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Asymmetric Transfer Hydrogenation of Allylic Alcohols

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Asymmetric Transfer Hydrogenation of Allylic Alcohols

BY

JOSEPH M. LAQUIDARA

Dissertation

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in the
Department of Chemistry and Biochemistry
of Seton Hall University

South Orange, New Jersey
May 2003
We certify that we have read this thesis and that in our opinion it is adequate in scientific scope and quality as a dissertation for the degree of Doctor of Philosophy.

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ABSTRACT

Asymmetric catalysis is recognized as one of the most useful and important chemical processes. For example, Knowles, Noyori, and Sharpless shared the 2001 Nobel Prize in recognition of their contribution to this area. Although Noyori and Knowles were recognized for their contribution to asymmetric hydrogenation with gaseous hydrogen there has been recent interest in asymmetric hydrogenation reactions that avoid gaseous hydrogen. These reactions are formally called asymmetric transfer hydrogenation (ATH) where the hydrogen source is the solvent (i.e., isopropyl alcohol) or a reagent such as triethylammonium formate. This field is dominated by examples of ATH of aldehydes and ketones and, to date, no examples of this reaction have been reported for allylic alcohols. Previously, we discovered the isomerization of geraniol (3,7-dimethyl-2,6-octadiene-1-ol) to the homoallylic alcohol γ-geraniol with the catalyst [RuCl₂((S)-(-)-tol-BINAP)]₂ N(C₂H₅)₃. However, when we attempted to improve the synthetic utility of this reaction with this catalyst (abbr. Ru-tol-BINAP) the unexpected hydrogenation product, citronellol, was obtained (140 °C neat, 3 days). Analysis indicated that citronellol was obtained in 27% yield and 50% ee (S) with Ru-(S)-tol-BINAP as the chiral catalyst. Further optimization of this novel reaction led us to the use of isopropyl alcohol as the solvent/hydrogen source and an in situ prepared catalyst (eq 1).

\[ \text{Geraniol} \xrightarrow{0.01 \text{ M IPA soln.} \; 2 \text{ eq KOH/Ru} \; S/C \; 10/1} \text{Citronellol} \]

95% yield 90% ee (R)
The result was the conversion of geraniol to citronellol in 95% yield and 90% ee (R).

Investigation of other chiral diphosphine ligands including DIOP, PHANEPHOS, Et-BPE, and Me-DUPHOS revealed good to low enantioselectivity. However, in the case of (S,S) iPr-DUPHOS, a double hydrogenation product, dihydrocitronellol, was obtained in 98% yield and 90% ee (R). Other allylic alcohols were evaluated and show a wide range of yields and enantioselectivities. In addition, the scope of this reaction was broadened to include an \( \alpha,\beta \)-unsaturated ester and acid, an unfunctionalized olefin (\textit{trans}-methyl stilbene) and an \( \alpha,\beta \)-unsaturated ketone (3-methyl-2-cyclohexen-1-one). The hydrogenated products were detected in all cases.

A mechanism is proposed to account for this new transfer hydrogenation reaction of allylic alcohol which is in good agreement with the mechanistic steps found in the well-studied transfer hydrogenation of carbonyl groups and the asymmetric hydrogenation reactions of olefins. Also, the enantioface discrimination of geraniol with the metal center appears to obey the ‘lock and key’ model which is similarly found in asymmetric hydrogenation.
Dedicated to the Blessed Trinity
ACKNOWLEDGEMENTS

My sincerest thanks goes to Dr. John R. Sowa Jr. for his commitment, encouragement, and selfless contribution toward my academic development. I am fortunate to have him as my mentor.

I am also appreciative of Merck & Co., Inc. for the permission to fulfill my residency requirement at Seton Hall University. A special thanks goes to Dr. Philip Eskola of Merck who supported this effort.

Finally my deepest gratitude goes to my wife, Lucy, who has been a source of strength and perspective throughout my struggle to achieve this goal.
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ABBREVIATIONS

(for chiral compounds, only one enantiomer is given)

ATH asymmetric transfer hydrogenation

BINAP (S)-2,2’-bis(diphenylphosphino)-1,1’-binaphthyl

COD 1,5-cyclooctadiene

DIOP (S,S)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DPPEA diphenylphosphinoethylamine

Et-BPE 1,2-bis((2S,5S)-2,5-diethylphospholano)ethane
iPr-DUPHOS  1,2-bis((2S,5S)-2,5-di-i-propylphospholano) benzene

Me-DUPHOS  1,2-bis((2S,5S)-2,5-dimethylphospholano) benzene

PHANEPHOS  (S)-4,12-bis(diphenylphosphino)-[2.2]-paracyclophane

tol-BINAP   (S)-2,2’-bis(di-p-tolylphosphino)-1,1’-binaphthyl
INTRODUCTION: A REVIEW OF THE LITERATURE

Asymmetric reduction is a valuable synthetic tool that has fundamental importance in such areas as the pharmaceutical chemistry. For instance, in 2000 the worldwide sales of single-enantiomer drugs reached 123 billion US dollars. The desire for stereoselective reductions continues to generate much interest in academia and industry and already much is known regarding this valuable and mature area of organic chemistry.

The field of asymmetric reduction involves the addition of hydrogen to an sp² hybridized carbon atom to form an sp³ hybridized carbon atom, which is in a lower oxidation state. This reduction involves the double bonds of carbon-carbon, carbon-oxygen, and carbon-nitrogen atoms. Asymmetry is achieved with the formation of a three-dimensional stereocenter from a two-dimensional prochiral planar center (Figure 1).

Figure 1. Asymmetric Hydrogenation Processes.

\[
\begin{align*}
\text{C(R)₂}\text{R₁R₂} & \quad + \quad [\text{H}] \quad \rightarrow \quad \text{CH(R)₂}\text{H₁H₂} \quad + \quad \text{CH(R)₂}\text{H₁H₂} \\
\text{O}\text{R₂R₁} & \quad + \quad [\text{H}] \quad \rightarrow \quad \text{OH}\text{H₁H₂} \quad + \quad \text{OH}\text{H₁H₂} \\
\text{NHR}\text{R₁R₂} & \quad + \quad [\text{H}] \quad \rightarrow \quad \text{NH₂R}\text{H₁H₂} \quad + \quad \text{NH₂R}\text{H₁H₂}
\end{align*}
\]

[H] = any hydrogen source

---

In Figure 1 [H] is designated as a hydrogen source and there are three methods where hydrogen can be incorporated into the double bond. These three make up the reaction types that define enantioselective or asymmetric reduction: they are known as enantioselective hydride reduction, asymmetric hydrogenation, and asymmetric transfer hydrogenation.

Enantioselective hydride reduction typically implies borane chemistry and most often use chiral oxazaborolidine to transfer the chirality of the reaction. The original condition used a stoichiometric amount of the chiral reductant but now only a catalytic amount of the oxazaborolidine is necessary, provided that borane is the actual reducing agent in stoichiometric quantity with the substrate (Figure 2).

**Figure 2.** Enantioselective Hydride Reduction.

\[
\text{O} \\
\text{0.1 mol catalyst,} \\
\text{THF} \\
\text{0.6 mol BH}_3\text{-THF} \\
\text{RT} \\
\text{1 minute} \\
\text{OH} \\
\text{99 % yield, 97 % ee} \\
\]

catalyst = \[
\begin{array}{c}
\text{N} \\
\text{B} \\
\text{O} \\
\text{Ph} \\
\text{Ph} \\
\text{H} \\
\text{H}
\end{array}
\]

oxazaborolidine

---

The major drawback with enantioselective hydride chemistry is the large quantity of hydride used. This translates into poor atom economy since much waste is involved in the reaction.

The second class of enantioselective reduction is asymmetric hydrogenation. This is the area in which the majority of asymmetric hydrogenation reactions are performed. It is the most mature, atom economical and synthetically useful of the three types of reactions. Gaseous hydrogen is the source of hydrogen in these reactions. Typically, only a very small amount of a chiral catalyst is required in the presence of the substrate in an appropriate solvent such as methanol. Hydrogen pressure varies but typically values from 1 to 4 atm up to 100 atm is most common. Excellent enantioselectivities have been reported and Figure 3 highlights some notable cases.

**Figure 3.** Highlights of Asymmetric Hydrogenation Reactions.
It is interesting to note that in many circumstances there exists an excess of hydrogen gas over the theoretical amount necessary for double bond reduction. For example, in a one litre autoclave containing 500 mL of 0.6 M substrate solution 0.3 moles of hydrogen gas is required. Yet if this vessel is pressurized with 30 and 100 atm of H₂ at 298 K the corresponding molar quantity of gas present is 0.7 and 2.2 moles H₂, respectively.

Asymmetric hydrogenation was first noted for reduction across carbon-carbon double bonds with transition metals that included ruthenium, rhodium, and iridium. Later the substrates were broadened to include carbonyls and imines. Chiral induction is achieved with chiral ligands that coordinate to the metal center and alter the steric environment of the catalyst to prefer coordination of one enantioface of the substrate. Hydrogenation only occurs on the substrate’s face that is attached to the catalyst, and only in cis orientation.

One of the first major achievements in asymmetric hydrogenation was demonstrated in the synthesis of a drug, L-DOPA, for Parkinson’s disease, that was discovered by W. S. Knowles and coworkers at Monsanto in the mid 1970’s that involved the asymmetric hydrogenation of an acylaminoacrylic acid (Figure 4a).

---

6 cf. 1.
The next great achievement in asymmetric hydrogenation was jettisoned by the development of the chiral ligand BINAP (2,2’-bis(diphenylphosphino)-1,1’-binaphthyl) by R. Noyori and coworkers in 1980. This opened new doors to asymmetric hydrogenation.

**Figure 4.** Commercial Applications of Asymmetric Hydrogenations.

a) R-(R,R)-DIPAMP

\[
\text{R-(R,R)-DIPAMP} = \begin{array}{c}
\text{P} \\
\text{C}_6\text{H}_5 \\
\text{P} \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_4\text{-}o\text{-OCH}_3 \\
\text{C}_6\text{H}_5
\end{array}
\]

\[
\begin{align*}
\text{(HO)}_2\text{C}_6\text{H}_3 & \underset{\text{Rh-(R,R)-DIPAMP}}{\xrightarrow{\text{3 atm. H}_2}} \text{H} \\
& \text{50 C} \\
& \text{MeOH}
\end{align*}
\]

\[
\text{COOH}
\]

\[
\text{NHOCH}_3
\]

\[
\text{(HO)}_2\text{C}_6\text{H}_3
\]

\[
\text{COOH}
\]

\[
\text{NH}_2
\]

\[
\text{L-DOPA} \ 94\%\text{ee}
\]

b) Ru-(S)-BINAP

\[
\text{(S)-BINAP} = \begin{array}{c}
\text{P}\text{(C}_6\text{H}_5\text{)}_2 \\
\text{P}\text{(C}_6\text{H}_5\text{)}_2
\end{array}
\]

\[
\begin{align*}
\text{COOH} & \underset{\text{Ru-(S)-BINAP}}{\xrightarrow{\text{135 atm. H}_2}} \text{COOH} \\
& \text{RT} \\
& \text{MeOH}
\end{align*}
\]

\[
\text{Naproxen} \ 97\%\text{ee}
\]

especially with ruthenium metal which behaves differently from rhodium in reactivity and its mechanism of hydrogenation. For instance, with ruthenium catalysis there is more

---

flexibility in substrate structure since there is no requirement that the substrate possess an α–amido functionality for reduction to occur as in rhodium catalysis. An industrial application of asymmetric hydrogenation with Ru-BINAP includes the preparation of the anti-inflammatory drug Naproxen shown in Figure 4b. The importance of asymmetric hydrogenation was readily made apparent when in 2001 the Nobel Prize in Chemistry went to W. S. Knowles and R. Noyori for their respective work in asymmetric hydrogenation. (The prize was also awarded to K. B. Sharpless for his work in asymmetric epoxidation.)

With the introduction of Ru-BINAP the scope of asymmetric hydrogenation was broadened to also include functionalized ketones in 1988 (Figure 5).

Figure 5. Asymmetric Hydrogenation of Functionalized Ketones.

\[ \text{[RuCl}(\text{p-cymene})(\text{S})\text{-BINAP}] \rightarrow \text{[RuCl}(\text{p-cymene})(\text{S})\text{-BINAP]} \]

9 cf. 5.
The success of these reactions required a closely positioned heteroatom to direct the substrate to the metal catalyst. It is important to know that with these catalyst systems, the Ru-BINAP complexes have just two coordination sites fixed (from the diphosphine atoms) with the remaining sites labile. Thus whether one refers to the asymmetric hydrogenation of an olefin or a functionalized ketone with Ru-BINAP the presumed substrate/catalyst intermediates are attached in trans coordination as depicted in Figure 6.12

**Figure 6.** Structural Comparison of Intermediates in Ru-BINAP Catalyzed Asymmetric Hydrogenation of Olefins and Functionalized Ketones.

![Figure 6](image)

Trans coordination of substrate with BINAP on each intermediate

This concept of trans coordination at the ruthenium metal will be cited throughout the body of this dissertation and will later support the mechanism proposed for the asymmetric transfer hydrogenation of allylic alcohols.

In 1995, the ability to hydrogenate unfunctionalized or simple ketones became possible with the addition of a bidentate amino ligand, ethylenediamine.13 Since then, chiral diamine ligands in conjunction with variations of the BINAP ligand have shown great efficiency and enantioselectivity of hydrogenation with unfunctionalized ketones.

---

In the case of unfunctionalized ketones the presumed substrate/catalyst intermediate can no longer adopt the structure shown in Figure 6 since the diamine ligand is tightly coordinated trans to the BINAP ligand. Thus, the only two open sites available on the ruthenium metal are trans to each other. The implications of this would be quite significant from a mechanistic aspect, although Noyori does not propose a mechanism for this reaction.

Shortly after his success with asymmetric hydrogenation, Noyori tried his Ru-diamine complexes into the blossoming field of asymmetric transfer hydrogenation (ATH). He made significant contributions in this area and in particular, he demonstrated that a

---

14 cf. 11c.
novel mechanism was evident for ketone ATH with Ru-diamine complexes, which will be discussed shortly.

‘ATH’ type reactions were already known for many decades as transfer hydrogenation reactions but without enantioselectivity. Two classes of reactions are grouped by their mechanism: the first group involves a concerted mechanism; and the second group involves a unique metal hydride species.

The first group is known as the Meerwein-Ponndorf-Verley (MPV) reduction which was developed independently in the mid 1920’s. This reaction uses a stoichiometric amount of aluminum tris(2-isopropoxide) as the reductant in isopropanol. The mechanism is believed to be a concerted process (Figure 8).

Figure 8. Meerwein-Ponndorf-Verley Reduction.

\[
\begin{align*}
\text{Meerwein, H.; Schmidt, R. \textit{Liebigs Ann. Chem.} \textbf{1925}, 444, 221.} \\
\text{Verley, A. \textit{Bull. Soc. Chim. Fr.} \textbf{1925}, 37, 537.} \\
\text{Ponndorf, W. \textit{Angew. Chem.} \textbf{1926}, 39, 138.}
\end{align*}
\]
To the best of our knowledge, the first example of an enantioselective and sub-stoichiometric MPV reduction was published in 1993 by D. Evans and coworkers where they used a chiral samarium complex in isopropanol (Figure 9).  

**Figure 9.** Enantioselective and Sub-stoichiometric MPV Reduction.

![Chemical structure](image)

Similar to the classical MPV reduction, the reaction with the samarium catalyst is thought to proceed through a concerted six-membered transition state where no metal hydride is ever formed.

Another example of a MPV reduction shows asymmetric amplification. Asymmetric amplification is a nonlinear effect where the enantiomeric purity of the product is greater than the enantiomeric purity of the sum of the catalyst species. C. Moeder et al. of Dr. Sowa’s research group has investigated the enantioselectivity of the reduction of acetophenone with a chiral borane complex that uses pinene as a ligand of 70 % ee to give

---


product of greater than 90 % ee (Figure 10). This is made possible by the fact that the statistical mix of chiral borane complexes show unequal reactivity with acetophenone to allow predominately one chiral species (+,+) to reduce acetophenone faster than either (+,-) or (-,-) complexes. (In this reaction, the hydride added to the double bond comes from the position geminal to the methyl group on the pinene ring.)

**Figure 10.** Asymmetric Amplification of Acetophenone Reduction with Chlorodiisopinocampheylborane.

The second group of transfer hydrogenation reactions is thought to proceed via a different mechanism where a metal hydride is formed. These reactions typically include transition metals such as ruthenium, rhodium, and nickel complexes.19 As in the case with the MPV reaction these reactions were also known for decades but without stereoselectivity.

In the early days the transfer hydrogenation reaction was a slow reaction to mature. In the early 1970’s the conditions required for the hydrogen transfer were unsuitable for most substrates, since the typical temperatures were from 160 to 200 °C, largely due to the absence of base and mismatched substrate to catalyst. For instance, α,β-unsaturated ketones and acids were matched with RuCl₂(PPh₃)₃ which does not have the best geometry

---


20
fit for bidentate olefin chelation (Figure 6). In 1991, Bäckvall and Chowdhury discovered what has become the current conditions for this reaction; the use isopropanol as the solvent and hydrogen source and the necessity of base. This reaction is now possible between room temperature and reflux (Figure 11).

**Figure 11.** Transfer Hydrogenation of Acetophenone.

![Transfer Hydrogenation of Acetophenone](image)

The proposed mechanism for transfer hydrogenation reactions in isopropanol is shown in Figure 12.

**Figure 12.** Conventional Mechanism for Transfer Hydrogenation

---


22 cf. 19.
The steps of the catalytic cycle are as follows: formation of a metal-alkoxide intermediate; \(\beta\)-hydride elimination (BHE); coordination of the ketone to the metal-hydride; migratory insertion of the hydride into the carbonyl carbon to form an alkoxide intermediate; release of product and return of the cycle by isopropanol. The involvement of a unique metal hydride species has not been unequivocally proven; but, studies implicate a hydride species in this mechanism.\(^{23}\)

Another popular hydrogen source for transfer hydrogenation reactions is formic acid with or without triethylamine.\(^{24}\) Interestingly, there is some confusion as to the possible mechanism with this hydrogen source. The literature reports a number of examples where the reactions were successfully run from room temperature up to 70 °C with excellent reactivity in standard glassware\(^{25}\), and yet two reports reveal the need for an autoclave due to the observation of a large pressure increase from the production of hydrogen gas at temperatures greater than 125 °C.\(^{26}\)

The question can then be raised, ‘Since there is a decomposition temperature at which molecular hydrogen is apparently formed and consumed at elevated temperature, does it also participate in the reaction unnoticed at lower temperature? The answer was given by Noyori in an experiment where formic acid was replaced by acetic acid (a non-reducing analogue) and the reaction placed under 20 atm of D\(_2\). The result was only 5 % yield was obtained. In another experiment, a formic acid/triethylamine mixture was used in


the presence of 65 atm of D₂ and at full conversion only a trace amount of deuterium was incorporated.  

The transition from transfer hydrogenation to asymmetric transfer hydrogenation (ATH) was a slow step up until the mid 1990’s. Prior, the best optical yield was 20 %; however, dramatic improvements were discovered with the use of Noyori’s chiral Ru-diamine that quickly launched ATH as a viable alternative to asymmetric hydrogenation.

Highlights of ATH reactions are shown in Figure 13.

**Figure 13.** Highlights of Asymmetric Transfer Hydrogenation Reactions.

<table>
<thead>
<tr>
<th>[H]</th>
<th>S/C/B</th>
<th>% Yield</th>
<th>% ee(config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPA</td>
<td>200/1/5</td>
<td>70</td>
<td>91(S)</td>
</tr>
<tr>
<td>HCOOH</td>
<td>200/1</td>
<td>75</td>
<td>91(S)</td>
</tr>
<tr>
<td>Et₃N 9eq</td>
<td>de &gt; 97%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

27 cf. 25a.
In ATH reactions with Ru-diamine, Noyori has proposed a mechanism different from Figure 12. This mechanism does not involve attachment of the substrate to the metal center but rather close participation with the amino group bound to the ruthenium (Figure 14).

**Figure 14.** Noyori’s Mechanism of ATH with Chiral Ru-diamine Catalyst.

The steps of the catalytic cycle are as follow: nucleophilic attack of base to form a 16 electron ruthenium complex; a concerted hydride transfer from isopropanol to reestablish an 18 electron saturated complex; and a concerted hydride transfer from the complex to

---

ketone to release product and return the cycle to the beginning. The concerted hydride transfer transition state and sense of asymmetric induction is shown in Figure 15.

**Figure 15.** Concerted Hydride Transfer Transition State and Sense of Asymmetric Induction.

These reactions also work well with chiral β-aminoalcohol ligands where presumably the same mechanism applies. In addition, Noyori’s Ru-diamine complexes work well with formic acid/triethylamine as the hydrogen source at low temperatures (i.e., 28 ºC).

Enantioselective reduction continues to mature into a extremely useful synthetic tool. Both asymmetric hydrogenation and ATH have proven their worthiness as unique and critical chemical processes.

For some time now, the chemical industry has become more conscious toward safety and efficiency. In that case ATH has offered great advances over asymmetric hydrogenation because the use of hydrogen gas is avoided. ATH is safer since there is no need for specialized reactors or equipment for handling this highly flammable and potentially dangerous gas. In addition, this translates into a more efficient chemical process.

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31 cf. 29a.
32 cf. 25.
since avoidance of specialized equipment means procedural simplicity. Certainly
asymmetric hydrogenation and to a much lesser extent, enantioselective hydride reduction,
have established niches in the chemical industry but increasingly ATH reactions are
demonstrating itself as a strong alternative. This study further supports that argument with
the introduction of a new reaction: the first ATH of allylic alcohols.
CHAPTER 1: ISOMERIZATION AND HYDROGENATION OF GERANIOL

INTRODUCTION

The asymmetric hydrogenation of geraniol with \([\text{Ru-(S)-(BINAP)(OAc)}_2]\) in methanol gives the monoreduction product, citronellol (Figure 3 (first example)). The enantioselectivity of this reaction was examined by Noyori at various hydrogen pressure and some interesting results were obtained in his experiments. At 100 atm of hydrogen citronellol of 98% ee was reported but at 4 atm of hydrogen the enantioselectivity dropped to 70% ee. No explanation was given for this discrepancy.\(^{33}\)

Several years after Noyori’s work, in collaboration with the Reaction Engineering Laboratory at Merck & Co., Inc., we pursued the investigation of the geraniol hydrogenation reaction from the experimental discovery that irreproducible enantioselectivities were obtained at a given hydrogen pressure. This was discovered when the time prior to the introduction of hydrogen gas was extended to allow for the ruthenium catalyst, \([\text{RuCl}_2(\text{S-tol-BINAP})_2\cdot\text{N(CH}_2\text{CH}_3)_2]\), to dissolve completely in methanol with geraniol also present. In this particular reaction lower ee was obtained than when the hydrogen gas was introduced sooner to the precatalyst/substrate mixture.

The hydrogenation of geraniol was investigated more closely and it became evident that a dramatic change in enantioselectivity was seen through the course of the entire reaction. At the beginning of the reaction citronellol that formed was the opposite

\(^{33}\) cf. 5, 43.
configuration than the citronellol formed at the end of the reaction. During the course of
the reaction the enantioselectivity was measured and is shown in Figure 16.\textsuperscript{34}

Figure 16. Change in Enantioselectivity During Course of Geraniol Hydrogenation

Isolation of the reaction mixture prior to full conversion revealed the formation of an
isomerization byproduct, γ-geraniol. When isolated γ-geraniol was hydrogenated it formed
citronellol of the opposite configuration than geraniol (Figure 17).

The isomerization and hydrogenation results were corroborated by an independent synthesis of $\gamma$-geraniol from the hydroboration of myrcene\textsuperscript{35} that was performed in the lab and shown in Figure 18.

Thus, the isomerization of geraniol to $\gamma$-geraniol competes with hydrogenation during the course of the reaction and especially in the beginning prior to pressurization with gas. Therefore, the results found by Noyori show a greater amount of isomerization occurs at lower hydrogen pressure which leads to a decrease in enantioselectivity.

RESULTS/DISCUSSION

The discovery of γ-geraniol found particular interest in the Sowa research group. We investigated the thermodynamics of the isomerization reaction. In the absence of hydrogen gas the isomerization reaction cleanly went to an equilibrium concentration of 18% γ-geraniol at 293 K and 22% γ-geraniol at 318 K. Application of the van’t Hoff-Isochore equation we obtain an enthalpy of isomerization of 1.79 kcal/mole higher in energy (Figure 19).\textsuperscript{36}

\textbf{Figure 19.} Enthalpy of Isomerization of Geraniol to γ-Geraniol.

\[
\frac{\text{dln}K}{dT} = \frac{-\Delta H^\circ}{RT^2} \quad \text{van’t Hoff-Isochore equation (K = eq. const., T = °K)}
\]

multiply both sides by dT and integrate:

\[
\ln \frac{K_2}{K_1} = -\Delta H^\circ \left( \frac{1}{T_2} - \frac{1}{T_1} \right)
\]

\[
\ln \frac{0.28}{0.22} = -\Delta H^\circ \left( \frac{1}{318} - \frac{1}{293} \right)
\]

\[
0.22 \times 1.97 = 1.97 \text{ cal.} \cdot \text{deg}^{-1} \cdot \text{mol}^{-1} \quad R = 1.97 \text{ cal.} \cdot \text{deg}^{-1} \cdot \text{mol}^{-1}
\]

\[
\Delta H^\circ = 1790 \text{ cal/mol}
\]

This is consistent with a comparison in the literature of the isomerization of 2-butene to 1-butene (1.99 kcal/mol). Interestingly, in no case did the isomerization to the aldehyde citronellal occur or the isomerization to the internal olefin (3,7-dimethyl-3,6-octadien-1-...
ol, (ocimenol)), which should be thermodynamically favorable based on Benson’s additivity rules of enthalpy of formation (Figure 20).

Figure 20. Benson’s Rules for Enthalpy of Formation.

Thus,

\[ \Delta H \text{ of geraniol to } \gamma\text{-geraniol is 0.39 kcal/mol.} \]
\[ \Delta H \text{ of geraniol to ocimenol is -1.13 kcal/mol.} \]
\[ \Delta H \text{ of geraniol to citronellal is -12.34 kcal/mol.} \]

The interest in \( \gamma \)-geraniol became even greater since it is not commercially available. We desired to explore this isomerization reaction for its synthetic utility. It was decided to change the solvent and temperature to see how the equilibrium concentration of geraniol to \( \gamma \)-geraniol was affected. Table 1 shows the results of a several solvents.

**Table 1.** Geraniol Isomerization with 1 mole % [RuCl\(_2\)(S)-(\text{-tol-BINAP})\]\(_2\).N(C\(_2\)H\(_5\))\(_3\) in Various Solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th># of Runs</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp ((^\circ)C)</th>
<th>% Isomerization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>MeOH</td>
<td>48</td>
<td>RT</td>
<td>16.1, 12.9</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>EtOH</td>
<td>48</td>
<td>RT</td>
<td>18.2, 18.4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>EtOH</td>
<td>1</td>
<td>45</td>
<td>10.4, 6.7</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>iPr-OH</td>
<td>2</td>
<td>45</td>
<td>1.9, 1.6</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>tBuOH</td>
<td>72</td>
<td>45</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>tBuOH/H(_2)O (95/5)</td>
<td>48</td>
<td>RT</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>tBuOH/acetaldehyde (95/5)</td>
<td>72</td>
<td>RT</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Isomerization occurred for each alcohol solvent that possessed an alpha hydrogen to the oxygen atom (oxidizeable solvent). However, in the case of \( t \)-butanol which does not contain an alpha hydrogen no isomerization occurred. Entry 6 was chosen in the hope of minimizing the differences in solvent polarity for a truer comparison since the polarity of a
mixture of 95/5 t-butanol/water is closer to the polarity of methanol. Still no isomerization occurred.

If only oxidizable solvents would permit isomerization one would expect evidence of the byproducts formaldehyde, acetaldehyde, and acetone from methanol, ethanol, and isopropanol, respectively (Figure 21).

**Figure 21.** Ruthenium Catalyzed Autooxidation of Oxidizable Solvents.

![Chemical reaction diagram](image)

Unfortunately, all attempts to find these solvent byproducts were unsuccessful. The only byproduct that could be found was ethyl acetate in the ethanol experiments in about 1% by weight with respect to the catalyst. Perhaps the acetaldehyde that was expected to form was transient and further reacted with ethanol through a proposed metal assisted nucleophilic substitution shown in Figure 22.

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* Neither did we find any diethyl acetal of acetaldehyde.
The decision to try entry 7 of Table 1 was based on the theory that was formulated thus far. If the isomerization in ethanol produced acetaldehyde that was either consumed or undetected, a reaction in a nonsolvent (\(t\)-butanol) should become possible in the presence of acetaldehyde. Indeed the isomerization did go to 7.4% conversion in this case.

One of the most intriguing aspects of this isomerization reaction is what did not form. In addition to no ocimenol, neither the aldehyde, citronellal, was present. Isomerization of allylic alcohols with ruthenium, rhodium, and nickel complexes customarily produce aldehydes or ketones, however, the isomerization of geraniol to citronellal is not a common reaction despite its favorable enthalpy (Figure 20). For
instance, Trost found no citronellal from the attempted isomerization of geraniol with 
CpRu(PPh₃)₂Cl in dioxane at 100 °C. Also no mention of any γ-geraniol was made 
either. The only examples in the literature that do describe the formation of citronellal from 
geraniol mention only a partial list of catalysts that enable this reaction under specialized 
conditions. For instance, the isomerization to citronellal can be obtained in 61 % yield 
with the preformed metal hydride catalyst, RhH(PPh₃)₃, in THF reflux for three hours.⁴¹a

On the other hand, the isomerization of diethylgeranylamine to (R)-citronellal 
enamine gives, upon hydrolysis, (R)-citronellal in 96% ee (Figure 23).

**Figure 23.** Isomerization of Diethylgeranylamine.

\[
\text{N(CH₂CH₃)₂} \quad \xrightarrow{[\text{Rh}((S)-\text{BINAP})(\text{COD})]\text{ClO₄}}} \quad \text{H}_3\text{O}^{+} \quad \text{96 % ee}
\]

This isomerization is catalyzed by [Rh((S)-BINAP)(COD)]ClO₄ in tetrahydrofuran and it is 
the first step in the production of (-)-menthol, the largest example of homogeneous 
asymmetric reaction in the world (nine ton scale).⁴² In this unique reaction the mechanism

---

has been shown to proceed through a nitrogen assisted intermediate which does not resemble the examples of allylic alcohol isomerizations reported in the literature.

The proposed mechanism for the isomerization of geraniol to γ-geraniol that we investigated may proceed as shown in Figure 24.

**Figure 24.** Proposed Mechanism for the Isomerization of Geraniol to γ-Geraniol.

The steps of the catalytic cycle are as follow: a) autooxidation of ethanol to form a ruthenium hydride; b) chelation with geraniol; c) migratory insertion of the hydride into the
olefin bond; and, d) β-hydride elimination to form γ-geraniol and return the cycle to the beginning. The only support for the ruthenium hydride/beta-hydride mechanism rather than a π-allyl mechanism is the experimental evidence of the failure of t-butanol to isomerize this substrate which strongly suggests the requirement of a unique ruthenium hydride species that forms via the autooxidation route. In the case of the π-allyl mechanism the ruthenium hydride would come directly from the allylic alcohol shown in Figure 25.

Figure 25. Requirement for π-Allyl Intermediate

\[ \text{[Ru]} + \text{OH} \rightarrow \text{[Ru]} - \text{H} \rightarrow \text{OH} \]

Based on the observation that the isomerization reaction is endothermic, an attempt was made to maximize the product yield at elevated temperature. A neat reaction was aged at 140 °C for three days in the hope of obtaining a better conversion of geraniol to γ-geraniol. Geraniol is also a primary alcohol and may be oxidized to activate the ruthenium catalyst into the hydride species; however, the results were astonishing. No γ-geraniol had formed; instead, numerous byproducts were formed and a major peak of 27 % (GC area) revealed the hydrogenated product citronellol. The ee of this product was measured and determined to be (R)-citronellol in 50 % ee.

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CONCLUSION

The asymmetric hydrogenation of geraniol is known to give citronellol that can vary in enantiomeric excess depending on hydrogen pressure used. Also, a change in the enantioselectivity at the same hydrogen pressure from one run to another was discovered by us in collaboration with researchers at Merck. When the reaction was more carefully monitored, we found the byproduct γ-geraniol was generated. It was observed that the concentration of γ-geraniol was greatest prior to the pressurization with hydrogen when only substrate, catalyst, and solvent were present. Further investigation revealed that when γ-geraniol was hydrogenated it formed citronellol of the opposite configuration than geraniol, thus, degrading the ee of the hydrogenation reaction at low hydrogen pressure.

This isomerization reaction was not only observed in methanol but also in ethanol and to a minor extent in isopropanol but not in t-butanol. The conclusion is that since t-butanol does not possess a hydrogen alpha to the oxygen there is no way for it to become oxidized and allow a ruthenium hydride catalyst to form. None of the expected byproducts from oxidized solvents were found but circumstantial evidence supports the beta-hydride mechanism believed for this reaction to occur.

The attempted improvement on the yield of γ-geraniol led to a neat reaction at elevated temperature which surprisingly formed citronellol instead. In addition, the ee of the citronellol was 50 % (R).

The amazing result appears, to the best of our knowledge, that this is the first example of a transfer hydrogenation of an allylic alcohol and, moreover, the first example of an asymmetric transfer hydrogenation (ATH) of an allylic alcohol. (This is based on a careful literature search on SciFinder and an extensive hand search of the literature of
The remainder of this thesis will be focused on the optimization of this reaction and application toward a broader range of substrates.
CHAPTER 2: ASYMMETRIC TRANSFER HYDROGENATION OF ALLYLIC ALCOHOLS

INTRODUCTION

To the best of our knowledge, transfer hydrogenation reactions of allylic alcohols have never been reported. Most of the transfer hydrogenation reactions in the literature are concerned with the reduction of ketones, aldehydes, and imines.\textsuperscript{44} Less common are the transfer hydrogenation of $\alpha,\beta$-unsaturated acids.\textsuperscript{45} However, no report has ever been published regarding the transfer hydrogenation of an allylic alcohol. Moreover, no ATH of an allylic alcohol has ever been described.

Indeed, it is worth mentioning that several articles on MPV reductions do mention the inactivity of the allylic bond. For example, in one paper, citral was readily reduced across the carbonyl moiety to form geraniol but did not show further reactivity with a modified MPV procedure that uses zeolite sieves.\textsuperscript{46} In another example, a heterogeneous MPV reaction using oxides of magnesium, aluminum, and calcium showed greater than a 90\% selective reduction of citral to geraniol but no citronellol formed.\textsuperscript{47}

In a similar case, a MPV reduction of cinnamaldehyde exclusively formed the allylic alcohol in 97\% yield but did not further react in the presence of aluminum $t$-

\textsuperscript{44} Palmer M. J.; Wills, M. Tetrahedron: Asymmetry 1999, 10, 2045.
\textsuperscript{46} Shabatai, J.; Lazar, R.; Biron, E. J. Mol. Catalysis 1984, 27, 35.
butoxide at room temperature. In this same article other allylic aldehydes and ketones gave only the monoreduced product with no mention of the fully saturated alcohol.

On the other hand, many reactions are known for the asymmetric hydrogenation of allylic alcohols. Examples abound for the hydrogenation of allylic alcohols with various transition metals, including ruthenium, rhodium, and iridium. Of particular interest, Noyori studied the hydrogenation of geraniol and nerol with Ru-BINAP(OAc), Also, Steven Bergens et al. examined the hydrogenation of geraniol with a cationic ruthenium catalyst, [Ru((R)-BINAP)(MeCN)(1-3:5,6-η-C8H11)](BF4). However, in no case does the literature describe any transfer hydrogenation of geraniol or for that matter any allylic alcohol.

The question now becomes, “did geraniol really undergo a transfer hydrogenation reaction and if so, could this be a synthetically useful reaction?”

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50 cf. 4a.
51 cf 4c.
RESULTS/DISCUSSION

While this project progressed it quickly became evident that a reliable measurement of product enantioselectivity was needed. Gas chromatographic analysis of citronellol on a chiral column (ChiralDEX B-TA column, 60 °C isocratic) was attempted but did not show baseline separation and was abandoned. Previously reported work with gas chromatographic separation of the diastereomeric amide derivative of citronelllic acid (from the oxidation of citronellol)\textsuperscript{52} and enantiomerically pure α-methylbenzylamine was partially successful but seemed unreliable since high temperatures were required to elute the diastereomers off the column. In addition, the \textsuperscript{1}H NMR of these diastereomers showed overlap which prevented the use of this technique. However, success was finally achieved by chiral HPLC with the preparation of the Mosher diastereomeric ester of citronellol with (S)-(+)\-methoxy-α-trifluoromethylphenylacetyl chloride (Figure 26).

**Figure 26.** Derivatization and ee Analysis.

Baseline separation was achieved with a Daicel Chiralcel OJ HPLC column. The validity of this analysis was then demonstrated with a racemic mixture of citronellol (Aldrich) that

\textsuperscript{52} Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399.
showed less than 3% ee and thus non-linear effects were absent from the derivatization reaction (Figure 27). In addition, because there was essentially no ee it was deduced that there was no significant difference in the extinction coefficient between the two diastereomers at 254 nm UV detection.

**Figure 27.** HPLC Analysis of (S)-Mosher Esters of Racemic Citronellol.

After the Mosher ester method for ee analysis was established the investigation of this potentially new ATH reaction was adapted to the conventional conditions for ATH with ketones. Immediately prior to this work we investigated the reduction of acetophenone and decided to retain some of the aspects of this work which seemed reasonable or showed promise.
In the ATH of ketones (such as acetophenone) with isopropyl alcohol as the hydrogen donor, there is a thermodynamically unfavorable equilibrium that poses a severe limitation. The byproduct of this reaction, acetone, has a similar oxidation potential to acetophenone, and thus competes for reduction. Therefore, it is customary to use a large excess of the donor molecule (isopropyl alcohol as a solvent) to help push the equilibrium concentration satisfactorily toward product formation. For instance, the calculated relative equilibrium ratios of sec-phenethanol: acetophenone in a 0.1 and 1.0 M substrate concentration in IPA are 98:2 and 80:20, respectively. On a practical level, it has been shown that the reaction may be driven to reasonable conversion by distillation of the acetone as it is formed. As a result of this thermodynamically unfavorable equilibrium all of the earlier ketone ATH experiments were run under gentle vacuum distillation (undetermined pressure) at 0.01 M in substrate. This is approximately 0.1 % by weight of acetophenone in isopropyl alcohol. This same substrate concentration was then used for all work with allylic alcohols.

From the beginning of this work we decided that commercially available chiral diphosphine ligands would be the best ligands for evaluation since much is already known about these ligands. In particular, Noyori’s BINAP ligand was well studied in the gaseous hydrogenation reaction of geraniol and this ligand was used in the isomerization work we performed. Similarly, the bulk of the literature described the use of ruthenium complexes for geraniol hydrogenation and so we chose to utilize ruthenium and diphosphine ligands for ATH studies. Finally, since recent mechanistic work by Noyori on the transfer

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53 cf. 16.
55 cf. 34.
hydrogenation reaction of ketones used ruthenium in their model, this mechanism was accepted as a good starting point for our investigation largely due to Noyori’s outstanding success in this field.

From the earliest work with ATH of ketones and then with allylic alcohols we prepared the catalyst precursor \textit{in situ}. The ruthenium metal used for the all the work for allylic alcohols was the ruthenium polymer \([\text{Ru(COD)Cl}_2]_n\). This is a convenient form of ruthenium that can be readily accessed by phosphine ligands to potentially make a reactive catalyst complex. The literature reports that simply refluxing the ruthenium polymer and ligand together in alcoholic solvent provides the desired complex, but in no case was isolation or characterization of the complex attempted\(^{56}\).

As previously stated we investigated the ATH of acetophenone. For the most part that work was unsuccessful with the exception of one encouraging result. The combined effect of \textit{tol}-BINAP and diphenylphosphinoethylamine (DPPEA) with ruthenium greatly increased the rate of acetophenone reduction (Table 2).

\begin{table}[h]
\centering
\begin{tabular}{lcccc}
Entry & Ligand 1 & Ligand 2 & % Yield\(^c\) & Time (h) \\
\hline
1 & \textit{tol}-BINAP & DPPEA & 46 & 2 \\
2 & \textit{tol}-BINAP & none & 47 & 17 \\
\end{tabular}
\end{table}

\textbf{Table 2.} Reactivity Enhancement of DPPEA on Asymmetric Transfer Hydrogenation (ATH) of Acetophenone\(^a\) to sec-Phenethanol with Precatalyst \(\text{RuCl}_2(\text{PPh}_3)_3\)^\textit{b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand 1</th>
<th>Ligand 2</th>
<th>% Yield(^c)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textit{tol}-BINAP</td>
<td>DPPEA</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>\textit{tol}-BINAP</td>
<td>none</td>
<td>47</td>
<td>17</td>
</tr>
</tbody>
</table>

\(^a\) 0.1 M substrate solution
\(^b\) Catalyst formed \textit{in situ} with one equivalent of ligand(s) at 100 °C
\(^c\) HPLC yield

\(^{56}\) cf. 45.
Assuming that both ligands adopted a trans relationship to the ruthenium metal, the expected complex is similar to the model shown by Noyori which includes a protonated nitrogen bound to a metal center (Figure 14). Therefore, our earliest explorations with geraniol retained the composition of both a diphosphine ligand and DPPEA.

One remaining aspect of the conventional ATH that is well known is the requirement of base for this reaction. Potassium hydroxide was employed as the base. A 0.1 M solution is frequently quoted in the literature and we retained this concentration from the earlier work that was done. Later we changed to a 0.05 M concentration because we suspected some problems with borderline insolubility of potassium hydroxide in isopropyl alcohol.

Now this question could be answered: “did geraniol really undergo a transfer hydrogenation reaction?” The answer: the reaction of a 0.1 M geraniol solution in isopropyl alcohol with two equivalents of potassium hydroxide per ruthenium complex containing tol-BINAP and DPPEA with a substrate/catalyst ratio of 100/1 at reflux for ten hours produced citronellol in 52% yield! Thus, similar conditions that give ATH for ketones give ATH for geraniol.

Exploration of this exciting new reaction was begun. For example, we examined the parameters that we felt would enhance the yield and enantioselectivity. The necessity for the presence of ruthenium and base were established as a requirement for this reaction to occur. Also, the concentration of base was found to be critical; an increase in base increased the rate of the desired reaction but, in addition, caused significant amounts of byproduct(s) to form. In addition, the qualitative observation that these reactions are
somewhat air sensitive led to a procedural modification later adopted for all the future work which greatly increased yields.

The requirement for ruthenium metal was quickly established. All ATH reactions suggest the requirement of a transition or main group metal to catalyze the reaction and this was also observed here (Table 3).

Table 3. The Requirement of Ruthenium Catalyst in the Asymmetric Transfer Hydrogenation (ATH) of Geraniol

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Ru (eq)</th>
<th>tolBINAP (eq)</th>
<th>Time (h)</th>
<th>% Conversion</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>57.0</td>
<td>56.0</td>
</tr>
</tbody>
</table>

*a0.1 M IPA solution, 100 °C  
bS/C/B 100/1/2.1 including 1 eq. each of diphenylphosphinoethylamine and CuCl

Table 4. The Requirement of Base for Asymmetric Transfer Hydrogenation (ATH) of Geraniol

<table>
<thead>
<tr>
<th>KOH</th>
<th>Time (h)</th>
<th>% Conversion</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>1.4</td>
<td>4</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>1.4</td>
<td>22</td>
<td>27</td>
<td>26</td>
</tr>
</tbody>
</table>

*a0.01 M IPA solution, 100 °C, substrate/Ru/DPPEA 100/1/1  
bmolar ratio of base/Ru
Although copper (I) chloride was present the results clearly indicate this reaction is transition metal catalyzed. Because the reactions are very air sensitive, we added CuCl as an oxygen scavenger in these early reactions. However, this additive seemed to have no effect and was abandoned. The requirement of the presence of base was also established and this is also a requirement with conventional transfer hydrogenation reactions (Table 4).

Interestingly, literature precedents for the reduction of ketones appeared to show the requirement of base more dramatically than the reaction of geraniol since 3% of citronellol was formed with no KOH. Perhaps the ligand DPPEA acts as a base to catalyze the reaction to some extent. In the literature it is clearly demonstrated that this reaction cannot proceed without base; for example, no cyclohexanol was noted in the attempted transfer hydrogenation of cyclohexanone without base after 6 hours at reflux. With base the reaction went to 89 % completion in 1 h.\footnote{57 cf. 21.}

The amount of base was also critically important. It was soon discovered that although the presence of base was necessary, excessive base was not advantageous. Table 5 shows that with even a minor increase in base there is the deleterious effect of byproduct formation.
Table 5: The Effect of Base on Asymmetric Transfer Hydrogenation (ATH) of Geraniol\textsuperscript{a}

<table>
<thead>
<tr>
<th>KOH\textsuperscript{b}</th>
<th>Time (h)</th>
<th>% Conversion</th>
<th>% Yield</th>
<th>% Byproducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4</td>
<td>2.5</td>
<td>87</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>2.1</td>
<td>2.5</td>
<td>99</td>
<td>96</td>
<td>3</td>
</tr>
<tr>
<td>2.9</td>
<td>2.5</td>
<td>78</td>
<td>66</td>
<td>12\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}0.01 M IPA solution, 100 °C, substrate/Ru 10/1
\textsuperscript{b}molar ratio of base/Ru
\textsuperscript{c}5.4 % γ-geraniol formed

Table 6: The Effect of Base on the Rate of Conversion of Asymmetric Transfer Hydrogenation (ATH) of Geraniol\textsuperscript{a}

<table>
<thead>
<tr>
<th>KOH\textsuperscript{b}</th>
<th>Time (h)</th>
<th>% Conversion</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4</td>
<td>3</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>85</td>
<td>43</td>
</tr>
</tbody>
</table>

\textsuperscript{a}0.01 M IPA solution, 100 °C, substrate/Ru 100/1
\textsuperscript{b}molar ratio of base/Ru

This byproduct, γ-geraniol, was observed in the isomerization reaction previously investigated. In addition, a second major byproduct of 4.8 % (probably ocimenol) in entry 3 was also detected. As a result of this competing side reaction there is a limit on the amount of base relative to substrate for those substrates capable of undergoing double bond isomerization. Another intriguing aspect of the concentration of base is the observation that an increase in base concentration increases the rate of conversion. Table 6 shows that in two ATH reactions of geraniol, the reaction with more base produced more product (as
well as \( \gamma \)-geraniol) in equal time. The significance of this result may become better utilized with substrates that cannot undergo isomerization. In these cases perhaps the increased reactivity with more base may translate into lower catalyst loading.

One aspect that became readily apparent with this new ATH was the qualitative sense that these reactions showed a significant degree of air sensitivity. Initially the procedure used for this work resembled that used for earlier work with ATH of acetophenone. Typically, the precatalyst composed of metal, ligands, and base in solvent was aged before it was added to degassed substrate to begin the reaction. Aliquots of the reaction solution were taken to determine conversion and it was noted that the reactions where more aliquots were taken showed lower conversion than ones with fewer samplings, particularly compared to ones with no sampling at all (Table 7).

**Table 7.** Sampling Sensitivity on the Asymmetric Transfer Hydrogenation (ATH) of Geraniol\(^a\)

<table>
<thead>
<tr>
<th>Aliquots Taken</th>
<th>Time (h)</th>
<th>% Conversion</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.5</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>54</td>
<td>54</td>
</tr>
</tbody>
</table>

\(^a\)0.01 M IPA solution, 100 °C, substrate/Ru/base 10/1/1.4

Despite the care taken to prevent air contamination the conversion always seemed to become sluggish after sampling. Eventually, the procedure was modified to eliminate contamination by air. The current procedure which is used for all of the remaining experiments in this dissertation involves combining all reagents together (precatalyst and
substrate) and degassing through three freeze-pump-thaw cycles before heating at 100 °C. A virgin septum was used in each case and no sampling was ever attempted because of the uncertainty of air contamination.

As stated earlier DPPEA was included in most of the initial ATH work and in particular all that we have discussed thus far. It was only found out much later that DPPEA was determined to be unnecessary and possibly deleterious. Since the original work on acetophenone ATH was so successful with DPPEA it was immediately carried over into the ATH of geraniol without question; however, as one can see by the results in Table 8 the incorporation of DPPEA reduces the enantioselectivity of the 3-phenyl-2-buten-1-ol reaction by about thirty percent and appears to reduce the enantioselectivity of the geraniol reaction by a few percentage points also.

**Table 8. Effect of DPPEA on the Asymmetric Transfer Hydrogenation (ATH) of Allylic Alcohol**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>DPPEA b</th>
<th>Time (h)</th>
<th>% Conversion</th>
<th>% Yield</th>
<th>% ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geraniol</td>
<td>Yes</td>
<td>2.5</td>
<td>98</td>
<td>94</td>
<td>78 (R)</td>
</tr>
<tr>
<td>Geraniol c</td>
<td>Yes</td>
<td>2.5</td>
<td>100</td>
<td>98</td>
<td>82 (S)</td>
</tr>
<tr>
<td>Geraniol</td>
<td>No</td>
<td>2</td>
<td>99</td>
<td>93</td>
<td>86 (R)</td>
</tr>
<tr>
<td>Geraniol d</td>
<td>No</td>
<td>2</td>
<td>100</td>
<td>95</td>
<td>90 (R)</td>
</tr>
<tr>
<td>3-phenyl-2-buten-1-ol d</td>
<td>No</td>
<td>12</td>
<td>100</td>
<td>99</td>
<td>72 (S)</td>
</tr>
</tbody>
</table>

a0.01 M IPA solution, 100 °C, substrate/Ru/base 10/1/2.1
b 1 eq. of DPPEA per Ru atom (where used) and 1 eq. (S)-tol-BINAP per Ru atom
c (R)-tol-BINAP used
d 2 eqs. (S) tol-BINAP used
The significance of this was initially found to be remarkable. Up to this point we accepted the working mechanism of this reaction as that given by Noyori (Figure 13) simply because of the great rate enhancement we found in our investigation with acetophenone ATH. Since the reaction works well without DPPEA, a nitrogen containing ligand is therefore unnecessary for the ATH of an allylic alcohol. This is not news for ATH since much of the literature prior to Noyori’s success describes transition metal catalysts without nitrogen containing ligands, but it became a cautionary note not to adopt so quickly a successful application from one area (the acetophenone work) to another area (allylic alcohol) so readily.

A closer look at the mechanism of Figure 13 that Noyori proposes is warranted. In his novel mechanism, he reveals that a coordinately saturated metal hydride transfers (in a concerted fashion) its hydrogen to the ketone substrate. This reaction works well with rhodium and ruthenium where the presumed hydride intermediates are octahedral and possess no vacant coordination sites (Figure 28).

**Figure 28.** Noyori’s Metal-Hydride Intermediates and Plausible Transition States.

![Figure 28](image-url)
As a result of this mechanism, the substrate does not become coordinated directly to the metal. If this same mechanism also applies with the catalysts we have chosen (Ru-tol-BINAP and DPPEA) then perhaps the improved reactivity with the earlier work on acetophenone supports Noyori’s mechanism. However, in the case of allylic alcohols, there is believed to be a directing influence of the hydroxyl group to the metal as seen in asymmetric hydrogenation. This would require two open \textit{cis} coordination sites which may not be available (Figure 29). Clearly an alternative mechanism must apply since the reaction is allowed but the fact remains that the presence of DPPEA leads to poorer enantioselectivity consistent with the proposal of a new mechanism.

\textbf{Figure 29.} Inability of [Ru-tol-BINAP(DPPEA)] to Chelate with Allylic Alcohol.

\begin{center}
\begin{tikzpicture}
\node[draw, shape=rectangle, rounded corners, minimum width=3cm, minimum height=1.5cm] (rectangle) at (0,0) {
\begin{tikzpicture}
\node[shape=circle,draw,fill=black] (iron) at (0,0) {$\text{Ru II, d}^{8}, 18e$};
\node[shape=regular polygon,regular polygon sides=6,draw] (pentagon) at (-1.5,0) {P$_{\text{X}}$};
\node[shape=regular polygon,regular polygon sides=6,draw] (pentagon) at (1.5,0) {P$_{\text{S}}$};
\draw (iron) -- (pentagon);
\draw (iron) -- (pentagon);
\end{tikzpicture}
};
\node at (0,-1.5) {X = anionic ligand};
\node at (0,-2) {S = neutral ligand};
\end{tikzpicture}
\end{center}

It is interesting to note that despite a somewhat lower ee with DPPEA (Table 8) in the ATH reactions at 10/1 S/C, it was discovered that in a 100/1 S/C reaction almost three times more citronellol was formed with DPPEA present than without it. In addition, the enantioselectivity at 100/1 remained very good (Table 9).
When we removed the DPPEA it was decided to maintain the stoichiometry of two ligands per ruthenium and thus two equivalents of diphosphine ligand per ruthenium were used. There seems to be a slight increase in the enantioselectivity of citronellol produced from ruthenium with two equivalents (90 % ee) than with one equivalent (86 %) of tol-BINAP as shown in Table 8.

One final optimization that was made before an in depth investigation began was selection of a substrate/catalyst ratio for these reactions. One chief concern was to drive this reaction to completion. In the practical application of ATH of a double bond there is virtually no way to separate starting material from product. Therefore, purification is a severe limitation. Fortunately, with gaseous hydrogenation and transfer hydrogenation reactions quantitative yields are more the rule than the exception. Therefore the necessity to achieve complete conversion led to a substrate/catalyst ratio of 10/1 to ensure full conversion in a reasonable time frame. A minor amount of work was attempted at greater substrate/catalyst ratios and noticeable decreases in the rate of this reaction were found in the ATH of geraniol with tol-BINAP as the ligand (Table 9).
At this stage the reaction was determined to be ‘optimized’. The stoichiometry of ligand and base to metal were set. The substrate concentration and catalyst ratio were fixed. The temperature of 100 °C was deemed most reasonable for a reaction time frame to get as much information as possible for as many substrates and ligands of interest. In addition, the procedure of using freeze-pump-thaw cycles was determined to afford the greatest protection against adventitious oxygen for these air sensitive reactions.

Table 10 shows the results of yield and enantioselectivity for the ATH of geraniol to produce citronellol with various ligands. The best yields were obtained with the ligands tol-BINAP and iPr-DuPHOS. Both gave very clean reactions while the other ligands showed either poor conversion or too many byproducts. Interestingly, with iPr-DuPHOS there was the greatly enhanced ATH of citronellol’s unfunctionalized double bond to form 3,7-dimethyl-octanol! When the reaction with iPr-DuPHOS was adjusted to a 2/1 substrate/catalyst ratio and aged for 24 h at 100 °C, the fully hydrogenated product could be produced in excellent yield (98 %) and ee (90 %).

The yields reported in Table 10 are GC yields that were not isolated with the exception of entry 5 which also included an isolated yield of 78% after column chromatography. We believe that the discrepancy is largely based on the reaction size. Should a larger reaction be run the yield would probably be closer to the yield obtained by GC. Most likely there was loss due to handling during vacuum distillation to remove isopropyl alcohol. Several attempts were made to improve the isolated yield by extraction of the reaction solution with hexanes followed by gentler concentration with a rotary evaporator. However, no better yield could be realized and certainly the limitations with extraction become very apparent with such a large excess of isopropyl alcohol, which is
Table 10. Asymmetric Transfer Hydrogenation (ATH) of Geraniol with Chiral Diphosphine Ligands$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>% Conv.</th>
<th>% Yield</th>
<th>% ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIOP</td>
<td>20</td>
<td>38</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PHANEPHOS</td>
<td>29</td>
<td>24</td>
<td>20</td>
<td>9 (R)</td>
</tr>
<tr>
<td>3</td>
<td>Me-DUPHOS</td>
<td>2</td>
<td>92</td>
<td>80</td>
<td>75 (R)</td>
</tr>
<tr>
<td>4</td>
<td>Et-BPE</td>
<td>2</td>
<td>80</td>
<td>56</td>
<td>31 (R)</td>
</tr>
<tr>
<td>5</td>
<td>tol-BINAP</td>
<td>2</td>
<td>100</td>
<td>95$^b$</td>
<td>90 (R)</td>
</tr>
<tr>
<td>6</td>
<td>(R)-BINAP</td>
<td>2</td>
<td>100</td>
<td>92</td>
<td>87 (S)</td>
</tr>
<tr>
<td>7</td>
<td>iPr-DUPHOS</td>
<td>2</td>
<td>100</td>
<td>50</td>
<td>84 (R)</td>
</tr>
<tr>
<td>8$^c$</td>
<td>iPr-DUPHOS</td>
<td>24</td>
<td>100</td>
<td>1.2</td>
<td>90 (R)</td>
</tr>
</tbody>
</table>

$^a$0.01 M IPA soln., 100 °C, S/C/B 10/1/2.1

$^b$78% isolated yield

$^c$98 % dihydrocitronellol at S/C/B 2/1/2.1
appreciably soluble in both organic and aqueous phases and not so easily separated from the product.

The enantioselectivity of this reaction also showed exceptional results with tol-BINAP and iPr-DuPHOS. There is similarity in terms of the direction of the ee with work found in the literature. For instance, Bergens shows the asymmetric hydrogenation of geraniol with 
\[
[Ru((R)-\text{BINAP})(\text{CH}_3\text{CN})(1-3:5,6-\eta-C_8H_{11})](\text{BF}_4)
\]
gives 86 % ee of S configuration.\(^{58}\) Noyori shows that, with 
\[
[Ru((S)-\text{BINAP})(\text{CH}_3\text{CO}_2)]
\]
an ee of 96% of R configuration is obtained.\(^{59}\) The literature reports usually BINAP but the more soluble version tol-BINAP was used (with one exception) in our studies.

As was shown in the review of the literature, isopropyl alcohol is not the only source of hydrogen but a mixture of formic acid with triethylamine is frequently used. Some work was tried with this mixed reagent and some startling observations were made. Caution! Within one-half hour at reaction temperature the experiments with formic acid/triethylamine either violently blew off the septa that were wired on or expanded these one-half inch septa to dimensions about two inches in diameter! (In no case was there ever the hint of over-pressurization with isopropyl alcohol.) Thus it appears that the temperature was high enough for decomposition to occur as was discussed in the introduction to this thesis.

The reactions that used formic acid/triethylamine produced low yields, the highest being 45 % of citronellol from one reaction before it blew out the septum at some unknown time before 12 h. It was then decided to run these reactions as an open system under argon

\(^{58}\) cf. 4c.  
\(^{59}\) cf 4a.
for safety. One reaction was run at 90 °C for 24 hours to obtain 35% product which gave zero ee. With that result the use of formic acid/triethylamine was quickly abandoned.

Now that two ligands, tol-BINAP and iPr-DuPHOS, were clearly efficient for the ATH of geraniol it was decided to apply these ligands to other substrates. Of course, uncertainty will always remain since one of the less effective ligands dropped from this investigation could have been well-suited to another substrate. However, in the interest of exploring the scope of this reaction within a reasonable time it appeared necessary to limit the remaining substrates to these two ligands.

The remaining substrates chosen were planned to offer a reasonable first trial investigation with this new reaction (Figure 30).

**Figure 30.** Substrates for Transfer Hydrogenation Reactions.

Nerol was chosen since it is the geometric isomer of geraniol and has been compared to geraniol asymmetric hydrogenation in the literature. Another allylic alcohol, 3-phenyl-2-butenoic acid, was picked because it too is trisubstituted and dramatically different due to the
large phenyl ring attachment. It was then decided that it might be worthwhile even at this early stage of investigation to include substrates that possess the allylic framework but are not alcohols. The α,β-unsaturated ester and acid were chosen based on the predicted coordination of the substrate-metal interaction. Another interesting substrate chosen was 3-methyl-2-cyclohexenone. This is an example of a molecule with two different functional groups capable of hydrogenation, an olefin and a carbonyl group. Both functional groups are prochiral and thus when fully hydrogenated two stereocenters form with four possible stereoisomers.

In the literature, Noyori used the monofunctional substrate, 3-methyl-2-cyclohexen-1-ol, that was hydrogenated under gaseous conditions. His interest was to examine the kinetic resolution of this reaction at one-half conversion. At 4 atm hydrogen pressure with the catalyst [Ru((R)-BINAP(CH₃CO₂)] he obtained a greater than 300:1 trans:cis ratio of one product in 99% ee. In addition, he was able to ‘recover’ unreacted starting material of high enantiomeric purity due to a large difference in the rates of hydrogenation between enantiomers (k_{fast}/k_{slow} = 74). This enabled him to hydrogenate the enantiomerically enriched substrate in situ with the catalyst of opposite configuration [Ru ((S)-BINAP(CH₃CO₂)] to obtain the other trans enantiomer (Figure 31).\textsuperscript{60}

\textsuperscript{60} cf. 4.
Figure 31. Kinetic Resolution of 3-Methyl-2-Cyclohexenol.

It was decided not to investigate the kinetic resolution as Noyori had done. This would require stopping the reaction at fifty percent conversion which would be considerably difficult. Our prior sampling procedure suffered from introducing air into this sensitive reaction and had therefore been abandoned. Also, we wanted to broaden the scope of this reaction and two different functional groups would offer a great opportunity to show the versatility of this reaction. In other words, a one-pot reaction for the ATH of a ketone and allylic alcohol! In truth, if one functional group is more reactive than the other functional group and shows enantioselectivity, then there exists the possibility of a double stereodifferentiation reaction where chiral catalyst and enantiomerically enriched allylic alcohol may react to form a fully saturated alcohol of high enantiomeric purity (Figure 32).
Figure 32. Double Stereodifferentiation of 3-Methyl-2-Cyclohexenone to 3-Methyl-2-Cyclohexanol.

One final substrate that was of interest was trans-methylstilbene which is an example of an unfunctionalized olefin. It was chosen to be evaluated with iPr-DuPHOS which showed the remarkable activity for hydrogenation of the remaining olefin bond in geraniol. This substrate was investigated by others using gaseous hydrogenation with chiral iridium catalysts.\textsuperscript{61}

The results of these ATH of various substrates with tol-BINAP and iPr-DuPHOS are shown in Table 11.

Table 11. Transfer Hydrogenations with Ru tolBINAP (1) and Ru iPrDUPHOS (2).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Time(h)</th>
<th>%Conversion</th>
<th>%Yield</th>
<th>%ee(config)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>100</td>
<td>95</td>
<td>90(R)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>50</td>
<td>80-84(R)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>100</td>
<td>96</td>
<td>93(S)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24</td>
<td>100</td>
<td>62</td>
<td>83(R)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>12</td>
<td>100</td>
<td>99</td>
<td>72(S)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>100</td>
<td>99</td>
<td>93(R)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>55</td>
<td>10</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>96</td>
<td>98</td>
<td>93</td>
<td>12(R)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>100</td>
<td>93</td>
<td>9(R)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24</td>
<td>18</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a0.01 M IPA soution, 100 deg C  
b2.5eq of base per substrate  
c%ee analysis of cis by $^{13}$C NMR, trans by GC
Geraniol hydrogenation was discussed previously. Nerol hydrogenation showed results consistent with that from the literature with tol-BINAP. With nerol the opposite configuration was obtained compared to that seen in the geraniol hydrogenation with tol-BINAP; however, with iPr-DuPHOS the same configuration is obtained with either geraniol or nerol. In addition, with iPr-DuPHOS the value of enantiomeric excess is about the same. The rationale for this stereochemical outcome will be discussed later. Finally, mention should be made that in no case of nerol ATH was any isomerization product discovered (i.e. γ-geraniol or ocimenol). This is consistent with previous work performed in our lab that showed that isomerization is only possible with geraniol, the E isomer.

It is also interesting to note the inherent limitation of this catalytic reaction. In the iPr-DuPHOS experiments there is only a twenty percent increase in yield between a reaction that was run for twenty-four hours than one at two hours. Thus it is evident the catalyst quickly loses its efficiency despite the high catalyst loading and care taken to avoid the introduction of oxygen into these reactions. This represents one of the areas where future research is needed to improve the efficiency of this catalytic reaction.

In the case of 3-phenyl-2-buten-1-ol both catalysts give excellent yield and good ee for tol-BINAP and excellent ee for iPr-DuPHOS. Reactions with the opposite configuration of each ligand were not attempted but would be assumed to show equal reactivity and enantioselectivity. In the case of iPr-DuPHOS it would be interesting to run a reaction with the Z isomer of this substrate. However, the E substrate was prepared in-house and what may possibly have been the Z isomer was present only in trace amounts

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that were too small for analysis. Preparation of the Z isomer would require a different synthetic strategy.

Interestingly, there may be a similarity between the E isomer of 3-phenyl-2-buten-1-ol and geraniol with their respective ability for isomerization. It was found that in the earlier reactions which were unoptimized and included the presence of DPPEA, unknown byproducts formed during the ATH of 3-phenyl-2-buten-1-ol with the ligand tol-BINAP. No investigation was made of the structure of the byproduct but it is probably the homoallylic alcohol, 3-phenyl-3-buten-1-ol. It would be interesting to know in the case of the Z isomer if isomerization would occur or if it behaved similarly as nerol and remained inactive.

The ee analysis was measured differently than with the previous substrates. Instead of the Mosher ester the acetate ester of 3-phenyl butanol separates directly on the Daicel Chiracel OJ column (an enantiomeric separation). It is also worth noting that before these ATH were attempted the ee analysis was thoroughly investigated. The separation of unreacted starting material which overlapped with the derivatized product was achieved by bromination of the double bond. The dibromo product elutes later and therefore the enantioselectivity during the course of this reaction could be measured. As it turned out, this was only necessary for the earlier reactions that used DPPEA which did not go to completion. Without DPPEA and with the improved procedure high conversions were obtained and rendered this extra step unnecessary.

In the next substrate, methyl 3-phenyl-2-butenoate, the similarity to the above allylic alcohol is readily apparent. It was envisioned that this substrate would potentially complex to the metal through its lone pair of electrons from the carbonyl oxygen to mimic the allylic
alcohol. Unfortunately, as shown in the table the reaction showed very poor yield. Two major byproducts were obtained. GC/MS of the reaction solution showed that formation of the isopropyl ester of both the starting material and the product occurred. Thus, at 100 °C transesterification occurred to a great extent. The reaction mixture contained 10% of the desired product, 45% starting material, 6% isopropyl-3-phenyl butanoate, and 34% isopropyl-3-phenyl-2-butenoate. Based on this result the concept of ATH of $\alpha,\beta$-unsaturated esters was quickly abandoned and the ligand iPr-DuPHOS was not evaluated.

No attempt was made to try this reaction with a formic acid/triethylamine mixture which was successfully performed by J. M. Brown and coworkers on $\alpha,\beta$-unsaturated acids at 70 °C, which gave excellent conversion and ee’s around 50 % with a notable exception of itaconic acid hydrogenation of 94 % ee.\(^{63}\)

In the case of the next substrate, 3-phenyl-2-butenoic acid, the first attempt at ATH was done at the standard S/C/B ratio of 10/1/2.1 where the amount of base used was calculated as the amount above that required to form the carboxylate salt. In other words, a reaction of 0.21 mmoles of substrate used about 5 mL of 0.05 M base. The initial result of this reaction gave only 30 % yield in twelve hours with iPr-DuPHOS. This seemed too sluggish for such a reactive ligand. It was then decided to add solid potassium hydroxide to the reaction flask. We decided to risk the chance of byproduct formation (i.e., isomerization) in the hope of obtaining a reasonable yield, and so we arbitrarily chose an overall S/C/B ratio of 10/1/25.0. Fortunately, byproduct formation was not a problem for either tol-BINAP or iPr-DuPHOS. The reaction with iPr-DuPHOS went to 100 %

\(^{63}\) cf. 45a.
conversion in 2 h but with low (9 % (R)) ee. It is unclear why the reaction with tol-BINAP was so slow (96 h, 12 % ee (R)), especially with the extra base.

The next substrate, 3-methyl-2-cyclohexenone, showed reactivity at both the olefin and carbonyl bonds. Significant amounts of byproducts were formed including the monoreacted 3-methyl-2-cyclohexenol at levels of 8.5 % with the tol-BINAP ligand and 6.8 % with the iPr-DuPHOS ligand. Only in one case was 3-methyl-cyclohexanone formed in about 1.4 % with a tol-BINAP reaction at 12 h that went to 63 % conversion. These byproducts suggest the carbonyl reduction occurs first but multiple pathways could not be conclusively ruled out (Figure 33).

**Figure 33.** Various Pathways for Hydrogenation.

Pathway 1:

Pathway 2:

Pathway 3:

Pathway 4:

One pertinent comment is that despite the slow reactivity of the tol-BINAP system compared to the iPr-DuPHOS system both show the same diastereoselectivity and very
similar enantioselectivity. The diastereoselectivity of this reaction with either ligand is 4:1 cis:trans.

A closer look at this reaction is warranted but first it would be instructive to review the results obtained by Noyori with asymmetric hydrogenation of racemic 3-methyl-2-cyclohexenol. Noyori’s work is an example of kinetic resolution and he stopped his reaction at 50 % conversion to obtain the maximum stereoselectivity. Figure 34 shows these results which demonstrate a diastereoselectivity of 300:1 trans:cis, and enantioselectivity of greater than 99 % ee. Figure 34 also shows the sense of chiral induction based on the presumed diastereomeric substrate/catalyst intermediates.

**Figure 34.** Enantioface Discrimination and Diastereoselectivity of Gaseous Hydrogenation of 3-Methyl-2-Cyclohexenol.

![Diagram of enantioface discrimination and diastereoselectivity](image)

There are clearly very different results obtained between Noyori’s work and ours. This is fascinating since one would predict the same sense of enantioface discrimination. In our ATH reactions reported here it is unclear what sense of enantioface discrimination is
described (Figure 35) since the presumed diastereomeric substrate/catalyst intermediate is greatly strained.

Figure 35. Enantioface Discrimination and Product Distribution for THR of 3-Methyl-2-Cyclohexenone.

Clearly the next series of experiments which would shed light on this would be kinetic resolution experiments on 3-methyl-2-cyclohexen-1-ol with our catalysts and conditions described here. This would remove any competition between the rates of olefin and carbonyl hydrogenation to eliminate questionable intermediates. The enantioselectivity of the cis product was determined by comparison of the proton decoupled $^{13}$C NMR of the Mosher ester of the saturated alcohol. Integration of what is believed to be one of the methylene carbons in the beta position to the hydroxyl group gave the best resolution. Figure 36 shows 17 % ee (R,R) with the tol-BINAP ligand. A racemic mixture of the Mosher ester gave 1.4 % ee, thus $^{13}$C NMR is a suitable method to determine enantioselectivity. The trans product was determined by gas chromatography of the Mosher ester of the saturated alcohol on a DB-23 column (J&W Scientific,15 m x 0.32 mm).
The final substrate investigated was picked solely for its evaluation with iPr-DuPHOS since this ligand showed remarkable reactivity with the unfunctionalized double bond in geraniol. The result of ATH of \textit{trans}-methylstilbene showed a very clean albeit sluggish reaction. This is not a major concern but unfortunately the ee analysis revealed no enantioselectivity for this reaction.

The proposed mechanism for the ATH of allylic alcohols is shown in Figure 37.
Figure 37. Proposed Mechanism for Transfer Hydrogenation of Allylic Alcohols.
Each step of this mechanism has precedence in the literature. The intermediates on the catalytic cycle are the same as that proposed for conventional ATH and gaseous hydrogenation reactions.

To begin, the precatalyst enters the cycle (a) with an open cis coordination site (1) prior to beta-hydride elimination (BHE). With BHE (b) a metal hydride (2) and acetone are formed. Next, the metal geometry must adopt a vacant site for cis coordination (3) to allow the hydroxyl group and olefin bond of the allylic alcohol bidentate chelation. Coordination of the prochiral allylic alcohol to the chiral metal center produces the diastereomeric intermediates (4) (only one shown in Figure 37). Migratory insertion of the hydride into the olefin bond forms the favored five membered ring intermediate (5). Protonolysis (f) of the intermediate gives the product and returns the cycle to the beginning. Throughout the catalytic cycle ruthenium remains in its 2+ oxidation state balanced by two anionic ligands as well as neutral ligands where (S) represents solvent molecules. Each complex with the exception of (5) achieves an 18 electron count; (5) achieves a 16 electron count.

The first two steps of this cycle involve a BHE followed by a fast hydride migration as with the case of a conventional transfer hydrogenation reaction (Figure 12). The third and fourth step are coordination of the allylic alcohol to the metal hydride followed by migratory insertion which is similar to the well-studied sequence in gaseous

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* The formalism used for transition metal complexes involves the 18-electron rule which supersedes the octet rule or Lewis formalism. The use of this rule not only applies to the transition metal but also affects each atom attached to the metal (i.e., ligand) making the Lewis formalism unsuitable. See a) Cotton, F. A.; Wilkinson, G. Advanced Inorganic Chemistry, 5th ed., Wiley, New York, 1988, 36. b) Lukehart, C. M. Fundamental Transition Metal Organometallic Chemistry, Brooks/Cole Publishing, California, 1985, 10.
hydrogenation. The final step involves protonolysis by isopropyl alcohol to form product and return the cycle to the beginning.

As stated earlier excess base is a problem since isomerization products are formed. According to the proposed mechanism the most likely intermediate to undergo isomerization is the intermediate prior to product formation where the carbon is attached to ruthenium with a sigma bond. A plausible mechanism for isomerization is shown in Figure 38.

**Figure 38.** Isomerization Competition with Product Formation.

The last step in our proposed mechanism has recently been investigated in the literature. Traditionally, the final step in a gaseous hydrogenation cycle is called a hydrogenolysis reaction where molecular hydrogen disproportionates to protonate the product and form a metal hydride that returns the cycle to its beginning. However, recently Noyori has shown that a minor pathway called protonolysis competes in the traditional gaseous hydrogenation

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64 cf. 5, 54.
mechanism to form as much as 31% product via a separate mechanism under hydrogen starved conditions (0.3 atm) (Figure 39).

**Figure 39.** Mechanism of Gaseous Hydrogenation of (Acylamino) Acrylic Esters in Methanol.
In this case Noyori determined through isotopic labeling experiments that a protic solvent such as methanol effectively competes with molecular hydrogen (Table 12).⁶⁵

**Table 12. Isotopic Distribution in Gaseous Hydrogenation of Methyl (Z)-α-(Acetomido)cinnamate**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>HD in CH₃OD</th>
<th>D₂ in CH₃OD</th>
<th>H₂ in CH₃OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>% enantiomeric excess</td>
<td>92</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>protium incorporation, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H in C(2)</td>
<td>41</td>
<td>0.5</td>
<td>84</td>
</tr>
<tr>
<td>H in C(3)</td>
<td>57</td>
<td>0.9</td>
<td>98</td>
</tr>
<tr>
<td>product distribution⁶, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>88</td>
<td>0.4</td>
</tr>
</tbody>
</table>

⁶ Reaction were carried out at 1 atm.
⁶ minor products of other deuterium distributions not shown.

As the table shows in the first experiment the distribution of labeled product show roughly a 40:60 distribution of protiums in the C2 and C3 positions that suggest that HD from the mechanism forms either metal hydride or metal deuteride and that protonation from hydrogenolysis can be from either H or D. The second experiment shows in a highly deuterated environment all the distribution is essentially with deuterium. However, in the third experiment H₂ does not exclusively form the non-deuterated product but a significant amount of participation from the solvent (protonolysis) has occurred since product #2 is formed in 14%. It is worth noting that Noyori did verify negligible gas-liquid and gas-gas isotope exchange for the validity of this experiment.

Based on this supporting evidence in the mechanism proposed here (Figure 37), protonolysis does occur with isopropyl alcohol and an experiment that should help elucidate this mechanism will be described below.

The stereochemical feature of the 3-methyl-2-cyclohexenone system which behaved very differently with tol-BINAP in the gaseous hydrogenation has been discussed. Fortunately, the results for geraniol and nerol are similar to that found in Noyori’s system with tol-BINAP. In both cases the chiral induction is similar, the ligand of S configuration with geraniol gives R citronellol and with nerol gives S citronellol. A schematic of the sense of stereochemical induction is pictured in Figure 40.
Although no optimization studies (i.e., molecular mechanics) have been done, the diastereomeric substrate/catalyst complex is most likely attached as the *trans* coordination.
which is probably the least congested structure. As can be see from Figure 40 both geraniol and nerol obey the same ‘chirality’ in the sense that both molecules appear to fit the chiral environment with their disubstituted groups on the olefin bond pointing away from the phenyl group of the tol-BINAP ligand. Interestingly, if one considers the possibility of a substrate/catalyst intermediate no longer trans coordinated but where the hydroxyl group attachment is $cis$ to both phosphines of the tol-BINAP ligand, the same stereochemical environment would also be expected as shown in Figure 41. The intermediate shown in Figure 41 may not be so unreasonable since the hydroxyl group is primary and may appear smaller than isopropyl alcohol.

On the other hand, the iPr-DuPHOS ligand shows mixed results. For the geraniol substrate it too is similar to the tol-BINAP example since the major enantiomer is produced from the intermediate where the olefin disubstitution is away from the chiral congestion. However, for nerol the opposite is true. The major enantiomer produced is from the intermediate that is more congested. Perhaps what is occurring is a significant rate difference between the minor diastereomer which is faster reacting and the major diastereomer which is slower reacting. Thus, the Curtin-Hammett principal is invoked to explain product formation (Figure 42).
Figure 41. Enantioface Discrimination for Ru -((S))-tol-BINAP with Hydroxyl Group Cis to Phosphine Atoms.

L = large, S = small substituents
Figure 42. Enantioface Discrimination for Ru -(S,S)-iPr-DUPHOS.

L = large, S = small substituents

In the case of 3-phenyl-2-buten-1-ol the tol-BINAP ligand shows greater product formation from the major diastereomer where the olefin disubstitution is away from the chiral congestion. However, this is not the case with 3-phenyl-2-butenoic acid. In this case the minor diastereomer preferentially leads to product but only 12% ee is obtained with tol-
BINAP and thus the chiral induction is not very effective with this substrate (and neither is the conversion itself).

Very high enantioselectivity was obtained in the reaction of 3-phenyl-2-buten-1-ol using iPr-DuPHOS. Once again the Curtin-Hammett principle is invoked here since the anticipated less stable intermediate forms the major product.

In the case of 3-phenyl-2-butoic acid the ee was as low as with tol-BINAP so no clear understanding could be determined from that reaction. Interestingly, this was a relatively fast reaction (two hours completion at 100 °C) which may show significant improvement in enantioselectivity if run at lower temperatures.

The chirality and stereochemical induction thus described postulates the idea of bidentate coordination. The concept of bidentate coordination comes from the requirement of the hydroxyl group as a directing group for an allylic alcohol; in the case of the α,β-unsaturated ester or acid, one oxygen of the carboxy group would function as the directing group. However, the iPr-DuPHOS has created some confusion with this working principle since apparently an isolated double bond is also reactive.

The requirement for bidentate chelation is necessary for the asymmetric hydrogenation of geraniol. The reactions of geraniol and homogeraniol proceed with excellent conversion and enantioselectivity; however, the extended bishomogeraniol does not react. It is believed that only through the directing ability of the hydroxyl group to chelate with the metal center can the reaction take place (Figure 43).66

66 cf. 5, 39.
Figure 43. Requirement of Bidentate Chelation for Asymmetric Hydrogenation.

Additional support for the bidentate requirement can also be seen in the literature regarding geraniol. In Figure 44, equation 1) shows that the aldehyde, citral, does not undergo further hydrogenation of its olefin bond with a catalyst that has presumably no vacant cis coordination site necessary for bidentate chelation. On the other hand, equation 2) involves a catalyst with an open cis coordination site that can accommodate chelation. Both reactions are run under identical conditions (4 atm H₂, RT); thus, additional support is given to the requirement of an available cis coordination site for bidentate chelation in the hydrogenation of allylic alcohols. 67

67 eq 1) cf. 4a. eq 2) cf. 13.
Figure 44. Additional Support for Bidentate Chelation.

One final concern that has surfaced regarding the supposed ATH of allylic alcohols should be discussed for anyone critical of this work. The literature has much information and studies on the isomerization of allylic alcohols to ketones and aldehydes, including the reluctant isomerization of geraniol to citronellal. That being the case the question arises, ‘do we really have a ATH of an allylic alcohol or is it an isomerization followed by a carbonyl reduction to give the saturated alcohol?’

To properly answer that question a deuterium isotopic labeling experiment needs to be done. Similar to Noyori’s investigation, the distribution of deuterium would (hopefully)
refute the ‘isomerization/reduction’ mechanism and substantiate the proposed mechanism in Figure 37.

The experiment we propose is very simple. If the ATH of geraniol is run in (CH₃)₂CDOD the distribution of deuterium would be different between an isomerization mechanism and the one we propose (Figure 45).

**Figure 45.** Is This an Isomerization/Carbonyl Reduction Reaction?

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68 cf. 39.
69 cf. 41.
CONCLUSION

The transfer hydrogenation reaction of allylic alcohols is an exciting new reaction. The initial investigation into this reaction shows promise and more exploration is warranted. The reaction uses a simple procedure that involves the in situ preparation of a ruthenium complex catalyst. A ruthenium polymer [(Ru(COD)Cl₂)n is combined with diphosphine ligand, substrate, and base in isopropyl alcohol. Air is removed by freeze/pump/thaw cycles and the reaction is heated at 100 °C. The procedural simplicity is similar to the ATH of known reactions with ketones, aldehydes, and imines. In addition, as in the case of these published reactions, base and transition metal are both needed.

Several allylic alcohols were investigated and show excellent conversion, product yield, and enantioselectivity with two selected ligands, tol-BINAP and iPr-DuPHOS. An initial screening with other diphosphine ligands showed good conversion and moderate to poor enantioselectivity. In addition, the reaction can be extended to other substrates including an α,β-unsaturated acid, and in the case of iPr-DuPHOS, an unfunctionalized olefin (trans-methylstilbene) although with no ee. A methyl ester did not work well in this reaction because of the extensive amount of the transesterified product, the isopropyl ester, which formed.

The reaction can also be extended as a one-pot hydrogenation of two functional groups, an olefin and a carbonyl group. In this case, 3-methyl-2-cyclohexenone was hydrogenated to obtain a double stereodifferentiation product. Interestingly, the diastereoselectivity of this reaction was very different from a similar reaction performed by Noyori with asymmetric hydrogenation.
Some of the limiting factors which govern this reaction are the low substrate/catalyst loading to achieve full conversion and the deleterious effect of isomerization for some substrates with excess base. There was some benefit seen in the presence of DPPEA as a coligand for conversion and product yield; however, the decrease in enantioselectivity more than offset this advantage.

Throughout the optimization of this reaction it became evident that air sensitivity was an issue. The reactions that gave the greatest conversion were those performed under the most stringent and simple conditions that involved freeze-pump-thaw cycles to remove air and the combination of all reagents at the start for the least intrusive reaction. In addition, sampling during the course of the reaction was eliminated to prevent accidental introduction of air.

The attempted use of formic acid/triethylamine resulted in an unsafe reaction at sealed conditions (100 °C). In an open system under argon the yield was very low and enantioselectivity was zero.

The proposed mechanism for this ATH involves key intermediates already postulated in the conventional ATH of ketones and gaseous hydrogenation reaction. The last step in our proposed mechanism involves a protonolysis step that has recently shown to be more competitive than hitherto believed in gaseous hydrogenation where solvent competes with molecular hydrogen for product formation.

The byproduct, γ-geraniol, found in the previous work on geraniol isomerization which ultimately led to the discovery of this reaction, was also noticed in the ATH of geraniol. The amount of byproduct increases with base, and it is probably a competition
reaction with the protonolysis step where BHE is more accessible under more basic conditions.

The stereochemical induction of this reaction is similar to those for geraniol and nerol with tol-BINAP under gaseous hydrogenation but show a deviation with iPr-DuPHOS. In this case with nerol the minor diastereomer forms the predominant product. A similar observation is also seen in 3-phenyl-2-buten-1-ol where the minor diastereomer forms the product in excellent ee. In these cases the Curtin-Hammett principle is invoked. The enantioselectivity in the case of the $\alpha,\beta$–unsaturated acid was so low with either ligand that no comment on chiral induction can be made.

Although no literature report has shown the ruthenium catalyzed ATH of an allylic alcohol there are ample studies on the isomerization of allylic alcohols catalyzed by ruthenium complexes. To confirm that the evidence found here is not a case of an isomerization followed by a reduction reaction, isotopic labeling experiments need to be performed. A simple experiment is devised where deuterated isopropyl alcohol can be used to further elucidate and support the proposed mechanism herein and show that indeed this is not an isomerization/reduction reaction but truly a new reaction, the transfer hydrogenation of allylic alcohol.
EXPERIMENTAL SECTION

General conditions

Nuclear magnetic resonance [\(^1\)H and \(^{13}\)C] spectra were measured on a Varian Unity Inova 500 MHz NMR spectrometer. Gas chromatographic analyses were measured on a Hewlett-Packard 5890 Series II equipped with a flame ionization detector. The column used for all the isomerization and hydrogenation analyses was a DB-5 column (J&W Scientific, 15 m x 0.32 mm) with the exception of the substrate 3-methyl-2-cyclohexenone which used a DB-23 column (J&W Scientific, 15 m x 0.32 mm) for hydrogenation and ee analyses of its Mosher ester. Mass spectroscopy was performed on a Hewlett-Packard 5971A mass detector attached to a Hewlett-Packard 5890 gas chromatograph equipped with a DB-1 column (J&W Scientific, 30 m x 0.32 mm). High performance liquid chromatography for all ee analyses were performed on a Hewlett-Packard 1050 Series instrument with a chiral column, Chiralcel OJ-H (Daicel, 250 mm x 4.6 mm). All chiral ligands were obtained from Strem Chemicals. All substrates were obtained from Aldrich with the exception of those prepared below. All solvents were ACS reagent grade and were used without further purification with the exception of hexane which was distilled prior to use. All transfer hydrogenation reactions were carried out using standard Schlenk glassware.

General Procedure for Geraniol Isomerization:

To a 50 mL Schlenk flask equipped with a magnetic stir bar is added 175 \(\mu\)L geraniol (1 mmol) in 10 mL solvent (0.1 M solution). The flask is sealed with a rubber septum and taken through two freeze-pump-thaw cycles with liquid nitrogen under a blanket of argon. The septum is removed and 10 mg of [RuCl\(_2\)-((S)-(-)-tol-BINAP)]\(_2\)-
N(C₂H₅)₃ (0.01 mmol) is added followed by two additional freeze-pump-thaw cycles. Reactions were stirred at room temperature or in an oil bath and aged. Afterwards, the flasks were removed from the bath, cooled, and opened to the atmosphere. GC measurements were taken directly from the crude reaction. ¹H NMR Lit.⁷⁰ (60 MHz, CCl₄) δ 4.80 (m, 1 H), 4.71 (br s, 2), 3.56 (t, 2 H, J = 7 Hz), 3.14 (s, 1 H), 2.20 (t, 2 H, J = 7 Hz), 1.87-2.15 (m, 4 H), 1.66 (s, 3H), 1.60 (s, 3 H)

**General Procedure for Transfer Hydrogenation:**

To a 50 mL Schlenk flask equipped with a magnetic stir bar is added 0.021 mmol [Ru(COD)Cl]₅, 0.038 mmol chiral ligand, 0.21 mmol substrate, 0.9 mL 0.05 M KOH in isopropanol, and 20 mL isopropanol. The flask is sealed with a latex septum and taken through three freeze-pump-thaw cycles with liquid nitrogen under a blanket of argon. Reactions were stirred in an oil bath at 100 °C, initially open to argon until reflux was noted and then changed to a closed system. For several minutes at the beginning of each reaction the flask was occasionally hand shaken to facilitate catalyst solubilization; otherwise, the ruthenium polymer had a tendency to aggregate in areas of insufficient mixing. The reactions were heated over various times. Afterwards, the flasks were removed from the bath, cooled, and opened to the atmosphere. The reaction mixture was concentrated using a rotary evaporator and then reconstituted with 20-40 mL of distilled hexane then reevaporated to an oil. The catalyst/ligand were filtered (whenever possible)

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⁸Same procedure used for acetophenone ATH shown in Table 2 using RuCl₂(PPh₃)₃.
and the filtrate reconcentrated and chromatographed (EM silica gel 60; hexane to 5% ethyl acetate/hexane).

**Preparation of methyl-3-phenyl-2-butenoate:**

A 250 mL 3-neck, round bottom flask equipped with magnetic stir bar, thermometer, and condenser, was charged with methyl diethylphosphonoacetate (15.5 mL, 88 mmol) followed by THF (130 mL). The flask was cooled to 5 °C and sodium hydride (60 % in mineral oil) (3.5 g, 88 mmol) was added in portions over 30 mins. The flask was warmed to about 25 °C and to this clear solution was added acetophenone (10.4 mL, 88 mmol) by addition funnel. The flask was heated to reflux for 8 h then quenched slowly with water. **Caution:** Vigorous gas evolution! The contents of the flask were then poured into water and extracted with ether and washed with 0.1 N HCl and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to obtain 15 g of a crude oil suitable for further preparations. Vacuum distillation and flash chromatography (100 % hexane) of a subsequent batch provided 540 mg of clear colorless oil (96 % GC purity) ¹H NMR (500 MHz, CDCl₃) δ 7.49-7.46 (m, 2H), 7.40-7.37 (m, 3H), 6.14 (s, 1H), 3.76 (s, 3H), 2.59 (s, 3H); MS m/z 176.

**Preparation of 3-phenyl-2-buten-1-ol:**

A 250 mL 3-neck, round bottom flask equipped with a magnetic stir bar and thermometer, was charged with methyl 3-phenyl-2-butenoate (14 g, 80 mmol), and 125 mL ether. The flask was cooled in an ice bath to 2 °C and lithium aluminum hydride (95 %) (3g, 320 mmol) was slowly added in portions so that a gentle reflux was obtained. The reaction was monitored by GC for the disappearance of starting material. Next, the flask was cooled in an ice bath to 5 °C then quenched slowly with 50 mL of saturated aqueous
Caution: Vigorous gas evolution! The contents were transferred to a separatory funnel, diluted with ether and washed with water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to obtain 10 g of an oil. Purification by flash chromatography with a Biotage 40XL cartridge (10 % ethyl acetate/hexane) yielded 1.7 g clear colorless oil (99 % purity GC). ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.41 (m, 2H), 7.35-7.33 (m, 2H), 7.29-7.27 (m, 1H), 6.01-5.98 (m, 1H), 4.38 (d, J = 14 Hz, 2H), 2.10 (s, 3H); MS m/z 148.

Preparation of 3-phenyl-2-butenoic acid:

A 50 mL single neck round bottom flask was charged with methyl 3-phenyl-2-butenoate (600 mg, crude), THF (2 mL), and 2 M NaOH (2.4 mL, 4.8 mmol) and refluxed for 3 h. The contents were diluted with ether and acidified with conc. HCl, extracted twice, washed with brine, dried over MgSO₄, filtered, and concentrated to obtain 270 mg white solid (99 % purity GC). ¹H NMR (500 MHz, CDCl₃) δ 7.52-7.49 (m, 2H), 7.42-7.39 (m, 3H), 6.19 (q, 1H), 2.62 (d, J = 2 Hz, 3H); MS m/z 162.

General Procedure for Preparation of Mosher Esters

A 10 mL single neck, round bottom flask equipped with a magnetic stir bar, was charged with product from transfer hydrogenation (about 25 mg), triethylamine (3 eq.), and CH₂Cl₂ (1 mL). The solution was cooled in an ice bath and to this was added dimethylaminopyridine (0.1 eq.), and (S)-(+)‐α-methoxy‐α-(trifluoromethyl)phenylacetyl chloride (1.5 eq.). The solution was heated to reflux for 4 h and monitored for starting material conversion greater than 98 % via GC. The reaction mixture was concentrated and
diluted with HPLC hexane and washed with saturated NaHCO₃, water, 0.1 N HCl, water, brine; dried over MgSO₄, filtered, and analyzed for ee purity.

**Preparation of 3-phenyl-1-butyl acetate.**

A 10 mL single neck, round bottom flask equipped with a magnetic bar, was charged with 3-phenyl-1-butanol (about 25 mg), triethylamine (6.5 eq.), and CH₂Cl₂ (1 mL). The solution was cooled in an ice bath and to this was added dimethylaminopyridine (0.1 eq.), and acetic anhydride (5 eq.). The solution was heated at reflux for 4 h. and monitored for GC conversion greater than 95%. The reaction mixture was concentrated and diluted with HPLC hexane and washed with saturated NaHCO₃, water, 0.1 N HCl, water, brine; dried over MgSO₄, filtered, and analyzed for ee purity.