Asymmetric Synthesis by Palladium (II) Catalysis: Chirality Transfer and New a Symmetric Catalytic System

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LOYOLA UNIVERSITY OF CHICAGO

ASYMMETRIC SYNTHESIS BY PALLADIUM (II) CATALYSIS:
CHIRALITY TRANSFER AND NEW A SYMMETRIC CATALYTIC SYSTEM

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
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DEPARTMENT OF CHEMISTRY

BY

OTHMAN HAMED

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ABSTRACT

This proposal is divided into two Parts: I. Exchange and oxidation of chiral allylic alcohols using chirality transfer. II. Asymmetric synthesis using Pd(II) catalysts with chiral auxiliaries.

Part I is divided into two sections: A. The determination of stereochemistries of hydroxypalladation using chirality transfer. B. Preparation of trichiral molecules. The allylic alcohols used for these studies included (R)-(−)-Z- and E-3-hexen-2-ol (13a), (R)-(−)-Z-4-hexen-3-ol (13b), (R)-Z- and E-3-penten-2-ol (17). The chiral alcohols were prepared by reduction of the corresponding alkynones with alpine-borane reagent to give the alkynones which were reduced with either Lindlar’s catalyst or LiAlH₄ to give the Z and E isomers respectively.

At low [Cr] PdCl₂ oxidizes 13a to a mixture of (R)-Z-4-hydroxy-2-hexanone (15a) and (R)-5-hydroxy-3-hexanone (15b). The configuration of 15a was consistent with syn hydroxypalladation. At high [Cr] (>2 M) PdCl₂ isomerizes 13b to (S)-Z-13a. This result is most consistent with anti hydroxypalladation. Thus the modes of addition are opposite at high and low [Cr].

(R)-Z- and (R)-E-17 were tested as new stereochemical probes to readily determine the modes of addition of various Pd(II) reagents to olefins under a variety of reaction conditions. Reaction of these alcohols with nucleophiles such as hydroxy, methoxy, acetoxy, phenyl and carboxmethoxy Pd(II) species gave the corresponding 2-pentanones whose absolute
configuration indicated the modes of addition. Generally the modes of addition were as expected but there were some surprises which require further investigation.

The oxidation of (R)-Z- and (R)-E-17 by PdCl$_4^{2-}$ under carbon monoxide pressure (3 atm.) produced 3,4-dicarbomethoxy-2-pentanols with 3 chiral centers. The chirality transfer to both the 3 and 4 positions was close to 100% for both geometric isomers. Tentative assignment of absolute configuration of the new chiral centers was carried out by NOE experiments. This reaction could be used to produce a number of new trichiral molecules.

In Part II two chiral syntheses are studied: A. Phenylation of olefins (Heck reaction). B. Oxidation of olefins by Pd(II) catalysts containing chiral ligands in the presence of CuCl$_2$ to give optically active chlorohydrins.
To my loving wife Mariam, and to our first child Assiya,  

who has brought inspiration to our lives
ACKNOWLEDGMENTS

Special thanks to my research director Dr. Patrick M. Henry for the opportunity to work in his research group. I am very grateful to him for his constant presence, his willingness to help at any time and his encouragement throughout this research project.

Thanks to Dr. Charles Thompson for his helpful suggestions in the synthesis of some of the organic compounds used in this research project. Thanks are extended to all of the my committee members, Dr. David S. Crumrine, Dr. Mary K. Boyd and Dr. William A. Donaldson for their many discussions and helpful suggestions which made for the successful completion of my work. Thanks to Dr. K. Zaw for his assistance in obtaining the $^1$H-$^1$H 2D NMR (NOESY) spectra. I would also like to thank my laboratory partners Arab El-Qisairi, Qijian Yu and Xiaoli Ma for their helpful suggestions and friendship.

I would also like to take this opportunity to thank the NMR lab managers Mr. Chris Clifford and Dr. David French for their help and support on the NMR spectrometer. Special thank also to the Stock room manager Mr. Hovis Imade for his cooperation and support during this work.
Asymmetric synthesis is presently a rapidly progressing field of synthetic organic chemistry. The amazing growth in this field is understood by the fact that nearly all natural products are chiral and their biological activities depend upon their recognition by chiral receptors. These chiral receptors will interact only with molecules of the proper absolute configuration.

In the food industry, for example, aspartame with an (S,S) absolute configuration is a commercial sweetener, while the (S,R) distereoisomer has a bitter taste. Another example is, thalidomide (next page). The (R)-enantiomer exhibits desirable analgesic properties but the (S)-enantiomer does not. Instead, this enantiomer is teratogenic and induces fetal malformations or death.

There are two major approaches to achieving enantiopure compounds: resolution or asymmetric synthesis. The latter involves the use of a chiral starting material or chiral reagent.
This thesis is aimed toward synthesis of chiral organic compounds using both procedures. It is divided into two parts. The first part, which involves chirality transfer, is aimed at preparing chiral compounds from chiral starting material. The second part of this thesis involves the use of chiral palladium catalysts in asymmetric phenylation and oxygenation of olefins.

\( \text{O} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{O} \)

\( \text{H} \quad \text{H} \quad \text{(S)- Thalidomide} \quad \text{(R)- Thalidomide} \)
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Mosher's Acid</td>
<td>(R)-(+)α-Methoxy-α-(trifluoromethyl)phenylacetic Acid</td>
</tr>
<tr>
<td>Eu(hfc)₃</td>
<td>Tris[3-((heptafluoropropyl)hydroxymethylene)camphorato]europium(III)</td>
</tr>
<tr>
<td>ee</td>
<td>Enantimetric Excess</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>2,4-DNP</td>
<td>2,4-Dinitrophenylhydrazine</td>
</tr>
<tr>
<td>1,3-BPP</td>
<td>1,3-bis(diphenylphosphino) propane</td>
</tr>
<tr>
<td>(S,S)-BDPP</td>
<td>(S,S)-2,4-bis(diphenylphosphino)pentane</td>
</tr>
<tr>
<td>(S,S)-Chiraphos</td>
<td>(S,S)-2,3-bis(diphenylphosphino)butane</td>
</tr>
<tr>
<td>((R)-Tol-BINAP)</td>
<td>(R)-(+)2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl</td>
</tr>
<tr>
<td>NMP</td>
<td>1-Methyl-2-Pyrrolidine</td>
</tr>
<tr>
<td>Pd(PPh₃)</td>
<td>Tetrakis(triphenylphosphine)palladium(0)</td>
</tr>
<tr>
<td>Pd(dba)₂</td>
<td>Bis(dibenzylidineacetone)palladium(0)</td>
</tr>
</tbody>
</table>

**Chirality transfer**

\[
\frac{\text{ee of the product}}{\text{ee of the starting material}} = \times 100\%
\]
PART ONE

ASYMMETRIC SYNTHESIS BY CHIRALITY TRANSFER
CHAPTER I
INTRODUCTION

1.1 General Palladium Chemistry

In recent years, transition metal catalysis has experienced rapid growth in the field of organic synthesis. It has been used to prepare many kinds of valuable, complex organic molecules such as alkaloids, terpenoids, steroids and other natural products. Among these transition metals, palladium is the most versatile. Palladium catalyzes many types of organic reactions and is particularly useful for carbon-carbon bond forming reactions.\textsuperscript{1-4} Palladium not only has wide-spread use for laboratory synthesis, but also is an important catalyst for industrial processes.

Palladium is a gray-white metal which is ductile and malleable. Palladium was discovered by W. H. Wollaston who named it after the asteroid Pallas that was discovered a short time earlier. Palladium is a relatively rare element, occurring to the extent of one part in about $10^{13}$ of the earth's crust. It is extracted from copper-nickel ores which are found mainly in Canada, South America, and Russia.\textsuperscript{1}

Palladium has two main stable oxidation states: the zero-valent state and the +2 state, and its facile redox interchange between the two oxidation states is responsible for the rich reaction chemistry that palladium complexes display. Each oxidation state has its own unique chemistry.
Palladium(0) complexes are nucleophiles and strong bases and most commonly are used to catalyze reactions involving organic halides, acetates, and triflates. The two most readily available complexes for palladium(0) are tetrakis(triphenylphosphine) palladium(0), Pd(PPh\(_3\))\(_4\), and bis(dibenzylideneacetone)palladium(0), Pd(dba)\(_2\). Tetrakis (triphenylphosphine) palladium(0), complex was first prepared by Malatesta and Angoletta in 1957 by reducing a Pd(II) complex in the presence of excess ligand (Equation I.1). The bisdibenzylidene acetone complex is prepared simply by boiling palladium(II) chloride and dba together in methanol which acts as a reducing agent (Equation I.2).

\[
\begin{align*}
2 (\text{Ph}_3\text{P})_2\text{PdCl}_2 + 4 \text{Ph}_3\text{P} + 5 \text{N}_2\text{H}_4 &\longrightarrow 2 (\text{Ph}_3\text{P})_4\text{Pd} + 4 \text{N}_2\text{H}_3\text{Cl} + \text{N}_2 \\
\text{PdCl}_2 + \text{Ph} + \text{NaOAc} + \text{MeOH} &\longrightarrow \text{Pd(dba)}_2 + \text{CH}_2\text{O} + 2\text{HCl}
\end{align*}
\]

Palladium (II) complexes are moderate to strong electrophiles depending on the counter-ion and tend to react with electron-rich organic compounds such as olefins and arenes. Commercially available salts are Pd(OAc)\(_2\), Pd(CF\(_3\)CO\(_2\))\(_2\) and (PdCl\(_2\))\(_n\). The former two are relatively soluble in organic solvents but (PdCl\(_2\))\(_n\) is insoluble in all solvents. It forms soluble solvates with nitriles or M\(_2\)PdCl\(_4\) complexes with sodium and lithium chloride. Palladium(II) chloride exists in two forms; \(\alpha\) and \(\beta\). The unstable \(\alpha\)-form is a linear chain of doubly chloride-bridge Pd(II)\(_n\)'s (Scheme I.1). The most stable commercially available form, \(\beta\)-form consist
of octahedral clusters of six Pd(II) atoms which are joined by chloride bridges. Palladium (II) chloride can be prepared by reacting palladium metal with chlorine at 300 °C. Pd(II) chloride is the most common starting material for Pd(II) complexes (Scheme I.2).

Pd(II) complexes most commonly are used to catalyze the oxidation of organic compounds. The oldest and the best known reaction is the oxidation of olefins to carbonyl compounds, often called the Wacker process. No doubt much of the impetus in palladium(II) catalysis research was provided by the disclosure of the Wacker process. This concentrated effort on palladium(II) catalysis has resulted in the discovery of a number of new reactions. One, which has commercial possibilities, is vinyl ester synthesis (Equation I.3). Closely
\[ C_2H_4 + 2 \text{OAc}^- \xrightarrow{\text{Pd(II)}} \text{O}_2 \rightarrow \text{H}_2\text{C} = \text{CHOAc} + \text{HOAc} \quad (1.3) \]

\[
\begin{array}{c}
\text{Ph} - \text{HgCl} + \text{RCH} = \text{CH}_2 \xrightarrow{\text{PdCl}_2} \text{RCH} = \text{CHPh} \\
\end{array}
\quad (1.4)
\]

related are the olefin arylation (Heck reaction, Equation 1.4)\(^{11}\) and the allylic alkylation reaction (Equation 1.5).\(^{12-15}\)

\[
\begin{array}{c}
\text{Y} - \text{X} + \text{Z} \xrightarrow{\text{L}_4\text{Pd}} \text{Y} - \text{X} \\
\end{array}
\quad (1.5)
\]

\(Z = \text{Br, Cl, OAc, OPh, OH, CN.}\)
\(X, Y = \text{CO}_2\text{R, COR, SO}_2\text{Ph, CN, NO}_2.\)

Carbon monoxide is involved in many of the new reactions, included is the aromatic acid synthesis (Equation I.6),\(^{16}\) isocyanate synthesis (Equation I.7)\(^{17}\) and lactam and lactone

\[
\text{Ph} - \text{HgCl} + \text{PdCl}_2 + \text{CO} \rightarrow \text{Ph} - \text{COCl} + \text{Pd}^0 + \text{HgCl}_2 \quad (1.6)
\]

\[
\text{RNH}_2 + \text{PdCl}_2 + \text{CO} \rightarrow \text{RNCO} + 2\text{HCl} + \text{Pd}^0 \quad (1.7)
\]
syntheses. In some cases, both olefin and CO are involved. This is the case in the carbonylation of olefins \(^\text{22}\) (Equation I.8).

\[
RCH=CH_2 + CO + \text{PdCl}_2 \rightarrow RCHC=CH_2\text{COCl} + \text{Pd}^0
\]  

(1.8)

A reaction that involves neither olefin nor CO is the aromatic coupling reaction (Equation I.9).\(^\text{23}\)

\[
\text{R}-\text{HgCl} + \text{PdCl}_2 \rightarrow \text{R}\text{R} + \text{Pd}^0 + \text{HCl} + \text{HgCl}_2
\]  

(1.9)

The examples given above are just a few of the many new Pd(II)-catalyzed reactions.\(^\text{1-4}\). The Pd(II) catalyzed reaction whose mechanism has been most extensively studied is the basic reaction of the Wacker process, the oxidation of ethene by palladium(II) chloride to acetaldehyde. The mechanism of this reaction will be the focus of the research described in this part of the thesis.

### 1.2 Oxidation of Olefins to Carbonyl Compounds

The palladium(II)-catalyzed oxidation of ethylene to acetaldehyde is called the Wacker process after the company that developed it. This oxidation is carried out in the presence of oxygen and cupric chloride. The CuCl\(_2\) re-oxidizes the Pd(0) formed in the ethylene oxidation back to the active Pd(II) state (Equation I.10). The catalytic cycle is completed by oxidation of CuCl formed back to CuCl\(_2\) by O\(_2\). The synthetic value of the reaction is that terminal alkenes,
can be oxidized to methyl ketones (Equation I.11). In methanol, the analogous reaction gives acetals and ketals.²⁴

\[
\text{C}_2\text{H}_4 + \frac{1}{2} \text{O}_2 \xrightarrow{\text{PdCl}_4^{2-} / \text{CuCl}_2, \text{H}_2\text{O}} \text{CH}_3\text{CHO}
\]  
(I.10)

\[
\text{RCH}=\text{CHR'} + \frac{1}{2} \text{O}_2 \xrightarrow{\text{PdCl}_4^{2-} / \text{CuCl}_2, \text{H}_2\text{O}} \text{CH}_3\text{COCHR'}
\]  
(I.11)

Although the mechanism of this reaction has attracted considerable attention, there is still disagreement concerning the steric course of the addition of metal and nucleophile to the double bond (Path A or B, Scheme I.3). For the palladium(II) catalyzed oxidation of acyclic
olefins in water and methanol, the rate expression for ethene is given by Equation I.12, where

\[
\frac{-d[C_2H_4]}{dt} = \frac{k[PdCl_4^{2-}][C_2H_4]}{[H^+][Cl^-]^2}
\]  

(I.12)

all workers agree the square chloride inhibition factor results from the two equilibria shown in Equation I.13 and I.14 to give 1a.

\[
PdCl_4^{2-} + C_2H_4 \rightleftharpoons PdCl_3(C_2H_4)^- + Cl^- \quad 1/[Cl^-] \text{ term (I.13)}
\]

\[
PdCl_3(C_2H_4)^- + H_2O \rightleftharpoons PdCl_3(C_2H_4)(H_2O)^- + Cl^- \quad 1/[Cl^-] \text{ term (I.14)}
\]

1a

However, it is the acid inhibition that has spawned controversy. The rate expression is consistent with the two routes shown in Scheme I.3. Path A involves anti attack by external solvent in an equilibrium step followed by rate determining decomposition to oxidation product. The equilibrium is required to explain the proton inhibition term. If hydroxypalladation were the slow step, there would be no proton inhibition term in the rate expression. Path B involves release of a proton in an acid-base equilibrium to give 1b, followed by syn addition of Pd(II) and coordinated hydroxide. In this case, the rate determining step could be hydroxypalladation although the kinetics do not require it to be. Note that the syn addition requires two coordination sites on 1b, one for olefin and one for hydroxyl, while the anti addition requires only one. This will be an important point in the following discussion.
The experimental arguments in favor of the syn addition mechanism are based on: (1) comparisons of kinetic and competitive isotope effects that indicate the hydride-shift step occurs after the rate determining step (Scheme I.3),\textsuperscript{26,27} (2) secondary isotope effects that are inconsistent with equilibrium hydroxypalladation,\textsuperscript{28} and (3) studies of the oxidation and isomerization of deuterated allylic alcohol.\textsuperscript{29}

The rate expression for the oxidation of allyl alcohol to Wacker products (Equation I.15) is given by Equation I.12. Thus the oxidation of allyl alcohol must proceed by the same

\[
\begin{align*}
\text{H}_2\text{C} &= \text{CHCH}_2\text{OH} \quad \text{PdCl}_4^{2-} \quad \text{H}_2\text{O} \quad \text{CH}_3\text{CCH}_2\text{OH} + \text{HOCH}_2\text{CH}_2\text{CH}
\end{align*}
\]

(1.15)

mechanism as other acyclic olefins. With allyl alcohol, equilibrium hydroxypalladation can be detected by the isomerization of allyl-1,1-\textit{d}_2 alcohol into allyl-3,3-\textit{d}_2 alcohol (Equation I.16). However, at [Cl\textsuperscript{−}] < 1.0 M no isomerization was observed, indicating that in this system, the hydroxypalladation is not an equilibrium process but rather the slow step of the oxidation.

\[
\begin{align*}
\text{H}_2\text{O} + \text{H}_2\text{C} &= \text{CHCD}_2\text{OH} + \text{Pd(II)} \quad \overset{k_1}{\underset{k_1^-}{\rightleftharpoons}} \quad \text{HOCH}_2\text{CHCD}_2\text{OH} + \text{H}^+ \\
\text{Pd(II)}
\end{align*}
\]

(1.16)

The evidence for anti hydroxypalladation arises from stereochemical studies.\textsuperscript{30-32} Since the aldehydes and ketones formed under Wacker conditions do not give stereochemical information, the substrate must be devised to give a product whose identity indicates formation
by syn or anti addition. The tacit assumption in these studies is that the mode of hydroxypalladation is independent of reaction conditions and substrate structure. It is this assumption that the writers, as well as the others,\(^\text{30}\) feel has led to significant confusion and misunderstanding in the field of palladium catalysis.

The most convincing argument for the anti addition route (Scheme I.3; Path A) is stereochemical studies at high [Cl\(^-\)] in the presence of CuCl\(_2\) conditions, under which ethene gives 2-chloroethanol. Using the CuCl\(_2\)-promoted reaction, Bäckvall, Åkemark and co-workers determined the stereochemistry of the hydroxypalladation at high [Cl\(^-\)]. The oxidation of Z- and E-ethene-\(\text{d}_2\) at high [Cl\(^-\)] in the presence of CuCl\(_2\) produced 2-chloroethanol-1,2-\(\text{d}_2\) with a configuration consistent only with anti hydroxypalladation (Scheme I.4). These workers make the assumption that the same intermediate which decomposed to acetaldehyde at low
[Cl\textsuperscript{−}] is the one intercepted by CuCl\textsubscript{2} at high [Cl\textsuperscript{−}]. This assumption appears to be reasonable but it is important to remember that 2-chloroethanol is only formed under high chloride conditions (>3 M). Since these chloride concentrations are much higher than those employed in the Wacker process, there is the possibility that the mode of addition is changed.

Isomerization studies with deuterated allyl alcohol under these high chloride conditions provide evidence that the intermediate which undergoes anti hydroxypalladation is not the same intermediate-producing acetaldehyde at low [Cl\textsuperscript{−}]. It was found that allyl alcohol-\textsuperscript{1,1-d\textsubscript{2}}, which is oxidized to Wacker product by the rate expression given by equation 1.12 at low [Cl\textsuperscript{−}], undergoes a non-oxidative isomerization and solvent exchange at high [Cl\textsuperscript{−}].\textsuperscript{33} The rate expression for the isomerization (Equation I.17) has only a single chloride inhibition and thus

\[
\frac{-d[C_3H_4D_2O]}{dt} = \frac{k[PdCl_4]^{-2}[C_3H_4D_2O]}{[Cl^{-}]}
\]  

(I.17)

becomes the predominant reaction at high [Cl\textsuperscript{−}]. The kinetics are consistent with the exchange proceeding by anti addition to a trichloropalladium(II) π-complex (2a) as shown in Equation I.18. Compound 3 is analogous to the intermediate in the ethene oxidation that is intercepted

\[
2a \quad \rightarrow \quad 2b
\]
by CuCl₂ to give 2-chloroethanol. If this analysis is correct, the stereochemistry at higher chloride is not related to the mode of addition at low chloride under Wacker conditions.

These two investigations serve to demonstrate the versatility in the modes of palladium catalysis. Further evidence in support of different modes of addition at high and low [Cl⁻] has been reported by Francis and Henry.³³,²⁴ Kinetic and stereochemical results from the investigation of the hydroxypalladation of the chiral allylic alcohol 2-(methyl-d₃)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol (4) showed that, at low chloride concentrations chiral 4a (Scheme I.5) gave exchange product with the same geometric configuration but with inversion of optical configuration. Furthermore, the rate of formation of inverted product was the same as the rate of isomerization indicating the addition of both Pd(II) and hydroxide was very stereospecific. This result is most consistent with syn addition to the most stable rotamer as shown in path B Scheme I.3.

On the other hand, at high [Cl⁻] the exchange occurred with retention of optical configuration and inversion of geometric configuration. As shown in scheme I.5 (next page), this result is most consistent with anti addition of water.

However, the most important results of the two studies is that stereochemistries of addition at high and low [Cl⁻] must be different. Since the stereochemistry of hydroxypalladation was determined independently to be anti at high [Cl⁻] it must be syn at low [Cl⁻].³² The mechanistic inference that can be deduced from the previous results is outlined as follows. As shown in Scheme I.3, syn attack requires two coordination sites which are open by the equilibrium shown in Equations I.13 and I.14. The net result is that the hydroxypalladation adduct (1') has a labile aquo ligand which makes it unstable to decomposition by hydride
transfer to yield aldehyde or ketone product. Thus, the same factor that encourages syn addition also encourages formation of carbonyl product. On the other hand, high chloride concentrations discourages syn addition because it removes labile coordination sites by reversing the equilibrium shown in Equation 1.14. The net result is that at high [Cl\textsuperscript{-}], the addition becomes anti (Equation 1.18). Since the lack of labile coordination sites stabilizes the intermediate, it does not readily decompose to carbonyl product by hydride shift. This implies that Pd(II) at high [Cl\textsuperscript{-}] becomes an exchange and isomerization catalyst and has a sufficient lifetime to be intercepted by CuCl\textsubscript{2} to produce saturated product.

The result at high [Cl\textsuperscript{-}] was confirmed by a study with a catalyst containing the neutral ligand pyridine (Py).\textsuperscript{34} This complex was chosen because, as shown in Scheme 1.6 (next page) the $\pi$-complex (6) from this catalyst will be neutral and thus not tend to lose a chloride from the coordination sphere to give a positively charged species. Therefore anti attack will be strongly encouraged. The hydroxypalladation adduct (7), from this catalyst, would have a single negative charge, and will not readily lose a chloride to yield an intermediate such as 1' (Scheme
I.3) with an available aquo coordination site required for hydride shift to produce a carbonyl product. Oxidation of ethylene by this complex occurred only at low [Cl⁻] (<0.05 M). Exchange studies with chiral 4a indicated that the reaction at high [Cl⁻] was a non-oxidative exchange which proceeded by anti addition. 35

I.3 Scope of The Research

This research involves synthetic utility of chirality transfer when chiral allylic alcohols are oxidized by Pd(II). The research has two divergent goals. The first is to define stereochemical paths and thus provide further mechanistic evidence for the modes of Pd(II) catalysis. The second goal is to develop new tools for natural product synthesis.
L3.1 Hydroxypalladation Studies

These studies can be best illustrated using an allylic alcohol, 1,1,1,5,5,5-hexafluoro-3-penten-2-ol (8), which has already been studied to a considerable extent by Francis and Henry (Scheme 1.7, next page). This allylic alcohol is a convenient substrate, since the presence of the trifluoromethyl group gives this allylic alcohol the necessary hydrolytic stability under the acid conditions of the Wacker oxidation and also provides considerable steric hindrance to rotation. Desktop energy calculations showed that the most stable rotamer is the one in which the OH and CF₃ groups are furthest from the CH₃ group on the olefin. When only one geometric isomer is present, the OH directs the Pd(II) moiety to one face or the other of the olefin. The actual face depends on the absolute configuration of the starting alcohol. The studies on this system showed that the isomer formed is the (S) with 98% selectivity.

The directing influence of the hydroxy group is predicted from Cram's rule and has been confirmed from several epoxidation reactions. In addition, partial 1,2 chirality transfer has been demonstrated for palladium(II)-catalyzed addition of a phenyl group (Heck reaction)
to chiral 3-methyl-but-3-en-2-ol. Further, there is evidence for a very strong directing effect of the hydroxy group from the studies on oxidation of deuteriated 2-cyclohexenol-1-d conducted by Henry and Zaw (Scheme I.8).

Scheme I.8

The simplest allylic alcohols which could be used for these studies are Z and E-3-hexen-2-ol or its allylic isomer, 4-hexen-3-ol. The reaction sequence with Z-4-hexen-3-ol (9) is shown in Equation I.19 assuming syn-hydroxypalladation.

The important result will be to establish absolute configuration and optical purity of 10a in order to determine its mode of formation. Thus did it arise from syn addition to the most stable rotamer and, is its optical purity high enough for asymmetric synthesis? It would
also be necessary to confirm that the absolute configuration of 10b, which did not arise from chirality transfer, has the same configuration as the starting allylic alcohol.

1.3.2 Other Pd(II) Reagents

One likely extension from these studies would use related Pd(II) reagents. One such reagent referred to above is phenylpalladium(II). Other reagents that could be of synthetic utility and considerable mechanistic interest are acetate and methoxide.

For these studies, it would be experimentally easier to employ Z- and E-3-penten-2-ol (11) since the rotation of the (S) and (R) configuration are known for both geometric isomers as well as the product when phenylpalladium(II) is the reagent. The reaction scheme is shown in Equation I.20 where X is the nucleophile and syn addition is used for purpose of illustration.

An especially interesting case is one where X is a carbonyl ester group. In this case, the Pd(II) reagent will be prepared by exchange of AcOHgCO₂R with Pd(II). If the carbonyl group in the product is reduced back to the alcohol, these monomers could be converted to chiral polyester polymers by self condensation of ester group with the alcohol group.
1.3.3 Preparation of Trisubstituted Organic Products

These studies would involve the synthesis of novel trichiral molecules by substitution on the middle carbon by several techniques. If the oxidation in Equation 1.21 is carried out at high [Cl] (>3.0 M) in the presence of CuCl₂, a 1,3-glycol with 3 chiral centers can be prepared.

(R)-Z-9

A particularly noteworthy case is the reaction of the original olefin 3-penten-2-ol in basic methanol with CO. In this case, chiral diester would be formed which could be used to prepare cross-linked chiral polymers.43-46
CHAPTER II

Pd(II) CATALYZED OXIDATION AND ISOMERIZATION OF CHIRAL ALLYLIC ALCOHOLS. EVIDENCE FOR DIFFERENT MODES OF ADDITION AT HIGH AND LOW [Cl\(^-\)]

II.1 Results and Discussion

The purpose of this study is to examine the Wacker oxidation of the chiral allylic alcohols 3-hexen-2-ol (13a) and 4-hexen-3-ol (13b) to obtain stereochemical information using the directing influence of the hydroxy group.

The basis of chirality transfer is the fact that a chiral allylic alcohol with restricted rotation will direct PdCl\(_2\)\(^-\) to one face of the olefin by hydrogen bonding between the alcohol hydrogen and a chloride on the Pd(II) to give a unique \(\pi\)-complex. The face to which the palladium(II) is directed will depend on the absolute configuration of the chiral alcohol carbon. Equation II.1 shows the specific \(\pi\)-complex formed for one absolute configuration. Attack of a nucleophile such as water on this \(\pi\)-complex will produce an intermediate hydroxypalladation adduct with an absolute configuration depending on the mode of addition of the nucleophile.
and the stereochemistry of the olefinic bond. Decomposition of the intermediate will thus give chiral products which will indicate the mode of addition. Note that the hydroxypalladation adducts can oxidatively decompose in two ways since there are two hydroxy reaction sites adjacent to the Pd(II). As shown in Equation II.2 the two products, 12a and 12b, will always be formed in approximately equal amounts. However, only 12a provides stereochemical information on the mode of addition.

The possible reaction sequences for syn and anti additions to the chiral allylic alcohols used in this study are outlined in Scheme II.1 on the following page. As shown in Scheme II.1, the face to which the Pd(II) is directed will depend on the absolute configuration of the starting alcohol. Anti hydroxypalladation of the most stable rotamer π-complex of (R)-(Z)-13 gives the adduct 14a that can either eliminate Pd(II)-OH from the original alcohol carbon in a anti fashion as required by the principle of microscopic reversibility to give the allylic isomer, (S)-(Z)-13, or oxidatively decompose to give the hydroxyketone, (S)-15. Alternately, syn addition affords intermediate 14b that can react to give the products (R)-(E)-13 and (R)-15. A less likely possibility is that addition occurs from the least stable isomer thereby reversing the syn and anti product outcomes. Thus syn addition would afford 14b and the resulting exchange

![Diagram](image-url)
and oxidation products, (R)-(E)-13 and (R)-15. However the determination of the relative modes of addition would not change except in the very unlikely event that one mode of addition occurs to one π-complex at low [Cl] and another mode of addition to the other π-complex at high [Cl].

The oxidation studies at low [Cl] were conducted using the two geometric isomers, (R)-(E)-13a and (R)-(E)-13a, (R1 = C2H5; R2 = CH3) as the substrates. (R)-3-Hexyn-2-ol was prepared by the reduction of 3-hexyn-2-one with (alpine-borane) reagent. A sample of (R)-Z-13a was prepared in 66% ee by reduction of the triple bond with Lindlar catalyst, and a sample of (R)-E-13a was prepared in 65% ee by reduction of the triple bond with LiAlH4.
As shown in Scheme II.1, oxidation of (R)-(−)-Z-13a at low [Cl\textsuperscript{−}] (0.1 M) gave a mixture of two products: 4-hydroxy-2-hexanone (15a: R\textsubscript{1} = C\textsubscript{2}H\textsubscript{5}; R\textsubscript{2} = CH\textsubscript{3}) and 5-hydroxy-3-hexanone (15b: R\textsubscript{1} = CH\textsubscript{3}; R\textsubscript{2} = C\textsubscript{2}H\textsubscript{5}) in relative yields of 57% and 43%, respectively. A pure sample of 15a was isolated from the reaction mixture by preparative gas chromatography. \textsuperscript{1}H NMR analysis of 15a in the presence of the chiral shift reagent Eu(hfc)\textsubscript{3}, indicated the presence of the two enantiomers S-15a and R-15a in the ratio: 1:2.45 (42% ee, Figure A.1, Appendix A), so the chirality transfer was 64%. The ee of 15b was determined in the same manner to be 38% (Figure A.2, Appendix A).

Oxidation of (R)-(−)-E-13a in the same manner used in the oxidation of (R)-(−)-Z-13a also gave a mixture of two products 15a and 15b. Gas chromatography and \textsuperscript{1}H NMR analysis showed that the two compounds, 15a and 15b, are present in relative yields of 29% and 71%, respectively. A pure sample of 15b was collected by preparative gas chromatography. \textsuperscript{1}H NMR analysis of the collected sample in the presence of the chiral shift reagent Eu(hfc)\textsubscript{3}, showed the two enantiomers, R-15b and S-15b, are present in the ratio: 2.3:1 (36% ee). The ee of 15a was determined in the same manner to be 28% (R configuration), which corresponds to a chirality transfer of 40%.

The absolute configuration of 15a and 15b was determined by converting them into their Mosher's esters.\textsuperscript{49} The configuration was determined to be R for compounds 15a and R for 15b when (R)-Z-13a was employed. The following discussion demonstrates the manner in which the absolute configuration was determined. The Fisher projections depicted in Scheme II.2 (next page) for the four diasteriomers (R,R)-15a, (R,S)-15a, (R,R)-15b and (R,S)-15b indicate that, in (R,S)-15a the methyl carbonyl group is deshielded in comparison to that of
(R,R)-15a since it is facing an aromatic ring. As shown in Figure A.1 (Appendix A), the two CH₃ signals derived from the Mosher's ester of 15a at 2.17 ppm and 2.12 ppm could be assigned to (R,S)-15a and (R,R)-15a, respectively. Also Scheme II.2 reveals that, in comparison to that of (R,S)-15a, the methoxy group in (R,R)-15a is deshielded since it is facing the carbonyl group. So the two -OCH₃ signals derived from Mosher's ester 15a at δ 3.81 ppm and δ 3.74 ppm in Figure A.3 (Appendix A) could be assigned to (R,R)-15a and (R,S)-15a, respectively. Furthermore, the C-6 methyl group in (R,R)-15b is deshielded in comparison to that for the (R,S)-15b, since, as shown in Scheme II.2, it is facing a phenyl
group. Referring to Figure A.2 (Appendix A), the two C-6 methyl groups derived from compound 15b at δ 1.89 ppm and at δ 1.83 ppm could be assigned to (R,R)-15b and (R,S)-15b, respectively. Since the areas under the peaks assigned for the R-enantiomers in Figures A.1, 2, and 3 (Appendix A) are larger than those assigned for the S-enantiomers we can conclude that, the absolute configuration of 15a and 15b are "R". The absolute configuration of 15a obtained from oxidation of (R)-(-)-E-13a was determined to be "R" by comparing its $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ with an authentic sample in the presence of Eu(hfc)$_3$.

These results are most consistent with syn addition to the most stable rotamer as shown in Scheme II.1.

The isomerization studies were carried out with (R)-(−)-Z-4-hexen-3-ol (13b; R$_1$ = CH$_3$; R$_2$ = C$_2$H$_5$), prepared in 76% ee by procedure analogs to that for 13a. The isomerization was conducted at high [Cl$^-$] (2.0 M). A pure sample of the isomerization product was isolated by preparative gas chromatography. $^1$H and $^{13}$C NMR analysis of the collected sample showed that the product is a 1:1 mixture of Z-4-hexen-3-ol (13b) and Z-3-hexen-2-ol (13a) (Figure A.4, Appendix A). Enantiomeric excesses for both compounds (Z)-13b and (Z)-13a, as determined by $^1$H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$, were 74% and 77%, respectively (Figure A.5, Appendix A). Therefore the chirality transfer is 100%. The absolute configuration of (Z)-13a and (Z)-13b were determined to be R and S, respectively, by comparing their $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ with those of an authentic samples in the presence of Eu(hfc)$_3$. The above results, which showed about 0% racemization, were obtained when the reaction mixture was left stirring for approximately 30 min. However
a small amount of racemization was observed when the reaction mixture was stirred for approximately 1 h.

A likely mechanism that account for these result is depicted in Scheme II.3. The

![Scheme II.3](image)

rotamer with the CH$_3$ on an opposite side of the C$_2$H$_5$ is the most stable one. This causes the hydroxy group in (R)-(Z)-13b to direct the PdCl$_2^{-}$ to the olefin face of the double bond to give the π-complex 16a, followed by anti addition of H$_2$O to give the oxypalladation intermediate, 16, which reverses the hydroxypalladation process to yield (S)-(Z)-13a as the exchange product. This mechanism is consistent with the kinetics shown in Equation I.17. The single chloride inhibition only allows for incorporation of olefin into the coordination sphere to give π-complex formation, which is always an intermediate in catalytic reactions of olefins with transition metals. The stability of the intermediate against the oxidative isomerization can be explained by the extra chloride in the coordination sphere of the intermediate. This extra chloride prevents decomposition by a β-hydride shift to give carbonyl products.
The stereochemical results of this work are in complete agreement with those of Francis and Henry, who showed that the isomerization of 2-(methyl-d3)-4-methyl-1,1,1,5,5,5 hexafluoro-3-penten-2-ol in aqueous solution catalyzed by PdCl42- at high and low [Cl-], give different stereochemical results.30,31 The addition is syn at low [Cl-] and anti at high [Cl-].

II.2 Experimental

II.2.1 Materials

All chemicals were from Aldrich Chemical Company, unless otherwise specified, and were used as received. 3-Hexyn-2-ol and 4-hexyn-3-ol were purchased from Lancaster Synthesis Inc. and used without further purification. Chromium trioxide was purchased from Fisher Scientific Company. Pd(OAc)2 was purchased from Alfa Aesar and used without further purification. THF was dried over sodium benzophenone ketyl, distilled and stored over CaH2 under Ar. All other chemicals were reagent grade. Stock solutions in water of the following composition were prepared: 0.2 M in K2PdCl4, and 0.2 M in HCl. Stock solutions in methanol of the following composition were prepared: 0.2 M in Li2PdCl4, and 0.2 M in LiCl. Reaction mixtures were prepared by diluting stock solutions.

II.2.2 Physical Measurements

1H NMR data were recorded on a Varian VXR 300 NMR spectrometer. 2D NOSEY experiments were carried out on GE OMEGA 500 NMR. All 1H NMR spectra in the presence of Eu(hfc)3 were carried out in CDCl3. GLC analysis were carried out using a GOW-MAC 350 gas chromatography fitted with Carbowax 10 M on 80-100 mesh Chromosorb W-NAW
columns. IR spectra were obtained on a ATI Mattson Genesis Series FT-IR or a Perkin Elmer 1310 Infrared spectrometer. All chemical shifts are reported relative to tetramethylsilane as internal standard.

II.2.3 Preparation of Pyridinium Chlorochromate

To 46.0 mL of 6.0 M HCl was added 25.0 g (0.25 mol) of CrO\textsubscript{3} rapidly with stirring. After about 5 min the homogenous solution was cooled to 0 °C followed by the careful addition of 16.3 mL pyridine (15.8 g, 0.2 mol) over approximately 10 min. Recooling to 0 °C produce a yellow orange solid which was collected by suction filtration and dried in vacuum.

II.2.4 Preparation of 3-Hexyn-2-one\textsuperscript{52}

In a 250-mL round bottomed flask fitted with a reflux condenser and magnetic stirring bar, 12.9 g (0.060 mol) of pyridinium chlorochromate in 50 mL CH\textsubscript{2}Cl\textsubscript{2} was suspended. 3-Hexyn-2-ol, 4.4 mL (3.9 g, 0.04 mol), in 10 mL of CH\textsubscript{2}Cl\textsubscript{2} was then added in one portion to the stirred mixture. After 2 h, 100 mL of ether was added and the supernatant was decanted from the black gum. Next the black gum was washed three times with 50 mL portions of ether. The combined ether washings were dried over MgSO\textsubscript{4} and the solvent was distilled. The residue upon distillation at 62 - 64 °C at 50 mm Hg (Lit\textsuperscript{60} b. p. 77 - 78 °C at 75 mm Hg) gave 3.0 g (0.03 mol) of 3-hexyn-2-one, 77% yield. \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta: 2.31 (q, 2H), 2.26 (s, 3H), 1.15 (t, 3H).

II.2.5 Preparation of (R)-3-Hexyn-2-ol

An oven-dried 500 mL round bottom flask equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser, and stopcock adapter connected to a mercury bubbler,
was assembled hot and flushed with a steam of Ar. After the apparatus was cooled, it was charged, via a double-ended syringe, with 309 mL of a 0.5 M THF solution of 9-BBN (0.152 mol). Then 27.0 mL (23.2 g, 0.17 mol) of α-pinene was added. After the solution was refluxed for 4 h, the excess α-pinene and THF were removed first by water aspirator and then by vacuum pump at 40 °C to provide a thick clear oil. The flask was then cooled in an ice bath and 12 mL (10.8 g, 0.108 mol) of 3-hexyn-2-one was added under Ar. Stirring was continued for 8 h, the first 2 h at 0 °C following by warming to room temperature. Then 8.4 mL of acetaldehyde was added to the solution and stirring was continued for another 1 h. Next, liberated α-pinene was removed under vacuum. Then 75 mL of THF and 57 mL of 3 M NaOH were added followed by dropwise addition of 57 mL of 30% H2O2. The mixture was stirred for 4 h at 40 °C and extracted with Et2O (3 x 50 mL). The ether layers were combined, dried over MgSO4, filtered and concentrated to yield an oil. Distillation at 72 - 74 °C at 50 mm Hg provided 7.7 g (0.79 mol) of 3-hexyn-2-ol, 73% yield. IR (neat): 3350, 3005, 2220, 720 cm⁻¹. ¹H NMR (CDCl₃) δ: 4.58 (q, 1H), 2.45 (b, 1H, OH), 2.25 (q, 2H), 1.63 (d, 3H), 1.67 (t, 3H). Optical rotation [α]D ³ 24 (neat) +18.8. Examination of the ¹H NMR spectrum in the presence of Eu(hfc)₃ indicated an enantiomeric mixture containing 84% (R) (68% ee).

II.2.6 Preparation of (R)-(−)-(Z)-3-Hexen-2-ol (13a)

A low pressure hydrogenation apparatus was charged with 10 mL of hexane, 3.5 mL (3.2 g, 0.032 mol) of (R)-(−)-3-hexyn-2-ol, 0.2 g of Pd on CaCO₃ poisoned with lead (Lindlar’s catalyst) and 20 drops of quinoline. The apparatus was evacuated and hydrogen was admitted to a pressure slightly above 1 atm. The contents of the flask was shaken until
absorption of hydrogen stopped. The catalyst was removed by filtration, hexane was distilled off and the residue, upon distillation at 80 - 82 °C produced 2.2 g (0.022 mol, 71% yield) of colorless liquid. GLC analysis of the product indicated it to be a 98% pure Z isomer. Optical rotation \[\alpha\]_D^{24} (neat) -6.20, \(^1\)H NMR (CDCl₃) δ: 5.43 (m, 2H), 4.65 (m, 1H), 2.12 (m, 2H), 1.90 (b, 1H, OH), 1.63 (d, 3H, J = 6.2 Hz), 1.00 (t, 3H, J = 7.2 Hz). \(^1\)H NMR (CDCl₃) study of the product in the presence of Eu(hfc)_₃ indicated the sample was 83% (R) (66% ee).

II.2.7 Preparation of (R)-(-)-E-3-Hexen-2-ol

A 100-mL flask was dried in an oven and cooled down to room temperature under a stream of Ar. The flask was equipped with a magnetic stirring bar and a refluxing condenser connected to a drying tube filled with anhydrous CaCl₂. Then 25 mL of dry THF was introduced into the flask followed by 1.3 g (30 mmol) of LiAlH₄ and 3.5 mL (3.2 g, 32 mmol) of (R)-(+)3-hexyn-2-ol. The mixture was refluxed for 3 h. Hydrolysis was affected by successive addition of H₂O (3.0 mL), 15% NaOH (2.0 mL) and H₂O (6.0 mL). The mixture was filtered and the precipitate was washed with ethyl ether (2 x 25 mL). The organic layers were combined and dried over anhydrous MgSO₄. The solvent was removed by distillation to give crude product which upon distillation at 82 - 84 °C at 50 mm Hg produced 2.5 g (77%) of a colorless liquid which was >98% pure E isomer by GLC. \(^1\)H NMR (CDCl₃) δ: 5.70 (m, 1H, J = 15.8 Hz and 6.6 Hz), 5.50 (m, 1H, J = 15.8 Hz and 7.2 Hz), 4.25 (m, 1H, J = 6.8), 2.05 (m, 2H), 1.26 (d, 3H, J = 6.2 Hz), 0.99 (t, 3H, J = 7.2 Hz). Study of the \(^1\)H NMR (CDCl₃) in the presence of the lanthanide shift reagent Eu(hfc)_₃ showed that the product is a mixture of two enantiomers containing 82.5 % (R) (65% ee).
II.2.8 Oxidation of (R)-(−)-(Z)-3-Hexen-2-ol (13a)

The reaction was carried out in an open round bottom flask. The reaction solution (50.0 mL) was 0.1 M in K₂PdCl₄, 0.1 M in HCl, and 0.1 M in benzoquinone. (R)-(−)-Z-13a 0.65 mL (0.11 M) was gradually added over a period of 20 min. The solution was stirred for another 20 min, Zn powder was added, and the mixture was stirred for another 10 min followed by extraction with ether (3 x 50 mL). The combined extracts were combined dried (MgSO₄, anhydrous). Analysis of the product by GLC and ¹H NMR showed that the product is a mixture of two compounds 15a and 15b in relative yields of 57% and 43%, respectively. Pure samples of 15a and 15b were obtained by preparative GLC. ¹H NMR (CDCl₃) of 15a: δ: 3.95 (m, 1H), 2.97 (bd, 1H, OH), 2.60 (dd, 2H), 2.19 (s, 3H), 1.50 (m, 2H), 0.95 (t, 3H). ¹³C NMR (CDCl₃) δ: 187.5, 63.9, 50.1, 36.7, 22.4, 7.6. ¹H NMR (CDCl₃) of 15b: δ: 4.25 (m, 1H), 3.28 (bd, 1H, OH), 2.55 (dd, 2H, J = 3.2 and 16.2), 2.45 (q, 2H, J = 7.1 Hz), 1.19 (d, 3H, J = 6.4 Hz), 1.07 (t, 3H, J = 7.3 Hz). ¹³C NMR (CDCl₃) of 15b: δ: 197.5, 64.2, 50.1, 37.2, 22.4, 7.5. The ee of 15a and 15b as determined by ¹H NMR (CDCl₃) in the presence of the lanthanide shift reagent Eu(hfc)₃ to be 42% and 38%, respectively.

II.2.9 Preparation of (R)-MTPA Derivative of 4-Hydroxy-2-hexanone (15a)

The reagents were injected by a syringe into a 1 mL conical vial fitted with a rubber septum in the following order, dry pyridine (300 µL), carbon tetrachloride (300 µL), (+)-MTPA-Cl (37 µL, 0.15 mmol), and 15 (11.5 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for about 48 h. Excess 3-dimethylethlamino-2-propylamine 24 µL (20 mg, 0.2 mmol) was added and the mixture was stirred for another 10 min. It was then
diluted with ether, washed with cold dilute HCl, cold saturated Na₂CO₃ and saturated NaCl, after drying over MgSO₄, the ether was removed under vacuum. The ¹H NMR (CDCl₃) spectrum of the residue was taken in the presence of Eu(hfc)₃.

II.2.10 Preparation of (R)-(+-)MTPA Derivative of 5-Hydroxy-3-hexanone (15b)

See preparation of (R)-(+-)MTPA derivative of 4-hydroxy-2-hexanone (II.2.9)

II.2.11 Oxidation of (R)-(+-)E-3-Hexen-2-ol

See oxidation of (R)-Z-13a. Oxidation of (R)-(E)-13a afforded 15a and 15b in 29% and 71% relative yields, respectively. The ee of 15a and 15b, as determined by ¹H NMR (CDCl₃) in the presence of the lanthanide shift reagent, were 28% and 36%, respectively.

II.2.12 Isomerization of (R)-(-)-(Z)-4-Hexen-3-ol (13b)

The reaction solution (25.0 mL H₂O) was 0.05 M in Li₂PdCl₄, 0.2 M in benzoquinone, 2.0 M in LiCl and 0.06 M in (R)-(->)-Z-(13b). LiClO₄ was added to bring the ionic strength (µ) to 2.0 M. The reaction mixture was stirred for 30 min at room temperature and CH₂Cl₂ was used to extract the product (3 x 30 mL). The extracts were combined, dried over MgSO₄ and evaporated. A pure sample of the product was collected by preparative gas chromatography. The product was identified by ¹H and ¹³C NMR to be a mixture of equal amounts of (R)-(->)-Z-(13b) and (S)-(->)-Z-(13a) as shown in Figure A.4 (Appendix A). The ee was determined by ¹H NMR (CDCl₃) in the presence of the chiral shift reagent Eu(hfc)₃.
III.1 Results and Discussion

The studies discussed in the previous chapter suggest that the oxidation of chiral allylic alcohols could be a general procedure for asymmetric synthesis.

In this chapter and the next one the use of chirality transfer to form optically active compounds with new carbon-carbon or carbon-oxygen bonds will be discussed.

The chiral allylic alcohols chosen for these studies were the geometric isomers (R)-(−)-Z and (+)-E-3-penten-2-ol (17), which were prepared by reduction of the corresponding pentyn-ol. A sample of propynylmagnesium bromide was prepared from propyne and ethylmagnesium bromide. This was reacted with acetaldehyde to give 3-pentyn-2-ol in 52% yield. 3-Pentyn-2-one was prepared by oxidation of the 3-pentyn-2-ol with pyridinium chlorochromate.\(^\text{52}\) (R)-(+)3-pentyn-2-ol was prepared by the reduction of 3-pentyn-2-one with (alpine-borane) reagent, which was prepared from (+)-\(\alpha\)-pinene and 9-BBN.\(^\text{47}\) A sample of (R)-(Z)-17 was prepared in 53% ee by reduction of the triple bond with Lindlar catalyst while a sample of (R)-(E)-17 was prepared in 52% ee by reduction with LiAlH\(_4\). GLC analysis showed that each sample was greater than 98% the desired double bond isomer.
Treatment of the geometric isomers (R)-Z and (R)-E-(17) with various nucleophiles in the presence of catalytic amount of Pd(II) gave various optically active β-substituted ketones (Equation III.1). Pure samples of the products were obtained by preparative GLC and identified by $^1$H and $^{13}$C NMR. The ee of the products were determined using $^1$H NMR in the presence of Eu(hfc)$_3$. The results from the (R)-Z-isomer are summarized in Table III.1 (next page), and those for the (R)-E- isomer in Table III.2 (next page).

![Chemical structure](image)

(R)-E-17: $R_1 = H$, $R_2 = Me$

(R)-Z-17: $R_1 = Me$, $R_2 = H$

X-Pd(II) $\rightarrow$

(X = OH, OCH$_3$, Ph, OAc, CO$_2$Me, $R_1 = H$, $R_2 = Me$

III.1.1 Hydroxylation of (R)-(−)-Z-17

As can be seen from Table III.1 (entry 1) hydroxylation of (R)-Z-17 gave 4-hydroxy-2-pentanone (18) in 34% ee (Figure B.1, Appendix B). The absolute configuration of 18 was determined to be R by converting the two enantiomers of 18 into their Mosher’s esters and determining the shift of the two-CH$_3$ signals in the presence of Eu(hfc)$_3$.

On the basis of the stereochemical result obtained above, the most reasonable pathway for the formation of R-18 is shown in Scheme III.1 (next page). As shown in Scheme III.1 the initial π-complex, 19, undergoes syn hydroxypalladation to the most stable rotamer to give the unsymmetrical intermediate, 20, with an absolute configuration of (R,R). Intermediate 20 then
### Table III.1. Results for the oxidation of (R)-Z-17 (ee = 53%) with various nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Species$^a$</th>
<th>X</th>
<th>Solvent</th>
<th>Configuration</th>
<th>%ee</th>
<th>Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li$_2$PdCl$_4$</td>
<td>OH</td>
<td>H$_2$O</td>
<td>R</td>
<td>34</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>CH$_3$O</td>
<td>CH$_3$OH</td>
<td>R</td>
<td>36</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>Li$_2$PdCl$_4$</td>
<td>CH$_3$O</td>
<td>CH$_3$OH</td>
<td>R</td>
<td>42</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Li$_2$PdCl$_4$</td>
<td>Ph</td>
<td>CH$_3$OH</td>
<td>R</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>Li$_2$Pd$_2$Cl$_6$</td>
<td>Ph</td>
<td>CH$_3$CN</td>
<td>R</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Li$_2$Pd$_2$(OAc)$_6$</td>
<td>OAc</td>
<td>HOAc</td>
<td>R</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>Li$_2$Pd$_2$Cl$_6$</td>
<td>OAc</td>
<td>HOAc</td>
<td>R</td>
<td>42</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>Li$_2$Pd$_2$Cl$_6$</td>
<td>OAc</td>
<td>HOAc</td>
<td>S</td>
<td>26</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>Li$_2$PdCl$_4$</td>
<td>CO$_2$Me</td>
<td>CH$_3$CN</td>
<td>R</td>
<td>26</td>
<td>49</td>
</tr>
</tbody>
</table>

$^a$ The formulas are the form of the catalytic species under the reaction conditions (see ref 1; pp 11-15). $^b$ Also 0.1 M in HCl. $^c$ State of catalyst unknown. $^d$ Also 0.8 M in LiOAc. $^e$ Also 1.0 M in LiCl.

### Table III.2. Results for the oxidation of (R)-E-17 (ee = 52%) with various nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Species$^a$</th>
<th>X</th>
<th>Solvent</th>
<th>Configuration</th>
<th>%ee</th>
<th>Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>CH$_3$O</td>
<td>CH$_3$OH</td>
<td>R</td>
<td>28</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Li$_2$PdCl$_4$</td>
<td>CH$_3$O</td>
<td>CH$_3$OH</td>
<td>R</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Li$_2$PdCl$_4$</td>
<td>Ph</td>
<td>CH$_3$OH</td>
<td>R</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Li$_2$Pd$_2$Cl$_6$</td>
<td>Ph</td>
<td>CH$_3$CN</td>
<td>R</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>Li$_2$Pd$_2$(OAc)$_6$</td>
<td>OAc</td>
<td>HOAc</td>
<td>R</td>
<td>12</td>
<td>23</td>
</tr>
</tbody>
</table>

$^a$ The formulas are the form of the catalytic species under the reaction conditions (see ref 1; pp 11-15). $^b$ State of catalyst unknown. $^c$ Also 0.8 M in LiOAc.
undergoes β-hydrogen elimination to give the final product R-18. Anti hydroxypalladation would give an intermediate with (R,S) absolute configuration, which, in the present case, would be symmetric and lead to a racemic product. So the results of this study are further evidence of syn addition to the most stable rotamer at low [Cl−].

Scheme III.1

III.1.2 Methoxylation of (R)-(−)-Z- and (R)-(E)-(−)-17

As shown in Table III.1 (entries 2 and 3) methoxylation of (R)-(−)-Z-(17) was carried out in methanol and catalyzed by either Pd(OAc)2 or Li2PdCl4 at low concentration of LiCl. When Pd(OAc)2 was used, two products were found: 4-methoxy-2-pentanone (21) and 3-penten-2-one (22) in 60% and 40% relative yields, respectively. When Li2PdCl4 was used, 21 was the only product.
The enantiomeric purity of 21 was determined to be 36% when the reaction was catalyzed by Pd(OAc)$_2$, and 42% when the reaction was catalyzed by Li$_2$PdCl$_4$ (Figure B.2, Appendix B). Thus the chirality transfer was 68% when Pd(OAc)$_2$ was used and 79% when Li$_2$PdCl$_4$ was employed. The absolute configuration of 21 was determined to be "R", by comparing its $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ with that of an authentic sample in the presence of Eu(hfc)$_3$.

An authentic sample of 21 was prepared by O-methylation of 18 in MeI in the presence of silver(I) oxide in the dark at 60 °C.\textsuperscript{45}

The most reasonable pathway for the later reaction is shown in Scheme III.2. The first...

Methoxylation of (R)-(+)E-(17) was carried out as above and the results are shown in Table III.2 (entries 1 and 2). When Pd(OAc)$_2$ was used, the product was a mixture of two compounds 21 and 22 in about 40% and 60% relative yields, respectively. The enantiomeric purity of 21 was determined to be 28% in the case of Pd(OAc)$_2$, and 8% in the case of Li$_2$PdCl$_4$. The absolute configuration of 21 was determined as before to be "R". These results are most consistent with syn addition to the most stable rotamer as shown in Scheme III.2.

The ally! ketone 22 is most likely formed by direct hydrogen extraction from the alcoholic carbon by Pd(II) as was suggested by previous workers. The most likely pathway for the formation of 22 is presented in Equation III.2

III.1.3 Phenylation of (R)-(−)-Z- and (R)-(+)E-17

As can be seen from Table III.1 (entries 3 and 4), phenylation of (R)-Z-17 was performed in two different solvents, methanol and acetonitrile. Methanol was chosen to perform the phenylation under conditions similar to that for Wacker process and acetonitrile was chosen to imitate the original Heck reaction. In both solvents CuCl$_2$ was used as re-
oxidant, triethylamine as a base and PhHgCl as the phenylating agent. In methanol the reaction was catalyzed by Li₂PdCl₄ while in acetonitrile LiPdCl₃ was used as a catalyst. The main product from these reactions was 4-phenyl-2-pentanone (31) which was purified by column chromatography. The ee of (31) from R-17 was determined to be 30% when the reaction was carried out in methanol (Figure B.3, Appendix B) and to be 36% when the reaction was performed in acetonitrile.

The absolute configuration of 31 was determined to be "R" by comparing its specific rotation [α] with that reported in the literature⁴⁰ and by comparing its ¹H NMR with that for an authentic sample both in the presence of Eu(hfc).³

A possible reaction pathway leading to R-23 is shown in Scheme III.3. The initial

\[
\text{Li}_2\text{PdCl}_4 + \text{PhHgCl} \xrightarrow{\text{MeOH}} \text{Ph-Pd-Cl}^2- + \text{Cl}^- + \text{CuCl}_2
\]

Scheme III.3

\[
\text{H}_3\text{C} = \text{C(Ph)(OH)} \xrightarrow{\text{Cl-Pd-Cl}} \text{R-23, ee} = 34\%
\]
phenylpalladium complex, 24, reacts with the olefin 17 to give the π-complex 25. Nucleophilic attack by a Ph group regioselectively at position 4 of the allyl alcohol 17 gives the intermediate 26 which undergoes decomposition to the final product 23.

When (R)-(+)E-17 was employed, the ee of 23 was determined to be 14% from methanol (Figure B.4, Appendix B) and 16% from acetonitrile (Table III.2, entries 3 and 4). The absolute configuration was determined as before to be "R". The absolute configuration is consistent with syn addition to the most stable rotamer as shown in Scheme III.3.

### III.1.4 Acetoxylation of (R)-(−)-Z- and -E-(+)-17

The acetoxylation of (R)-(−)-Z-17 (ee = 53%) was carried out in acetic acid in the presence of LiOAc and a catalytic amount of Pd(OAc)$_2$. Benzoquinone and MnO$_2$ were added as re-oxidants. The product of this reaction was identified to be 4-acetoxy-2-pentanone (27). As shown in Table III.1 (entry 6) the ee of 27 was determined to be 28% (Figure B.5, Appendix B). The absolute configuration of 27 was determined to be "R" by comparing the $^1$H NMR spectrum of 27 in the presence of Eu(hfc)$_3$ with that of an authentic sample in the presence of Eu(hfc)$_3$. The authentic sample was prepared by an O-acylation of (R)-4-hydroxy-2-pentanone (18) by reaction with acetyl chloride in CCl$_4$ in the presence of pyridine. R configuration of 27 is most consistent with syn addition to the most stable rotamer. The reaction pathway is depicted in Scheme III.4 (next page). Again, the first step involves the coordination of the olefin to give the π-complex, 28a. The most stable rotamer of complexed olefin undergoes syn
acetate attack to give the intermediate, 29a, which undergoes Wacker type oxidation to give 4-acetoxy-2-pentanone (27).

Acetoxylation of (R)-E-17 in the same way gave 27 in 12% ee with "R" absolute configuration. Again R configuration of 27 is most consistent with syn addition to the most stable rotamer as shown in Scheme III.4.

Scheme III.4

\[
\begin{align*}
\text{CH}_3 & \quad \text{OH} & & \quad \text{Pd(OAc)}_2 & & \quad \text{HOAc} & \\
\text{C} = \text{C} & & \quad \text{H} & & \quad \text{Pd} & & \quad \text{OAc}^- \\
(R)^{-}(-)(Z)^{-}17 & & & & 27 & & \text{ee} = 28\%
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H} & & \quad \text{Pd} & & \quad \text{OAc} \\
\text{C} & & \quad \text{OH} & & \quad \text{OAc} \\
27 & & & & 28a & & \text{LiOAc}
\end{align*}
\]

In another reaction the acetoxylation of (R)-Z-17 was carried out in acetic acid with a catalytic amount of Li$_2$PdCl$_4$ in the presence of LiOAc. The enantiomeric excess of the
product was determined to be 42% (Figure B.6, Appendix B) and the absolute configuration was found to be "R" (Table III.1, entry 7) by comparing the $^1$H NMR spectrum of the product with that of an authentic sample in the presence of Eu(hfc)$_3$.

Performing the same reaction in the presence of LiCl (1 M) changes the steric course of the nucleophilic attack and gives S-27 with an ee of 26% (Figure B.7, Appendix B).

A likely mechanism which accounts for the result (Scheme III.5) is that the chloride

Scheme III.5

\[
\begin{align*}
\text{(R)-(−)-(Z)-17} & \quad + \quad \text{PdCl}_2 \\
\text{[LiCl] = 1M} & \quad \text{[LiCl] = 1M} \\
\text{S-27} & \quad \text{Pd}^0 \\
\text{Pd}^0 + \text{benzoquinone} & \quad \text{Pd}^{II} + \text{hydroquinone}
\end{align*}
\]
ions effectively block the coordination of acetate to palladium and hence hinders the syn migration path. Thus in the absence of the chloride ion the attack was mainly syn on the π-complex 28a and in the presence of the chloride ion both syn and anti attack occurs. The mode of addition depends on the chloride ion concentration; increasing the chloride ion concentration increases the extent of anti attack.

**III.1.5 Carbonylation of (R)-(−)-Z-17**

The carbonylation of R-Z-(17) was carried out in acetonitrile in the presence of carbomethoxy mercuric chloride, 30, as the carbomethoxyating agent. The reaction was catalyzed by Li₂PdCl₄. The product was a mixture of two compounds. The first compound which was present in 80% relative yield was identified by GLC to be 3-penten-2-one (22). The second product was identified to be 4-carbomethoxy-2-pentanone (31), its ee was determined to be 26% (Table III.1, entry 9). The absolute configuration was not determined. However, from the previous results we can conclude that, the absolute configuration is “R” and the reaction proceeds as shown in Scheme III.6 (next page). In the first step the palladium catalyst exchanges carbomethoxy group with compound 38, followed by the formation of the π-complex 32, nucleophilic attack of the carbomethoxy group regioselectively, at position 4 of the substrate (R)-Z-17 gives the σ-alkyl complex 33 which subsequently undergoes oxidation to give the product 31.

The above procedure was tested in other solvents such as methanol and THF. The best yield was obtained in acetonitrile solvent.
Since the above procedure resulted in forming (31) in a very low yield, other procedures were tested. In one reaction, carbomethoxymercuric acetate was used as carbomethoxylating agent. The reaction was carried out in methanol and catalyzed by 

\[
\text{LiPdCl}_3 + \text{MeO}_2\text{CHgCl} \rightarrow \text{MeO}_2\text{C-Pd-Cl}^{(\text{R}-\text{Z}-17)} \rightarrow \text{MeO}_2\text{C-Pd-Cl}^{32} \\
\text{Pd}(\text{OAc})_2. \quad \text{Analysis of the product by GLC showed that, compound (31) was not present. In other similar reactions re-oxidants such as CuCl}_2 \text{ and benzoquinone were used, but again no (31) was formed.}
\]

III.2 Experimental

III.2.1 Preparation of 3-Pentyn-2-ol

A clean oven dried 3-necked one litre flask equipped with a magnetic stirring bar, a dropping funnel, and a reflux condenser connected with a drying tube filled with anhydrous
CaCl₂, was used for this experiment. Acetaldehyde (27.8 mL, 22.0 g, 0.5 mol) in 50 mL anhydrous ether was gradually added to a solution of propenylmagnesium bromide obtained by passing propyne into a solution of ethylmagnesium bromide (from Mg 12.15 g (0.5 mol) and ethyl bromide 54.5 g (0.5 mol)) in 500 mL of anhydrous ether at 0 °C. After 5 hours of stirring, ice-cold saturated aqueous ammonium chloride (500 mL) was added. The ethereal layer was separated, dried over anhydrous MgSO₄ and fractionated, giving 21.9 g (52%) of 3-pentyn-2-ol, b.p. 117 - 119 °C (Lit 61 118 - 121 °C).

IR (neat): 3350, 2220 cm⁻¹.

### III.2.2 Preparation of 3-Pentyn-2-one

In a 500-mL round bottomed flask fitted with a reflux condenser and magnetic stirring bar was suspended 64.6 g (0.3 mol) of pyridinium chlorochromate in 100 mL of CH₂Cl₂. 3-Pentyn-2-ol (19 mL, 16.8 g, 0.2 mol) in 20 mL of CH₂Cl₂ was added in one portion to the magnetically stirred solution. After 2 hr, 200 mL of ether was added and the supernatant decanted from the black gum. The insoluble black gum was washed 3 times with 100 mL portions of ether. The combined ether was dried over MgSO₄ and removed by distillation. The residue upon distillation at 56 - 58 °C at 50 mm Hg gave 12.3 g (0.15 mol) of 3-pentyn-2-one, 75% yield. ¹H NMR (CDCl₃) δ: 2.02 (s, 3H), 2.32 (s, 3H).

### III.2.3 Preparation of (R)-(+) 3-Pentyn-2-ol

An oven-dried 500 mL 3-necked round bottom flask, equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser, and stopcock adapter connected to a mercury
bubbler was assembled hot and flushed with a stream of Ar. After the apparatus cooled, it was charged, via a double-ended syringe, with 303 mL of a 0.5 M THF solution of 9-BBN (0.15 mol). Then 27.0 mL (23.2 g, 0.17 mol) of α-pinene was added. After the solution was refluxed for 4 h, the excess α-pinene and THF were removed first by water aspirator followed by vacuum pump at 40 °C to provide a clear thick oil. The vacuum was released with Ar. The flask was cooled to 0 °C (ice bath) and 10.2 mL (8.9 g, 0.108 mol) of 3-pentyn-2-one was added. Stirring was continued for 8 h, the first 2 h at 0 °C. Then 8.4 mL of acetaldehyde was added to the solution and stirring continued for another 1 h. Liberated α-pinene was then removed by vacuum, and 75 mL of THF was added followed by 57 mL of 3 M NaOH. Then 57 mL of 30% H₂O₂ was added dropwise. The mixture was stirred for 4 h at 40 °C, and extracted with Et₂O (3 x 50 mL). The ether layers were combined and dried over MgSO₄, filtered and concentrated by rotary evaporation to give an oil. Distillation at 64 - 66 °C at 50 mm Hg provided 6.3 g (76 mmol) of 3-pentyn-2-ol, 70% yield. IR (neat): 3350, 3005, 2220, 720 cm⁻¹. ¹H NMR (CDCl₃) δ: 4.48 (m, 1H), 2.55 (variable, broad, 1H, OH), 1.82 (s, 3H), 1.42 (d, 3H). Optical rotation [α]²⁴ D +19.71 (neat). Examination of the ¹H NMR spectrum in the presence of Eu(hfc)₃ indicated an enantiomeric mixture of 78.5% (R) and 21.5% (S), (57% ee).

III.2.4 Preparation of (R)-(−)-(Z)-3-penten-2-ol (17)

A low pressure hydrogenation flask of the hydrogenation apparatus was charged with 5 mL of hexane, 2.2 mL (2.1 g, 25 mmol) of (R)-(−)-3-pentyn-2-ol, 0.1 g of Pd on CaCO₃
poisoned with Pb (Lindlar's catalyst) and two drops of quinoline. The apparatus was evacuated and hydrogen was admitted to a pressure slightly above 1 atm. The contents of the flask was shaken until absorption of hydrogen stopped. The catalyst was removed by filtration, hexane was distilled off and the residue upon distillation at 61 - 63 °C at 50 mm Hg (Lit b.p 118 - 121 °C) gave 1.5 g (70%) of a colorless liquid. GLC analysis of the product indicated it to be 98% pure Z isomer.

Optical rotation $[\alpha]_D^{24}$ -7.91 (neat), IR (neat): 3350, 3005, 1605, 720 cm$^{-1}$. $^1$H NMR (CDCl$_3$) δ: 5.52 (m, 1H), 5.40 (m, 1H), 4.65 (dq, J = 18.60 Hz and 6.28 Hz, 1H), 2.15 (br, 1H, OH), 1.68 (d, J = 6.50 Hz, 3H), 1.25 (d, J = 6.35 Hz, 3H). NMR study of the product in the presence of Eu(hfc)$_3$ indicated the sample was 78.3% (R) (56.6% ee).

**III.2.5 Preparation of (R)-(+)-(E)-3-penten-2-ol (17)**

A 100-mL flask was dried in an oven and cooled down to room temperature under a stream of argon. The flask was equipped with a magnetic stirring bar, and a refluxing condenser connected to drying tube of CaCl$_2$ (anhydrous). A 200 mL sample of dry THF was introduced into the flask followed by 1.3 g (0.3 mol) of LiAlH$_4$ and 3.5 mL (3.2 g, 38 mmol) of (R)-(+)3-pentyn-2-ol. The mixture was stirred for 3 h at room temperature. Hydrolysis was affected by careful dropwise addition of H$_2$O (3.0 mL), 15% NaOH (2.0 mL) and H$_2$O (6.0 mL). The mixture was filtered and the precipitate was washed with ethyl ether (2 x 30 mL). The organic layers were combined dried over anhydrous MgSO$_4$ and distilled off. The residue upon distillation at 62 - 64 °C at 50 mm Hg gave 2.5 g (77%) of a colorless liquid which was >98% pure E isomer by GLC.
Optical rotation $[\alpha]_D^{24} + 4.95$ (c = 5, methanol). IR (neat): 3350, 3005, 1605, 980 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) $\delta$: 5.7 (dd, $J = 6.32$ Hz and 15.30 Hz, 1H), 5.52 (dq, $J = 6.43$ Hz and 15.30 Hz, 1H), 4.25 (dq, $J = 6.30$ Hz and 19.00 Hz, 1H), 2.10 (br, 1H, OH), 1.54 (d, $J = 6.45$ Hz, 3H), 1.22 (d, $J = 6.50$ Hz, 3H). Study of the $^1$H NMR in the presence of the lanthanide shift reagent Eu(hfc)$_3$ showed that the product is a mixture of the two enantiomers containing 76.5% (R) (53% ee).

III.2.6 Oxidation of (R)-(−)-(Z)-3-penten-2-ol

See oxidation of (R)-(−)-Z-3-hexen-2-ol (II.2.8).

Oxidation of (R)-(−)-(Z)-17 1.0 mL (0.89 g, 0.10 mol) afforded 0.65 g of 4-hydroxy-2-pentanone (18) (65% yield). The ee (34%) of 18 was determined by $^1$H NMR in the presence of Eu(hfc)$_3$. The absolute configuration was determined to be "R" by converting the two enantiomers of 18 into their Mosher's ester and determining the shift of the two-CH$_3$ signals in the presence of Eu(hfc)$_3$. $^1$H NMR (CDCl$_3$) $\delta$: 4.2 (m, 1H), 3.05 (b, 1H), 2.07 (dd, 2H, $J = 3.2$ and 13.1), 2.16 (S, 3H), 1.69 (d, 3H, $J = 6.3$). $^{13}$C NMR (CDCl$_3$) $\delta$: 209.6, 83.8, 51.4, 30.75, 22.36.

III.2.7 Pd(OAc)$_2$ Catalyzed Methoxylation of (R)-(−)-Z-(17)

To a solution of 0.25 mL (0.21 g, 2.5 mmol) of (R)-(−)-Z-17 (ee = 53%) in 5.0 mL methanol under Ar, was added 0.63 g (2.5 mmol) of Pd(OAc)$_2$. After stirring for 2 h at room temperature the mixture became black. The stirring was continued for another 10 h. The reaction mixture then diluted with water and filtered to remove the black precipitate. The
filtrate was extracted with CH$_2$Cl$_2$ (3 x 10 mL). CH$_2$Cl$_2$ layers were combined, dried over MgSO$_4$ and evaporated to yield 0.21 g (47%) of yellow liquid. Analysis by gas chromatography and NMR identified one product as 21. $^1$H NMR (CDCl$_3$) $\delta$: 3.78 (m, 1H), 3.29 (s, 3H), 2.70 (dd, 1H), 2.40 (dd, 1H), 2.15 (s, 3H), 1.15 (d, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$: 207.2, 73.2, 56.3, 50.6, 31.1, 19.13. The other compound was identified as 22 in 40% yield. $^1$H NMR (CDCl$_3$) $\delta$: 6.82 (m, 1H), 6.1 (dd, 1H), 2.2 (s, 3H), 1.90 (d, 3H).

III.2.8 Pd(OAc)$_2$ Catalyzed Methoxylation of (R)-(+)E-17

See methoxylation of (R)-(−)-Z-17 (III.2.7). Mass of the product was 0.156 g (35%, yield).

Analysis of the product by gas chromatography and $^1$H NMR showed the presence of 18 and 19 in a 1:2.3 ratio.

III.2.9 Li$_2$PdCl$_4$ Catalyzed Methoxylation of (R)-(−)-Z-17

A solution of 0.1 M Li$_2$PdCl$_4$, 0.1 M LiCl, and 0.1 M benzoquinone in 25 mL methanol was prepared. To this solution was added 0.35 mL (0.3 g, 0.35 mmol) of (R)-(−)-Z-17 (ee = 53%). The system was placed under Ar and stirred for 8 h at room temperature. The mixture was then diluted with water and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic phase was dried over MgSO$_4$ and solvent removed by distillation. Analysis of the residue by gas chromatography showed the presence of 21 and 22 in 95% and 5% relative yields, respectively. A pure sample of 22 was collected by preparative gas chromatography.
III.2.10 Li₂PdCl₄ Catalyzed Methoxylation of (R)-(+)−E-17

See Li₂PdCl₄ catalyzed methoxylation of (R)-(−)-Z-17.

III.2.11 Preparation of An authentic Sample of (R)-4-Methoxy-2-pentanone

O-Methylation of (R)-4-Hydroxy-2-Pentanone (18)

A 25 mL flask, equipped with a magnetic stirring bar and a refluxing condenser connected to a mercury bubbler, was charged with 5.0 mL methyl iodide, 0.17 mL (0.16 g, 1.6 mmol) of (R)-18, 0.15 g CaSO₄, and 0.37 g of silver(I) oxide. The stirred mixture was heated in the absence of light in a 60 °C oil bath for 27 h. Then 20 mL of ethyl ether was added, the mixture was filtered by suction using sintered glass funnel and the solid residue was washed with two-20 mL portions of ethyl ether. The ether washes were combined, and solvent removed by distillation. A pure sample of the product was obtained from the residue by preparative gas chromatography.

III.2.12 LiPdCl₃ Catalyzed Phenylation of (R)-(−)-Z-(17)

To a stirred solution of (R)-(−)-Z-17 (ee = 53%), 1.89 mL (1.68 g, 20 mmol) in 5.0 mL acetonitrile under Ar at room temperature were sequentially added Et₃N, 2.7 mL (3.3 g, 20 mL), phenylmercuric chloride, 2.73 g (20 mmol), cupric chloride 2.73 g (20 mmol) and 20 mL of 0.1 M LiPdCl₃ in acetonitrile. The reaction mixture was stirred overnight. Water (50 mL) was added and the insoluble material and the aqueous solution were extracted with hexane (3 x 50 mL). The combined extracts were washed twice with water and dried over MgSO₄. After evaporation of solvent, the yellow oily material was purified twice by column chromatography.
(silica gel, 8/2 hexane/Et$_2$O) to give 1.5 g (53% yield) of 4-phenyl-2-pentanone (23). IR (neat): 3030, 3010, 2990, 1720 cm$^{-1}$. $^1$H NMR (CDCl$_3$) $\delta$: 7.22 (m, 5H), 3.30 (m, 1H), 2.7 (dd, 2H), 2.07 (s, 3H), 1.69 (d, 3H). $^1$C NMR (CDCl$_3$) $\delta$: 143.0, 128.6, 126.6, 45.8, 42.3, 38.9, 31.2.

Optical rotation $[\alpha]_D^{24} +6.45$ (c = 5, cyclohexane). Lanthanide shift determination showed the presence of R (68%) and S (32%), (36% ee).

III.2.13 LiPdCl$_3$ Catalyzed Phenylation of (R)-(+-)-E-17

See phenylation of (R)-(+-)-Z-17 (previous page).

A 1.89 mL (1.68 g, 0.02 mol) sample of (R)-E-17 (ee = 51%) afforded 1.4 g (50% yield) of 4-phenyl-2-pentanone (23). Lanthanide shift determination showed the product to be 58% (R) and 42% (S), (16% ee).

III.2.14 Li$_2$PdCl$_4$ Catalyzed Phenylation of (R)-(+-)-Z-17

To a stirred solution of 0.1 M Li$_2$PdCl$_4$ in methanol (25.0 mL) was added 0.5 mL (3.7 mmol) Et$_3$N, 1.1 g (3.5 mmol) PhHgCl and 0.35 mL (0.3 g, 3.5 mmol) (R)-(+-)-Z-17 (ee = 53%). After stirring for 2 h at room temperature the reaction was diluted with water. The precipitate was removed by filtration and the filtrate and the precipitate were extracted with ether (3 x 30 mL). The ether layers were combined, dried over MgSO$_4$ and solvent removed under vacuum. The residue was purified twice by column chromatography (silica gel, 8/2 hexane/ether) to give 0.47 g (84% yield) of 4-phenyl-2-pentanone (23). $^1$H NMR determination in the presence of Eu(hfc)$_3$ showed the presence of the two enantiomers R and S, (30% ee).
III.2.15 Li₂PdCl₄ Catalyzed Phenylation of (R)-(+)−E-(17)

See phenylation of (R)-(−)−Z-17 (III.2.14). 0.35 mL of (R)-E-17 (ee = 53%) afforded 0.38 g (68% yield) of 23.

¹H NMR study of 23 in the presence of Eu(hfc)₃ showed the presence of the two enantiomers R and S, (14% ee).

III.2.16 Pd(OAc)₂ Catalyzed Acetoxylation of (R)-(−)-Z-17

To a stirred solution of Pd(OAc)₂ (0.1 g, 0.44 mmol), LiOAc.2H₂O (0.41 g, 4.0 mmol), and benzoquinone 0.11 g, (1 mmol) in acetic acid (5.0 mL) was added MnO₂ (0.36 g, 3 mmol) followed by 0.31 mL (0.26 g, 3 mmol) (R)-(−)-Z-17 (ee = 53%). The reaction was stirred at room temperature for 12 h, diluted with water (10 mL), extracted with petroleum ether-ether (1:1) (3 x 30 mL). The combined extracts were washed with saturated NaCl (2 x 30 mL), saturated NaHCO₃ (2 x 30 mL) and finally water (2 x 10 mL). The organic phase was dried (MgSO₄) and evaporated to give 0.33 g (76.4%, yield) of 27. ¹H NMR (CDCl₃) δ: 5.25 (m, 1H), 2.78 (dd, 1H), 2.55 (dd, 1H), 2.15 (s, 3H), 1.96 (s, 3H), 1.25 (d, 3H). ¹³C NMR (CDCl₃) δ: 20.7 (C=O), 21.2 (acetoxy methyl), 30.5 (C-1), 49.5 (C-3), 67.0 (C-4), 170.1 (acetoxy carbonyl), 205.2 (C-2).

III.2.17 Pd(OAc)₂ Catalyzed Acetoxylation of (R)-(−)-E-17

See acetoxylation of (R)-(−)-Z-17 (III.2.16). 0.3 mL of (R)-E-17 afforded 0.30 g (70%, yield) of 27.
III.2.18 Li₂PdCl₄ Catalyzed Acetoxylation of (R)-(−)-(Z)-17

See acetoxylation of (R)-(−)-(Z)-17. A 0.3 mL (0.28 g, 3 mmol) sample of (R)-(Z)-17 afforded 0.36 g (83% yield) of 27 with an ee of 42%.

III.2.19 Li₂PdCl₄ Catalyzed Acetoxylation of (R)-(−)-(Z)-17 in The Presence of LiCl

Same as Li₂PdCl₄ catalyzed acetoxylation of (R)-(−)-(Z)-17 except in this case the reaction was carried out in the presence of LiCl (1.0 M), 0.2 mL (0.17 g, 3 mmol) of (R)-(Z)-17 afforded 0.15 g (42% yield) of 27. A pure sample of the product was obtained by GLC, the ee (32%) of the product was determined by ¹H NMR in the presence of Eu(hfc)₃. The absolute configuration of 27 was found to be S.

III.2.20 Preparation of An Authentic Sample of 4-Acetoxy-2-pentanone

An oven-dried 25 mL flask, equipped with a rubber septum and a magnetic stirring bar, was charged with 1.5 mL CC₄, 1.5 mL pyridine, 0.11 mL (0.102 g, 1 mmol) of R-4-hydroxy-2-pentanone (R-18), and 0.085 mL (0.0942 g) of acetylchloride. The mixture was stirred at room temperature for 1 h. It was then diluted with ether, washed with cold diluted HCl, cold saturated NaHCO₃, H₂O and dried over MgSO₄. Ether was removed by distillation. A pure sample of the product was collected by GLC.

III.2.21 Preparation of Carbomethoxymercuric Acetate

A mixture of methanol (50 mL) and mercuric acetate (10.0 g) was stirred under about 2 atm of CO at room temperature for 48 h. The reaction mixture was then filtered to remove
the unreacted mercuric acetate and the filtrate was diluted with 200 mL ether. The resulting mixture was placed in the refrigerator to complete the crystallization of the product. The white shiny crystals were filtered, washed with ether and air dried. $^1$H NMR (CDCl$_3$) $\delta$: 3.76 (s, 3H), 2.07 (s, 3H).

III.2.22 Preparation of Carbomethoxymercuric Chloride (30)

A solution of carbomethoxymercuric acetate (2.0 g) in 10 mL methanol was prepared. To this solution was added a solution of NaCl (0.5 g) in H$_2$O (5.0 mL). The resulting solution was placed in the refrigerator for 12 h. The resulting white solid was filtered and dried under vacuum. $^1$H NMR (CDCl$_3$) $\delta$: 3.76 (s, 3H).

III.2.23 LiPdCl$_3$ Catalyzed Carbonylation of (R)-(−)-Z-17

A mixture of (R)-Z-17 (0.3 mL, 0.25 g, 3.0 mmol), 35 (0.75 g, 2.54 mmol), bezoquinone (0.35 g, 3.26 mmol), and 25 mL of 0.1 M LiPdCl$_3$ in acetonitrile solution was stirred at room temperature under Ar for 24 h. The reaction mixture was then filtered to remove the black precipitate and the solvent was evaporated under reduced pressure. The residue was extracted with ether. The combined ether extracts washed with dilute potassium cyanide and dried over magnesium sulfate. Removal of ether afforded 73 mg of crude product. A pure sample of the product (31) was obtained by GLC. $^1$H NMR of 31 (CDCl$_3$) $\delta$: 3.66 (s, 3H), 2.88 (m, 2H), 2.50 (m, 1H), 2.15 (s, 3H), 1.64 (d, 3H). The ee of 31 (26%) was determined by $^1$H NMR in the presence of the Eu(hfc)$_3$. 
CHAPTER IV
PALLADIUM (II)-CATALYZED SYNTHESIS OF OPTICALLY
ACTIVE 3,4-DICARBOMETHOXY-2-PENTANOL
A STUDY USING CHIRALITY TRANSFER

IV.1 Results And Discussion

Olefins are dicarbonylated catalytically by a PdCl₂ - CuCl₂ system in methanol under basic condition at low CO pressure (3 atm) to give diesters.⁴⁵,⁴⁶ The overall stereochemistry of addition is syn. While chirality transfer usually involves transfer of optical activity from one carbon to another, this system would involve novel double insertions of CO to give saturated products containing three chiral centers. The substrate for these studies are (R)-(Z)- and -(E)-3-penten-2-ol (17). Since the addition of the carbomethoxy group would be expected to be syn from the most stable π-complex, the reaction Scheme for (R)-Z-17 is shown in Scheme IV.1 (next page). The initial π-complex, 35a, reacts with methanol solvent to produce the carbomethoxy π-complex 36a which reacts by syn addition of the carbomethoxy group to give the intermediate 27a. The adduct 37a then undergoes further syn addition of CO to give 38a which decomposes to the final product, 34. As shown in Scheme IV.1, the face to which the Pd(II) is directed in the π-complexes, 35 and 36, will depend on the absolute configuration of the starting alcohol, 17. The most stable complex is that which has the two methyl groups furthest apart. As shown in Scheme IV.1, (R)-Z-17 would be expected to give the (2R, 3R,
4R) isomer. An analogous pathway for the (R)-E-17, shown in Scheme IV.2 (next page), would predict that the (2R, 3S, 4R) isomer would be formed.

Dicarbonylation of both isomers was carried out at 25 °C in a solution which was 0.06 M in PdCl₄²⁻, 1.0 M in sodium acetate and 1 M in cupric chloride under about 3 atm of carbon monoxide pressure. Anhydrous sodium acetate was used to prevent the methoxylation and CuCl₂ was used as re-oxidant. (R)-Z-17 (ee = 62%) gave 4-methoxy-2-pentanone 21, 4-acetoxy-2-pentanone 27, and 3,4-dicarbomethoxy-2-pentanol 34 in relative yields of 10%, 10% and 80%, respectively. A pure sample of 34 was collected by preparative GLC and the enantiomeric purity determined by ¹H and ¹³C NMR in the presence of chiral shift reagent
Scheme IV.2

\[
\begin{align*}
\text{(R)-(E)-17} & \quad + \text{PdCl}_2^2 + \text{CO} & \rightarrow \text{CO} \quad \text{(R)-(E)-17} & \quad + \text{PdCl}_2^2 + \text{CO} & \rightarrow \text{CO} \\
\end{align*}
\]

Eu(hfc)$_3$. It was found to be 62% ee at the alcoholic carbon, C-2, 58% ee at the C-3 and 62% ee at C-4 (Figure B.8, Appendix B). The chirality transfer is thus 100% at C-4.

The dicarbonylation of (R)-(+)E-17 (ee = 58%) gave 21, 27, 4-carbomethoxy-2-pentanone, 31, and 34 in relative yields of 5%, 20%, 30% and 45%, respectively. A pure sample of 34 was prepared as described above was found to have an ee of 58% at C-2, 62% at C-3, and 58% at C-4 (Figure B.9, Appendix B). Thus the chirality transfer was again 100% at C-4.

The absolute configuration of the product 34 from the carbonylation of (R)-Z- and (R)-E-17 was determined by $^1$H-$^1$H 2D NOESY NMR. The NOE assignments for the most stable rotamers of the two products are shown in the next page. These assignments are in
agreement with all the information from $^1$H-$^1$H NOSEY NMR shown in Figures IV.1 and 2. Figure IV.1 shows the spectra of 34 from (R)-Z-17. The intersecting lines indicated the location of possible NOE interactions. As predicted for (2R, 3R, 4R)-34, none were found.

Figure III.2 shows the spectra of 34 from (R)-E-17. As predicted for (2R, 3S, 4R), there are NOE interactions between the hydrogens on C$_2$-C$_3$ and C$_3$-C$_4$. The assignment of absolute configuration is consistent with the expected initial syn addition of the elements of the carbometoxy-Pd(II) moiety shown in Scheme IV.1 and 2.

There is always a possibility the reaction proceeds via a syn addition from the least stable isomer as shown in Scheme IV.3, page 59. If that's the case, the absolute configuration of 34 will be (2S, 3S, 4R) when (R)-Z-17 is used and (2S, 3R, 4R) when (R)-E-17 is used. The NOE interaction for these configurations are shown below.
Figure IV.1. NOESY spectrum for compound 34 obtained from carbonylation of (R)-Z-17. Intersecting lines indicate where the NOE interaction would have appeared.
Figure IV.2. NOESY spectrum for compound 34 obtained from carbonylation of (R)-E-17. Intersecting lines indicate where the NOE interaction would have appeared.
The NOE interaction in the (2S, 3S, 4R)-34 product are between the hydrogen on C2-C3 carbons while for the (2S, 3R, 4R)-34 product the interactions involve the C3-C4 carbons. As can be seen from Figures IV.1 and 2, these are not the observed NOE interactions.

The fact that the starting materials are not pure enantiomers does not affect the NOE results. Thus (S)-Z-17 undergoes carbonylation in the fashion shown in Scheme IV.1 to produce (2S, 3S, 4S)-34 (Scheme IV.3) which will display no NOE interactions. On the other hand, (S)-E-17 gives (2S, 3R, 4S)-34 which has the same NOE interactions as (2R, 3S, 4R)-34.

![Scheme IV.3](image-url)
A similar dicarbonylation was carried out with (S)-Z-17 (ee = 64%), GLC indicated the product contained more than 90% 34. A pure sample of 34 was obtained by preparative GLC. The enatiomeric purity of 34 as determined by $^1$H NMR in the presence of Eu(hfc)$_3$. It was 64% at C-2, 66% at C-3 and 64% at C-4 (Figure 10.B, Appendix B). The chirality transfer was again 100% at C-4.

The absolute configuration of 34 determined to be (2S, 3S, 4S) by comparing its $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ with that of an authentic sample obtained from (R)-Z-17.

The dicarbonylation was also carried out with (R)-2-cyclopenten-1-ol (35). A sample of R-35 was prepared in 24% ee by isomerization of the achiral cyclopentene oxide catalyzed by vitamin B$_{12}$.\textsuperscript{58}

Dicarbonylation of R-35 gave two products in 35% and 65%, relative yields as shown by GLC. The two products were identified by $^1$H and $^{13}$C NMR to be 3-carbomethoxy cyclopentan-2-one (36) and 2,3-dicarbomethoxy-1-pentanol (37), respectively (Equation IV.1).

\begin{equation}
\begin{array}{c}
\text{35} \\
\text{H} \\
\text{HO} \\
\text{PdCl$_2$} \\
\text{CO, MeOH} \\
\text{MeCO$_2$} \\
\text{36} \\
\text{H} \\
\text{MeCO$_2$} \\
\text{37} \\
\text{H} \\
\text{OH} \\
\text{CO$_2$Me}
\end{array}
\end{equation}

The ee of 37 was determined to be 24% at C-1, 22% at C-2 and 22% at C-3. The $J$ values of H$_2$ were determine to be 15.6 and 8.0 Hz, these values are consistent with syn stereochemistry.
between H₁, H₂ and H₃ as shown below. Since the absolute configuration at C-1 is known (R), the absolute configurations at C-2 and C-3 must be R and S, respectively.

The stereochemistry of the product 36 is consistent with a mechanism which requires initial π-complexation of the cyclic olefin directed by the hydroxy group followed by syn dicarbomethoxylation in a fashion analogous to that shown in Schemes IV.1 and IV.2.

![Chemical Structure](image)

**IV.2 Experimental**

**IV.2.1 Preparation of R-2-Cyclopenten-1-ol (34)**

To 15 mL methanol in a 100-mL flask under Ar were added in succession, 1.0 g (0.64 mmol) vitamin of B₁₂, 1.2 g of NH₄Cl and 1.0 g of mossy Zn. After stirring for 10 min cyclopentene oxide (2.5 mL, 28.0 mol) was added. The produced solution was stirred at room temperature for about 48 h, then the flask was opened and Et₂O (150 mL) was added. The produced colorless solution was decanted and the precipitate was extracted with Et₂O (3 x 15 mL). The combined ether solution was washed with saturated NaCl solution (3 x 10 mL) and dried over MgSO₄. Evaporation of Et₂O gave 2-cyclopenten-1-ol (34) (1.7 g, 72%). The ee was determined by ¹H NMR in the presence of Eu(hfc)₃ to be 24%.
IV.2.2 PdCl₂ Catalyzed Dicarbomethoxylation of (R)-(−)-Z-17

A 100 mL, two-necked flask equipped with magnetic stirring bar, septum and balloon, was charged with 10 mL methanol, 1.34 g (10 mmol) anhydrous sodium acetate, and 0.1 g PdCl₂. The air in the flask was replaced by CO by evacuating on an aspirator and then pressuring with about 2 atmospheres of CO through a needle. Then 0.51 mL (0.43 g, 5 mmol) of (R)-(−)-Z-17 (ee = 62%) was injected and the CO pressure was raised to about 3 atm. The reaction mixture was stirred at room temperature for 72 h. Product was isolated by collecting the precipitate using gravity filtration and washing it with methanol. Methanol was evaporated under vacuum and the residue extracted with petroleum ether. The petroleum ether extracts were combined, filtered and solvent removed under vacuum. A pure sample of the product was collected by preparative gas chromatography. The product was identified as 34 by ¹H and ¹³C NMR. ¹H NMR (CDCl₃) δ: 3.95 (m, 1H), 3.74(s, 3), 3.29 (s, 3H), 3.08 (s, 1H), 2.85 (m, 1H), 2.42 (dd, 1H), 1.36 (d, 3H), 1.20 (d, 3H); ¹³C (CDCl₃) δ: 16.63 (C-1 methyl), 22.40 (C-5 methyl), 51.73 (C-3 methyne), 56.8 (C-4 methyne), 58.4 (C-3 carbomethoxylate methyl), 66.1 (C-4, carbomethoxylate methyl), 76.5 (C-2, methyne), 168.6 (C-4, carboxylate carbonyl), 174.4 (C-3, carboxylate carbonyl).

IV.2.3 PdCl₂ Catalyzed Dicabonylation of (R)-(−)-E-17

See dicarbonylation of (R)-(−)-Z-17.

IV.2.4 PdCl₂ Catalyzed Dicabonylation of (R)-34

Dicarbonylation of (R)-34 as shown in IV.2.2 afforded 3-carbomethoxycyclopenten-2-one (35) and 2,3-dicarbomethoxyxycyclopenten-1-ol (36) in 35% and 65%, relative yield (85% total chemical yield). Spectral data of the products were as follows.
3-Carbomethoxycyclopenten-2-one (35): $^1$H NMR (CHCl$_3$) $\delta$: 3.71 (s, 3H), 3.12 (m, 1H), 2.48 (t, 3H), 2.4-2.06 (m, 4H). $^{13}$C NMR (CHCl$_3$) $\delta$: 206.8, 174.3, 41.2, 40.8, 37.5, 26.6.

2,3-Dicarbomethoxycyclopenten-1-ol (36): $^1$H NMR (CHCl$_3$) $\delta$: 4.40 (m, 1H) 3.66 (s, 3H), 3.64 (s, 3H), 3.31 (s, 1H, OH), 3.18 (q, $J$ = 15.6 and 8.0 Hz, 1H), 3.10 (dd, $J$ = 8.2 and 3.5, 1H), 2.00-2.16 (m, 4H). $^{13}$C NMR (CHCl$_3$) $\delta$: 26.4 (C-4), 30.7 (C-5), 45.7(C-3), 51.0 (C-2), 52.8 (C-3, carbomethoxy methyl), 57.0 (C-2, carbomethoxy methyl), 84.4 (C-1), 172.7 (C-3, carboxylate carbonyl), 173.8 (C-2, carboxylate carbonyl).
Figure A.1. Illustrative part of the \(^1\)H NMR spectrum of Mosher's ester of 15a in the presence of Eu(hfc)\(_3\). The spectrum shows the resolved methyl carbonyl protons. The methyl carbonyl protons of the (R,R) diastereomer appear at lower field than those of the (R,S) diastereomer.
Figure A.2. Illustrative part of the $^1$H NMR spectrum of Mosher's ester of 15b in the presence of Eu(hfc)$_3$. The spectrum shows the resolved C-5 methyl protons. The C-5 methyl protons of the (R,R) diastereomers appear at higher field than those of the (R,S) diastereomers.
Figure A.3 Illustrative part of the $^1$H NMR spectrum of Mosher's ester of 15a in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methoxy protons. The methoxy protons of the (R,R) diastereomer appear at higher field than those of the (R,S) diastereomer.
Figure A.4. $^1$H and $^{13}$C NMR spectrum of the product obtained from the isomerization of (R)-Z-13b. The spectrum shows that the product is a mixture of 50% of each of (R)-(-)-Z-4-hexen-3-ol and (S)-(E)-3-hexen-2-ol (13a).
Figure A.5. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of the product obtained from isomerization of (R)-Z-13b. The spectrum shows the resolved C-3 and C-2 proton in (S)-Z-13a and (R)-Z-13b, respectively.
Appendix B
Figure B.1. Illustrative part of the $^1$H NMR spectrum of 18 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methyl and carbonyl protons. The R enantiomer appear in higher yield than the S enantiomer.
Figure B.2. Illustrative part of the $^1$H NMR spectrum of 21 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methoxy and carbonyl protons. The R enantiomer appear in higher yield than the S enantiomer.
Figure B.3. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of 23 obtained from phenylation of (R)-Z-17. The spectrum shows the resolved C-5 protons. The C-5 protons of the R enantiomer appear at lower field than those of the S enantiomer.
Figure B.4. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of 23 obtained from phenylation of (R)-E-17. The spectrum shows the resolved C-5 protons. The C-5 protons of the R enantiomer appear at lower field than those of the S enantiomer.
Figure B.5. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of 27 obtained from acetoxylation of (R)-Z-17. The spectrum shows the resolved C-4 acetoxy methyl- and carbonyl methyl-protons. The R enantiomer present in higher yield.
Figure B.6. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of 27 obtained from acetoxylation of (R)-Z-17. The spectrum shows the resolved C-4 acetoxy methyl- and carbonyl methyl-protons. The R enatiomer present in higher yield.
Figure B.7. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of 27 obtained from acetoxylation of (R)-Z-17 in the presence of 1 M LiCl. The spectrum shows the resolved carbonyl methyl- and the acetoxy methyl-protons. The S enantiomer present in higher yield.
Figure B.8. Illustrative part of the $^1$H NMR spectrum of 34 in the presence of Eu(hfc)$_3$ obtained from dicarbonylation of (R)-Z-17. The spectrum shows the resolved C-3 and C-4 carbomethoxylate methyls protons.
Figure B.9. Illustrative part of the $^1$H NMR spectrum of 34 in the presence of Eu(hfc)$_2$ obtained from dicarbonylation of (R)-E-17. The spectrum shows the resolved C-3 and C-4 carbomethoxylate methyl protons.
Figure B.10. Illustrative part of the $^1$H NMR spectrum of 34 in the presence of Eu(hfc)$_3$ obtained from dicarbonylation of (S)-Z-17. The spectrum shows the resolved C-3 and C-4 carbomethoxylate methyls protons.
REFERENCES


(24) Reference 1, pages 133-147.

(25) Another possible mechanism is external attack of RO'. But it is unlikely because the concentration of RO' would be very low under the acid conditions of the oxidation. In two aqueous cases, it has been shown to be impossible because the attack would have to be faster than a diffusion controlled process in aqueous solution.


(31) Bäckvall, J. E.; Åkemark, B.; Ljunggren, S. D. *J. Am. Chem. Soc.* **1979**, *101*, 241. In order to explain the isotope effects, which require the hydride shift to occur after the rate determining step, without invoking a third chloride inhibition, these workers proposed that loss of chloride from 1 is the slow step of the reaction.


(47) Midland, M. M; Tramonato, A.; Kazubuski, A.; Graham, R. S.; Tsai, D. J. S.; Ordin,


(54) NOE has been used previously to assign absolute configuration of cyclic systems\(^{55,56}\) and the theory for acyclic systems such as compound 25 with restricted rotation has recently been presented.\(^{57}\)


PART TWO

CATALYTIC ASYMMETRIC PHENYLATION AND

OXIDATION OF OLEFINs
CHAPTER I

INTRODUCTION

1.1 Background

The concept of asymmetric synthesis have been known for more than 90 years. In 1894 Emil Fischer proposed that chlorophyll acting as an asymmetric catalyst was responsible for the production of optically active sugars from carbon dioxide and water in plants.¹

Asymmetric synthesis was first described in 1904 by Marckwald as the process for the formation of an optically active compound through reaction of an achiral substrate with a chiral reagent.² This definition was expanded by Morrison and Mosher in 1971 when they defined it as a reaction where an a chiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are formed in unequal amounts.³

In the early part of this century asymmetric induction was thought of as some mysterious unsymmetrical force acting on molecules.¹ Not until the late forties when Meerwein-Pondrof-Verley and Grignard proposed that asymmetric induction could be rationalized in terms of steric interactions in the transition state.¹,² Since then the field of asymmetric synthesis has undergone radical changes and a number of methods have been developed to achieve asymmetric induction.⁴⁻¹¹

In the field of catalytic asymmetric synthesis important progress was made in the late 1980’s when it was found that a number of asymmetric reactions could be performed by
catalytic amounts of chiral transition metal complexes. This kind of asymmetric synthesis is very important since one chiral molecule can create millions of chiral product molecules. Examples of these types of reactions are asymmetric hydrogenation and dihydroxylation epoxidation of olefins.

Among the several catalytic asymmetric reactions developed recently the most important are those involving oxygenation of olefins and creation of quaternary carbon center. A large number of biological active natural products contain chiral alcohol or quaternary carbon atom(s). This part of the thesis focuses on these two enantioselective catalyzed reactions.

I.2 Asymmetric Arylation and Alkenylation of Olefins (Heck Reaction)

The coupling of an olefin with an arylPdX or vinylPdX reagent is called the Heck reaction. The catalytic cycle of the reaction (Scheme I.1) involves the oxidative addition of
RX to the palladium(0) complex (it is called oxidative addition because the metal is formally oxidized from Pd(0) to Pd(II)), followed by coordination of olefin to give the \(\pi\)-olefin palladium complex (1). Nucleophilic attack by \(\text{R}^+\) group on the complexed olefin gives the \(\sigma\)-alkylpalladium intermediate (2) which subsequently undergoes a \(\beta\)-hydrogen elimination reaction to produce an arylated or alkenylated olefin.

The first example of an asymmetric Heck reaction was reported in 1989 by Shibasaki and Overman. They independently showed that optically active cis-decaline (4) can be prepared in 64% ee and 70% yield from alkenyl iodide (3) in the presence of the chiral catalyst PdCl\(_2\)(R)-BINAP (Equation I.1).\(^{13,14}\) In another report it was shown that, by using the silver salt Ag\(_3\)PO\(_4\) as a base, the ee of 4 could be as high as 80%.\(^{15}\) Using alkenyltriflate (5) instead of alkenyl iodide, the ee of 4 reached 90% even without a silver salt (equation I.2).\(^{16}\)
The improvement in the ee was related to the triflate. Since triflate is a good leaving group, 5 is immediately transferred into the 16-electron complex 6 responsible for high ee.

Another example of this type of cyclization is the formation of the bicyclo cis-hydrindan (8) system. Treatment of the iodide 7a with PdCl₂((R)-BINAP), Ag₂PO₄ and CaCO₃ in NMP at 60° for 68 h gave the cis-hydrindans 8 in 86% ee (Equation I.3). The alkenyl triflate 7b in this case gave a less satisfactory result (73% ee, 63% yield).

\[ \begin{align*}
\text{7a: } & R = I \\
\text{7b: } & R = \text{OTf}
\end{align*} \]

An indolizidine derivative (10) was prepared in 25-86% ee (Equation I.4). The % ee of 10 was shown to be base- and solvent-dependent. The highest ee was attained when Ag.zeolite was used as a base in DMSO-DMF (1:1). The reaction is depicted in the following diagrams:

\[ \begin{align*}
\text{9} & \xrightarrow{\text{R--CO..(L4)}} \text{10}
\end{align*} \]
An interesting double cyclization giving a chiral quaternary carbon was also reported (Equation I.5).\textsuperscript{19} The Pd(OAc)\textsubscript{2}.DIOP catalyzed cyclization of 11 in benzene at room temperature to give 12 (45% ee, >90% yield).

All the previous examples involved an intramolecular asymmetric Heck reaction. However, no example of intermolecular asymmetric Heck reaction was reported until very recently. In 1991 Ozawa \textit{et al.} used Pd(OAc)\textsubscript{2}((R)-BINAP) prepared \textit{in situ} from Pd(OAc)\textsubscript{2} and (R)-BINAP to synthesize the optically active 2,3-dihydrofuran (15) in 87-94% ee (Equation I.6).\textsuperscript{20,21}

Another example of the intermolecular asymmetric Heck reaction was reported by Ozawa \textit{et al.} They showed that, treatment of 2,3-dihydrofuran (14) with aryltriflates in benzene in the presence of catalytic amount of the chiral Pd(OAc)\textsubscript{2}(R)-BINAP gives (R)-2-
aryl-2,5-dihydrofuran (16) and its regioisomer (S)-2-aryl-2,5-dihydrofuran (17) (Equation I.7). The enantiomeric purity of 16 exceeded 96% ee.

\[
\begin{align*}
\text{14} &\quad \text{ArOTf} &\quad \text{16} &\quad \text{17} \\
&\quad &\quad &\quad \\
&\quad &\quad (I.7)
\end{align*}
\]

These are just few examples of the many reports of the asymmetric Heck reaction.

1.3 Asymmetric Oxygenation of Olefins

The first enantioslective oxygenation of unsaturated compounds appeared in 1965 using percamphoric acid as an oxidant. An enantioselectivity of 8% was achieved. Much later, in 1980, Katuski and Sharpless reported that the combination of a titanium (IV) alkoxide, an optically active tartrate ester and t-butylhydroperoxide was capable of epoxidizing a wide variety of allylic alcohols in good yield with enantioselectivity greater than 90% (Scheme I.2). This method of epoxidation was initially developed with stoichiometric amounts of

Scheme I.2
tartarate catalyst. Today, it is usually performed in the presence of catalytic amount of Ti(o-i-Pr)$_4$ and diethyl or diisopropyl tartarate. The Sharpless method is now very popular and has been used in industry.\textsuperscript{32} Despite its usefulness, the Sharpless epoxidation is largely restricted to oxidation of allylic alcohols.

Another method of asymmetric oxygenation was developed by Jacobsen and co-workers. The Jacobsen oxygenation is performed with sodium hypochlorite or iodosylbenzene in the presence of manganese (III) complexes bearing chiral ligands derived from salen or cyclohexyldiamine (Scheme I.3).\textsuperscript{33-36}

\textbf{Scheme I.3}

More recent improvements involve the use of osmium tetroxide coordinated to a chiral ligand derived from dihydroquinidine or dihydroquinone (Scheme I.4, next page). Oxygenation by OsO$_4$ is usually conducted with either stoichiometric or catalytic amounts of osmium complex in the presence of cooxidant such as N-methylmorpholine-N-oxide (NMO).\textsuperscript{37-40}
The last two methods do not suffer from the limitation of the Sharpless epoxidation for which the presence of OH is necessary to obtain enantioselectivity. Thus the asymmetric oxygenation by these two methods is a general reaction, a trait which makes them useful for the preparation of a wide variety of chiral biological active compounds.

Scheme I.4

I.4 Scope of the Study

I.4.1 Asymmetric Arylation of Olefins

As discussed in the introduction, in order for the asymmetric Heck reaction to proceed, in addition to a chiral bidentate ligand, two coordination sites must be available on Pd, one for the olefin and the other for the aryl. This could occur via a partial dissociation of the neutral ligand (Path A, Scheme I.5, next page) or via dissociation of an ionic ligand (Path B, Scheme I.5, next page). Path A leads to an intermediate with a partially coordinated chiral bidentate ligand and thus, only low asymmetric induction may achieved. Path B leads to a Pd(I) intermediate, which has a square-planner structure convenient for high asymmetric induction.

As discussed in the introduction, Path B is encouraged by silver salts or by substituting aryl triflates for arylhalides. Another approach would involve using relatively labile ligands
such as acetate and preparing the aryl Pd(II) intermediate by exchange of Pd(II) with aryl mercurial as in the original Heck reaction (Scheme I.1). The lability of the acetate ligand could be enhanced by adding an acid such as methanesulfonic acid or acetic acid.

Scheme I.5

Although the use of mercurials for bulk chemicals may not be feasible, it could be practical for the production of more valuable chiral compounds. The reaction is catalytic in Pd(II), since the Hg(II) regenerates Pd(II) from Pd(0), giving Hg(0) that can be re-oxidized by nitric acid. Z-3-penten-2-ol (19) was chosen for this study since the optical isomers of the carbonyl product are known.
I.4.2 Asymmetric Oxidation of Olefins

As discussed previously (Part one, I.1), the success of the Wacker process as an efficient industrial method for oxidation of ethene to acetaldehyde has initiated an intense study of palladium catalyzed organic reactions.\textsuperscript{41,43} This has led to the development of a number of new palladium-promoted or catalyzed reactions of olefins.\textsuperscript{42-45} As shown in the Introduction of Part I of this thesis, one of these procedures involved increasing the chloride concentration. Another involved adding a neutral ligand, such as an amine or phosphine, to the coordination sphere of the palladium (II).\textsuperscript{46-47}

The stage is now set for the development of chiral catalysts. If the amine or phosphine ligand is now replaced with a chiral amine or phosphine ligand the potential now exists for asymmetric oxidation of olefins to give chiral chlorohydrins which can be converted to chiral epoxides. The reaction is shown in Equation I.9 using propene as the olefin. This procedure

\[
PdCl_3L^* + CH_3CH\equivCH_2 \xrightarrow{CuCl_2 \text{H}_2O} CH_2=CHCH_2Cl \xrightarrow{NaOH \text{H}_3C\text{Cl}} \text{H}_3C\text{CH}_2\text{CH}_2\text{O} \quad \text{(I.9)}
\]

would have the advantage over the titanium diethyltartrate complex catalyzed t-butyl peroxide epoxidation in that it would not be limited to allylic alcohols.\textsuperscript{7} On the other hand the reaction could be used for allylic alcohols or their derivatives. Thus the oxidation of allylic alcohol itself, followed by conversion to the epoxide, would give chiral-Glycidols. The chlorohydrin from the allyl $\alpha$-naphthyl ether could be converted to chiral-Propranolol which is used in the treatment of heart disease and hypertension.
The study will include palladium catalysts containing chiral chelating diphosphine ligands to see if the oxidation still occurs. The intermediate oxidation adduct should be very stable and very selectively intercepted by CuCl$_2$. This catalyst should give higher optical yield with chiral diphosphines than the one with chiral mono-amine or phosphines. The initial studies will be conducted with simple diphosphine such as 1,3-bis(diphenylphosphino)propane to see how well the CuCl$_2$ promoted reaction proceeds with the chiral diphosphine systems.

One problem which is likely to arise is that the diphosphine complex is neutral and thus probably insoluble in water solvent. Mixed aqueous solvent could be employed to increase the solubility or sulfonated diphosphines could be employed in place of the neutral one.
II.1 Results and Discussion

II.1.1 Asymmetric Arylation by KPdCl₃((S)-N,N-dimethylphenyethylamine) (21)

The substrates chosen for these studies were Z-3-penten-2-ol (19) and E-4-hexen-3-ol (20). The preparation of these substrates are described in Part I of this thesis (pages 21 and 45). Complex 21 was prepared by stirring equimolar amounts of K₂PdCl₄ and (S)-N,N-dimethylphenyethylamine in THF under Ar at room temperature for 24 h.

Asymmetric arylation was performed in THF in the presence of PhHgCl as a phenylating agent, triethylamine as a base, cupric chloride as a re-oxidant and catalytic amounts of 21. The product was purified by column chromatography (hexane/ether, 80/20). ¹H and ¹³C NMR analysis showed the presence of 4-phenyl-2-pentanone (22) and biphenyl.

The ee (24%) of 22 was determined by ¹H NMR in the presence of the lanthanide shift reagent Eu(hfc)₃. The absolute configuration of 22 was determined to be “S” by comparing the ¹H NMR spectrum of 22 in the presence of Eu(hfc)₃ with that of an authentic sample in the presence of Eu(hfc)₃. The reaction probably proceeds as shown in Scheme II.1 (next page). In the first step palladium complex 21 exchanges phenyl with PhHgCl followed by coordination of the substrate 19 to give the π-olefin complex 23. Syn nucleophilic attack of the Ph group at
position 4 of the olefinic substrate gives the σ-alkyl complex 24, which undergoes β-hydride elimination to give the final product 22.

Asymmetric arylation of E-4-hexen-3-ol (20) was carried out as above to give 5-phenyl-3-hexanone 24 in 43% yield and 15% ee as determined by \(^1\)H NMR in the presence of Eu(hfc)_3. The absolute configuration was not determined.

The low enantioselectivity was expected because the chiral ligand was a monodentate ligand which tends to give low ee's. In order to enhance the enantioselectivity, a chiral bidentate ligand was employed. The bidentate ligand chosen for this study was (R,R)-1,2-cyclohexanediameine.

### 11.2.2 Asymmetric Arylation by PdCl\(_2\)((1R,2R)-1,2\)-Cyclohexanediameine) (25)

PdCl\(_2\)((1R,2R)-1,2\)-cyclohexanediameine) (25) was prepared by stirring K\(_2\)PdCl\(_4\) and
excess (1R,2R)-1,2-cyclohexanediamine with heating in acidic aqueous solution. The complex 25 was identified by $^1$H and $^{13}$C NMR. Solubility tests for complex 25 showed that, it is only soluble in DMF and DMSO.

Asymmetric arylation of 19 in DMF at 60 °C in the presence of PhHgCl, triethylamine and catalytic amounts of 25 afforded 22 in 10% yield with an ee of 0% as determined by $^1$H NMR in the presence of Eu(hfc)$_3$.

The low enantioselectivity of 22 could be attributed to the presence of the chloride ion. Since the chloride-Pd(II) bond is a strong, the reaction is forced to follow path A (Scheme I.5, Page 86). Thus coordination of olefin occurs via dissociation of the chiral diamine ligand.

In order to enhance the yield and the enantioselectivity, the reaction was performed in the presence of Ag$_2$CO$_3$ as a base instead of triethylamine. Overman et al. and Hallberg el al. showed that silver salts enhance the rate of Heck arylation and suppress alkene isomerization.$^{14,49,50}$ So in the presence of silver salt the cation intermediate [ArPd(olefin) amine]$^+$ was expected to be formed without partial dissociation of the amine ligand, leading to a high enantioselectivity. These reaction conditions gave the product 22 in 58% yield. The ee of 22 was determined by $^1$H NMR to be 10%. Thus the yield was enhanced but the ee was not.

The low enantioselectivity in this case could be related to the following: i) the complex 25 used in this reaction may have lost its optically activity during the preparation. It was prepared in acidic aqueous medium at about 60 °C. ii) The size of the chiral bidentate ligand used may not be big enough to induce optical activity.
To overcome these problems the catalyst Pd(OAc)$_2$(S)-BINAP (26) was employed. Since this catalyst has an acetate ligand which is a good leaving group and a chiral bidentate ligand which is very effective in asymmetric induction, it should be a good chiral catalyst.$^{22-24}$

II.2.3 Asymmetric Arylation By Pd(OAc)$_2$(S)-BINAP (28)

The substrates chosen for this study were Z-3-penten-2-ol (19), Z-3-hexen-2-ol (26), and 2-cyclopenten-1-ol (27). The preparation of substrate 26 was described earlier (page 28). The preparation of Substrate 27 has been described in the literature.$^{51}$ Catalyst 28 was generated in situ from Pd(OAc)$_2$ and (S)-BINAP in benzene.$^{52}$ The results of these studies are summarized in Table II.1 (next page).

The arylation reaction was first carried out with substrate 19. Arylation of 19 with PhHgOAc in benzene containing triethylamine and catalytic amount of Pd(OAc)$_2$(S)-BINAP at 40 °C gave 22 in about 22% yield and 44% ee (Figure C.1, Appendix C).

A similar reaction was carried out in the presence of Proton Sponge (1,8-bis-(dimethylamino)naphthalene). Use of Proton Sponge resulted in the formation of 22 in 28% yield and 48% ee (Figure C.2, Appendix C). The absolute configuration was determined to be “S”. When the reaction was carried out in methanol, the ee did not change but the yield decreased to 15%.

Phenylation of 26 in the same way in the presence of Proton Sponge (Equation II.1)
gave 4-phenyl-2-hexanone (32) in 17% yield and 26% ee (Figure C.3, appendix C). 2-Cyclopenten-1-ol (27) gave 3-phenylcyclopentanone (33) in 32% yield (Equation II.2) and 68% ee (Figure C.4, Appendix C).

\[
\begin{align*}
\text{OH} & \quad \text{Pd(OAc)}_2\text{H}_{(S)-(BINAP)} \quad \text{PhHgOAc, Proton sponge} \\
27 & \quad \text{33}
\end{align*}
\]

(II.2)

Table II.1 Phenylation of Various Allyl Alcohols Catalyzed By Pd(OAc)$_2$((S)-BINAP)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Base</th>
<th>Product</th>
<th>yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>benzene</td>
<td>Et$_3$N</td>
<td>22</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>benzene</td>
<td>proton sponge</td>
<td>22</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>3*</td>
<td>19</td>
<td>benzene</td>
<td>proton sponge</td>
<td>22</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>THF</td>
<td>benzoquinone</td>
<td>22</td>
<td>------</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>methanol</td>
<td>benzoquinone</td>
<td>22</td>
<td>------</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>methanol</td>
<td>proton sponge</td>
<td>22</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>benzene</td>
<td>proton sponge</td>
<td>32</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>benzene</td>
<td>proton sponge</td>
<td>33</td>
<td>32</td>
<td>68</td>
</tr>
</tbody>
</table>

* This reaction was carried out in the presence of methanesulfonic acid (5 equiv/equiv of Pd).

Thus Proton Sponge enhanced enatioselectivity, but not as much as described. The reason could be related to the presence of the acetate group. Previous investigators showed that the acetate group has the ability to make a tight ion pair with the 16-electron Pd(I) intermediate (29) responsible for high ee's. This interaction could cause the ee to be low.
A possible way of overcoming the acetate-Pd(I) interaction is by adding an acid to the reaction mixture. A reaction similar to the previous one was carried out in the presence of methanesulfonic acid (5 equiv/equiv of Pd) resulted in the formation of 22 in 32% yield and 58% ee (Figure C.5, Appendix C).

Another reaction (entry 4) carried out in THF in the presence of methanesulfonic acid using benzoquinone as a re-oxidant and base produced 22 in very low yield and about 10% ee. When the same reaction was carried in methanol, 22 was again produced in a very low yield and 0% ee (Figure C.6, Appendix C).

The phenylation reaction must involve [PhPd(II)(OAc)(BINAP)], which is formed by exchange of phenyl between PhHgOAc and catalyst 28 as shown in Scheme II.2. Coordination of 19 and subsequent β-hydrogen elimination process provides arylation product 22.

Scheme II.2

![Scheme II.2 Image]
The improvement in the ee by using Proton Sponge could be related to the fact that Proton Sponge is one of the strongest bases ($pK_a = 12.34^{23}$) in trapping protons in organic solvents. The isomerization shown in Scheme II.3 which causes racemization is prevented.

**Scheme II.3**

Scheme II.4 (next page) shows the two possible modes for coordination of the substrate Z-3-penten-2-ol (19) to the [PdPh{(S)-BINAP}]$^+$ moiety. In mode A, 19 combines with the palladium center through the $si$ face and in mode B through the $re$ face. The olefin coordination in mode A followed by olefin-insertion and $\beta$-elimination reaction forms the phenylation product with $S$ configuration. In contrast, the olefin coordination in mode B lead to the phenylation product with $R$ configuration. The enantioslectivity results show that mode A is preferable to mode B. This could be due to the fact the chiral cavity created around palladium by the (S)-BINAP ligand favors the attack of palladium the $si$ face over the $re$ face of the substrate 19.

In conclusion, various $\beta$-phenylketones were synthesized in modest enantioselectivity using the asymmetric Heck type reaction. In addition the effect of acid and base on the asymmetric induction was determined.
II.2 Experimental

II.2.1 Materials

All chemicals were from Aldrich Chemical Company, unless otherwise specified, and were used as received. Pd(OAc)$_2$ was purchased from Alfa Aesar and used without further purification. PdCl$_2$ was purchased from Alfa Aesar and used without further purification. (S)-BINAP (S,S)-BDPP, (S,S)-Chiraphos and (R)-Tol-BINAP were obtained from Strem Chemical Inc. and used without further purification. Benzene was distilled and stored over CaH$_2$ under an Ar atmosphere. THF was dried over sodium benzophenone ketyl and distilled and stored over CaH$_2$ under Ar. All other chemicals were of reagent grade.
II.2.2 Physical Measurements

$^1$H NMR data were recorded on a Varian VXR 300 and 400S NMR spectrometer. Chemical shifts are reported in $\delta$ (ppm) referenced to an internal SiMe$_4$ standard for $^1$H NMR and to an external 85% H$_3$PO$_4$ standard for $^{31}$P NMR. IR spectra were obtained on a ATI Mattson Genesis Series FT-IR or a Perkin Elmer 1310 Infrared spectrometer. GLC analysis were carried out using a GOW-MAC 350 gas chromatography fitted with Carbowax 10 M on 80-100 mesh Chromosorb W-NAW columns.

II.2.3 Preparation of Pd(II) complex 21

A 0.72 g (2.19 mmol) sample of K$_2$PdCl$_4$ and 0.36 mL (0.33 g, 2.19 mmol) of (S)-(−)-N,N-dimethyl-1-phenethylamine were suspended in 15 mL of dry THF under Ar and stirred at room temperature for 24 h. The resulting brownish yellow solid was collected by filtration, washed with Et$_2$O and dried under vacuum to give 0.51 g (72% yield) of 21, m.p 142-145° dec. $^1$H NMR (CDCl$_3$) $\delta$: 7.50 (m, 5H), 4.28 (q, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 1.29 (d, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$: 129.2, 128.4, 128.3, 65.4, 41.9, 38.6, 16.1.

II.2.4 Preparation of Dichloro((1R,2R)-1,2-diaminecyclohexane)Pd(II) (25)

Excess (1R,2R)-(−)-1,2-diaminocyclohexane 1.37 g (12.0 mmol) was added with stirring to an aqueous solution of K$_2$PdCl$_4$ (2.61 g, 8.00 mmol). The initial pink- to brown-precipitate, was re-dissolved with stirring aided by warming to give a very pale yellow solution. After filtration, concentrated hydrochloric acid was added dropwise until the solution was acidic. The solution turned bright yellow and a yellow solid precipitated. The precipitate was
filtered, washed well with cold water, acetone and then Et$_2$O, and air dried to give 2.47 g (85%), mp 324-327° dec, $^1$H NMR (DMSO) $\delta$: 5.00 (d, 2H), 4.70 (t, 2H), 2.15 (t, 2H), 1.8 (m, 2H), 1.50 (m, 2H), 1.15 (t, 2H), 0.90 (m, 2H). $^{13}$C NMR (DMSO): 61.0, 32.2, 23.7.

II.2.5 Palladium Complex 21 Catalyzed Phenylation of Z-3-penten-2-ol (19)

To 0.2 g (0.3 mmol) of Pd complex 21 in 20 mL dry THF were sequentially added 4.6 g (15 mmol) phenylmercuric chloride, 2.1 g (15 mmol) cupric chloride and 1.9 mL (1.7 g, 20 mmol) of Z-3-penten-2-ol (19). The mixture was stirred under Ar at room temperature for 12 h. A portion of 50 mL water was added and the resulting insoluble material and the aqueous solution were extracted with ether (3 x 50 mL). The combined organic layers were washed with water, dried (MgSO$_4$, anhydrous) and filtered. The filtrate was concentrated to dryness to give a yellow oily material which was subjected to column chromatography (silica gel; 9/1 hexane /Et$_2$O) to give 1.1g (45% yield) of 4-phenyl-2-pentanone 22. $[\alpha]^2_4 +0.733$ (c = 5, cyclohexane). IR (neat): 3020, 2990, 1720 cm$^{-1}$. $^1$H NMR (CDCl$_3$) $\delta$: 7.30 (m, 5H), 3.30 (m, 1H), 2.70 (dd, 2H), 2.07 (s, 3H), 1.69 (d, 3H). Examination of the $^1$H NMR spectrum in the presence of the lanthanide shift reagent Eu(hfc)$_3$ indicated an enantiomeric mixture of 62% (S) and 38% (R), (24% ee).

II.2.6 Palladium Complex 21 Catalyzed Phenylation of E-4-Hexene-3-ol (20)

See section II.2.5, palladium complex 21 catalyzed phenylation of Z-3-penten-2-ol.

A 1.5 mL sample of 20 (1.3 g, 15 mmol) afforded 1.06 g (43% yield) of 5-phenyl-3-hexanone. $[\alpha]_D^{24} +1.26$ (c = 2.5, cyclohexanol). The ee was determined as before to be 15%.
IR(neat) cm⁻¹: 3015, 2985, 1715. ¹H NMR (CDCl₃) δ: 7.26 (m, 5H), 3.35 (m, 1H), 2.70 (dd, 2H), 2.35 (q, 2H), 1.262 (d, 3H), 0.986 (t, 3H).

II.2.7 Palladium Complex 25 Catalyzed Phenylation of Z-3-Penten-2-ol (19)

To 0.2 g (0.687 mmol) of Pd complex 25 in 15 mL dry DMF was added 4.6 g (15 mmol) phenylmercuric chloride, 2.1 mL (15 mmol) triethyl amine, and 1.9 mL (1.7 g, 20 mmol) of Z-3-penten-2-ol. The mixture was stirred under Ar at 60 °C for 12 h and subsequently cooled to 20 °C. A 50 mL aliquot of H₂O was added and the resulting insoluble material and the aqueous solution were extracted with hexane (3 x 50 mL). The combined organic layers were washed with water, dried over MgSO₄ and filtered. The filtrate was concentrated to dryness to give a yellow oily material which was subjected to column chromatography (silica gel; 9/1 hexane/Et₂O). 4-Phenyl-2-pentanone (22) was attained in 10% yield and 0% ee as determined by ¹H NMR.

II.2.8 Pd(OAc)₂((S)-BINAP) Complex (28) Catalyzed Phenylation of Z-3-Penten-2-ol

To a stirred solution of Pd(OAc)₂ (0.0207 g, 0.10 mmol) and (S)-BINAP (0.0747 g, 0.12 mmol), in benzene (4 mL) under Ar at room temperature, were sequentially added Et₃N (0.41 mL, 0.51 g, 3.0 mmol), PhHgOAc (0.6 g, 1.77 mmol) and Z-3-penten-2-ol (0.4 mL, 4.0 mmol). The reaction mixture was stirred at 40 °C under Ar for 48 h. It was then diluted with petroleum ether (50 mL) and the resulting black solid was removed by filtration. The filtrate was concentrated to dryness to give yellow oily material, which was subjected to column chromatography (silica gel, 8/2 hexane/ether) to give 61.0 mg (22% yield) of 22. The enantiomeric purity of 22 (44%) was determined as before by ¹H NMR (CDCl₃) using the
optically active NMR shift reagent Eu(hfc)$_3$. In the $^1$H NMR analysis, the carbonylmethyl protons and the C-5 protons of R-22 appeared at higher field than those of S-22 (Figure C.1 Appendix C).

The reaction with Proton Sponge was performed as above. The crude product was purified by column chromatography (silica gel, CH$_2$Cl$_2$) to remove the ammonium salt and Proton sponge. The elute was concentrated and further purified by column chromatography (silica gel, 8/2 hexane/ether) to give 79.0 mg (28% yield) of S-22. The ee was determined to be 48%.

A similar reaction was performed in methanol in which methanesulfonic acid and benzoquinone were substituted for Proton sponge. The crude product was purified as before to give 14.5 mg of 22 with an ee of 0%. When the same reaction carried out in THF, the yield was 10% and the ee was 8%.

**II.2.9 Pd(OAc)$_2$((S)-BINAP) Complex (28) Catalyzed Phenylation of Z-3-Hexen-2-ol (26)**

See Pd(OAc)$_2$((S)-BINAP) complex (28) catalyzed phenylation of Z-3-penten-2-ol (II.2.8).

Phenylation of (26) gave 4-phenyl-3-hexanone (32) in 17% yield. $^1$H NMR (CDCl$_3$) $\delta$: 7.20-7.38 (m, 5H), 3.10 (m, 1H), 2.8 (d, 2H), 2.08 (s, 3H), 1.65 (m, 2H), 0.85 (t, 3H).
II.2.10 Pd(OAc)$_2$((S)-BINAP) (28) Catalyzed Phenylation of 2-Cyclopenten-1-ol (27)

See Pd(OAc)$_2$((S)-BINAP) complex (28) catalyzed phenylation of Z-3-penten-2-ol (II.2.8).

Phenylation of 2-cyclopenten-1-ol (27) gave 3-phenylcyclopentanone (33) in 32% yield. $^1$H NMR (CDCl$_3$) $\delta$: 7.18-7.36 (m, 5H), 3.40 (m, 1H), 2.60 (dd, 1H), 2.20-2.50 (m, 4H), 1.95 (m, 1H). C$^{13}$ NMR (CDCl$_3$) $\delta$: 217.8, 143.0, 128.6, 126.6, 45.8, 42.3, 38.9, 31.2.
CHAPTER III
HYDROXYCHLIRONATION OF OLEFINS

III.1 Result and Discussion

III.1.1 Potassium Trichloro (S)-N,N-dimethyl-1-phenethylamine Pd(II) Catalyzed Oxidation of Olefins

The first catalyst to be tried in these oxidation studies was Cl$_3$PdL$^*$ (L$^*$ = N,N-dimethylphenethylamine) (21). Complex 21 was prepared by the procedure described in Chapter II (page 101). The olefins chosen for this study were propene and methyl vinyl ketone (35). Initial studies on the oxidation of propene was carried out at different concentrations of CuCl$_2$ and LiCl to find at what concentrations the yields of chloropropanol will be the highest. The results of these studies showed that, the maximum yield of hydroxychlorinated propylene is obtained at 6.0 M and 0.2 M concentrations of CuCl$_2$ and LiCl, respectively.

Oxidation of propylene under these conditions gave acetone, 2-chloro-1-propanol (36), and 1-chloro-2-propanol (37) in relative yields of 15%, 18%, and 67%, respectively as shown by GLC and $^1$H NMR of the 2,4-DNP derivative. A pure sample of 37 was collected by preparative GLC. $^1$H NMR analysis of the collected sample in the presence of the lanthanide shift reagent Eu(hfc)$_3$ showed the presence of two enatiomers in relative yields of 45.6% and 54.4 %, (8.8% ee). Because of its low yield, isolation of 36 was difficult and its % ee was not determined.
Oxidation of methyl vinyl ketone 35 afforded only 4-chloro-3-hydroxy-2-butanone (40) as shown by GLC and $^1$H and $^{13}$C NMR. The ee (12%) of 40 was determined by $^1$H NMR.

The absolute configuration of 37 and 40 are not determined. The reaction probably proceeds as shown in Scheme III.1. As can be seen from Scheme III.1, displacement of chloride in complex 21 by olefin produces the intermediate neutral $\pi$-complex, 38, which undergoes anti hydroxypalladation at either end of the double bond (path a and b) to give the relatively stable adducts 39. This adduct can either revert to 38 or, if CuCl$_2$ is present, be intercepted to produce chloropropanol. The intermediate 39 is assumed to be in equilibrium with 38 because 39 is stabilized against decomposition to ketone.

The above results were disappointing on two accounts. First, the low ee's achieved for the chlorohydrins, 37 and 40 were expected for a catalyst with a monodentate ligand. Second,
the formation of the other positional isomer 36 in 18% was also expected. Since the monodentate ligand is not big enough to stop the Pd(II) moiety completely from adding to the inner side of the double bond of the olefin (path b, Scheme III.1).

The use of chiral bidentate ligands could overcome these problems. Initial studies were carried out with the chelating chiral diamine, (1R,2R)-(−)-1,2-diaminocyclohexane (N*-N*) and with the non-chiral diphosphine, 1,3-bis(diphenylphosphino)propane (1,3-BPP). The complexes [PdCl(N*-N*)] and [PdCl(1,3-BPP)] were prepared and characterized by $^1$H, $^{31}$P and $^{13}$C NMR. Unfortunately these complexes are insoluble in aqueous solution. This problem was solved by sulfonating the aryl ring of the diphosphine ligands as shown in Scheme III.2.

Scheme III.2

\[
\text{PPh}_2 \quad \text{PPh}_2 \quad \overset{1. \text{H}_2\text{SO}_4: \text{SO}_3 20\%}{\rightarrow} \quad \text{PAr}_2 \quad \text{PAr}_2 \\
\text{1,3-bis(diphenylphosphino)propane = 1,3-BPP}
\]

\[
\text{Ar} = \begin{array}{c}
\text{Ar} \\
\text{SO}_3 \text{Na}^+ 
\end{array}
\]
III.1.2 Chiral Tetrasulfonated Phosphines: Synthesis and Use in Asymmetric Synthesis

Sulfonation of the 1,3-BPP (41) was carried out in concentrated sulfuric acid containing 20% SO₃ in the manner described for the diphoshine.⁹,¹⁰ The sulfonated diphosphine ligand was characterized by ³¹P, ¹H and ¹³C NMR.

The catalyst used in this study was prepared by mixing equimolar amounts of, Li₂PdCl₄ and sulfonated ligand 41 in distilled degassed water. The oxidation was performed in a water-THF mixture (4:1 ratio by volume) in the presence of CuCl₂ and LiCl at concentrations of 6.0 M and 0.2 M, respectively. It was previously shown that the maximum yield of the hydroxychlorinated product was obtained at these concentrations. Analysis of the product by GLC showed the presence of three products; acetone, 36, and 37 in relative yields of 5%, 7% and 88%, respectively.

The purpose of this initial study was to see if the oxidation in the presence of sulfonated bidentate ligands will occur. Thus the oxidation works very well with the sulfonated diphosphine ligand and a yield of > 85% of hydroxychlorinated product could be obtained. Attention was now turned to the asymmetric oxidation of olefins by a Pd(II) catalyst coordinated to a tetrasulfonated chiral diphosphine ligand.

The ligands chosen for this purpose were (S,S)-2,4-bis(diphenylphosphino)pentane ((S,S)-BDPP) (40), (S,S)-2,3-bis(diphenylphosphino)butane ((S,S)-Chiraphos) (41), and (R)-(+)2,2’-bis(di-p-tolylphosphino)-1,1’-binaphthyl ((R)-Tol-BINAP) (42). Sulfonation of these three ligands were carried out in a fashion similar to that used in the sulfonation of 1,3-bis(diphenylphosphino)propane (Scheme III.2). Sulfonation of (S,S)-BDPP gave a mixture of 18.5% mono-, 6.5% di-, 20% tri- and 55% tetrasulfonated diphosphine as determined by ³¹P
NMR. Sulfonation of (S,S)-Chiraphos gave the tetrasulfonated diphosphine in 76% yield and a 23% mixture of mono-, di-, and tri-sulfonated phosphines. However, sulfonation of (R)-Tol-BINAP gave only one product, which was identified by $^{31}$P and $^1$H NMR to be tetrasulfonated (R)-Tol-BINAP (Figure D.1, Appendix D). The $^{31}$P{$^1$H} NMR data of the sulfonated phosphines are shown in Table III.1.

Table III.1. $^{31}$P{$^1$H} NMR Data of the Prepared Tetrasulfonated Diphosphines and the Corresponding Pd(II) Complexes.

<table>
<thead>
<tr>
<th>Tetrasulfonated ligand</th>
<th>$\delta$(P) (D$_2$O)$_a$</th>
<th>PdCl$_2$ + sulfonated ligand</th>
<th>$\delta$(P) (D$_2$O)$_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>-16.31</td>
<td>41</td>
<td>14.00</td>
</tr>
<tr>
<td>42</td>
<td>0.65</td>
<td>42</td>
<td>27.00</td>
</tr>
<tr>
<td>43</td>
<td>-9.96</td>
<td>43</td>
<td>57.90</td>
</tr>
<tr>
<td>44</td>
<td>-16.30</td>
<td>44</td>
<td>16.70</td>
</tr>
</tbody>
</table>

$^a$ In ppm relative to the external H$_3$PO$_4$

Catalytic Studies

The tetrasulfonated chiral diphosphine-Pd(II) catalysts were prepared as described above. The $^{31}$P{$^1$H} NMR data of the prepared catalysts are summarized in Table III.1. These catalysts were used in the asymmetric oxidation of propylene, methyl vinyl ketone (35), and allyl phenyl ether (45). Oxidation of these substrates were carried out in water-THF mixtures in the presence of CuCl$_2$ and LiCl at concentrations of 6.0 M and 0.2 M, respectively. The results of these studies are summarized in Table III.2 (next page).
Oxidation of propylene gave a mixture of three products, acetone, 36, and 37 in relative yields of 5%, 7% and 88%, respectively. A pure sample of 37 was collected by preparative GLC. Analysis of the collected sample by $^1$H NMR in the presence of chiral shift reagent Eu(hfc)$_3$ showed that, the ee of 37 is 28% when sulfonated (S,S)-BDPP ligand was used, 46% when sulfonated (S,S)-Chiraphos ligand was employed and 44% when sulfonated (R)-Tol-BINAP was used.

<p>| Table II.2 Oxidation of Various Olefins Using Chiral Pd(II) Complexes |</p>
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>H$_2$O/THF</th>
<th>Product</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Propylene</td>
<td>42$^*$</td>
<td>4/1</td>
<td>Me</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>Propylene</td>
<td>43$^b$</td>
<td>4/1</td>
<td>Me</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>Propylene</td>
<td>44$^c$</td>
<td>4/1</td>
<td>Me</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>Methyl vinyl ketone (35)</td>
<td>43</td>
<td>4/1</td>
<td>CH$_3$CO</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>44</td>
<td>4/1</td>
<td>CH$_3$CO</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Allyl phenyl ether (45)</td>
<td>44</td>
<td>3/2</td>
<td>PhOCH$_2$</td>
<td>68</td>
</tr>
</tbody>
</table>

$^*$ = (S,S)-BDPP. $^b$ = (S,S)-CHIRAPHOS. $^c$ = (R)-Tol-BINAP.

Oxidation of methyl vinyl ketone (Equation III.1) afforded only one product by GLC analysis. A pure sample of the product was obtained by preparative GLC. $^1$H and $^{13}$C NMR analysis of the obtained product showed that, the compound is 4-chloro-3-hydroxy-2-butanone (40). The ee was determined to be 64% when the sulfonated (S,S)-Chiraphos was used (Figure D.2, Appendix D) and 76% when tetrasulfonated (R)-Tol-BINAP was used (Figure D.3, Appendix D).
The absence of the other positional isomer 3-chloro-4-hydroxy-2-butanone could result from the bulk of the Pd(II) moiety containing the large phosphine. This size would favor addition to the less hindered side of the olefin. This same effect is apparent in the oxidation of propylene. When a monodentate ligand is used the positional isomer 36 was produced in 17% yield but when the bidentate ligand was used isomer 36 was obtained in only 7% yield.

Oxidation of allyl phenyl ether (45) in the presence of tetrasulfonated (R)-Tol-BINAP afforded two products in relative yields of 84 and 16%. The compounds were identified by $^1$H and $^{13}$C NMR to be 1-chloro-2-propanol phenyl ether (48) and phenoxyacetone (Equation III.2). The ee of 48 was found to be 68% (Figure D.4, Appendix D). The absolute configuration was not determined.

The reaction pathway for propene is shown in Scheme III.3 (next page). As shown in Scheme III.3, the initial complex is neutral so the displacement of a chloride by olefin gives the
positively charged π-complex (46). This is followed by attack of water to either end of the double bond (path a and path b). The presence of the positive charge on the π-complex (46) makes the attack of water much more facile than the attack of water on the π-complex in Scheme III.1. Attack of water on the π-complex (46) give the hydroxypalladation adduct (47). Attack of chloride on the adduct (47) give the hydroxychlorinated product.
The results from these studies show that the enantioselectivities of the products are affected by both steric and electronic factors. As can be seen from Table III.2, the enantioselectivity increases with the size of the ligand and the substrate. Previous researchers related this to the steric interaction between the ligand and the substrate in the transition state.\textsuperscript{53,54} The higher the steric interaction the higher will be the enantioselectivity.

The highest ee was obtained from methyl vinyl ketone \textsuperscript{35} (Table III.2). This is consistent with the results obtained by Ozawa \textit{et al.} who showed that substrates with electron withdrawing groups at the vinyl carbon proceed with extremely high enantioselectivity.\textsuperscript{21}

In summary, various chlorohydrins were prepared in modest enantioselectivities by asymmetric oxidation of olefins. Next, the extent of asymmetric induction in the oxidation of olefins using a non-sulfonated (R)-Tol-BINAP ligand in mixed aqueous solvent was investigated.

\textbf{III.1.3 \textit{PdCl}_2(R)-Tol-BINAP (49) Catalyzed Oxidation of Olefins}}

The oxidation studies were performed using the substrates propylene, methyl vinyl ketone \textsuperscript{35}, allyl phenyl ether \textsuperscript{45} and 2,3-dihydrofuran \textsuperscript{50}. Catalyst (49) was generated \textit{in situ} from \textit{PdCl}_2(CH_3CN)_2 and (R)-Tol-BINAP in THF. The oxidation was carried out as above in THF- water solution (2 : 1) in the presence of CuCl\textsubscript{2} (4.0 M) and LiCl (0.2 M). Pure samples of the products were obtained by GLC. The products were identified by $^1$H and $^{13}$C NMR. The ee's were determined by $^1$H and $^{13}$C NMR using the chiral shift reagent, Eu(hfc)_3. The results are summarized in Table III.3.
Table III.3 Oxidation of Various Olefins Using PdCl₂(R)-Tol-BINAP Complex

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>THF/H₂O</th>
<th>Product</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Propylene</td>
<td>2/1</td>
<td>37</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>35 a</td>
<td>2/1</td>
<td>40</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>45 b</td>
<td>2/1</td>
<td>48</td>
<td>35</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>50 c</td>
<td>2/1</td>
<td>51</td>
<td>75</td>
<td>64</td>
</tr>
</tbody>
</table>

a 35: methyl vinyl Ketone. b 45: allyl phenyl ether. c 50: 2,3-dihydrofuran.

Oxidation of propylene gave 36, 37, and acetone in relative yield of 55%, 10% and 35%, respectively. The ee of 37 was determined to be 56%. The absolute configuration of 37 was determined to be "R" as follows. A pure sample of 37 obtained by preparative GLC was converted into propylene oxide by reacting it with 5% NaOH solution. The ¹H NMR spectrum of the prepared oxide in the presence of Eu(hfc)₃ was compared with that of an authentic sample from Aldrich in the presence of Eu(hfc)₃ (Figure III.1, next page). Oxidation of methyl vinyl ketone (45) gave 3-chloro-2-hydroxy-2-butanone (40) as the only product in 82% ee and in 78% chemical yield (Figure D.5, Appendix D). Allyl phenyl ether (45) gave 48 in 80% ee and 35% chemical yield (Figure D.6, Appendix D): The low yield in this case could be related to low solubility of the substrate 45 in the reaction mixture. Oxidation of 2,3-dihydrofuran (Equation III.3) gave three products in total chemical yield of 75%. The three products were

\[
PdCl₂(R)-Tol-BINAP \xrightarrow{CuCl₂, LiCl, THF-H₂O} \text{Cl} \quad \text{H₂} \quad \text{OH} \quad \text{Cl} \quad \text{CO} \quad \text{O} \]

\[
50 \quad 51 \quad 52 \quad 53
\]
Figure III.1.A. Illustration part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$, of an authentic sample of cyclopropene oxide with S absolute configuration.

Figure III.1.B. Illustrative part of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$ of the prepared cyclopropene oxide. The spectrum shows that cyclopropene oxide has an opposite absolute configuration to that shown in Figure III.1 A.
identified to be 3-chloro-2-hydroxytetrahydrofuran (51), the positional isomer 2-chloro-3-
hydroxytetrahydrofuran (52) and 3-oxo-tetrahydrofuran (53). The three compounds are
present in 20%, 75% and 5%, respectively. The ee of 52 was determined to be 66% at C-2 and
46% at C-3 (Figure D.7, Appendix D). \(^1\)H NMR analysis showed that H\(_1\) and H\(_2\) have an E
stereochemistry (\(J_{1,2} = 2.93\) Hz).\(^5^5\)

Based on the experimental results, the reaction probably proceeds in a fashion
analogous to that presented in Scheme III.3.

In conclusion, a catalytic asymmetric synthesis utilizing a Wacker-type reaction has
been realized for the first time. Various chlorohydrins have been prepared with modest
enantioselectivities using chiral tetrasulfonated diphosphine ligands. However, modest to
excellent enantioselectivities have been obtained using non-sulfonated (R)-Tol-BINAP ligand.

III.2 Experimental

III.2.1 Oxidation of Propene Catalyzed by Pd(II) Complex 21

The reaction was carried out in a 250-mL two necked cone-shaped flask with indented
sides to increase the efficiency of stirring. The O\(_2\) uptake was measured by means of a gas
buret thermostated at the reaction temperature (the apparatus is described in Figure III.1, next
page). The flask was equipped with magnetic stirring bar, subseal septum and vacuum
adapter. The flask was charged with H\(_2\)O (25.0 mL), CuCl\(_2\) (6.0 M), LiCl (0.2 M), and Pd(II)
complex 21 (0.15 g). The flask was then placed in constant temperature bath and connected to
the gas uptake system. The system was then evacuated for 10 min on the vacuum line with the
stirrer running. The stirring was then stopped and the system pressurized to 1.0 atmosphere
Figure III.2 Gas uptake apparatus used for propylene and oxygen uptake.
with propylene. The mercury in the gas buret and the leveling bulb were then equalized, and a reading taken. The stirrer was turned on to start the reaction. The pressure was kept constant by continuously leveling the mercury in the gas buret and bulb. The reaction allowed to run under these conditions until the reaction mixture was at least 0.25 M in total oxidation product. The oxidation product was separated from the mixture by continuous extraction with ether overnight. The ether solution was dried over anhydrous MgSO₄, and the solvent removed by distillation. GLC analysis and preparation of the 2,4-DNP derivative, showed the presence of acetone, 2-chlororo-1-propanol (36) and 1-chloro-2-propanol (37) in relative yields of 15%, 18% and 67%, respectively. A pure sample of the product 37 was collected by preparative GLC and analyzed by ¹H NMR. Analysis of the sample by ¹H NMR in the presence of Eu(hfc)₃ showed the ee to be 8.8%.

III.2.2 Oxidation of Methyl Vinyl Ketone Catalyzed by Pd(II) Complex 34

Oxidation of methyl vinyl ketone by the procedure described previously (III.2.3) afforded only one product. Analysis by GLC ¹H and ¹³C NMR showed the product to be 4-chloro-3-hydroxy-2-butanone (40). ¹H NMR (CDCl₃) δ: 4.30 (t, 1H), 3.90 (dd, 2H), 2.40 (s, 3H). ¹³C NMR (CDCl₃) δ: 203.0, 62.5, 63.7, 27.6.

III.2.3 Preparation of Tetrasulfonated Phosphine

General Procedure

To 1 mmol diphosphine in 0.5 mL sulfuric acid in a two necked 50 mL flask under Ar at 0 °C, 6.0 mL of sulfuric acid containing 20% SO₃ was added slowly. After 5 days of stirring
at room temperature the mixture was poured slowly onto 50 g of ice and neutralized with 20% 
NaOH at 0 °C. After filtration the solution was poured into 50 mL of methanol and the solid
precipitate was extracted with methanol (2 x 50 mL). The layers were combined and the
solvent evaporated under vacuum. The residue was then dissolved in a minimum amount of
water and poured into methanol. The solid which produced was removed by filtration and the
filtrate evaporated to gave the crude tetrasulfonated diphosphine. Pure samples of sulfonated
diphosphine was obtained by repeatedly recrystallizing the crude product from aqueous
methanol.

III.2.3.1 Preparation of Tetrasulfonated 1,3-BPP

$^{13}$P NMR (D$_2$O) $\delta$: -16.32. $^1$H NMR (D$_2$O) $\delta$: 7.65 (m, 8H), 7.25 (m, 8H), 2.05
(t,4H), 1.31(m, 2H); $^{13}$C NMR (D$_2$O, DMSO) $\delta$: 21.5 (s, C-2), 29.5 (t, C-1,C-1'), 127.8 (s, C-
4 ar.), 130.6 (s, C-5 ar.) 130.88 (d, C-2 ar.), 136.1 (d, C-6 ar.), 139.5 (d, C-1 ar.), 145 (d, C-3
ar.).

III.2.3.2 Preparation of Tetrasulfonated (S,S)-BDPP

$^{13}$P NMR (D$_2$O) $\delta$: 0.65. $^1$H NMR (D$_2$O) $\delta$: 8.4-7.8 (m, 8H), 7.5-7.2 (m, 8H), 1.1 (m,
2H), 2.5 (m, 2H), 0.85 (b, 6H).

III.2.3.3 Preparation of Tetrasulfonated (S,S)-Chiraphos

$^{13}$P NMR (D$_2$O) $\delta$: -9.96. $^1$H NMR (D$_2$O) $\delta$: 7.70-6.90 (m, 16H), 2.20 (b, 2H), 0.84
(b, 6H)
III.2.3.4 Preparation of Tetrasulfonated (R)-Tol-BINAP

$^{13}$P NMR (D$_2$O) δ: -16.3. $^1$H NMR (D$_2$O) δ: 8.60 (d, 4H), 7.80 (d, 4H), 7.40 (b, 4H), 6.90-6.40 (m, 12H), 3.20 (s, 3H).

III.2.4 Preparation of Tetrasulfonated Diphosphine-PdCl$_2$

General Procedure

A) To an aqueous solution of 0.1 M of K$_2$PdCl$_4$ (0.1 mmol in 1 mL H$_2$O) under Ar was added a solution of tetrasulfonated diphosphine (0.1 mmol in 4 mL H$_2$O). The resulting solution was stirred for 1 h. Then it was transferred to the oxidation apparatus to be used in situ.

B) To a solution of PdCl$_2$(PhCN)$_2$ (0.01 mmol) in benzene (1 mL) under Ar was added a solution of tetrasulfonated diphosphine (0.012 mmol in 5 mL degassed H$_2$O). The mixture was stirred for 1 h. Then the aqueous layer was transferred via a syringe to the oxidation apparatus to be used in situ.

The complexes were characterized by $^{31}$P NMR. The results are summarized in Table III.1

III.2.5 PdCl$_2$ Tetrasulfonated Diphosphine Catalyzed Oxidation of Olefins

General Procedure

The reaction was carried out in a 250-mL two necked cone-shaped flask with indented sides to increase the efficiency of stirring. The gas uptake was measured by means of a gas buret thermostated at the reaction temperature. The flask was equipped with a magnetic stirring bar, subseal septum and vacuum adapter. The flask was then charged with H$_2$O (20.0
mL), CuCl₂ (6.0 M), LiCl (0.2 M), and PdCl₂ tetrasulfonated diphosphine (prepared above in 5.0 mL H₂O). The flask was then placed in constant temperature bath and connected to the gas uptake system, and the system was evacuated for 10 min on the vacuum line with the stirrer running. The stirring was stopped and the system pressurized to 1.0 atmosphere with propene (the other olefins were added to the reaction mixture by a syringe and the reaction was carried out under 1 atmosphere of O₂). The mercury in the gas buret and the leveling bulb were then equalized, and a reading taken. The stirrer was turned on to start the reaction. The pressure was kept constant by continuously leveling the mercury in the gas buret and bulb. The reaction allowed to run under these conditions until the reaction mixture was at least 0.25 M in total oxidation product (7-10 days). The oxidation product was separated from the mixture by continuous extraction with ether overnight. The ether was dried over anhydrous MgSO₄, and removed by distillation. Analysis of the product was carried out by gas chromatography ¹H and ¹³C NMR. The results are summarized in Table III.2.

**PdCl₂ Tetrasulfonated (R)-Tol-BINAP Catalyzed Oxidation of Allyl Phenyl Ether (45)**

Oxidation of allyl phenyl ether (45) as before gave two products in relative yields of 84 and 16%. Pure samples of these two compounds were obtained by preparative GLC. The compounds were identified by ¹H and ¹³C NMR to be 1-chloro-2-propanol phenyl ether (48) and phenoxy acetone, respectively. ¹H NMR of 47 (CDCl₃) δ: 7.33 (t, 2H), 7.00 (t, 1H), 6.90 (d, 2H), 4.25 (m, 1H), 4.10 (dd, 1H), 3.60 (m, 2H), 2.55 (db, 1H, OH). ¹³C NMR of 47 (CDCl₃) δ: 129.5, 121.4, 114.6, 70.0, 68.5, 46.0.
III.2.6 PdCl₂(R)-Tol-BINAP Catalyzed Oxidation of Olefins

The procedure was similar to that described in section III.2.7.

The catalyst was prepared by adding (R)-Tol-BINAP (117.0 mg, 0.172 mmol) to a solution of PdCl₂(CH₃CN)₂ (39.0 mg, 0.15 mmol) in THF (5 mL). The solution was stirred under Ar at room temperature for about 30 min. The yellow clear solution which was produced transferred to the oxidation apparatus to be used in situ. The results of these studies are summarized in Table III.3.

Oxidation of 2,3-dihydrofuran (50) afforded three products in relative yields of 20%, 75% and 5%. The products were identified by ¹H and ¹³C NMR to be 3-oxo-tetrahydrofuran (53), 3-chloro-2-hydroxy-tetrahydrofuran (51) and 2-chloro-3-hydroxy-tetrahydrofuran (52), respectively. Spectral data of the products were as follows.

3-Chloro-2-hydroxy-tetrahydrofuran (51): ¹H NMR (CHCl₃) δ: 5.48 (d, J₁,₂ = 2.93 Hz, 1H), 4.26 (d, 1H), 4.19 (m, 2H), 2.78 (b, 1H, OH), 2.65 (m, 1H), 2.15 (dd, 1H); ¹³C NMR (CDCl₃) δ: 103.2, 67.1, 61.1, 33.0.

3-oxo-tetrahydrofuran (53): ¹H NMR (CHCl₃) δ: 5.10 (dd, 2H), 3.70 (m, 2H), 2.02 (m, 2H); ¹³C NMR (CDCl₃) δ: 207.3, 103.6, 62.6, 32.4.
Figure C.1. Illustrative part of the $^1$H NMR spectrum of 22 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methyl carbonyl protons. The spectrum shows that 22 has an ee of 42% with S absolute configuration.
Figure C.2. Illustrative part of the $^1$H NMR spectrum of 22 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved C-5 protons. The spectrum shows that 22 has an ee of 48% with S absolute configuration.
Figure C.3. Illustrative part of the $^1$H NMR spectrum of 32 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methyl carbonyl protons. The spectrum shows that 32 has an ee of 26%.
Figure C.4. Illustrative part of the $^1$H NMR spectrum of 33 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved ortho-aromatic protons. The spectrum shows that 33 has an ee of 68%.
Figure C.5. Illustrative part of the \(^1\)H NMR spectrum of 22 in the presence of Eu(hfc)_3. The spectrum shows the resolved methyl carbonyl protons. The spectrum shows that 22 has an ee of 58% with S absolute configuration.
Figure C.6. Illustrative part of the $^1$H NMR spectrum of 22 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methyl carbonyl protons. The spectrum shows that 22 has an ee of 0%.
APPENDIX D
Figure D.1. $^1$H and $^{13}$C NMR spectra of tetrasulfonated-(R)-Tol-BINAP.
Figure D.2. Illustrative part of the $^1$H NMR spectrum of 40 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methyl protons. The spectrum shows that compound 40 has an ee of 64%
Figure D.3. Illustrative part of the $^1$H NMR spectrum of 40 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved methyl protons. The spectrum shows that compound 40 has an ee of 76%.
Figure D.4. Illustrative part of the $^1$H NMR spectrum of 48 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved C-2 proton. The spectrum shows that compound 48 has an ee of 68%
Figure D.5. Illustrative part of the $^1$H NMR spectrum of 40 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved C-3 proton. The spectrum shows that compound 40 has an ee of 82%
Figure D.6. Illustrative part of the $^1$H NMR spectrum of 48 in the presence of Eu(hfc)$_3$. The spectrum shows the resolved C-2 proton. The spectrum shows that compound 48 has an ee of 80%.
Figure D.7. Illustrative part of the $^{13}\text{C}$ NMR spectrum of 51 in the presence of $\text{Eu(hfc)}_3$. The spectrum shows the resolved C-1 and C-2. The spectrum shows that compound 51 has an ee of 64% at C-1 and 46% at C-2.
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The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.