Asymmetric Transfer Hydrogenation of Allylic Alcohols With Homogeneous Chiral Ruthenium Catalysts: A Proposed Mechanism

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ASYMMETRIC TRANSFER HYDROGENATION OF ALLYLIC ALCOHOLS WITH HOMOGENEOUS CHIRAL RUTHENIUM CATALYSTS: A PROPOSED MECHANISM

by

MARIE G. BEAUCHAMPS

DISSERTATION

A thesis submitted in partial fulfillment of the requirements for the degree of Doctoral of Philosophy

In the Department of Chemistry and Biochemistry

Seton Hall University

South Orange, New Jersey

May, 2009
We certify that we have read this thesis and that in our opinion it is sufficient in scientific scope and quality for a dissertation for the degree of Doctoral of Philosophy.

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This thesis is dedicated

To my daughter Nathalie Beauchamps

To my nephew David Moore

and

To my nieces Katchina, Shannah and Sarah

I hope they can all be inspired by this work.
Abstract

Optically active alcohols are useful building blocks for the synthesis of biologically active and structurally interesting compounds. These types of compounds have been prepared by asymmetric hydrogenation of olefins (eq. 1), and enantioselective hydrogenation of ketones and alpha or beta-keto esters using gaseous hydrogen with homogeneous and heterogeneous catalyst systems.

Eq. 1

\[
\text{Geraniol} + H_2 \xrightarrow{(S)\text{-BinapRu(OAc)}_2} \text{Citronellol}
\]

100% yield, 96-99% ee

In addition to straightforward asymmetric hydrogenation, which results in high enantioselectivity, there has been recent interest in the preparation of these compounds using asymmetric transfer hydrogenation (ATH) where the hydrogen source comes from a solvent.

This method has been extensively used for aldehydes and ketones because of the favorable properties of the hydrogen donor as well as the operational simplicity. Recent work in our group has shown that this reaction is amenable to a new class of substrates, allylic alcohols (eq. 2). Geraniol was converted to citronellol in 90 – 95 % yield and 95 –

---

98 % ee (R) using isopropyl alcohol as the solvent/hydrogen source and an in situ prepared catalyst Ru-(S)-tolBINAP.

Eq. 2

\[
\begin{align*}
\text{Geraniol} & \xrightarrow{\text{Ru-(S)-tolBINAP}} \text{(R)-Citronellol} \\
0.01 \text{ M IPA soln.} & \quad 2 \text{ eq KOH/Ru} \\
\text{S/C 10/1} & \\
90-95\% \text{ yield} & \quad 95-98\% \text{ ee}
\end{align*}
\]

An investigation on the mechanism of this ATH reaction was conducted. The results from the deuterated experiments lead us to propose that the olefin isomerizes to the enol followed by a transfer hydrogenation reaction (eq. 3). The isomerization takes place by a metal-assisted 1,3-hydrogen shift via a \(\pi\)-allyl intermediate. The transfer hydrogenation step is in good agreement with the mechanistic steps found in the well-studied transfer hydrogenation of carbonyl groups.

Eq. 3
Acknowledgments

Thanks to my mentor Prof. John R. Sowa Jr. for his guidance, encouragement and countless lectures toward my academic education. Thank you for being such a wonderful mentor.

Thanks to my family, particularly to my sister Alexandra Pierre who took good care of my daughter, Nathalie, while I was doing my research in the lab. Without her help and continuous prayers, I would not have the strength to accomplish this goal.
# Table of Contents

Title page ........................................................................................................... 1
Approval page .................................................................................................... 2
Dedication ........................................................................................................... 3
Abstract .............................................................................................................. 4
Acknowledgments .............................................................................................. 6
Table of contents ............................................................................................... 7
List of schemes .................................................................................................. 8
List of figures ...................................................................................................... 10
List of tables ...................................................................................................... 12
Chapter 1: A review of asymmetric hydrogenation & asymmetric transfer hydrogenation .............................................................. 13
Chapter 2: Chiral method development .................................................................. 42
Chapter 3: Asymmetric transfer hydrogenation of allylic alcohols ...................... 71
Experimental Section ......................................................................................... 111
Appendix .............................................................................................................. 118
### List of Schemes

**Scheme 1.1:** Preparation of Wilkinson’s Triphenylphosphine/Rh Catalyst Complexes ................................................................. 14

**Scheme 1.2:** Asymmetric Hydrogenation with Chiral Phosphine Ligands .......................................................................................................................... 16

**Scheme 1.3:** Asymmetric Hydrogenation with Chiral Phosphine/Rh Catalysts .......................................................................................................................... 16

**Scheme 1.4:** The Use of CAMP in L-DOPA Synthesis ................................................................................................................................. 18

**Scheme 1.5:** Asymmetric Hydrogenation with DIOP ................................................................................................................................. 19

**Scheme 1.6:** Asymmetric Hydrogenation of Functionalized Olefins with Ru-BINAP .......................................................................................................................... 21

**Scheme 1.7:** Asymmetric Hydrogenation of Functionalized Ketones with RuBINAP .......................................................................................................................... 22

**Scheme 1.8:** Application of Ru-BINAP in Commercial Syntheses ................................................................................................................................. 24

**Scheme 1.9:** Asymmetric Hydrogenation of Simple Ketones with Ru-BINAP/Diamine .......................................................................................................................... 26

**Scheme 1.10:** Transfer Hydrogenation with Metal Alkoxide Catalysts ................................................................................................................................. 31

**Scheme 1.11:** Transfer Hydrogenation with a Chiral Samarium Catalyst ................................................................................................................................. 33

**Scheme 1.12:** Transfer Hydrogenation with an Iridium-Hydride Catalyst ................................................................................................................................. 34

**Scheme 1.13:** Transfer Hydrogenation with RuCl₂(PPh₃)₃ ................................................................................................................................. 36

**Scheme 1.14:** Transfer Hydrogenation with RuCl(arene)/Chiral Ligand Complexes ................................................................................................................................. 37

**Scheme 2.1:** Reaction of 1-Phenylethylamine (21) with the Chiral Derivatizing Agent (CDA) (−)-Myrtenal (20) ................................................................................................................................. 57
Scheme 2.2: Derivatization of Citronellol with R-Mosher Acid Chloride.....................60

Scheme 2.3: Derivatization of Citronellol with
S-Naproxen........................................................................................................63

Scheme 3.1: First Example of Ruthenium Catalyzed Asymmetric Transfer
Hydrogenation (ATH) of an Allylic Alcohol......................................................72

Scheme 3.2: Baylis-Hillman Reaction with a Chiral
Solvent........................................................................................................83

Scheme 3.3: Chemical Structures of [(S)-tol-BINAP]Ru(II)Cl₂ (Complex A),
[(R)-BINAP]Ru(II)Cl₂ (Complex B) and [(S)-BINAP]Ru(II)Cl₂ (Complex C)........86

Scheme 3.4: Hydrogenation of α,β-Unsaturated Amino Acids with Ru₂Cl₄[(-)-
BINAP]₂(NEt₃)......................................................................................87

Scheme 3.5: Reciprocal Relationship Between Nerol and Geraniol.....................90

Scheme 3.6: Preparation of γ-Geraniol..................................................................91

Scheme 3.7: Asymmetric Isomerization of Geraniol with Rh-BINAP.........................95

Scheme 3.8: Asymmetric Isomerization of Geraniol.............................................98

Scheme 3.9: Potential Products from the ATH with Deuterated IPA.......................99

Scheme 3.10: Asymmetric Transfer Hydrogenation of Geraniol with
Deuterated IPA..............................................................................................100

Scheme 3.11: Isomerization/ATH of Allylic Alcohols Via π-Allyl Mechanism with
d₈-IPA........................................................................................................106

Scheme 3.12: Proposed Mechanism for Asymmetric Transfer Hydrogenation........107
List of Figures

Figure 1.1: The Mechanism of Hydrogenation with Wilkinson’s Tris-(triphenylphosphine)chlororhodium(I) Catalyst.................................................................15

Figure 1.2: Phosphine Ligands Screened in the Asymmetric Hydrogenation Step in L-DOPA Synthesis..................................................................................18

Figure 1.3: The Use of Biphosphine Ligands in Asymmetric Hydrogenation...........20

Figure 1.4: The Mechanism of BINAPRu(II) Catalyzed Hydrogenation of β-Keto Esters...............................................................................................................24

Figure 1.5: a) Non-classical Metal-Ligand Bifunctional Mechanism and Conventional [2+2] Mechanism. b) Catalytic Cycle of Hydrogenation of Ketones with BINAPRu(II)/Diamine.................................................................27

Figure 1.6: Application of BINAP/Diamine-Ruthenium Complexes in Commercial Compounds..........................................................................................28

Figure 1.7: Meerwein-Ponndorf-Verley (MPV) Mechanism...........................................32

Figure 1.8: Conventional Mechanism of Transition-Metal-Catalyzed Transfer Hydrogenation with Isopropanol........................................................................38

Figure 1.9: Non-Classical Metal-Ligand Bifunctional Mechanism of Transfer Hydrogenation with Isopropanol.............................................................39

Figure 2.1: Application of Different GC Chiral Stationary Phases from 1/01 to 7/04....48

Figure 2.2: Proton NMR of N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-y1)methylene)-1-phenylethanamine (22).................................................................58

Figure 2.3: Carbon NMR of N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-y1)methylene)-1-phenylethanamine (22).................................................................58

Figure 2.4: HPLC Chromatogram of Citronellyl-Mosher Esters...............................61

Figure 2.5: 13C NMR Segment of Sample (b) [(S)-Naproxen Citronellyl Ester]........65
Figure 2.6: Comparison of Standard Citronellol Samples (a, b, c and d) with their (S)-Naproxen Esters Results from $^{13}$C NMR.................................................................65

Figure 2.7: Comparison of Standard Citronellol Samples (A, B, C, D and E) with the Chiral GC Results..............................................................................................................68

Figure 2.8: Chiral GC of 1 M Citronellol in Methanol........................................................................69

Figure 3.1: Ligands Used in Table 3.1 and Table 3.2........................................................................74

Figure 3.2: Substrates Used in Table 3.2..........................................................................................76

Figure 3.3: Proposed Mechanism for Asymmetric Isomerization of Allylic Alcohols...............................97

Figure 3.4: Segment of GC/MS of d$_3$-citronellol........................................................................101

Figure 3.5: The $^1$H NMR of d$_3$-citronellol................................................................................102

Figure 3.6: $^{13}$C NMR of d$_3$-citronellol......................................................................................103

Figure 3.7: Enlarged $^{13}$C NMR of d$_3$-citronellol........................................................................103

Figure 3.8: Enlarged HMQC NMR of d$_3$-citronellol......................................................................104

Figure 3.9: Enlarged HMQC NMR of Regular Citronellol............................................................105

Figure 3.10: $^2$H NMR of d$_3$-citronellol......................................................................................105
List of Tables

Table 1.1: Transfer Hydrogenation with RuCl(arene)/Chiral Ligand Complexes .......37

Table 2.1: Differences in Pharmacodynamic Action ...........................................43

Table 2.2: Derivatized Cyclodextrins and their Recent Applications in Chiral GC ......49

Table 2.3: Common Chiral Lanthanide Shift Reagents ........................................56

Table 2.4: Comparison of Standard Citronellol Samples (a, b, c and d) with the (S)-Naproxen Esters Results from $^{13}$C NMR ..............................................................64

Table 2.5: Comparison of Standard Citronellol samples (A, B, C, D and E) with the Chiral GC Results ...........................................................................................................68

Table 3.1: Evaluation of Various Ligands in the ATH of Geraniol .......................73

Table 3.2: Transfer Hydrogenation with Ru/tol-BINAP (A) and Ru/iPrDUPHOS (B) ...75

Table 3.3: Transfer Hydrogenation with Ru/tol-BINAP in Mixed Solvents .............78

Table 3.4: Transfer Hydrogenation with Ru/tol-BINAP in Cyclohexanol ...............81

Table 3.5: Asymmetric Transfer Hydrogenation with Chiral Solvents ..................84

Table 3.6: ATH with Pre-made Catalyst [(S)-BINAP]Ru(II)Cl$_2$ (Complex C in Figure 3.3) Compared with in situ Prepared Catalyst B .............................................87

Table 3.7: ATH with Pre-made Catalyst [(S)-BINAP]Ru(II)Cl$_2$ ............................89

Table 3.8: Asymmetric Transfer Hydrogenation of $\gamma$-Geraniol with Two Equivalents of Base ..................................................................................................................92

Table 3.9: Asymmetric Transfer Hydrogenation of $\gamma$-Geraniol with Four Equivalents of Base ..........................................................................................................................93

Table 3.10: Asymmetric Isomerization of Allylic Alcohols with HRh(CO)(PPh$_3$)$_3$/DIOP Catalyst System .................................................................95
CHAPTER 1: A REVIEW OF ASYMMETRIC HYDROGENATION AND
ASYMMETRIC TRANSFER HYDROGENATION

1.1 Introduction

Asymmetric hydrogenation is an important tool in synthetic organic chemistry. It has dramatically changed the procedures of chemical synthesis since its modest beginnings in the 1960s. It all began by the discovery of Wilkinson that triphenylphosphine/Rh complexes could catalyze hydrogenation of olefins in solution.\(^5\) The field really got underway when Knowles and Horner reported the first examples of asymmetric hydrogenation of prochiral olefins with chiral phosphine/Rh complexes in 1968.\(^5\) Asymmetric catalysis became so important in organic synthesis that three researchers in this area were awarded with the 2001 Nobel Prize in chemistry,\(^6\) which was shared among William S. Knowles and Ryoji Noyori for their work on catalytic asymmetric hydrogenation reactions and Barry K. Sharpless for his work on catalytic asymmetric epoxidation reactions. Today, about half of the commercial drugs in use are chiral\(^7\) and in 2005, the worldwide sales of single-enantiomer drugs reached 225 billion US dollars based on estimates from Technology Catalysts International (TCI).\(^8\) In this chapter, the origin, the use and the mechanism of various types of homogeneous asymmetric reductions will be reviewed.

1.2 Overview of Asymmetric Hydrogenation

1.2.1 Wilkinson’s Catalysts

---


\(^6\) http://nobelprize.org/nobel_prizes/chemistry/laureates/

The first efficient catalysts in the homogeneous hydrogenation of unsaturated compounds were reported by Geoffrey Wilkinson in 1966 with the discovery of its tris(triphenylphosphine)halogenorhodium(I) complexes. Previous catalysts, particularly the cobalt(II)-cyanide system, had limited use as they were efficient only in the reduction of conjugated double bonds (butadiene, α,β-unsaturated acids and aldehydes), but not in isolated ethylenic linkages.

Scheme 1.1: Preparation of Wilkinson’s Triphenylphosphine/Rh Catalyst Complexes.

\[
\text{RhX}_3(\text{H}_2\text{O})_3 + \text{CH}_3\text{CH}_2\text{OH} + 3 \text{PPh}_3 \rightarrow \text{RhX(PPh}_3)_3 + \text{CH}_3\text{CHO} + 2 \text{HCl} + 3 \text{H}_2\text{O}
\]

\[
(X = \text{Cl, Br, I})
\]

The Wilkinson’s catalysts were prepared by the reaction of excess triphenylphosphine with rhodium(III) halide in ethanol (Scheme 1.1). In homogeneous solution, the tris(triphenylphosphine) complexes were reported to be exceedingly active catalysts for rapid homogeneous hydrogenation of unsaturated compounds containing isolated olefinic and acetylenic linkages.

The mechanism (Figure 1.1) involves the initial dissociation of one or two triphenylphosphine ligands to give 14 or 12-electron complexes, respectively. Oxidative addition of hydrogen to the metal center generates the 16 electron Rh complex. Subsequent insertion of the olefin follow by reductive elimination results in the formation of the reduced product.

8 http://www.pharmatech.com/
1.2.2 Asymmetric Hydrogenation with Chiral Phosphine Ligands

The first examples of catalytic asymmetric hydrogenation were reported by Knowles and Horner in 1968 with the synthesis of their chiral phosphine/rhodium complexes.\(^{11}\) Knowles reported the hydrogenation of α-phenylacrylic acid with 0.15 mole % of RhCl\(_3\)L\(_3\) (L = (-)-methylpropyl-phenylphosphine), which gave 2-phenylpropanoic acid in 15% ee at 60 °C, and the hydrogenation of itaconic acid to succinic acid in 3% ee at 25 and 60 °C (Scheme 1.2).\(^{11}\) That same year, Horner reported that α-ethylstyrene and
α-methoxystyrene could be hydrogenated to (S)-(+-)-2-phenylbutane in 7 – 8 % ee and (R)-(+-)-1-methoxy-1-phenylethane in 3 – 4 % ee, respectively, in the presence of 0.5 mole % of the same chiral ligand at normal pressure and room temperature.\textsuperscript{11b}

**Scheme 1.2: Asymmetric Hydrogenation with Chiral Phosphine Ligands.**

\[
\begin{align*}
\text{COOH} & \quad \text{RhC}_3\text{L}_3 \quad \text{MeOH} \quad 60^\circ \text{C} \\
& \quad \text{H}_2 \quad 15\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{COOH} & \quad \text{RhC}_3\text{L}_3 \quad \text{MeOH} \quad 25-60^\circ \text{C} \\
& \quad \text{H}_2 \quad 3\% \text{ ee}
\end{align*}
\]

**Scheme 1.3: Asymmetric Hydrogenation with Chiral Phosphine/Rh Catalysts.**

\[
\begin{align*}
\text{HOOC} & \quad \text{NHCOR}^5 \quad \text{Rh} \quad \text{H}_2, \quad 0.05\% \quad \text{[Rh} \quad \text{(1,5-cyclo-octadiene)\text{Cl}\text{L}]} \\
& \quad \text{10-55 psi} \quad \text{Alcoholic solvent, 25-50}^\circ \text{C} \\
& \quad \text{HOOC} \quad \text{NHCOR}^5 \quad \text{~80\% ee}
\end{align*}
\]

\[R^4 = \text{H, Ph, MeO}^4\text{-(OH)}\text{-C}_6\text{H}_3, \text{MeO}^4\text{-(AcO)}\text{-C}_6\text{H}_3\]

\[R^5 = \text{Ph, Me}\]

\[L = \begin{array}{c}
\text{P} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3
\end{array} \]

\[75-95\% \text{ ee}\]

\[R^1 = \text{m-anisyl, o-anisyl, Me, Cyclohexyl}\]

\[R^2 = \text{Me, Ph, cyclohexyl}\]

\[R^3 = \text{Ph, Pr, Pr', Me}\]

\[\text{CAMP}\]

A few years later, Knowles and coworkers synthesized a new series of chiral phosphine ligands, which gave moderate to good enantiomeric excess. This resulted in the discovery of o-anisylmethylcyclohexylphosphine (CAMP), giving 80% enantiomeric excess (Scheme 1.3).

Several α-acylaminoacrylic acids were hydrogenated to their corresponding α-amino acids using 0.05 mole % of the rhodium catalysts under 10 - 55 psi of hydrogen at 25 - 50 °C. Of particular interest were the high optical purities obtained with o-anisylmethylcyclohexylphosphine (CAMP) when applied to various acylphenylalanine substrates. These yields ranging from 85 - 90 % show that almost complete stereospecificity was achieved considering that the phosphine ligand was only 95% ee. On the other hand, the lower optical yields, <90% ee, indicate that the ligand is not the only factor influencing the outcome of the product.

The o-anisylmethylcyclohexylphosphine (CAMP) catalyst gained its major importance when it was applied to the preparation of commercial drug L-DOPA, an anti-Parkinson drug (Scheme 1.4).

Several catalysts (Figure 1.2) were screened in the hydrogenation step, the key step in L-DOPA synthesis, and the best enantiomeric excess (88%) was then obtained with CAMP, which resulted in an isolated yield of about 70%. This was the first time enzymatic-like selectivity was obtained with a man-made catalyst. Later, the ligand was replaced with 1,2-bis(phenylorthoanisylphosphino)ethane (DIPAMP), which gave 95% ee and an isolated yield of 75 - 80%.

---

Scheme 1.4: The Use of CAMP in L-DOPA Synthesis.

Figure 1.2: Phosphine Ligands Screened in the Asymmetric Hydrogenation Step in L-DOPA Synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>88</td>
</tr>
</tbody>
</table>

(R,R)-DIPAMP 95% ee
1.2.3 Asymmetric Hydrogenation with C₂-Chiral Biphosphine Ligands

The field of asymmetric hydrogenation really got underway with the discovery of the first active C₂-chiral biphosphine ligand 4,5-Bis-[(diphenylphosphanyl)-methyl]-2,2-dimethyl-[1,3]dioxolane (DIOP). Previous example of C₂-chiral phosphine ligand (Entry 1, Figure 1.2) resulted in no enantioselectivity. It was believed that to get enantioselectivity, the chirality needed to be directly on the phosphorous atom, but Kagan’s discovery of the DIOP ligand has proven otherwise.

The active catalyst was prepared in situ by adding two equivalents of DIOP to a benzene-ethanol solution of [Rh-(cyclooctene)₂Cl]₂. The resulting solution catalyzed the hydrogenation of α,β-unsaturated carboxylic acids in 95% yields and 63 – 72 % ee (Scheme 1.5).

Scheme 1.5: Asymmetric Hydrogenation with DIOP.

\[
\begin{array}{c}
\text{R}_1\text{R}_2^1
\end{array}
\xrightarrow{[\text{Rh(I)}(\text{L})\text{Csolvent}], 3.3 \text{ mol }%} \begin{array}{c}
\text{R}_1\text{R}_2
\end{array}
\]

95% Yield, 63-72% ee

(1) \( \text{R}_1 = \text{H}, \text{R}_2 = \text{Ph} \)
(2) \( \text{R}_1 = \text{Ph}, \text{R}_2 = \text{NHAc} \)
(3) \( \text{R}_1 = \text{H}, \text{R}_2 = \text{NHOCH₂Ph} \)

\[L = \begin{array}{c}
\text{CH}_2\text{P(C}_6\text{H}_5)_2
\end{array}\]

\[\text{(R,R)-DIOP}\]

These results have generated a lot of interest and for the next decade many efficient C₂-chiral biphosphine ligands were discovered. However, these ligands were useful only on enamides, enol esters and carboxylic acids (Figure 1.3). Other compounds like α-arylacrylic acids and unfunctionalized olefins worked poorly or were simply inactive.

Figure 1.3: The Use of Diphosphine Ligands in Asymmetric Hydrogenation.
It wasn’t until 1980 - 1986 that the scope of asymmetric hydrogenation was expanded with the discovery of ruthenium 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (Ru/BINAP) complexes. This axially di-symmetric C₂ biphosphine ligand coupled with ruthenium allows asymmetric hydrogenation of a wide range of functionalized olefins including α-arylacrylic acids, α,β- and β,γ-unsaturated carboxylic acids, allyl and homo-
allylic alcohols, 2-acyl-benzylidene-1,2,3,4-tetrahydroisoquinolines, α- and β-
amino acids, as well as α-amino phosphonic acids (Scheme 1.6).\textsuperscript{15}

The Ru-BINAP complexes were also useful in the asymmetric hydrogenation of a
wide range of functionalized ketones, wherein coordination of nitrogen, oxygen, and
halogen groups near the carbonyl group directed the reactivity and stereoselectivity of the
product (Scheme 1.7). The reactions are normally conducted in alcoholic solvents under 4
- 100 atm hydrogen pressure at room temperature to give the corresponding alcohols in 90
- 100 % ee.\textsuperscript{15}

\textbf{Scheme 1.7: Asymmetric Hydrogenation of Functionalized Ketones with Ru-BINAP.}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.7.png}
\end{center}

The 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) worked well with Rh (I) and Ru (II) but gave opposite enantiomers. This is due to the operation of different catalytic cycles, a dihydride mechanism for Rh (I) versus a monohydride pathway for Ru (II). The dihydride mechanism for Rh (I) (similar to Figure 1.1) proceeds via oxidative addition of H₂ to diastereomeric Rh-substrate chelate complexes, followed by stepwise transfer of the hydrides to the coordinated olefin; which involves a +1/+3 redox process. In contrast to the monohydride pathway for Ru(II), the ruthenium center remains in the +2 oxidation state throughout the catalytic cycle. Figure 1.4 illustrates the mechanism of Ru(II)BINAP.¹⁵

The reaction has been shown to proceed via a ruthenium intermediate 2 formed by heterolysis of H₂ by the Ru complex 1. Interaction of 2 with the β-keto ester forms complex 3. Protonation of the keto oxygen follow by hydride transfer generates the Ru-hydroxy ester 4, which interacts with a solvent molecule to release the chiral β-hydroxy ester. The cationic ruthenium 5 reacts with another hydrogen molecule to regenerate 2, which reenters the catalytic cycle.

The Ru-BINAP complexes have some important applications in the synthesis of many commercial compounds.⁷ For example, the anti-inflammatory drug Naproxen can be obtained in 97 % ee from the corresponding α-aryl-acrylic acid using this catalyst.¹⁶ Similarly, citronellol can be obtained in 96 – 98 % ee from geraniol or nerol without over reduction to the dihydrocitronellol¹⁷ (Scheme 1.8).

**Figure 1.4:** The Mechanism of Ru(II)BINAP Catalyzed Hydrogenation of β-Keto Esters.

\[
\text{RuC}_2(\text{BINAP})(\text{solvent})_2 + \text{H}_2 \rightarrow \text{RuHCl(BINAP)(solvent)}_2
\]

**Scheme 1.8:** Application of Ru-BINAP in Commercial Syntheses.

- Geraniol > 30 atm. H₂ MeOH
  - [(R)-citronellol]
    - 99% yield
    - 96-98% ee

- 135 atm. H₂ MeOH
  - (S)-naproxen 97% ee
The Ru-BINAP system was considered a major breakthrough for extending the scope of asymmetric hydrogenation to a variety of functionalized olefins and ketones. None of the previous chiral ligands (mono- and bi-phosphine) offered this kind of diversity. The Ru-BINAP system is thought to come close as a universal asymmetric hydrogenation catalyst. However, this catalyst system was not efficient in the hydrogenation of non-functionalized ketones, particularly with acetophenone.\textsuperscript{7}

1.2.4 Asymmetric Hydrogenation with BINAP/Diamine Ligands

In 1995, the hydrogenation of simple ketones became possible with the discovery of BINAP/diamine-ruthenium complexes. These catalysts, particularly RuCl\textsubscript{2}(xyl-BINAP)-DAIPEN, were very efficient in the presence of a strong base (KOH, KOtBu) in the enantioselective hydrogenation of a range of aromatic, heteroaromatic, and olefinic ketones in isopropanol.\textsuperscript{15} For example, acetophenone and its derivatives can be hydrogenated to the corresponding alcohols in 94 – 96 % ee. In addition, α,β-unsaturated ketones can now be hydrogenated in the presence of a weaker base (K\textsubscript{2}CO\textsubscript{3}) to give the corresponding chiral allylic alcohols (Scheme 1.9).\textsuperscript{18}

The mechanism of the BINAP/diamine-ruthenium reduction is shown to be different from the amine-free BINAP reduction. The high reactivity and chemoselectivity of the BINAP/diamine system is due to a bifunctional mechanism (Figure 1.5).\textsuperscript{7}
Scheme 1.9: Asymmetric Hydrogenation of Simple Ketones with Ru-BINAP/Diamine.

\[
\text{Scheme 1.9: Asymmetric Hydrogenation of Simple Ketones with Ru-BINAP/Diamine.}
\]

\[
\begin{align*}
\text{Ru-(S)-XylBINAP-DAIPEN} & \quad \xrightarrow{8 \text{ atm. } H_2} \quad \text{OH} \\
\text{Ru-(S)-XylBINAP-DAIPEN} & \quad \xrightarrow{10 \text{ atm. } H_2} \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
X = H, \text{ Cl}, \text{ Br}, \text{ CH}_3\text{O} & \quad \xrightarrow{\text{IPA, KOC(\text{CH}_3)_3}} \quad 100\% \text{ yield} \\
\text{C}_6\text{H}_5\text{H} & \quad \xrightarrow{\text{IPA, K}_2\text{CO}_3} \quad 100\% \text{ yield, } 96\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \xrightarrow{\text{IPA, K}_2\text{CO}_3} \quad 100\% \text{ yield, } 90\% \text{ ee}
\end{align*}
\]


Figure 1.5 (a) shows the six-membered ring intermediate describing a Ru hydride species possessing an NH$_2$ ligand, whose protons (Ru-H and N-H) are simultaneously transferred to the C=O linkage, without direct coordination of the carbonyl substrate to the metal. Figure 1.5 (b) shows a more detailed mechanism. The 18-electron ruthenium hydride 2 reacts with the carbonyl group via the six-membered ring intermediate shown.
in Figure 1.5 (a) to give the product alcohol and the 16-electron complex 3. The high turnover efficiency of this catalyst system is believed to originate from the alternating charge arrangement of \( \text{H}^5 \), \( \text{Ru}^{5+} \), \( \text{N}^5 \), \( \text{H}^{5+} \) on the six-membered ring intermediate. Therefore, the hydride at the ruthenium center has sufficient nucleophilicity and the NH hydrogen-bonding ability activate the carbonyl substrate. The ruthenium complex 3 reacts with \( \text{H}_2 \) in the presence of base and a protic solvent to regenerate 2, which goes back to the catalytic cycle via complex 4 and complex 5.\(^7\),\(^15\)

**Figure 1.6**: Application of BINAP/Diamine-Ruthenium Complexes in Commercial Compounds.

\[
\begin{align*}
\text{(S)-orphenadrine: } & \ R^1 = \text{CH}_3, \ R^2 = \text{H} \\
\text{(R)-neobenodine: } & \ R^1 = \text{H}, \ R^2 = \text{CH}_3 \\
\text{fluoxetine hydrochloride: } & \ \text{antidepressant agent} \\
\text{denopamine hydrochloride: } & \ \text{beta}_1\text{-receptor agonist} \\
\text{BMS 181100: } & \ \text{antipsychotic agent}
\end{align*}
\]
The BINAP/diamine-ruthenium complexes have many industrial applications. For example, (R)-neobenodine, a β₁-receptor agonist, can be synthesized by doing asymmetric hydrogenation of \(o\)-bromo-\(p\')-methylbenzophenone as a key step.\(^{19}\) Other applications include (R)-denopamine, another β₁-receptor agonist, the antidepressant (R)-fluoxetine, the antipsychotic BMS 181100, and (S)-duloxetine, a potent inhibitor of serotonin and norepinephrine (Figure 1.6).\(^{7}\)

1.2.5 Summary of Asymmetric Hydrogenation

Asymmetric hydrogenation is an important tool in organic synthesis. Since the discovery of the first chiral phosphine/Rh complexes in the late 1960s, this field in organic synthesis has enabled efficient synthetic routes, including the asymmetric synthesis of many medicinally and industrially important compounds. Over the years, asymmetric reduction has expanded to various types of substrates, which include functionalized olefins, functionalized ketones and simple ketones. These transformations became possible with the discovery of more reactive and chemoselective ligand-catalyst systems.

The chiral mono-phosphine ligands/rhodium catalyst systems (Figure 1.2), particularly CAMP, gave moderate enantioselectivity (−80%) in the asymmetric reduction of unsaturated amino acids and carboxylic acids. Later, the enantioselectivity was increased to up to 99\% ee with the discovery of the diphosphine ligands (Figure 1.3). The asymmetric reduction of a broader range of olefins (Scheme 1.6) and functionalized ketones (Scheme 1.7) became possible with the discovery of the BINAP/ruthenium catalyst system. Today, even the long time challenging α-phenylacrylic acid and its

derivatives as well as various simple ketones (Scheme 1.9) can be hydrogenated in high yield and good enantiomeric excess (90 – 96 %) with the BINAP/diamine ruthenium complexes.

Despite the high reactivity and chemoselectivity obtained with these catalyst systems, safer procedures are desired among organic chemists. Most asymmetric hydrogenations are conducted under high pressure, thus, special equipment is required. An alternate procedure is Asymmetric Transfer Hydrogenation (ATH), which eliminates the need for high pressure vessels. An overview on ATH follows below.

1.3 Overview of Asymmetric Transfer Hydrogenation

Asymmetric transfer hydrogenation is also a well studied area in organic chemistry. It is a convenient method to reduce carbonyls, imines and activated olefins without the use of hydrogen pressure or hazardous reducing agents. In recent years, asymmetric transfer hydrogenation has been classified second to gaseous hydrogenation among the methodologies suitable for this purpose. This method is being extensively studied because of the low cost and favorable properties of the hydrogen donor as well as operational simplicity. Transfer hydrogenation can take place under two major types of mechanisms: metal-template concerted process [Meerwein-Ponndorf-Verley (MPV) reduction] and metal hydride mediated process (hydridic reduction). An overview of these two processes is given in the following section.

---

1.3.1 Meerwein-Ponndorf-Verley (MPV) Reduction

The first example of transfer hydrogenation is dated back to 1925 when Meerwein and Schmidt performed the hydrogenation of an aldehyde with aluminum ethoxide in ethanol. The same year, Verley reported the reduction of butyraldehyde using the same aluminum ethoxide in the presence of geraniol as a hydrogen donor. A year later, 1926, Ponndorf extended the scope to the reduction to ketones with aluminum isopropoxide in isopropanol (Scheme 1.10). A major drawback of these types of reductions is that a stoichiometric amount of the metal catalyst is required.

Scheme 1.10: Transfer Hydrogenation with Metal Alkoxide Catalysts.

\[
\begin{align*}
\text{R} & \quad \text{H} & \quad \text{R} & \quad \text{H} \\
\text{EtOH} & \quad \text{A(OEt)}_3 & \quad + \text{acetaldehyde} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{CH}_3 & \quad \text{R} & \quad \text{CH}_3 \\
\text{IPA/reflux} & \quad \text{A(PrO)}_3 & \quad + \text{acetone} \\
\end{align*}
\]

The mechanism of this reaction, known as MPV mechanism, proceeds through a concerted six-membered ring transition state (Figure 1.7). The alcohol reactant coordinates to the metal to form 7. The carbonyl is activated upon coordination to 7 to form 8, which undergoes rearrangement to form 10 via the six membered-ring.

intermediate 9. Both the carbonyl compound and the reducing alcohol are bound to the metal via the six-membered ring intermediate and the reduction occurs without the formation of any metal hydride.

**Figure 1.7:** Meerwein-Ponndorf-Verley (MPV) Mechanism.

An enantioselective example of the Meerwein-Ponndorf-Verley (MPV) type of reduction was reported in 1993 by David Evans. Following Kagand's lead in his C2 chiral backbone catalyst, chiral samarium(III) was able to reduce carbonyl groups in high enantioselectivity via transfer hydrogenation using the MPV mechanism. Several aryl ketones were converted to their corresponding alcohols in high enantiomeric excess when 5 mole % of the samarium catalyst was used in the presence of isopropyl alcohol as hydrogen donor at ambient temperatures (Scheme 1.11).

---

Unlike the previous stoichiometric examples with aluminum alkoxides, this MPV reduction is catalytic in samarium. However, the samarium catalyst seems to have a special affinity for isopropyl alcohol as the hydrogen source; other alcohols such as 3-pentanol, cyclopentanol, or benzhydrol were ineffective.
1.3.2 Transfer Hydrogenation via Metal-Hydride Mediated Mechanism

The second category of transfer hydrogenation involves the formation of a metal hydride by interaction of the hydrogen donor with the catalyst, which subsequently transfers the hydride to the substrate. This mechanism is typical for transition metals [Ru (II), Rh (I), Ir(I)] and depending on the metal, a mono or dihydride metal species may be involved. The most popular hydrogen donors include formic acid/triethylamine and isopropyl alcohol (IPA). During the process of transfer hydrogenation with IPA, the IPA oxidizes to acetone, which also competes for hydrogen and as a result makes transfer hydrogenation a reversible process. The equilibrium of the reaction can be shifted toward the desired product by using IPA as the reaction solvent.

Scheme 1.12: Transfer Hydrogenation with Iridium-Hydride Catalyst.

![Scheme 1.12: Transfer Hydrogenation with Iridium-Hydride Catalyst.]

Early examples of transition metal catalyzed transfer hydrogenation were reported by Henbest in the 1960s. For example, the carbon-carbon double bond in benzylideneacetophenone and related compounds was reduced with 5 mole % of the

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acidic iridium catalyst in boiling isopropyl alcohol (IPA) (Scheme 1.12). The metal hydride HIrCl₂(Me₂SO₃)₃ was believed to be generated from an acidic solution of iridium tetrachloride/dimethylsulfoxide in boiling IPA.

In 1991, metal-hydride transfer hydrogenation was optimized with the addition of a strong base. Aliphatic and aromatic ketones were reduced with 0.1 mole % of RuCl₂(PPh₃)₃ and 2.4 mole % of sodium hydroxide in isopropyl alcohol at 82 °C (Scheme 1.13). The reactions remained in equilibrium giving up to 89% conversion. However, distillation of the by-product acetone resulted in full conversion of the substrates. This was an upgrade compared to the previous non basic reactions, which required high temperature (150 - 200 °C). The base was believed to generate a more nucleophilic alkoxide ion, which resulted in faster attack to the metal, thus enhancing the reaction rate.

Transition metal-catalyzed transfer hydrogenation may result in the formation of chiral products if conducted in the presence of chiral ligands. The ligands feature various combinations of phosphorous, nitrogen, oxygen, or sulfur. Many prochiral ketones, imines and activated olefins, which are limited to conjugated acid and amino acid derivatives, may be hydrogenated via asymmetric transfer hydrogenation. The enantiomeric excess (ee) of the product depends on the substrate type, the catalyst and the reaction conditions.

For example, the carbonyl group in acetophenone can be reduced with 1 mole % of (1R,2S)-(+) cis-1-amino-2-indanol, L₁, 0.25 mole % of the ruthenium complex

---

[RuCl$_2$(p-cymene)]$_2$ A and 2.5 mole % of KOH in isopropanol at room temperature to give 70% yield and 91% ee (Table 1.1, entry 1 and Scheme 1.14). At lower temperature (0 °C), the same reaction gave 49% yield with a slight increase in the enantiomeric excess to 93% (Table 1.1, Entry 2). When the ligand was substituted with the less rigid (R)-phenylglycinol, L$_2$, the enantiomeric excess dropped to 23% but the yield increased to 95% at room temperature (Table 1.1, entry 3). The use of another ruthenium arene complex [RuCl$_2$(mesitylene)]$_2$ B gave 73% yield and 82% ee (Table 1.1, entry 4). When the catalyst was replaced with ruthenium arene complex B and (S,S)-TsDPEN, L$_3$, the yield and the enantiomeric excess increased to 95% yield and 97% ee (Table 1.1, entry 5). This last result is comparable to what obtained from gaseous hydrogenation (Scheme 1.9, eq. 1). The rate and enantioselectivity of asymmetric transfer hydrogenation may also be affected by the bulkiness and electronic properties of the substrate.

**Scheme 1.13:** Transfer Hydrogenation with RuCl$_2$(PPh$_3$)$_3$.

---


Scheme 1.14: Transfer Hydrogenation with RuCl(arene)/Chiral Ligand Complexes.

\[
\begin{align*}
\text{Scheme 1.14: Transfer Hydrogenation with RuCl(arene)/Chiral Ligand Complexes.} \\
\text{IPA, KOH para-cymene} \\
\text{RuCl}(p\text{-cymene})L \\
\text{or} \\
\text{RuCl(mesitylene)L} \\
\text{L1 = \includegraphics[width=2cm]{l1}} \\
\text{L2 = \includegraphics[width=2cm]{l2}} \\
\text{L3 = \includegraphics[width=2cm]{l3}} \\
\text{A = \includegraphics[width=1cm]{a}} \\
\text{B = \includegraphics[width=1cm]{b}} \\
\end{align*}
\]

Table 1.1: Transfer Hydrogenation with RuCl(arene)/Chiral Ligand Complexes.

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Ru complex</th>
<th>Ligand</th>
<th>Temp. °C</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>L1</td>
<td>Rt</td>
<td>70</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>L1</td>
<td>0</td>
<td>49</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>L2</td>
<td>Rt</td>
<td>95</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>L1</td>
<td>Rt</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>L3</td>
<td>Rt</td>
<td>95</td>
<td>97</td>
</tr>
</tbody>
</table>
The mechanism of the metal-hydride mediated transfer hydrogenation may involve direct coordination of the substrate to the metal center (the inner sphere mechanism) or hydrogen bonding and dipolar interactions of the substrate with two different sites of the catalyst (metal-ligand bifunctional catalysis, outer sphere mechanism) depending on the structure of the ligand.\textsuperscript{20a, 27, 33} In the inner sphere mechanism, the metal may form a monohydride (MH) or dihydride (MH\textsubscript{2}) species depending on the metal. It has been proven via deuterium experiments that rhodium- and iridium-catalyzed reactions follow the monohydride pathway\textsuperscript{34} where ruthenium follows the dihydride pathway.\textsuperscript{27}

Regardless of the metal species, the conventional (inner sphere) mechanism of transition-metal-catalyzed transfer hydrogenation involves direct coordination of the substrate to the metal. Figure 1.8 outlines the mechanism of transfer hydrogenation with isopropanol and transition metal, in which X represents a halide. Base is required to
generate the isopropoxide ion, which coordinates to the metal and then undergoes β-
elimination to generate the metal hydride (15) and acetone. Coordination of the substrate,
which, in this example, occurs through the carbonyl group, to the metal center followed
by a hydride transfer gave intermediate (17). Hydrogenolysis of (17) gives the reduced
product (18) and the catalyst goes back to the start of the cycle.33

The non-classical (metal-ligand bifunctional catalysis, outer sphere) mechanism
occurs with diamine catalysts such as Ru-(S)-XylBINAP-DAIPEN (Figure 1.9), which
Noyori terms a metal ligand bifunctional catalyst.27 Theoretical calculations along with
experimental findings suggest that the hydrogenation of the carbonyl group takes place
via the six-membered ring transition state shown in Figure 1.9(a).33 The 18-electron metal
hydride complex is regenerated by dehydrogenation of isopropanol with the 16-electron
metal amide via the same six-membered ring. The reaction involves the participation of
both the metal and the ligand. Neither the substrate (carbonyl) nor the hydrogen donor
(isopropanol) interacts directly with the metal center. The reduction occurs in the outer
sphere of the metal hydride complex.33

1.3.3 Summary of Asymmetric Transfer Hydrogenation

Transfer hydrogenation occurs via two major pathways, the Meerwein-Ponndorf-
Verley (MPV) pathway, where a metal hydride is never formed and the hydridic pathway,
which occurs via the formation of a metal hydride. Within the hydridic pathway, there are
two mechanisms: the conventional metal hydride mechanism (inner sphere), which
involves direct coordination of the substrate with the metal and the metal-ligand
bifunctional mechanism (outer sphere), where the substrate doesn’t directly coordinate to
the metal center.\textsuperscript{27} Like in asymmetric hydrogenation, asymmetric transfer hydrogenation (ATH) transforms prochiral substrates to their reduced products in high yield and enantiomeric excess with the help of chiral ligands.

There are many advantages associated with the asymmetric transfer hydrogenation reaction. It is a cheaper, safer and the yield and enantiomeric excess are comparable to that obtained from gaseous hydrogenation. Extensive effort is given to this area in organic synthesis due to the low cost and favorable properties of the hydrogen donor as well as the operational simplicity.\textsuperscript{20b}

\textbf{1.4 Conclusion}

Asymmetric catalysis is a powerful tool in organic synthesis.\textsuperscript{33} Since its modest beginning in the 1960s, this field in organic chemistry has revolutionized the way synthetic organic chemists operate. Continuous effort is given to this area and many catalysts have been developed to improve the reactivity and enantioselectivity of the reaction to practical levels.

Lately, new catalysts are being used in transfer hydrogenation, which often result in similar yield and enantioselectivity without the danger associated with the high pressure in gaseous hydrogenation. Several catalysts have been reported to be efficient in the asymmetric transfer hydrogenation of carbonyls, imines, and activated olefins like conjugated carboxylic acid and amino acid derivatives. However, there has not been any example of asymmetric transfer hydrogenation of an allylic compound. In this thesis, the synthetic and mechanistic aspects asymmetric transfer hydrogenation of allylic alcohols with ruthenium catalysts will be presented.
CHAPTER 2: CHIRAL METHOD DEVELOPMENT

2.1 Introduction

At the early stage of this project, the enantiomeric purity was determined by derivatizing the reduced product (citronellol) with (S)-Mosher acid chloride, [S-(+)-methoxy-trifluoromethylphenylacetyl chloride], followed by chromatographic separation of the diastereomers. The diastereomers, S-Mosher-S-citronellol and S-Mosher-R-citronellol, were separated using a Daicel Chiralcel OJ HPLC column. This method was used at the beginning of the project but was considered expensive and unreliable due to the discrepancy obtained when coupled the racemic citronellol with the S-Mosher acid chloride; a 5 – 6 % diastereomeric excess (de) was obtained. Searching for a cheaper and more reliable chiral separation method became our first priority.

2.1.1 Background

Chirality is now a major theme in the discovery, development, and commercialization of new drugs. About half of drugs in use are chiral and about 25% of them are administered as pure enantiomers due to their chemical and pharmacological behavior.\(^{35}\) It is well know that in most cases the pharmacological activity is restricted to one of the enantiomers (eutomer) whereas the other enantiomer (distomer) has either no activity or can even be toxic (Table 2.1).\(^{36}\) For example, in the late 1960s thalidomide (Softenon\(^{®}\)) was found to be a seriously teratogenic for causing birth defects in more than 10,000 babies as it was prescribed for morning sickness to pregnant women.\(^{37}\) It was later

\(^{37}\) http://www.chem.yale.edu/-cheml25/125/thalidomide/thalidomide.html
discovered that these anomalies were due to a single enantiomer of this chiral molecule. Consequently, the separation of enantiomers has become a major field in pharmaceutical industries.

**Table 2.1: Differences in Pharmacodynamic Action.**

<table>
<thead>
<tr>
<th>Isomers Producing Different types of Toxicity</th>
<th>Chemical</th>
<th>Effect of (+)-isomer</th>
<th>Effect of (-)-isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Teratogenic</td>
<td>Nonteratogenic?</td>
<td></td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>Peripheral effect least potent</td>
<td>Most potent (ten-fold)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isomers Producing Different types of Therapeutic Effect</th>
<th>Chemical</th>
<th>Effect of (+)-isomer</th>
<th>Effect of (-)-isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxy-N-methylmorphinan</td>
<td>Analgesic</td>
<td>Antitussive</td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Local anaesthetic &amp; vasoconstrictor</td>
<td>Local anesthetic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>One Isomer Responsible for The Therapeutic Action, The Other Toxic</th>
<th>Chemical</th>
<th>Therapeutic effect</th>
<th>Toxic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>Analgesic/hypnotic ((+) -form)</td>
<td>CNS stimulation ((-) -form)</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>Reduction of intraocular pressure (RS-forms)</td>
<td>β-Andrenergic antagonism (S-form)</td>
<td></td>
</tr>
<tr>
<td>Dialkylphosphates</td>
<td>Pepticides in insects (no therapeutic benefit)</td>
<td>Inhibition of neurotoxic esterase leading to neurophaty ((-) -form)</td>
<td></td>
</tr>
</tbody>
</table>

It is worth noting that racemic thalidomide (Thalomid®) in combination with dexamethasone is now one of the best treatments in the market for multiple myeloma (bone marrow cancer). It is also used to treat and prevent the debilitating and disfiguring skin sores caused by erythema nodosum leprosum (ENL), an inflammatory complication.
of leprosy.\textsuperscript{38} Thalidomide is being sold as a chiral mixture because it racemizes in the body. Therefore, it passes the Food and Drug Administration (FDA) guidelines for the development and commercialization of chiral drugs.\textsuperscript{39} It is preferred that new drugs only contain the active enantiomer when it is demonstrated that it is not converted to the distomer \textit{in vivo} or during storage. For the registration procedure, the FDA requires a chiral method capable to qualify the distomer from the eutomer. As a result, more industries are dedicated to the separation of stereoisomers.

2.1.2 \textit{Major Types of Chiral Techniques}

There are many techniques for the analysis and separation of chiral molecules. Some non-chromatographic techniques include polarimetry and nuclear magnetic resonance (NMR) spectroscopy. The disadvantages of these techniques are the need of an enantiomerically pure reference sample and the enantiomers are not separated during the analysis. The most popular types of chiral techniques are gas chromatography (GC) and high performance liquid chromatography (HPLC). These techniques are preferred because pure enantiomers are not required and the separation of the enantiomers does take place.\textsuperscript{40} Furthermore, these chromatographic techniques can be used to prepare enantiomerically pure molecules.

\textsuperscript{38} http://www.thalomid.com/
\textsuperscript{39} http://www.fda.gov/cder/guidance/stereo.htm
2.1.3 Chiral HPLC as a Separation Technique

Chiral HPLC is one of the best and most widely used chiral separation techniques. The separation can be direct, which involves the use of a chiral stationary phase (CSP) or chiral mobile phase (CMP), or indirect, which involves derivatization of the enantiomers prior to analysis.\(^40\) The separation of enantiomers over the CSP is well understood. The enantiomer that forms the stronger association with the CSP will be the more strongly retained, thus, it will have a longer retention time \((t_R)\). The enantioselectivity \((a)\) of the chiral chromatography system is then expressed as the ratio of the retention factors of the two enantiomers (Eq. 2.1).\(^41\), \(^42\)

\[
\alpha = \frac{(t_R(R) - t_0)}{(t_R(S) - t_0)}
\]

where \(t_0 = \text{void time}\) and \(t_R = \text{retention time of the enantiomers } R \text{ and } S.\)

This ratio may sometimes be close to the value of the thermodynamic enantioselectivity of the association of the CSP with the enantiomers. On the other hand, the more polar mobile phase reduces the \(t_R\) of the enantiomer that forms the stronger association with the CSP. Therefore, the effective enantioselectivity of the chromatographic system will be proportional to the ratio of the enantioselectivity of the association processes in the stationary and mobile phases (Eq. 2.2).\(^41\), \(^42\)

There are many other factors that can affect the retention, resolution, and stereoselectivity of chiral compounds. Some of these factors include temperature, flow-

rate, mobile phase composition, and pH. For example, some enantiomers contain amino or hydroxy groups that might hydrogen bonds with the stationary phase; the pH of the mobile phase can increase the solvation of the enantiomers, thus, enhance the peak shape and \( t_R \). A similar effect can be obtained by increasing the temperature of the column, increasing the flow-rate, or increasing the polarity of the mobile phase. Although the pH and temperature have a great effect on the peak shape, they have a small effect on the \( t_R \). The flow-rate and the mobile phase composition have greater effects on the \( t_R \). Steric repulsion and the pH, ion strength and temperature of the mobile phase all affect the resolution of enantiomers.

Despite the great understanding of the chiral HPLC system, a successful chiral separation is often not predictable based on the CSP structures. Finding the right CSP for the separation of enantiomers can be very difficult. In most cases, the chiral separation is obtained by trying various CSPs. One can understand the interactions among the enantiomers, the CSP, and the mobile phase, but still has difficulty of obtaining a successful enantioseparation. The decision of choosing the right CSP relies mostly on empirical data or by using predictive empirical rules that have been developed based on empirical structures.

### 2.1.4 Chiral GC as a Separation Technique

Chiral GC is another efficient and reliable technique for the separation and quantitation of enantiomers and diastereomers. It is mainly used for volatile and thermally stable solutes. In general, the retention time (\( t_R \)) of the solute is determined by

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the solute’s boiling point; except where there are specific interactions with the stationary phase, which is the basis of chiral separation. Just as in the chiral HPLC, enantiomers can be separated by either direct or indirect methods in the GC. The indirect methods involve derivatization of the enantiomers to diastereomers using a homochiral reagent, followed by separation on an achiral GC column. The direct separation is the most desired method; the success relies on direct separation of the enantiomers using a chiral stationary phase (CSP). In this method, the enantiomers form rapid and reversible transient diastereomers with the CSP. It is a straightforward method and avoids all problems associated with the chiral derivatization process in the indirect method. Except for very polar compounds, such as alcohols, amines, and acids, no pre-column derivatization is required to separate enantiomers.

Based on the interaction with the enantiomers, the CSPs are divided in three major categories: 1) diamine and amino acid derivatives which form hydrogen bonds with the analytes; 2) chiral metal complexes which coordinate to the analytes; and 3) cyclodextrin (CD) derivatives which separate enantiomers by dipole-dipole interactions, or by forming an inclusion complex with the analytes. Among the three types of chiral selectors, the CD derivatives remain the most popular CSPs in enantioselective GC (Figure 2.1).\(^4\)

Figure 2.1: Application of Different GC Chiral Stationary Phases from 1/01 to 7/04.

Figure 2.1 summarizes a survey on publications discussing separation of enantiomers with various chiral capillary GC. From January 2001 to July 2004, the use of chiral metal stationary phases has dramatically diminished; the amino acid derivatives CSPs are limited to specific applications; but the CD derivatives account for nearly 90% of successful enantiomeric GC separations.

Chiral stationary phases based on CD derivatives remain popular in recent years due to their versatility. Their applications cover almost all the fields where other CSPs are applied. There are many types and sizes of CSPs based on CD derivatives. Depending on the cavity size and percentage of cyclodextrins (α, β, or γ), different enantiomeric selectivities are obtained. It is also believed that the type, the site, the percentage, and the degree of substitution on positions (2-, 3-, and 6-position of glucose unit of CD) of the

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substituents all influence the enantioselectivity of the CSP. Therefore, the synthesis of the CD derivatives must be carefully controlled and final structures must be fully characterized to avoid reproducibility problems.\textsuperscript{46} A list of CD derivatives and their recent applications are summarized in Table 2.2.\textsuperscript{44}

**Table 2.2:** Derivatized Cyclodextrins and their Recent Applications in Chiral GC.\textsuperscript{44}

<table>
<thead>
<tr>
<th>GC chiral selector</th>
<th>Coated or bonded</th>
<th>Trademark</th>
<th>Vendor</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexakis (2,6-di-O-pentyl-3-$O$-trifluoroacetyl)-$\alpha$-cyclodextrin</td>
<td>Coated</td>
<td>Chiraldex A-TA</td>
<td>ASTEC</td>
<td>Nitroalkenes</td>
</tr>
<tr>
<td>Hexakis (2,3,6-tri-$O$-pentyl)-$\alpha$-cyclodextrin</td>
<td>Coated</td>
<td>Lipodex A</td>
<td>Macherey-Nagel</td>
<td>$\alpha$-Ketoester hydrogenation</td>
</tr>
</tbody>
</table>

| Heptakis (2,3-di-
| O-methyl-6-O-tert-
| butyldimethylsilyl) | Coated | β-DEX325 Chiraldex B-
| | | -DM Cyclosil-B Hydromex
| | | β-6TBDM9 Rt-bDEXsm
| | | BGB-176 | SUPELCO ASTEC J&W Scientific Macherey-Nagel Restek BGB Analytik | Lactone thio, thiono, dithioderivatives Bicyclic γ-lactone γ-Butyrolactone derivatives β-Irones PCBs Diterpene Bicycloheptane α-HCHs CTTs Metolachlor Polychlorinated Bipyrrrole Sesquiterpenes Essential oils Monoterpenes Sulfoxides and sulfinate esters 1,2-O-isopropylidene-sn-glycerol Flavour Secondary alcohols Sex pheromone Positional isomers Pesticides Fragrances Methyl dihydromjasmonates |
| β-cyclodextrin | | | | | |
| Heptakis (2,3-di-
| O-ethyl-6-
| O-tert-
| butyldimethylsilyl) | Coated | Rt-βDEXse EtTBS-β-CD Restek MeGA | Monoterpene, Chiral alcohols 3-Hydroxy acids Positional isomers Essential oils |
| -β-cyclodextrin | | | | | |
| Heptakis (2,3-di-
| O-acetyl-6-O-tert-
<p>| butyldimethylsilyl) | Coated | β-DEX225 Rt-βDEXsa | SUPELCO Restek | Lactone thio, thiono, dithioderivatives β, γ-Lactones Monoterpenes Sex pheromones 3-Hydroxy acids Aroma |
| -β-cyclodextrin | | | | | |</p>
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<td>ASTEC</td>
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<td>Heptakis(2,6-di-O-nonyl-3-O-trifluoroacetyl)-β-CD</td>
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<td>Chira ldex BTA</td>
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<tr>
<td>Heptakis (2,6-di-O-pentyl-3-O-trifluoroacetyl)-β-cyclodextrin</td>
<td>Coated</td>
<td>Chira ldex BTA</td>
<td>Coated</td>
</tr>
<tr>
<td>Heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin</td>
<td>Coated</td>
<td>Varian/Chrom Pack</td>
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<td>Chiral acids</td>
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<td>Terpenes</td>
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<td>Mandelates and its analogs</td>
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<td>Odorants</td>
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<td>Sex pheromones</td>
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<td>Bonding</td>
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<tr>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin</td>
<td>Bonded</td>
</tr>
<tr>
<td>Heptakis (2,3,6-tri-O-tert-butylidimethylsilyl)-β-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Heptakis (2,3,6-tri-O-ethyl)-β-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>(S)-Hydroxypropyl derivatized)-β-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (bis-tertbutyldimethylsilyl)-γ-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (2,3-di-O-acetyl-6-O-tert-butylidimethylsilyl)-γ-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (2,6-di-O-methyl-3-O-pentyl)-γ-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (2,6-di-O-pentyl-3-O-trifluoroacetyl)-γ-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (2,6-di-O-propionyl)-γ-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (2,3,6-tri-O-ethyl)-(\gamma)-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Octakis (3-O-butanoyl-2,6-di-O-pentyl)-(\gamma)-cyclodextrin</td>
<td>Coated</td>
</tr>
<tr>
<td>Octakis (2,3-di-O-pentyl-6-O-methyl)-(\gamma)-cyclodextrin</td>
<td>Coated</td>
</tr>
</tbody>
</table>

As shown in Table 2.2 the CD derivatives CSPs are applied in the separation of a broad range of chiral molecules including essential oils, flavours and fragrances, alcoholic beverages, clinical chemistry, terpenoids, and pesticides. For example, volatile chiral sulfoxides, which are important bioactive compounds, are easily separated with heptakis(2,2-di-O-pentyl-3-trifluoroacetyl)-\(\gamma\)-cyclodextrin (DPTFA - GCD). Mandelate analogs, which are important intermediates in pharmaceutical chemistry, are separated on both heptakis(2,3,6-tri-O-methyl)-\(\beta\)-cyclodextrin (PMBCD) and heptakis(2,6-di-O-nonyl-3-O-trifluoroacetyl-\(\beta\)-cyclodextrin (DNTBCD). Both coated and bonded PMBCD phases are suitable for the separation of saturated chiral aliphatic hydrocarbons, geometrical isomers of furan derivatives, positional isomers of xylenes and...
dimethylnaphthalenes, aryl- and heteroarylcarbinol, and α-hydroxyl fatty acid esters.\textsuperscript{49}

The octakis(3-O-butanoyl-2,6-di-n-pentyl)-γ-cyclodextrin phase is extremely useful in the separation of chiral halogenomethanes and various chlorinated and fluorinated ethers (inhalation anesthetics).\textsuperscript{50} Therefore, CD based CSPs are classified as the most powerful tool in GC for separation on enantiomers.

\subsection*{2.1.5 NMR in Chiral Analysis}

Nuclear Resonance Magnetic (NMR) spectroscopy is one of the most important methods used to determined optical purity of different classes of compounds. Although it is easily accessible, the NMR does not differentiate enantiomers.\textsuperscript{51} Derivatization with a pure chiral auxiliary reagent to produce diastereomers must be performed prior to analysis. The chemical shifts of the diastereotopic nuclei will be different, which under the ideal condition results in baseline separation. Integration of the S and R diastereotopic nuclei leads directly to the estimation of enantiomeric purity.

One type of chiral auxiliary agent used in NMR is the chiral lanthanide shift reagents. The lanthanide forms diastereomeric complexes \textit{in situ} with the substrate enantiomers and may be used directly.\textsuperscript{52} There are many kinds of lanthanide shift

\begin{itemize}
\item \textsuperscript{52} Parker, D. Chem. Rev. 1991, 91, 1441.
\end{itemize}

54
reagents, the most common ones are shown in Table 2.3. Addition of lanthanide shift reagent to an organic compound results in the resolution and the chemical shift of the enantiomeric signals move to lower frequencies. The lanthanide forms a weak addition complex with a large variety of organic compounds (alkenes, arenes, allenes) that is in fast exchange with the unbound organic substrate. This fast exchange results in line broadening of the signals, which makes it often preferable to acquire spectra on a 100-MHz instrument rather than a 500-MHz instrument where line broadening is 25 times more severe.\textsuperscript{52} The line broadening represents a major disadvantage in this method. Even when special care is taken in the data acquisition (use of dry shift reagent, use of Gaussian line narrowing methods and base-line correction routines), the % error may be as high as 10% especially when the ee is >90%.

Nuclear magnetic resonance (NMR) spectroscopy is based on the net absorption of energy in the radiofrequency region of the electromagnetic spectrum by the nuclei of certain elements in a molecule. All nuclei are assigned a spin quantum number, $I$, on the basis of the number of protons and neutrons in the nucleus. The number of permitted orientations in space that can be adopted by a nucleus subjected to a magnetic field is given by $(2I + 1)$. For $I = 1/2$, two orientations or energy levels are possible. Therefore, nuclei with even numbers of both protons and neutrons, for example $^{12}$C, $^{16}$O, and $^{32}$S, have a spin quantum number of zero, no spin angular momentum, cannot give an NMR spectrum; where nuclei with a spin quantum number of $1/2$, including proton, carbon-13, phosphorus-31 and fluorine-19, will give an NMR spectrum.\textsuperscript{43} Any nucleus capable of giving an NMR spectrum can be used to identify the structure and optical purity of
organic compounds. However, because $^1$H and $^{13}$C are the most widely studied spectra, they remain the most popular tools for the determination of chiral purity.

**Table 2.3:** Common Chiral Lanthanide Shift Reagents.\(^5\)

<table>
<thead>
<tr>
<th>Structure of L in LnL(_3)</th>
<th>Lanthanon</th>
<th>Abreviation(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Europium (Eu)</td>
<td>Eu[pvc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Europium (Eu)</td>
<td>Eu[tfc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Praseodymium (Pr)</td>
<td>Pr[tfc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Ytterbium (Yb)</td>
<td>Yb[tfc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Europium (Eu)</td>
<td>Eu[hfc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Praseodymium (Pr)</td>
<td>Pr[hfc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Ytterbium (Yb)</td>
<td>Yb[hfc(_3)]</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>Eu</td>
<td>Eu[dcm(_3)]</td>
</tr>
</tbody>
</table>

\(^{a}\text{pvc} = \text{pivaloy-d-camphorato};\ \text{tfc} = \text{trifluorohydroxymethylene-d-camphorato};\ \text{hfc} = \text{heptafluorohydroxymethylene-d-camphorato};\ \text{dcm} = \text{dicamphoyl-d-methanato}.

Nuclei of a particular element that are in different environments generally experience slightly different applied magnetic field strengths due to the shielding and deshielding effects of nearby electrons. Consequently, their resonance frequencies vary and each frequency is defined by a characteristic chemical shift value. On the other hand,
the chemical shift of a particular element, whether chiral or achiral, remains unchanged in similar environment. After derivatization, the introduction of a second chiral center changes the environment of the first chiral center along with some neighboring (diastereotopic) elements in the same molecule. As a result, two different chemical shifts may be obtained for the diastereotopic nuclei. For example, Figure 2.2 and Figure 2.3 show the proton and carbon NMR spectra of N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methylene)-1-phenylethanamine, 22, (Scheme 2.1).\textsuperscript{51}

**Scheme 2.1:** Reaction of 1-phenylethylamine (21) with the Chiral Derivatizing Agent (CDA) (−)-myrtenal (20).

\[
\begin{align*}
\text{(CDA) (−)-myrtenal} \quad & \quad + \quad \text{1-phenylethylamine} \quad \rightarrow \quad \text{H}_2\text{O}
\end{align*}
\]

Three samples of 1-phenylethylamine 21 were prepared in three different ratio of R:S enantiomers as follows: (a) 50:50, (b) 33.4:66.6, and (c) 14.4:85.6. After derivatization with (1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-enc-2-carbaldehyde, commonly known as (CDA) (−)-myrtenal 20, the resulting diastereomers were analyzed by proton and carbon NMR. In the proton NMR (Figure 2.2), the spectral region of the imine proton (7.88 ppm) is shown and the diastereomeric ratios are found very close to the enantiomeric values: (a) 50.5:49.5, (b) 34.3:65.7, and (c) 15.7:84.3. In the carbon NMR (Figure 2.3), the spectral region of C3=N-C (159.0–161.7 ppm) and C=N-CI (67.8–70.5 ppm) are shown. The ratios are also found to be consistent with the expected values: (a) 50.3:49.7 for C3 and 49.5:50.5 for C1; (b) 34.5:65.5 for C3 and 34.3:65.7 for
C1; and (c) 15.1:84.9 for C3 and 15.8:84.2 for C1. Better baseline resolution occurs in the $^{13}$C experiments.

**Figure 2.2:** Proton NMR of N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methylene)-1-phenylethanamine (22).$^{51}$

![Proton NMR spectra](image)

**Figure 2.3:** Carbon NMR of N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methylene)-1-phenylethanamine (22).$^{51}$

![Carbon NMR spectra](image)

Nuclear magnetic resonance (NMR) spectrometry also has its disadvantages. Resolution of the diastereotopic protons is not always obtained. In the above example
with 1-phenylethylamine, complete baseline separation was not achieved in the proton NMR (Figure 2.2); integration and determination of the R:S ratio was possible by using automated deconvolution and integration. Other examples in the same study resulted in complete overlap of the diastereotopic protons; $^{13}$C NMR was used in those cases, yet the difference in the expected ratios was as high as 6% in some cases. These errors are not only due to poor resolution of the diastereotopic peaks; impurities in the chiral resolving agent combined with different reactivity of the enantiomers contribute to the discrepancy.

2.2 Results and Discussions

2.2.1 Derivatization with Mosher Acid Chloride and Diastereomeric Excess Determination by HPLC

2.2.1.1 Introduction

Mosher acid ($\alpha$-methoxytrifluorophenylacetic acid) was first used by Harry S. Mosher as a chiral derivatizing agent in the late 1960s.$^{53}$ The chiral reagent reacts with alcohols or amines of unknown stereochemistries to form esters and amides. The absolute configuration of the ester or amide is then determined by proton NMR spectroscopy.$^{54}$ To increase the reactivity of the Mosher acid, it is often converted to the acid chloride prior to the coupling reactions.$^{55}$

One of the most popular methods used to determine the enantiomeric purity of citronellol is by derivatizing it with the (R) or (S)-Mosher acid chloride. In our case, the (R)-Mosher acid chloride was used (Scheme 2.2). The R-citronellyl-R-Mosher ester and

the S-citronellyl-R-Mosher ester are diastereomers, thus could be separated with an achiral column. However, attempts to separate these diastereomers using C18 columns were unsuccessful. We found that they could be separated using a chiral HPLC column.

**Scheme 2.2: Derivatization of Citronellol with R-Mosher Acid Chloride.**

![Scheme 2.2: Derivatization of Citronellol with R-Mosher Acid Chloride.](image)

2.2.1.2 Results and Discussion

Figure 2.4 shows the chromatogram of the citronellyl-Mosher esters. This particular example is from the reaction of a mixture of 41:59 R:S citronellol. After derivatization with R-Mosher acid chloride (3 equiv), a ratio of 43.1:56.9 of RR:RS diastereomers was obtained at 210 nm and 42.5:57.5 of RR:RS was obtained at 220 nm with a range of 3.7 to 4.8% difference from the expected ratio. This percent difference was even larger (6%)\(^56\) when 1.5 equiv of Mosher acid chloride was used in the derivatization reaction.


\(^{56}\) Laquidara, J. M. Ph. D. Dissertation, Department of Chemistry and Biochemistry, Seton Hall University, South Orange, NJ, 2003.
Although satisfactory baseline separation was obtained from the Diacel Chiracel OJ-H HPLC column, finding a better chiral method was still needed. The 5% to 6% difference was too high for our purpose since we were expected citronellol as high as 98% ee from the transfer hydrogenation reaction. In addition, to reduce the discrepancy in the reactivity of the R and S enantiomeris of citronellol, a large excess (about ten equiv) of the pure (>99% ee) Mosher acid chloride would have to be used. That would require about 556 mg of the Mosher acid chloride for each reaction of 35 mg of citronellol. The cost of the Mosher acid chloride from Aldrich is $292/500 mg. Therefore each derivatization would cost over $324 for a more accurate result; or a minimum of $49 if only 1.5 equiv of the Mosher acid chloride is used, which gives a 6% difference.
toluene, resulted in the decomposition of the starting material; the product was never obtained. Our initial work with oxalyl chloride in refluxed methylene chloride were also unsuccessful. Maybe higher temperatures were damaging to the reaction. So we decided to conduct the reaction at room temperature following Nagasawa's procedure with neat oxalyl chloride.\textsuperscript{58a} The problem with this procedure is that the product was obtained as a slurry; filtration of the slurry gave a yellow solid in very low yield. Using Wang's isolation procedure (see Section 2.2.2.3 below),\textsuperscript{58b} (S)-Naproxen acid chloride was obtained as a white needle-shaped crystals in 88\% yield. Subsequent treatment with citronellol gave the diastereomeric esters, which were analyzed by NMR.

**Scheme 2.3: Derivatization of Citronellol with S-Naproxen.**

\[\text{Scheme 2.3: Derivatization of Citronellol with S-Naproxen.}\]

\[
\begin{align*}
(S)-\text{Naproxen} & \quad \overset{\text{C},\text{O}}{\text{C}} \quad \text{neat rt} \quad \overset{\text{H}_3\text{C}}{\text{C}} \\
\text{23} & \quad \overset{\text{Et}_3\text{N} \ 3 \text{ eq}}{\text{Et}_3\text{N} \ 3 \text{ eq}} \quad \overset{\text{DMAP} \ 0.1 \text{ eq}}{\text{DMAP} \ 0.1 \text{ eq}} \quad \overset{\text{CH}_2\text{C}_2}{\text{CH}_2\text{C}_2} \quad \overset{\text{reflux}}{\text{reflux}} \\
& \quad \overset{\text{Step 2}}{\text{Step 2}} \\
& \quad \overset{\text{Step 1}}{\text{Step 1}} \\
& \quad \overset{\text{28}}{\text{28}} \\
& \quad \overset{\text{29}}{\text{29}}
\end{align*}
\]

2.2.2.2 Results and Discussion

Four different samples of citronellol were prepared in the following ratios of R:S enantiomers: (a) Aldrich racemic citronellol assumed to be 50:50, (b) 36.28:63.72, (c)
All four samples were converted to the (S)-Naproxen ester and the resulting diastereomers were analyzed by $^{13}\text{C}$ NMR (Table 2.4). The proton NMR was not utilized because the (S)-Naproxen citronellyl ester diastereomers completely overlap giving one set of signals. The carbon NMR mostly overlaps; but, four carbons gave partial to complete separation with the best separation occurring for C3 of the citronellyl chain, at 29.66 (R) to 29.7 (S) ppm (Figure 2.5).

**Table 2.4:** Comparison of Standard Citronellol Samples (a, b, c and d) with the (S)-Naproxen Esters Results from $^{13}\text{C}$ NMR.

<table>
<thead>
<tr>
<th>Samples</th>
<th>% (R)-Citronellol prepared</th>
<th>$^{13}\text{C}$ NMR of (R)-citronellyl-(S)-Naproxen</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>50</td>
<td>49.58</td>
<td>0.42</td>
</tr>
<tr>
<td>B</td>
<td>36.28</td>
<td>32.22</td>
<td>4.06</td>
</tr>
<tr>
<td>C</td>
<td>14</td>
<td>6.14</td>
<td>7.86</td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Integration of the two diastereomeric peaks of C3 in 29 is summarized in Table 2.4 and Figure 2.6. The $^{13}\text{C}$ NMR integration of C3 of the (S)-Naproxen citronellyl ester gave the following R:S ratios: (a) 49.58:50.42, (b) 32.22:67.78, (c) 6.14:93.86, and (d) was difficult to integrate. The NMR result for sample (a) was in agreement with the standard racemic citronellol, but the % difference for sample (b) was 4.06% and 7.86% for sample (c). It was difficult to integrate sample (d) because there wasn’t any baseline separation; the (R) signal was too small. These results indicate that the derivatization method with (S)-Naproxen followed by $^{13}\text{C}$ NMR analysis is useful to determine up to
36:64 R:S citronellol ratio. Any larger ratio would result in a % difference greater than 4%.

**Figure 2.5:** $^{13}$C NMR Segment of Sample (b) [(S)-Naproxen Citronellyl Ester].

**Figure 2.6:** Comparison of Standard Citronellol Samples (a, b, c and d) with their (S)-Naproxen Esters Results from $^{13}$C NMR.
This behavior was previously investigated in our group in the reaction of S-Naproxen acid with sec-phenylethanol.\textsuperscript{59} It was found that S-sec-phenylethanol reacts 4.5 times faster than R-sec-phenylethanol with S-Naproxen. Therefore, incomplete reaction during derivatization leads to residual unreacted alcohol (R-sec-phenylethanol), which results in further discrepancy of the diastereomeric purity. It was then concluded that the optimum amount of the resolving agent needed was ten equivalents.

### 2.2.2.3 Conclusions

Although S-Naproxen is about 100 times cheaper than the Mosher acid chloride, it didn't meet our needs. Our NMR results show large discrepancies between the standard citronellol enantiomers and the S-Naproxen diastereomers. The higher the enantiomeric excess, the greater the discrepancy. In addition, it was difficult to obtain a signal for the minor diastereomer when the ee was >95%. In the future, however, it may be possible to obtain better results if we follow improvements suggested by Li Li\textsuperscript{59} and use more concentrated samples and long acquisition times to increase the $^{13}$C NMR sensitivity. However, this method was rejected and the desire to find a better and cheaper chiral separation method was still present. We wanted to find a method capable of determining enantiomeric excess greater than 95% ee with less than 5% difference.

\textsuperscript{59} Li, L. Ph. D. Dissertation, Department of Chemistry and Biochemistry, Seton Hall University, South
2.2.3 Direct Separation on Chiral GC Column

2.2.3.1 Introduction

Direct chromatographic separation of enantiomers is the most desirable method by most analytical chemists. In most cases the method is faster and more reliable than performing a derivatization. As mentioned above, derivation of citronellol with Mosher acid chloride and Naproxen results in various levels of error and were not reliable at high enantiomeric excess. Therefore, it was decided to determine the ee of the crude citronellol using a chiral GC column without derivatization.

2.2.3.2 Results and Discussion

To validate the chiral GC method, five standards of citronellol were analyzed. Three samples were prepared and the racemic and enantiomerically pure S-citronellol from Aldrich were also analyzed which gave a total of five standards in the following ratios of R:S enantiomers: (A) racemic citronellol assumed to be 50:50, (B) 5.46:94.54, (C) 3.48:96.52, (D) 2.43:97.57, and (E) S-citronellol (sold as >98% ee) 1:99 (Table 2.5).

All samples were prepared in three different concentrations in methanol (0.01 M, 0.02 M and 0.1 M) and the % ee reported is the average of three data points. These concentrations were selected based on our reaction concentration (0.01 to 0.1 M), but, excellent baseline separation can be obtained for racemic citronellol at 1 M concentration (Figure 2.8). The chiral GC results for the standard citronellol samples (A, B, C, D and E) are summarized in Table 2.5 and a schematic representation of these results is shown in Figure 2.7.
Table 2.5: Comparison of Standard Citronellol samples (A, B, C, D and E) with the Chiral GC Results.

<table>
<thead>
<tr>
<th>Sample #</th>
<th>% S</th>
<th>% R</th>
<th>Cal. % ee (S)</th>
<th>Found % ee (S)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-citronellol</td>
<td>~ 50</td>
<td>~ 50</td>
<td>0</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>B</td>
<td>94.54</td>
<td>5.46</td>
<td>89.08</td>
<td>89.00</td>
<td>-0.08</td>
</tr>
<tr>
<td>C</td>
<td>96.52</td>
<td>3.48</td>
<td>93.04</td>
<td>93.14</td>
<td>0.1</td>
</tr>
<tr>
<td>D</td>
<td>97.57</td>
<td>2.43</td>
<td>95.14</td>
<td>95.59</td>
<td>0.45</td>
</tr>
<tr>
<td>S-citronellol</td>
<td>~ 99</td>
<td>~ 1</td>
<td>&gt; 98</td>
<td>97.91</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

Figure 2.7: Comparison of Standard Citronellol Samples (A, B, C, D and E) with the Chiral GC Results.

The ee found for the racemic citronellol is very close to the expected value, giving a difference of less than 0.1%. The S-citronellol from Aldrich has an optical purity of
≥98%. Our chiral GC method revealed 97.91% (S), with a difference of -0.09%. Sample B was found to have a difference of 0.08% and sample C 0.1%. The largest % difference was obtained from sample D, which was 0.45%. In summary, the ee found for all the purchased and prepared standards using our chiral GC method were very close to the expected values. In addition, the cost of a RT-BetaDEXsa column is less than $700. However, it is recommended to use proper care to extend the life of this column. For a short-term standby mode, it is suggested to leave the column in the GC with the carrier gas flow on at an oven temperature of 100 - 150 °C. For long-term storage, it is recommended to remove the column from the GC and store away from strong light.60

Figure 2.8: Chiral GC of 1 M Citronellol in Methanol. Chromatographic conditions: RT-BetaDEXsa column, 30 m x 0.32 mm ID x 0.25 mm; inlet, split mode (50:1), 150 °C; column, isothermal 80 °C, He flow 30 mL/min, 15 psi, 120 min; detector 150 °C; 10 µl injection.

60 http://www.restek.com/
2.3 Conclusions

Three chiral methods were tested in the separation of R and S enantiomers of citronellol. Our validation studies reveal that direct separation using a chiral GC column was the most reliable method. The RT-BetaDEXsa GC column gives baseline separation for citronellol of ≥98% ee with less than 0.5% error. This method is faster, cheaper and more reliable than doing derivatization with either Mosher acid chloride or S-Naproxen.

Derivatization with the Mosher acid chloride gave a moderate HPLC baseline separation for the diastereomers with a 5 – 6% difference when using racemic citronellol. We did not investigate how this percent error would change at higher R:S or S:R ratios of citronellol. However, this method was abandoned due to the high cost of the Mosher acid chloride, $292/500 mg.

S-Naproxen is a cheaper derivatizing agent; it is nearly 100 times cheaper than the Mosher acid chloride. The $^{13}$C NMR of the diastereomers of the racemic citronellol gave good baseline separation with a 0.42% difference. However, this error got larger at higher R:S citronellol ratios. A 7.86% difference was obtained from a 14:86 R:S citronellol mixture and this method failed to give any result for a 6:94 R:S citronellol mixture.

As shown above, the chiral GC method gave excellent baseline separation for citronellol of ≥98% ee with a difference of 0.09%. The largest difference obtained with this method was 0.45%, which may be related to some measurement errors. The errors associated with unreacted citronellol or with different rates of reaction of the chiral auxiliary during derivatization were no longer a problem. This method is direct, fast and reliable. So it was decided to determine the enantiomeric excess of our reaction mixtures by chiral GC.
CHAPTER 3: ASYMMETRIC TRANSFER HYDROGENATION OF ALLYLIC ALCOHOLS

3.1 Introduction

Asymmetric transfer hydrogenation (ATH) is an alternate process of performing asymmetric hydrogenation of prochiral substrates in high yield and enantioselectivity without the danger associated with hydrogen gas. Most ATH reactions are conducted in the presence of IPA or formic acid/triethyl amine mixtures as hydrogen donors, which eliminates the need for a pressure vessel. ATH is a safer, cheaper and an operationally simpler process. There have been many examples of transfer hydrogenation reactions in the literature. The reduction of ketones, aldehydes and imines are among the most common examples\textsuperscript{20a, 25, 28, 31, 32, 61} and the reduction of \(\alpha,\beta\)-unsaturated acids are less common.\textsuperscript{20a, 62} Furthermore, there have been examples of transfer hydrogenation of allylic alcohols.\textsuperscript{63} However, those examples resulted in no enantioselectivity.

Ruthenium catalyzed asymmetric transfer hydrogenation (ATH) of allylic alcohols is a novel reaction. The reaction was discovered in our research group by Joseph Laquidara while he was doing his Ph.D. with Prof. John R. Sowa. While attempting to isomerize geraniol to \(\gamma\)-geraniol with the [RuCl\(_2\)((S)-(\cdot)-\text{tolBINAP})]_2\text{N}(\text{C}_2\text{H}_5)_3\) catalyst, instead of obtaining \(\gamma\)-geraniol, citronellol was obtained in 27\% yield and 50\% ee. To our knowledge, this is the first example of asymmetric transfer reduction of an allylic alcohol.

3.1.1 Project origin

There has been some interest in our group to isomerize geraniol to $\gamma$-geraniol and the thermodynamic concentration of geraniol to $\gamma$-geraniol under various conditions has been investigated. For example, geraniol was converted to $\gamma$-geraniol in 18% yield using catalytic amount of $[\text{RuCl}_2((S)-(\cdot)-(\cdot)-\text{tolBINAP})]_2\text{N}((\text{C}_2\text{H}_5)_3$ in MeOH at room temperature. At 45 °C, the amount of geraniol increased to 22%. However, as discussed above, in a neat reaction at 140 °C, the reduced product, citronellol, was obtained in 27% yield and 50% ee (R) (Scheme 3.1).

**Scheme 3.1:** First Example of Ruthenium Catalyzed Asymmetric Transfer Hydrogenation (ATH) of an Allylic Alcohol.

Soon after this initial result, extensive effort was put into the optimization of this reaction. Based on previous literature references, it was decided to use isopropanol as hydrogen donor and potassium hydroxide as base in the reaction. The focus of the optimization work was to find a good ruthenium/ligand catalyst system, as well as, the
optimum temperature, which could result in higher yields and ee's. Table 3.1 summarizes the results of some of the ligands screened in this reaction. Using 0.01 M geraniol in isopropanol and a substrate/[Ru(COD)Cl2]/KOH/ligand molar ratio of 10/1/2.1/2, it was demonstrated that (S)-tolBINAP (A, Figure 3.1) gave the best yield (95%) and enantiomeric excess (90% ee) (entry 5, Table 3.1).

Table 3.1: Evaluation of Various Ligands in the ATH of Geraniol.

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

a0.01 M solution in IPA, (geraniol/[Ru(COD)Cl2]2/KOH/ligand molar ratio = 10/1/2.1/2).
bGC yields measured on a DB-5 column (J&W Scientific, 15 m x 0.32 mm). cee analysis measured on the (R) Mosher ester on a Chiralcel OJ-H column (Daicel, 250 mm x 4.6 mm). d78% isolated yield by column chromatography. e98 % dihydrocitronellol formed, (geraniol/[Ru(COD)Cl2]2/KOH/ligand molar ratio = 2/1/2.1/2).

The reaction with (S,S)-iPrDUPHOS (B, Figure 3.1) went to 100% conversion but without regioselectivity (entries 7 and 8, Table 3.1). This ligand resulted in the reduction of the second double bond of geraniol to give dihydrocitronellol (3,7-dimethyl-octan-1-
However, this result suggests that this ligand produces a more powerful catalyst which is able to reduce functionalized and unfunctionalized alkene groups.

**Figure 3.1:** Ligands Used in Table 3.1 and Table 3.2.

Several substrates (Figure 3.2) were evaluated in this reaction using two of the most reactive ligands, S-tolBINAP and (S,S)-iPrDUPHOS (Table 3.2). It has been demonstrated that the allylic bond of several allylic alcohols (geraniol, nerol, 3-phenyl-2-buten-1-ol) can be converted to their saturated alcohols in excellent yields (95 – 99 %) and moderate to good ee (72 – 93 %) with S-tolBINAP. Lower yields were obtained for geraniol and nerol with iPr-DUPHOS, but this catalyst was proven to be the best for 3-phenyl-2-buten-1-ol, giving 99% yield and 93% ee. An α,β-unsaturated carboxylic acid, was also converted to the reduced product in excellent yield, but in low enantioselectivity with both ligands. The reaction with 3-methylcyclohex-2-enone resulted in double
reduction of the olefinic and the carbonyl groups in high yield with both ligands (97 – 98 % yield), but the diastereoselectivity was significantly lower (4:1, cis:trans) compared to what was obtained from gaseous hydrogenation (1:3000 cis:trans). Lastly, the reduction of the double bond in trans-methylstilbene resulted in low conversion, only 18% in 24 h (entry 11, Table 3.2).

Table 3.2: Transfer Hydrogenation with Ru/tolBINAP (A) and Ru/iPrDUPHOS (B).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Ligand</th>
<th>Time (h) (% Conv)</th>
<th>% Product (%) ee, config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>geraniol</td>
<td>A</td>
<td>2 (100)</td>
<td>95 (90, R)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>B</td>
<td>2 (100)</td>
<td>50 (80-84, R)</td>
</tr>
<tr>
<td>3</td>
<td>nerol</td>
<td>A</td>
<td>2 (100)</td>
<td>96 (93, S)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>B</td>
<td>24 (100)</td>
<td>62 (83 R)</td>
</tr>
<tr>
<td>5</td>
<td>3-phenyl-2-buten-1-ol</td>
<td>A</td>
<td>12 (100)</td>
<td>99 (72, S)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>B</td>
<td>2 (100)</td>
<td>99 (93, R)</td>
</tr>
<tr>
<td>7</td>
<td>3-phenylbut-2-enoic acid</td>
<td>A</td>
<td>96 (98)</td>
<td>93 (12, R)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>B</td>
<td>2 (100)</td>
<td>96 (9, R)</td>
</tr>
<tr>
<td>9</td>
<td>3-methylcyclohex-2-enone</td>
<td>A</td>
<td>48 (97)</td>
<td>23 cis (17, S,R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 trans, (16, R,R)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>B</td>
<td>1 (98)</td>
<td>34 cis (8, S,R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9 trans (14, R,R)</td>
</tr>
<tr>
<td>11</td>
<td>trans-methylstilbene</td>
<td>B</td>
<td>24 (18)</td>
<td>18 (0)</td>
</tr>
</tbody>
</table>

a0.01 M solution in IPA, [substrate/[Ru(COD)Cl₂]₆/KOH/ligand molar ratio = 10/1/2/1/2]. bGC yields measured with a DB-5 column (J&W Scientific, 15m x 0.32mm). cee analysis of entries 1-4 measured on the (R) Mosher ester on an OJ-H column; ee analysis of entry 5 and 6 measured on the acetate on an OJ-H column; ee analysis of entries 7, 8 and 11 measured directly on an OJ-H column; ee analysis of entries 9 and 10 measured on the (R) Mosher ester where the ee of the cis isomer was measured by GC analysis on a DB-23 column (J&W Scientific, 15m x 0.32mm) and the ee of the trans isomer was measured by proton decoupled ¹³C NMR. d2.5 equiv. of KOH per substrate was used.
Figure 3.2: Substrates Used in Table 3.2.\textsuperscript{56}

It is worth noting that the configuration of the products obtained from nerol and geraniol were consistent with the gaseous hydrogenation; but the result for 3-methylcyclohex-2-enone, which gave a very low stereoselectivity, clearly indicated that our system was different. Therefore, it was imperative to understand the mechanism of our system.

3.1.2 Project Goals

The main objective of this project was to understand the mechanism of this interesting and potentially useful ruthenium/BINAP asymmetric transfer hydrogenation (ATH) reaction. To meet this objective, the effects of various hydrogen donors, including cyclic and chiral alcohols, at different concentrations and temperatures have been studied. The asymmetric transfer hydrogenation of a homoallylic alcohol, $\gamma$-geraniol, has been
conducted and compared to the result of the gaseous hydrogenation reaction. The effects of a commercial catalyst, [(S)-BINAP]Ru(II)Cl₂, which may have a similar structure to our in situ-prepared catalyst⁶⁴, has been investigated. In addition, we have studied the isomerization of geraniol in the absence of a hydrogen donor and with a deuterated donor.

3.2 Results and Discussion

3.2.1 Asymmetric Transfer Hydrogenation with Mixed Solvents

Using the optimized conditions with 0.01 M geraniol with a substrate/[Ru(COD)Cl₂]/KOH/(S)-tolBINAP molar ratio of 10/1/2/2, several solvents were screened for effectiveness in the ATH reaction. Since the purpose of the isopropyl alcohol (IPA) is to transfer hydrogen in the reaction, we wanted to investigate the effects of different solvents while using IPA as a reagent. Thus, we added >100 equiv of IPA to serve as the reductant.

As shown in Table 3.3, the reactions in dimethylformamide (DMF), tert-butanol and toluene (entries 2 - 4) resulted in 85 to >99 % conversion. However, the downside of these reactions is that they all resulted in lower ee and the conversions were very slow. These results clearly indicate that the large excess, such as complete use of the IPA as a solvent, is needed for faster conversion and higher ee.

There seems to be a direct relation between the rate of conversion and the enantioselectivity. Although a large excess IPA (112 equiv) is being used in these reactions, the conversion of geraniol to citronellol in the mixed solvents media is very

---

slow. In some cases, for example in 1,2-dimethoxyethane (entry 6, Table 3.3), the reaction went to only 2% conversion.

**Table 3.3: Transfer Hydrogenation with Ru/tolBINAP in Mixed Solvents.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>% Conv.</th>
<th>% ee&lt;sup&gt;b&lt;/sup&gt; (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPA</td>
<td>2</td>
<td>100</td>
<td>97&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>61</td>
<td>89</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOH</td>
<td>39</td>
<td>85</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>94</td>
<td>&gt;99</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>DCM&lt;sup&gt;*&lt;/sup&gt;</td>
<td>116</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>1,2-Dimethoxyethane</td>
<td>117</td>
<td>&lt;2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Reaction performed at 40 °C.

<sup>*</sup>GC conversions measured with a HP-5 column (J&W Scientific, 15 m x 0.32 mm).

<sup>#</sup>ee measured on RT-BetaDEXsa GC column, 30 m x 0.32 mm ID x 0.25 mm.

<sup>b</sup>ee measured by derivatization with Mosher acid chloride.

The amount of IPA in the reaction may be important in the conversion rate. However, since the conversion is different with different solvents, there might be a solubility issue or a solvent interaction with the catalyst system. If any of the reagents, KOH, (S)-tolBINAP, or [Ru(COD)Cl<sub>2</sub>]<sub>n</sub>, have low solubility in the solvent, that will
result in slower conversion. In addition, if the solvents have greater affinity for the catalyst than IPA, that may result in less reactive sites for the reaction to occur, thus slower conversion.

Why would a slower reaction rate affect the enantioselectivity? It is well known that transfer hydrogenation with IPA is a reversible process.\textsuperscript{20a} At low IPA concentrations, the enol intermediate (f) in our proposed mechanism (Scheme 3.12) may go back to the allylic intermediate (b). Depending on the conformation of the reversibly formed allylic intermediate (\textit{cis} or \textit{trans}), the (S) or the (R) product may be obtained. This point will be further clarified when the proposed mechanism is discussed in Section 3.2.8.

We've already demonstrated that asymmetric transfer hydrogenation of geraniol (trans) and nerol (cis) with (S)-"tolBINAP gives opposite configurations of citronellol (Table 3.2, entries 1 and 4). Similarly, transfer hydrogenation of the cis and trans isomers of the reversibly formed allylic intermediate (b in Scheme 3.12) gives both (S) and (R) citronellol, which results in lower ee. Therefore, slow reactions give lower ee's.

The reaction didn't go in methylene chloride (entry 5, Table 3.3), however, this is likely due to the lower temperature used, 40 °C. In 1,2-dimethoxyethane (entry 6, Table 3.3), the reaction went to only 2% conversion after 117 hours at 100 °C. This is an example of a solvent that has strong affinity for the catalyst. The oxygens in the 1,2-dimethoxyethane may chelate the ruthenium center to give the inactive catalyst II below.

A similar diamine catalyst to II, Ru-(S)-"XylBINAP-DAIPEN (I), has been reported to be very active in the reduction of carbonyl groups under gaseous and transfer hydrogenation conditions.\textsuperscript{7,15} The nitrogen groups in the diamine catalyst are believe to take part in the hydrogenation process (metal-ligand bifunctional mechanism Figure 1.9). This
mechanism doesn’t involve coordination of the substrate to the metal center. The hydrogenation is believed to take place via a six-membered ring transition state intermediate (Figure 1.9). If II is generated with 1,2-dimethoxyethane, it may not be able to catalyze the isomerization step of the allylic alcohol to the carbonyl prior to transfer hydrogenation, which we are proposing as the mechanistic route of our ATH reaction (Section 3.2.8). The isomerization step requires coordination of the substrate to the metal center.

\[ \text{Ru-(S)-XylBINAP-DAIPEN (I) Active} \]

\[ \text{Ru-(I) inactive} \]

3.2.2 Asymmetric Transfer Hydrogenation with a Cyclic Alcohol Donor

Another study we wanted to conduct was the effect of a cyclic hydrogen donor in our system. Cyclohexanol was selected because of its high melting point of 20 - 22 °C. Its use in our reaction as a hydrogen donor would eliminate the cryogenic conditions needed to freeze IPA (m. p. = -89.5 °C) during the degassing process. The required freeze-pump-thaw could easily be done in an ice-water bath instead of the liquid nitrogen bath used for IPA.
Table 3.4: Transfer Hydrogenation with Ru/(S)-tolBINAP in Cyclohexanol.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>% Conv.</th>
<th>% ee&lt;sup&gt;b&lt;/sup&gt; (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>2</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>2 - 43</td>
<td>4 - 38</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>67</td>
<td>72 - 74</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>160</td>
<td>4</td>
<td>92</td>
<td>66</td>
</tr>
<tr>
<td>5*</td>
<td>160</td>
<td>4</td>
<td>100</td>
<td>26</td>
</tr>
<tr>
<td>6*</td>
<td>160</td>
<td>4</td>
<td>100</td>
<td>24</td>
</tr>
<tr>
<td>7*,*</td>
<td>160</td>
<td>8</td>
<td>100</td>
<td>11</td>
</tr>
</tbody>
</table>

<sup>®</sup> 10 mM concentration. <sup>*</sup> 20 mM concentration. <sup>#</sup> 100 mM concentration.<br><sup>®</sup> Deuterated cyclohexanol.<br><sup>®</sup> GC conversions measured with a HP-5 column (J&W Scientific, 15 m x 0.32 mm).<br><sup>®</sup> ee measured on RT-BetaDEXsa GC column, 30 m x 0.32 mm ID x 0.25 mm.

Using our best conditions (substrate/[Ru(COD)Cl₂]ₙ/KOH/(S)-tolBINAP molar ratio = 10/1/2/2), we conducted the reactions in 0.01 M geraniol in cyclohexanol. The results are summarized in Table 3.4. To have a direct comparison with IPA, the first reaction was set at 100 °C for two hours (entry 2). This reaction went to only 4% conversion and the ee wasn’t determined.
To increase the conversion, we decided to increase the temperature of the reaction. At 160 °C (entry 4), the reaction went to 92% conversion in 4 hours and the ee was 66%. At a higher concentration, 0.02 M (entry 5), the reaction went to 100% conversion in 4 hours, but the ee dropped to 26%. This is a very clear example that higher concentration results in lower ee. However, this trend doesn’t seem to continue beyond 0.02 M concentration. At 0.1 M concentration, the ee remained at 24% (entry 6). Entry 7 shows the reaction with $d_{12}$-cyclohexanol at 0.1 M concentration which was conducted in an 8 hour reaction time. This reaction results in lower ee (11%) than the non-deuterated reaction at the same concentration (entry 6). This might be the result of the difference of reaction time or subtle differences in cyclohexanol versus $d_{12}$-cyclohexanol.

3.2.3 The Effects of Chiral Alcohol in Asymmetric Transfer Hydrogenation

The use of chiral solvents in asymmetric synthesis is well known.65 For example Vo-Thanh reported a Baylis-Hillman reaction of benzaldehyde and methyl acrylate in the presence of a chiral ionic liquid to give the alkoxyester in 44% ee (Scheme 3.2).66 The chirality of the product came from the ionic liquid solvent, which was the only source of chirality in the reaction. Likewise, we wanted to investigate the effect of a chiral solvent in the enantioselectivity of our ATH reaction.

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To conduct this study, we selected 2-pentanol, which was used as solvent as well as hydrogen donor in the reaction. The solvent 2-pentanol was selected to conduct this study because of the following reasons: first, the (S) and (R) enantiomers are commercially available; second, it is the closest secondary alcohol to IPA that has a higher melting point (-50 °C) than IPA (-89.5 °C), 2-butanol has a melting point of -115 °C. The use of 2-pentanol allowed the freeze-pump-thaw process in dry ice/acetone bath (-78 °C) instead of the liquid nitrogen bath used for IPA.

Using 2-pentanol, we ran the reactions at 0.01 M concentration of geraniol and a substrate/[Ru(COD)Cl]_2/KOH/(S)-tolBINAP molar ratio of 10/1/2/2. The results are summarized in Table 3.5. The reaction in racemic 2-pentanol went to 84% conversion and 79% ee at 100 °C in 2 hours (entry 1, Table 3.5). At 120 °C, the reaction with racemic 2-pentanol went to 98 - 100 % conversion and 77% ee in 4 hours (entry 2, Table 3.5). This ee result was promising as it suggested that there could be improvement if a pure chiral 2-pentanol was used.
Table 3.5: Asymmetric Transfer Hydrogenation with Chiral Solvents.

![Chemical structure of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>% Conv.</th>
<th>ee&lt;sub&gt;b&lt;/sub&gt; (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-pentanol</td>
<td>100</td>
<td>2</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>2-pentanol</td>
<td>120</td>
<td>4</td>
<td>98-100</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>(S)-2-pentanol</td>
<td>120</td>
<td>2</td>
<td>86</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>(S)-2-pentanol</td>
<td>120</td>
<td>4</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>(R)-2-pentanol</td>
<td>120</td>
<td>2</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>(R)-2-pentanol</td>
<td>120</td>
<td>4</td>
<td>100</td>
<td>26</td>
</tr>
</tbody>
</table>

<sup>a</sup>GC conversions measured with a HP-5 column (J&W Scientific, 15 m x 0.32 mm).

<sup>b</sup>ee analysis measured with a GC Column RT-BetaDEXsa 30 m x 0.32 mm ID x 0.25 mm.

The reaction with (S)-2-pentanol gave 86 – 100 % conversion and 69 - 72 % ee in 2 - 4 hours at 120 °C (entries 3 and 4, Table 3.5). The reaction with (R)-2-pentanol was slower and resulted in only 50% conversion and 2% ee after 2 hours (entry 5, Table 3.5) compared to the 86% conversion obtained with (S)-2-pentanol. This reaction went to 100% conversion and 26% ee in 4 hours under the same conditions (entry 6, Table 3.5). These results indicate a striking difference in the selectivity of (S)-2-pentanol versus (R)-2-pentanol with the Ru/(S)-tolBINAP catalyst system as (S)-2-pentanol is a better match. Although we were hoping that the ee would increase with a properly matched chiral
solvent, we found that racemic 2-pentanol is as efficient as the (S)-2-pentanol, therefore there is no advantage of using a chiral solvent as the hydrogen donor.

It is also worth noting that the reactions with the (S) and (R)-2-pentanol were conducted in a much lower scale (1/8) of the one with racemic 2-pentanol. It was difficult to measure some of the reagents at that scale. This might be the reason why the ee from the (S)-2-pentanol is slightly lower rather than being equal to what was obtained from racemic 2-pentanol.

3.2.4 Asymmetric Transfer Hydrogenation with Pre-Made Catalyst, [(S-)-BINAP]]

Ru(II)Cl₂

Since the catalyst cocktail method of combining [RuCODCl₂]ₙ with (S)-tolBinap leads to an imprecisely defined catalyst precursor, we were interested in performing the asymmetric transfer hydrogenation with a pre-made catalyst with known structure. Our Ru/(S)-tolBINAP catalyst is prepared in situ from commercially available ruthenium cyclooctadiene dichloride polymer, [RuCODCl₂]ₙ, and (S)-tolBINAP, which presumably forms [(S)-tolBINAP]Ru(II)Cl₂, complex A shown in Scheme 3.3. In the presence of (R)-BINAP, the catalyst species would then be [(R)-BINAP]Ru(II)Cl₂, complex B in Scheme 3.3. These structures were supported by Ikariya who demonstrated that a dimer of complex B, Ru₂Cl₄[(−)-BINAP]₂(NEt₃), can be obtained with similar starting materials in the presence of triethylamine in refluxed toluene.⁶⁴ According to Ikariya, the dimer should provide a co-ordinatively unsaturated ruthenium species, RuCl₂L₂ (L = phosphine ligand), which is similar to our proposed complexes A and B. Also, the dimer, Ru₂Cl₄[(−)-
BINAP$_2$(NEt$_3$), is known to exhibit excellent catalytic activity and high stereoselectivity for the hydrogenation of α,β-unsaturated amino acids (Scheme 3.4).$^{64}$

To investigate that the structures of our \textit{in situ} prepared catalysts are complexes A and B (Scheme 3.3), we tried our ATH reaction with a commercially available catalyst, [(S)-BINAP]Ru(II)Cl$_2$, complex C in Scheme 3.3. This catalyst has the same configuration as our \textit{in situ} prepared catalyst A, but they are slightly different chemically because of the difference between a tolyl-substituted ancillary group and a phenyl group. To have a more exacting comparison, the results obtained with the commercial catalyst C will be compared to the reaction with [RuCODCl$_2$]$_n$(R)-BINAP, entry 6 in Table 3.1.

Scheme 3.4: Hydrogenation of α,β-Unsaturated Amino Acids with Ru$_2$Cl$_4$[(-)-BINAP]$_2$(NEt$_3$).$^{64}$

\[
\begin{align*}
\text{NHCOR}^2 & \quad \rightarrow \quad \text{NHCOR}^2 \\
\text{R}^1 & \quad \text{CO}_2\text{H} \\
\text{Ru}_2\text{Cl}_4[(-)-\text{BINAP}]_2(\text{NEt}_3) & \quad \text{H}_2, \text{EtN}_3 \\
\text{R}^1 & \quad \text{CO}_2\text{H}
\end{align*}
\]

a: R$^1$ = Ph, R$^2$ = Me
b: R$^1$ = R$^2$ = Ph
c: R$^1$ = H, R$^2$ = Me

86% ee
92% ee
76% ee

Table 3.6: ATH with Pre-made Catalyst [(S)-BINAP]Ru(II)Cl$_2$ (Complex C in Figure 3.3) Compared with in situ Prepared Catalyst B.

Table:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate (concentration)</th>
<th>% Conv.$^a$</th>
<th>% ee$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>Geraniol (0.01 M)</td>
<td>100</td>
<td>87 (S)$^c$$^d$</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>Geraniol (0.01 M)</td>
<td>100</td>
<td>90 (R)</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>Nerol (0.01 M)</td>
<td>100</td>
<td>91 (S)</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>Geraniol (0.02 M)</td>
<td>100</td>
<td>92.8 (R)</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>Geraniol (0.1 M)</td>
<td>100</td>
<td>93.4 (R)</td>
</tr>
</tbody>
</table>

$^a$GC conversions measured with a HP-5 column (J&W Scientific, 15 m x 0.32 mm).
$^b$ee analysis measured with a GC Column RT-BetaDEXsa 30 m x 0.32 mm ID x 0.25 mm.  
$^c$ee analysis measured on the (R)-Mosher ester on a Chiralcel OJ-H column (Daicel, 250 mm x 4.6 mm).
$^d$GC conversions measured with a DB-5 column (J&W Scientific, 15 m x 0.32 mm).
It has already been demonstrated that tolBINAP gives slightly better enantioselectivity than BINAP (Table 3.1). Here we want to compare the results from two sterically similar Ru/BINAP catalysts: the pre-made catalyst [(S)-BINAP[Ru(II)Cl₂ (C)] and our in situ prepared catalyst [(R)-BINAP[Ru(II)Cl₂ (B)]. As shown in Table 3.6, commercially available catalyst (S)-BINAP[Ru(II)Cl₂ (C) was able to fully convert geraniol to (R)-citronellol in 90% ee (entry 2). This result is slightly higher than that obtained from our in situ prepared catalyst B (87% ee) with, of course, the opposite configuration. The commercial catalyst (C) was also able to convert nerol to (S)-citronellol in 91% ee (entry 3). The only difference is that this catalyst offers the advantage of maintaining the enantioselectivity at higher concentration. At 0.02 M and 0.1 M geraniol, catalyst C gives (R)-citronellol in 92.8% and 93.4% ee, respectively, with a slightly increase in ee compared to the reaction at 0.01 M concentration. This is likely due to a higher concentration of the "active" catalyst species that is obtained from the pure precatalyst compared to what is obtained from the catalyst cocktail.

To further test the efficiency of the commercial catalyst, we decided to run a set of experiments without the three freeze-pump-thaws. In this series, the IPA was degassed with argon for 1 hour and the reagents were charged under argon. Under these conditions, the pre-made catalyst, [(S)-BINAP[Ru(II)Cl₂], was able to give citronellol in 95% conversion and 91.7% ee in two hours (Table 3.7). This kind of conversion was never obtained under similar conditions with our in situ prepared catalysts. This suggests that the cryogenic freeze-pump-thaw procedure is necessary for the preparation of the catalyst, but not for the transfer hydrogenation reaction.
Table 3.7: ATH with Pre-made Catalyst [(S)-BINAP]Ru(II)Cl₂.

![Reaction schematic](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min.)</th>
<th>% Conv.*</th>
<th>% ee b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>80.3</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>80.5</td>
<td>91.6</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>88.5</td>
<td>92.2</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>95</td>
<td>91.7</td>
</tr>
</tbody>
</table>

*aGC conversions measured with a HP-5 column (J&W Scientific, 15 m x 0.32 mm).

b ee analysis measured with a GC Column RT-BetaDEXsa 30 m x 0.32 mm ID x 0.25 mm.

In Table 3.7, we explore the effect of reaction time on reaction conversion and ee. Each data point in Table 3.7 represents a separate reaction. Like with the *in situ* prepared catalyst, attempts to sample the reaction mixture result in deactivation of the catalyst. That is additional evidence suggesting the structural similarity between the commercial and the pre-made catalysts.

### 3.2.5 Asymmetric Transfer Hydrogenation of γ-Geraniol

In gaseous hydrogenation, there is a reciprocal relationship between nerol and geraniol. These two substrates give opposite configuration of citronellol after hydrogenation with either (S) or (R) Ru/BINAP catalyst (Scheme 3.5).³ A similar observation was made in our transfer hydrogenation system (Table 3.1, entry 5 and 6 and
Table 3.2, entry 1 and 3). In contrast, in the presence of the (S)-Ru/BINAP, γ-geraniol gives (S)-citronellol in 85 - 93 % ee (Scheme 3.5). We wanted to investigate if this relation also exists in our transfer hydrogenation system.

Since γ-geraniol is not commercially available, we prepared it following the conditions shown in Scheme 3.6. The reaction is a one-pot synthesis, which involves the in situ preparation of disiamylborane (31) starting with commercially available isoprene (30). Treatment of 31 with myrcene gives the trialkylborane (32), which subsequently hydrolyses to the crude product. Purification of the crude by fractional distillation gives γ-geraniol (33) in 15% yield and 97% purity (GC area percentage).

Scheme 3.5: Reciprocal Relationship Between Nerol and Geraniol.

---

Attempts to perform transfer hydrogenation of γ-geraniol under our best conditions with substrate/[Ru(COD)Cl₂]₂/KOH/(S)-tolBINAP molar ratio = 10/1/2/2, result in 40.7% conversion to citronellol after 2 hour at 100 °C. Prolonged heating of the reaction mixture for up to 6 hours results in 50.6% conversion to citronellol (Table 3.8). As usual, each data point represents a separate reaction; attempts to withdraw samples from the ongoing reactions result in deactivation of the catalyst.

An interesting observation we made in the transfer hydrogenation of γ-geraniol with two equiv of base (that is, with respect to the catalyst load) is the formation of small amounts of nerol and geraniol in every reaction. With two equiv of base, the amount of geraniol formed in every reaction exceeds the amount of nerol formed; as a result the (R)-citronellol is obtained in a small excess (19 – 34 % ee). Thus, γ-geraniol gives low ee under ATH conditions and the chiral direction is different from that of the hydrogenation reaction, 85 – 93 % ee (S). In fact, the chiral direction seems to correlate with the slight excess of geraniol detected in the reaction.
Table 3.8: Asymmetric Transfer Hydrogenation of $\gamma$-Geraniol with Two Equivalents of Base.

In an attempt to increase the conversion of $\gamma$-geraniol, the amount of base was increased to four equiv. with a substrate/[Ru(COD)Cl$_2$]$\_n$/KOH/(S)-tolBINAP molar ratio of 10/1/4/2. In two hours, the reaction went to 87.93% conversion; more than double of the percent conversion obtained with two equiv of base over the same period of time. On the other hand, the amount of (R)-citronellol produced in every reaction decreases in a manner that directly corresponds to the lower amount of geraniol and increasing amount.
of nerol produced in the reactions with four equiv of base. This set of experiments results
in very low ee, which shifts from 9.72% (S) to 8.2% (R) citronellol (Table 3.9).

Table 3.9: Asymmetric Transfer Hydrogenation of γ-Geraniol with Four Equiv of Base.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>γ-geraniol a</th>
<th>nerol a</th>
<th>geraniol a</th>
<th>citronellol a</th>
<th>% ee b</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>96.71</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>15</td>
<td>45.03</td>
<td>1.13</td>
<td>1.21</td>
<td>44.53</td>
<td>4.18 (S)</td>
</tr>
<tr>
<td>30</td>
<td>24.7</td>
<td>1.46</td>
<td>1.04</td>
<td>59.42</td>
<td>9.72 (S)</td>
</tr>
<tr>
<td>60</td>
<td>18.96</td>
<td>0.61</td>
<td>0.31</td>
<td>53.47</td>
<td>0.86 (S)</td>
</tr>
<tr>
<td>120</td>
<td>12.07</td>
<td>0.57</td>
<td>0.24</td>
<td>64.17</td>
<td>7.44 (S)</td>
</tr>
<tr>
<td>240</td>
<td>21.71</td>
<td>1.39</td>
<td>0.76</td>
<td>60.69</td>
<td>1.72 (R)</td>
</tr>
<tr>
<td>360</td>
<td>12.82</td>
<td>1.41</td>
<td>0.88</td>
<td>64.18</td>
<td>8.2 (R)</td>
</tr>
</tbody>
</table>

aGC conversions measured with a HP-5 column (J&W Scientific, 15 m x 0.32 mm).
bee analysis measured with a GC Column RT-BetaDEXsa 30 m x 0.32 mm ID x 0.25 mm.

Our results indicate that ATH of the homo-allylic alcohol γ-geraniol is possible,
however, the reaction is relatively slower compare to the ATH of nerol and geraniol and
the enantioselectivity obtained is very low and sensitive to the concentration of base. This leads us to believe that the mechanism of our ATH system is different from the gaseous hydrogenation. In addition, all the reactions with γ-geraniol generate small amounts of nerol and geraniol. Therefore, we think that the ATH of γ-geraniol may take place via isomerizing to nerol and geraniol prior to ATH. Knowing that the ATH of nerol and geraniol give opposite configuration of citronellol (S) and (R), respectively, isomerization of γ-geraniol to both nerol and geraniol prior to ATH would result in what we observe in our experiments; low enantioselectivity.

3.2.6 Isomerization of Geraniol

Transition metal catalyzed isomerization of allylic alcohols to carbonyl compounds is well known. Many examples of primary, secondary and cyclic alcohols have been reported to oxidize under intramolecular redox processes. The earliest examples of allylic alcohol isomerization were reported by Botteghi and Giacomelli in 1976. These examples had limited success in terms of conversion and enantioselectivity. For example, HRh(CO)(PPh3)3/DIOP catalyses the isomerization of 2-methylbut-2-en-1-ol to the corresponding aldehyde in 98% conversion and 4% ee. A similar reaction resulted in 0% conversion when there was a phenyl group attached on the allylic bond (Table 3.10).

Table 3.10: Asymmetric Isomerization of Allylic Alcohols with HRh(CO)(PPh$_3$)$_3$/DIOP Catalyst System.$^{59}$

\[
\begin{align*}
\text{Entry} & \quad \text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 & \quad \text{Time (h)} & \quad \% \text{ Conv.} & \quad \% \text{ ee} & \quad \text{Config.} \\
1 & \text{Me} & \text{H} & \text{Me} & 55 & 98 & 4 & \text{S} \\
2 & \text{H} & \text{H} & \text{Et} & 55 & 100 & 3 & \text{R} \\
3 & \text{Me} & \text{Et} & \text{H} & 400 & 63 & 2 & \text{R} \\
4 & \text{Ph} & \text{Me} & \text{H} & 180 & 0 & - & - \\
\end{align*}
\]

Scheme 3.7: Asymmetric Isomerization of Geraniol with Rh-BINAP.$^{70,71}$

Another example includes cationic-Rh-BINAP catalyzed isomerization of geraniol to citronellal in 70% yield and 37% ee (Scheme 3.7).$^{70}$ This yield is considerably lower

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$^{70}$ Tani, K. Pure & Appl. Chem. 1985, 57, 1845.
compared to the excellent yield obtained with the corresponding allylic amines; the major step in the industrial synthesis of menthol and other terpenes, which proceeds in 100% yield and 95–99 % ee.\textsuperscript{71}

The mechanism of the isomerization of geraniol to citronellal is believed to proceed via the same route as the isomerization of geranylamine, where the nitrogen atom plays an important role.\textsuperscript{71} There is no experimental evidence on how the hydrogen transfer takes place, but two types of mechanisms have been proposed (Figure 3.3).\textsuperscript{69c} The type I mechanism takes place via an alkylmetal intermediate. In this case, the catalyst is a metal-hydride [M-H], which is either isolated or generated \textit{in situ}. The type II mechanism takes place via a \(\pi\)-allyl intermediate. In this case, the transition metal [M] leads the migration of the hydrogen from position 1 to position 3 of the allylic alcohol via a \(\pi\)-allyl metal hydride intermediate.

In our system and the presence of a hydrogen donor, geraniol is converted to citronellol; the aldehyde citronellal has never been detected in the reactions using the ATH conditions of catalyst, hydrogen donor and base. To see if isomerization was taking place in our ATH reactions, we decided to run a reaction in the absence of the hydrogen donor, IPA. The isomerization reaction was conducted in t-butanol, a non-oxidizable alcohol. Using a substrate/[Ru(COD)Cl\textsubscript{2}]\textsubscript{6}/KOH/(S)-tolBINAP molar ratio of 10/1/2/2, geraniol (1) was converted to citronellal (34) in 21% yield (Scheme 3.8). This reaction also gave citronellol (2) in 13% yield and 77% ee. This result is reminiscent, \textit{vide supra}, to the origin of this project where geraniol acts as a hydrogen donor to give citronellol in

27% yield and 50% ee (Scheme 3.1). In this reaction, we were able to identify all the major components of the isomerization reaction: the isomerized product citronellal (34), the reduced product citronellol (2) and the oxidized product citral (35), which was obtained in equal amount as citronellol, 13% yield.

Figure 3.3: Proposed Mechanism for Asymmetric Isomerization of Allylic Alcohols.
Scheme 3.8: Asymmetric Isomerization of Geraniol.

In an attempt to prevent the transfer hydrogenation from occurring, we repeated the isomerization reaction without base, but, this resulted in 0% conversion (Scheme 3.8). Isomerization of geraniol to citronellal is possible with our Ru-BINAP catalyst system. However, the isomerized product was never detected in our reaction system. If citronellal is an intermediate, it may be rapidly hydrogenated in the presence of the hydrogen donor, IPA.

3.2.7 Deuterium Experiments

To investigate which pathway our asymmetric transfer hydrogenation follows, we conducted a series of deuteration experiments. These will provide two key answers: first, the transfer of deuterium to the substrate will confirm that the alcohol is the hydrogen source in the reaction, second, the position of the deuteriums on the reduced product will
tell which path the reaction follows. Some of the possible outcomes of the deuterium experiment are highlighted in Scheme 3.9.

Scheme 3.9: Potential Products from the ATH with Deuterated IPA.

*Via direct allylic*

\[
\begin{align*}
    \text{Product } A & : R-D-D-\text{OH} \\
    \text{via direct allylic} & : R-\text{OH} \rightarrow R-D-D-\text{OH}
\end{align*}
\]

*Via isomerization with a metal deuteride (M-D), metal ligand intermediate*

\[
\begin{align*}
    \text{Product } B & : R-D-D-\text{OH} \\
    \text{via isomerization with a metal deuteride (M-D), metal ligand intermediate} & : R-\text{OH} \rightarrow R-D-D-\text{OH}
\end{align*}
\]

*Via isomerization with a metal (M), \(\alpha\)-allyl isomerization*

\[
\begin{align*}
    \text{Product } C & : R-D-D-\text{OH} \\
    \text{via isomerization with a metal (M), } \alpha\text{-allyl isomerization} & : R-\text{OH} \rightarrow R-D-D-\text{OH}
\end{align*}
\]
For simplicity, we are leaving the possibility of deuterium exchange until later. If the reaction goes via direct hydrogenation of the C=C, the deuteriums will transfer directly across the double bond of the allylic alcohol and product A will be formed (Scheme 3.9). If the allylic bond isomerizes to the enol, via the Type I M-H mechanism proposed in Figure 3.3, prior to transfer hydrogenation, product B will be formed. Under the same isomerization pathway, if the enol tautomerizes to the aldehyde prior to transfer hydrogenation, product C will be formed. However, if the isomerization takes place via the Type II \( \pi \)-allyl mechanism in Figure 3.3, transfer hydrogenation of the enol and the aldehyde will give products D and E, respectively.

Using our optimum conditions, substrate/[Ru(COD)Cl\(_2\)]\(_n\)/KOH/(S)-tolBINAP molar ratio = 10/1/2/2, the asymmetric transfer hydrogenation of geraniol was conducted in \( d_3 \)-isopropanol to give \( d_3 \)-citronellol (36) in 86% yield and 98% ee (Scheme 3.10). This product was characterized by GC/MS and various NMR experiments.

**Scheme 3.10:** Asymmetric Transfer Hydrogenation of Geraniol with Deuterated IPA.

This experiment answers our first question regarding whether transfer hydrogenation took place. The GC/MS of the product shows a mass of 159, which indicates the formation of \( d_3 \)-citronellol (Figure 3.4). The presence of deuterium on the
product indicates that deuterium did transfer from d$_8$-IPA to geraniol, giving d$_3$-citronellol.

The second question on how the transfer hydrogenation occurs will be answered in the following discussion. The proton NMR of the product (Figure 3.5) shows a signal at 3.64 - 3.67 ppm that integrates as 0.98. This indicates the absence of one proton or the presence of one deuterium on C1. In regular citronellol, that signal integrates for two protons. In addition, the signals of the C3' protons at 0.89 - 0.92 ppm, which integrates as 3.2, and occurs as show a doublet. The multiplicity of the C3' protons indicates the presence of one proton (no deuterium) on C3, which eliminates the possibility of direct addition of hydrogen to the C=C.

Figure 3.4: Segment of GC/MS of d$_3$-citronellol.
The $^{13}$C NMR shows a tremendous suppression of C1 and C2 (Figure 3.6). This indicates the presence of deuterium at these two locations. Furthermore, deuterium couples with carbon, as a result the deuterium-carbon peaks will split. Sure enough, a closer look at C1 (Figure 3.7) reveals a triple with a $J_{CD} = 21$ which matches the literature reference for the CD coupling constant ($J_{CD} = 20-30$ Hz). Thus, this confirms the presence of one deuterium on C1. A closer look at C2 (Figure 3.7) shows a multiplet. Since the deuteriums on C2 are diastereotopic (alpha to the chiral center), it is reasonable to suggest that the multiplet is an overlap of two triplets; a typical pattern for CDD'. The $^{13}$C NMR clearly indicates the location of the three deuteriums on our d$_3$-citronellol.

---

To confirm the absence of protons on C2, we decided to run an HMQC NMR of our d₃-citronellol and compare this spectrum to that of regular citronellol. HMQC
(Heteronuclear Multiple-Quantum Coherence) is a two-dimensional inverse proton-carbon correlation technique.\textsuperscript{73} This NMR experiment is selective for direct C-H bonds. Therefore, every carbon that is directly attached to a hydrogen (but not a deuterium) will show a correlation. In the enlarged HMQC spectrum of citronellol (Figure 3.9), we see the correlations for the two diastereotopic protons on C2. These two correlations are reduced to a trace signals in our d$_3$-citronellol product (Figure 3.8).

**Figure 3.8:** Enlarged HMQC NMR of d$_3$-citronellol.

A more direct analysis of the d$_3$-citronellol is the $^2$H NMR shown in Figure 3.10. Integration of the 3.64 ppm deuterium of C1 for 1 deuterium results in simultaneous integration of the 1.34 and 1.56 ppm deuteriums of C2 as 1.61 deuteriums which is close to the expected value of 2 deuteriums. This result confirms that the major product formed

---

from our d₈-IPA experiment is indeed compound 36 in Scheme 3.8. The two small signals at 0.86 and 1.1 ppm do not seem to be related to the product.

**Figure 3.9:** Enlarged HMQC NMR of Regular Citronellol.

![HMQC NMR of Regular Citronellol](image)

**Figure 3.10:** ²H NMR of d₃-citronellol.

![²H NMR of d₃-citronellol](image)
The position of the deuterium on the product helped us determine which pathway the hydrogenation followed. Going back to Scheme 3.9, we can eliminate the first three possibilities, since our product (36) doesn’t have any deuterium on C3. Therefore, we can say that neither direct hydrogenation of the C=C bond, nor a Type I metal hydride (M-H) isomerization followed by transfer hydrogenation is the mechanistic route of our system. The isomerization in our system must have been taken place via the Type II π-allyl mechanism (Scheme 3.11). The enol then leaves the catalytic cycle and undergoes tautomerization in the presence of the deuterated solvent to generate the aldehyde, which reenters the catalytic cycle for transfer hydrogenation.

**Scheme 3.11:** Isomerization/ATH of Allylic Alcohols Via π-Allyl Mechanism with d₈-IPA.

Scheme 3.12 summarizes the mechanism of the ATH reaction. Starting with the allylic alcohol a, a base generates the alkoxide b, which coordinates to a selective side of
the ruthenium complex to produce c. A π-allyl intermediate d is generated, which subsequently undergoes a metal-mediated 1,3-hydrogen shift (the chiral induction step) to give the chiral intermediate e. β-elimination releases the chiral enol f. This concludes the isomerization part of the process. In the presence of a deuterated alcohol (DOR), the enol f undergoes deuterium exchange follow by tautomerization, which enables incorporation of deuterium on C2 to give the aldehyde g. Transfer hydrogenation of g follow by an aqueous workup gives the d₃-citronellol product h. This experiment clearly indicates the isomerization as the chiral induction step. Remarkably the direction of chirality is the same as the gaseous hydrogenation even though the mechanism is different from what occurs in gaseous hydrogenation.

Scheme 3.12: Proposed Mechanism for Asymmetric Transfer Hydrogenation.

It is unclear if all these steps are reversible. However, it is well known that transfer hydrogenation with IPA is a reversible process. In addition, our experiments in low IPA concentration, which are slow in conversion rate, result in lower ee. This leads us to believe that under low IPA concentration or low hydrogen donor concentration, the aldehyde g, which is in equilibrium with f, goes back to the alkoxide b. During the reverse process, the alkoxide may switch from the original trans to cis configuration. This
might be the source of the low enantioselectivities obtained in the reactions with low IPA concentrations (Table 3.3) or the slow reactions with cyclohexanol and 2-pentanol (Tables 3.4 and 3.5).

We do have evidence that our ATH reaction mechanism involves isomerization of the allylic bond to aldehyde prior to hydrogenation. Both steps, the isomerization of allylic alcohols to aldehydes\(^{69, 70}\) and the transfer hydrogenation of carbonyls to alcohols,\(^{28, 31, 32}\) have been reported. However, none of these reports has mentioned the reduction of an allylic alcohol. In addition, the isomerized product was never detected in our reaction mixtures. Yes, we do have isomerization prior to ATH, but we could not make this distinction if we did not perform the mechanistic study. Our observation is that allylic alcohols undergo asymmetric transfer hydrogenation in the presence of Ru/BINAP and IPA as hydrogen donor.

3.3 Conclusions

In conclusion, asymmetric transfer hydrogenation of allylic alcohols is possible and the product can be obtained in high yield and excellent enantioselectivity. The yield and the chiral direction of the product is the exact same as the gaseous hydrogenation reaction. For example, \([\text{RuCODCl}_2]_\alpha/(S)-\text{tolBINAP}\) catalyzes the asymmetric transfer hydrogenation of geraniol to (R)-citronellol in 90 - 95 % yield and 95 - 98 % ee. This yield and enantioselectivity rival gaseous asymmetric hydrogenations of allylic alcohols. However, a significant advantage of this ATH reaction is that it eliminates the high hydrogen pressures (>30 atm)\(^3\) used for the same transformation.
This asymmetric transfer hydrogenation reaction is not limited to isopropanol as hydrogen donor. Other alcohols, such as racemic and chiral 2-pentanol and cyclohexanol, can also be used. In our study with the 2-pentanol, we have demonstrated that a chiral solvent is not required to enhance the enantioselectivity. The racemic alcohol can provide the same enantioselectivity as the most active chiral alcohol. In our study with cyclohexanol, we have demonstrated that the freeze-pump-thaws can be done under non-cryogenic conditions. The freeze-pump-thaws can be done at the melting point of the solvent used.

Most of our experiments are done with the [RuCODCl₂]₆/(S)-tolBINAP catalyst system as it gave the best yield and the best ee during our screening process. However, other ligands including BINAP, (S,S)-MeDUPHOS and (S,S)-iPrDUPHOS can also be used. In addition, we have demonstrated that a pre-made catalyst, [(S)-BINAP]Ru(II)Cl₂, can work efficiently in our system. This catalyst gives the same yield and chiral configuration as our in situ prepared catalyst; which suggests that the structure of our active catalyst may also be a [BINAP]Ru(II)Cl₂ complex. Other experiments with this catalyst without the freeze-pump-thaws resulted in no major changes in yield, ee and it was possible to increase in substrate to catalyst ratio without affecting ee. Therefore, the freeze-pump-thaw process is required only for the in situ preparation of the catalyst.

Our deuterium experiment indicates that the mechanism occurs through an isomerization process, which is very different form the gaseous hydrogenation mechanism. Considering that the yield, the chirality and the ee of our product is the exact same as the gaseous hydrogenation, and given the fact that transfer hydrogenation is a
safer procedure, this reaction is a potential route for asymmetric reduction of allylic alcohols.
EXPERIMENTAL SECTION

I. Chiral Method Development

A) Derivatization with Mosher Acid Chloride

Reagents

All chemicals were purchased from Aldrich. The R-(+)-methoxy-trifluoromethylphenylacetyl chloride had an optical purity of 98% and a GC assay of 98%. The 4-(dimethylamino)pyridine (DMAP) and the triethylamine (TEA) were reagent grades with chromatographic purities greater than 99%.

Chromatographic Conditions

The reaction was monitored by gas chromatography, Hewlett-Packard 5890 Series II equipped with a flame ionization detector. The column used was a DB-5, J&W Scientific, 15 m x 0.32 mm. The chromatographic conditions were: split mode inlet (250:1), 250 °C; column temperature 60 - 175 °C at 3 °C/min, He flow 30 mL/min, 15 psi; detector 250 °C; 10 µl injection. The diastereomeric purity was determined on a Hewlett-Packard 1050 Series high performance liquid chromatography (HPLC). The column used was a Diacel Chiralcel OJ-H, 250 mm x 4.6 mm. The mobile phase was a mixture of HPLC grade hexanes and ethyl alcohol (EtOH), 90:10 to 50:50 EtOH:hexanes, 0.6 mL/min, 20 minute gradient; room temperature; 210 and 220 nm. The diastereomeric excess was calculated based on HPLC area percent of the R-Mosher-R-citronellyl ester and R-Mosher-S-citronellyl ester.

Reaction Conditions

To an ice cold solution of citronellol (35 mg, 0.22 mmol) in 3.5 mL dichloromethane (DCM) at 0 °C, was added (R)-Mosher acid chloride (123.5 µl, 0.66
mmol), triethylamine (92 µl, 0.66 mmol), and 4-dimethylaminopyridine (2.7 mg, 0.022 mmol). The mixture was refluxed for 4 hours or until GC revealed less than 1% citronellol. After cooling to room temperature (rt), hexanes (5 mL) was added and the reaction mixture was washed with saturated sodium bicarbonate (NaHCO₃), water, 0.1 normal aqueous hydrochloric acid (HCl), and water, respectively. The organic was dried over magnesium sulfate (MgSO₄), filtered, and then concentrated to a crude oil. Without further purification, the crude oil was diluted in 1:1 HPLC grade EtOH:hexanes and analyzed by HPLC for diastereometric purity.

B) Derivatization with S-Naproxen

Reagents

The (S)-Naproxen was isolated from commercially available drug Aleve®. All other reagents, the oxalyl chloride, the triethylamine (TEA) and the 4-(dimethylamino)pyridine (DMAP) were purchased from Aldrich with purities greater than 99%.

Analytical Conditions

The first step of the reaction (Scheme 2.3) was monitored by TLC using 85:15/hexanes:acetone. The melting point of the acid chloride product (28) was compared to the literature value (91 - 94 °C). The second step was monitored by GC for the disappearance of citronellol (23) on a Hewlett-Packard 5890 Series II equipped with a flame ionization detector. A DB-5, J&W Scientific, 15 m x 0.32 mm column was used. The chromatographic conditions were: split mode inlet (250:1), 250 °C; column temperature 60 - 175 °C at 3 °C/min, He flow 30 mL/min, 15 psi; detector 250 °C; 10 µl injection.
During the chromatographic purification, TLC was used to analyze the purity of the fractions. Satisfactory separation was obtained using 7:3 hexanes:acetone plus 1 drop phosphoric acid (H₃PO₄) in the TLC analysis. The final product S-Naproxen-ester 29 was characterized using a 500 MHz Varian NMR equipped with Inova software in deuterated chloroform (CDCl₃). The relaxation time was 1 second for both proton and carbon experiments, with 8 and 256 scans, respectively.

**Reaction Conditions**

**Step 1: Preparation of (S)-Naproxen Acid Chloride**

Ten equiv of oxalyl chloride (1.41 mL, 13 mmol) was added to solid (S)-Naproxen (300 mg, 1.3 mmol). The mixture was stirred at room temperature (rt) for 30 min and formed a solution. The excess oxalyl chloride was removed under reduced pressure at rt. Four volumes of dichloromethane (1.2 mL) were added, and then hexanes (30 mL) was added in small portions. The mixture was chilled over ice for one hour to allow precipitation of the product. The solvent was decanted and the product was dried under nitrogen flow overnight to afford S-Naproxen acid chloride as a white needle shaped product (280 mg, 88% yield, mp 91 - 94 °C).

**Step 2: Preparation of (S)-Citronellyl-Naproxen Ester**

To a cold solution of citronellol (35 mg, 0.22 mmol) in 5 mL dichloromethane (DCM) at 0 °C, (S)-Naproxen acid chloride (81 mg, 0.34 mmol), triethylamine (92 µL, 0.66 mmol), and 4-dimethylaminopyridine (2.7 mg, 0.022 mmol) were added. The mixture was refluxed for 4 - 5 h or until GC revealed less than 1% citronellol. After cooling to room temperature (rt), hexanes (5 mL) was added and the residual salt was removed by filtration. The filtrate was concentrated to a crude oil, which was purified
through a silica gel plug using hexanes. The enriched fractions were combined and concentrated to dryness. The diastereomeric purity was determined by $^{13}$C NMR in CDCl$_3$.

**C) Chiral GC**

*Analytical Conditions*

All reactions were monitored by gas chromatography, Hewlett-Packard 5890 Series II equipped with a flame ionization detector. The column used was a HP-5, J&W Scientific, 30 m x 0.32 mm. The chromatographic conditions were: split mode inlet (250:1), 250 °C; column temperature 60 - 175 °C at 3 °C/min, He flow 30 mL/min, 15 psi; detector 250 °C; 10 µl injection. The enantiomeric excess of the crude citronellol was measured using a RT -BetaDEXsa column, 30 m x 0.32 mm ID x 0.25 mm, obtained from Restek. The Chromatographic conditions were as follow: inlet, split mode (50:1), 150 °C; column, isothermal 80 °C, He flow 30 mL/min, 15 psi, 120 min; detector 150 °C; 10 µl injection.

**II. Asymmetric Transfer Hydrogenation**

*General Procedure for Transfer Hydrogenation and Derivatization with Mosher Acid Chloride*

*Reagents*

Geraniol (trans-3,7-dimethyl-2,6-octadien-1-ol) (98% purity) dichloro-ruthenium-(II)-1,5-cyclooctadiene complex, [RuCODCl$_2$)$_n$, (95% purity) and the ligand (S)-(−)-2,2′-bis(di-p-toly1phosphino)-1,1′-binaphthyl, (S)-tolBINAP, 97% purity) were purchased
from Aldrich. The pre-made catalyst, dichloro-[(S)-(-)-2,2'-bis(diphenylphosphino-1,1'-binaphthyl)ruthenium(II), [(S)-BINAP]Ru(II)Cl₂, was obtained from Strem in 95% assay. Potassium hydroxide, technical grade, was purchased from Fisher. The solvents, 1,2-dimethoxyethane and the N,N-dimethylformamide (DMF), each in anhydrous grade and >99.5% assay were purchased from Aldrich. The hexanes and the ethanol, HPLC grade, and all the other solvents (isopropanol, t-butanol, toluene, dichloromethane, cyclohexanol, 2-pentanol), were purchased as ACS Grade solvents from Fisher. The enantiomers of 2-pentanol, 98% assay, were purchased from Aldrich with optical activities of [α]₂⁵° of +13° (S) and -13° (R). The deuterated solvents, d₈-isopropanol, d₁₂-cyclohexanol and d₁-chloroform, were purchased from Aldrich with isotopic purities of 99.5%, 98% and 99.96%, respectively. The R-(+)-methoxy-trifluoromethylphenylacetyl chloride ((R)-Mosher acid chloride, optical purity 98% and GC assay 98%), the 4-dimethylaminopyridine (DMAP) and the triethylamine (TEA), reagent grades (>99% purity), were purchased from Aldrich.

**Analytical Conditions**

All reactions were monitored by gas chromatography, using a Hewlett-Packard 5890 Series II gas chromatography equipped with a flame ionization detector. The column used was a HP-5, J&W Scientific, 30 m x 0.32 mm. The chromatographic conditions were: split mode inlet (250:1), 250 °C; column temperature 60 - 175 °C at 3 °C/min, He flow 30 mL/min, 15 psi; detector 250 °C; 10 μl injection.

The GC-MS analyses were performed on HP 5890 GC system equipped with an HP 5971A Mass Selective Detector and a 70 eV electron-impact ion source.
The enantiomeric purity of the crude citronellol was measured using a RT-BetaDEXsa 30 m x 0.32 mm ID x 0.25 mm obtained from Restek, Bellefonte, PA. The chromatographic conditions were: split mode inlet (50:1), 150 °C; isothermal 80 °C, He flow 30 mL/min, 15 psi, 120 min; detector 150 °C; 10 μl injection.

The diastereomeric purity of the Mosher ester of citronellol was determined on a Hewlett-Packard 1050 Series high performance liquid chromatography (HPLC). The column used was Chiralcel OJ-H, 250 mm x 4.6 mm obtained from Daicel Chemical Industries, Fort Lee, NJ. The mobile phase was a mixture of HPLC grade hexanes:ethyl alcohol, 90:10 to 50:50, 0.6 mL/min, 20 minute gradient; room temperature; 210 and 220 nm. The diastereomeric excess was calculated based on HPLC area percent of the R-Mosher-R-citronellyl ester and R-Mosher-S-citronellyl ester. All products were characterized using a 500 MHz Varian NMR equipped with Inova software in deuterated chloroform (CDCl₃), except for the deuterated product d₃-citronellol, which was characterized using a 300 MHz Bruker NMR equipped with TopSpin software.

**Reaction Conditions**

- **Asymmetric Transfer Hydrogenation**

Unless specifically indicated, all reactions were performed in a 50 mL Schlenk flask equipped with a teflon-coated magnetic stirrer bar. The reagents were added under a continuous flow of argon while the flask was placed over a liquid nitrogen bath. The reagents, 0.023 mmol [Ru(COD)Cl]₉, 0.046 mmol chiral ligand, 0.23 mmol substrate, 0.046 mmol KOH and 20 mL isopropanol, were added in no particular order. The flask was then sealed with a latex septum and subjected to three freeze-pump-thaw cycles using vacuum and argon. The flask was then placed in a silicone oil bath at 100 °C while
under a slight overpressure of argon and as soon as the solvent started to boil, the reaction system was closed and the mixture was stirred for 2 hours. At the end of the reaction, the flask was removed from the oil bath and brought to room temperature before opening to the atmosphere. The isopropanol was removed under reduced pressure and the reaction mixture was reconstituted with 2 mL of hexanes. Residual catalyst and solids were removed by filtration through a silica gel plug using 0% to 5% ethyl acetate in hexanes and the filtrate was concentrated to dryness under reduced pressure.

- **Derivatization with Mosher Acid Chloride**

  Same as in the Chiral Method Development Section.
Appendix

NMR Spectra

and

Chiral GC Chromatogram
Proton NMR of Citronellol Made by Asymmetric Transfer Hydrogenation
Carbon NMR of Citronellol Made by Asymmetric Transfer Hydrogenation
gCOSY NMR of Citronellol Made by Asymmetric Transfer Hydrogenation
Proton NMR of γ-Geraniol

Sample: PROTON
SPECIAL

Data: 04-20-2006

Solvent: CDCl3
Gain: 0.010

Frequency: 399.468 MHz
Flags: n

Sample:

ppm

5
4
3
2
1
0
1
2
3
4
5
6
7
8
9

8.76
7.00
5.12
3.71
3.09
2.38
1.91
1.39
1.00
0.68
0.54
0.30
Carbon NMR of γ-Geraniol
Proton NMR of Citronellol R-Mosher Ester (de by HPLC = 85% RR)
Proton NMR of β-Citronellol S-Naproxen Ester
Carbon NMR of β-Citronellol S-Naproxen Ester
Carbon NMR of S-Citronellol S-Naproxen Ester
Proton NMR 1,2,2-trideuterium-3,7-dimethyloct-6-en-1-ol (d3-Citronellol)
Carbon NMR of 1,2,2-trideuterium-3,7-dimethyl-6-ene-1-ol (d3-Citronellol)
HMQC NMR of 1,2,2-trideuterium-3,7-dimethyloct-6-en-1-ol (d3-Citronellol)
Deuterium NMR of 1,2,2-trideuterium-3,7-dimethyl-6-en-1-01 (d3-Citronellol)
Chiral CG Chromatogram of S-Citronellol, R-Citronellol, Geraniol and Nerol
Chiral GC of Citronellol (ee > 98% R)

Data File: C:\CHEM32\DATA\GMB-1-31-08\MARIE_GC 2008-01-31 17-09-24\005F0501.D
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Inj. Volume : External
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Last changed : 1/31/2008 5:05:38 PM by MB
Analysis Method : C:\CHEM32\DATA\GMB-1-31-08\MARIE_GC 2008-01-31 17-09-24\GLUTARIMIDE_FID.M
Last changed : 1/31/2008 5:05:38 PM by MB
(modified after loading)

Area Percent Report

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Multiplier : 1.0000  Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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