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Synthesis, separation and reactivities of multidentate phosphine ligands and investigation into dirhodium hydroformylation and hydrocarboxylation catalysis

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SYNTHESIS, SEPARATION, AND REACTIVITIES OF MULTIDENTATE PHOSPHINE LIGANDS AND INVESTIGATION INTO DIRHODIUM HYDROFORMYLATION AND HYDROCARBOXYLATION CATALYSIS

A Dissertation

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ABSTRACT

A dirhodium homogeneous hydroformylation catalyst based on a tetraphosphine ligand, rac-Et₂CH₂P(Ph)₂CH₂P(Ph)₂Et₂, rac-et,ph-P₄, is under investigation. The ligand synthesis produces a racemic mixture and a facile and efficient method of separation of the racemic and meso diastereomers was achieved through reaction of et,ph-P₄ with two equivalents of NiCl₂ in EtOH to yield an almost quantitatively isolable precipitate of meso-Ni₂Cl₄(et,ph-P₄) and the soluble rac-Ni₂Cl₄(et,ph-P₄). Subsequent cyanolysis of these complexes liberates the et,ph-P₄ ligand, and the formation of a thermodynamically favored racemic monometallic intermediate during cyanolysis facilitates isomerization of meso to racemic ligand.

The addition of even small amounts of PPh₃ to the dirhodium tetraphosphine hydroformylation catalyst synthesized from the diastereomerically pure rac-et,ph-P₄ causes a dramatic drop in the aldehyde linear to branched regioselectivity (25:1 to 3:1) in acetone solvent (90 ºC, 6.1 bar, 1-hexene). The results indicate extremely effective inhibition of the regioselective bimetallic hydroformylation catalyst and the formation of an inefficient monometallic catalyst system, but not fragmentation to generate free RhH(CO)(PPh₃)₂ catalysts.

For the dirhodium hydroformylation catalyst the addition of 30% water (by volume) to the acetone solvent gives the highest rate (73 min⁻¹) and highest selectivity (33:1 linear:branched (L:B) aldehyde ratio, <1% isomerization or hydrogenation products) as compared to that in acetone with initial TOF of 20 min⁻¹, 25:1 L:B, 2.5% isomerization, and 3.4% alkene hydrogenation for 1-hexene. The dramatic improvement is the result of the more polar water-acetone solvent system preventing phosphine ligand dissociation from the dirhodium catalyst and subsequent formation of inactive species. Comparisons of the catalytic results in water-acetone to those of four representative monometallic, rhodium, modified phosphine systems indicate that
the dirhodium catalyst is one of the fastest and the most selective catalyst overall. The
drhodium catalyst also converts aldehydes, but more interestingly alkenes, to carboxylic acids in
the presence of water and under hydrogen-depleted conditions. Alkenes are converted via a
novel tandem catalysis reaction first involving hydroformylation then aldehyde-water shift
catalysis.
CHAPTER 1: HYDROFORMYLATION

1.1. Introduction to Hydroformylation

Hydroformylation, or the oxo reaction, is the most widely used homogeneous catalytic industrial process for the production of aldehydes.\textsuperscript{1,1} Discovered in 1938 by Otto Roelen at Ruhrchemie, it is the reaction of alkenes with hydrogen and carbon monoxide in the presence of a catalyst to yield either linear (normal) or branched (iso) aldehydes. For most applications the best hydroformylation catalysts are those that produce the highest ratio of linear to branched products and the fewest side reactions. The side reactions produce alkene isomerization products (internal alkenes) and alkene hydrogenation products (hydrocarbons), as indicated in Scheme 1.1.

Following Roelen’s discovery, hydroformylation became the dominant homogeneous catalytic process for producing aldehydes and over 12 billion pounds of aldehydes are produced through this process each year. Common commercial catalysts are based on cobalt or rhodium hydride carbonyl complexes and often utilize phosphite or phosphine ligands to enhance the rate or the linear to branched regioselectivity. Aldehydes are used to produce alcohols and carboxylic acids, which are used in the production of fatty acids,\textsuperscript{1,2} plasticizers, detergents, surfactants, lubricants, and solvents.\textsuperscript{1,3}
The generally-accepted mechanism for the cobalt-catalyzed reaction was provided by Heck and Breslow$^{1,4}$ and is shown in Scheme 1.2.

**Scheme 1.2.** Cobalt-catalyzed hydroformylation mechanism.

The basic steps of the catalytic cycle include generation of a cobalt hydride from a mono- or bimetallic cobalt carbonyl complex, alkene coordination to the metal center via an open coordination site provided by CO ligand dissociation, alkene insertion into the metal-hydrogen bond, CO coordination and insertion into the metal-alkyl bond to form an acyl complex, oxidative addition of hydrogen, and the reductive elimination of the aldehyde product and regeneration of the active catalyst.

Cobalt catalyst systems dominated hydroformylation until the 1970’s. In the late 1960’s some corporations, influenced by the work of Osborn, Young and Wilkinson, began using rhodium catalyst systems.$^{1,5}$ They reported that the Rh/PPh$_3$ catalyst system was highly selective and far more active than their cobalt counterparts, even when used under mild conditions.
Although Wilkinson proposed several mechanisms for the Rh/PPh\textsubscript{3} catalyst systems, the generally accepted mechanism for Rh/PPh\textsubscript{3}-catalyzed hydroformylation is shown in Scheme 1.3. Note that the mechanism is analogous to the cobalt-catalyzed mechanism described by Scheme 1.2, with PPh\textsubscript{3} ligands replacing the less sterically influential CO ligands.

![Scheme 1.3. Rh/PPh\textsubscript{3}-catalyzed hydroformylation mechanism.](image)

The Rh/PPh\textsubscript{3} system is commonly used. The Dow Chemical Company likely uses HRh(CO)(PPh\textsubscript{3})\textsubscript{2} as their catalyst system (although they might be using a bulky bisphosphite catalyst) and has a hydroformylation plant in Taft, Louisiana that produces over 100,000 tons of aldehyde annually. Roy Pruett at Union Carbide (now Dow) patented the key discovery that a large excess of PPh\textsubscript{3} (at constant concentration of 0.4 M or higher) was required to produce a selective, active, and more stable catalyst.\textsuperscript{1,6} Excess PPh\textsubscript{3} stabilizes the Rh complex, minimizing the formation of unsaturated 14e\textsuperscript{-} complexes that promote the fragmentation of PPh\textsubscript{3} which
ultimately leads to the formation of phosphide-bridged Rh dimers and clusters, which are poor or inactive hydroformylation catalysts.

The goal in designing an effective catalyst system is to optimize the production of the desired products under the mildest (cheapest) conditions. Since higher turnover frequencies, higher linear to branched ratios, and low production of side reaction products are usually required, much effort has been expended to attempt to design catalyst systems with these goals in mind.

Designing new, modified ligand systems is a common approach to improving the catalysis. Systems based on phosphite ligands, which are relatively poor donors and therefore promote facile CO dissociation and thus higher turnover frequencies, usually offer poorer regioselectivity and are subject to undesirable side reactions such as hydrolysis and alcoholysis,\(^1,7\) and are subject to fragmentation that leads to lowered selectivity or inactivity. Contrarily, most of the best modified phosphine ligand systems offer excellent selectivity, but are often difficult to synthesize and generally offer lower rates than phosphite systems and deactivate relatively easily.\(^1,7,1.8\) Other approaches to improve the catalysis involve solvent system modifications which can lower the cost of separation of the products as well as increases in rate, selectivity and longevity of the catalysts; development of systems that perform switchable-reaction catalysis; development of asymmetric systems; and development of systems able to perform tandem catalysis. Research continues in the design of new ligands and catalyst systems for the further improvement of hydroformylation catalysis.

1.2. **Multimetallic Catalysis and Stanley’s Bimetallic Catalyst**

A novel approach to improving hydroformylation results is to design an entirely new catalyst that may more easily facilitate the required steps of the mechanism, rather than focusing
strictly on varying electronic and steric influences through the design and synthesis of exotic phosphite and phosphine ligands. One such idea is to employ a bimetallic system. The use of transition metal dimers and cluster species for homogeneous catalysis has attracted considerable interest due to the species’ numerous potential advantages which include the capacity to support multielectron transfers, the ability to form multicenter metal-to-ligand bonds that may help activate substituents, the potential to use metal-metal bonds as stabilizing and/or reactive sites, and the potential ability to use mixed metal systems where two or more different metals can be used to selectively activate different substrates.\textsuperscript{1,9}

Interest in bimetallic cooperativity in hydroformylation catalysis is evident in Heck’s original 1961 mechanism for HCo(CO)$_4$-catalyzed hydroformylation (Scheme 1.2) where, in addition to the now commonly accepted monometallic mechanism for both Co and Rh catalysts, he proposed a bimetallic pathway in which the intermolecular hydride transfer from HCo(CO)$_4$ to Co(acyl)(CO)$_4$ leads to the reductive elimination of aldehyde and formation of Co$_2$(CO)$_8$ as shown in Scheme 1.4.\textsuperscript{1,4}

![Scheme 1.4](image)

**Scheme 1.4.** Formation of Heck’s proposed bimetallic cobalt complex.

Heck did not favor the bimetallic mechanism due to the relatively low concentrations of the reactant species involved and subsequent spectroscopic studies have confirmed that the monometallic pathway is most probable.\textsuperscript{1,10} Regardless, even if the bimetallic pathway were taken by some of the complexes it is relatively unimportant and uninteresting with regard to the concept of bimetallic hydroformylation. The formation of the bimetallic or subsequent
decomposition to the monometallic carbonyl precursor species is not the rate-determining step of
the overall reaction, and minimal cobalt is consumed at any given time from the monometallic,
catalytically active species.\textsuperscript{1,10} Furthermore, the bimetallic complex would not interfere with any
of the steps of the catalytic cycle.

Although numerous investigations have been performed, dimers and cluster compounds
have failed, generally, to produce rates and regioselectivities superior or even comparable to the
monometallic cobalt or rhodium hydroformylation systems.\textsuperscript{1,11} For instance, Pittman used cobalt
clusters containing three and four metal atoms to hydroformylate 1-pentene, however, the
regioselectivity was a low 5:1 linear to branched ratio for the production of hexanal.\textsuperscript{1,12} Another
system, reported by Suss-Fink, utilizes the cluster [HRu\textsubscript{3}(CO)\textsubscript{11}]\textsuperscript{-} to produce virtually pure linear
aldehyde (70:1 linear to branched ratio), however, the system performs only 50 turnovers in 66
hours.\textsuperscript{1,11}

The one known example of a good polymetallic hydroformylation catalyst is the bimetallic
rhodium catalyst developed by Stanley. His strategy was to attempt to produce bimetallic
cooperativity between two metals by tethering them together using a bridging ligand system.
Stanley designed a novel binucleating tetraphosphine ligand

\[(\text{Et}_2\text{CH}_2\text{CH}_2)(\text{Ph})\text{PCH}_2\text{P}(\text{Ph})(\text{CH}_2\text{CH}_2\text{PEt}_2), (\text{et,ph-P}_4)\]

to strongly chelate and bridge two metal
centers via a single, conformationally flexible methylene bridge in order to explore bimetallic
cooperativity in hydroformylation catalysis.\textsuperscript{1,13} The two internal phosphines in the et,ph-P\textsubscript{4}
ligand are chiral, leading to two diastereomeric forms which retain their diastereomerism when
bound to two metal centers, as shown in Figure 1.1. The catalyst precursor, 1r, (Figure 1.2) is
formed by treating the tetraphosphine ligand with two equivalents of Rh(nbd)\textsubscript{2}\textsuperscript{+} and when
subjected to 50:50 H\textsubscript{2}/CO (syn gas) the active catalyst is generated \textit{in situ}. 
Figure 1.1. The diastereomers of the et,ph-P4 ligand and the display of diastereomerism when bound to two metal centers.

Figure 1.2. The catalyst precursor, 1r.

Reaction studies on this bimetallic system have indicated that it provides comparable or superior performance relative to the commercial monometallic catalysts in terms of rates and regioselectivity. In addition, the racemic dinuclear complex displays the most dramatic example of bimetallic cooperativity ever seen in a homogeneous catalyst. The racemic form of the catalyst is considerably more active than that employing the meso diastereomer. This is likely due to the racemic catalyst’s ability to more easily, relative to the meso, form a doubly bridged hydrido-carbonyl species, \([\text{rac}-\{\text{Rh}_2\text{H}_2(\mu-\text{CO})_2(\text{CO})_2(\text{et,ph-P4})\}]^{2+}\), 2r, (Fig. 1.3, phenyl rings and hydrocarbon arms omitted for clarity), which favors the intramolecular hydride transfer that facilitates the hydroformylation.
The racemic catalyst is more likely to form this species than the meso catalyst because of the stereochemical orientation of the phosphine chelate rings and the proximity of the ligands to the rhodium metal centers. The racemic conformation more readily allows the interaction or transfer of ligands from one metal center with or to the other, as shown in Figure 1.4, which indicates potential for both CO and hydride bridges. Due to the orientation of the ligands in the racemic complex, a doubly bridging complex may form which promotes the intramolecular hydride transfer that is required for the reductive elimination of the aldehyde product and represents a form of bimetallic cooperativity.

FT-IR in situ spectroscopic studies have clearly indicated the importance of dicationic bimetallic complexes in the hydroformylation, with the activity of the catalyst directly related to the presence and intensity of the bridging carbonyl bands in the IR. In situ high pressure NMR studies do not appear to directly show what is believed to be the active catalyst $[rac\text{-}Rh_2H_2(\mu-\text{CO})_2(\text{CO})_2(\text{et,ph-P4})]^{2+}$, $2r$, (Et and Ph groups omitted for clarity).
CO\textsubscript{2}(CO)\textsubscript{2}(\text{et,ph-P4})\textsuperscript{2+}, \textbf{2r}. The presence, however, of the starting pentacarbonyl complex, [\textit{rac}-Rh\textsubscript{2}(CO)\textsubscript{5}(\text{et,ph-P4})]\textsuperscript{2+}, \textbf{3r}, and closed mode [\textit{rac}-Rh\textsubscript{2}(\mu-CO)(CO)\textsubscript{2}(\text{et,ph-P4})]\textsuperscript{2+}, \textbf{4r*}, both point to the presence of the proposed active hydride catalyst \textbf{2r}. The proposed mechanism for hydroformylation by the bimetallic system is shown in Scheme 1.5.

\begin{center}
\includegraphics[width=\textwidth]{scheme15.png}
\end{center}

\textbf{Scheme 1.5.} Proposed bimetallic dicationic hydroformylation mechanism, Et and Ph groups omitted for clarity.

The mechanism begins with the pentacarbonyl complex, [\textit{rac}-Rh\textsubscript{2}(CO)\textsubscript{5}(\text{et,ph-P4})]\textsuperscript{2+}, \textbf{3r}. Oxidative addition of hydrogen produces a Rh(I)/Rh(III) mixed oxidation state complex, [Rh\textsubscript{2}H\textsubscript{2}(CO)\textsubscript{4}(\text{et,ph-P4})]\textsuperscript{2+}, \textbf{A}, and an intramolecular hydride transfer between the rhodium metal centers, via complex \textbf{B}, generates the proposed active catalyst, \textbf{2r}. Carbonyl dissociation allows alkene coordination, yielding complex \textbf{C}. The alkene undergoes a migratory insertion, providing the alkyl complex \textbf{D}, whereupon carbonyl ligand coordination leads to migratory insertion into...
the metal-alkyl bond to produce the acyl ligand on complex E. Another intramolecular hydride transfer occurs between the metal centers to reductively eliminate the final aldehyde product, producing $4r^*$, which can accept a CO ligand and rotate to the open-mode complex, $3r$, or directly react with H$_2$ to ultimately reform complex $2r$. Although more steps are involved due to the intramolecular transfers, the basic steps fulfill the same requirements for hydroformylation as the simple monometallic mechanisms previously discussed, including generation of a hydride-containing species, the opening of a coordination site and alkene coordination, migratory insertion to form an alkyl complex, migratory insertion to provide an acyl complex, reductive elimination of the aldehyde product, and catalyst regeneration.

Stanley’s bimetallic catalyst is not yet fully understood or near becoming a commercially applicable hydroformylation catalyst. Investigations into a variety of aspects of its chemistry, including synthesis improvements, further characterization, side-reaction and fragmentation studies, the use of different substrates, the use of different solvent systems, applicability to other types of catalysis, and the use of variant ligand systems, for example, are important and underway or planned.

To facilitate easier and larger-scale synthesis of the bimetallic catalyst, an investigation and optimization of the separation of the diastereomers of the required et,ph-P4 ligand was completed. A study of the addition of the PPh$_3$ ligand to the bimetallic catalyst was performed, resulting in new information about catalyst fragmentation and deactivation. An extensive study of the beneficial effect of using a polar solvent system indicated that the polarity aids in preventing catalyst decomposition and produces conditions under which the bimetallic catalyst outperforms in rate and overall selectivity some of the best monometallic Rh/ligand systems. Further investigation into the novel tandem catalysis that produces carboxylic acids from alkenes.
discovered by Dr. Novella Bridges led to the development of procedural modifications such as constant gas purging and demonstrated the ability of the catalyst to directly convert aldehydes to carboxylic acids.

1.3. Conclusions

Although a well-established and widely used industrial process, hydroformylation continues to be the subject of extensive research. Some of the current challenges include separating of the products from the crude input stream or solvent, improving regio- and chemoselectivities, decreasing the rate of decomposition of the catalysts, designing catalysts for different substrates such as internal alkenes, developing asymmetric catalysts, inducing related reactions such as hydrogenation or hydrocarboxylation, and decreasing the overall cost of the catalysis. Research on Stanley’s novel bimetallic system employing the tetradentate phosphine ligand continues and is addressing the challenges posed to all of homogeneous hydroformylation research.

1.4. References

1.8. Private communication with George G. Stanley.


CHAPTER 2: SEPARATION OF THE DIASTEREOMERS OF THE ET,PH-P4 LIGAND AND A STUDY OF MONOMERIC COMPLEXES OF Ni(SCN)$_2$ AND RAC-ET,PH-P4 LIGAND

2.1. Introduction

The synthesis, characterization, and use of the et,ph-P4 ligand has been previously studied and reported. The separation of the diastereomers of the ligand is essential in order to use the rac-et,ph-P4 ligand to make an active and selective dirhodium catalyst for hydroformylation and hydrocarboxylation. An efficient and cost-effective method of separation is needed if the et,ph-P4 ligand, or variant thereof, is ever to be implemented industrially. The structures of the diastereomers appear in Figure 1.1.

Separation of the diastereomers of the et,ph-P4 ligand has been reported through simple crystallization and through the use of NiCl$_2$ and Ni(SCN)$_2$ bimetallic complexes. Although separation has been achieved, the previous procedures suffer from inconsistent and often low yields or were only suitable for small scale separations. The level of ligand purity obtained was also highly inconsistent. To rectify the yield and purity problems, the separation chemistry was extensively reexamined. et,Ph-P4 ligand separations through the use of both nickel chloride and nickel thiocyanate complexes were achieved in much higher yield than previously observed, with the nickel chloride route providing a better overall separation. The overall scheme is indicated in Scheme 2.1.

2.2. Nickel Chloride Separation Methods

2.2.1. Bimetallic Racemic and Meso Nickel Chloride Complexes

Treating the mixed-et,ph-P4 ligand with two equivalents of NiCl$_2$ or Ni(SCN)$_2$ produces bimetallic et,ph-P4 complexes in quantitative yield. The racemic and meso nickel complexes have different solubilities that provide a convenient way to separate the complexes. Although
the original published procedure did provide an effective separation, it was not optimized, was difficult to use on a large scale, and provided generally low yields of pure racemic ligand.

\[
\begin{align*}
\text{et,ph-P4} & \quad \text{NiCl}_2 \\
\text{rac} & \quad \text{meso} \\
\text{mixed-Ni}_2\text{Cl}_4(\text{et,ph-P4}) & \\
\text{filtrate + 250 eq CN⁻} & \quad \text{solid + 50 eq CN⁻} \\
\text{rac-(et,ph-P4)} & \quad \text{meso-(et,ph-P4)} \\
80\% \text{ yield} & \quad 45\% \text{ yield} \\
>95\% \text{ rac} & \quad >95\% \text{ meso} \\
\text{Catalyst Precursor, 1r} & \quad \text{rac-(et,ph-P4)} \\
70\% \text{ yield} & \quad 1.1-1.4 \text{ rac:meso}
\end{align*}
\]

**Scheme 2.1.** Summary of the separation of the et,ph-P4 ligand using NiCl₂.

The reaction of two equivalents of NiCl₂ with mixed-et,ph-P4 in EtOH produces meso-Ni₂Cl₄(et,ph-P4), 5m, and rac-Ni₂Cl₄(et,ph-P4), 5r. After the dropwise addition of the ligand to the rapidly stirred nickel chloride solution, the mixture is allowed to stir rapidly for 24 hours, during which nearly quantitative separation of the meso and racemic complexes occurs; the meso complex is less soluble than the racemic and precipitates as an orange powder. The yield of isolated meso-Ni₂Cl₄(et,ph-P4) obtained by vacuum filtration is always >90%. The filtrate, which contains the rac-Ni₂Cl₄(et, ph-P4), can be concentrated to a black amorphous tarry substance, which still contains variable amounts of EtOH so the yield cannot be accurately determined. The structures and $^{31}$P NMR spectra are similar to those already published.
After experimenting with numerous solvents and concentrations, it was determined that the optimal solvent for the separation is EtOH, (although MeOH affords only slightly lower yield), and that 260 mL EtOH is required per each 10 g of mixed ligand. At higher concentrations, (lower volumes), no separation occurs. Instead, the solution remains black and tarry and no precipitate of 5m forms. This is likely due to the reversible formation of nickel-P4 oligomers, which are indicated by the complex $^{31}$P NMR spectrum. However, subsequent addition of the appropriate amount of solvent and overnight stirring produces the desired separation.

2.2.2. Cyanolysis of rac-Ni$_2$Cl$_4$(et, ph-P4)

Cyanolysis of Ni$_2$Cl$_4$(et,ph-P4) is a convenient method to remove the nickel from the ligand. The previous published cyanolysis procedure for 5r afforded only a 45% yield. The method employed heat, low concentrations of cyanide, and an H$_2$O/benzene solvent system. All of these factors contributed to the low yield and have now been corrected to provide an optimized procedure for obtaining pure rac-et,ph-P4.

Heating during the cyanolysis procedure is unnecessary, as the strongly sigma-donating anionic cyanide will readily replace the phosphine ligands. In addition, decomposition of NaCN occurs at higher temperatures.

Higher concentrations of CN$^-$ provide better yields for the liberation of the racemic ligand from the nickel complex. This is due to a shift of the reaction equilibrium because the reverse reaction with the strongly chelating et,ph-P4 ligand is also favorable. A stable intermediate nickel complex can form, which is rac,trans-Ni(CN)$_2$(η$_{2.5}$et,ph-P4), 6r. This complex was isolated previously and the crystallographic data and spectra match the previously published results. This complex consumes some of the ligand, but reaction with more CN$^-$
liberates the phosphine ligand, providing higher yields. Extensive experimentation with the addition of CN\(^-\) resulted in a procedure that employs two separate CN\(^-\) additions. The first addition of 133 equivalents serves to liberate some of the ligand and to produce \(6r\) and the orange, square-planar \([\text{Ni(CN)}_4]^2^-\). Further addition of CN\(^-\) (150 equivalents) frees the remaining coordinated ligand from \(6r\). In addition, the higher cyanide ion concentration favors the formation of \([\text{Ni(CN)}_5]^3^-\), as evidenced by the solution turning from orange to red. With a single addition, the purity of the product is decreased because most of the coordinated ligand is liberated directly from the bimetallic complexes \(5r\) and the small quantity of \(5m\). The formation of \(6r\) causes a higher amount of ligand to be racemic. Higher cyanide concentrations provide similar results, but the minimal amount is used because of the toxicity of cyanide.

In order for \(6r\) to efficiently further react with CN\(^-\) it must be completely dissolved. It is insoluble in H\(_2\)O but soluble in MeOH. Therefore a 2.5:1 ratio of H\(_2\)O:MeOH is employed, keeping \(6r\) in solution. A benefit provided by the formation of the trans-\(\text{Ni(CN)}_2(\text{et,ph-P4})\) intermediate is that the formation of the racemic complex is favored over the meso. A partial isomerization of meso to racemic ligand occurs during the formation of the trans-\(\text{Ni(CN)}_2(\text{et,ph-P4})\). Some meso-\(\text{Ni}_2\text{Cl}_4(\text{et,ph-P4})\) is in solution, since <100% of meso-\(\text{Ni}_2\text{Cl}_4(\text{et,ph-P4})\) is recovered during the filtration step. However, after both CN\(^-\) additions <5% meso ligand remains. The meso ligand undergoes partial isomerization to form the more thermodynamically stable \(6r\). Further evidence of this was encountered in the cyanolysis of \(5m\), which can produce racemic:meso ligand in excess of 7:3. The metal-assisted isomerization of meso- to rac-\(\text{et,ph-P4}\) is not unprecedented; the formation of \([\text{rac-RhCl}_2(\eta^4-\text{et,ph-P4})]^+\) from pure meso-\(\text{et,ph-P4}\), \([\text{Rh(nbd)}_2]^+\) and DCM was observed with no evidence of the formation of a corresponding meso complex.\(^{2,5}\) The Rh-mediated isomerization is significant in that it may lead to a facile synthesis
of the active and selective racemic bimetallic rhodium catalyst precursor. Unfortunately, the 18 e\textsuperscript{-} rhodium dichloride species is extremely unreactive and we have yet to successfully use it to provide catalyst precursor, free ligand, or any other complexes, yet demonstrated that metal-mediated isomerization of the et,ph-P\textsubscript{4} ligand is feasible.\textsuperscript{2.5,2.6}

The removal of the free et,ph-P\textsubscript{4} ligand from the H\textsubscript{2}O/MeOH solvent is achieved through extractions with benzene. Hexane can also be employed to extract the ligand, however, isolated yields are 20-30\% lower. Previous work involved hexane because the rac-Ni(CN)\textsubscript{2}(\eta\textsuperscript{2.5}-et,ph-P\textsubscript{4}), 6\textsubscript{r}, is more soluble in benzene than hexane and contaminated the benzene extractions.\textsuperscript{2.4} Because of the modification above, which included MeOH in the solvent to keep 6\textsubscript{r} dissolved, combined with a second CN\textsuperscript{-} addition to further react with the rac-Ni(CN)\textsubscript{2}(et,ph-P\textsubscript{4}), the use of benzene as the extractant no longer poses a problem.

2.2.3. Cyanolysis of meso-Ni\textsubscript{2}Cl\textsubscript{4}(et,ph-P\textsubscript{4}) to Yield meso-(et,ph-P\textsubscript{4})

The removal of the nickel from the 5\textsubscript{m} through cyanolysis has never worked consistently. Although the meso ligand is not desirable for use in hydroformylation, it may be potentially interesting or useful in other applications.\textsuperscript{2.7}

The main obstacle encountered during the cyanolysis of meso-Ni\textsubscript{2}Cl\textsubscript{4}(et,ph-P\textsubscript{4}) to produce meso-et,ph-P\textsubscript{4} is that the formation of the intermediate rac,trans-Ni(CN)\textsubscript{2}(\eta\textsuperscript{2.5}et,ph-P\textsubscript{4}), 6\textsubscript{r}, is thermodynamically favored over meso,trans-Ni(CN)\textsubscript{2}(\eta\textsuperscript{2.5}et,ph-P\textsubscript{4}), 6\textsubscript{m}. Therefore, some of the meso ligand is isomerized to racemic ligand during the cyanolysis. In order to avoid this isomerization problem, the meso-Ni\textsubscript{2}Cl\textsubscript{4}(et,ph-P\textsubscript{4}) complex, 5\textsubscript{m}, can be added dropwise with stirring to a solution of NaCN in 2:1 H\textsubscript{2}O and MeOH. This minimizes the formation of 6\textsubscript{m} where we believe the meso to rac isomerization is occurring. This pushes the reaction to form [Ni(CN)]\textsuperscript{2-}, [Ni(CN)]\textsuperscript{3-}, and mostly free meso-et,ph-P\textsubscript{4}. The saturation of the aqueous layer
with cyanide or other salt predictably aids the extraction process somewhat, providing approximately 5-10% higher yields of the *meso* et,ph-P4 ligand.

Benzene and hexane are both suitable solvents for the extraction of *meso*-et,ph-P4. The *meso*-et,ph-P4 is considerably more soluble in the aqueous layer than the *racemic* and therefore the yield of *meso* ligand after the extraction is generally lower relative to the *racemic* (45-65% for *meso*, in contrast to 75-87% for *racemic*). As previously published, free *meso* ligand is evident in $^{31}$P NMR spectra of the aqueous layer both before and after extraction. In addition, the purity of the isolated *meso* ligand is typically lower than that of the *racemic* ligand due to the *meso* to *racemic* nickel-mediated isomerization that occurs. The yield and purity is further decreased because the *racemic* ligand is more soluble in the organic extractions than the *meso* ligand. Recrystallization of the extracted *meso* ligand from hexane, however, does provide > 99% pure *meso* ligand typically in 30-60% yield.

### 2.2.4. Cyanolysis of *meso*-Ni$_2$Cl$_4$(et,ph-P4) to Yield *rac*- (et,ph-P4)

During the investigation of the cyanolysis of 5m to produce *meso*-et,ph-P4 occasionally unexpectedly high amounts of *racemic* ligand were obtained, (30-60% *racemic* ligand), even though the Ni$_2$Cl$_4$(et,ph-P4) complex was purely *meso* based on $^{31}$P NMR spectra. This surprising result further supports the partial *meso* to *racemic* isomerization as previously discussed. If the *meso* ligand is being converted to *racemic* ligand, then it would be possible to isolate the more desirable pure *racemic* ligand from *meso*-Ni$_2$Cl$_4$(et,ph-P4). In addition, this discovery may preclude the necessity of separating 5r and 5m and may eventually lead to a single cyanolysis of the unseparated bimetallic nickel complexes.

Slow addition of NaCN to *meso*-Ni$_2$Cl$_4$(et,ph-P4) in H$_2$O provides the optimal condition to form 6r. During the addition both 6m and 6r form as an orange precipitate, however, the
formation of \(6r\) is favored. Further addition of NaCN frees the ligand. During the formation of \(6r\), some ligand is isomerized. However, the highest level of purity regularly achieved was a 70:30 racemic to meso mixture, although purity as high as 4:1 has been obtained using the same procedure.\(^2,8\) The direct liberation of free meso ligand and the limited formation and subsequent cyanolysis of \(6m\) prohibits higher purity achievement.

### 2.2.5. Meso,trans-Ni(CN)\(_2\)(\(\eta\)\(^{2.5}\)et,ph-P\(_4\))

The formation of \(6r\) was discovered during the initial separation scheme.\(^2,2\) However, the meso analogue was unknown. That >70% racemic could not be obtained from pure meso nickel complex \(5m\) raised a question whether the meso analogue existed and was playing a role, or whether the meso ligand was directly released by the nickel during cyanolysis. Meso,trans-Ni(CN)\(_2\)(\(\eta\)\(^{2.5}\)et,ph-P\(_4\)), \(6m\), crystallizes out of H\(_2\)O as clear needles, as opposed to rac-Ni(CN)\(_2\)(et,ph-P\(_4\)), which crystallizes as orange crystals. The \(^{31}\)P spectrum for \(6m\) is presented in Figure 2.1 and the crystallographic information is presented in Figure 2.2 and Tables 2.1 and 2.2 for both \(6r\) and \(6m\).

Several interesting structural features are found in trans-[Ni(CN)\(_2\)(\(\eta\)\(^{2.5}\)et,ph-P\(_4\))]. The geometry about the metal center is clearly distorted from square planar toward square pyramidal with average P2-Ni-P4 and C1-Ni-C2 angles of 166° and 156°, respectively (Table 2.2). There is a weak interaction of the P1 phosphine lone pair with the empty p\(_z\) orbital of the nickel at the axial position. The average Ni-P\(_\text{ext}\) basal bond distance of 2.18 Å falls right in the range of normal Ni(II)-P bonds. The 2.395(2) and 2.345(3) Å distances (\(6r\) and \(6m\), respectively) from the nickel to the internal phosphorus atom (P1) suggests a weaker but definite bonding interaction. This longer and weaker Ni-P1 apical bond is the reason that we use the \(\eta\)\(^{2.5}\) bonding
nomenclature for the et,ph-P4 ligand to the nickel center. Weak apical interactions in Ni(II) complexes with phosphine ligands have been reported before by several groups.  

**Figure 2.1.** $^{31}$P NMR spectrum of 6m. Phosphorus assignments correspond to numbering system in ORTEP plot of 6m in Figure 2.2.

**Figure 2.2.** ORTEP plots of 6r and 6m, hydrogen atoms are omitted for clarity.
Table 2.1. Key crystallographic data for 6r and 6m.

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<th>6r•(THF)</th>
<th>6m•(H2O)</th>
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<td>100 K</td>
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<td>Kappa-CCD</td>
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<td>0.71073 (Mo)</td>
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2.3. Nickel Thiocyanate Separation Methods

2.3.1. Bimetallic Racemic and Meso Nickel Thiocyanate Complexes

As previously reported, bimetallic nickel complexes can be obtained through the reaction of mixed-et,ph-P4 with two equivalents of Ni(SCN)\(_2\) in EtOH, but the reaction was reexamined since the procedure offered low and inconsistent yield and purity. The reaction is complex enough that an entire Ph.D. dissertation was devoted to its study, yet no publishable results or consistently usable procedures resulted.\(^{2,4}\) Similar to the reaction of the ligand with NiCl\(_2\), the reaction with Ni(SCN)\(_2\) results in a separation of the racemic and the meso complexes, based on the nickel complexes’ different solubilities. The meso-Ni\(_2\)(SCN)\(_4\)(et,ph-P4) is much less soluble in EtOH than the rac-Ni\(_2\)(SCN)\(_4\)(et,ph-P4).
Table 2.2. Selected bond distances (Å) and angles (°) for 6r and 6m.

<table>
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<tr>
<th></th>
<th>6r• (THF)</th>
<th>6m• (H₂O)</th>
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<tr>
<td>Ni–P1</td>
<td>2.395(2)</td>
<td>2.348(3)</td>
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<td>Ni–P2</td>
<td>2.183(2)</td>
<td>2.195(3)</td>
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<td>Ni–P4</td>
<td>2.186(2)</td>
<td>2.170(3)</td>
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<tr>
<td>N1–C1</td>
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<tr>
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<tr>
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<td>87.54(7)</td>
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<td>155.3(5)</td>
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<td>176.0(3)</td>
<td>175.3(10)</td>
</tr>
<tr>
<td>Ni-C2-N2</td>
<td>178.7(3)</td>
<td>179.3(10)</td>
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<tr>
<td>P1–C′–P3</td>
<td>122.1(3)</td>
<td>113.4(5)</td>
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</table>

Numerous solvents and volumes were used, with EtOH providing the highest yield. After 24 hours of rapid stirring, a brown precipitate of mostly meso-Ni₂(SCN)₄(et,ph-P₄) forms and can be easily isolated by vacuum filtration. The filtrate contains the rac-Ni₂(SCN)₄(et,ph-P₄), along with other nickel-ligand complexes and decomposition products. Similar to the nickel chloride procedure, >90% yield is obtained for the meso complex, but the yield of the racemic complex cannot be accurately measured due to variable solvent incorporation. Analogous to the nickel chloride procedure, 260 mL EtOH is required per 10 g of mixed ligand for optimal separation—higher concentrations prevent any separation from occurring and lower.
concentrations predictably produce less precipitate. The formation of decomposition products that decrease the overall yield and purity prevents the nickel thiocyanate procedure from being as useful as the nickel chloride procedure.

2.3.2. Cyanolysis of rac-Ni$_2$(SCN)$_4$(et,ph-P4)

The cyanolysis of rac-Ni$_2$(SCN)$_4$(et,ph-P4) has been previously examined.$^{2,4}$ The reported procedure has proven to be inconsistent and unreliable, providing yields of 0-50% and often impure free ligand. Therefore, a detailed refinement of these procedures was investigated. The results from the nickel chloride investigation were applied to the nickel thiocyanate procedure with some success. Employing a procedure similar to that used for the cyanolysis of rac-Ni$_2$Cl$_4$(et,ph-P4), yields of 60-75% rac-et,ph-P4 are obtained, with purity ranging from 70-90%. Various permutations of the nickel chloride cyanolysis procedure were attempted but with less successful results.

The high degree of variability of the reaction and relatively low yield and purity of the final ligand are due to several factors. Unlike the nickel chloride route, the nickel thiocyanate route involves the NCS$^-$ ligand, which is considerably more reactive than the chloride. Unwanted side reactions occur with the sulfur atom. The formation of rac-et,ph-P3,P$_{int}$=S and associated nickel complexes is known to occur, and often contaminates the final free ligand. In addition, the initial separation of racemic and meso nickel complexes is fraught with unusual side reactions that are difficult to control.$^{2,4}$

2.3.3. Cyanolysis of meso-Ni$_2$(SCN)$_4$(et,ph-P4)

The cyanolysis of the meso-Ni$_2$(SCN)$_4$(et,ph-P4) complex was investigated to determine if pure racemic or pure meso-(et,ph-P4) could be obtained. Although a variety of methods were investigated, the most successful methods were adopted from the nickel chloride procedures.
The purest meso ligand achieved was 60% purity (40% yield), although after recrystallization in hexane the purity is >98% and yields are typically 30-50%. Isolated racemic ligand was typically 40-60% in diastereomeric purity and in 30-50% yield.

2.4. Introduction to Monomeric Complexes of Ni(SCN)$_2$ and Rac-et,ph-P4 Ligand

Effective separation of the racemic and meso diastereomers of the et,ph-P4 ligand has been a somewhat elusive goal. As previously discussed, several methods have been explored, with mostly unsatisfactory results, including separation through recrystallization of the mixed ligand, and through the use of Ni(II) compounds such as Ni(SCN)$_2$ and NiCl$_2$. Although the NiCl$_2$ method provides the most pure and most consistent yields of the separated ligand, interesting aspects of the reaction with Ni(SCN)$_2$ were reexamined.

The separation of the et,ph-P4 ligand through the use of Ni(SCN)$_2$ was investigated with both one equivalent and two equivalents of Ni(SCN)$_2$. With the use of one equivalent, a monomeric complex with the ligand is formed, whereas with two equivalents, a bimetallic complex forms. The reaction of one equivalent of Ni(SCN)$_2$ with meso ligand consistently yields the monometallic meso-Ni(SCN)(η$_3$-et,ph-P3), (Figure 2.3).

![Figure 2.3. The monometallic meso nickel thiocyanate complex.](image)

Although the use of the bimetallic complex is more successful in the separation of the diastereomers of the ligand, the use of one equivalent of racemic ligand provided some highly unusual results, including the surprising selective formation of P=S and P=O bonds on one of the internal phosphorus atoms of the ligand. The complexes rac-[Ni(SCN)(η$_3$-et,ph-P3,
P_{int=S})[NCS], 7, and rac-[Ni(SCN)(\eta^3\,-\text{et-P3}, P_{int}=O)][NCS], 8, were formed. In addition, previous results indicate that Ni_2(SCN)_2(\mu,SCH_3)(\text{et-P4})^+, 9, is formed. Figure 2.4 indicates the structures of these complexes.

Figure 2.4. Structural drawings of complexes 7, 8, and 9.

In order to understand the formation of 7, 8, and 9, consistently reproducible syntheses of the complexes were necessary. The original procedure, which was intended for use for the separation of diastereomers, provided a starting point by which to begin the investigation. Although the original procedure does produce the desired complexes 7, 8, and 9, it was neither carefully investigated nor optimized for their production since they are undesirable in the separation of the diastereomers.

Optimization of the procedure was obtained through the use of a slight excess of rac-et,ph-P4 ligand. Without a slight (5-10%) excess of the ligand, the majority of the ligand is consumed forming the bimetallic rac-Ni_2(SCN)_4(et,ph-P4) complex. This complex is relatively stable and without the presence of other coordinating ligands, will not react further, and therefore it is not useful in the investigation of 7, 8, and 9. Slight excess of ligand helps ensures that all of the Ni(SCN)_2 will be consumed with minimal formation of the bimetallic complexes. Optimization also included that the nickel thiocyanate solution be added dropwise to the stirred et,ph-P4 solution, as opposed to the previous procedure. This promotes monomeric complexes over bimetallic complexes, due to the low concentration of Ni(SCN)_2 in solution.
In order that the desired complexes form, the solution must be allowed to stir for a minimum of 3-5 days. Prior to that, $^{31}$P NMR spectra reveal two very broad doublets at 55.9 and 49.5 ppm, respectively, and free ligand at -19.3, -26.1, and -27.3 ppm, as previously reported.$^{2,4}$

The broad peaks’ disappearance coincides with the formation of new species, proposed complexes 7, 8, and 9. The $^{31}$P NMR spectrum indicates no free ligand, as shown in Figure 2.5. The $^{31}$P NMR spectrum of the solution after 3-5 days indicates the presence of at least 4 main species. Three of the complexes are Ni$_2$(SCN)$_4$(et,ph-P4), 7, 8, and a fourth may be 9, although the assignment of 9 is tentative since it had not previously been spectroscopically characterized (although a crystal structure determination was done).$^{2,4}$ The formation of these compounds is almost completely unexpected.

We suspected that the EtOH solvent played a major role in the formation of these unusual complexes, so different solvents were employed. If the oxygen atom in the P=O is coming from EtOH, it would likely not be observed when using other solvents such as MeOH or THF. Both of these solvents were used, and, as expected, complexes 7, 8, and 9 were not formed, even after
30 days of reaction. However, upon addition of several drops of EtOH to the experiment conducted in MeOH, within 24 hours of stirring complexes 7 and 8 had formed, as evidenced by $^{31}$P NMR. This confirms that EtOH is required for the reactions. After 3 days the spectrum did not change, which is likely due to the EtOH being the limiting reagent of the reaction.

While it appeared that EtOH was a reactant, it was also possible that H$_2$O or dissolved O$_2$ were playing a role. The EtOH used for the experiments was anhydrous, exposed to molecular sieves, and subjected to freeze/thaw cycles and N$_2$ bubbling to attempt to eliminate these potential factors. In addition, experiments in EtOH with added H$_2$O were performed, and the results indicate that the water has no effect, or possibly a slightly slowing effect, on the formation of the complexes. With 0.5 mL water added to a 2 mL EtOH solution, the length of time required to produce the complexes 7, 8, and 9 increased to 7 days. The slowing of the reaction to form the complexes when H$_2$O is present is not very surprising since the EtOH concentration is effectively lowered. The fact that water is a non-factor was also confirmed by the addition of H$_2$O to the experiment performed in MeOH which had no effect as the complexes were not formed, whereas the addition of anhydrous, degassed EtOH did cause the formation of the complexes.

The formation of 9 is still under investigation. The original crystal structure indicated a bridging SCH$_3$.$^{2,4}$ The origin of the CH$_3$ group is unknown. A possible explanation is that it is actually a SCH$_2$CH$_3$ group, and that there is a severe disorder of the terminal methyl group in the crystal. If it is a SCH$_2$CH$_3$ group, it is probably a result of a nickel-assisted sulfur-transfer reaction with the EtOH solvent. It may also be possible that the SCN$^-$ group was reduced to SCH$_3$ and NH$_3$, but that seems unlikely since there are no good reducing agents present. Without more data, the definitive structure of this complex will not be known.
In order to more closely examine the structures and to help elucidate from where the atoms were coming, the reaction was performed in $^{13}\text{C}$-labeled EtOH in order to use $^{13}\text{C}$ NMR spectroscopy. Although the exact procedure was used that produces the complexes in standard EtOH, unfortunately, none of the complexes were produced even after 30 days of reaction. The experiments were repeated with three different batches of $^{13}\text{C}$-labeled EtOH from two different vendors. In addition, even after the addition of non-labeled EtOH, the complexes were not produced. The most likely explanation is that an inhibitor is present in the $^{13}\text{C}$-labeled EtOH, although GC/MS spectroscopy revealed no unexpected species. Although a small amount of water is present in the labeled EtOH, and, as previously discussed with regard to the non-labeled EtOH, water does not stop the reaction but only slows it. GC/MS as well as $^1\text{H}$ and $^{13}\text{C}$ NMR spectroscopy revealed no other species, so extremely low concentrations must be able to produce the inhibitory effect, if they are indeed the culprit. Another possibility raised by these experiments is that an impurity in the non-labeled EtOH causes the reaction. However, GC/MS nor $^1\text{H}$ NMR spectroscopy revealed another species, although there may indeed be one in very low concentrations. This seems unlikely, however, as differing purities of standard EtOH from differing vendors were used, and all were able to produce the complexes under investigation.

Formation of $\text{rac-}[\text{Ni(SCN)}(\eta^3\text{-et,ph-P3, P}_{\text{m}}=\text{S})]$ indicates that sulfur is being transferred from the thiocyanate group to the phosphorus. There are no probable sources of sulfur other than the thiocyanate group. The sulfur transfer does not occur with the bimetallic $\text{rac-Ni}_2(\text{et,ph-P4})(\text{SCN})_4$, nor does it occur with the monomeric or bimetallic $\text{meso-et,ph-P4}$ ligand complexes. In addition, it does not occur in solution lacking Ni(SCN)$_2$, and seems to require EtOH. The lone pair on the phosphorus atom P3 of the $\text{racemic}$ ligand must interact with the nickel center in
some way in the presence of EtOH to facilitate the transfer of the sulfur atom from the thiocyanate to the phosphine, as indicated by the dotted line in Figure 2.6.

![Figure 2.6. Potential lone pair interaction.](image)

The formation of the P=S bond indicates that cyanide is liberated, however, there is no evidence of cyanide-containing nickel-phosphine complexes. If cyanide was liberated one might expect species such as rac-Ni(CN)₂(et,ph-P₄) to form, but ³¹P NMR spectra do not show such complexes. Possible explanations include that concentrations of cyanide are so low that little rac,trans-Ni(CN)₂(η²⁻⁵et,ph-P₄), 6r, forms. In addition, it is possible that the cyanide could displace the entire phosphine ligand, producing [Ni(CN)₄]²⁻ and free et,ph-P₄, however, ³¹P NMR spectra do not indicate free ligand. Another possibility is that HCN is evolved and lost from solution. Another plausible explanation which is supported by ³¹P NMR spectroscopy is that some of the unidentified, low-intensity, very broad peaks may be lower-symmetry oligomeric nickel-phosphine complexes containing one or more cyanide moieties.

The oxygen atom in rac-[Ni(SCN)(η³⁻et,ph-P₃, P₃⁻=O)], 8, is probably derived from the EtOH solvent and the ethyl group becomes part of the bridging SCH₂CH₃ of 9, assuming, of course that the bridging -SR group is actually -SCH₂CH₃, (which preliminary crystallography has indicated is –SCH₃). Until more crystals or spectroscopic evidence can obtained, this will be difficult to prove.

The ratio of the quantities of 7, 8, and 9 as well as their rates of growth should offer information concerning what reactions are occurring to produce them. Both complexes 7 and 9
are produced after several days of reaction but do not continue to be produced. Complex 8 is produced after 7 and 9, and its quantity continues to slowly increase for 2 weeks. This indicates that complexes 8 and 9 may not be produced together from the decomposition of EtOH. No other constant ratio or highly correlated trends have been observed for the complexes, indicating that the production of these complexes may not be correlated. Highly complex chemistry is occurring that may warrant further investigation.

2.5. Conclusions

The separation of the diastereomers of mixed-(et,ph-P4) should be performed using the new nickel chloride procedure. The procedure avoids the complications of the nickel thiocyanate route and produces consistently higher yields. The new procedures rely on the knowledge of the formation and properties of the intermediate species 6r and 6m. In addition, the partial isomerization, mediated by intermediate nickel complexes, of the meso- to rac-et,ph-P4 provides a viable route by which to ultimately obtain even higher than 50% yield pure racemic ligand from the synthesis of mixed-et,ph-P4.

2.6. References


CHAPTER 3: THE UNUSUAL EFFECT OF PPH₃ ON A DIRHODIUM HYDROFORMYLATION CATALYST

3.1. Introduction

Stanley’s bimetallic [\(\text{rac-Rh}_2(\text{nbd})_2(\text{et,ph-P4})\)](\(\text{BF}_4\))₂ is the catalyst precursor to a highly selective and active bimetallic hydroformylation catalyst for 1-alkenes. Studies have indicated that the active catalyst, generated \textit{in situ} (90°C, 6.1 bar \(\text{H}_2/\text{CO}\)), exhibits bimetallic cooperativity.\(^1\) That bimetallic cooperativity occurs is strongly supported by the high linear to branched ratios of the aldehyde products for the catalyst (27:1 for 1-hexene), whereas monometallic analogs using \(\text{R}_2\text{PCH}_2\text{CH}_2\text{PR}_2\) ligands provide low selectivity of 3:1, as well as low activity (one turnover per hour) and high side reactions (70% isomerization and hydrogenation).\(^2\)

Although other bimetallic hydroformylation catalysts have been proposed, such as Heck’s cobalt catalyst system,\(^3\) there are no other catalysts known to operate via bimetallic cooperativity. Interestingly, Kalck reported an active thiolate-bridged dirhodium catalyst, \(\text{Rh}_2(\mu-\text{SR})_2(\text{CO})_4\), that was proposed to operate via bimetallic cooperativity.\(^4\) However, the system was unusual as it had little or no activity until \(\text{PPh}_3\) is added and then its activity and selectivity was almost identical to the classic and well-understood Rh/PPh₃ catalyst system. It was subsequently shown that the thiolate-bridged complex readily fragments and that the \(\text{PPh}_3\) is necessary to produce the active catalyst, which is indeed the ubiquitous \(\text{RhH(CO)(PPh}_3\))₂ monometallic catalyst.\(^5\)\(^6\)

What would the effect of the \(\text{PPh}_3\) ligand be on a completely different system, such as Stanley’s bimetallic catalyst system, which has already been shown to operate differently than the monometallic Rh/PPh₃ system (or Kalck’s supposed bimetallic system)? Generally, in monometallic rhodium-based PPh₃ systems, increasing the concentration of \(\text{PPh}_3\) lowers the rate
but increases the selectivity. An investigation into the effect of PPh$_3$ on Stanley’s bimetallic rhodium hydroformylation catalyst could serve to provide information that could be used to improve upon the already impressive hydroformylation capabilities of the catalyst, offer new mechanistic information about how the catalyst functions, or provide new insights into possible methods of catalyst deactivation. Previous exploratory work indicated that PPh$_3$ may enhance the rate of hydroformylation.$^{3,7}$

Surprisingly, the addition of even small amounts of PPh$_3$ causes a dramatic drop in rate and selectivity. Although not of particular interest to the world of hydroformylation catalysis, studies using PPh$_3$ with the bimetallic catalyst do provide additional mechanistic and fragmentation information about the bimetallic system. This information further supports the accepted proposed bimetallic mechanism, provides details with respect to decomposition routes, aids in experimental troubleshooting, and may ultimately lead to the design of an even more robust bimetallic system.

3.2. Hydroformylation Results

Hydroformylation runs were performed under the relatively mild standard conditions (90°C, 6.1 bar H$_2$/CO, 1mM catalyst, 1000 equiv. alkene) with the bimetallic hydroformylation catalyst precursor, [rac-Rh$_2$(nbd)$_2$(et,ph-P4)](BF$_4$)$_2$, the monometallic precursor Rh(acac)(CO)$_2$, and cationic [Rh(nbd)$_2$](BF$_4$)$_2$, with varying amounts of PPh$_3$ and PEt$_3$ present. The results are presented in Table 3.1.

Interestingly, the addition of 2 equivalents of PPh$_3$ to the bimetallic catalyst causes a dramatic drop in the L:B aldehyde regioselectivity from 24.9 to 3.1 and a reduction by 51% in the initial TOF to 590/hr. Increasing amounts of PPh$_3$ lead to steadily decreasing catalytic rates
until 100 equivalents, at which virtually no hydroformylation is observed. This is in stark contrast to the results observed for Kalck’s bimetallic Rh$_2$(μ-SR)$_2$(CO)$_4$ system that is inactive.

Table 3.1. Hydroformylation of 1-hexene in acetone.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Equiv. PPh$_3$</th>
<th>Equiv. PEt$_3$</th>
<th>Initial TOF$^b$ (hr$^{-1}$)</th>
<th>Aldehyde L:B Selectivity</th>
<th>% Alkene Isomer$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimetallic</td>
<td>0</td>
<td>0</td>
<td>1200</td>
<td>25</td>
<td>2.5</td>
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<td>Bimetallic</td>
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<td>0</td>
<td>590</td>
<td>3.1</td>
<td>5.0</td>
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<td>10</td>
<td>0</td>
<td>220</td>
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<td>100</td>
<td>0</td>
<td>0</td>
<td>--</td>
<td>0</td>
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<td>--</td>
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<td>1.1</td>
<td>3100</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
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<td>100</td>
<td>1.1</td>
<td>780</td>
<td>4.9</td>
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<tr>
<td>Mono</td>
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<td>2.2</td>
<td>2000</td>
<td>3.0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Mono</td>
<td>100</td>
<td>2.2</td>
<td>450</td>
<td>3.6</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Mono(+)$^d$</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>1.6</td>
<td>80</td>
</tr>
<tr>
<td>Mono(+)$^d$</td>
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<td>0</td>
<td>300</td>
<td>4.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Mono(+)$^d$</td>
<td>10</td>
<td>2.2</td>
<td>180</td>
<td>3.3</td>
<td>1.7</td>
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<td>Mono(+)$^d$</td>
<td>100</td>
<td>2.2</td>
<td>180</td>
<td>3.1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

$^a$ equivalents of PPh$_3$ or PEt$_3$ added relative to the amount of rhodium catalyst precursor  
$^b$ TOF = turnover frequency; an average of at least three consistent runs; approximately a 5% error on the rates, which have been rounded off to reflect this.  
$^c$ isomerization  
$^d$ cationic precursor [Rh(nbd)$_2$](BF$_4$) (nbd = norbornadiene)

until the addition of PPh$_3$, and then the rate and selectivity increase with increasing amounts of added PPh$_3$ up to a point analogous to the monometallic Rh/PPh$_3$ catalyst system. Van Leeuwen
and Claver have demonstrated that Kalek’s bimetallic system readily fragments and reacts with PPh\textsubscript{3} to generate the classic monometallic HRh(CO)\textsubscript{x}(PPh\textsubscript{3})\textsubscript{y} (x = 1-2; y = 3 – x) catalyst.\textsuperscript{3,6}

Surprisingly, even the addition of only 0.5 equivalents of PPh\textsubscript{3} causes a dramatic drop in the regioselectivity and catalyst activity as shown in Table 3.1. The steady deactivation and essentially constant low regioselectivity of our bimetallic system with increasing amounts of PPh\textsubscript{3} is not consistent with simple fragmentation to a monometallic Wilkinson-like catalyst system. This is illustrated by the parallel runs with the monometallic precursor Rh(acac)(CO)\textsubscript{2} and PPh\textsubscript{3} (Table 3.1). At low PPh\textsubscript{3} ratios an extremely active, but short-lived, catalyst with relatively low selectivity is generated. At 100 equivalents of PPh\textsubscript{3} the catalyst starts to slow down and the aldehyde L:B regioselectivity starts to increase. At 400 equivalents (0.4 M) of PPh\textsubscript{3} the catalyst initial TOF has deceased to 700/hr, but the L:B regioselectivity has increased to 9.1. Incidentally, commercial Rh/PPh\textsubscript{3} hydroformylation processes are typically run with 0.4 M PPh\textsubscript{3} up to 50% PPh\textsubscript{3} by solution weight when the highest L:B aldehyde regioselectivities are needed.\textsuperscript{3,3}

3.3. Implications of the Results Observed upon Addition of PPh\textsubscript{3}

The L:B aldehyde regioselectivity data strongly indicates that the addition of even small amounts of PPh\textsubscript{3} strongly inhibits the highly regioselective bimetallic catalyst and generates an alternate catalyst with far lower regioselectivity. The rate and regioselectivity data, however, indicate that this alternate catalyst is not HRh(CO)\textsubscript{4}, HRh(CO)\textsubscript{2}(PPh\textsubscript{3}), or HRh(CO)(PPh\textsubscript{3})\textsubscript{2}. Even assuming that fragmentation is generating very low concentrations of a monometallic rhodium carbonyl complex that could be intercepted by PPh\textsubscript{3}, the rate and regioselectivity should increase as the PPh\textsubscript{3} concentration increases within the range studied. Instead, the bimetallic
catalytic run with 100 equivalents of PPh$_3$ is essentially inactive for hydroformylation catalysis, which is completely inconsistent with Rh/PPh$_3$-type catalysts.

The mechanism of the bimetallic catalysis was examined to determine how the PPh$_3$ affects the catalytic cycle. The proposed bimetallic hydroformylation catalytic cycle is shown in Scheme 1.5 (see Chapter 1) and presented again here for further discussion as Scheme 3.1.

**Scheme 3.1.** Proposed bimetallic dicationic hydroformylation mechanism, Et and Ph groups of the et,ph-P4 ligand omitted for clarity.

The *in situ* NMR studies indicate that the resting state of the catalyst appears to be the open-mode dicationic carbonyl complex $[rac$-$Rh_2(CO)_5$(et,ph-P4)]$^{2+}$, 3r, which has been crystallographically characterized. There is a very facile CO-based on-off equilibrium between the tetracarbonyl, pentacarbonyl 3r, and the transient hexacarbonyl bimetallic
complexes. The localized cationic charge on each rhodium atom compensates for the strongly electron-donating nature of the et,ph-P4 ligand reducing the CO π-backbonding and enabling CO dissociation. Oxidative addition of H₂ to one of the Rh centers generates the dihydride complex A. This can readily rotate to form the bridged complex B, which can rearrange to form the symmetric Rh(II) terminal dihydride complex 2r. Alkene coordination to form C is followed by a migratory insertion of the alkene into the Rh-H bond, generating the alkyl complex D. CO coordination is followed by migratory insertion into the Rh-alkyl bond to produce the acyl complex E. This can then perform a bimetallic reductive elimination of the aldehyde to form the bridging carbonyl Rh(I) complex 4r, that can break open to form 3r or directly react with H₂ to lead to the active catalyst, the hydride complex 2r.

One obvious effect of added PPh₃ on this catalytic cycle would be to simply block the axial coordination site provided by CO dissociation and thus prevent formation of the alkene complex C. However, this should simply slow down the catalyst (the axial sites are quite labile) and not affect the regioselectivity. Aside from binding-site blocking effects, PPh₃ should not have great impact on most of the other steps of this bimetallic catalytic cycle. The high regioselectivity of the bimetallic catalyst is believed to arise from the Rh-Rh bond, bridging carbonyls, and Rh(II) oxidation state. These work together to create an extremely well-defined binding site that does not electronically reorganize or distort upon coordination of the alkene to the empty axial coordination site maximizing the steric directing effects of the relatively small ethyl and phenyl groups, thus providing high regioselectivity. This is quite unlike square-planar Rh(I) monometallic catalysts that electronically distort upon coordination of the alkene to form a 5-coordinate geometry, which is illustrated in Scheme 3.2. The electronic distortion of a square-planar complex to a 5-coordinate structure causes the sterically directing
R-groups on the phosphine ligands to be moved further away from the alkene. This minimizes the phosphine ligands steric orienting effects for the subsequent hydride-alkene migratory insertion that is the regioselectivity-determining step, thus lowering regioselectivity.

Scheme 3.2. Distortion of monometallic catalysts and lack thereof for the bimetallic catalyst.

In addition to the inhibitory effect of PPh$_3$, our catalytic data suggests that PPh$_3$ causes a decomposition of the bimetallic catalyst into another structure that has low regioselectivity and moderate activity, but one that is eventually completely inhibited by increasing amounts of PPh$_3$. The most likely entry point for disrupting the formation of the Rh-Rh bonded complex 2r involves the starting carbonyl complex 3r. PPh$_3$ coordination could easily disrupt the rotation to the closed-mode complex B after oxidative addition of H$_2$. Molecular modeling studies indicate that this open- to closed-mode rotation is strongly influenced by steric effects. For example, the simple tetracarbonyl [rac-Rh$_2$(CO)$_6$(et,ph-P$_4$)]$^{2+}$ (or pentacarbonyl 3r) shows no sign of rotation into a bridged-carbonyl structure such as 4r* (Scheme 3.1) in the presence of CO. Only when H$_2$ is added do we observe rhodium complexes with bridging carbonyls. Indeed the activity of the catalyst appears to directly coincide with the presence and intensity of the bridging carbonyl
bands in the IR spectrum. The modeling studies clearly demonstrate that it is much easier for the bimetallic complex to rotate into a closed-mode structure when there are two comparatively small hydride ligands present on the one rhodium center instead of larger carbonyls. If a PPh$_3$ ligand were present on one or both of the Rh centers it could easily sterically block the complex from forming a closed-mode Rh-Rh bonded structure, as discussed previously, that facilitates high catalyst activity and regioselectivity.

The coordination of PPh$_3$ is proposed to break the bimetallic catalyst chelate structure to form, in essence, a monometallic catalyst center with one PEt$_3$-like alkylated phosphine and a PPh$_3$, 10. Further phosphine addition would produce a saturated center resembling HRhPEt$_3$CO(PPh$_3$)$_2$, 11. The monometallic center should catalytically resemble the monometallic Rh/PPh$_3$ system. The coordination and subsequent opening is shown in Scheme 3.3 for one half of 3r, although it could occur at both Rh centers.

![Scheme 3.3](image)

**Scheme 3.3.** The creation of an effectively monometallic catalyst.

A key feature is that one also has to have loss of a proton in order to generate a neutral mono-hydride complex. Cationic monometallic precursors like [Rh(nbd)$_2$]$^+$, as shown in Table 3.1, typically generate poor hydroformylation catalysts unless one can deprotonate the resulting
saturated cationic Rh(III) dihydrides such as [RhH$_2$(CO)$_2$(PPh$_3$)$_2$]$^+$ produced from the oxidative addition of H$_2$.$^{3,9}$ PPh$_3$ is barely basic enough to accomplish this, with 10 equivalents producing a catalyst that only marginally performs hydroformylation, instead producing alkene isomerization. The addition of 90 more equivalents of PPh$_3$, however, does shift the deprotonation equilibrium enough to give modest hydroformylation activity and dramatically reduced alkene isomerization side reactions (Table 3.1).

The bimetallic catalyst avoids this “trap” by performing an intramolecular hydride transfer from complex A in Scheme 3.1 to ultimately form the symmetrical bimetallic dihydride complex 2r- this is one of the key bimetallic cooperativity steps. While PPh$_3$ can deprotonate [RhH$_2$(CO)$_2$(PPh$_3$)$_2$]$^+$ when present in high enough concentrations, it is likely not effective in deprotonating the less acidic cationic dihydride precursor that leads to 7 due to the more strongly donating et,ph-P4 ligand. The considerably more basic et,ph-P4 ligand may, however, well be able to act as a suitable base for this deprotonation. Indeed, the internal free phosphine in 7 is well situated to act as an intramolecular deprotonating agent, although not drawn as such in Scheme 3.3.

These mechanistic proposals have been tested by the addition of 1.1 and 2.2 eq. of PEt$_3$ to the neutral and cationic monometallic precursor catalytic reactions (Table 3.1). In the case of Rh(CO)$_2$(acac), the addition of PEt$_3$ causes a dramatic drop in activity and a small change in regioselectivity. For example, the initial TOF with 100 equivalents PPh$_3$ drops from 6300 to 450 when 2.2 equivalents of PEt$_3$ are added, while the selectivity dropped from 5.0 to 3.6. The deprotonating ability of 2.2 equivalents of PEt$_3$ (one to deprotonate, one to coordinate to the Rh, presumably) was tested on the cationic [Rh(nbd)$_2$]$^+$ precursor system. The rate increased (with 10 equivalents of PPh$_3$ present) from 2 to 180. Comparing this to the 10 equivalents of PPh$_3$ and
1.1 equivalents of PEt$_3$ Rh(CO)$_2$(acac) experiment that has an initial rate of 3100 clearly demonstrates that the PEt$_3$ is only partially deprotonating the cationic rhodium complex and that there is an equilibrium between the cationic and neutral catalyst species.

The experiments with PEt$_3$ offer, at minimum, quite reasonable support for the proposed formation of an inefficient monometallic-like catalyst from the bimetallic catalyst similar to 7 in the presence of PPh$_3$. The essentially complete catalytic inhibition upon addition of 100 equivalents of PPh$_3$ is consistent with the coordination of a second or third PPh$_3$ to generate a 4- or 5-coordinate sterically hindered monometallic-like catalyst like 10, which should indeed be inactive for hydroformylation. The inability of the PEt$_3$ model system to mimic the zero activity with 100 eq. of PPh$_3$ is reasonable given that PEt$_3$ is certainly not the same as an $\eta^1$-et,ph-P4 ligand that has a cationic Rh(CO)$_3$ (or another variant) coordinated to the other side, as proposed for 10 and 11. The dramatic regioselectivity-lowering effect of even 0.5 equivalents of added PPh$_3$ to the bimetallic catalyst must point to the extremely efficient inhibition of the active and selective catalyst, which is indeed present in relatively small concentrations compared to the total amount of catalyst precursor used.

### 3.4. Catalysis Troubleshooting Using Information from PPh$_3$ Experiments

Subsequent to the majority of the experiments using PPh$_3$, catalysis experiments using the bimetallic catalyst were providing results inconsistently and at odds with those previously expected, obtained, and published. Often the bimetallic catalyst (which $^{31}$P NMR spectroscopy indicated >99% purity) surprisingly yielded 0 turnovers per minute. Relatively extensive troubleshooting was rigorously pursued to determine the source of the inconsistency. Process of elimination indicated that the inconsistencies were unrelated to any common or obvious problem including solvent impurities, decomposed catalyst precursor, incorrect syn gas
mixture, syn gas impurities, malfunctioning equipment, or improper experimental procedural execution. The reaction vessel and alkene injection reservoir were contaminated with PPh₃. Yellow (rhodium-containing) acetone washings from the reservoir were indicated by ³¹P NMR spectroscopy to indeed contain free PPh₃. The presence of the PPh₃ provided an easy explanation for the lower rates; enough PPh₃ was present to interfere with the bimetallic catalyst, and subsequent washings and experiments decreased the quantity of PPh₃ present. Over time, the rates increased as more and more PPh₃ was removed, further indicating that even trace amounts of PPh₃ partially deactivate the bimetallic catalyst. Due to this, special protocols are now in place to prevent cross-contamination of any of the catalysis equipment by the PPh₃ ligand.

3.5. Conclusion

There is no reason to add PPh₃ to Stanley’s bimetallic hydroformylation catalyst. Even small amounts of PPh₃ disrupt the highly active and regioselective bimetallic catalyst though a combination of blocking effects that includes coordination to the bimetallic binding site and inhibition of the formation of the closed-mode catalyst. PPh₃ is proposed to disrupt the bimetallic catalyst to generate what is effectively a very poor monometallic catalyst that involves the electron-rich alkylated PEt₃-like arm of the et,ph-P₄ ligand and one or more coordinated PPh₃ ligands. The electron-rich et,ph-P₄ ligand is also proposed to help deprotonate the cationic monometallic center to generate an active neutral mono-hydride HRh(CO)(η¹-et,ph-P₄)(PPh₃) species, which is moderately active for hydroformylation, but provides poor regioselectivity. Continued addition of PPh₃ rapidly leads to catalyst deactivation by forming the tris-phosphine complex HRh(CO)(η¹-et,ph-P₄)(PPh₃)₂. The bimetallic catalyst is so sensitive to the deactivation by PPh₃ that special procedures have been introduced to prevent cross-
contamination. In situ NMR and FT-IR studies are planned to further probe the validity of these proposals.

3.6. References


(b) Kalck, P. Polyhedron. 1988, 7, 2441.


CHAPTER 4: POLAR PHASE HYDROFORMYLATION: THE DRAMATIC EFFECT OF WATER ON A DIRHODIUM CATALYST

4.1. Introduction

A persistent challenge in the use of homogeneous catalysis is the removal of the aldehyde products from the catalyst solution. While homogeneous catalysis offers an efficiency advantage with regard to the interaction of the catalyst with the substrate, heterogeneous systems are already phase-separated: the aldehyde products are liquid and the catalyst is fixed to a solid support. Research into the development of facile separation methods involves investigating different reaction solvent systems and modified catalysts. Some research of note includes aqueous-phase catalysis using water-soluble tris-sulfonated triphenylphosphine (TPPTS), \(^{4,1}\) supported aqueous-phase variants, \(^{4,2}\) fluorocarbon solvents and fluorocarbon soluble rhodium catalysts, \(^{4,3}\) catalysis in liquid or supercritical \(\text{CO}_2\), \(^{4,4}\) and the use of ionic liquids. \(^{4,5}\) The water soluble Rh/TPPTS catalyst system is used commercially by Celanese (originally developed by Rhurchemie using the TPPTS ligand from Rohn Poulanc) to hydroformylate propylene to butylaldehyde, which does phase separate from the aqueous solvent. But this system is severely limited by the lack of solubility of longer chain alkenes into the water. 1-Butene is the longest alkene that shows appreciable solubility and activity for hydroformylation in water using the Rh/TPPTS catalyst. Industry would very much like to combine product phase separation along with use of longer chain alkenes like 1-hexene to 1-dodecene for hydroformylation. The other technologies mentioned like fluorous phase catalysis, supercritical \(\text{CO}_2\), and ionic liquids all suffer from low reaction rate, low product linear to branched (L:B) regioselectivities, catalyst-solvent fragmentation reactions, or various combinations of these problems.

The novel \([\text{rac-Rh}_2\text{H}_2(\mu-\text{CO})(\text{et,ph-P4})](\text{BF}_4)_2\) catalyst developed in our group is no different from the vast majority of homogeneous systems in that separation of the product from
the reaction solution is a major problem. The dicationic dirhodium catalyst works best in polar solvents such as acetone or DMF. Acetone is the solvent used most regularly because of its polarity, low cost, and low health hazards. Medium-chain alkene substrates, such as 1-hexene, are miscible in acetone, as are the aldehyde products. Increasing the polarity of the acetone solvent through the addition of water, for example, would hopefully cause phase separation of the non-polar aldehyde products from the more polar catalyst water-acetone solution. Thus the addition of water to the acetone solvent could potentially provide a very simple solution to the much-sought phase separation of the aldehyde products from the catalyst solution.

In order to probe the feasibility of increasing the polarity of the solvent in order to phase-separate the non-polar products, Dr. Novella Bridges conducted some exploratory experiments with a mixed solvent system of acetone and water. She demonstrated that the polar phase solvent system was a feasible system as it increased the rate of hydroformylation and fortuitously led to the accidental production of carboxylic acid (see Chapter 5).

4.2. Polar Phase Experiments

In order to optimize the amount of water (and thus the polarity of the catalyst solution), experiments were conducted with varying amounts of water to determine what quantity would provide the best rate, selectivities, and separation of the product aldehyde. The catalytic data for the hydroformylation of 1-hexene and 1-octene in acetone or DMF with the addition of water is shown in Table 4.1.

4.3. Discussion of Results and Comparison to Monometallic Phosphine-based Rhodium Hydroformylation Catalysts

Thirty percent water in acetone gave the fastest rate (73 min⁻¹), and highest selectivity, (33:1 linear:branched [L:B] aldehyde ratio), and virtually no alkene isomerization and hydrogenation side reactions. This is in marked contrast to the runs in pure acetone that give an
initial TOF of only 20 min, 25:1 L:B aldehyde regioselectivity, 2.5% alkene isomerization, and 3.4% alkene hydrogenation.

**Table 4.1.** Hydroformylation data for 1-hexene and 1-octene.

<table>
<thead>
<tr>
<th>Alkene (1 M)</th>
<th>Solvent</th>
<th>% H₂Oa</th>
<th>TOF (min⁻¹)b</th>
<th>L:Bd</th>
<th>% isoede</th>
<th>% hydrof</th>
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<tbody>
<tr>
<td>1-hexene</td>
<td>acetone</td>
<td>0</td>
<td>20(1)</td>
<td>25:1</td>
<td>2.5</td>
<td>3.4</td>
</tr>
<tr>
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<td>acetone</td>
<td>10</td>
<td>23(1)</td>
<td>30:1</td>
<td>1.5</td>
<td>&lt;1</td>
</tr>
<tr>
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<td>acetone</td>
<td>20</td>
<td>48(0)</td>
<td>26:1</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene</td>
<td>acetone</td>
<td>30</td>
<td>73(1)</td>
<td>33:1</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene</td>
<td>acetone</td>
<td>40</td>
<td>48(1)</td>
<td>32:1</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene</td>
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<td>2.3</td>
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</tr>
<tr>
<td>1-hexene</td>
<td>acetone</td>
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<td>5.0(4)</td>
<td>--</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene</td>
<td>acetone</td>
<td>100</td>
<td>0</td>
<td>--</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene (2M)</td>
<td>acetone</td>
<td>0</td>
<td>30</td>
<td>26:1</td>
<td>2.0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>1-hexene (2M)</td>
<td>acetone</td>
<td>30</td>
<td>106(10)</td>
<td>31:1</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene</td>
<td>DMF</td>
<td>0</td>
<td>12(1)</td>
<td>22:1</td>
<td>2.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-hexene</td>
<td>DMF</td>
<td>30</td>
<td>18(1)</td>
<td>25:1</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-octene</td>
<td>acetone</td>
<td>0</td>
<td>11(1)</td>
<td>26:1</td>
<td>11</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-octene</td>
<td>acetone</td>
<td>30</td>
<td>13(0)</td>
<td>28:1</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-octene</td>
<td>DMF</td>
<td>0</td>
<td>8.3(1)</td>
<td>29:1</td>
<td>1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>1-octene</td>
<td>DMF</td>
<td>30</td>
<td>10(1)</td>
<td>28:1</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

---

*a* 90°C, 90 psig 1:1 H₂/CO (constant pressure), 1 mM catalyst, 1 M alkene, 1000 rpm, [rac-Rh₂(nbd)₂(et,ph-P4)][BF₄]₂ (nbd = norbornadiene) as the catalyst precursor, number in parenthesis is the standard deviation in the last significant figure (from at least 3 consistent catalytic runs)  
b volume %  
c initial turnover frequency (min⁻¹), numbers in parentheses represent the standard deviation of the last digit or digits  
d aldehyde product linear to branched ratio  
e % alkene isomerization  
f % alkene hydrogenation
The temperature and pressure conditions for this reaction are not yet optimized and the current 90º C and 90 psig (6.2 bar) of 1:1 H₂/CO represents rather mild conditions for rhodium-catalyzed hydroformylation.

The poorer hydroformylation that results as the water content is increased past 30% is likely caused by the decreasing solubility of the alkenes in the polar acetone/water solvent system. Pure water is a very poor solvent for the bimetallic catalyst with 1-hexene due to the very low solubility of 1-hexene in water. This insolubility of non-polar substrates is a major limitation of the current water-soluble Rh/TPPTS catalyst as only smaller chain alkenes like propylene that have reasonable solubilities in water can be used.

The combination of extremely high rate, excellent regioselectivity, and the elimination of side reactions makes our dirhodium catalyst in 30% water-acetone one of the fastest and most selective overall hydroformylation catalysts known. In order to make comparisons to other systems and further investigate the results, some of the best monometallic Rh/phosphine ligand combinations known were tested. The ligands chosen include triphenylphosphine, Eastman Chemical’s Bisbi bisphosphine,⁴,⁷ the related Naphos ligand that has been studied for hydroformylation separately by Herrmann and Beller,⁴,⁸ and van Leeuwen’s Xantphos ligand⁴,⁹,¹⁰ (Figure 4.1).

**Figure 4.1.** Monometallic Rh system ligands used for comparison.
The solvent used for each ligand system was identical to the control value (0% water) and the experimentally discovered optimal value for the dirhodium catalyst with 1-hexene (30% water). The results are shown in Table 4.2.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>% H₂O</th>
<th>TOF</th>
<th>L:B</th>
<th>% iso</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Rh₂P₄]²⁺</td>
<td>acetone</td>
<td>0</td>
<td>20(1)</td>
<td>25:1</td>
<td>2.5</td>
</tr>
<tr>
<td>[Rh₂P₄]²⁺</td>
<td>acetone</td>
<td>30</td>
<td>73(1)</td>
<td>33:1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Rh/PPh₃ f</td>
<td>acetone</td>
<td>0</td>
<td>13(1)</td>
<td>9.1:1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Rh/PPh₃ f</td>
<td>acetone</td>
<td>30</td>
<td>17(1)</td>
<td>14:1</td>
<td>1</td>
</tr>
<tr>
<td>Rh/Bisbi g</td>
<td>acetone</td>
<td>0</td>
<td>25(2)</td>
<td>70:1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Rh/Bisbi g</td>
<td>acetone</td>
<td>30</td>
<td>37(1)</td>
<td>80:1</td>
<td>2</td>
</tr>
<tr>
<td>Rh/Naphos g</td>
<td>acetone</td>
<td>0</td>
<td>27(1)</td>
<td>120:1</td>
<td>1.5</td>
</tr>
<tr>
<td>Rh/Naphos g</td>
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<td>30</td>
<td>35(1)</td>
<td>100:1</td>
<td>2.2</td>
</tr>
<tr>
<td>Rh/Xantphos g</td>
<td>acetone</td>
<td>0</td>
<td>13(2)</td>
<td>80:1</td>
<td>5</td>
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<td>Rh/Xantphos g</td>
<td>acetone</td>
<td>30</td>
<td>28(1)</td>
<td>60:1</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

a 1 mM catalyst, 1000 rpm stirring, catalysis performed under constant pressure in the autoclave, number in parenthesis is the standard deviation in the last significant figure (from at least 3 consistent catalytic runs) b volume % c initial turnover frequency (min⁻¹), numbers in parentheses represent the standard deviation of the last digit d aldehyde product linear to branched ratio e % alkene isomerization f 0.4 M PPh₃ (400 equivalents) g 5 equivalents of ligand, Rh(CO)₂(acac) precursor

The results clearly indicate that our dirhodium catalyst has the highest turnover frequency and the fewest side reactions. Although the regioselectivity appears to be considerably higher for the Rh/Naphos catalyst (120:1 L:B) in pure acetone, this represents a linear aldehyde amount of 99.2% compared to 97.1% for our bimetallic catalyst (33:1 L:B). The higher aldehyde
product regioselectivity for Rh/Naphos is partially offset by the 1.5% alkene isomerization that lowers the overall chemoselectivity and conversion of starting alkene to product.

Surprisingly, added water increases the initial TOF for the neutral, monometallic Rh catalysts. There are 31, 48 and 30% rate increases for the PPh₃, Bisbi, and Naphos-based catalysts, respectively, upon addition of 30% water to the acetone solvent. The L:B aldehyde regioselectivity increases moderately for PPh₃ and slightly for Bisbi, but decreases a bit for Naphos. Somewhat higher alkene isomerization is seen for all three of these systems with the addition of water. Because the catalytic rate is first order in alkene for each of these systems, a local increase in the non-polar alkene concentration around the non-polar catalyst enhanced by the polar solvent could explain the modest rate increases seen for these systems. Water is definitely causing this effect as the monometallic catalysts have similar activity and selectivity in either pure acetone or toluene. In congruence with this concentration effect, the regioselectivities of these monometallic catalysts also increases, which is expected for higher ligand:Rh ratios.

One reason why to initiate these studies was to see if phase separation of the less polar aldehyde products from the very polar water-acetone solvent system could be achieved. This does indeed occur for the runs using water at or in excess of 20% of the solvent volume. Samples taken during and at the end of the catalysis show clear phase separation of the aldehyde organic layer and the water-acetone solvent. The final solution from experiments using 30% water in acetone is biphasic, with a light yellow polar phase containing mostly acetone and water (with trace aldehyde), and a brown non-polar phase consisting of the non-polar aldehyde products and the rhodium catalyst (Figure 4.2). The preferred solubility of the catalyst in the aldehyde product layer indicates that the catalyst-product separation problem inherent in most
hydroformylation catalyst systems is not solved. The dirhodium catalyst system needs to be redesigned to be considerably more polar so it will have a strong preference to remain in the water-acetone solvent layer.

![Figure 4.2](image.png)

**Figure 4.2.** Pictorial depiction of phase separation of the products and the catalyst.

Although alkene concentration effects are the most likely source of the rate increases in the presence of water for the monometallic catalysts, the more dramatic doubling of rate for the Rh/Xantphos system (115% initial TOF increase) is likely due to the additional effect of the water hydrogen-bonding to the oxygen of the coordinated Xantphos ligand. This water-Xantphos interaction should inhibit the potential Rh-O bonding interaction, shown in Figure 4.3, that tends to saturate the Rh center preventing alkene coordination. van Leeuwen and coworkers have demonstrated that this Rh-O interaction does occur for cationic Rh(I) complexes, but they did not think it was significant for the neutral HRh(CO)(Xantphos) catalyst. Once again, even relatively weak Rh-O bonding in the HRh(CO)(Xantphos) catalyst would likely lower the rate by generating a saturated 18 e⁻ complex as opposed to the unsaturated and more reactive 16 e⁻ complex shown to the left in Figure 4.3, and indeed van Leeuwen’s system runs considerably more slowly in the absence of water. There is also a significant decrease in the alkene isomerization side reaction for Rh/Xantphos upon the addition of 30% water from 5% to less
than 0.5%. One might wonder why a bisphosphine ligand would be designed containing an oxygen atom with potentially coordinating lone pairs of electrons in close proximity to the metal center, but the Xantphos ligand framework requires a sterically small group in this position and a saturated CH₂ bridge does not produce a good Rh hydroformylation catalyst. Piet van Leeuwen has privately communicated that the Xantphos ligand with a sulfur atom replacing the O atom is also a very poor hydroformylation catalyst, providing further support for our proposal for Rh-O interactions in the neutral catalyst.

\[ \text{Figure 4.3. Rh-O Xantphos interaction equilibrium.} \]

Why does added water have such a large effect on the bimetallic catalyst? This is proposed to be mainly due to effective inhibition of the fragmentation of the catalyst into inactive complexes. In situ NMR spectroscopic studies have indicated that when the catalyst precursor, 1r, sits under H₂/CO the following complexes are formed:

\[ \text{Figure 4.4. Proposed decomposition products.} \]

We believe that these are formed via dissociation of one of the external phosphine arms of the et,ph-P₄ ligand in the bimetallic catalyst, which allows eventual loss of one of the rhodium
atoms. The dissociation of the essentially non-polar diethyl-substituted phosphine arm is more favorable in less polar solvents such as pure acetone. The resulting monometallic Rh intermediate can either dimerize to ultimately form the double-ligand dirhodium complex \(11\), or the et,ph-P4 ligand can wrap around the single rhodium center to form the \(\eta^4\)-coordinated 18 e-saturated monometallic complex \(12\), (Scheme 4.1). Although we have not yet isolated either of these complexes, we have identified the closely related complexes: \([\text{rac,rac}-\text{Rh}_2(\text{et,ph-P4})_2]^{2+}\) and \([\text{rac-RhCl}_2(\eta^4-\text{et,ph-P4})]^+\).4.11

**Scheme 4.1.** Proposed formation of hydroformylation-inactive complexes \(12\) and \(13\).

The dramatically enhanced activity and reduced side reactions when water is added likely results from inhibition of the initial phosphine dissociation from \(2r\). \(^{31}\text{P}\) NMR experiments were conducted to probe the validity of the more prevalent formation of the inactive decomposition products in pure acetone as compared to that in acetone-water. Figure 4.5 shows the \(^{31}\text{P}\) NMR spectrum of the bimetallic catalyst precursor, \(1r\), in acetone after 24 hours of soaking under 250 psig \(\text{H}_2/\text{CO}\). The spectrum indicates a variety of decomposition products which have been characterized. \(^{31}\text{P}\) NMR data indicates that fewer species are present (only two very broad peak
resonances at 50 and 75 ppm) when 30% water (by volume) in acetone after 24 hours of soaking under 250 psig H₂/CO is used. There is no evidence of the formation of complexes 12 or 13. However, the 30% water-acetone NMR studies are challenging due to the considerably lower solubility of the dirhodium catalyst in this polar phase solvent. For example, in pure acetone a saturated catalyst solution has a concentration of about 50 mM, whereas 5 mM is the maximum in 30% water-acetone. Future studies will require a higher field NMR to compensate for the order of magnitude decrease in catalyst concentration for the 30% water-acetone studies. Fewer products are indicated in the 30% water system, which indeed proves to be the more active and selective system, even regardless of the exact character of the rhodium complexes.

![Figure 4.5. 31P NMR spectrum of 1r after 24 hours of soaking.](image-url)
It has long been known that the phosphine dissociation equilibrium in the water soluble HRh(CO)(TPPTS)$_3$ hydroformylation catalyst is considerably slower in water than the analogous PPh$_3$ dissociation equilibria in organic solvents. Thus, less excess TPPTS ligand is required for this aqueous phase hydroformylation catalyst system compared to the excess PPh$_3$ required for organic phase rhodium hydroformylation. A similar ligand dissociation effect could be operating for the bimetallic catalyst as well.

The bimetallic catalyst steadily deactivates during soaking in pure acetone under 45-90 psig H$_2$/CO at 90 ºC, losing 80% of its activity within 50 minutes and becoming completely inactive after 80 minutes. Indeed, in just the first 15-20 min it takes to heat the autoclave containing the catalyst solution to the operating temperature of 90 ºC the catalyst solution is starting to decompose. In stark contrast, the presence of 30% water effectively inhibits the phosphine dissociation and subsequent formation of poor or inactive hydroformylation complexes. Only a small 10% decrease in activity is observed after a full two hours of soaking the dirhodium catalyst solution under syn gas at 90ºC. The improved stability of the catalyst in 30% water-acetone is further indicated by the fact that we can easily perform 10,000 turnovers using 0.1 mM catalyst and 1.0 M 1-hexene (initial TOF = 60(3) min$^{-1}$, L:B = 29:1, 2% alkene isomerization, > 0.1% alkene hydrogenation).\textsuperscript{4,12}

We believe that the increase in initial TOF in 30% water-acetone compared to pure acetone indicates that 78% of 1r is being deactivated during the 20 min period that the autoclave is being heated to 90ºC. Thus the high initial TOF, regioselectivity, and chemoselectivity for 1r in 30% water-acetone reflects the intrinsic activity and selectivity of the dirhodium et,ph-P4 catalyst for hydroformylation. In the presence of 1-alkene substrate almost all monometallic hydroformylation catalysts show dramatically reduced fragmentation reactions. This is one of
the factors that contribute to the success of performing 10,000 turnovers, as mentioned above.

Monometallic Rh hydroformylation catalysts typically decompose from Rh-induced phosphine
fragmentations that either yield phosphido-bridged dimers and clusters or partially alkylated
phosphines that are poor ligands for hydroformylation catalysis. We have never observed any
Rh-induced et,ph-P4 fragmentations under our normal and quite mild operating conditions.

4.4. Conclusions

The addition of 30% water by volume to acetone creates a remarkably effective polar
phase solvent system for our dicationic dirhodium tetraphosphine hydroformylation catalyst.
The initial turnover frequency increases by 265% (to 73 min\(^{-1}\), or 4,380 hr\(^{-1}\)) for the
hydroformylation of 1-hexene relative to pure acetone (20 min\(^{-1}\), or 1,200 hr\(^{-1}\)). The
regioselectivity increases to 33:1 and unwanted side reactions are essentially eliminated.

Comparisons with monometallic rhodium catalysts demonstrate that this polar phase bimetallic
catalyst is one of the fastest and most selective hydroformylation systems known. In the future,
in\(\textit{situ}\) FT-IR spectroscopy studies and further NMR spectroscopy studies on this system may
provide more insight or confirmation of the current hypotheses of catalyst deactivation. Further
use of this information may lead to the design of even more efficient solvent systems that may be
used for a variety of catalyst systems and possibly ultimately lead to the achievement of the
original purpose of the investigation—facile separation of the aldehyde products from the solvent
and catalyst. In addition, this information might also be used to design even better
tetraphosphine ligands that do not dissociate as readily in less polar solvents, allowing the
production of far more active and selective catalysts.

4.5. References


(b) Bianchini, C., Giambastiani, G. *Chemtracts*. 2003, 16, 301-309.


CHAPTER 5: HYDROCARBOXYLATION AND ALDEHYDE-WATER SHIFT CATALYSIS BY A DIRHODIUM HYDROFORMYLATION CATALYST

5.1. Introduction to Hydrocarboxylation and Aldehyde-Water Shift Catalysis

Hydrocarboxylation is a generic term referring to the production of carboxylic acids or esters. The most difficult and sought of these reactions is the conversion of alkenes, CO, and water to carboxylic acids (Scheme 5.1). It can be considered a “holy grail” reaction in that it involves the catalytic activation of water and has previously only been performed under very forcing conditions and generally with poor selectivity. Although hydrocarboxylation (sometimes also referred to as hydrocarbonylation) catalysis has been known for a long time and was used industrially for the production of acrylic acid from acetylene, it typically requires high temperature, pressures, and strong acid co-catalysts that present major corrosion problems.5,1

![Scheme 5.1](image)

**Scheme 5.1.** Hydrocarboxylation catalysis to produce carboxylic acids.

A very unusual accidental discovery in our lab using the dirhodium et,ph-P4 catalyst system may have solved the hydrocarboxylation problem via a novel tandem catalysis reaction involving both hydroformylation and aldehyde-water shift catalysis. The aldehyde-water shift reaction is essentially without precedent and represents a breakthrough in catalysis due to its rate and selectivity, no requirement for promoters, and use of water as a H₂ source.

5.1.1. Background

The production of carboxylic acids from alkenes has been extensively studied since its discovery by Reppe in 1953.5,1,5,2 Reppe used a simple Ni(CO)₄-based system that produces
simple carboxylic acids such as propionic acid using ethylene as the alkene substrate. Simple nickel (and cobalt) systems such as Reppe’s require high temperatures of 200-300 °C and a high pressures of 200-300 atm of CO yet still provide poor chemo- and regioselectivity when alkenes with more than three-carbons are used. In addition, these systems require the presence of a strong acid, HX, X typically being iodide, to generate the active catalyst, HMX(CO)₂, from the starting metal carbonyl complex. Heck’s proposed mechanism for Ni-catalyzed hydrocarboxylation⁵.³ is shown in Scheme 5.2. Alternatively, the acid can generate an alkyl halide from the starting alkene substrate that oxidatively adds to the metal center. Following migratory insertion of CO, an acyl halide is reductively eliminated (Scheme 5.3) and converted to carboxylic acid by reaction with water, which regenerates the strong acid HX.

\[
\text{Scheme 5.2. Heck’s proposed mechanism for hydrocarboxylation.}
\]
Scheme 5.3. Activation of alkene by strong acid and hydrocarboxylation.

The well-studied Monsanto Acetic Acid Process also produces carboxylic acid from MeOH and CO in an analogous manner. It uses a strong acid, HI, and Rh or Ir carbonyl complexes to convert methanol to acetic acid, although the process is applicable to longer chain alcohols (although it usually demonstrates poor selectivity). The strong acid is required to generate a reactive methyl iodide intermediate from the alcohol, which after oxidative addition to the metal center undergoes migratory insertion of CO and then reductive elimination as an acyl iodide. The acyl iodide reacts with water to produce acetic acid (and regenerates HI). The strong acid is required to activate the initial substrate, which also forms water which is required to convert the acyl species to carboxylic acid. The proposed mechanism is shown in Scheme 5.4.

Scheme 5.4. Proposed mechanism for the Monsanto Acetic Acid Process.
Modified Rh-catalyst systems exist that can convert alkenes, water, and CO to carboxylic acids. Zoeller at Eastman Chemicals patented phosphine-modified \([\text{RhI}_2(\text{CO})_2]\) catalysts that, like the previously discussed systems, require strong acids as promoters.\(^5\) These modified systems operate under relatively milder conditions of 190 °C and 27.2 atm CO, but provide only 6.7 L:B selectivity with 56 TO/hr using PPh\(_3\) as the phosphine, or 4.6 L:B selectivity at 135 TO/hr using diphenylphosphinebutane, both with 1-hexene as the alkene substrate. Pruchnik reported a carboxylic acid-producing Rh hydroformylation catalyst based on a cationic monodentate phosphine ligand (and iodide counter anion), however the regioselectivity is a very low 1.1 L:B and conversion to the carboxylic acid is only 27% for 1-hexene.\(^6\) Several Pd catalysts also exist that operate under relatively mild conditions, (90-120 °C, 40-70 atm CO) and they also require strong acids and/or other promoters such as metal halides.\(^5\) In addition, the Pd catalysts readily isomerize alkenes, are generally not regioselective, and are typically slow even for short-chained alkenes.

### 5.1.2. Previous Work Using the Dirhodium Catalyst System

During the original investigation into the feasibility of the use of a polar solvent system with our bimetallic catalyst, Dr. Novella Bridges made a remarkable yet accidental discovery: variable amounts of carboxylic acid was evident in the GC trace of a polar-phase hydroformylation experiment.\(^5\)\(^,\)\(^8\) The production of carboxylic acids under the mild hydroformylation conditions used (90 °C, 90 psig 1:1 H\(_2\) /CO at constant pressure, 1 M alkene, 1000 rpm, 0.1 mM \([\text{rac-Rh}_2(\text{nb}d)_2(\text{et,ph-P}4)](\text{BF}_4)_2\) as the catalyst precursor), is extremely unexpected and virtually without precedent.

After considerable further study, Dr. Bridges discovered that a leak was present in the autoclave system. Examination of routine uptake curves makes this observation relatively
obvious as leaking autoclaves never stop appearing to consume $\text{H}_2/\text{CO}$ gas. Figure 5.1 shows one of Dr. Bridges’ uptake curves presented in her dissertation indicating a leak, and also shows the uptake curve of a standard hydroformylation experiment using a properly sealed autoclave.

Upon repairing the leaking autoclave, Dr. Bridges observed that there was no more carboxylic acid production. Since acid production does not occur under normal “leak-free” hydroformylation conditions, the question of interest was how the carboxylic acid was produced and how this was related to the leak in the autoclave. The direct involvement of $\text{O}_2$ to oxidize the aldehyde to carboxylic acid was quickly ruled out as the leak in the autoclave could not allow any $\text{O}_2$ to enter the autoclave.

GC analysis of the catalyst mixture when carboxylic acid was produced indicated nothing unexpected until the majority of the alkene was consumed, at which time carboxylic acid production commenced and the amount of aldehyde product present decreased by the same amount as the carboxylic acid being produced. This key observation indicated that the catalysis occurring involved the reaction of aldehyde with water to produce the carboxylic acid and $\text{H}_2$. This reaction is shown in Scheme 5.5 and is a new type of catalytic reaction that we call
aldehyde-water shift catalysis, in analogy with the well-known water-gas shift reaction: CO + H₂O $\rightleftharpoons$ CO₂ + H₂.⁵⁻⁹

\[
\begin{array}{c}
\text{H} & \text{O} \quad \text{R} \\
\text{H} \quad \text{O} \quad \text{R} \\
\text{catalyst}
\end{array}
\]

*Aldehyde-Water Shift Rxn*

Scheme 5.5. Aldehyde-water shift catalysis producing acid and hydrogen.

The proposal was made that the leak may have served to allow excess hydrogen gas to escape creating conditions that allowed this new catalytic reaction to occur. The inhibition of the aldehyde-water shift catalysis by hydrogen could be solved by the constant purging of hydrogen, which the fortuitous leak accomplished. Since the leak was somewhat random and certainly not regulated it lead to variable production of carboxylic acid, thus a better method of inducing the acid production was sought.

A logical first attempt to consistently produce carboxylic acid was to switch to pure CO (from the 1:1 H₂/CO syn gas mixture used during normal hydroformylation experiments) when there was approximately 20% alkene remaining from the initial hydroformylation catalysis. The smaller amount of alkene present would continue to be hydroformylated leading to H₂-depletion in the autoclave, which we believed would initiate the aldehyde-water shift catalysis. Dr. Bridges performed a series of experiments in which syn gas was used for zero, five, ten, or fifteen minutes (and then switched to pure CO at constant pressure of 90 psig). No carboxylic acid was produced except with ten minutes of syn gas before the switch to pure CO. This corresponded to approximately 80% conversion of the initial 1000 equivalents (1 M) of 1-hexene added to the catalyst solution. Ten minutes of hydroformylation using 1:1 H₂/CO, followed by a switch in the gas feed to pure CO provides the conditions required to consistently produce carboxylic acid at
90°C and 90 psig pressure. We typically convert 99+% of the 1-hexene to aldehyde (25:1 L:B regioselectivity), and then 70-80% of the aldehyde to carboxylic acid with > 25:1 L:B regioselectivity. Dr. Bridges reported in her dissertation an initial TOF of 2100 hr\(^{-1}\) for the aldehyde-water shift catalysis, while I observe an initial TOF of 1700 hr\(^{-1}\), also with > 25:1 L:B selectivity and virtually no side reactions.

The production of carboxylic acid from alkene occurs through a novel two-stage tandem catalysis. The first stage is hydroformylation, the conversion of H\(_2\), CO, and alkene to aldehyde. The second step is aldehyde-water shift catalysis, the conversion of aldehyde and water to produce carboxylic acid and hydrogen. The overall reaction combines alkene, CO, and water to produce carboxylic acid as shown in Scheme 5.6.

The thermodynamics of the aldehyde-water shift reaction is favorable: \(\Delta H_{\text{rxn}}\) is \(-9.6\) KJ/mol, \(\Delta S_{\text{rxn}}\) is \(+51.9\) J/mol and the overall \(\Delta G_{\text{rxn}}\) is \(-28.4\) KJ/mol. The water-gas shift reaction, CO + H\(_2\)O \(\rightleftharpoons\) CO\(_2\) + H\(_2\), has \(\Delta H_{\text{rxn}} = +2.8\) KJ/mol, \(\Delta S_{\text{rxn}} = +75.8\) J/mol and the overall \(\Delta G_{\text{rxn}} = -24.7\) KJ/mol. However, the water gas shift reaction is considerably more dependent on entropic factors that are not as forcing for gases dissolved in solution. This may
explain why the water-gas shift reaction can readily proceed in either direction, depending on conditions, while we have only observed the forward reaction for the aldehyde-water shift catalysis.

The proposed mechanism for the aldehyde-water shift reaction is presented in Scheme 5.7. To the starting tetracarbonyl species \(4r^*\), aldehyde coordinates to one of the unsaturated 16 e\(^{-}\) Rh(I) centers to form 14. Nucleophilic attack by water made easier by the cationic charge on the Rh activating the aldehyde (complex 15) and the loss of a water proton to become a monocationic complex yields complex 16. Ligand dissociation of CO opens a coordination site (complex 17) which facilitates \(\beta\)-hydride elimination to form a hydride complex with a still-coordinated carboxylic acid, complex 18. Dissociation of the carboxylic acid and protonation of the relatively basic hydride (complex 19) yields free carboxylic acid and hydrogen as well as regeneration of a dicationic complex; coordination of CO again produces the starting complex \(4r^*\).

\[ \text{Scheme 5.7. Proposed aldehyde-water shift mechanism.} \]
Zakiya Wilson in our group has performed Density Functional Theory (DFT) calculations using Gaussian 98 on the bridged carbonyl complex \([\text{rac-Rh}_2(\mu-\text{CO})_2(\text{CO})_2(\text{et,ph-P}4)]^{2+}\), 4r*. The lowest unoccupied molecular orbital (LUMO) for this complex is shown in Figure 5.9. Two different views with the ball and stick models are shown for reference. Although a line is shown between the Rh centers, there is no formal Rh-Rh bond. We believe that this orbital offers the key explanation for why the closed-mode bridged carbonyl complex 4r* plays a critical role as the catalyst in the activation of the aldehyde in the aldehyde-water shift catalysis. This LUMO is composed of an empty Rh \(p_z\) orbital (the two phosphines and terminal CO ligands define the \(xy\) plane) strongly bonding to both the terminal and bridging CO \(\pi^*\) MO’s. It is the bridging CO’s that link both Rh centers together in this LUMO allowing all 4 CO ligand \(p^*\) systems to be linked together. This lowers the energy of this LUMO by 0.8 eV relative to the open mode tetracarbonyl complex \([\text{rac-Rh}_2(\text{CO})_4(\text{et,ph-P}4)]^{2+}\), where only two of the terminal CO ligands show significant contributions to the LUMO.

The cooperativity of both rhodium centers and all four CO ligands in the LUMO shown in Figure 5.2 allows this orbital to be a considerably stronger acceptor that can drain more electron density from the aldehyde, enough to activate it for nucleophilic attack by water and the subsequent deprotonation step to make the alkoxide bound intermediate. This nicely corresponds to the experimental work where we find that the open-mode carbonyl catalyst precursor, \([\text{rac-Rh}_2(\text{CO})_4(\text{et,ph-P}4)]^{2+}\), does not catalyze the reaction between aldehyde and water, nor alkene, water and CO in the absence of any H\(_2\) gas. The H\(_2\) gas is necessary to react with the dirhodium complex and reduce the steric and electronic barriers, allowing it to close up to form the important bridged carbonyl species that we propose are the actual catalysts for the aldehyde-water shift catalysis. In the presence of too much H\(_2\), however, the concentration of
[rac-Rh₂(µ-CO)₂(CO)₂(et,ph-P4)]²⁺, 4r*, is very low – too low to effectively perform aldehyde-water shift catalysis.

![Figure 5.2. LUMO for [rac-Rh₂(µ-CO)₂(CO)₂(et,ph-P4)]²⁺, 4r*, as calculated from a Gaussian 98 DFT calculation by Ms. Zakiya Wilson. Color coding for ball and stick diagram: Rh = blue, P = orange, O = red, C = grey, H = white.](image)

We also believe that alkene inhibits the coordination of aldehyde to [rac-Rh₂(µ-CO)₂(CO)₂(et,ph-P4)]²⁺. This nicely explains the failure of Dr. Bridges catalytic runs with only 5 min of hydroformylation prior to shifting to a pure CO atmosphere and why too rapid changes from syn gas to pure CO result in little or no acid production. The presence of unhydroformylated alkene, which cannot hydroformylate due to H₂–depletion, inhibits the coordination of the aldehyde to the catalyst.
5.2. Aldehyde-Water Shift Catalysis Experiments

Clearly the tandem catalytic production of carboxylic acid from alkenes, CO, and water with our bimetallic system is far superior to any of the monometallic systems discussed in the introduction with regards to rate, chemo- and regioselectivity, and mild conditions being used. In addition to its superior performance and no requirement for strong acid promoters such as HI, the reaction is extremely interesting because it may involve the direct activation of water by the catalyst. Extensive experimentation is required to characterize, probe, and optimize a new reaction such as aldehyde-water shift catalysis. Additional experiments were required to confirm the previous results, quantify the reagents during the reaction, attempt to optimize the acid production, and to explore related reactions with other substrates.

5.2.1. Confirmation of Reproducibility and Quantitative Analysis

The first task was to confirm the production of the carboxylic acid and the reproducibility of the results obtained by Dr. Bridges. A series of experiments were performed confirming that her results were indeed both valid and reproducible. More information was required however, in order to understand and optimize the reaction. The first task was to obtain a quantitative mass balance of the reactants and products during the course of the reaction. Careful gas chromatography methods were created and a quantitative mass balance was performed using these methods that provided accountability for the reactants and products during the course of the reaction to within 7%, which is considered very good for this type of catalytic experiment (Figure 5.3). The information offered by this plot indicates that carboxylic acid production occurs after 72% of the initial alkene substrate is converted to aldehyde, which is after 10 min of reaction time when the syn gas is switched to pure CO. The hydrogen produced by the aldehyde-water shift reaction feeds the complete hydroformylation of the starting alkene.
During the initial 10 min after substrate addition, conditions are identical to those for hydroformylation, and the initial TOF for hydroformylation is approximately 4200 hr\(^{-1}\) (as reflected by syn gas consumption) providing regioselectivity of 28:1. The conversion of aldehyde to acid, commencing after 10 min, has an initial rate of approximately 1700 hr\(^{-1}\), (from GC analysis) providing regioselectivity of 60:1.

The tandem reaction is not as reproducible as standard hydroformylation experiments. More mechanical manipulation is necessary in order to change gases, and timing is critical. For example, approximately 25% of the experiments performed with 10 min gas change failed to produce significant quantities of carboxylic acid (although some alkene is always hydroformylated). The reaction procedure and conditions are not optimal, but provide a basis for pursuing understanding and optimization of the reaction.

5.2.2. Direct Conversion of the Aldehyde and Purge Rate Studies

An investigation into the direct conversion of aldehyde to carboxylic acid was performed to provide additional information about the system and to determine if it was indeed possible. If
the catalysis is indeed operating via a two-stage process, then either of the two processes should theoretically operate independently under the appropriate conditions. The hydroformylation stage for Stanley’s bimetallic catalyst is well-documented. The second stage is, as mentioned previously, virtually without precedent. The difficult task was to create the conditions required for conversion to carboxylic acids since the reaction produces reaction-inhibiting H₂. Under normal hydroformylation conditions the presence of 1:1 H₂/CO (the H₂ in particular) prevents aldehyde-water shift catalysis from occurring. After many unsuccessful attempts to convert pure aldehyde and water to carboxylic acid and H₂, a simple experiment was devised. After the initial catalyst precursor ([rac-Rh₂(nbd)₂(et,ph-P₄)](BF₄)₂) soaks under 1:1 H₂/CO at 90 ºC to generate the active catalyst, the feed gas is switched to pure CO and a needle valve is employed to constantly purge the reaction vessel. A purge rate of 4-5 psig/min provided good conditions for aldehyde-water shift catalysis, however, only a maximum of 75% conversion to acid was achieved, although at 70:1 L:B (from 50:1 heptanal) at an initial TOF of approximately 1000 TO/hr (from GC analysis) and with undetectable side products. The aldehyde-water shift catalysis is quite sensitive to reaction conditions and both timing and purge rates are critical to achieve good conversion.

An interesting observation was that the carboxylic acid L:B ratio exceeded the L:B ratio of the starting aldehyde, both for the tandem catalysis when starting with alkene, or when starting with pure aldehyde. Starting with as low as 25:1 linear:branched heptanal provides >60:1 linear:branched heptanoic acid. This is a result of faster conversion of the less sterically hindered linear aldehyde relative to the already small amount of bulkier branched substrate.

The success of using a gas purge for the direct conversion of aldehydes and water to carboxylic acids and H₂ led to investigations using purge rates for the tandem catalytic reaction
involving the overall conversion of alkenes, CO, and H₂O to carboxylic acids. The leak that initially led to Dr. Bridges’ accidental discovery of the aldehyde-water shift catalysis was in essence a slow purge. Indeed, a 2-5 psig/min purge rate when 1:1 H₂/CO is used also provides reaction conditions under which carboxylic acid is produced, although in only 50% or less yield. We believe that the incomplete conversion to carboxylic acid is due to the rapid aldehyde-water shift catalysis that builds up H₂ much faster than the purging can deplete, leading to catalyst inhibition. Although the purging should eventually flush out this excess H₂, the reaction does not restart even after three hours of additional purging. In addition, the use of faster purge rates to maintain low hydrogen concentrations depletes the system of the relatively volatile water-acetone solvent and reactants. We are in the process of installing a new water-cooled high-pressure condenser system for one of the autoclaves that should allow considerably faster purge rates and maintain the solvent and reactants in the autoclave with minimal losses.

5.2.3. The Use of Different Substrates

For the bimetallic system to be of much use or interest to the catalysis community, it should work with a variety of substrates. Unfortunately, without a reasonable understanding of the conditions required for optimizing the reaction with one substrate, it is somewhat difficult to apply the catalysis to other substrates. A series of experiments was performed to investigate whether acetaldehyde and water could be converted to acetic acid and H₂. Benchtop reactions were performed, using lower temperature (75 ºC) and bubbled gases (as opposed to standard conditions of 90 ºC, 90 psig syn gas). Similar to reactions performed with 1-hexene under these conditions, no catalysis was observed, presumably due to the catalyst not being activated under such mild conditions.
However, in experiments performed using autoclave conditions similar to those with heptanal as the substrate and a purge rate of 1 psig/min, at least 10% conversion (100 turnovers) to acetic acid was achieved (as measured by GC analysis). Higher purge rates facilitate the rapid escape of the very volatile substrate due to its low boiling point (78 °C). Although the 10% conversion clearly indicates that the reaction is not optimized, it certainly demonstrates that the reaction is occurring. The conversion estimate is a conservative one due to the volatility of both reactant and product and the difficulty of accurately controlling the purging with a simple needle valve. Because acetaldehyde can be converted, it is reasonable to assume that any aldehyde that is soluble in the catalyst solvent solution can be converted to carboxylic acid by the bimetallic catalyst. The importance of the successful conversion of acetaldehyde and water to acetic acid and H₂ lies in the potential conversion of formaldehyde and water to formic acid and H₂. The formic acid can be readily decomposed by a variety of catalysts (probably including our dirhodium system) to another equivalent of H₂ and CO₂. The overall reaction is shown in Scheme 5.8.

![Scheme 5.8](image)

**Scheme 5.8.** Conversion of formaldehyde and water to formic acid and H₂, followed by decomposition of the formic acid to another H₂ and one equivalent of CO₂.

Formaldehyde-water represents one of the highest H₂ storage liquids on a per gram basis making it a very attractive candidate for fuel cells. Formaldehyde-water is less flammable
relative to MeOH (one of the frontrunners for fuel cell use) and the toxicity of formaldehyde can be significantly reduced through the use of paraformaldehyde that readily decomposes back to formaldehyde around 80 °C.

5.2.4. Future Work

In the future, the most important aspect is to create conditions under which the reaction can reach full conversion with a variety of different substrates. In order to produce the correct conditions for the reaction, a more sophisticated autoclave flow reactor system is required. First, a more precise and accurate purge control is required than the manual (and somewhat inconsistent) needle valve. An electronically controlled precision mass flow meter should provide the required control. Second, a high pressure condenser is required at the outlet of the reaction vessel to prevent the loss of solvent, reactants and products that becomes increasingly problematic with higher purge rates and lower boiling substrates. Lastly, a back-pressure regulator is required to work in tandem with the mass flow meter/controller to allow a constant purge flow and yet maintain a constant pressure inside the reaction vessel. Prof. Stanley has purchased these items along with a new computerized process controller, and through their use the reaction should be optimized and made more industrially applicable than the current techniques involving timing patterns of gas switching and manual purging using needle valves.

5.3. Conclusions

Stanley’s bimetallic hydroformylation catalyst also performs aldehyde-water shift catalysis under hydrogen deficient conditions. It produces carboxylic acids from alkenes, CO, and water via a novel two-stage reaction (hydroformylation and aldehyde-water shift catalysis) with unprecedented rate, selectivity, and with virtually no side products. The reaction is unique in that it requires no strong acid promoters and relies on the catalyst’s ability to directly utilize
Further study of the system will lead to the optimization of the reaction and allow its application to catalysis of other substrates.

5.4. References


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CHAPTER 6: EXPERIMENTAL PROCEDURES

6.1. General Synthesis Notes

All synthetic procedures were performed using standard Schlenk and dry box techniques. All solvents and chemicals used were purchased from Aldrich 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 ($^1$H) spectrometer. Chemical shifts are reported relative to H$_3$PO$_4$ (external standard).

6.2. Synthesis of the et,Ph-P4 Ligand

All synthetic techniques for the synthesis of et,ph-P4 have been previously reported multiple times and were used with only minor adjustments, such as batch size or the use of correct synthetic technique.$^{6.1, 6.2}$

6.3. Separation of the Diastereomers of the et,Ph-P4 Ligand Using Nickel Chloride

6.3.1. Synthesis of Ni$_2$Cl$_4$(et,ph-P4)

A 125 mL EtOH solution of mixed ligand (10.01 g, 0.02155 mol) was added dropwise to a rapidly stirred clear green solution of NiCl$_2$$\cdot$6H$_2$O (10.30 g, 0.431 mol) in 135 mL EtOH. The solution turned dark red as the ligand solution was added. An orange precipitate began to form after the addition was complete. After the mixture was stirred for 24 hours, the orange precipitate was collected by filtration and washed with three ca. 30 mL portions of EtOH to give 7.32 g (92.8% yield) of meso-Ni$_2$Cl$_4$(et,ph-P4). Yields are typically 90-96%. The filtrate was concentrated down to a dark red amorphous solid of mainly rac-Ni$_2$Cl$_4$(et,ph-P4).

6.3.2. Removal of Nickel from rac-Ni$_2$Cl$_4$(et,ph-P4)

A Schlenk flask containing rac-Ni$_2$Cl$_4$(et,ph-P4) (2.00 g, 2.77 mmol) was charged with a solution of NaCN (18.1 g, 0.369 mol, 133 equiv.) in 125 mL H$_2$O and 50 mL MeOH. The
resulting orange solution was stirred slowly for three hours, during which it became increasingly red. The flask was then charged with more NaCN (20.4 g, 0.416 mol, 150 equiv.) and allowed to slowly stir until all the NaCN dissolved (ca. 15 minutes.) The free rac-et,ph-P4 was extracted into three 100 mL portions of benzene. The slightly-yellow extracted solution was then passed through a small neutral alumina column to remove the yellow tint, which has been previously reported. The clear solution was then concentrated to yield a clear viscous liquid (1.16 g, 2.50 mmol, 85.2%) of free racemic ligand. Yields are typically 75-87% and the purity level, based on $^{31}$P NMR, is typically >95%.

6.3.3. Removal of Nickel from meso-Ni$_2$Cl$_4$(et,ph-P4) to Provide meso-(et,ph-P4)

A Schlenk flask was charged with 40 mL H$_2$O, 20 mL MeOH and NaCN (20 g, 0.40 mol, 400 equiv.) To the cloudy white cyanide solution 30 mL of a brown 3:1 solution of H$_2$O and MeOH containing meso-Ni$_2$Cl$_4$(et,ph-P4) (0.75 g, 1.04 mmol) was added dropwise with rapid stirring. Upon addition, the cloudy cyanide solution turned light orange. After slow overnight stirring, the mixture was extracted with three 75 mL portions of hexane. The slightly-yellow extracted solution was then passed through a neutral alumina column to remove the yellow tint. The clear solution was then concentrated to yield a cloudy, highly viscous substance (0.30 g, 0.647 mmol, 62.2% yield). Yields are typically 45-65% and the purity level, based on $^{31}$P NMR, is typically 75%. Recrystallization of the extracted ligand (.30 g, .647 mmol) from hexane (ca. 25 mL) provided 99% pure meso ligand, a white powder, based on $^{31}$P NMR, (.25 g, .539 mmol, 51% yield). Yields after recrystallization are typically 30-60% and purity is >98%.

6.3.4. Removal of Nickel from meso-Ni$_2$Cl$_4$(et,ph-P4) to Provide rac-(et,ph-P4)

A Schlenk flask was charged with meso-Ni$_2$Cl$_4$(et,ph-P4) (1.0g, 1.385 mmol) and 20 mL H$_2$O. After stirring for 1 hour to dissolve the meso-Ni$_2$Cl$_4$(et,ph-P4), a 10 mL H$_2$O solution of
NaCN (0.35 g, 0.00714 mol, 5.2 equiv.) was added dropwise with stirring. During the addition, an orange precipitate formed, which is \textit{rac}-Ni(CN)$_2$(et,ph-P4). 20 mL MeOH was added to dissolve the precipitate. More NaCN was added (3.50 g, 0.0714 mol, 52 equiv.) to free the ligand. The ligand was extracted with 3 50 mL portions of benzene. The slightly-yellow extracted solution was then passed through a neutral alumina column to remove the yellow tint. The clear solution was concentrated to yield a clear viscous liquid (0.41 g, 0.875 mmol, 70% yield). Yields are typically 60-75% and usually contain 1:1 to 1:1.4 \textit{rac}:meso.

### 6.4. Separation of the Diastereomers of the et,Ph-P4 Ligand Using Nickel Thiocyanate

#### 6.4.1. Synthesis of Ni$_2$(SCN)$_4$(et,ph-P4)

A cloudy gray/green solution of Ni(SCN)$_2$ (7.53 g, .0431mol) in 135 mL EtOH was allowed to stir rapidly for 2 hours. A 125 mL EtOH solution of mixed (et,ph-P4) (10.0 g, .02155 mol) was added dropwise to the rapidly stirred Ni(SCN)$_2$ solution. The solution turned orange as the ligand solution was added. An orange precipitate began to form after the addition was complete. After the mixture was stirred for 24 hours, the orange precipitate was collected by filtration and washed with three ca. 30 mL portions of EtOH to give 7.8 g (45% yield) of mainly meso-Ni$_2$(SCN)$_4$(et,ph-P4). The filtrate was concentrated down to a dark red amorphous solid of mainly \textit{rac}-Ni$_2$(SCN)$_4$(et,ph-P4).

#### 6.4.2. Removal of Nickel from rac-Ni$_2$(SCN)$_4$(et,ph-P4)

A Schlenk flask containing \textit{rac}-Ni$_2$(SCN)$_4$(et,ph-P4) (2.00 g, 2.46 mmol) was charged with a solution of NaCN (16.0 g, 0.327 mol, 133 equiv.) in 125 mL H$_2$O and 50 mL MeOH. The resulting brown solution was stirred slowly for three hours, during which it became increasingly red. The flask was then charged with more NaCN (18.1 g, 0.369 mol, 150 equiv.) and allowed to slowly stir until all the NaCN dissolved (ca. 15 minutes.) The mixture was extracted with three
100 mL portions of benzene. The slightly-yellow extracted solution was then passed through a small neutral alumina column to remove the yellow tint. The clear solution was then concentrated to yield a clear viscous liquid (0.80 g, 1.72 mmol, 70%) of free rac-(et,ph-P4). Yields are typically 60-75% and the purity level, based on $^{31}$P NMR, is typically 70-90%.

6.4.3. Removal of Nickel from meso-Ni$_2$(SCN)$_4$(et,ph-P4)

Producing free meso ligand by the same procedure as used in the nickel chloride procedure produces results in 40-60% pure meso ligand in 35-65% yield. After recrystallization from hexane >98% pure meso ligand is produced in 30-60% yield.

Producing free rac ligand by the same procedure as used in the nickel chloride procedure produces results in 40-60% pure rac ligand in 30-60% yield.

6.5. Synthesis of Monometallic Nickel Thiocyanate Complexes

Ni(SCN)$_2$ (.048 g, .00276 mol) in 2 mL solvent was allowed to stir for 1 hour. To a rapidly stirring 2 mL clear solution of >95% (rac to meso) rac-et,ph-P4 (.122 g, .000262 mol, .95 equiv.), the Ni(SCN)$_2$ solution was added dropwise over 5 minutes. The resulting dark, reddish-brown solution was allowed to stir for varying lengths of time and using the following solvents: THF, EtOH/H$_2$O, MeOH, MeOH/EtOH.

6.6. Hydroformylation and Hydrocarboxylation Catalytic Experiments

Procedures employed are similar to those previously reported.$^6$ Experiments were performed in 150 mL stainless steel autoclaves from Parr and controlled by Parr 4850 controllers. The autoclaves were loaded under an inert atmosphere with standard reaction conditions of 1.0 mM catalyst, 80 mL solvent (including 5.0 mL toluene as an internal standard). In the case of monometallic catalysts, 5 eq of ligand was also loaded unless otherwise noted. The autoclaves were then purged three times with $N_2$, closed, and the catalyst solution soaked for
20 min with H₂/CO at 45 psig as the temperature ramped to 90 C. After 20 minutes, the pressure of the reaction vessel was decreased to 45 psig and 1000 equivalents of 1-hexene (99+%, run through a neutral alumina column immediately prior to use, 8.9 x 10⁻² moles, 11.2 mL) were pushed in by 90 psig H₂/CO. In the case of the hydrocarboxylation experiments, multiple variables were adjusted subsequent to the injection of the substrate, including switching from syn gas to pure CO, adjusting the flow of gas through the reaction vessel, or adjusting the pressure of gas maintained in the vessel. The progress of the reactions was measured by logging the syn gas uptake from the reservoir that is connected to a two-stage regulator that delivers the gas at a constant pressure of 90 psig. Reaction conditions were maintained and logged by the Parr 4850 controller during the catalytic run, transferred to a PC, and analyzed using Microsoft Excel. Products were analyzed by gas chromatography using a Hewlett Packard 5890 Series II Gas Chromatograph equipped with a DB-1 capillary column for calculation of regioslectivity, final conversion, 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 characterization was performed on a Hewlett Packard 5890 Series II Gas Chromatograph/Mass Spectrometer equipped with a DB-5 capillary column as well as a Bruker 250 MHz NMR spectrometer.

6.7. References


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VITA

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