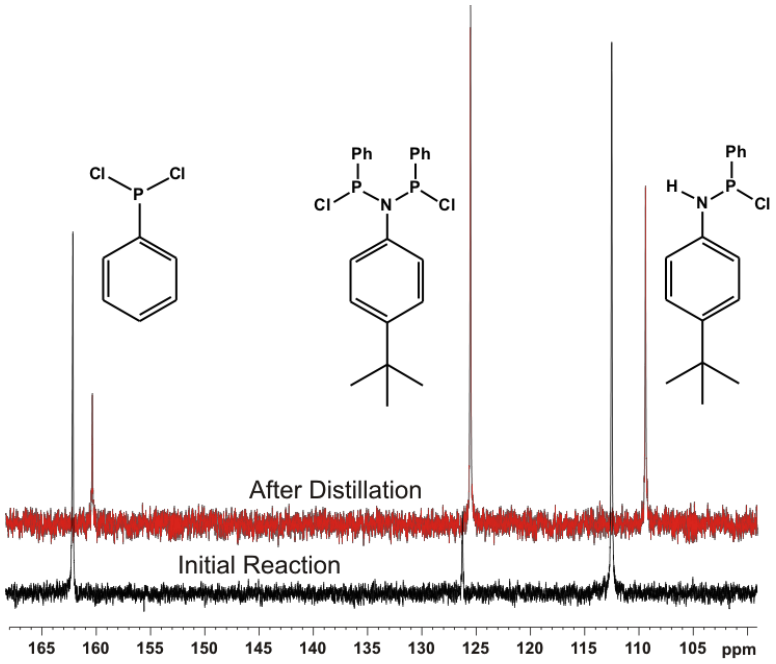


Figure 3.10. $^{31}P\{^{1}H\}$ NMR of the initial reaction to form *p-tert*-butyl aniline bridge and after distillation.

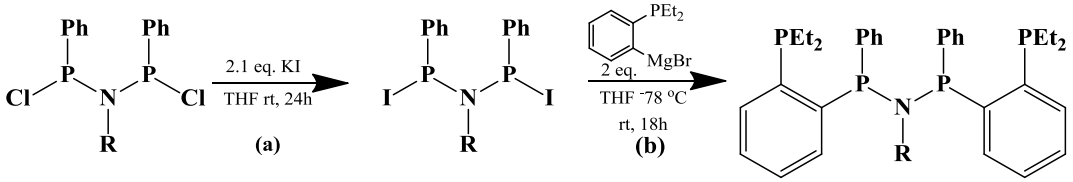
An attempt to remove the $PhPCl_2$ by vacuum distillation (heated only to 85 °C to prevent decomposition) was made, but without success. However, all the peaks in the NMR spectra changed. There was a decrease in the $PhPCl_2$ peak, an increase of the peak at 126 ppm, and a decrease in the peak at 112 ppm. It is possible that the reaction requires more vigorous conditions to go to completion and that the peak at 112 ppm is the intermediate compound to the amine bridge. The coupling step (Scheme 3.7b) was attempted between the cyclohexyl and tert-

butyl amine bridges (both not purified) and the short arm but was unsuccessful after stirring at room temperature for 24 hours. The crude reaction mixture contained only the initial reactants when analyzed by $^{31}P\{^{1}H\}$ NMR. Refluxing the mixture for an additional 24 hours was attempted.in hopes that more vigorous reaction conditions would cause the desired reaction to occur, but with no success.

P(III)-N bonds are displayed as single bonds but analysis of the bond length shows that there is some double bond character present. A P-N single bond is approximately 1.75 Å – 1.80 Å, whereas the P-N bond lengths in PNP ligands are approximately 1.60 Å – 1.69 Å. Partial double bond character most likely occurs because of the π-interaction between the *p* orbital of the nitrogen and an empty *d* orbital of each of the phosphorus atoms. Furthermore, the decrease in reactivity of the phosphorus atoms on the bridge is due to the presence of the nitrogen center. The lone pair on the nitrogen atom increases the nucleophilicity of the phosphorus atoms. Normally, the phosphorus can act as an electrophile in a substitution reaction because of the empty *d* orbitals, but an increase in nucleophilicity will make the phosphorus, in turn, less susceptible to nucleophilic attack.

The Finkelstein reaction is a reaction in which an alkyl chloride or alkyl bromide is treated with sodium iodide (or potassium iodide) in acetone to afford an alkyl iodide.[3,15] The transformation can occur by an S_N1 or S_N2 reaction depending on the nature of the alkyl halide. This reaction is an equilibrium reaction that follows Le Chatelier's principle. Sodium iodide is much more soluble in acetone than sodium chloride and bromide and the precipitation of these salts drives the reaction to completion by removing the chloride and bromide ions from solution. This same methodology was applied to the amine bridge in hopes that the phosphorus centers would be more reactive to nucleophilic attack with replacement of the chlorines for the better

leaving group, iodine. The amine bridge was allowed to stir in the presence of KI for 24 hours in THF (Scheme 3.8a). As time progressed, the solution became more orange and a yellow precipitate formed, which is indicative of the less soluble KCl. The reaction was monitored by $^{31}P\{^{1}H\}$NMR, but due to poor spectra, proof of a halide exchange is not definitive. The last coupling step (Scheme 3.8b) has been performed without purification of the iodine-containing bridge and isolation of the product was attempted.



Scheme 3.8. Synthesis of RN-P4-Ph utilizing the Finkelstein reaction.

The product that was formed from this reaction was more soluble in the aqueous layer than the organic layer and remained in the aqueous layer after workup. This was not noticed until the aqueous layer was neutralized with bleach before discarding. This sequence of reactions needs to be performed again and careful isolation of each intermediate must done in order to obtain clear evidence that the desired products are being made. Also, the amine bridge was thought to be pure when the initial Finkelstein-type reaction was performed, however there was unreacted $PhPCl_2$ present from the synthesis of the bridge that could have affected the reaction.

3.6. Future Work

This work has not yet afforded us with the RN-P4-Ph ligands, which is the ultimate goal for this project. Synthesis of the large arm through the protected derivative followed by direct coupling with the primary amine has been performed, but cleaner methods of separating the deprotected moiety should be studied. The Finkelstein-type reaction to give the desired ligand has

been done, but more work is needed to demonstrate whether the RN-P4-Ph ligand was indeed made.

If one of these paths is successful, separation of the isomers is the next challenge. Solvent crystallization will be attempted first since it gives a reasonable separation of the et,ph-P4 ligand. Separation of the isomers may be possible by HPLC, which should also be attempted. To date, no real effort has been made to achieve a resolution of the ligand isomers with chiral resolving agents. Diastereomeric crystallization of chiral molecules by way of chiral resolving agents is an older, well known method to obtain the desired compound. This process is performed by a trial-and-error basis due to the large number of resolving agents and solvent variations. The most likely chiral compounds to give the desired separation are carboxylic acids, such as tartaric acids and amino acids. This may be a good project to invest time into as it might prove very beneficial to our ligand separation problems.

3.7. References

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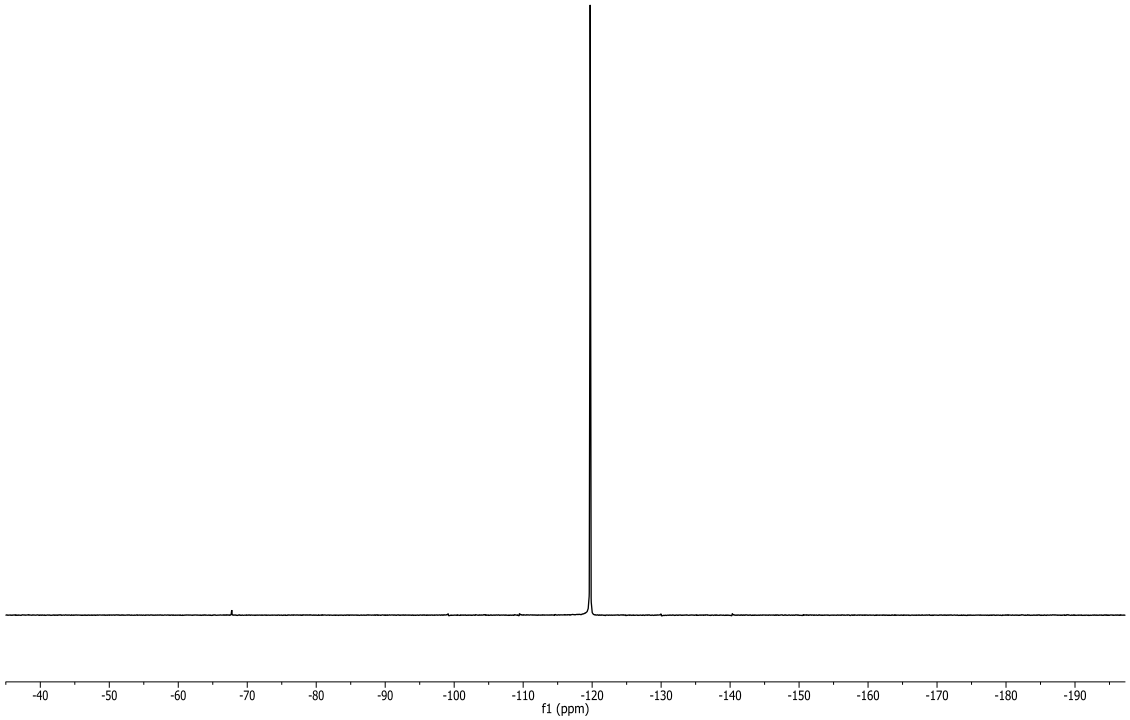
CHAPTER 4. EXPERIMENTAL

4.1 General Notes

All synthetic procedures were performed using standard Schlenk and dry box techniques. All solvents and chemicals used were purchased from Aldrich, Alfa Aesar, or Matrix scientific and used without further purification unless otherwise noted. ^{1}H and ^{31}P NMR spectra were recorded on a Bruker 250 MHz and 400 MHz (1H) spectrometer. All ^{13}C NMR spectra were recorded on a bruker 400 MHz spectrometer. ^{31}P chemical shifts are reported relative to H_3PO_4 (external standard) and dichlorophenylphosphine(internal standard where applicable).

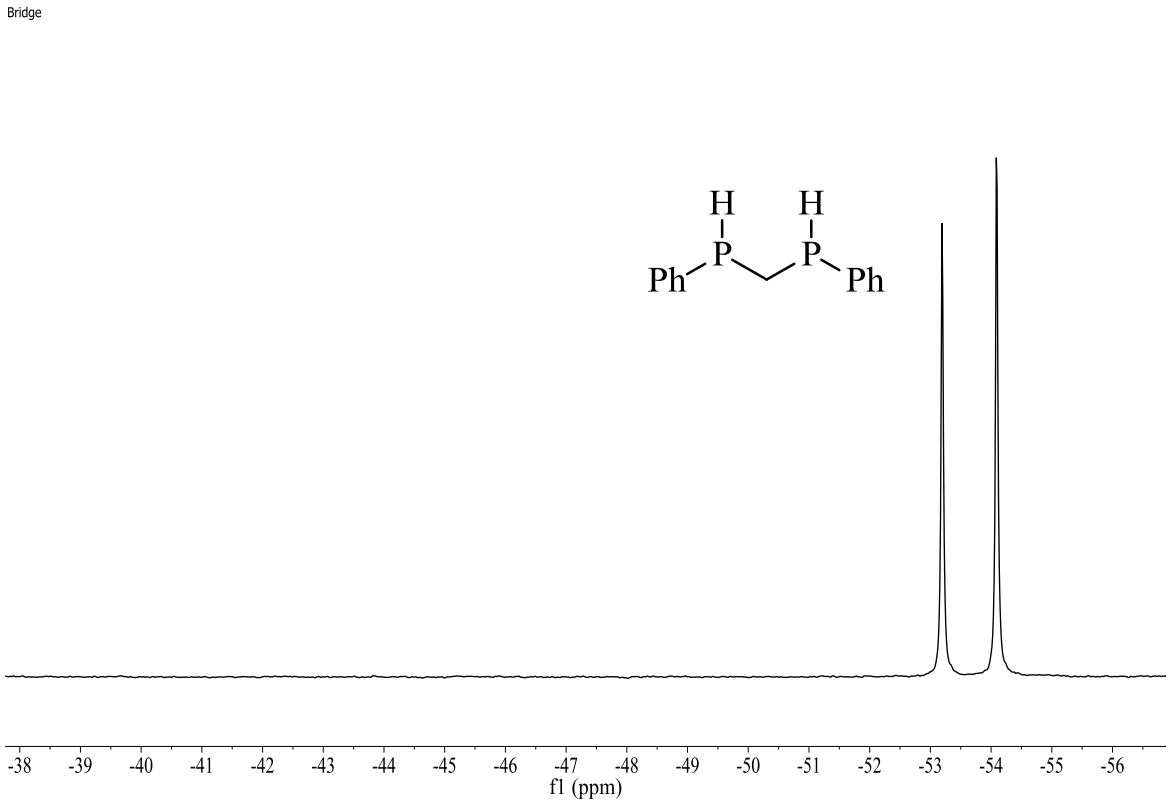
4.2 Synthetic procedures related to the synthesis of et,ph-P4

4.2.1 Phenylphosphine



In a 250 mL Schlenk flask, Dichlorophenylphosphine (36.3 g, 203 mmol) and 150 mL of tglyme were added. To a separate 500 mL Schlenk Flask equipped with a stirbar, LAH (9 g, 237 mmol) and 300 mL of tglyme were added. Both flasks were placed in an ice bath 20 minutes prior to the addition of the dichlorophenylphosphine solution to the vigorously stirring LAH solution at a rate of 2-3 drops per second with a large bore cannula. Upon completion of the addition, the reaction flask was allowed to come to room temperature and stir overnight and the product was obtained by trap-to trap distillation. Acceptable yields are between 80-83% and greater than 99% purity.

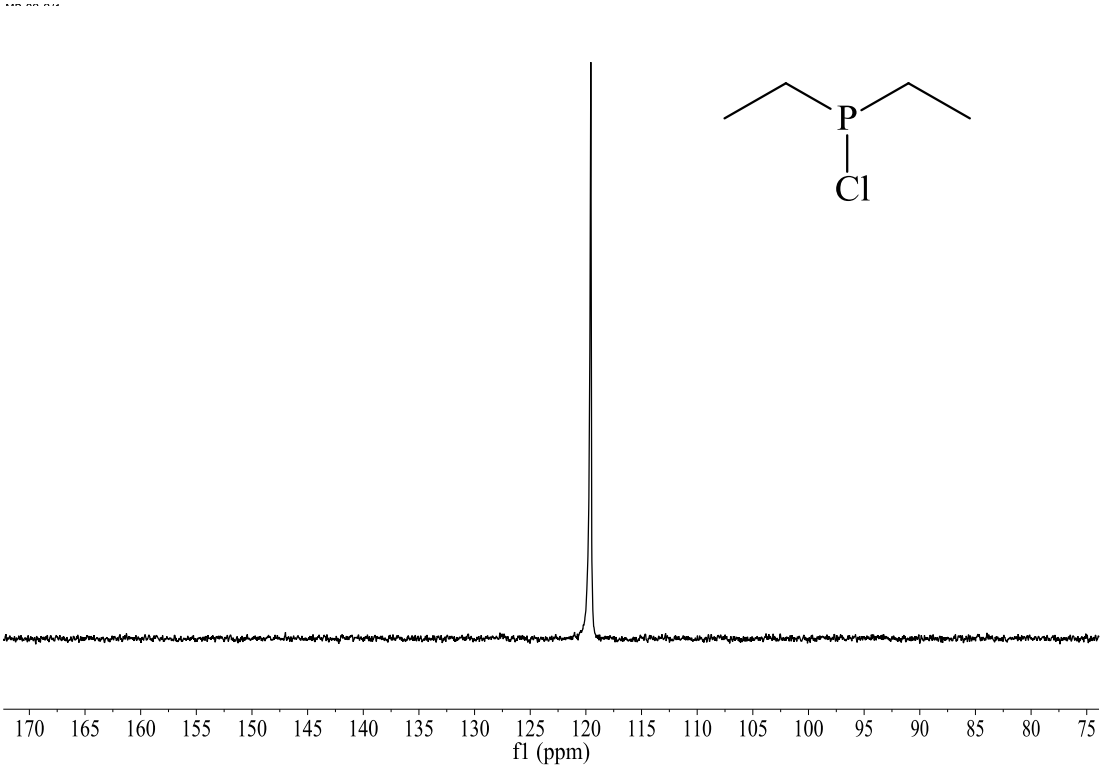
4.2.2 Methylenebis(phenylphosphine)



In a 250 mL Schlenk flask potassium hydroxide (28.6g, 477mmol) was dissolved in sufficient water to give a 56% solution. This solution is to be placed in an ice bath and degassed for at least 20 minutes. In a 500 mL Schlenk flask equipped with a stirbar phenylphosphine

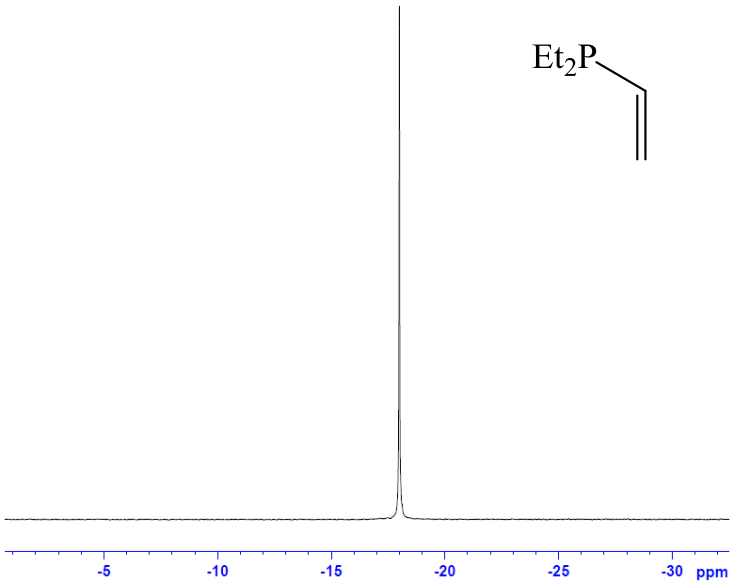
(15g, 136mm), dichloromethane (5.79g, 68.1mm), and 150 mL of DMF were added and cooled in an ice bath as well. With both flasks in an ice bath the KOH solution was added to the vigorously stirring phenylphosphine solution at a rate of 2-3 drops per second with a medium bore cannula. Upon completion of the addition, the reaction flask was allowed to warm to room temperature and continue stirring for 6 hours. 100mL of degassed distilled water was added to the solution to quench the reaction as well as dissolve the produced salts. The product was extracted from the aqueous solution with pentane or low boiling petroleum ether. The organic fractions were dried over sodium sulfate and concentrated to yield the semi-pure product. Stirring the crude mixture under vacuum removes volatile impurities gives the pure desired product. Acceptable yields are between 40-50% and >90% purity.

4.2.3 Diethylchlorophosphine



In a Schlenk flask equipped with a stirbar, phosphorous trichloride (30.24g, 220mmol) and 40 mL of tglyme were added and cooled to 0 C. To a separate Schlenk flask a diethyl zinc (29.93g, 242mmol) and 50 mL of tglyme were added and cooled to 0 C--*A 10% excess of the diethyl zinc must be used or yields will be poor*. While maintaining ice baths the zinc solution was added to the vigorously stirring phosphine solution by cannula at a rate of 2 drops per second. After completion of the addition, the resulting solution was allowed to warm to room temperature and the product was collected by trap-to-trap distillation. Acceptable yields are >80% and >99% purity.

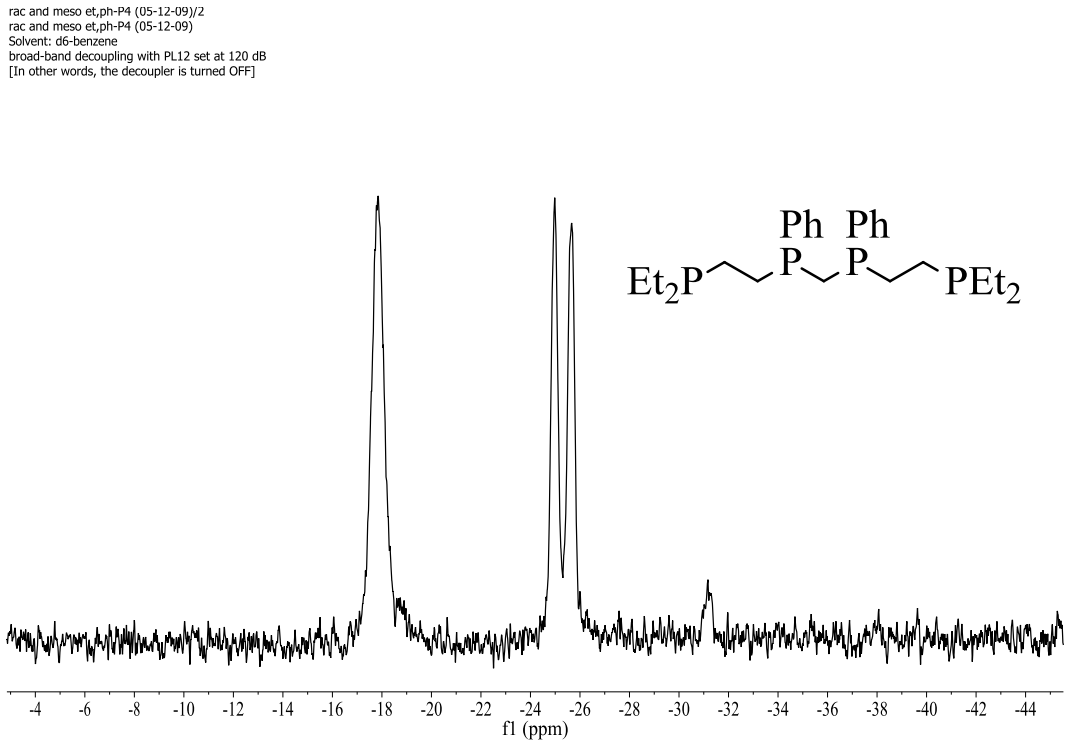
4.2.4 Vinyldiethylphosphine



To a solution of vinyl magnesium bromide (137mL of a 1M THF solution), an equal volume of tglyme was added to a Schlenk flask equipped with a stirrbar. Vacuum distillation was used to remove at least 95% of the THF. To a separate Schlenk flask, diethylchlorophosphine (12.32 g, 101mmol) and 30 mL of tglyme were added. Both solutions were placed in ice baths and the phosphine solution was added to the vigorously stirring

Grignard solution by cannula at a rate of 2-3 drops per second. Upon completion of the addition, the reaction was allowed to warm to room temperature and the product was collected by trap-to-trap distillation. Acceptable yields are >70% with >99% purity

4.2.5 Et, Ph-P4



In a Schlenk flask equipped with a stirbar, vinyldiethylphosphine (8.3g, 71.5mmol) and methylene bis(phenylphosphine) (7.96g, 34.5mmol) were added. The sealed flask was placed in in the beam of UV light (xenon bulb) with stirring for a minimum of 8 hours. Excess vinyl was removed by reduced pressure to give the rac, meso mixture of the ligand. Yields are typically quantitative with >97% purity.

4.2.6 Separation of the rac/meso-et,Ph-P4 diastereomers

A mixture of racemic and meso ligand were diluted with approximately three times its volume in hexane and the resulting solution was placed in a freezer overnight. While keeping

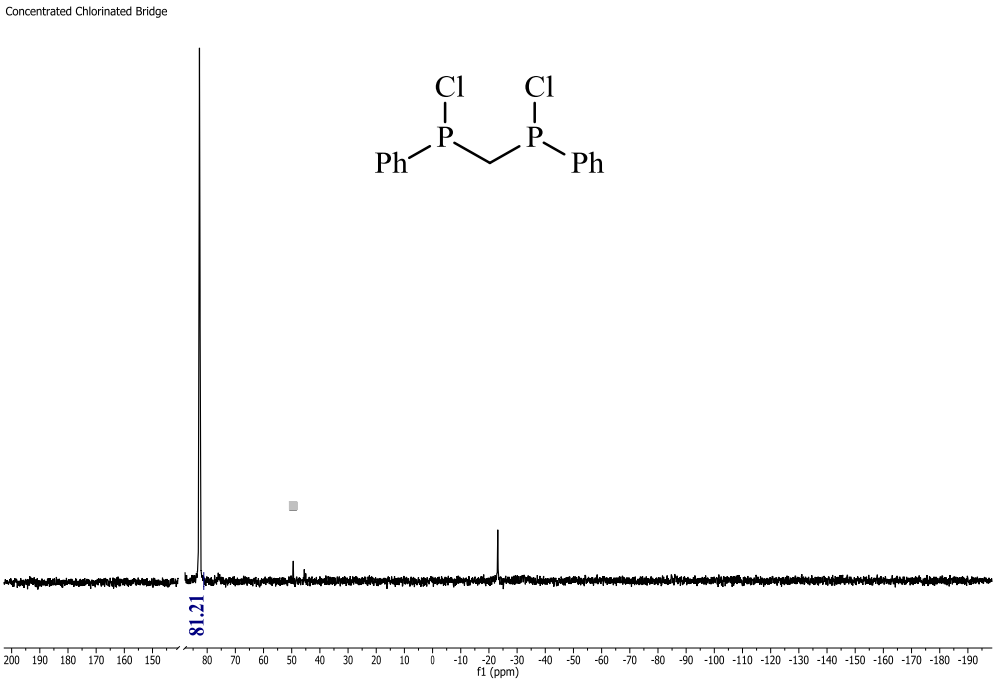
the flask at ice bath temperatures, the racemic ligand and hexanes transferred to a different flask via cannula to leave approximately 70% meso ligand behind—white solid at temperatures below -15. Hexane was again added to the flask containing the meso and both flasks were placed in the freezer again overnight. This process of separating the diastereomers from one another is performed until the racemic ligands purity is >80% purity.

4.3 Synthetic procedures related to the synthesis of et,ph-P4-Ph

4.3.1 General Considerations

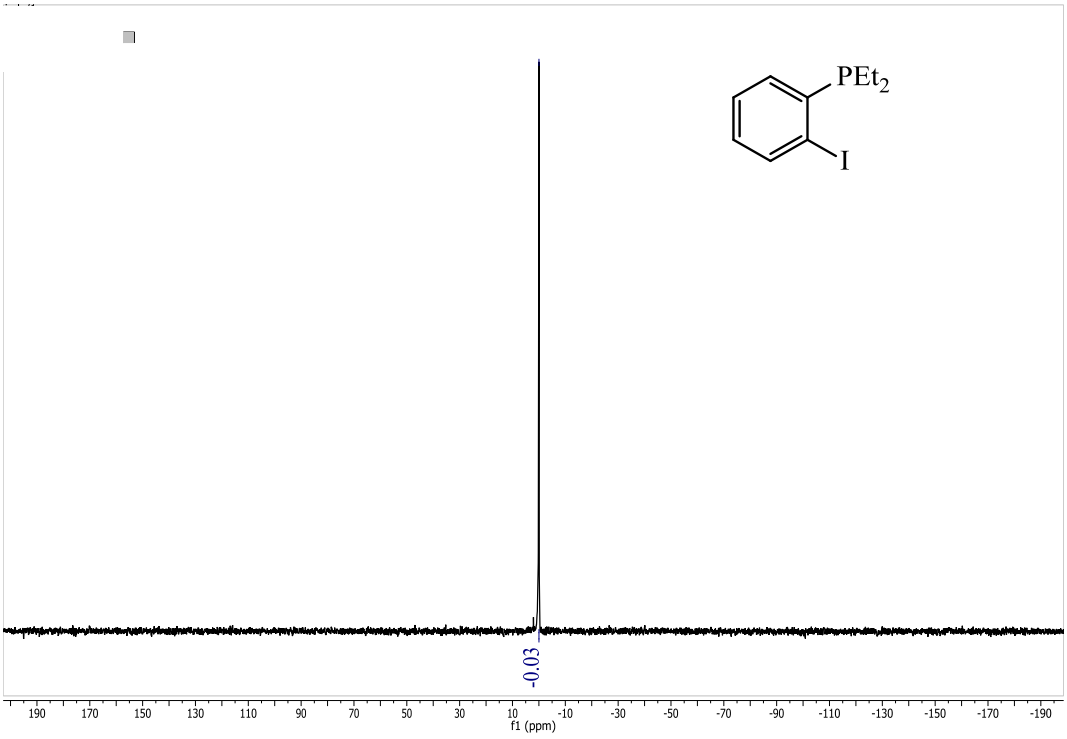
Phenylphosphine and methylene bis(phenylphosphine) are prepared by the same methods listed in **5.2** and will not be repeated. Most of these reactions are light as well as moisture and air sensitive and required wrapping flasks in aluminum foil works to minimize exposure to light. (***ls***) will be at the end of the experiment name indicating light sensitive precautions must be taken.

4.3.2 Methylenebis(chlorophenylphosphine)



Methylene bis(phenylphosphine) (5.62g), hexachloroethane(12.23g), and 50 mL of diethyl ether were added to a Schlenk flask equipped with a stirbar. This solution was allowed to reflux for at least 24 hours. Crude NMR should be taken to determine the completion of the reaction. Upon completion of the reaction approximately half the solvent used was removed under vacuum leaving behind the solvent and initiating the precipitation of byproducts. The solid byproducts were removed by gravity filtration with a celite plug. The remaining solvent was removed under vacuum. It should be noted that this reaction should not be allowed to approach 70 ^{o}C at any point. Temperatures above this mark will begin to decompose the chlorinated bridge product. Yields were quantitative with >90% purity.

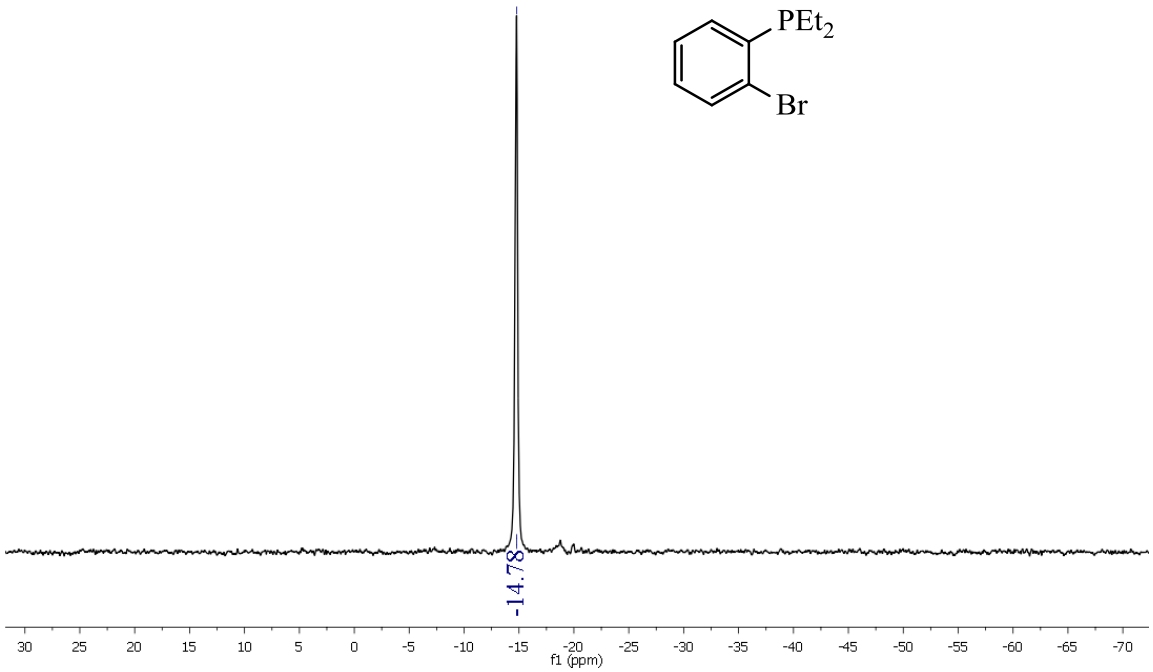
4.3.3 1-diethylphosphino-2-iodobenzene



A 1M THF solution containing diiodobenzene(15.087g, 45.7mmol) was cooled to 0 ^{o}C and slowly treated with a 0.73M(62.6 ml, 45.7mmol) isopropylmagnesium bromide solution by

cannula at a rate of 2 drop per second. The reaction was kept at 0 C with moderate stirring for a minimum of 4 hours. This reaction flask was subsequently cooled to -25 C. A cooled 1M THF solution containing diethylchlorophosphine (5.7g, 45.7mmol) was slowly added to the Grignard solution by cannula at the previously stated rate. Upon completion of the addition, this reaction was allowed to warm to room temp and stir overnight and subsequently quenched with degassed water. The product was obtained alkane solvent extraction and concentrated by vacuum distillation. The product was further purified by purified by a short path vacuum distillation with a boiling point between 116-122 ^{o}C at 0.8 torr. Product yields are typically 70-75% with >99% purity.

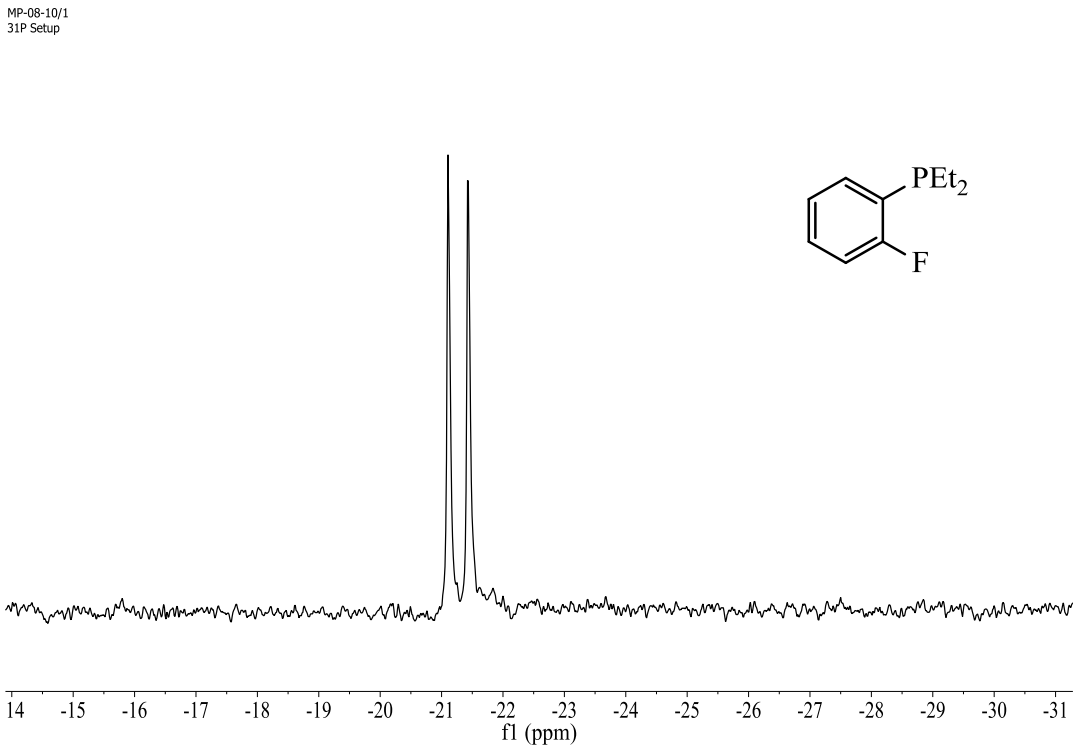
4.3.4 1-diethylphosphino-2-bromobenzene



A 1M THF solution containing 1-bromo-2-iodobenzene (60.45g, 214mmol) was cooled to 0 ^{o}C and subsequently treated with 203 mL(221mmol) of 1.09M isopropylmagnesium bromide by cannula at a rate of 2-4 drops per second. The reaction is allowed to stir at 0 ^{o}C for a

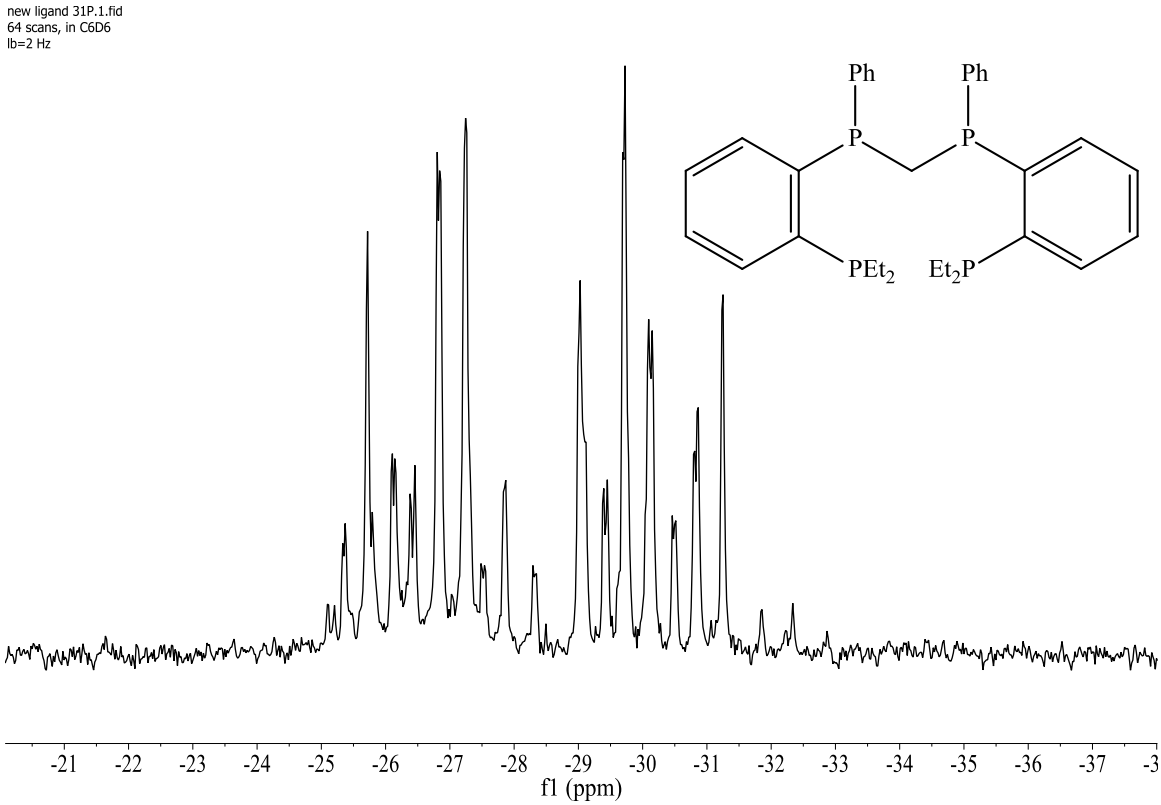
minimum of 4 hours and then cooled to -25 ^{o}C. A cooled 1M THF solution containing diethylchlorophosphine (26.61g, 214 mmol) was slowly added to the Grignard solution via cannula at the previously stated rate. Upon completion of the addition, this reaction was allowed to warm to room temp and stir overnight, followed by quenching unreacted Grignard reagent with degassed water. The product was obtained via solvent extraction and concentrated by vacuum distillation. The product was further purified by short path vacuum distillation with a boiling point of 110 ^{o}C. Product yields are typically 70-72% with >99% purity.

4.3.5 1-diethylphosphino-2-fluorobenzene



This compound was prepared using the same methods for species 5.3.3 and 5.3.4. Product yields are typically 70-73% with >99% purity.

4.3.6 Attempted synthesis of rac,meso-et,ph-P4-Ph



A 1M THF solution of 1-diethylphosphino-2-iodobenzene (4g) was slowly treated with a 0.5M THF isopropylmagnesium bromide (26mL) solution. After stirring at 0 C for 6 hours, the Grignard solution was held at 0 C and added to a 1M Methylene bis(chlorophenylphosphine)(2.g) solution which had a maintained temperature of -25 C. Distilled water was added to the solution to quench unreacted Grignard. The organic layer was extracted and the aqueous layer was washed with three 10mL equivalents of diethyl ether. The combined organic layers were combined, dried over sodium sulfate, and run through an alumina column. Solvents were removed by vacuum distillation and unreacted iodobenzene was removed via short path distillation, leaving behind a white paste with a slightly brown hue. ^{31}P NMR yielded second order coupling, but the desired product was confirmed via a crystal structure by Dr. Alexandre Monteil.

4.3.7 Attempts toward the separation of the rac,meso-et,ph-P4-Ph diastereomers

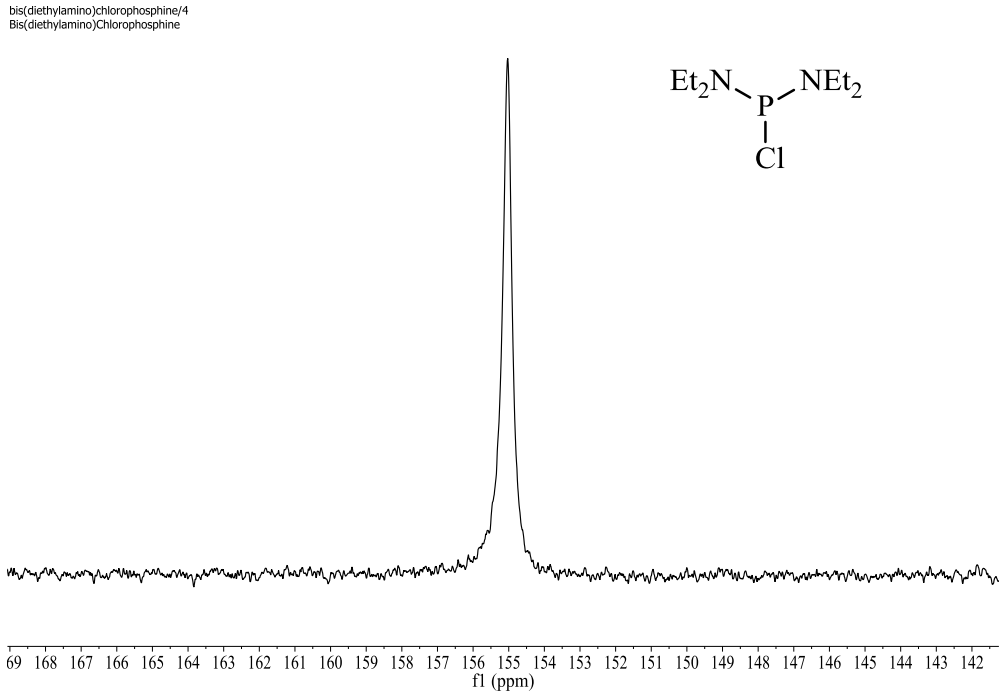
Ethers, toluene, pentane, hexanes, petroleum ether, C1-C4 alcohols, and mixed ratios of these various solvents were unsuccessfully used in the method commonly used to separate the et,ph-P4 diastereomoers. At the milligram scale some successes were made in better purifying P4, but when approaching the multi-gram scale there were no promising results. Neutral and basic alumina columns, as well as nickel complexation were used to separate the diastereomers but met no success. Attempting to distill the neat product resulted in the decomposition of the product.

4.4 Synthetic procedures related to modifying the traditional methylene bridge

4.4.1 General Considerations

To avoid writing a separate experimental for each modified phenylphosphine species, [R] will be used 5.4.2A to summarize the following: N,N-dimethyl, tert-butyl, ethyl ester, and nitro. 5.4.2B and onward [R] Tert-butyl and N,N-dimethyl substituted phenylphosphines as they were the only successfully synthesized species. Though synthesis of bis((4-(tert-butyl)phenyl)phosphino)methane was successful by ^{31}P NMR, the product could not be isolated from any crude yield, making further exploration into ligands derived from bridges of this type unable to be performed.

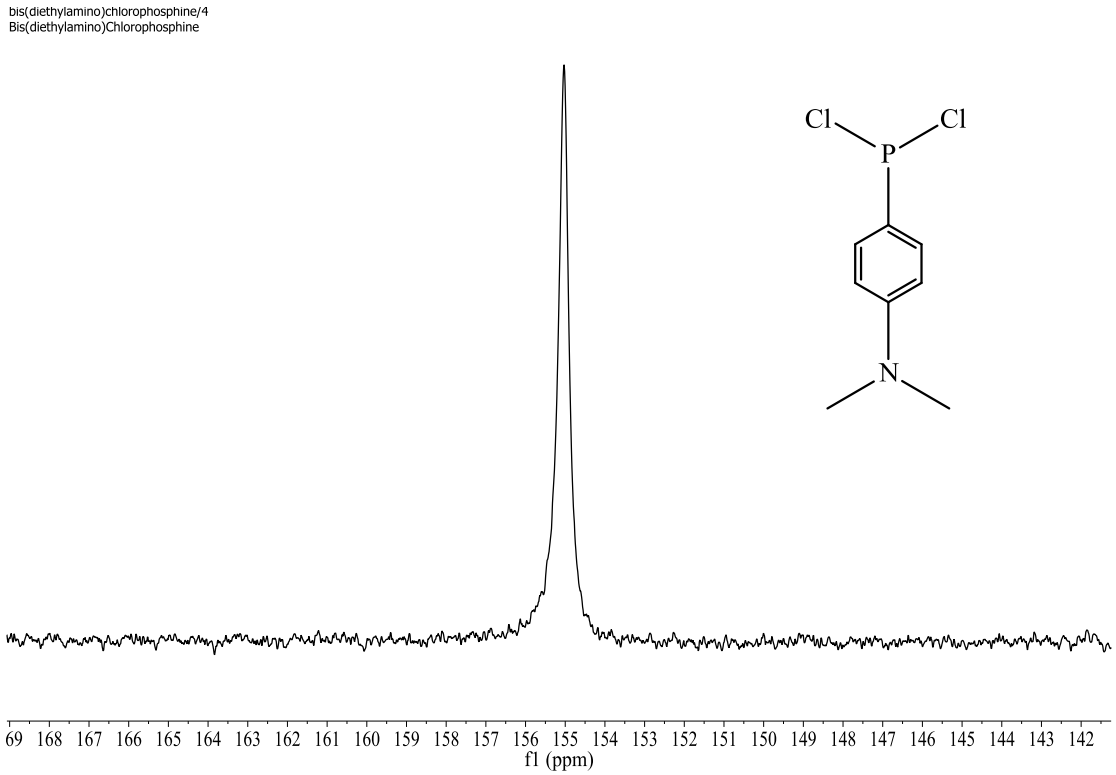
4.4.2 bis(diethylamino)chlorophosphine



This addition was carried out at -78 ^{o}C. A 10M, Diethylamine (147g, 2010 mmol) petroleum ether solution was slowly added to a vigorously stirring 0.1M phosphorus trichloride(43.8mL, 502 mmol) petroleum ether solution at a rate of 2 drops per second with a large bore cannula. Upon completion of the addition, the reaction was allowed to warm to room temperature and stir overnight. Ammonium salts were filtered of and washed with additional petroleum ether. The liquid product was concentrated and vacuum distilled at 90 ^{o}C to acquire the protected phosphine. Yields were between 70-75% with greater than 90% purity.

4.4.3 Modification of phenylphosphine

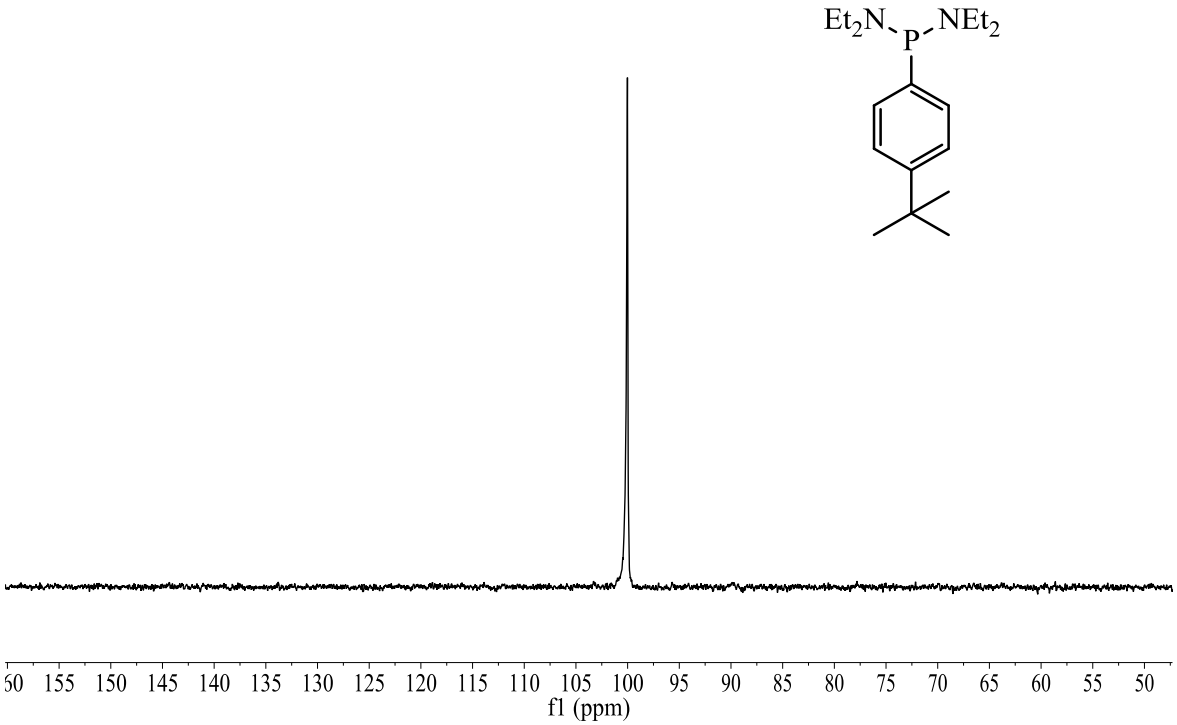
4.4.3A 4-(dichlorophosphino)-N,N-dimethylaniline



A 1M THF solution containing 4-bromo-N,N-dimethylaniline(10g, 49.9mmol) was cooled to 0 ^{o}C and slowly treated with 0.894M isopropylmagnesium bromide (55.9 ml, 49.9mmol) by cannula at a rate of 2 drop per second. The reaction was kept at 0 C with moderate stirring for a minimum of 4 hours. This reaction flask was subsequently cooled to -25 C and slowly added to a 1M THF solution containing phosphorous trichloride (7.55, 54.89mmol). Upon completion of the addition, this reaction was allowed to warm to room temp and stir overnight. The product concentrated by vacuum distillation and filtered by suction with a fine fritted funnel. The

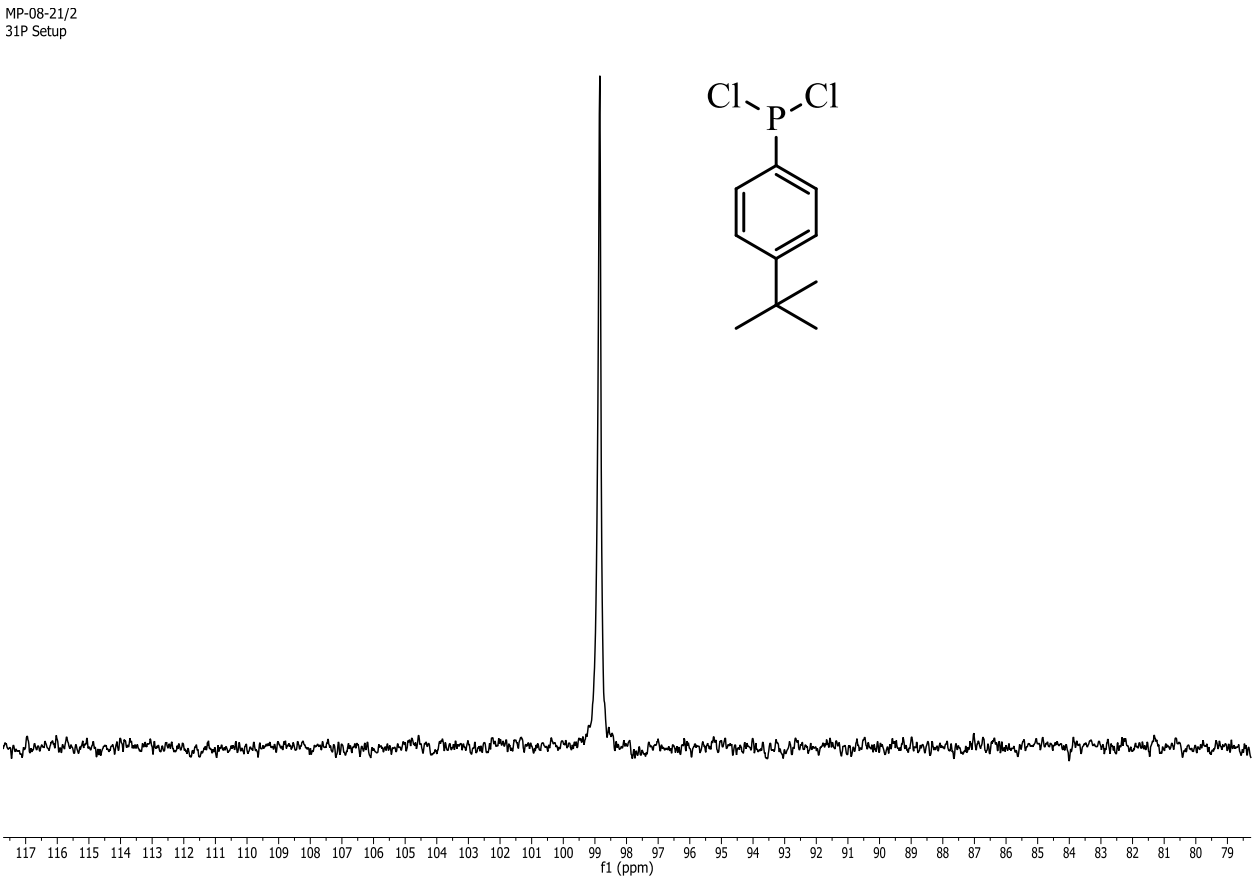
product was further purified by purified by a short path vacuum distillation with a boiling point between 70-75 ^{o}C at 0.8 torr. Product yields were typically 60-63% with >98% purity.

4.4.3B 1-(4-(tert-butyl)phenyl)-N,N,N',N'-tetraethylphosphinediamine



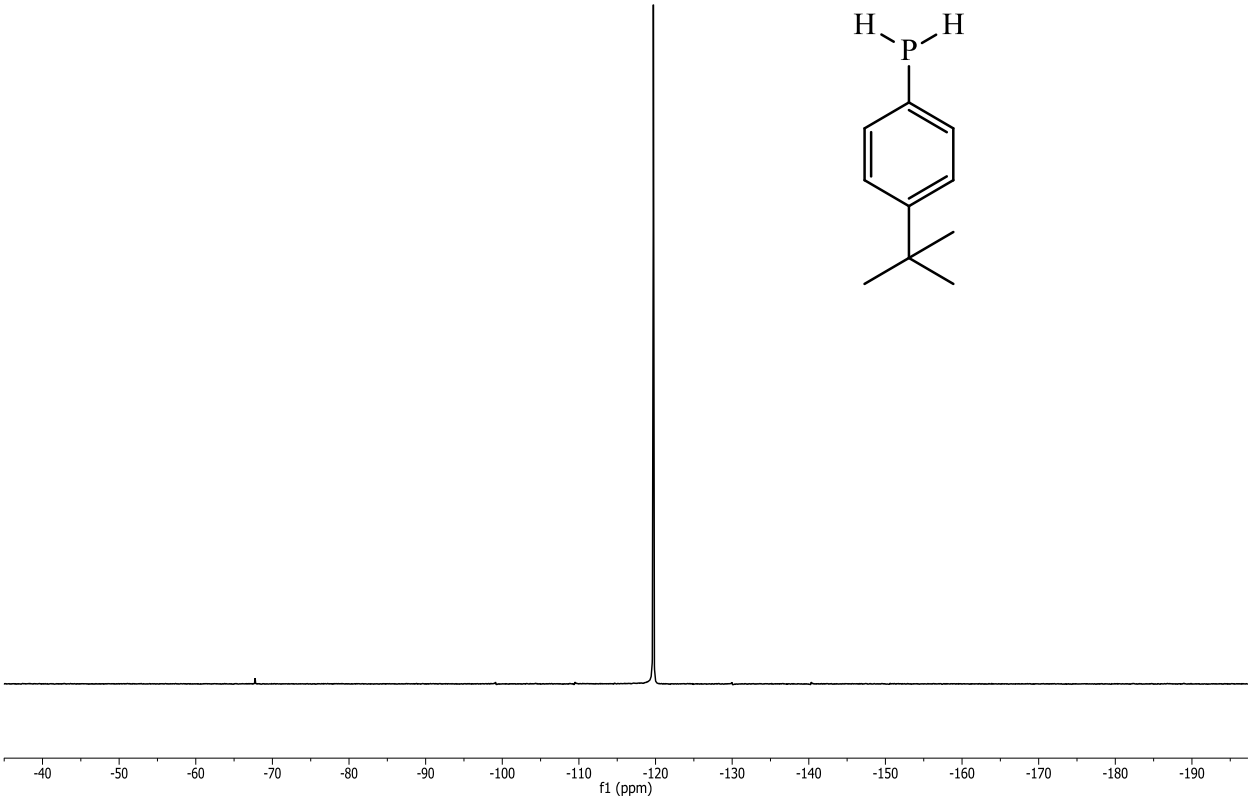
A 2M ethereal solution of bis(diethylamino)chlorophosphine (39.58g, 188mmol) was added to a 0.9M ethereal solution of 4-tertbutylmagnesium bromide (179ml, 188mmol) at $^{-}$78 ^{o}C. The mixture was allowed to warm to room temperature and stir overnight. The reactants were then filtered with a coarse fritted funnel and concentrated by vacuum distillation. Pure product was obtained by short path distillation with a boiling point range of 145-150 ^{o}C(0.8torr). Product yields were typically 72-75% with >99% purity.

4.4.3C (4-(tert-butyl)phenyl)dichlorophosphine



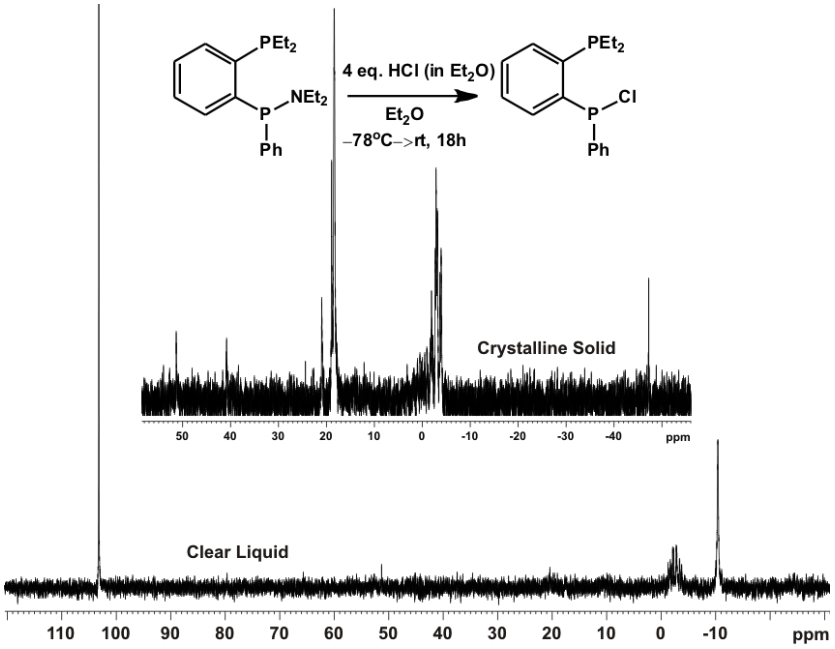
A 1M (4-(tert-butyl)phenyl)-N,N,N',N'-tetraethylphosphinediamine **(**42.5g, 138mmol) ethereal solution was slowly added to a vigorously stirring 2M ethereal HCl solution (276 mL, 551mmol). The resulting solution was allowed to warm to room temperature and stir for at least 18 hours. The crude product was separated from the resulting ammonium salts with a coarse fritted funnel and concentrated. Product was purified by short path distillation with a boiling point of 93-95 ^{o}C(0.8torr) with yields of 77-80% with >99% purity.

4.4.3D (4-(tert-butyl)phenyl) phosphine



In a 250 mL Schlenk flask, (4-(tert-butyl)phenyl)dichlorophosphine (15g, 63.8mmol) and sufficient THF to afford a 1M solution were added. To a separate 500 mL Schlenk Flask equipped with a stirbar, LAH (2.91g, 76.6mmol) and double the volume of THF used for (4-(tert-butyl)phenyl)dichlorophosphine were added. Both flasks were placed in an ice bath 20 minutes prior to the addition of the 4-r-dichlorophenylphosphine solution to the vigorously stirring LAH solution at a rate of 2-3 drops per second via a large bore cannula. Upon completion of the addition, the reaction flask was allowed to come to room temperature and stir overnight. The THF solvent was exchanged for hexane, followed by quenching of excess LAH with degassed H_2O. Product was removed from the crude mixture via solvent extraction and purified by short path distillation. Yields were typically 70% and >99% purity.

4.4.4 Attempted Synthesis of Chloro(2-(diethylphosphino)phenyl)phenylphosphine



A solution of (2-bromophenyl)diethylphosphine (5.87 g, 24.0 mmol) in THF (80 mL) was cooled to 0 oC. A 0.67 M THF solution of isopropylmagnesium bromide was added to the phosphine mixture via cannula. The resulting solution was stirred at 0 ^{o}C for 6H. This solution was then slowly added via cannula to a -78 ^{o}C THF solution of chloro(N, N-diethylamino)phenylphosphine (5.23g, 24.3 mmol, 50 mL THF). The resulting mixture was allowed to warm to room temperature as it stirred overnight. This reaction was quenched with DI water and the organic portion was collected. The aqueous layer was extracted with 3 50 mL portions of diethyl ether. The combined organic extracts were dried over sodium sulfate and filtered through a funnel. Solvent was removed by vacuum distillation. Yields varied between 30-50% but NMR results were consistent.

4.5 Catalytic Runs

4.5.1. General Considerations

All solvents and chemicals were purchased from Aldrich and used without further purification (aside from degassing) unless otherwise noted. $Rh(acac)(CO)_2$ was donated by Celanese, $[Rh(nbd)_2](BF_4)$ and **[*rac*-Rh_2(nbd)$_2$(et,ph-P4)](BF_4)$_2$**were prepared according to the procedure described in section 4.2.7, and the purity was checked by ^{1}H NMR spectroscopy. PPh_3 and PEt_3 ligands were purchased from Aldrich. All procedures were performed under inert atmosphere of nitrogen gas unless noted otherwise.

4.5.2. Catalytic Experiments

Catalytic experiments were performed in 150 mL stainless steel autoclaves from Parr and operated by Parr 4850 controllers. The autoclaves were loaded under inert atmosphere with 1.0 mM catalyst, 80 mL solvent (75 mL of acetone and 5.0 mL of toluene as an internal standard). PPh_3 (0.5 to 400 equiv.) was then added, and in the case of monometallic catalysts (Table 3.2, entries 3-6 and 9-10), PEt_3 (1.1 or 2.2 equiv. to compensate for its volatility and sensitivity to oxygen) was also added. The autoclaves were then purged three times with 1:1 H_2/CO, closed, and the catalyst solution soaked with stirring (1000 rpm) for 20 min under 45 psig 1:1 H_2/CO as the temperature was progressively increased to 90 ^{o}C.

After 20 min, the pressure of the reaction vessel was decreased to ~45 psig and 1000 equivalents (1.0 M) of 1-hexene (99+%, passed through a neutral alumina column immediately prior to use in order to remove peroxides, 8.9 μ 10^{-2} mol, 11.2 mL) were pressure added to the autoclave by 90 psig of H_2/CO. The progress of the reaction was monitored by gas uptake from the higher pressure gas storage reservoir connected to a two- stage regulator delivering synthesis gas at a constant pressure of 90 psig to the reaction vessel (see Figure 4.37). Pressures in the

autoclave and gas storage reservoir were monitored by electronic pressure transducers. Reaction conditions (pressure of autoclave and reservoir, temperature of autoclave and reservoir, and time) were monitored and logged by the Parr 4850 controller during the entire length of the catalytic run, transferred to a PC, and analyzed using Microsoft Excel. Data was typically collected every 1 min during a run.

Products were analyzed using a Hewlett Packard 5890 Series II Gas Chromatograph equipped with a DB-1 capillary column for calculation of final conversion, regioselectivity, isomerization, and hydrogenation. Chromatography data was collected using National Instruments Virtual Bench software, converted to usable format using Microsoft Excel, and analyzed using GRAMS 32 version 5 by Galactic Software. Further confirmation of reactant and product characterization was performed on a Hewlett Packard 5890 Series II Gas Chromatograph/Mass Spectrometer equipped with a DB-5 capillary column as well as ^{1}H NMR spectroscopy on a Bruker DPX-250 spectrometer (250 MHz). Occasional blank autoclave runs confirm that no impurities or deposits inside the autoclave were causing any competing catalytic reactions.

VITA

Marc A. Peterson was born in 1983 and raised in Bunkie, Louisiana. He graduated from Bunkie High School in Bunkie Louisiana in May of 2001. In August of 2001 he attended Southern University and A & M College where received a Bachelor of Science Degree in Chemistry in July of 2005. In August of 2005, he enrolled in Louisiana State University and A & M College to pursue his Doctor of Philosophy Degree under the supervision of Professor George G. Stanley.