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ASYMMETRIC HOMOGENEOUS HYDROGENATION

WITH CHIRAL PHOSPHINE-RHODIUM(I) CATALYSTS

BY

SUSAN J. HATHAWAY
B.A., SUNY at Potsdam, 1971
M.A., SUNY at Potsdam, 1973

A DISSERTATION

Submitted to the University of New Hampshire
in Partial Fulfillment of
the Requirements for the Degree of

Doctor of Philosophy
in
Chemistry

May, 1978

This thesis has been examined and approved.

Thesis director, James D. Morrison
Professor of Chemistry

Kenneth K. Andersen, Professor of Chemistry

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Alexander R. Amell, Professor of Chemistry

Arthur E. Teeri, Professor of Biochemistry

May 8, 1978
Date

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There are rare individuals who can truly be called teachers. It is to one of these persons, Dr. James D. Morrison, that I wish to express my lasting and sincere gratitude. For his giving of much time and energy in the course of this study and for his friendship and guidance I now tender my heartfelt thanks.

I would also like to express my sincere appreciation to the chemistry faculty for their devotion to duty even when faced with a former biologist.

TO MY PARENTS

WHO HAVE WAITED SO PATIENTLY,

FOR SO LONG

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ABSTRACT

ASYMMETRIC HOMOGENEOUS HYDROGENATION WITH CHIRAL
PHOSPHINE-RHODIUM(I) CATALYSTS

by

SUSAN J. HATHAWAY

Asymmetric homogeneous hydrogenation with chiral phosphine-rhodium(I) catalysts has been investigated.

The syntheses of two new chiral phosphine ligands, 2-phenylbis(diphenylphosphino)butane (SUPHOS) and carvomenthyl-diphenylphosphine (CMDPP) are described. Alternate syntheses of 2-phenyl-1-diphenylphosphinobutane (BUPHOS) and neomenthyl-diphenylphosphine (NMDPP), previously prepared in this laboratory, are also described.

Asymmetric homogeneous hydrogenations of both E and Z isomers of α- and β-methylcinnamic acids, (Z)-α-acetamidocinnamic acid, (E)- and (Z)-ethyl 3-acetoxybut-2-enoate, (Z)-methyl 3-acetoxybut-2-enoate, (E)- and (Z)-ethyl 3-acetoxyhex-2-enoate, (Z)-ethyl 3-acetoxytridec-2-enoate, (Z)-ethyl 3-acetoxytetradec-2-enoate, and (Z)-ethyl 3-acetoxy-cinnamate were carried out.

Hydrogenations of the α,β-unsaturated acids were performed with the ligands prepared in this study and o-anisylcyclohexylmethylphosphine (ACMP), 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), and 1,2-ethanediylbis[(o-methoxyphenyl)phenylphosphine] (DIPAMP). Hydrogenation of (E)-α-methylcinnamic acid with a neutral Rh/NMDPP catalyst

gave up to 63% ee. When preformed cationic catalysts were used, the highest optical yield (39% ee) was observed in the reduction of (E)-β-methylcinnamic acid with $[Rh(COD)(CMDPP)]^+BF_4^-$. The influence of substrate geometry (E/Z) on both chemical and optical yield varied from substrate to substrate.

Hydrogenations of (Z)-α-acetamidocinnamic acid with neutral Wilkinson-type catalysts containing BUPHOS, SUPHOS, NMDPP, and CMDPP gave products having low optical purities (0-12% ee).

The results of hydrogenation of enol acetate substrates with eleven different chiral Rh(I) phosphine catalysts showed BUPHOS to be the most successful ligand, when both chemical and optical yields are considered. Several catalysts gave large amounts of hydrogenolysis (20-65%). Successful reductions were achieved with ethyl-3-acetoxybut-2-enoate and ethyl 3-acetoxyhex-2-enoate but long chain aliphatic enol acetates did not undergo hydrogenation.

Hydrogenation of (Z)-ethyl 3-acetoxycinnamate with Rh/ACMP gave a specific rotation nearly seven times the literature value for the maximum rotation of ethyl 3-acetoxyhydrocinnamate. The synthesis of chiral ethyl-3-acetoxyhydrocinnamate was investigated and the source of the literature error was found to be associated with by-product formation during the esterification of the chiral β-hydroxy acid precursor. Using the chiral shift reagent, $Eu(dcm)_3$, the maximum rotation value was determined to be nearly twelve times that previously reported for the acetoxy ester.

INTRODUCTION

Chiral compounds are essential in the synthesis of pharmaceuticals, flavors, fragrances, and natural products. The classical methods of producing optically active molecules are the manual separation of enantiomeric crystal forms (not often used; Pasteur's manual separation of D and L forms of tartaric acid was the first), resolution by physical separation of diastereomeric derivatives,[1,2] thermodynamically controlled asymmetric transformations, and kinetically controlled asymmetric transformations. The last category includes asymmetric synthesis.

An asymmetric synthesis is defined as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts."[3] It is possible to obtain 100% conversion of a prochiral substrate to one chiral product by asymmetric synthesis. However, only a few nonenzymatic syntheses are this efficient. The loss of at least 50% of the starting material that is unavoidable in resolutions of racemic compounds can therefore be circumvented. The economic factor is an important driving force for the development of this kind of process since there is no waste of materials.

A good example of the impact of an efficient asymmetric synthesis is the production of chiral essential amino acids.[4] In the last few years interest in adequate world-wide nutrition has been growing and with it the price of commodities such as soybeans (rich in essential amino acids) has increased with this demand. The desire to produce L-amino acids inexpensively has resulted in the development of an efficient

1

catalytic asymmetric synthesis by the Monsanto Company (to be described in detail later).

Asymmetric synthesis occurs when diastereomeric transition states are formed between a reagent and a substrate, one of which is chiral.[5] The magnitude of the energy difference between diastereomeric transition states determines the excess of one stereoisomer over the other. Reagents (chemical, organismic, or enzymatic) are sought which will maximize the energy differences. Rationally designed syntheses attempt to make use of steric hindrance or in some other way facilitate the use of a lower energy pathway. However, it is not always possible to design an efficient asymmetric synthesis. Good attempts can be made though, given a system with a known mechanism and a normally stereoselective outcome.

It is important to use chiral reagents efficiently, that is, to be able to recycle them. Only rarely is it desirable to create one chiral center from the destruction of another. Obviously, then, one of the best ways to use chiral reagents is as catalysts. Chiral catalysts have already achieved a high degree of success. Asymmetric Wilkinson-type catalysts for homogeneous hydrogenation developed by Dr. William S. Knowles at the Monsanto Co. are good examples.[6] The Knowles catalysts have made possible the direct catalytic synthesis of D- and L-amino acid derivatives with stereoselectivities heretofore observed only in enzymatic processes (greater than 95%). The process has been applied successfully to the large scale manufacture of L-dopa, an amino acid drug used in the treatment of Parkinson's Disease. As a result of the economic leverage of the Knowles process the Monsanto Co. has become the only manufacturer of L-dopa in the United States and the leading world-wide producer. The practical formation of one or the other of two enantiomers in greater

than 90% excess is the mark of an elegant asymmetric synthesis. The

Knowles process is even more impressive because it is catalytic.

HISTORICAL

Wilkinson Catalysts

Synthesis of the Original Catalyst

The original Wilkinson catalyst, tris(triphenylphosphine)-chlororhodium(I) was well described in 1966.[7] The catalyst was prepared by allowing an excess of triphenylphosphine to react with rhodium(III) chloride hydrate in ethanol to form $RhCl(PPh_3)_3$, a dark burgundy-red crystalline complex. This complex, under one atmosphere of hydrogen at room temperature and in a suitable solvent (_i.e._ benzene) formed an octahedral dihydrido rhodium(III) complex (Figure 1) which was capable of rapid homogeneous hydrogenation of certain alkenes and alkynes.
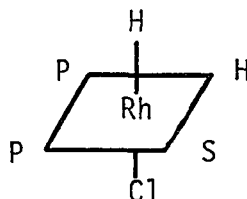
Figure 1. Octahedral dihydrido rhodium(III) complex.

An Alternate Synthesis of Wilkinson-Type Catalysts

Subsequent to Wilkinson's pioneering investigations with triphenylphosphine it was found that catalytically active dihydrido Rh

4

complexes of a variety of 3° phosphines could be obtained from an easily prepared precursor, $[Rh(diene)Cl]_2$.[8,9] This bridged Rh(I) dimer was most effective when the diene was 1,5-cyclooctadiene (COD) (Figure 2). The system most commonly employed now for in situ homogeneous hydrogenations involves the addition of two molar equivalents of a 3° monophosphine or 1 molar equivalent of a diphosphine to 0.5 equivalent of $[Rh(COD)Cl]_2$.
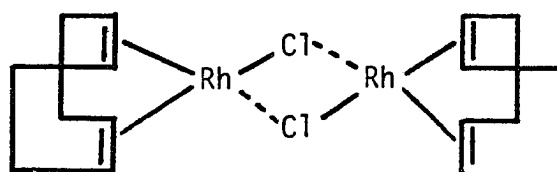
Figure 2. Preformed catalyst precursor, $[Rh(COD)Cl]_2$.

Synthetic Utility

Wilkinson-type catalysts have been found to effect rapid cis homogeneous hydrogenation of olefins and alkynes. Early rate studies of the hydrogenation of 1-heptene, cyclohexene, and 1-hexyne with the original catalyst were conducted to determine the dependence on such factors as catalyst and substrate concentration, pressure, and temperature. It was shown that at a catalyst concentration of 10^{-3} M in benzene, and at one atmosphere of hydrogen and 25°, olefins would hydrogenate so rapidly that the solution would boil. Wilkinson-type catalysts exhibit high specificity in the reduction of carbon-carbon double bonds in the presence of other

functional groups. They also are specific for unhindered olefins. Unlike most heterogeneous catalysts they are not poisoned by divalent sulfur.[20]

Mechanism of Action

Cationic Versus Neutral Catalyst Species. The Wilkinson catalyst can exist as either a cationic or neutral species. The neutral species, $RhCl(PPh_3)_3$, was described by Wilkinson. It was discovered that similar hydrogenation results could be obtained when a cationic catalyst, $[Rh(diene)L_n]^+A^-$ (L=tertiary phosphine ligand with n=1,2; $A^-=ClO_4^-$, BF_4^-, or PF_6^-) was used.[10] Both cationic and neutral catalysts are currently used. A cationic phosphine containing catalyst has the advantage of being air stable while the free phosphine used to form the neutral catalyst is air sensitive. Numerous studies have been conducted to determine the efficacy of one species over the other but no conclusive evidence has yet been presented. There are still unresolved questions about the precise nature of the catalytic process for the two species, although certain generalities have been elucidated.

The Mechanism Proposed by Wilkinson. Wilkinson proposed a catalysis mechanism that is shown in Figure 3.[7] His first assumption was that the complex, $RhClL_3$, initially underwent essentially complete dissociation of a phosphine ligand to give an unsaturated complex $RhClL_2$. This assumption has been proved wrong.[11] The dissociation of a ligand has been found to be very unfavorable and to occur in less than

$$RhClL_3 \rightleftharpoons RhClL_2 + L$$

$$RhClL_2 \underset{}{\overset{H_2}{\rightleftharpoons}} H_2RhClL_2$$

01 ⇅ (a)   (b) ↓ 01

$$(01)RhClL_2 \overset{H_2}{\longrightarrow} RhClL_2 + paraffin$$
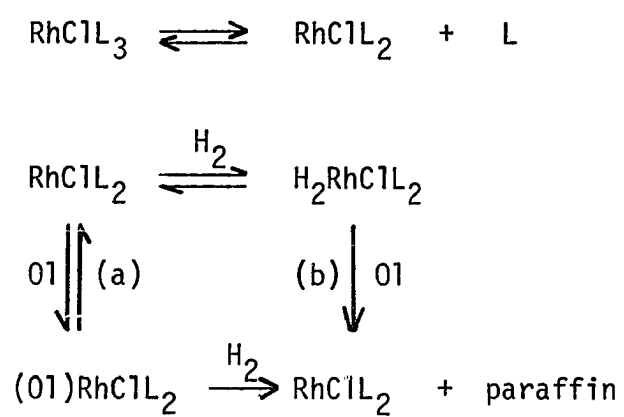
01 = olefin

L = PPh_3

Figure 3. Original mechanism proposed by Wilkinson.

5%. It was further proposed that the unsaturated complex could promote
hydrogenation by one of two pathways, one involving olefin coordination
as a first step (a, in Figure 3) and the other involving oxidative
addition of hydrogen as a first step (b, in Figure 3).

These mechanistic alternatives, and others involving oxidative
addition of hydrogen prior to ligand dissociation (see below) have been
reviewed. Their relative importance is still open to debate. However,
as will be shown, there is common agreement that at some point in the
sequence there is oxidative addition of a hydrogen molecule and disso-
ciation of one phosphine ligand to form a dihydrido olefin rhodium(III)
complex (A, in Figure 4). The coordinated olefin inserts into a Rh-H
bond to give an alkyl rhodium intermediate (B, in Figure 4),and then via
reductive elimination an unsaturated catalytic species (C, in Figure 4)
is regenerated and saturated product is released.

Mechanistic Alternatives. A mechanism proposed by Dolcetti and
Hoffman is shown in Figure 5.[11] It is a well established fact that
$RhCl(PPh_3)_3$ is a square planar Rh(I) complex. Whether this complex first
undergoes oxidative addition of H_2 to form the octahedral dihydride Rh(III)
complex (step 1) or whether the olefin adds first (step 7) is uncertain.
Whichever takes place first, it is postulated that the dissociation of a
phosphine ligand (L) occurs subsequently (steps 2 and 8). (A solvent
molecule would occupy a position in the coordination sphere of the
octahedral complex at this point.) In step 3 the olefin adds to the
active dihydride species or alternatively, in step 9, H_2 adds to form the
Rh(III) dihydride. Through stages 4, 5 and 6 the pathway is the same
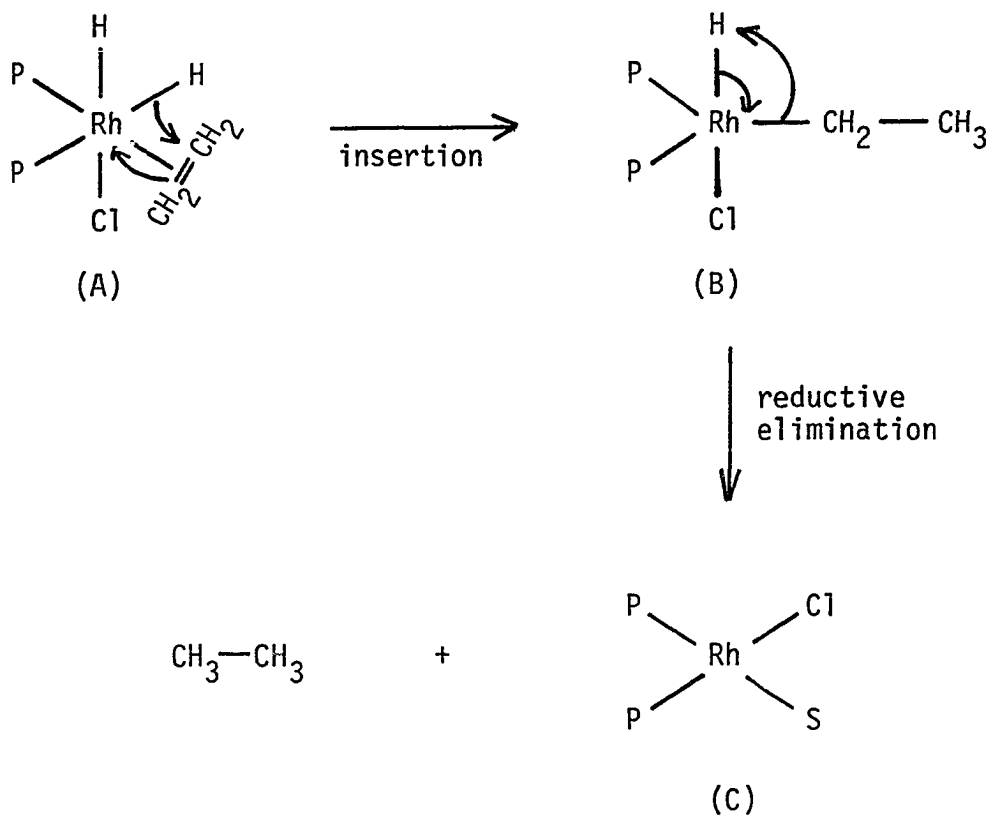
Figure 4. Insertion of an olefin followed by reductive elimination to regenerate the catalyst and release the saturated product.

RCH_2CH_3

$RhClL_3$

H_2 $RCH=CH_2$

(6)

(1)   (7)

$RCH_2CH_2RhHClL_3$

H_2RhClL_3 $(RCH=CH_2)RhClL_3$

L   (5)

(2)   L   (8)

$RCH_2CH_2RhHClL_2$

H_2RhClL_2 $(RCH=CH_2)RhClL_2$

(4)

(3)   (9)

$H_2RhClL(CH_2=CHR)$

$CH_2=CHR$ H_2
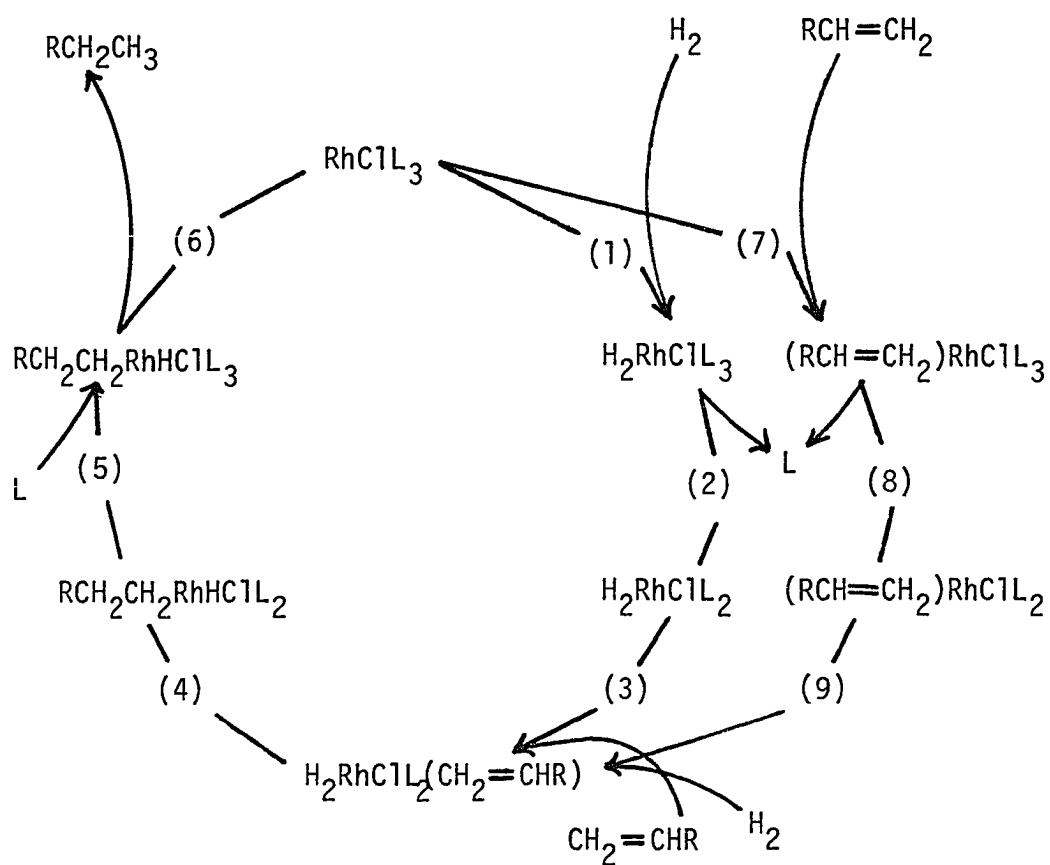
Figure 5. The mechanism proposed by Dolcetti and Hoffman for the neutral Wilkinson catalyst.

regardless of the preceding steps with insertion of the olefin to form the sigma bonded alkyl then reductive elimination of the alkane and regeneration of the active catalyst (regains the formerly dissociated ligand).

The Mechanism Proposed by Schrock and Osborn for the Cationic Wilkinson Catalyst. In 1976, Schrock and Osborn proposed a mechanism for homogeneous hydrogenations involving cationic complexes (Figure 6).[10] The initial 6 steps are essentially the same as those shown in Figure 3 for the neutral catalyst except that the complex is cationic and the problem of ligand dissociation is avoided by not designating the number of ligands present. The difference is seen with the complex $[RhH_2L_n]^+Cl^-$ which can by loss of HCl become the neutral species $RhHL_n$ (step 7). This species can then add olefin in step 8 to form $RhHL_n(Ol)$ which can undergo insertion (step 9) to form an alkyl rhodium complex, $RhRL_n$. Addition of H_2 (step 10) to form RhH_2L_n (where rhodium is once again in the plus three state) allows reductive elimination of RH (the saturated product) and regeneration of $RhHL_n$. This "side" mechanism (steps 7-11) has been found to be associated with the isomerization of unsaturated substrates; it can be suppressed by keeping the reaction medium acidic. Whichever reduction pathway is active in steps 1-6, the process is known to be slower than that in the "side mechanism", but it does not cause the isomerization of substrates.
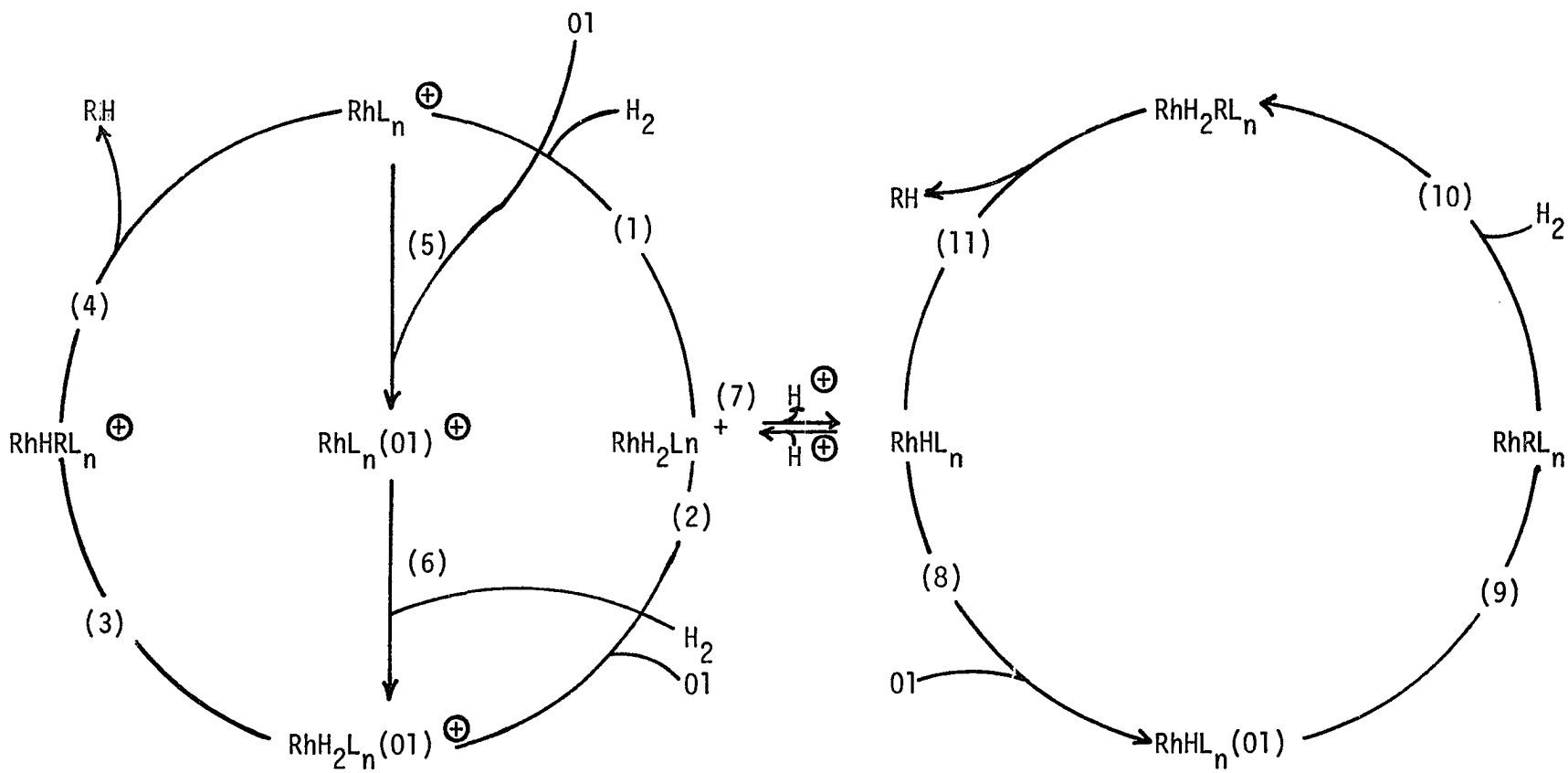
Figure 6. The mechanism proposed by Schrock and Osborn for the cationic Wilkinson catalyst.

Chiral Wilkinson-Type Catalysts

Chiral Ligands

With the success of achiral Wilkinson-type catalysts in the hydrogenation of carbon-carbon double bonds it was logical that there should be a progression to the design of chiral systems. Several workers recognized the potential value of incorporating chiral phosphine ligands into the Wilkinson catalyst system thereby producing an asymmetric homogeneous hydrogenation catalyst.

There have been many studies of such systems. The chiral phosphine, phosphinite, and aminophosphine ligands that have been used to prepare chiral catalysts for the hydrogenation of carbon-carbon double bonds are listed in Figure 7.

General Methods of Ligand Synthesis

P-Chiral Ligands. The variety of chiral ligands that could be synthesized for use in the Wilkinson-type catalyst is limited only by the imagination and skill of the synthetic chemist. The first researchers in this area attacked the synthesis problem by making ligands that were chiral at phosphorus (P-chiral). These P-chiral ligands were prepared using Mislow's scheme for the synthesis of optically active phosphine oxides which, in turn, can be deoxygenated stereospecifically to chiral phosphines (Figure 8).[42,43,44]

The syntheses of two P-chiral ligands, o-anisylcyclohexylmethylphenylphosphine (ACMP or CAMP) (2) and 1,2-ethanediylbis-[(o-methoxyphenyl)phenylphosphine] (DIPAMP) (12), both synthesized by

OMe
|
Me—P

Ph—P—Me
|
n—Pr

C₆H₁₁
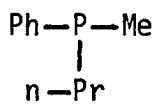
(+)-(S)-Methylphenyl-n-propyl-
phosphine (Ref. 9)

(+)-(R)-ACMP   (Ref. 12, 13)

1

2

OMe
|
Me—P

Me—P—i—Pr
|
Ph

Ph
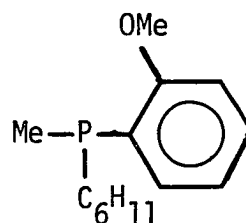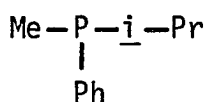
(-)-Methylisopropylphenyl-
phosphine (Ref. 8) 90%
optical purity
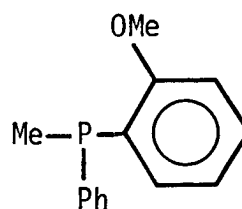
o-Anisylmethylphenylphosphine
(Ref. 8) 95% optical purity

3

4

OMe

Me—P

Me—P—C₆H₁₁
|
Ph

Ph
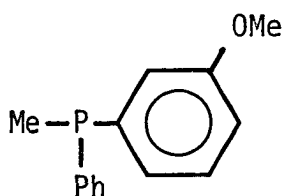
m-Anisylmethylphenylphosphine
(Ref. 8) 80% optical purity
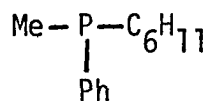
Cyclohexylmethylphenylphosphine
(Ref. 8) 75% optical purity

5

6a

Figure 7.   Chiral phosphine, phosphinite, and phosphinamide ligands
used for asymmetric homogeneous hydrogenation of carbon-
carbon double bonds with the Wilkinson-type catalyst.*

Figure 7 Continued.

OMe

Me —P—Ph
|
Et

i—Pr—P
|
Ph
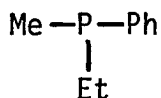
(R)-Ethylmethylphenylphosphine
(Ref. 50)

o-Anisylisopropylphenyl-
phosphine (Ref. 8) 80%
optical purity

6b

7

OMe

Me —P
|
n—Pr

OMe

PhCH₂—P
|
Me
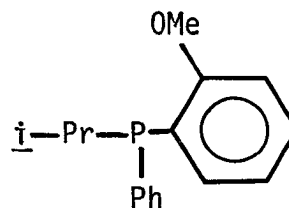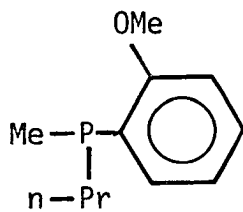
o-Anisylmethyl-n-propylphosphine
(Ref. 8) 95% optical purity
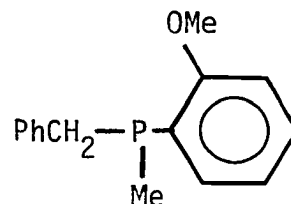
o-Anisylbenzylmethylphosphine
(Ref. 12)

8

9

OMe

CH_3
|
P—CH₂CH—CH₃
|
Me

$PhCH_2$—P—Ph
|
Me
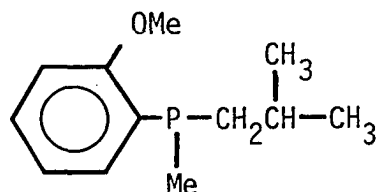
o-Anisylisobutylmethylphosphine
(Ref. 12)
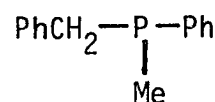
(R)-Benzylmethylphenyl-
phosphine (Ref. 14)

$[\alpha]_D^{25}$ 84° (c 1.3, toluene)

10

11

Figure 7 Continued.
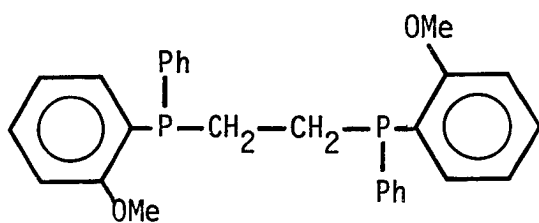
(-)-(R,R)-DIPAMP   (Ref. 16)

12
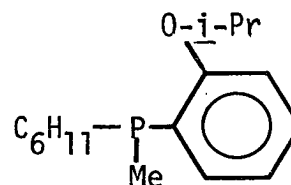
Cyclohexyl-o-isopropoxyphenyl-
methylphosphine   (Ref. 13, 17)

13a
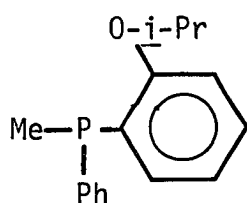
o-Isopropoxyphenylmethylphenyl-
phosphine   (Ref. 13)

13b
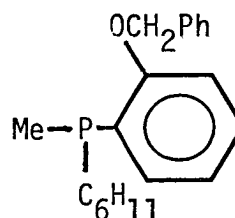
o-Benzyloxyphenylcyclohexyl-
methylphosphine   (Ref. 13)

13c
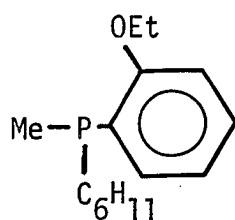
Cyclohexyl-o-ethoxyphenylmethyl-
phosphine   (Ref. 13)

13d
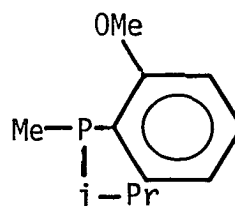
o-Anisylisopropylmethylphosphine
(Ref. 13)

13e

Figure 7 Continued.
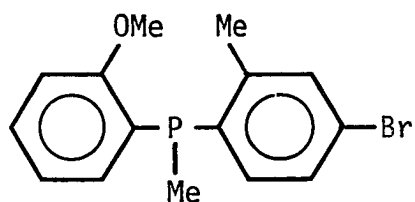
o-Anisylmethyl-2-methyl-4-
bromophenylphosphine (Ref. 13)

<u>13f</u>
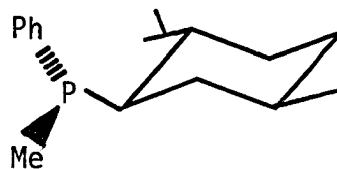
(S)-MMPP (Ref. 18) 96%
optical purity (R)$_p$ also
synthesized

<u>14</u>

Et—CH—CH$_2$PPh$_2$
      |
      Me
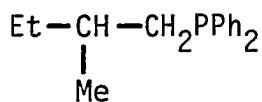
(+)-(S)-2-Methylbutyldiphenyl-
phosphine (Ref. 15)

<u>15</u>

Ph—CH—CH$_2$PPh$_2$
      |
      Et
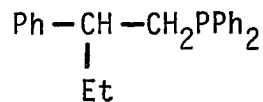
(+)-(S)-2-Phenylbutyldiphenyl-
phosphine (Ref. 15)

<u>16**</u>

Me—CH—C$_6$H$_{13}$
      |
      PPh$_2$
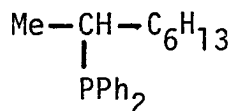
(+)-2-Octyldiphenylphosphine
(Ref. 15)

<u>17</u>
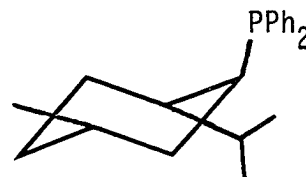
(+)-(1R,3S,4S)-NMDPP (Ref. 15)

<u>18</u>

Figure 7 Continued.

$$Ph-P-(CH_2CH-Et)_2$$

with Me on the P
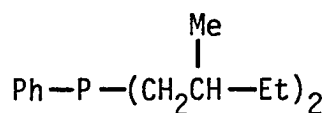
Bis(sec-butyl)phenylphosphine
(Ref. 6)

19
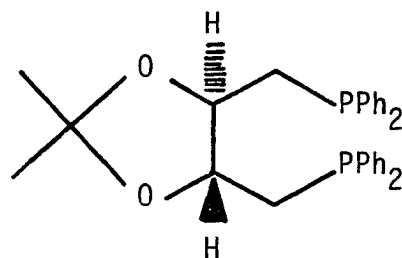
(-)-(2R,3R)-DIOP   (Ref. 19)

20
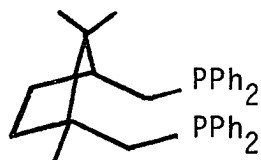
(+)-CAMPHOS   (Ref. 20)

21

(-)-MDPP   (Ref. 20)

22
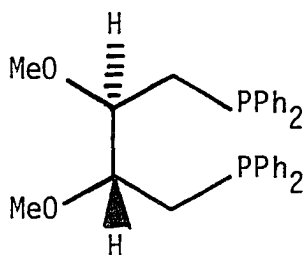
(+)-2,3-Dimethoxy-1,4-bis-
(diphenylphosphino)butane
(Ref. 19) $[\alpha]_D$ 4.0° ($\underline{c}$ 2.45,
benzene)

23
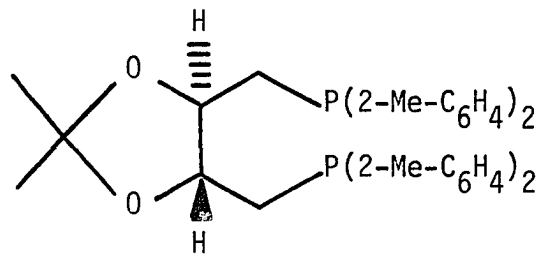
(-)-2,3-0-Isopropylidene-1,4-
bis(di-o-tolylphosphino)butane
(Ref. 21) $[\alpha]_D^{22}$ -13.5° ($\underline{c}$ 2.2,
benzene)

24

Figure 7 Continued.
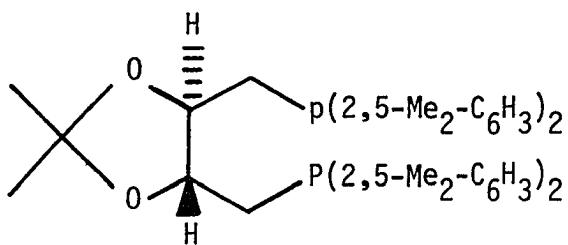
(-)-2,3-0-Isopropylidene-1,4-
bis(di-2,5-dimethylphenylphos-
phino)butane (Ref. 21)
$[\alpha]_D^{22}$ -18.9° ($\underline{c}$ 1.6, benzene)

25
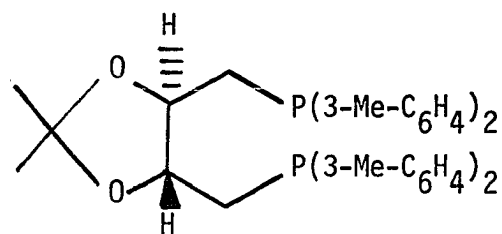
(-)-2,3-0-Isopropylidene-1,4-
bis(di-$\underline{m}$-tolylphosphino)butane
(Ref. 21, 22) $[\alpha]_D^{22}$ -3.46°
($\underline{c}$ 2, benzene)

26
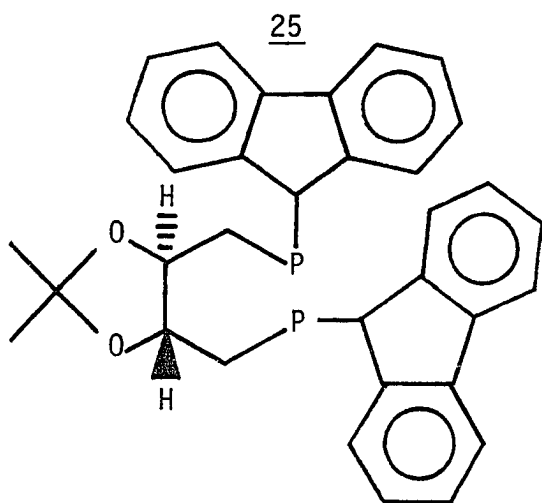
(-)-2,3-0-Isopropylidene-1,4-
bis(2,2'-biphenylphosphino)-
butane (Ref. 21, 22)
$[\alpha]_D^{22}$ -65.5° ($\underline{c}$ 2, benzene)

27
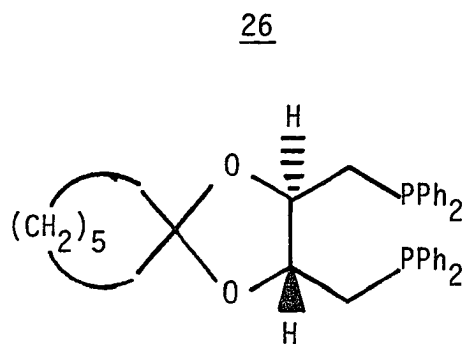
(-)-2,3-0-Cyclohexyl-1,4-
bis(diphenylphosphino)butane
(Ref. 21) $[\alpha]_D^{22}$ -18.7°
($\underline{c}$ 2, benzene)

28
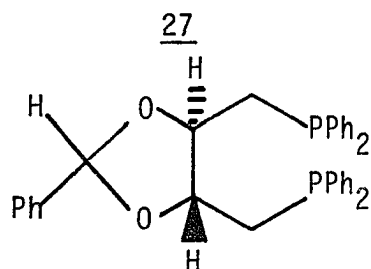
(-)-2,3-0-Benzyl-1,4-bis-
(diphenylphosphino)butane
(Ref. 21) $[\alpha]_D^{22}$ -26.0°
($\underline{c}$ 2, benzene)

29
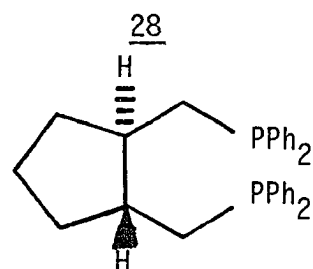
(-)-(1R,2R)-trans-1,2-Bis-
(diphenylphosphinomethyl)
cyclopentane (Ref. 21)
$[\alpha]_D^{22}$ -25.9° ($\underline{c}$ 1, benzene)

30

Figure 7 Continued.
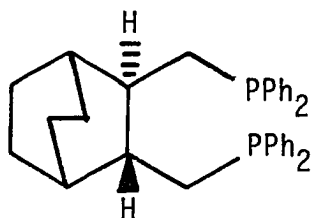
(-)-1,2-Bis(diphenylphosphino-
methyl)bicyclo[2.2.2]octene
(Ref. 21) $[\alpha]_D^{22}$ -20.0°
(c 1, benzene)

31
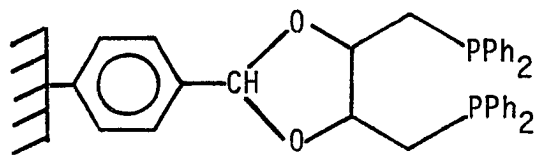
(Ref. 23)

32
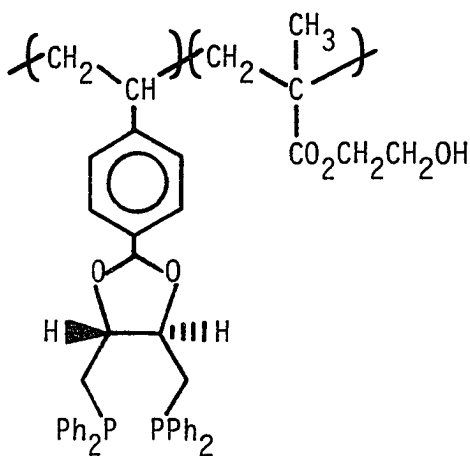
(Ref. 24)

33
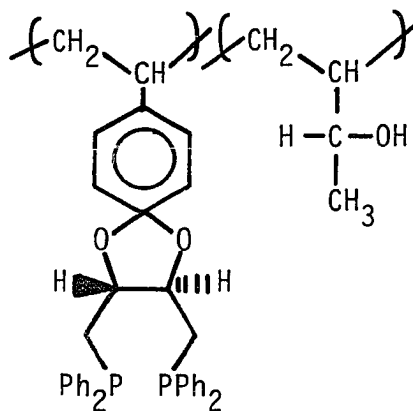
(Ref. 25)

34
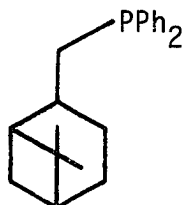
(-)-cis-Myrtanyldiphenyl-
phosphine (Ref. 26)

35
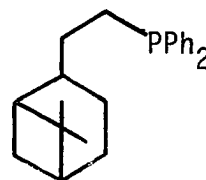
(-)-cis-Dihydronopyldiphenyl-
phosphine (Ref. 26)

36

Figure 7 Continued.
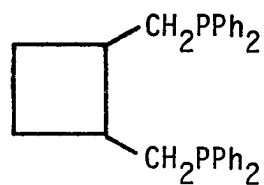
(1R,2R)-<u>trans</u>-1,2-Bis(diphenyl-phosphinomethyl)cyclobutane
(Ref. 27)

<u>37</u>
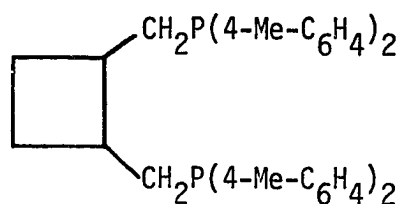
(1R,2R)-<u>trans</u>-1,2-Bis(ditolyl-phosphinomethyl)cyclobutane
(Ref. 27)

<u>38</u>
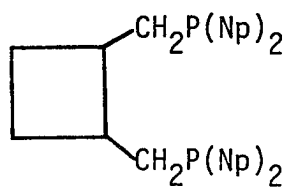
(1R,2R)-<u>trans</u>-1,2-Bis(dinaphthyl-phosphinomethyl)cyclobutane
(Ref. 27)

<u>39</u>
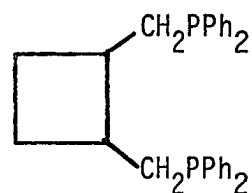
(1R,2R)-<u>trans</u>-1,2-Bis(diphenyl-methyl)cyclohexane (Ref. 28)

<u>40</u>
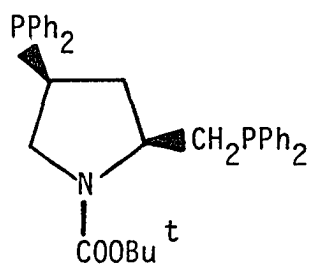
(-)-(2S,4S)-BPPM (Ref. 29)

<u>41</u>
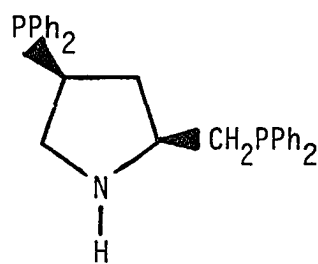
(-)-(2S,4S)-PPM (Ref. 29)

<u>42</u>

Figure 7 Continued.

PPh$_2$

(2S,4S)-PPM   (Ref. 30)

CH_3—CH—CH_2—PPh_2
|
Ph

(R)-PROPHOS   (Ref. 31)

<u>43</u>

<u>44</u>

CH_3—CH—CH—CH_3
| |
$PPh_2 PPh_2$
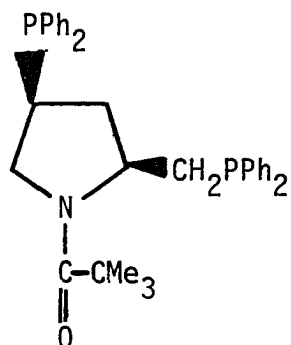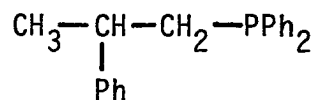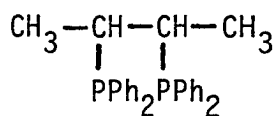
(-)-(2S,3S)-CHIRAPHOS   (Ref. 31)
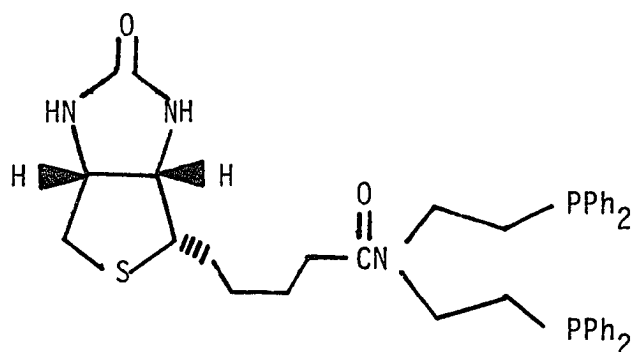
N,N-Bis(2-diphenylphosphino-
ethyl)biotinamide   (Ref. 42)

<u>45</u>

<u>46</u>

CH_2PPh_2
CH_2PPh_2

(-)-(S)-NAPHOS(1,1)   (Ref. 33)

Fe
PPh_2
PPh_2
CH—NMe_2
|
Me

(+)-(S)-(R)-BPPFA   (Ref. 34)

<u>47</u>
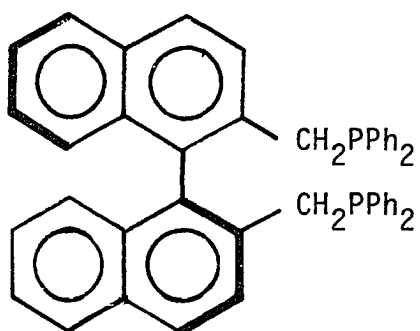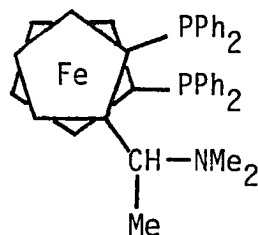
<u>48</u>

Figure 7 Continued.
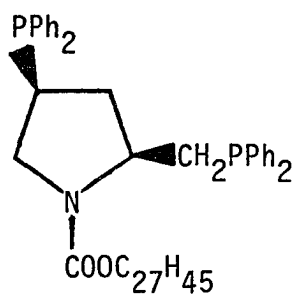
(-)-(2S,4S)-CPPM   (Ref. 35)
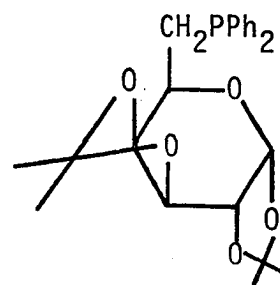
6-Deoxy-1,2,3,4-di-0-iso-
propylidene-6-diphenylphosphino-
α-D-galactopyranose   (Ref. 36)

<u>49</u>

<u>50</u>
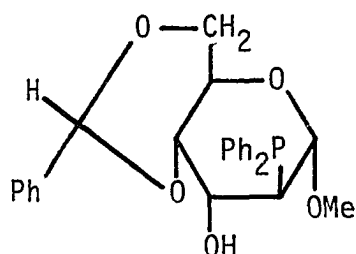
Methyl-4,6-0-benzylidene-2-
deoxy-2-diphenylphosphino-
α-D-altropyranoside   (Ref. 36)

(+)-(1S,2S)-BDPCH   (Ref. 37)

<u>51</u>
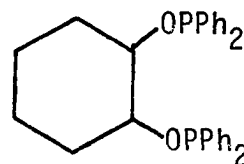
<u>52</u>
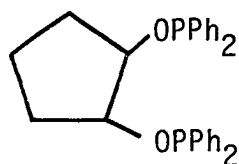
(+)-<u>trans</u>-BDPCP   (Ref. 38)
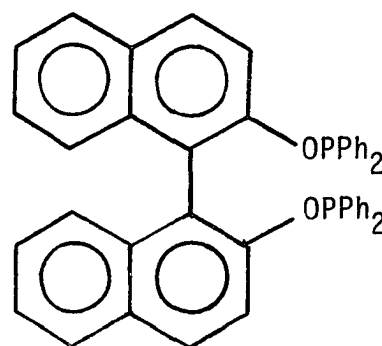
(-)-1,1'-Bi-2-naphthylbis-
(diphenylphosphinite)   (Ref. 39)

<u>53</u>

<u>54</u>

Figure 7 Continued.

CH$_2$OCPh$_3$

(structure with pyranose ring, OPPh$_2$, OPPh$_2$)

(Ref. 40)

55

CH$_3$ CH$_3$
| |
Ph—CH   Ph   CH—Ph
| | |
N — P — N
| |
Me   Me
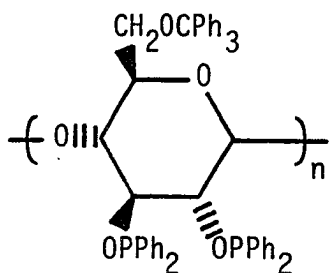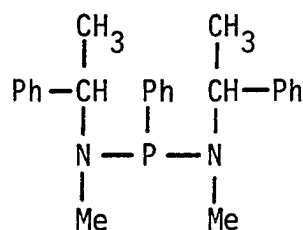
Phenylphosphonous acid bis-
[N-methyl-(S)-α-phenethylamide]
(Ref. 41)

56

CH$_3$ CH$_3$
| |
Ph—CH   Ph   CH—Ph
| | |
N — P — N
| |
CH$_2$———CH$_2$
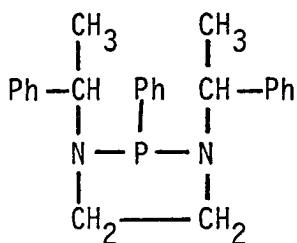
[(S)-α-Phenylethyl]-2-phenyl-
2-phosphaimidazolidine
(Ref. 41)

57

CH$_3$ PPh$_2$
| |
Ph—CH—N—CH$_2$—CH$_2$—N—CH—Ph
        | |
       PPh$_2$ CH$_3$

(Ref. 41)

58

CH$_3$—CH—N—PPh$_2$
       | |
       Ph Et
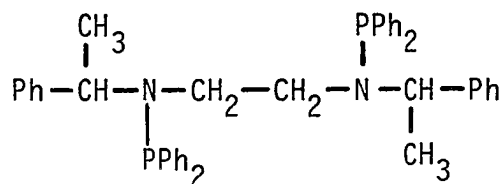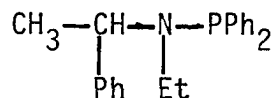
(+)-(R)-Ethyl-N-(α-methylbenzyl)-
diphenylphosphine (Ref. 15)

59

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*Data concerning configuration, rotation, and optical purity was not
available for all ligands. Data is given where available.

**Renumbered and referred to as <u>80</u> in Results and Discussion when
prepared <u>via</u> the tosylate in this study.

$$Ph-PCl_2 \quad \xrightarrow[C_5H_5N]{CH_3OH} \quad Ph-P(OCH_3)_2$$

$$\downarrow CH_3I$$

$$\overset{O}{\underset{CH_3}{\overset{\|}{Ph-P-Cl}}} \quad \xleftarrow{PCl_5} \quad \overset{O}{\underset{CH_3}{\overset{\|}{Ph-P-OCH_3}}}$$

$$\downarrow \quad \begin{array}{l} (-)\text{-menthol} \\ C_5H_5N \end{array}$$

$$\overset{O}{\underset{CH_3}{\overset{\|}{Ph-P-O-menthyl}}} \quad \xrightarrow{\text{resolution}} \quad \overset{O}{\underset{CH_3}{\overset{\|}{Ph^{||||}P-O-Men}}} + \overset{O}{\underset{Ph}{\overset{\|}{CH_3^{||||}P-O-Men}}}$$

$$(R) \qquad\qquad (S)$$

$$\overset{O}{\underset{Ph}{\overset{\|}{CH_3^{||||}P-O-Men}}} \quad \xrightarrow{RMgX} \quad \overset{O}{\underset{CH_3}{\overset{\|}{Ph^{||||}P-R}}} \quad \xrightarrow{HSiCl_3{*}} \quad \overset{\cdot\cdot}{\underset{CH_3}{\overset{|}{Ph^{||||}P-R}}}$$
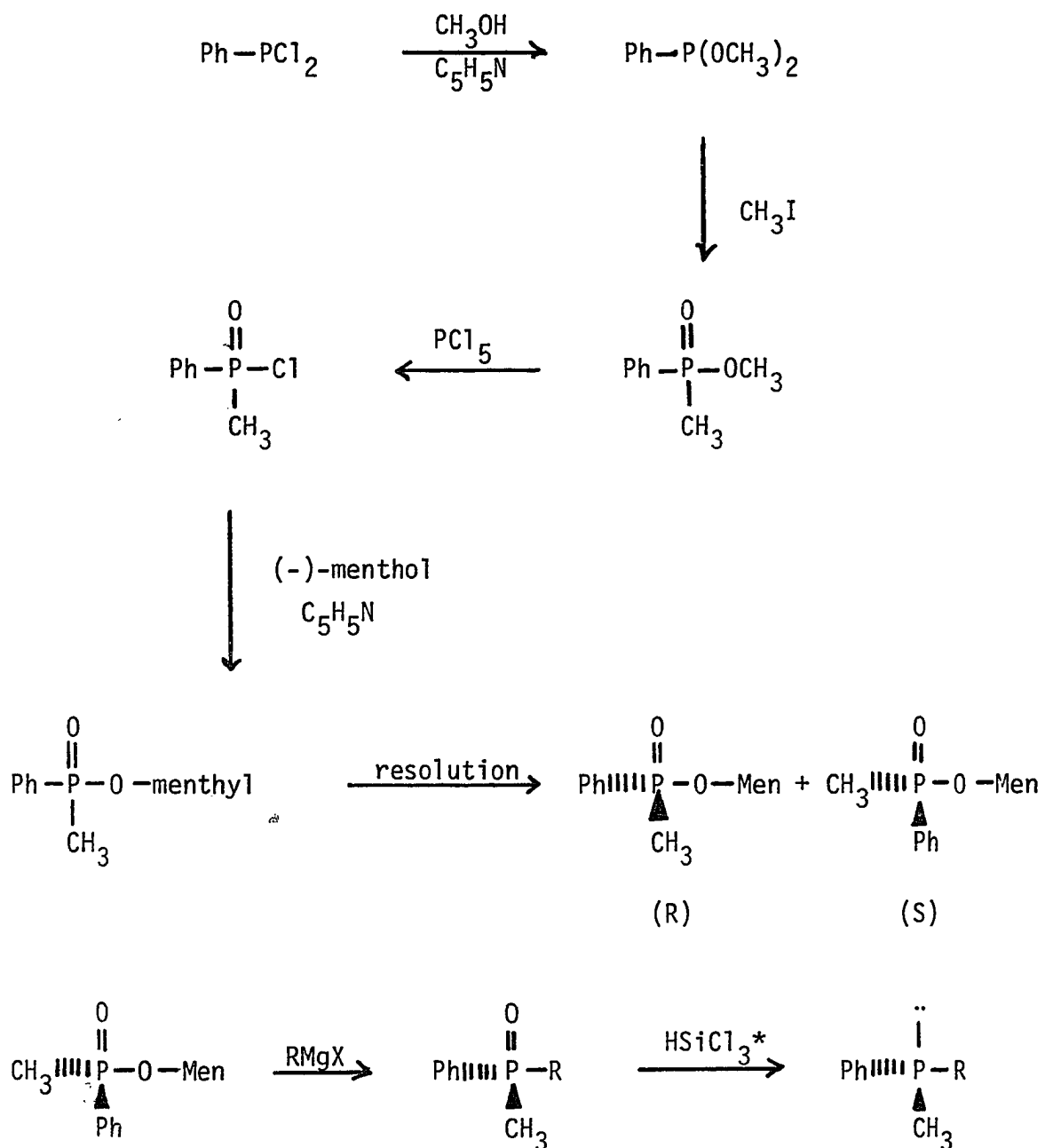
Figure 8.   Mislow's procedure for preparation of optically active phosphines.

*Conditions are also available for deoxygenation with inversion (see text).

Knowles and coworkers at Monsanto, will be described in detail. Catalysts prepared from these ligands have been highly effective for the asymmetric homogeneous hydrogenation of α-acetamidoacrylic acids. The synthesis of ACMP is illustrated in Figure 9.[13] The R menthyl phosphinate was obtained by fractional crystallization of the mixture of diastereomeric esters from α- or β-pinene. The R ester was then allowed to react with an o-anisyl Grignard reagent to displace menthol. The benzene ring of the resulting diaryl phosphine oxide was selectively hydrogenated with rhodium on carbon and the monoaryl phosphine oxide was deoxygenated with trichlorosilane and triethylamine (inversion) to give the R phosphine. DIPAMP is prepared from the ACMP precursor diaryl phosphine oxide, as shown in Figure 10.[46] Neither ACMP nor DIPAMP is commercially available and both syntheses are tedious, therefore, these ligands have not been tested as extensively as some others (e.g., DIOP, see below).

C-Chiral Ligands. As is obvious from Figure 7 a great variety of ligands chiral at carbon (C-chiral) is available. One method of synthesizing C-chiral phosphines is used more often than any other due to its general utility in preparing ligands not chiral at phosphorus. The procedure was used by Kagan for the synthesis of the highly successful C-chiral ligand 2,3-0-isopropylidene-1,4-bis(diphenylphosphino)butane (DIOP) (20).[19] The synthesis of DIOP involves formation of a tosylate which is allowed to react with diphenylphosphide anion to form the desired phosphine (20) (Figure 11).[47] Tosylate displacement procedures have been used to prepare many of the C-chiral ligands shown in Figure 7. The polymer supported DIOP derivative (32) was prepared in a similar manner (Figure 12).[23]

Ph
|
O=P⦀CH₃
▲
OMen

―MgBr

OCH₃

OCH₃
O=P⦀⦀CH₃
▲
Ph

(R)ₚ

H₂

Rh/C

HSiCl₃

Et₃N

OCH₃
O=P⦀⦀CH₃
▲

: ―P⦀ CH₃
OCH₃

(+)-(R)-ACMP

(R)ₚ

Men = 1-menthyl
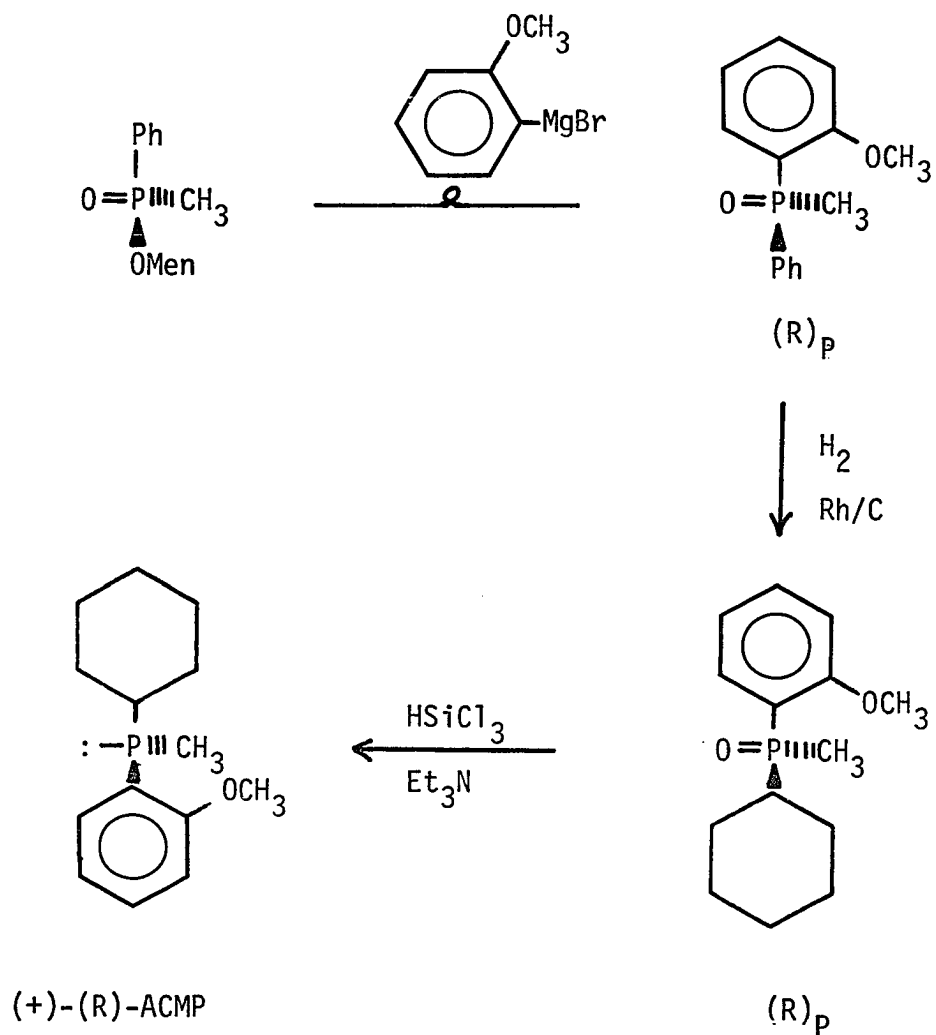
Figure 9.   The synthesis of ACMP.

Ph
|
O=P|||||CH$_3$
▲
OMen

—MgBr

$^OCH_3$

Ph
|
O=P||||CH$_3$
▲
Ph

$^OCH_3$

1) LiN($\underline{i}$C$_3$H$_7$)$_2$

2) Cu(II)

$_OCH_3$

(O=P|||| CH$_2$)$_2$
▲
Ph

(R, R)

Ph
|
(:P—CH$_2$)$_2$
▲
OCH$_3$

HSiCl$_3$
tributylamine
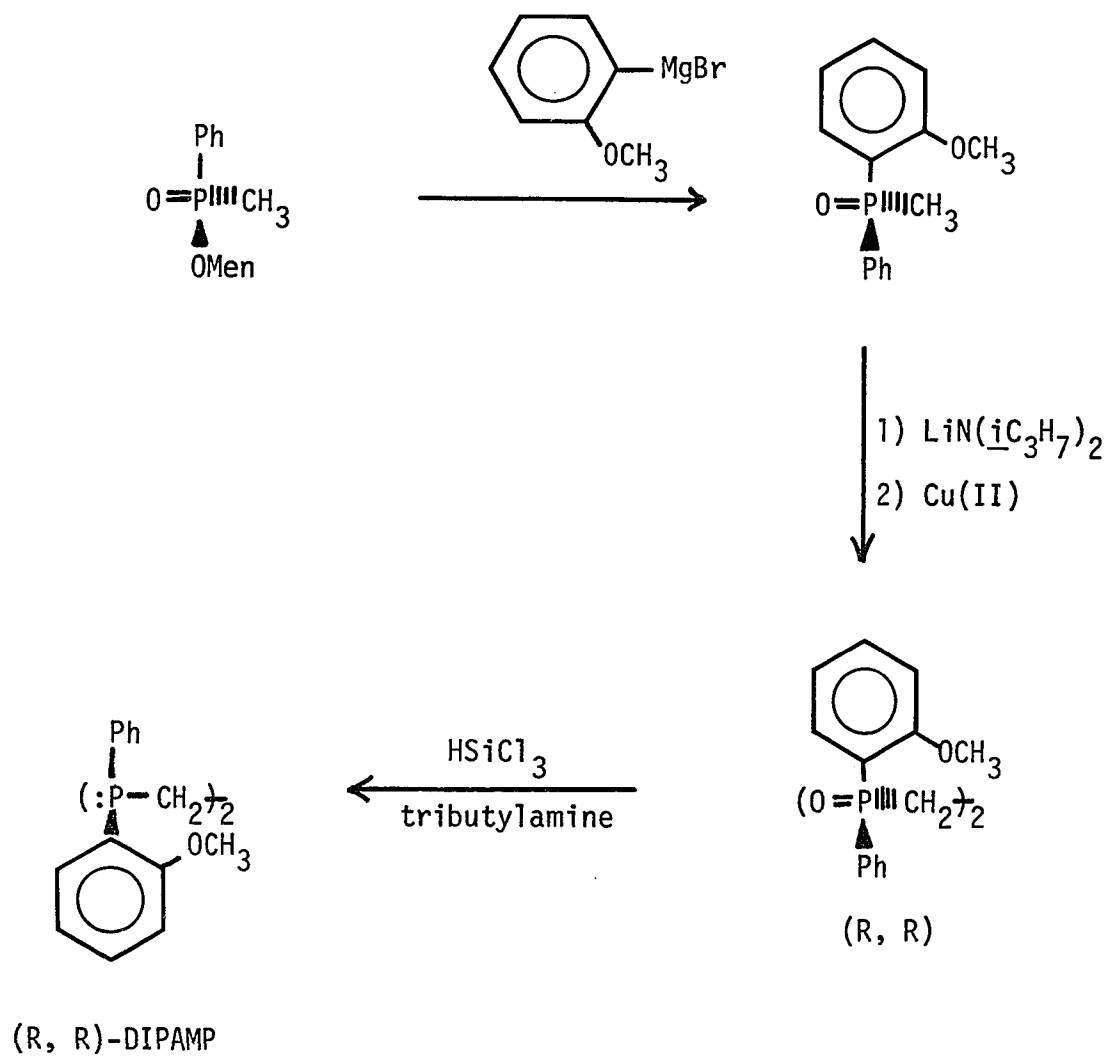
(R, R)-DIPAMP

Figure 10.   The synthesis of DIPAMP.

COOH
HCOH
HOCH
COOH

xs.

OMe   OMe

CH₃CCH₃

pTsOH (cat.)
C₆H₁₂ (solvent)

→

(dioxolane ester structure with COOEt groups)

1) LiAlH₄

2) NaOH

(dioxolane diol structure, CH₂OH)

TosCl
C₅H₅N

(dioxolane ditosylate structure, CH₂OTs)

M⁺
PPh₂⁻
THF

(dioxolane diphosphine structure, PPh₂)

M = Li, Na, K

(-)-(R, R)-DIOP
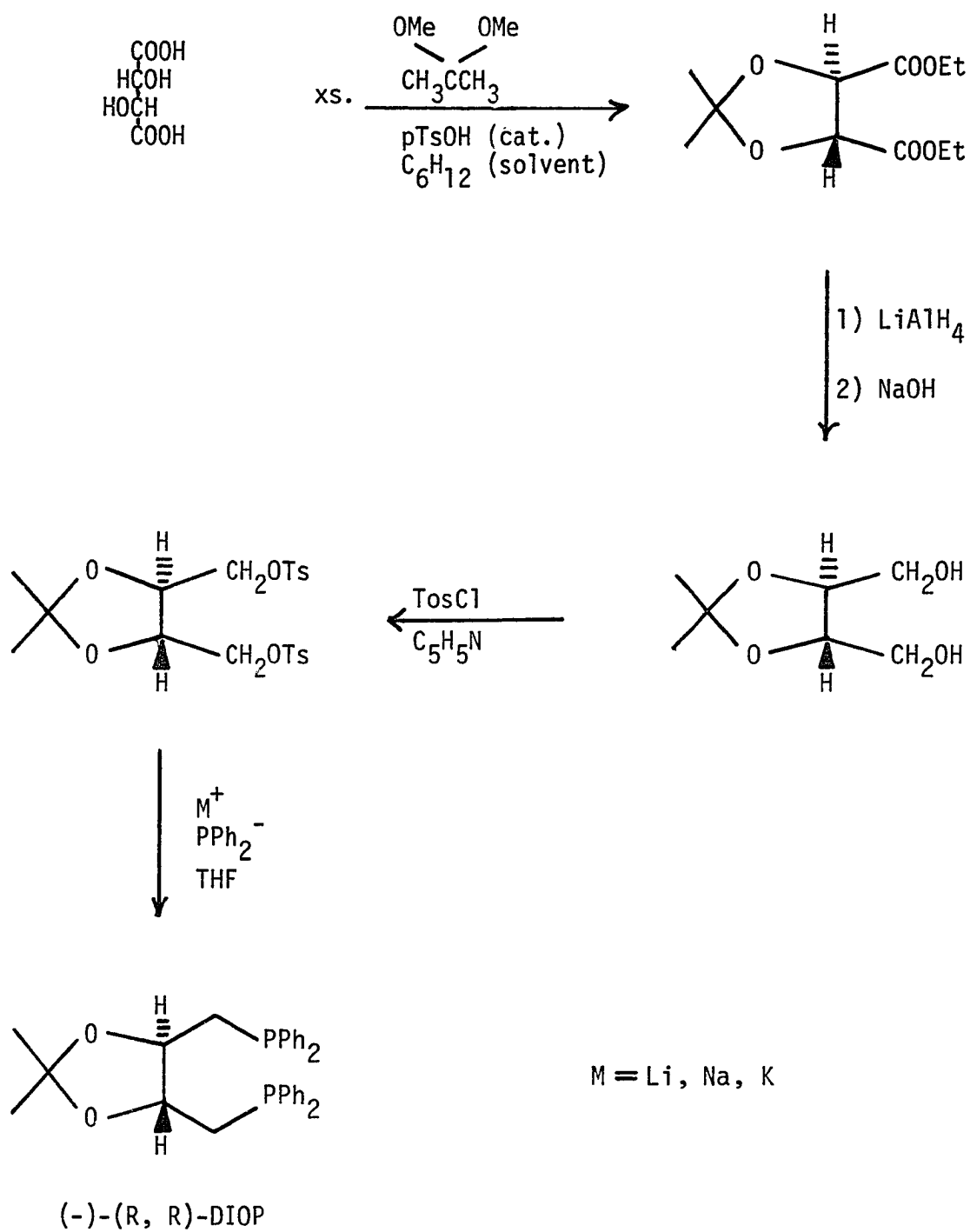
Figure 11.   The synthesis of DIOP.
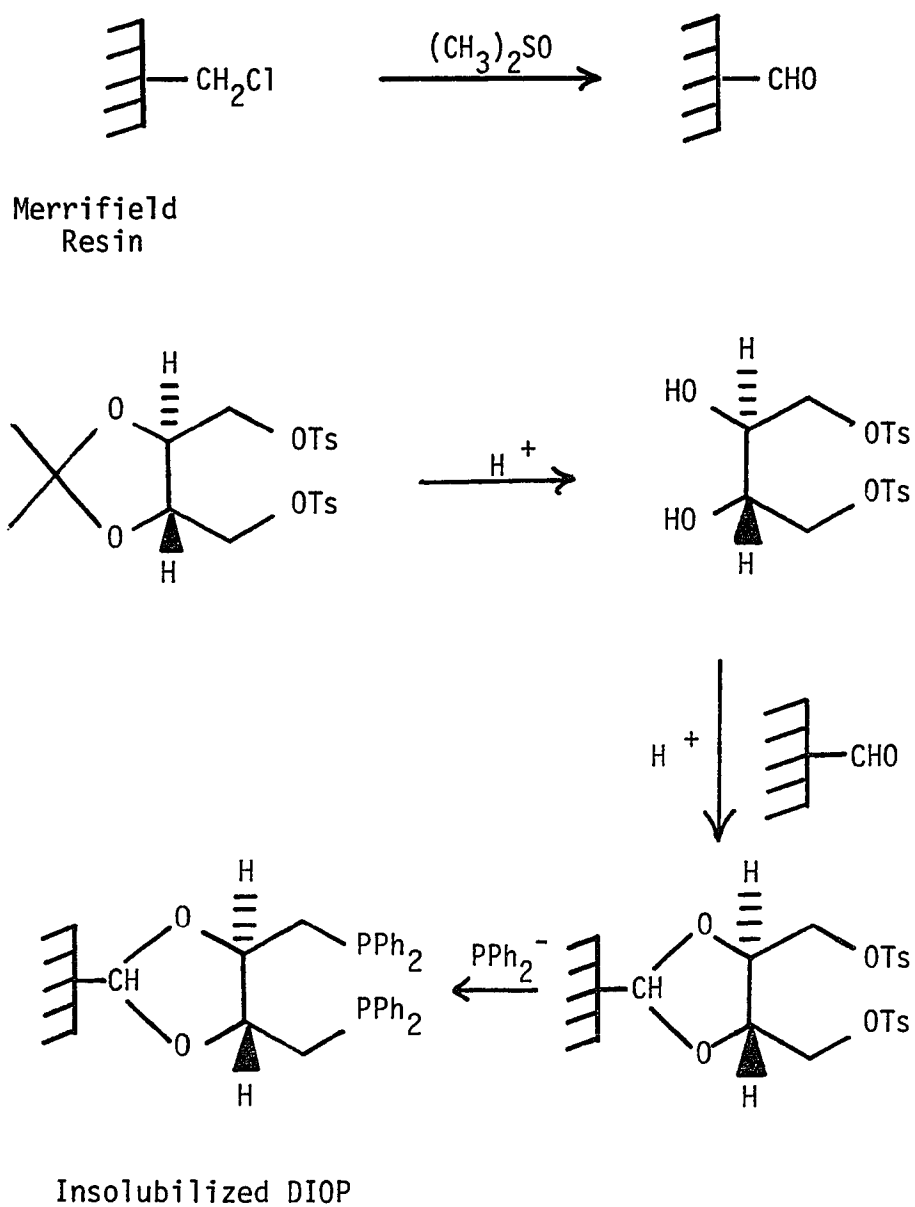
Figure 12. Preparation of polymer-supported DIOP.

Neomenthyldiphenylphosphine (NMDPP) (18) has been prepared by
conversion of menthol to menthyl chloride followed by displacement with
phosphide anion.[20] This procedure, modifications of which have been
used to synthesize other phosphines (e.g., 22), has been well reviewed.[48,49]

The synthesis of one other C-chiral ligand deserves specific
comment. (2S,3S)-Bis-(diphenylphosphino)butane (CHIRAPHOS) (45) was
prepared according to the general tosylate displacement procedure.[31]
However, the isolation and purification procedure is worth special notice.
The phosphine was separated from by-products as an insoluble nickel(II)
complex which was then freed with cyanide ion. Yields of 20-30% of
CHIRAPHOS were obtained in this manner.

C-Chiral Plus P-Chiral Ligands. One ligand that is chiral at
both phosphorus and carbon has been reported. Menthylmethylphenylphosphine
(MMPP) (14)[18] was synthesized from neomenthyl chloride via reaction with
sodium methylphenylphosphide. This reaction produced a mixture of epimers
(R_p and S_p) which were converted to their respective phosphine oxides and
then separated by chromatography on silica gel. After separation the
phosphine oxides were reduced with phenylsilane to give the free phosphines.
Under the reducing conditions S_p-MMPP was stereochemically stable but the
R_p isomer underwent 13-25% epimerization.

Tertiary Phosphines having Axial Chirality. The ligand (-)-(S)-
2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl [NAPHOS(1,1)] (47) was
the first reported example of a chiral phosphine possessing axial
chirality.[33] This ligand was prepared via an Arbuzov reaction between
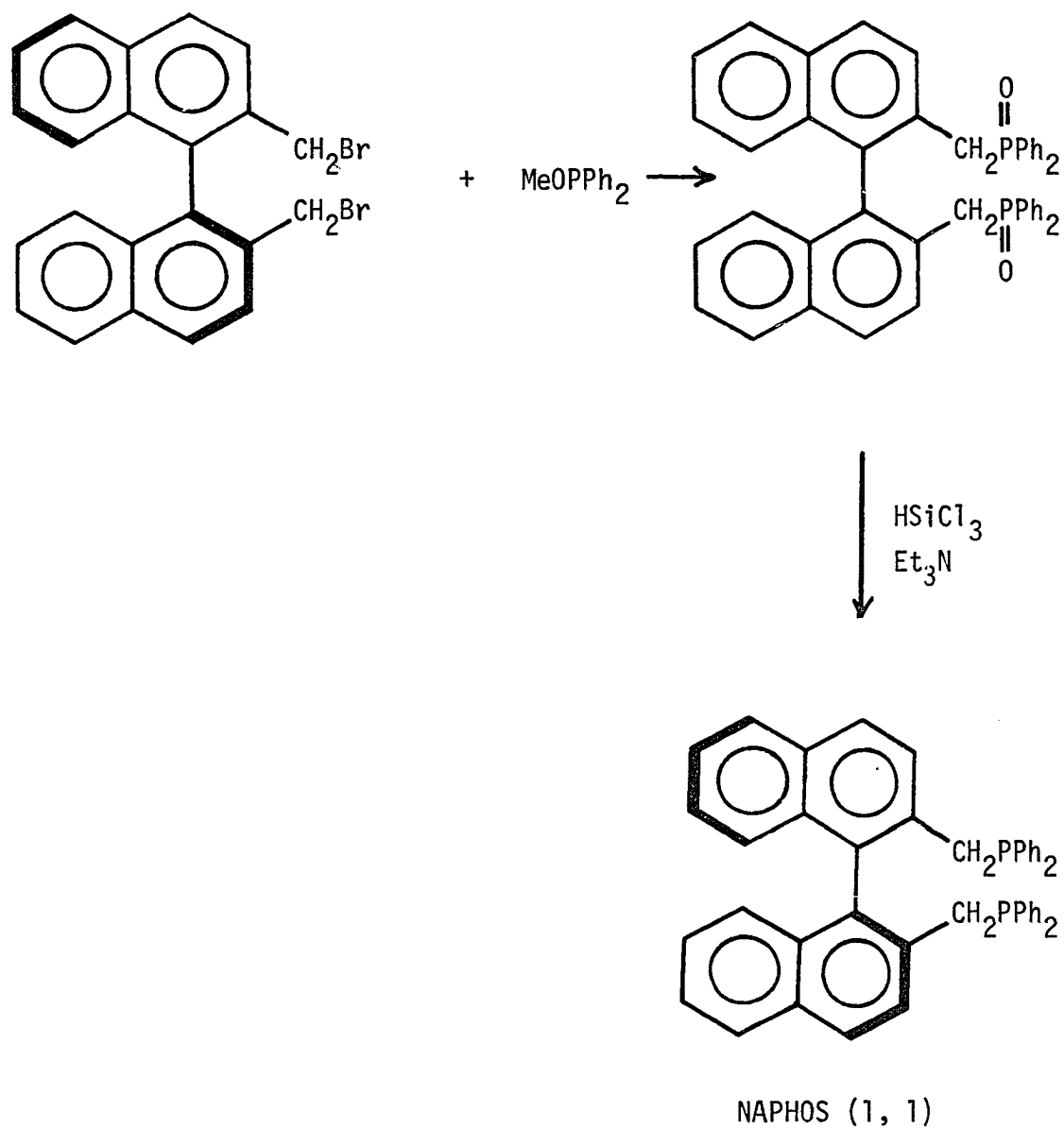
Figure 13. The synthesis of NAPHOS (1, 1).

(S)-(-)-2,2'-bis(bromomethyl)-1,1'-binaphthyl and methyldiphenylphosphinite

to give a phosphine oxide which was, in turn, reduced with $HSiCl_3$-Et_3N

(Figure 13).

Ferrocenyl Plus C-Chiral Ligands. Planar chirality is exhibited

by substituted ferrocenes. In the case of ligand (48) there is a center

of chirality at carbon as well.[34] The ligand (S)-α-[(R)-1',2-bis(diphenyl-

phosphino)-ferrocenyl]ethyldimethylamine (BPPFA) is prepared by stepwise

lithiation of (S)-α-ferrocenylethyldimethylamine with n-butyl lithium

and n-butyl lithium in TMEDA, followed by introduction of a diphenyl-

phosphino group into each cyclopentadienyl ring (Figure 13).

1) n-BuLi, Et_2O
2) n-BuLi, TMEDA/Et_2O
3) Ph_2PCl
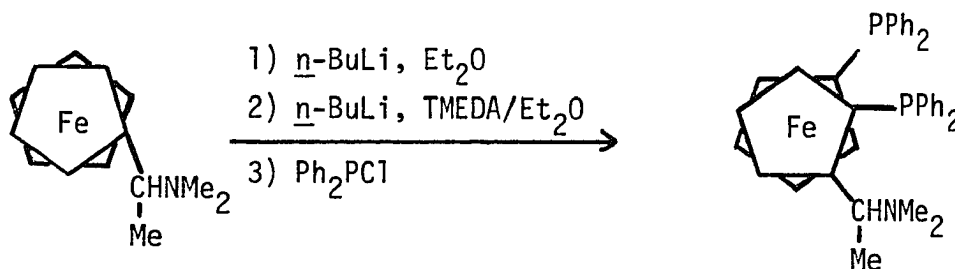
Figure 14. Synthesis of (S)-(R)-BPPFA.

Chiral Phosphinite Ligands. It has been found that phosphinites

are also effective as ligands in Wilkinson-type catalytic systems. Chiral

phosphinites are very simply prepared from an optically active alcohol and

chlorodiphenylphosphine. In Figure 15 the preparation of (+)-trans-1,2-

bis(diphenylphosphinoxy)-cyclohexane (BDPCH) (52) is shown.[37]
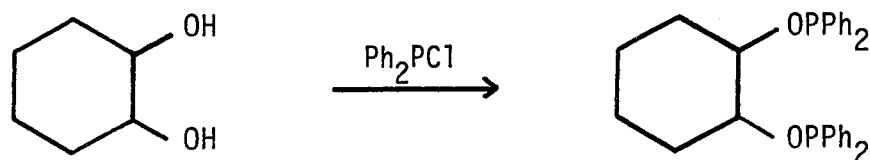
Figure 15. Preparation of (+)-(1S,2S)-BDPCH.

Chiral Aminophosphine Ligands. Amino and diaminophosphines have also been employed successfully as ligands in Wilkinson-type catalyst systems. A general procedure for preparing this type of ligand is shown in Figure 16. A chiral amine, (S)-(-)-N-methyl-α-phenylethylamine, was allowed to react with dichlorophenylphosphine to form phenylphosphonous acid bis[N-methyl-(S)-α-phenylethylamide](56).[41]
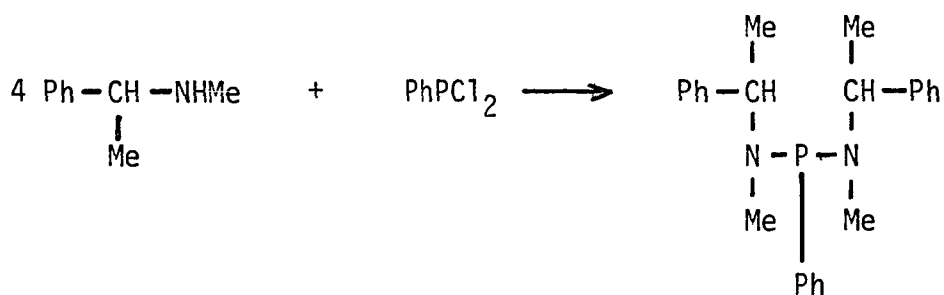
Figure 16. Preparation of a diaminophosphine ligand.

Substrates for Chiral Hydrogenation Studies

Unfunctionalized Olefins

Very few unfunctionalized olefins have been studied because initial examples showed that the paraffin products are of low optical purity. Furthermore, optically active paraffins are of little practical value. Simple olefins that have been asymmetrically hydrogenated are listed in Table 1. The highest % ee was obtained with a Rh/phosphinite catalyst though none of the results are outstanding.

Monofunctionalized Olefins

Enol Ethers. The reduction of α-methoxystyrene (60) was one of the first monofunctional olefin hydrogenations reported.[9] A 3-4% ee of (R)-(+)-1-methoxy-1-phenylethane was observed with a catalyst containing (+)-(S)-methylphenyl-n-propylphosphine. Reduction of the same substituted styrene with a rhodium catalyst containing ligand (52) or (53) gave approximately a 9% ee of the R isomer.[38]

$$Ph-\underset{\underset{OMe}{|}}{C}=CH_2$$

60
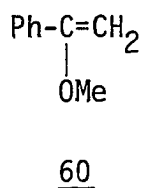
Silyl Enol Ethers. Three different silyl enol ethers have been hydrogenated with a catalyst containing (-)-DIOP (20) (Table 2).[50] The

Table 1. Reduction of unfunctionalized olefins with Wilkinson-type catalysts.

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
1	$PhC(Et)=CH_2$	1	S	7-8	9
2	"	52	R	33	36
3	"	53	"	60	37
4	"	20	S	25	"
5	"	32	"	1	46
6	"	49	"	25	35
7	$CH_3(CH_2)_3-C(Et)=CH_2$	49	"	6	"
8	$\underline{cis}-CH_3CH=C(Ph)CH_3$	53	"	14	36
9	$CH_3CH_2C(Ph)=CH_2$	55	-	49	40

Table 2. (-)-DIOP-Rhodium(I) catalyzed asymmetric hydrogenations of silyl enol ethers.

Entry	Substrate	Product Config.	Product % ee
1	2—Naph—C=CH$_2$ (OSiMe$_3$)	R	7
2	Ph—C=CH$_2$ (OSiMe$_3$)	R	7
3	Bu—C=CH$_2$ (OSiMe$_3$)	S	8

optical yields for all of these hydrogenations were low, but were higher than the values obtained with catalysts containing a number of other phosphines. Hydrogenations performed with catalysts containing other C-chiral (18) or P-chiral ligands (1), (6b), (11) gave less than 4% optical yield.

Enamides. Enamides have been found to be good prochiral substrates for the asymmetric synthesis of optically active amides and amines. A large number of enamides have been reduced with the Wilkinson-type catalyst containing either (+)-DIOP (20) or (-)-DIPAMP (12). The optical yields vary greatly but as high as 92% ee has been obtained in the reduction of 1-acetamido-1-phenylpropene (61b) (entry 2, Table 3).

$$\text{Ph} \diagdown \atop \text{AcNH} \diagup C = C - CH_3$$
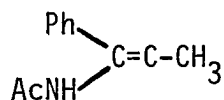
61b

Variations in optical yield are observed depending on solvent and whether the catalyst is cationic or neutral. These differences will be discussed later.

Carboxylic Acids and Esters. The monofunctional substrates that have been studied the most extensively are α,β-unsaturated carboxylic acids and esters. These substrates are easily obtained; many are natural products or are easily synthesized. They give a wide range of optical

Table 3. Reduction of enamides with (+)-DIOP/Rh and (-)-DIPAMP/Rh catalysts.

a: R=H, R'=Me
b: R=R'=Me
c: R=Me, R'=Ph
d: R=Me, R'=i-Pr
e: R=Et, R'=Me
f: R=C_6H_{11}, R'=Me
g: R=H, R'=Et
h: R=Ph, R'=Me

61a-h

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
1	61a	(+)-20*	R	68	52
2	61b	=	=	92	=
3	61d	=	=	90	=
4	61e	=	=	90	=
5	61f	=	=	82	=

Table 3 Continued.

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
6	61a	(+)-20	R	45	22
7	61b	"	"	83	"
8	61c	"	"	≥73 ± 3	51
9	61d	"	"	85 ± 4	"
10	61g	"	S	14	"
11	61h	"	"	6	"
12	(E)-62	"	"	15	"
13	(Z)-62	"	R	1	"
14	63	"	-	10	"
15	(E)-62	(-)-12	R	9	46
16	(Z)-62	"	"	51	"

*These ligands were used in a preformed cationic catalyst; all other catalysts were prepared in situ from [Rh(alkene)$_2$Cl]$_2$ and phosphine.

40

yields. Substrates that have been reduced are listed in Figure 17. Results for a large number of different ligands are shown in Table 4.

Some tentative generalities can be drawn from the results presently available. The highest optical yields are observed for reduction of (E)-β-methylcinnamic acid (69a) with Rh/(R)- or (S)-MMPP. This same ligand also gives 61% ee with (E)-α-methylcinnamic acid. The only other results that are greater than 60% ee are those obtained with these same substrates and Rh/NMDPP (18). Also, Rh/DIOP (20) is especially successful in the reduction of atropic acid (63% ee). With any particular ligand, it appears that E isomers of α,β-unsaturated acids hydrogenate to give products having higher % ee values. The presence of an aryl group in the substrate seems to promote high asymmetric induction.

Difunctional Olefins

Substrates that are Amino Acid Precursors. Most catalysts are tested for their ability to hydrogenate amino acid precursors in high chemical and optical yield. A large variety of these substrates have been examined but two substrates have usually been used to test new ligands. In Table 5 these two substrates, α-acetamidoacrylic acid (71) and (Z)-α-acetamidocinnamic acid (72) are listed with the results obtained upon hydrogenation with a Wilkinson-type catalyst containing every ligand that has been tested on these substrates. This table has been compiled in an attempt to give a common basis for comparing the efficiency of existing chiral ligands.
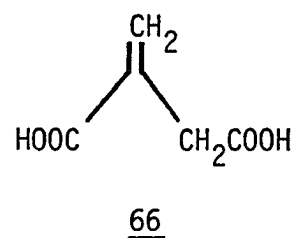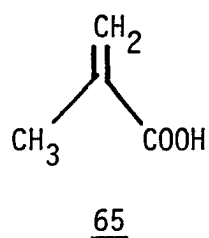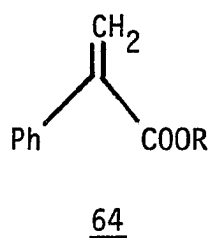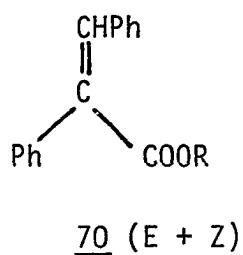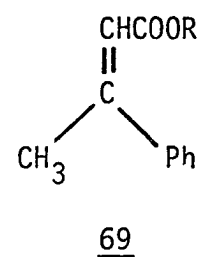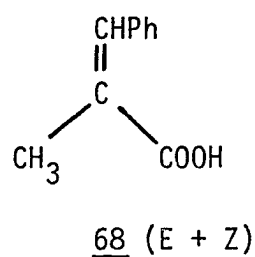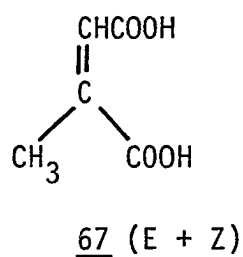
Figure 17. α,β-Unsaturated carboxylic acid and ester substrates used in asymmetric homogeneous hydrogenation.

Table 4. Results of the hydrogenation of α,β-unsaturated carboxylic acids and esters with various chiral Wilkinson-type catalysts.*

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
1	64a	20	S	44	49
2	"	18	"	30	"
3	"	22	-	0	"
4	"	21	S	6	"
5	"	3	"	15	6
6	"	19	-	1	6
7	"	(S)-14	R	14	18
8	"	(R)-14	S	28	18
9	"	20	"	63, 60	22, 19, 13
10	"	2	-	12	13
11	"	33	S	58-62	53, 24
12	"	50	R	17	36
13	"	51	S	2	"

43

Table 4 Continued.

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
14	64b	34	S	59(63)	25
15	65	20	R	7	22
16	=	50	S	33	36
17	66	51	=	39	=
18	=	18	R	8	49
19	=	22	=	18	=
20	=	21	=	11	=
21	=	3	-	3	6
22	=	(R)-14	S	52	18
23	=	50	R	7	36
24	=	51	S	18	=
25	(E)-67	18	R	6	49
26	=	22	S	7	=
27	=	21	R	2	=
28	(E)-68	2	=	12	=

Table 4 Continued.

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
29	(E)-68	20	S	25	49
30	=	18	R	60	=
31	=	22	S	17	=
32	=	21	R	15	=
33	(Z)-68	2	=	24	=
34	=	20	=	33	=
35	=	18	=	25	=
36	=	22	-	0	=
37	=	21	S	23	=
38	(E)-68	12	R	1	46
39	(Z)-68	12	=	<1	46
40	(E)-68	14	=	61	18
41	(E)-69a	2	S	37	49
42	=	20	R	14	=
43	=	18	S	62	=

Table 4 Continued.

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
44	(E)-69a	20	S	1	49
45	"	21	=	10	=
46	(Z)-69a	2	R	13	=
47	"	20	S	28	=
48	"	18	R	31	=
49	"	22	S	31	=
50	"	21	R	11	=
51	"	(S)-14	=	67	18
52	"	(R)-14	S	71	18
53	"	20	R	24	21
54	"	25	=	12	21
55	69b	54	-	44	39
56	(E)-70	2	S	24	49
57	"	20	R	15	=
58	"	18	S	34	=

Table 4 Continued.

Entry	Substrate	Catalyst Ligand	Product Config.	Product % ee	Ref.
59	(E)-70	22	R	27	49
60	"	21	S	12	"
61	(Z)-70	2	R	2	"
62	"	21	S	1	"
63	"	18	"	9	"
64	"	22	"	3	"
65	"	21	"	14	"

*Reaction conditions are widely varied for this series of hydrogenations but temperatures and pressures tend to be higher than those used with other substrates. References should be checked for specific conditions.

Table 5. Results of the hydrogenation of α-acetamidoacrylic acid (71) and α-acetamidocinnamic acid (72). A comparison of ligand effectiveness with two "standard substrates".

$$CH_2{=}C\begin{array}{l}\diagup NHAc\\ \diagdown COOH\end{array}$$

71

$$\begin{array}{l}Ph\\ H\end{array}{>}C{=}C\begin{array}{l}\diagup NHAc\\ \diagdown COOH\end{array}$$

72
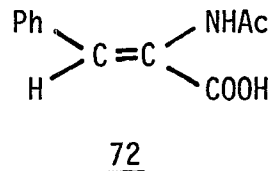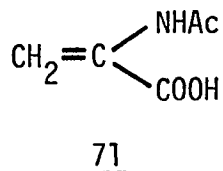
Entry	Catalyst Ligand	Substrate	Product Config.	Product % ee	Ref.
1	2	71	-	60	8
		72	S	54-88	13,12
2	12	71			
		72(Z,E)	(Z)S,(E)S	(Z)94,(E)47(96)	
3	13a	71			
		72	R,S	(R)40,(S)46	13
4	13d	71			
		72	R	83	13
5	14	71			
		72	R	44	18
6	20*	71	"	73(61-83,42(S),60(S))	19,13,22,52
		72	"	72(82,58(S),81(S), 44(S),49(S),60(S))	21,22,55,52

48

Table 5 Continued.

Entry	Catalyst Ligand	Substrate	Product Config.	Product % ee	Ref.
7	24	71 72	R	27	22
8	25	71 72	=	44	=
9	26	71 72	=	88	=
10	27	71 72	= S	34 28(25)	21 22,32
11	30	71 72	R =	65(72) 83	21,28 13
12	31	71 72	=	74	21
13	33	71 72	= =	52-60 86	24,53 24,53
14	34	71 72	= =	24-78 83(81)	25 =
15	37	71 72	= =	72 86(70,82)	28 28,27
16	40	71 72	S =	40 35	28 11

Table 5 Continued.

Entry	Catalyst Ligand	Substrate	Product Config.	Product % ee	Ref.
17	41	71			
		72	R	2-91	29
18	42	71			
		72	S	6	"
19	45	71	R	88-91	31
		72	"	74-89	"
20	46	71	S	2-44	42
		72			
21	47	71			
		72	"	54	33
22	48	71			
		72	"	89-93	34
23	50	71			
		72	R	6	36
24	51	71			
		72	"	2	"
25	54	71	-	6	39
		72	-	9	"
26	58	71			
		72	R	80	41

*(-)-DIOP gives (R)-phenylalanine. (+)-DIOP gives (S)-phenylalanine.

It is evident from the data in Table 5 that some ligands are clearly superior to others for the reduction of acylaminoacrylic substrates. It is possible to obtain nearly optically pure alanine or phenylalanine through the correct choice of ligand and reaction conditions. Of the ligands that are available commercially DIOP (20) is best. This is not a bad choice considering that an 82% optically pure amino acid (phenylalanine) can be obtained. If the ligands are to be synthesized then CHIRAPHOS (45), ACMP (2), DIPAMP (12) or BPPM (41) would be good choices with CHIRAPHOS or BPPM being somewhat less difficult to synthesize. Substrate structure must also be taken into consideration. Reduction of (Z)-(72) with Rh/DIPAMP gives 94% ee product whereas (E)-(72) yields only 57% ee phenylalanine. The subject of substrate geometry will be covered more fully in the section on Structure-Activity Relationships.

It is not possible from examination of the available data to say that any particular type of ligand (e.g., phosphine, phosphinite, amino-phosphine) is superior to any other. In general, the phosphinite ligands studied to date seem to be less effective, whereas the ferrocenyl and aminophosphinyl ligands are as effective, and in many cases more effective, than the P-chiral and C-chiral phosphines.

Media effects on optical yields are great, as can be seen from the data for ligand (41) (entry 17). The optical purity varies from 2-91% depending on solvent and the presence or absence of triethylamine in the hydrogenation mixture. (A more detailed discussion of these effects will be taken up later.)

Substrates (71) and (72) have been reduced with catalysts contain-ing many different ligands, but there are a number of other substrates

that have been reduced with a less varied list of chiral catalysts. A compilation of these results is shown in Table 6.

The most efficient ligands for asymmetric induction are ACMP ($\underline{2}$), DIPAMP ($\underline{12}$), DIOP ($\underline{20}$), and CHIRAPHOS ($\underline{45}$). Since two of these are P-chiral and two are C-chiral it is obvious that the nature of the chiral center is not critical. It might be argued that because DIPAMP, DIOP, and CHIRAPHOS all possess a C_2 axis of symmetry the number of diastereomeric chelates is reduced and this could be at least partially responsible for the higher asymmetric bias. However, some ligands that also possess a C_2 axis don't begin to achieve the high asymmetric induction generally seen in catalysts containing the aforementioned ligands. Furthermore, ACMP is not a chelating ligand and does not have a C_2 axis, yet it is as effective as DIPAMP, DIOP and CHIRAPHOS in many instances. Thus, an argument for greater catalyst effectiveness based solely on the symmetry character of the ligand is not sufficient to explain the general behavior observed. It cannot be said that the presence of a potentially coordinating oxygen atom makes a ligand more effective since CHIRAPHOS (100% ee with leucine) contains only hydrocarbon residues.

Tetrasubstituted olefinic amino acid precursors will not hydrogenate in this system. Also, optical yields are usually lower when large ester or amide functions are present in the substrate. Optical yields in reductions of multifunctional amide-containing acid substrates are greater than those for monofunctional amide or acid substrates and un-functionalized olefins. Apparently, an extra coordination is observed through the amide function (see last section). The effects of E/Z isomerism, substrate ionization and steric bulk, and media effects will be discussed

Table 6. Results for the hydrogenation of a variety of amino acid precursors with several chiral Wilkinson-type catalysts (excluding results presented in Table 5 for two "standard substrates").

$$R-CH=C\underset{R''}{\overset{NHCR'\overset{O}{\overset{\parallel}{}}}{}}$$
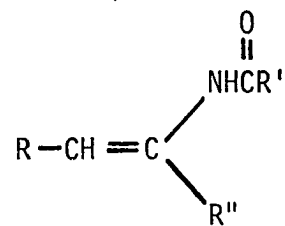
Entry	Catalyst Ligand	Substrate R	R'	R"	Product Config.	Product % ee	Ref.
1	1	3-MeO-4-(OH)C_6H_3	Ph	COOH	-	28	8
2	2	"	"	"	-	87,90	"
3	2	"	Me	"	-	77,85,88	"
4	2	Ph	Ph	"	-	85	"
5	2	3-MeO-4-(OAc)C_6H_3	Me	"	-	88	12
6	"	p-Cl-C_6H_4	"	"	-	77	"
7	"	3-(1-acetyl-indolyl)	"	"	-	60	"
8	2	Ph	"	$CONH_2$	"	70	13
9	2	"	"	COOMe	"	60	"
10	3	3-MeO-4-(OH)C_6H_3	Ph	COOH	-	28	8

Table 6 Continued.

Entry	Catalyst Ligand	Substrate R	R'	R''	Product Config.	Product % ee	Ref.
11	4	3-MeO-4-(OH)C$_6$H$_3$	Ph	COOH	-	58	8
12	4	"	Me	"	-	55	"
13	5	"	Ph	"	-	1	"
14	6a	"	"	"	-	32	"
15	7	"	"	"	-	1	"
16	8	"	Me	"	-	20	"
17	9	3-MeO-4-(OAc)C$_6$H$_3$	"	"	-	47	12
18	9	3-MeO-4-(OH)C$_6$H$_3$	Ph	"	S	47	13
19	10	3-MeO-4-(OAc)C$_6$H$_3$	Me	"	-	49	12
20	10	3-MeO-4-(OH)C$_6$H$_3$	Ph	"	S	49	13
21	12	(Z)-Ph	Me	COOMe	=	96	46
22	=	(E)-"	"	"	=	23	"
23	=	(Z)-"	Ph	COOH	=	66,78,93	"
24	=	(E)-"	"	"	=	39	"
25	=	(Z)-"	"	CN	=	86,89	"

Table 6 Continued.

Entry	Catalyst Ligand	Substrate R	R'	R''	Product Config.	Product % ee	Ref.
26	12	(Z)-Ph	OEt	COOEt		89	46
27	=	(Z)- "	C(S)OEt	"	S	56,62	=
28	=	H	CH_2Cl	COOH	=	95	=
29	=	(Z)-i-Pr	Ph	$CONH_2$	=	95	=
30	=	3-MeO-4-(OAc)C_6H_3	Me	COOH	=	89-94	16
31	=	3-(1-acetyl-indolyl)	=	=	=	94	=
32	=	3-MeO-4-(OH)C_6H_3	Ph	=	=	88	13
33	13b	=	=	=	=	37	=
34	13c	=	=	=	=	3,49	=
35	13d	=	=	=	=	71	=
36	13e	=	=	=	=	85	=
37	13f	=	=	=	=	74	=
38	20	3-AcO-4-(MeOC_6H_3)	Me	=	R	60	=
39	=	=	=	=	=	84	21
40	=	H	CH_2Ph	=	=	68	19

56

Table 6 Continued.

Entry	Catalyst Ligand	Substrate R	R'	R''	Product Config.	Product % ee	Ref.
41	20	Ph	CH_2Ph	COOMe	S	8,14	52
42	=	3-MeO-4-(OAc)C_6H_3	Me	COOH	=	84	=
43	=	Ph	=	$CONH_2$	R	71	22
44	=	=	=	COOMe	=	55	=
45	=	=	Ph	COOH	=	64	=
46	=	p-OH-Ph	=	=	=	80	48
47	=	3,4-$(CH_2O_2)C_6H_3$	Me	=	=	79	=
48	=	p-OH-Ph	=	=	=	62	=
49	=	i-Pr	=	=	=	22	=
50	=	Ph	=	COOMenthyl	=	53	56
51	(+)-20*	=	=	=	S	77	=
52	20	=	=	COOBornyl	R	64	=
53	(+)-20	=	=	=	S	50	=
54	20	(Z)-Ph	=	COOH	R	82	57
55	=	=	=	COOMe	=	69	=

Table 6 Continued.

Entry	Catalyst Ligand	Substrate R	R'	R''	Product Config.	Product % ee	Ref.
56	20	(Z)-Ph	Me	COOEt	R	7	57
57	"	"	"	COOi-Pr	"	76	"
58	"	"	"	COOt-Bu	"	77	"
59	"	"	"	COO-1-Adamantyl	"	71	"
60	(+)-20	"	H	COOMe	S	58	54
61	"	"	Me	"	"	69	"
62	"	"	CF$_3$	"	R	22	"
63	"	"	i-Pr	"	S	15	"
64	"	"	t-Bu	"	-	0	"
65	"	"	1-Adamantyl	"	-	0	"
66	"	"	Ph	"	S	35	"
67	20	3-indolyl	"	COOH	R	65	27
68	"	"	Me	"	"	67	"
69	"	(Z)-Ph	Ph	"	S	70	55
70	"	(E)-Ph	"	"	"	25	"

Table 6 Continued.

Entry	Catalyst Ligand	Substrate			Product Config.	Product % ee	Ref.
		R	R'	R''			
71	20	(Z)-Ph	p-OCH₃C₆H₄	COOH	S	64	55
72	"	"	p-CH₃C₆H₄	"	"	45	"
73	"	"	p-ClC₆H₄	"	"	59	"
74	"	"	p-NO₂C₆H₄	"	"	69	"
75	"	"	Ph	COOMe	"	38	"
76	"	(E)-Ph	"	"	"	5	"
77	"	(Z)-Ph	p-OCH₃C₆H₄	"	"	30	"
78	"	"	p-CH₃C₆H₄	"	"	34	"
79	"	"	p-ClC₆H₄	"	"	35	"
80	"	"	p-NO₂C₆H₄	"	"	36	"
81	26	3-AcO-4-(MeO)C₆H₃	Me	COOH	R	90	21
82	26	3-MeO-4-(OAc)C₆H₃	"	"	–	90	22
83	27	3-AcO-4-(MeO)C₆H₃	"	"	S	14	21
84	27	3-MeO-4-(OAc)C₆H₃	"	"	"	14	22
85	34	p-OH-Ph	"	"	R	71	25

Table 6 Continued.

Entry	Catalyst Ligand	Substrate R	R'	R''	Product Config.	Product %ee	Ref.
86	34	3-MeO-4-(OAc)C$_6$H$_3$	Me	COOH	R	79	25
87	37	p-OH-Ph	=	=	S	86,8	27
88	=	3-Me-4-(OH)C$_6$H$_3$	=	=	R	89	=
89	=	"	Ph	=	=	76	=
90	37	3,4-(CH$_2$O$_2$)C$_6$H$_3$	Me	=	=	89	=
91	=	3-indolyl	=	=	=	67	=
92	=	"	Ph	=	=	70	=
93	42	Ph	Me	COOMe	S,R	(S)7,(R)15	29
94	=	3,4-(CH$_2$O$_2$)C$_6$H$_3$	=	COOH	R	32,83	=
95	=	3-MeO-4-(OAc)C$_6$H$_3$	=	=	=	86	=
96	=	4-OAcC$_6$H$_4$	=	=	=	87	=
97	45	Ph	Ph	=	=	99	31
98	=	"	=	COOEt	=	83	=
99	=	i-Pr	=	COOH	=	87	=
100	=	"	Me	=	=	100	=

Table 6 Continued.

Entry	Catalyst Ligand	Substrate			Product Config.	Product % ee	Ref.
		R	R'	R"			
101	45	p-OHC$_6$H$_4$	Me	COOH	R	88	31
102	"	"	Ph	"	"	92	"
103	"	p-OAcC$_6$H$_4$	Me	"	"	74	"
104	"	3-Me-4-(OAC)C$_6$H$_4$	"	"	"	80	"
105	48	4-OAcC$_6$H$_4$	"	"	S	8,38,87	34
106	"	3-MeO-4-(OAc)C$_6$H$_3$	"	"	"	36,86	"
107	"	3,4-(CH$_2$O$_2$)C$_6$H$_3$	"	"	"	52	"
108	54	Ph	"	COOMe	-	76	39
109	"	H	"	"	-	76	"
110	56	Ph	"	"	R	4-20	41
111	57	"	"	"	-	-	"
112	58	"	"	"	R	9,66,83	"

*(-)-DIOP (20) is used unless otherwise indicated as (+)-(20).

60

fully in the section in Structure-Activity Relationships.

Enol Acetates. One other class of difunctional olefin, enol acetates, has been hydrogenated by chiral Wilkinson-type systems. Enol acetates have received very little attention relative to other substrates. Results with only two ligands, (73) and (74), have been reported.[46] The (Z)-α-enol acetate (73) when hydrogenated in the presence of a catalyst prepared from ligand (12) gave about 90% ee but the (Z)- and (E)-β-enol acetates (74) were hydrogenated only sluggishly compared to (Z)-(73) and less than 10% ee was observed in both cases.

Ph-CH=C-COOEt
|
OAc

Ethyl-2-acetyloxy-3-phenyl-
propenoate

73

Ph-C=CH-COOEt
|
OAc

Ethyl-3-acetyloxy-3-phenyl-
propenoate

74
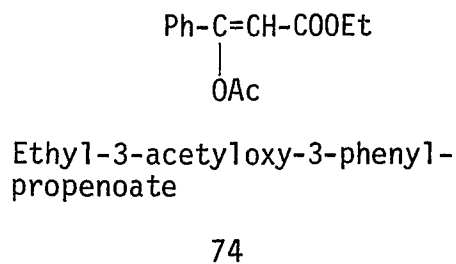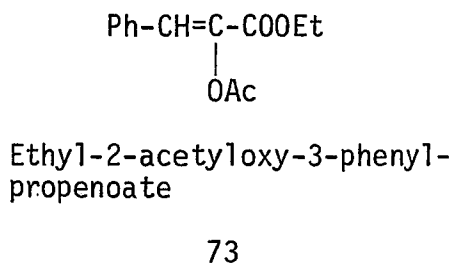
Structure-Activity Relationships

E/Z Isomerism. Early studies did not consider the matter of E and Z isomerism in substrates. As more examples were reported the very great influence of substrate geometry on the degree of asymmetric bias became apparent (see preceding tables for specific data). Which diastereomeric form will give the higher % ee with a particular ligand varies with substrate type. Entries, 12, 13, 15, and 16 in Table 3 show the influence of enamide substrate geometry even though the % ee values are not high. With enamides there is no predictable outcome; e.g., (+)-DIOP (20) with enamide (E)-(62) shows 15% ee while with (Z)-(62) 1% ee is

observed. Conversely, reduction of (Z)-(62) with Rh/DIPAMP (12) gives 51% ee while the E substrate gives only 9% ee. Thus there is a reversal of preferred enamide substrate geometry depending on the ligand used.

In the reduction of α,β-unsaturated carboxylic acids and esters the E substrates seem to give higher asymmetric bias. The two ligands that are outstanding are (+)-NMDPP (18) and the structurally similar MMPP (14). Consistently, these ligands have given better results with the substituted cinnamic acids than other ligands. However, the highest optical yields with atropic acid (64a) are observed when DIOP (20) and the polymer supported DIOP ligands (33, 34) are used.

In many published hydrogenations of α-acetamidocinnamic acids, (Table 5) the substrate geometry has not been specified, but in cases where both E and Z isomers were hydrogenated with a catalyst containing the same ligand, a much higher % ee was observed for the Z isomer; for example, entry 2, Table 5: 94% ee (Z) versus 47% ee (E); also, Table 6, entries 21-27, 29, 54-66, 69-80.

Effects of Amide and Acetate Functionalities. The presence of functionalities on a substrate that can coordinate to the catalyst promotes high asymmetric bias. Such coordination reduces the number of ways in which the olefinic grouping can coordinate to the metal. The more specific the approach of the substrate to the catalyst must be, the better will be the chances of a high optical yield. Coordination of amide and acetate functions in substrates that are amino acid precursors and enol acetates, respectively, serves this purpose well. Their "extra coordination"

is believed to be responsibile for the much higher optical yields observed with these substrates as opposed to those observed with substrates lacking such groups (see last section).

The Effect of Substrate Functional Group Charge State and Steric Bulk. In the reduction of α,β-unsaturated acids added triethylamine affects the optical yield. When a small amount of triethylamine was added to the hydrogenation solution, prior to reduction, a much higher % ee was observed. This effect has been attributed to the added restriction imposed by coordination of the carboxylate anion to the catalyst during hydrogenation.

The % ee obtained in chiral reductions of amino acid precursors is also affected by the steric bulk of ester or amide functions in the substrate (Table 7, entries 54-65). One can speculate that this may be a reflection of a loosening of the complex coordination sphere to accomodate the bulkier substrate. In this event, steric interactions between substrate and chiral ligands might be less severe and prochiral recognition could be less effective. Alternatively, the bulk effect may be more specifically related to the lack of "extra coordination" to the hindered ester or amide which would result in the absence of a directing effect for olefin coordination. In reality, probably both aspects are operative.

Media Effects

The nature of the solvent greatly affects asymmetric hydrogenation. Solvent effects have not been systematically studied yet nor are they

understood. The effect of this variable, is dramatized by entry 111 in Table 6; 9% ee (benzene), 83% ee (methanol). Some of the large variations in % ee values apparent from the data in Tables 4, 5, and 6 can be attributed to such effects. A few comparisons have been made but the best solvent cannot be generalized; because the solvent effect is both ligand and substrate dependent. The most frequently used solvents are benzene, methanol, ethanol, benzene-ethanol, and benzene-methanol. Before planning an asymmetric hydrogenation one should check the literature for optimum results with similar catalysts and substrates in order to choose the best solvent system.

Changing from a polar to a non-polar solvent can also result in a change in the configuration of the product. It is conceivable that in a polar solvent such as methanol, Cl^- dissociates from the catalyst complex (Figure 1) (leaves the coordination sphere), thus forming a cationic species, whereas in a non-polar solvent such as benzene, Cl^- would be expected to remain within the coordination sphere of rhodium. Not enough is known about the mechanism at this time to postulate why in some cases a cationic catalyst may be more effective than a neutral one and vice versa.

Effects of temperature and pressure have not yet been well studied and vary widely for different systems. One advantage of the Monsanto DIPAMP system, however, is its lack of sensitivity to such effects.

Rationalizations for Asymmetric Induction

in Olefin Hydrogenations

Glaser's Stereocorrelation Model

Glaser's stereocorrelation model for the rhodium-DIOP complex can be used to predict the configuration of the product in some asymmetric homogeneous hydrogenations.[28] Using CPK-type space-filling models of the rhodium-DIOP complex the conformation shown in Figure 18 was chosen as most desirable. As seen in (73), due to the rigidity of the dioxolan ring in the ligand the seven-membered ring coordinating rhodium is forced to assume a twisted chair form. This constraint forces one phenyl of the diphenylphosphino group in the foreground of (73) to be pushed forward into the "belt region" of the complex toward coordination site A in (74), thus sterically hindering it. It is assumed, therefore, that site A will probably be occupied by hydrogen while the less hindered site B will be occupied by the olefin. There is still the matter of the small or the large group facing rhodium when there is a prochiral olefin. In the achiral case (when the phosphines are not chiral) then two enantiomeric pairs of diastereomers are possible (75a-d). However, when the phosphines are chiral then four diastereomers are possible (76a-d). It is the pre-dominance of two diastereomers that will form one enantiomeric product, over the other two that will form the other enantiomer that causes the asymmetric synthesis. If the chiral ligands fail to produce a preferred diastereomer then no asymmetric induction occurs and the result is a racemic product.

Glaser used this model to predict the stereochemical outcome of 24 asymmetric homogeneous hydrogenations and hydrosilylations using DIOP
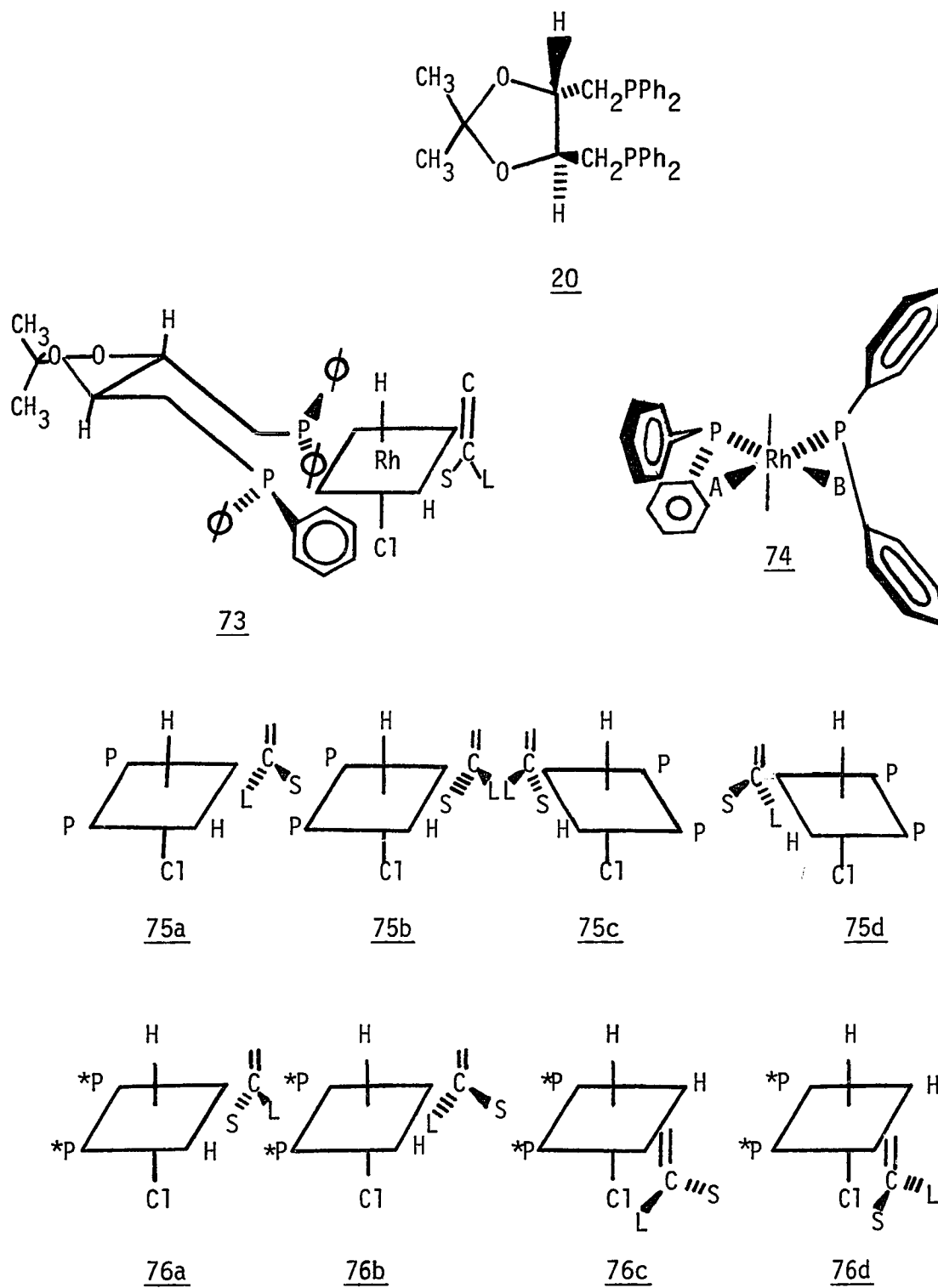
Figure 18.   Glaser's model for predicting product configuration.

as the ligand and correctly predicted the configuration of the product in all but three cases.

Knowles' Stereocorrelation Model

Knowles' stereocorrelation model for the Rh/DIPAMP catalyst proposes a bisphosphine-rhodium catalyst complex that presents alternating "edges" and "faces" of phenyl rings to a substrate so as to favor an approach by one of the prochiral faces that is less crowded than the other (Figure 19). For example, hydrogenation of (Z)-α-acylaminoacrylic substrates with the Rh/DIPAMP catalyst gives the S isomer of the product amino acids. This can be explained by viewing the catalyst and substrate as in Figure 19.
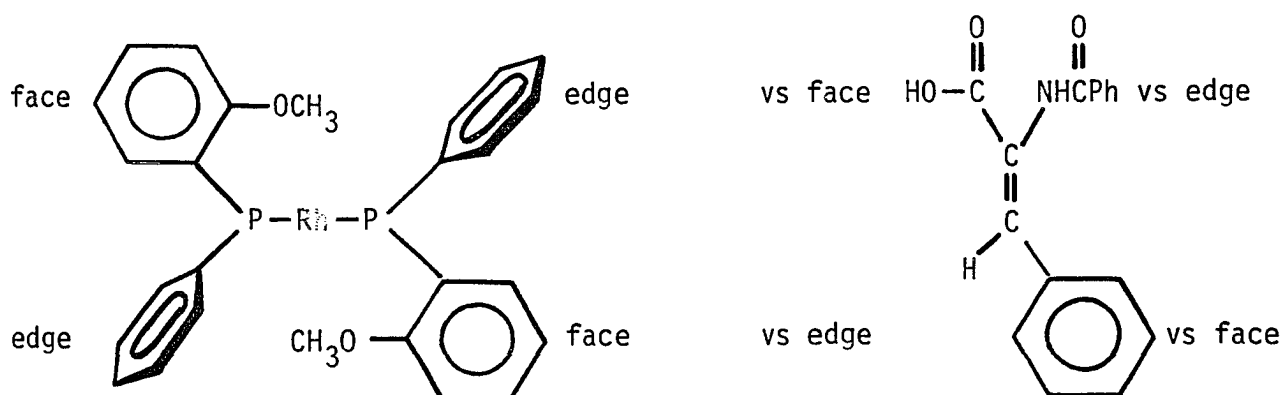
Figure 19. Knowles' stereocorrelation model for the Rh-DIPAMP catalyst complex.

The catalyst assumes the conformation whereby the four phenyl rings show

alternating edges and faces with the phenyl rings substituted with methoxyl groups being the faces and the unsubstituted phenyls being the edges. The oxygens in the methoxyl group are not close enough to the Rh to enter its coordination sphere but some kind of interaction is assumed to occur that causes these groups to be held in a flat face-exposed position. When looking at (Z)-α-benzamidocinnamic acid in a flat conformation it is readily seen that with the carboxyl, the olefin, and the phenyl coplanar and with the amide projecting on one side it is easiest for the substrate to approach the catalyst with the amide oxygen bonding to an axial position of the rhodium and the olefin occupying an equatorial position. This arrangement imposes added rigidity on the approach of substrate and catalyst. It also lines up the larger phenyl and carboxyl groups in the substrate with the face exposed phenyls of the catalyst and puts the sterically less pretentious hydrogen and amide functions over edge phenyls. (The amide function is "smaller" than COOH because it is able to rotate away from the edge phenyl.) In this position the re face of the substrate is toward the metal and will be hydrogenated to give the S product. If the substrate is turned over to expose the si face to hydrogenation then the flat part of the substrate molecule (carboxyl, olefin, and phenyl) has to approach edge phenyls and hydrogenation is much slower. Use of (E)-α-benzamidocinnamic acid rather than the Z isomer results in loss of linearity and planarity and the phenyl is then juxta-positioned with an edge catalyst phenyl and hydrogenation is slower but the S isomer of product is still obtained.

RESULTS AND DISCUSSION

The purpose of this study was to design and prepare new chiral phosphine ligands for use in the Wilkinson-type catalyst system and to test their efficiency with a variety of different substrates.

Chiral Phosphine Ligands

An alternate Synthesis of BUPHOS

The C-chiral phosphine, 2-phenylbutyldiphenylphosphine (BUPHOS) was first prepared by Burnett.[15] His synthetic scheme involved the reaction of lithium diphenylphosphide with chiral 1-chloro-2-phenylbutane to form the phosphine.

A preparation of BUPHOS <u>via</u> the tosylate, a process analogous to that described previously for DIOP, was investigated. A sample of optically pure (+)-2-phenylbutyric acid (<u>77</u>) was reduced with LiAlH$_4$ to give 2-phenylbutanol (<u>78</u>). The alcohol was converted to the tosylate (<u>79</u>) by a standard tosylation procedure. The tosylate was allowed t., react with potassium diphenylphosphide in THF to form BUPHOS (<u>80</u>) in 44% yield (Figure 20).

Preparation of BUPHOS by the tosylation route rather than the chloride route offers no advantage in overall yield from chiral 2-phenylbutyric acid. However, the tosylation route is somewhat simpler in terms of the synthetic manipulations involved. For this reason, other phosphine ligands were prepared by tosylation.

68

COOH
|
Ph—CH
|
CH$_2$
|
CH$_3$

$\xrightarrow{\text{LiAlH}_4}$

CH$_2$OH
|
Ph—CH
|
CH$_2$
|
CH$_3$

77   78

|
TosCl

C$_5$H$_5$N

↓

CH$_2$—PPh$_2$
|
Ph—CH
|
CH$_3$
|
CH$_3$

$\xleftarrow{\text{K}^+\text{PPh}_2^-}$

CH$_2$OTs
|
Ph—CH
|
CH$_2$
|
CH$_3$

BUPHOS   79

80
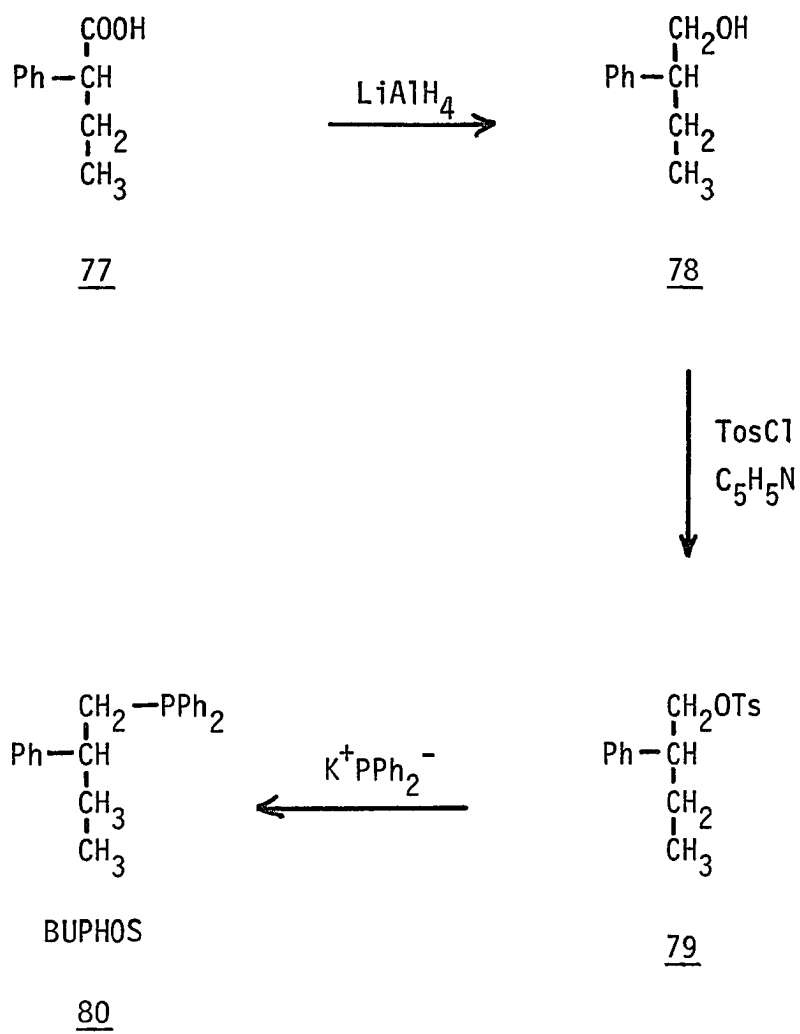
Figure 20.   The synthesis of BUPHOS.

It was also found that the counterion in the phosphide displacement step was important. Kagan's synthesis of DIOP gave the best results when the cation was sodium.[19] In Masler's synthesis of CAMPHOS <u>via</u> tosylation, the best yield of phosphine was observed when potassium was the cation.[20] Potassium diphenylphosphide also gave a higher yield than did sodium diphenylphosphide in the BUPHOS synthesis (Figure 20).

The Synthesis of SUPHOS

In order to compare structurally similar mono- and diphosphines, the diphosphine, 2-phenylbis(1,4-diphenylphosphino)butane (SUPHOS) (<u>84</u>) was prepared. The carbon skeleton of SUPHOS is identical to that of BUPHOS but there is an additional diphenylphosphino group present in SUPHOS which can act as a chelating ligand.

The synthesis of SUPHOS (<u>84</u>) (Figure 21) involved a procedure analogous to that described for BUPHOS. A sample of racemic 2-phenyl-succinic acid (<u>81</u>) was resolved with (-)-α-methylbenzylamine and the plus isomer of (<u>81</u>) was obtained in better than 98% optical purity. A sample of 73% ee material was also obtained and treated in the same manner to prepare 73% ee SUPHOS. The optically active diacid was reduced with liquid $LiAlH_4$ to give 2-phenyl-1,4-butanediol (<u>82</u>). Problems were encountered in the reduction step due to the condition of the $LiAlH_4$. Initially, the reduction was attempted with powdered $LiAlH_4$ and no reduction was observed. Using a sample of liquid $LiAlH_4$ which had partially evaporated and precipitated on standing, again, no reduction was observed, even though active $LiAlH_4$ was left at the end of the reaction.

$$Ph-\overset{\displaystyle COOH}{\underset{\displaystyle COOH}{\overset{|}{\underset{|}{\underset{\displaystyle CH_2}{\overset{\displaystyle |}{C}H}}}}} \quad \xrightarrow{\text{LiAlH}_4} \quad Ph-\overset{\displaystyle CH_2OH}{\underset{\displaystyle CH_2OH}{\overset{|}{\underset{|}{\underset{\displaystyle CH_2}{\overset{\displaystyle |}{C}H}}}}}$$

<u>81</u>   <u>82</u>

TosCl
C_5H_5N

$$Ph-\overset{\displaystyle CH_2-PPh_2}{\underset{\displaystyle CH_2-PPh_2}{\overset{|}{\underset{|}{\underset{\displaystyle CH_2}{\overset{\displaystyle |}{C}H}}}}} \quad \xleftarrow{\text{K}^+\text{PPh}_2{}^-} \quad Ph-\overset{\displaystyle CH_2OTs}{\underset{\displaystyle CH_2OTs}{\overset{|}{\underset{|}{\underset{\displaystyle CH_2}{\overset{\displaystyle |}{C}H}}}}}$$

SUPHOS   <u>83</u>

<u>84</u>
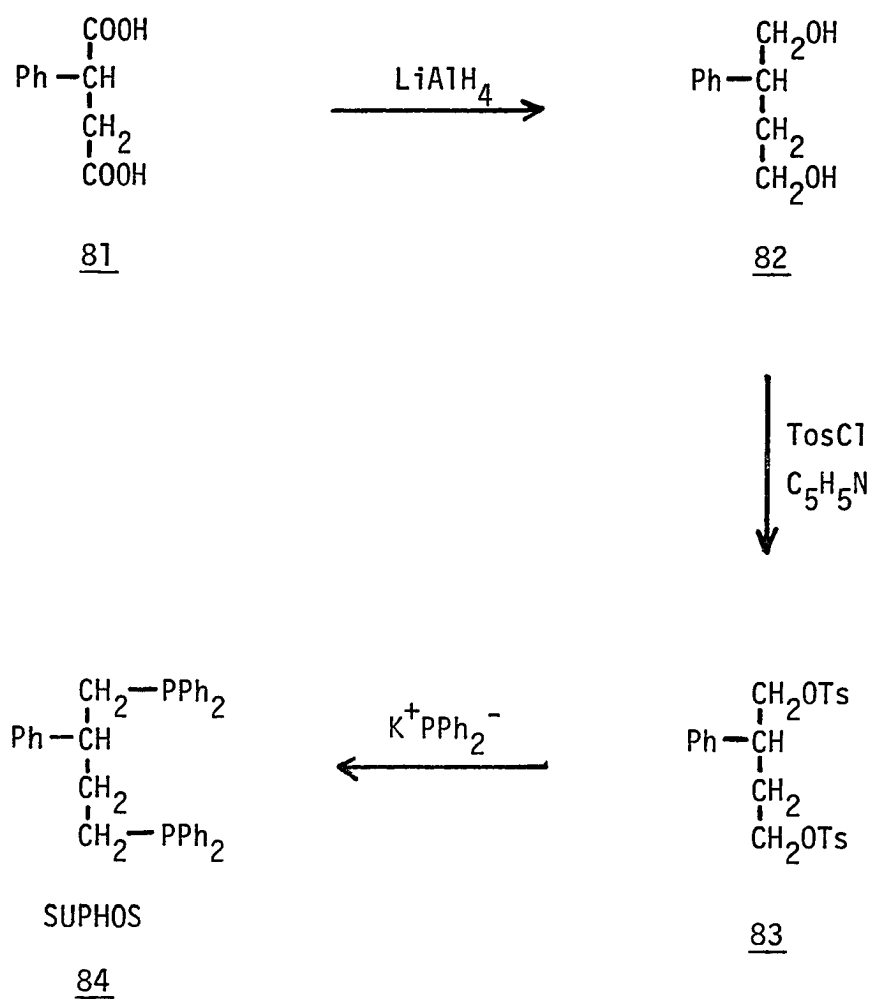
Figure 21.   The synthesis of SUPHOS.

Some reduction did occur when a freshly opened bottle of liquid LiAlH$_4$ which had not precipitated or evaporated was employed, but yields were low. There does not appear to be an unequivocal explanation for this behavior. It was thought that some diol might have been trapped in the copious lithium and aluminum salts produced during the work-up. For this reason, an acidic work-up was attempted but no better results were obtained than with a basic work-up. In an acid medium it is possible that there was dehydration of any diol that was formed.

The diol proved to be non-distillable. A heavy grease which remained as the pot residue upon attempted distillation was analyzed by ir and appeared to be an alcohol; no COOH or alkene bands were present in the spectrum. The crude diol (82) was subjected to tosylation directly. The tosylate (83) was then treated with potassium diphenylphosphide to form SUPHOS (84) in a low overall yield (10%). The yield was greatly lowered by the difficulties encountered in the LiAlH$_4$ reduction as well as the usually observed low yield in the phosphide displacement.

A comparison of the hydrogenating ability of BUPHOS and SUPHOS will be discussed later in the section on asymmetric homogeneous hydrogenations.

An Alternate Synthesis of NMDPP

The successful preparation of BUPHOS by the tosylate method made it seem worthwhile to attempt the synthesis of NMDPP (18) by this procedure. Direct conversion of (-)-menthol to menthyl tosylate followed by reaction with potassium diphenylphosphide (Figure 22) is a much simpler scheme than
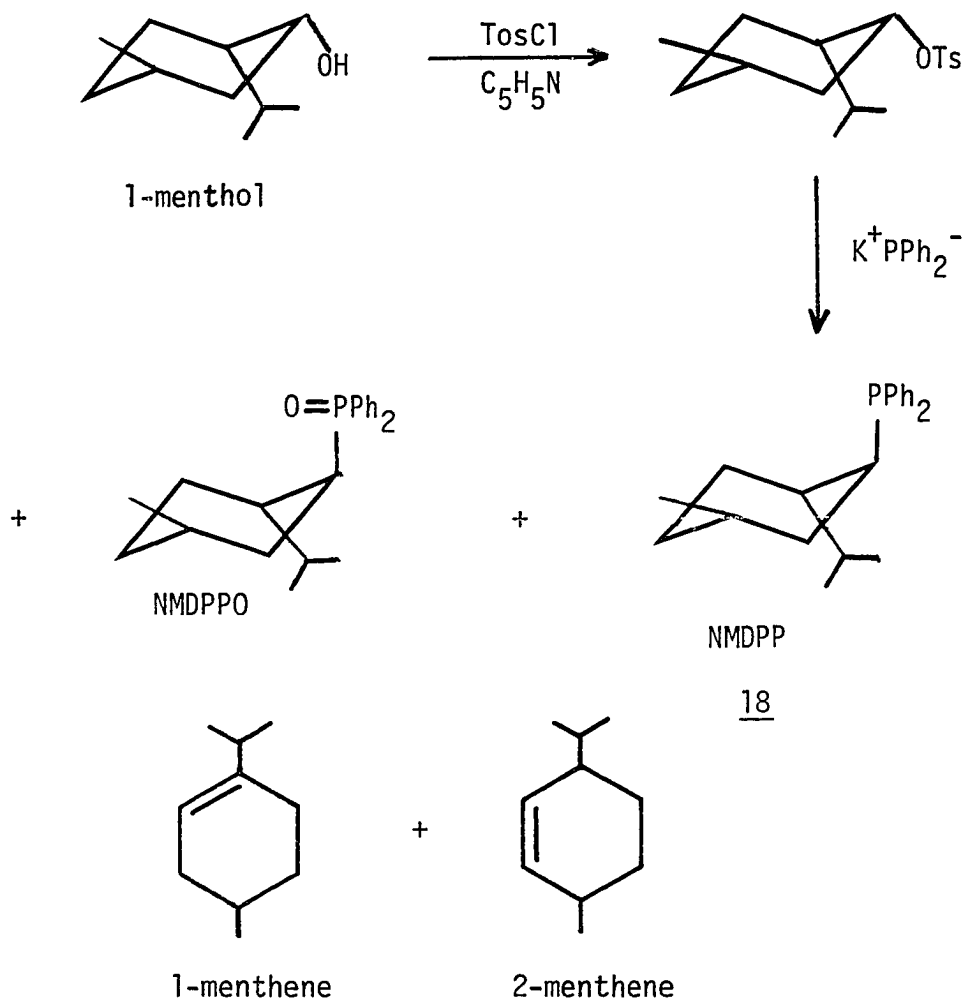
Figure 22. Alternate synthesis of NMDPP and observed by-products.

that used by Masler for the preparation of NMDPP (preparation discussed in historical section). However, the yield of NMDPP prepared in this manner was very low (10%), and analysis by glpc indicated the presence of 15% neomenthyldiphenylphosphine oxide (NMDPPO) in the product. The value of this synthetic method is debatable. It is a much easier preparation but the yield is much lower because elimination competes with displacement.

The Synthesis of CMDPP

In our efforts to determine the features that make a good chiral phosphine ligand, we decided to prepare carvomenthyldiphenylphosphine (CMDPP) (94). CMDPP is a structural isomer of NMDPP. The methyl and isopropyl groups on the cyclohexane ring are interchanged in the two compounds. The synthesis designed for CMDPP involved a tosylation procedure analogous to that described for the preparation of NMDPP (Figure 22). However, no precursor alcohol of the required stereochemistry was commercially available. (-)-Carvone was chosen as the naturally-occurring compound that could be converted most inexpensively and easily to the required alcohol.

The preparation of carvomenthol (88) from (-)-carvone (85) is shown in Figure 23. A sample of (-)-carvone was reduced with sodium in ethanol[59] to give a mixture of dihydrocarveol (86) (95%) and neodihydro-carveol (87) (5%). No attempt was made to separate the isomers at this point due to the small amount of the undesired alcohol present. Attempts to reduce dihydrocarveol with hydrogen in the presence of acidic $PdCl_2$ and gum arabic were unsuccessful and unreacted dihydrocarveol was

Na
absolute
EtOH

95%
dihydrocarveol

5%
neodihydrocarveol

85

86

87

H_2, 5% Pd/C
EtOH

carvomenthol

neocarvomenthol

neoisocarvo-
menthol

isocarvomenthol

88

89

90

91

+

92
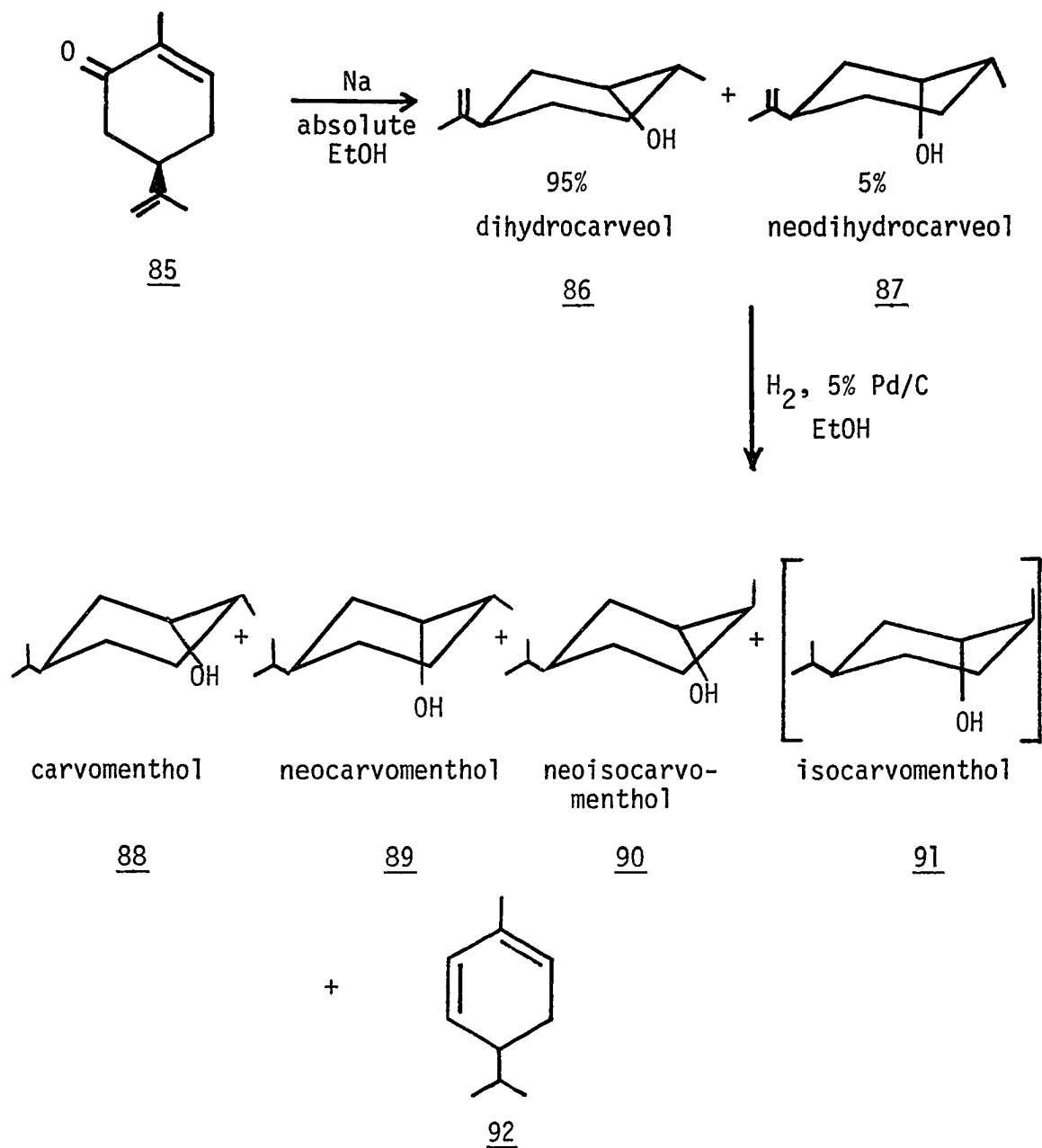
Figure 23. The synthesis of carvomenthol.*

*There is a disagreement in the literature as to the naming of the carvomenthols. The convention described by Schroeter and Eliel is followed.[62]

recovered.[60] Dihydrocarveol was successfully reduced with hydrogen and 5% Pd/C catalyst to give a mixture of the expected alcohol, carvomenthol (88) and neocarvomenthol (89).[61]

It was evident from tlc analysis that the product was a mixture of at least two alcohols (two spots). In order to prepare a large sample of the pure alcohol (88) it was necessary to purify the distilled product mixture by preparative hplc. When a sample was analyzed on a Porasil column (analytical hplc) four different peaks were observed. Separation by preparative hplc of 33 g of alcohol mixture on silica gel in 80/20 hexane/ethyl acetate yielded four fractions including 18.7 g of (88) and 9.85 g from the three other fractions. The products from these three fractions were determined to be the dehydration product 1,2,5,6-menthadiene (92), neocarvomenthol (89), and neoisocarvomenthol (90) (Figure 23). It was not possible to determine by nmr which fraction was (90) and which was (89). It was assumed that isocarvomenthol (91) was not found because the diaxial compound would be least likely to be formed.

Purified carvomenthol (88) was converted to carvomenthyl tosylate (93) as shown in Figure 24. The tosylate was then allowed to react with potassium diphenylphosphide to yield CMDPP (94).
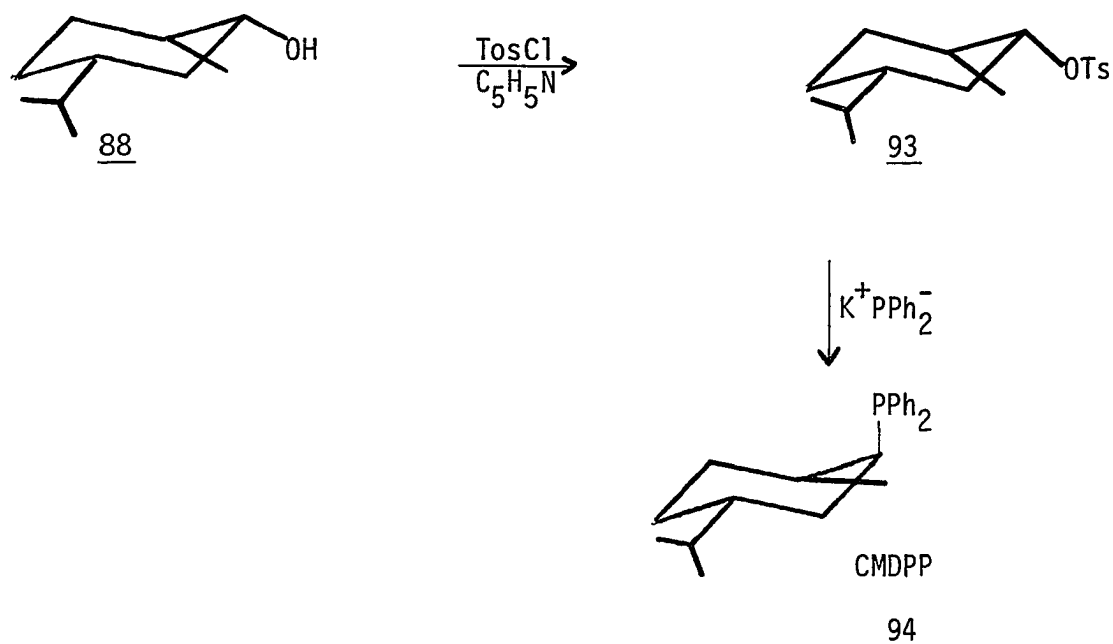
Figure 24. The synthesis of CMDPP from carvomenthol.

A low yield (14%) of CMDPP was obtained. This was slightly higher than the yield observed for the analogous reaction of neomenthyl tosylate to form NMDPP. The higher yield in this case may be attributable to a less sterically hindered reaction site (the α-alkyl substituent is methyl rather than isopropyl).

An Attempted Synthesis of PPDPP

It was hoped that a ligand could be synthesized using the product from the 1,4-addition of phenylmagnesium bromide to the naturally occurring terpene, pulegone (95). The less expensive enantiomer (+)-pulegone, was treated with phenylmagnesium bromide in the presence of copper(I) chloride as described by Ensley[63,64] to give a good yield (65%) of 2-(2-phenylpropyl)-5-methylcyclohexanone (96) (Figure 25). The approximately 1:1 mixture of
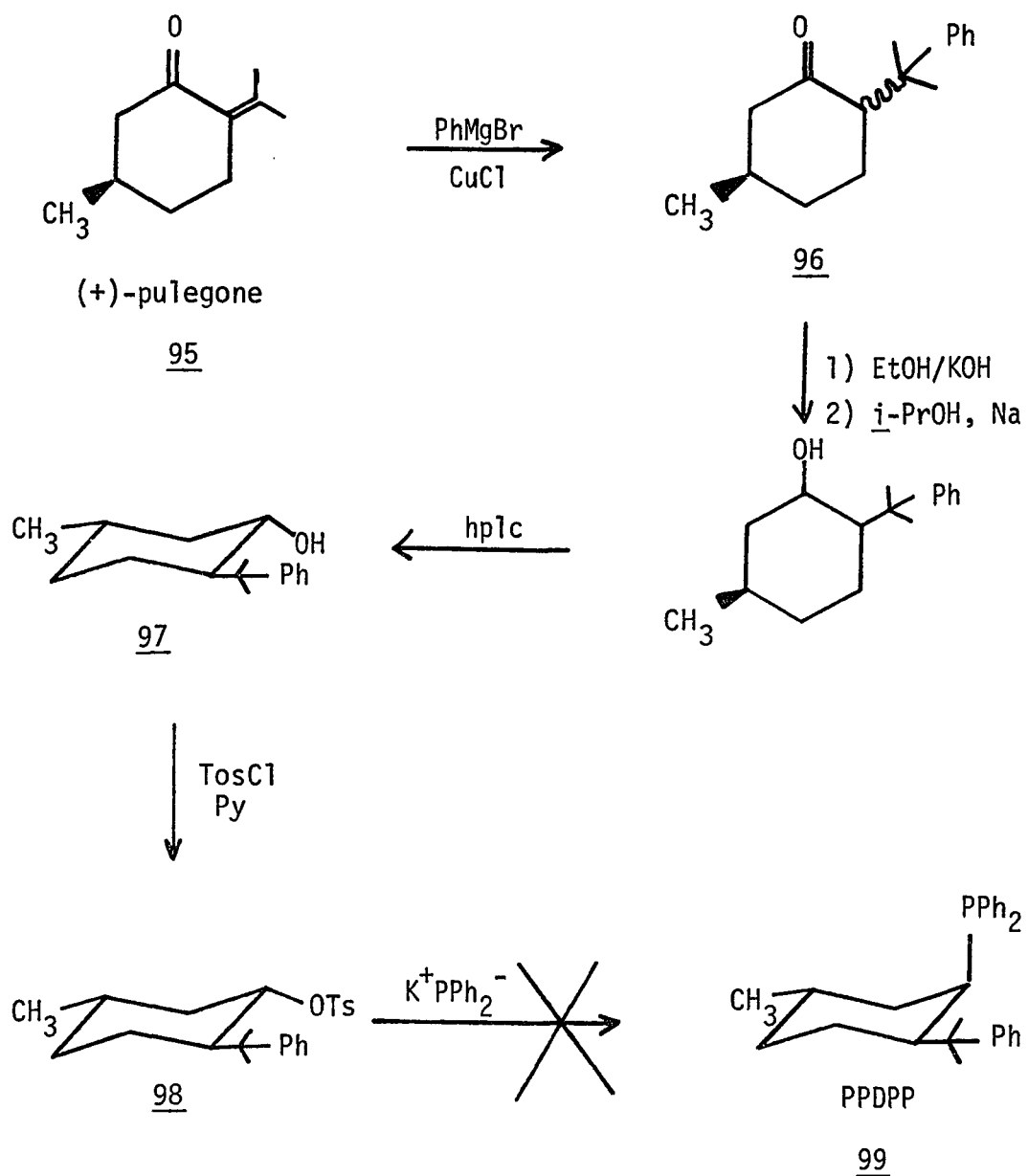
Figure 25.   Preparation of 2-(2-phenylpropyl)-5-methylcyclohexyldiphenyl-
             phosphine from (+)-pulegone.

cis and trans ketones was equilibrated to what has been reported to be

an 85:15 mixture (the more stable trans isomer in excess) by treatment

with ethanolic potassium hydroxide.[65] Subsequent reduction with sodium

and 2- propanol in refluxing toluene[66] gave a mixture of alcohol epimers

(97) (Figure 25). It has been reported by Ensley[63] that due to more

rapid reduction of the trans isomer to alcohol further equilibration

occurs during reduction and mainly one alcohol isomer is obtained. In

Ensley's work the desired epimer was isolated by standard open column

chromatographic techniques (silica gel, with ethyl ether:petroleum

ether eluent[64]).

In order to convert the alcohol (97) to a phosphine ligand it

was necessary to have a relatively large quantity of the alcohol. Prepara-

tive hplc was chosen for the purification rather than standard methods

which would have required many repeated separations due to the scale

limitations. A sample of 33 g of 2-(2-phenylpropyl)-5-methylcyclohexanol,

prepared as described above was purified by preparative hplc using a

90/10 hexane/ethyl acetate solvent system. After separation about 63%

of the all equatorial alcohol was obtained plus, in contrast to Ensley's

results, 15% each of two other isomers, possessing either an axial

hydroxyl or an axial methyl group. About 7% of other by-products was

obtained in three other fractions which were identified as dehydration

products and one unidentified compound (Figure 26).

The alcohol was converted via a standard tosylation procedure to

the tosylate (98) which was then allowed to react with potassium diphenyl-

phosphide in an attempt to form 2-(2-phenylpropyl)-5-methylcyclohexyl-

diphenylphosphine (PPDPP) (99) with the configuration shown in Figure 25.
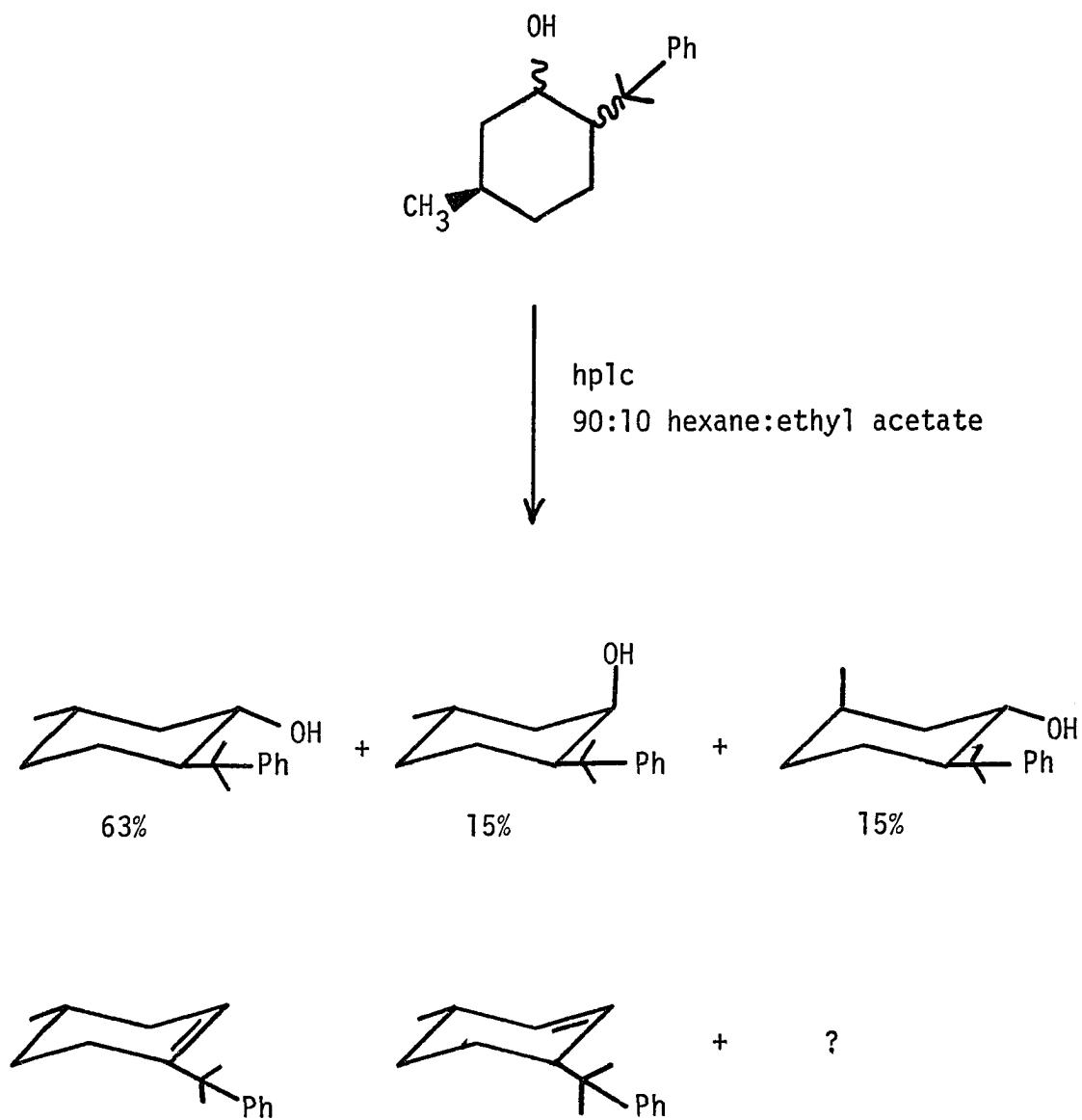
Figure 26. Purification of 2-(2-phenylpropyl)-5-methylcyclohexanol by hplc.

Several attempts to accomplish the S_N2 displacement with phosphide anion resulted in recovery of only a few percent of a white solid which proved to be elimination products contaminated with diphenylphosphine oxide. It appears that the tosylate is too sterically hindered to allow S_N2 displacement.

Asymmetric Homogeneous Hydrogenations

Use of Cationic vs In Situ Catalysts

Several workers have investigated the use of cationic and neutral catalysts in an attempt to ascertain the differences in hydrogenation performance. It has already been noted (see historical section) that the preformed cationic catalysts have the advantage of not being air sensitive. No general statement can be made about whether or not different percent ee values may be obtained with a cationic catalyst as compared to a neutral in situ catalyst that a difference is observed.

In this study, an attempt was made to run hydrogenations with both neutral and cationic catalyst species to determine possible differences. The ligands DIOP (20), NMDPP (18), and CMDPP (94) were converted to preformed cationic catalysts[67] (see below). Hydrogenation results with these cationic catalysts were compared with those obtained with neutral catalysts containing the same ligands. These comparisons will be discussed in the section on hydrogenation of α,β-unsaturated acids. Attempts to form cationic Rh catalysts with BUPHOS (80) and SUPHOS (84) were unsuccessful.

$$[Rh(COD)Cl]_2 + Phosphine \xrightarrow{NaBF_4} [Rh(COD)(Phosphine)_n]^+BF_4^-$$
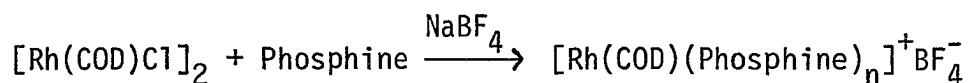
Reductions of α,β-Unsaturated Acids

A series of hydrogenations involving (E)- and (Z)- α- and
β-methylcinnamic acids were performed with catalysts containing previously
reported ligands[20] as well as those prepared in this study. The structures
of the substrates used, also listed in the historical section, are shown
again here for convenience.
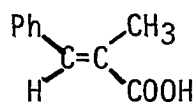
(E)-68
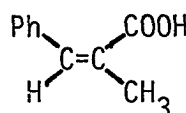
(Z)-68
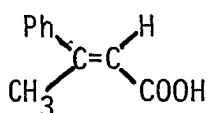
(E)-69
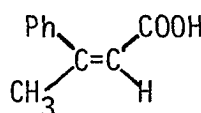
(Z)-69

Most of the hydrogenation were performed at 300 psig and 60° for
24 hr. Under these conditions, neutral catalysts containing the ligands
NMDPP (18), DIOP (20), BUPHOS (80), SUPHOS (84), and CMDPP (94) completely
reduced the substrate (E)-α-methylcinnamic acid (68) (Table 7). The
products obtained with (18), (84), and (94) were all of the R configuration
with the highest percent ee observed for the catalyst containing NMDPP
(18). Ethyl-2-methyl-3-phenylpropanoic acid of the S configuration was
obtained upon reduction of (E)-(68) with Rh/(20). However, the R isomer

Table 7. Reduction of α-methylcinnamic acid (68) with a series of neutral and cationic Rh catalysts.[a]

Substrate	Catalyst Ligand	% Reduction	Product % ee	Product Config.
(E)-68	18	100	63	R
"	20	"	25	S
"	80	"	-	-
"	84	"	8	R
"	94	"	28	"
"	12[b]	30	-	-[d]
"	18[b]	56	-	-[d]
"	94[b]	100	19	R
"	"[b,c]	90	23	"
"	12[b,c]	17	-	-[d]
"	20[b,c]	5	-	-[d]
(Z)-68[e]	20	100	33	R

a) Hydrogenations were run at 300 psig of hydrogen, and 50 for 24 hr in the presence of triethylamine unless otherwise noted.
b) Cationic catalyst.
c) These hydrogenations were run at 45 psig of hydrogen, otherwise conditions were the same as described in footnote a.
d) Because of the low yield no rotation data were taken.
e) Additional comparative data of this kind are listed in Table 4.

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was obtained when (Z)-(68) was reduced with Rh/(20) indicating that the approach of the Z isomer to the catalyst was different from that of the E isomer. Reduction of (E)-(68) with Rh/BUPHOS (80) showed no asymmetric induction, Rh/SUPHOS (84) gave a very low value, and Rh/CMDPP (94) a slightly higher ee (28%).

Generally, neutral catalyst species hydrogenated α-methylcinnamic acid more efficiently (higher reduction yields) than did cationic species. Cationic catalysts containing DIPAMP (12), NMDPP (18), and DIOP (20) ligands gave very little reduction whereas Rh/CMDPP gave complete reduction. CMDPP was also the only ligand effective at low pressures (45 psig); 90% reduction and 23% ee.

The hydrogenation data obtained with (E)- and (Z)-β-methylcinnamic acids are shown in Table 8. With these substrates, in contrast to the α-methylcinnamic acids (Table 7), reduction of the Z-isomer with Rh/DIOP (20) gave a higher percent ee than reduction of the E isomer. The same tendency was observed when the catalyst was Rh/ACMP (2). A reversal in product configuration was also observed with DIOP and ACMP catalysts when the substrate geometry was changed from E to Z.

The results of hydrogenations with ligands (80) and (84) are unspectacular (3% ee) but once again, the value with a neutral Rh/CMDPP catalyst is much higher (39% ee). As in the case of the α-methylcinnamic acid substrates, the cationic complexes containing NMDPP (18) and DIPAMP (12), gave low percent reduction. Only the cationic catalyst containing CMDPP (94) gave complete reduction but with a lower ee (19%) than was observed for the neutral catalyst (39%).

Table 8. Reduction of (E)- and (Z)-β-methylcinnamic acid with a series of neutral and cationic catalysts.[a]

Substrate	Catalyst Ligand	% Reduction	Product % ee	Product Config.
(E)-69	20	100	5	R
(Z)-69	"	"	28	S
(E)-69	2[b]	"	13	R
(Z)-69	"[b]	"	37	S
(E)-69	80	"	3	"
"	84	"	3	"
"	94	"	39	"
"	"[b]	"	19	"
"	12[b]	33	-	_[c]
"	18[b]	50	-	_[c]

a) Hydrogenations were run at 300 psig of H_2, and 50° for 24 hr in the presence of Et_3N.
b) These ligands were used in cationic catalyst species.
c) Because of the low yield, no rotation data were taken.

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In all reductions of substrates (68) and (69) without added triethylamine, little or no hydrogenation occurred.

Reductions of (Z)-α-Acetamidocinnamic Acid

(Z)-α-acetamidocinnamic acid (72) has been reduced with the Wilkinson-type catalyst containing a large number of the chiral ligands that have been synthesized (Table 5). Therefore, it was decided to test the ligands from this study on the phenylalanine precursor (Table 9). A check on the system and procedure was carried out with a sample of the DIPAMP (12) catalyst. The result obtained, 93% ee of the S isomer, is in agreement with the value reported by Knowles.[46] Reduction of (72) with Rh/DIOP (20) also gave results in agreement with literature values (76%ee).[19]

$$\begin{array}{c} Ph \quad\quad NHAc \\ C{=}C \\ H \quad\quad COOH \end{array}$$
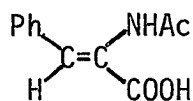
72

Results obtained upon hydrogenation of (72) with catalysts containing the ligands prepared at New Hampshire were not spectacular (Table 9). The percent ee values ranged from 1-12%. "Unnatural" N-acetyl-D-phenylalanine was the predominant enantiomer produced. The less sterically hindered ligand, CMDPP (94), once again proved its hydrogenation efficiency (100% reduction) as did BUPHOS (80). The much more hindered ligands NMDPP (18) and SUPHOS (84) were incapable of completely reducing (72) even though many attempts to do so (varying the phosphine to rhodium

Table 9. Reduction of (Z)-α-acetamidocinnamic acid with a series of neutral and cationic catalysts.[a]

Ligand	% Reduction	Product % ee	Product Config.
12[b]	100	93	S
20	"	76	R
18	25	0	-
18[b]	10-15	0	-
80	100	8	R
84	75	12	"
84[c]	75	6	"
94	100	5	"

a) Hydrogenations were run at 3 atm of H_2, and 50° for 24 hr.
b) These ligands were used as cationic catalyst species.
c) 73% ee.

ratio, increased reduction times) were unsuccessful and are not reported here. From these results, it is evident that none of the New Hampshire ligands tested (NMDPP, CMDPP, BUPHOS, SUPHOS) is very effective in catalytic reductions of (Z)-α-acetamidocinnamic acid.

Reductions of Enol Acetates

Aliphatic Enol Acetates

The preparation of chiral β-hydroxy acid derivatives via the asymmetric homogeneous hydrogenation of enol acetates was attempted during this study. A series of enol acetates, varying in the length of the aliphatic chain, were prepared. Due to difficulties in the synthesis of the long chain enol acetates, most of the work was done with short chain analogues. The enol acetate substrates that were used are shown in Figure 27.

The substrate most commonly used was (Z)-ethyl 3-acetoxybut-2-enoate (Z-100); it was easily synthesized as shown in Figure 28. The β-keto ester, ethyl acetoacetate, was purchased and was converted to the Z-enol acetate in an acid catalyzed reaction. The Z-isomer is presumed to form preferentially due to the formation of the hydrogen-bonded intermediate (105).[68]

105
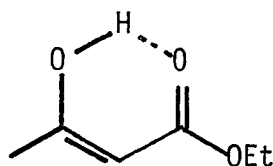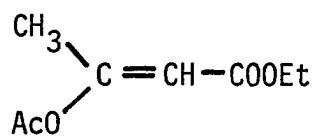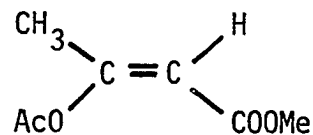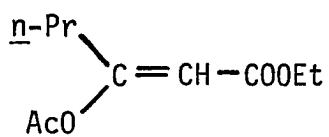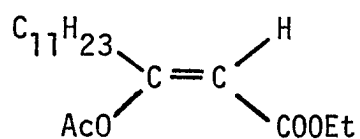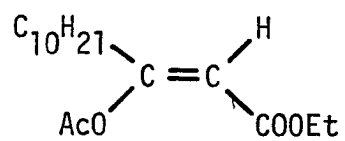
Figure 27. Aliphatic enol acetates studied as precursors of optically active β-hydroxy acid derivatives.

In order to prepare the E isomer, the reaction was run under basic conditions (Figure 28). The E isomer is presumed to form preferentially due to the presence of the solvent separated ion intermediate (106),[69] in the basic media.
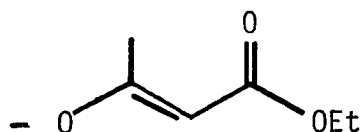
106

Neither the acid nor base synthesis is stereospecific; the observed · stereoselectivities were; 18:1, Z:E and 1:15, Z:E, respectively. Both procedures gave good yields (greater than 80%). (E)- and (Z)-ethyl 3-acetoxyhex-2-enoate (102) were prepared from ethyl butyrylacetate by the same procedures. Also, the (Z)-methyl ester (101) was prepared from methyl acetoacetate by the procedure described for the synthesis of (Z)-(100).

The synthesis of the long chain enol acetates, (103) and (104), was not as simple as that of the shorter analogues. The β-keto esters had to be prepared since they were not commercially available. The synthetic scheme used for ethyl 3-ketotetradecanoate and ethyl 3-acetoxytetradec-2-enoate is shown in Figure 29.[70,71,72] The procedure described by Rathke was used to prepare lithio ethyl acetate. Addition of either lauroyl chloride or undecanoyl chloride to lithio ethyl acetate yielded ethyl 3-ketotetradecanoate or ethyl 3-ketotridecanoate, respectively.

$$\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OEt} \quad \xrightarrow[\underline{p}\text{-TsOH, }\Delta]{\text{CH}_2=\overset{\text{OAc}}{\underset{}{\text{C}}}-\text{CH}_3}$$

$$\underset{\text{AcO}}{\overset{\text{CH}_3}{>}}\text{C}=\text{C}\underset{\text{COOEt}}{\overset{\text{H}}{<}}$$

(Z)-100

18:1 Z:E

$$\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_2\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OEt} \quad \xrightarrow[\text{HMPA, Et}_3\text{N}]{\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Cl}}$$

$$\underset{\text{AcO}}{\overset{\text{CH}_3}{>}}\text{C}=\text{C}\underset{\text{H}}{\overset{\text{COOEt}}{<}}$$

(E)-100

1:15 Z:E
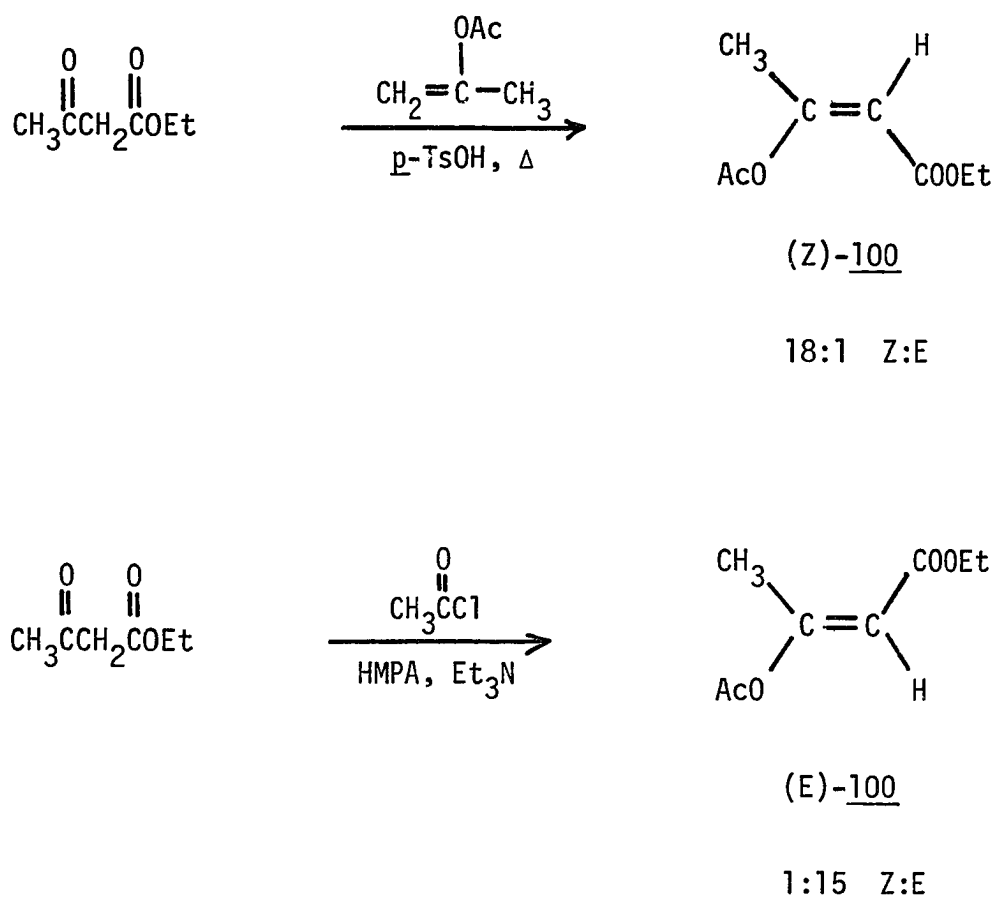
Figure 28.   The synthesis of (E)- and (Z)-ethyl-3-acetoxybut-2-enoate.

$$CH_3-(CH_2)_{10}-COOH \xrightarrow{SOCl_2} CH_3-(CH_2)_{10}-\overset{\overset{O}{\|}}{C}-Cl$$

lauric acid   lauroyl chloride

$$\underline{n}\text{-BuLi} + C_6H_{11}NH(\underline{i}-Pr) \longrightarrow C_6H_{11}-N^--\underline{i}-Pr$$

$$\downarrow CH_3COOEt$$

$$CH_3-(CH_2)_{10}-\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OEt \xleftarrow{CH_3-(CH_2)_{10}-\overset{\overset{O}{\|}}{C}Cl} {}^-CH_2COOEt$$

ethyl 3-ketotetradecanoate   lithio ethyl acetate

$$\downarrow \begin{array}{c} \overset{OAc}{\underset{|}{}} \\ CH_2=C-CH_3 \\ \underline{p}\text{-TsOH, } \Delta \end{array}$$

$$\underset{AcO}{\overset{CH_3-(CH_2)_{10}}{}} C=C \underset{COOEt}{\overset{H}{}}$$

$$\underline{103}$$
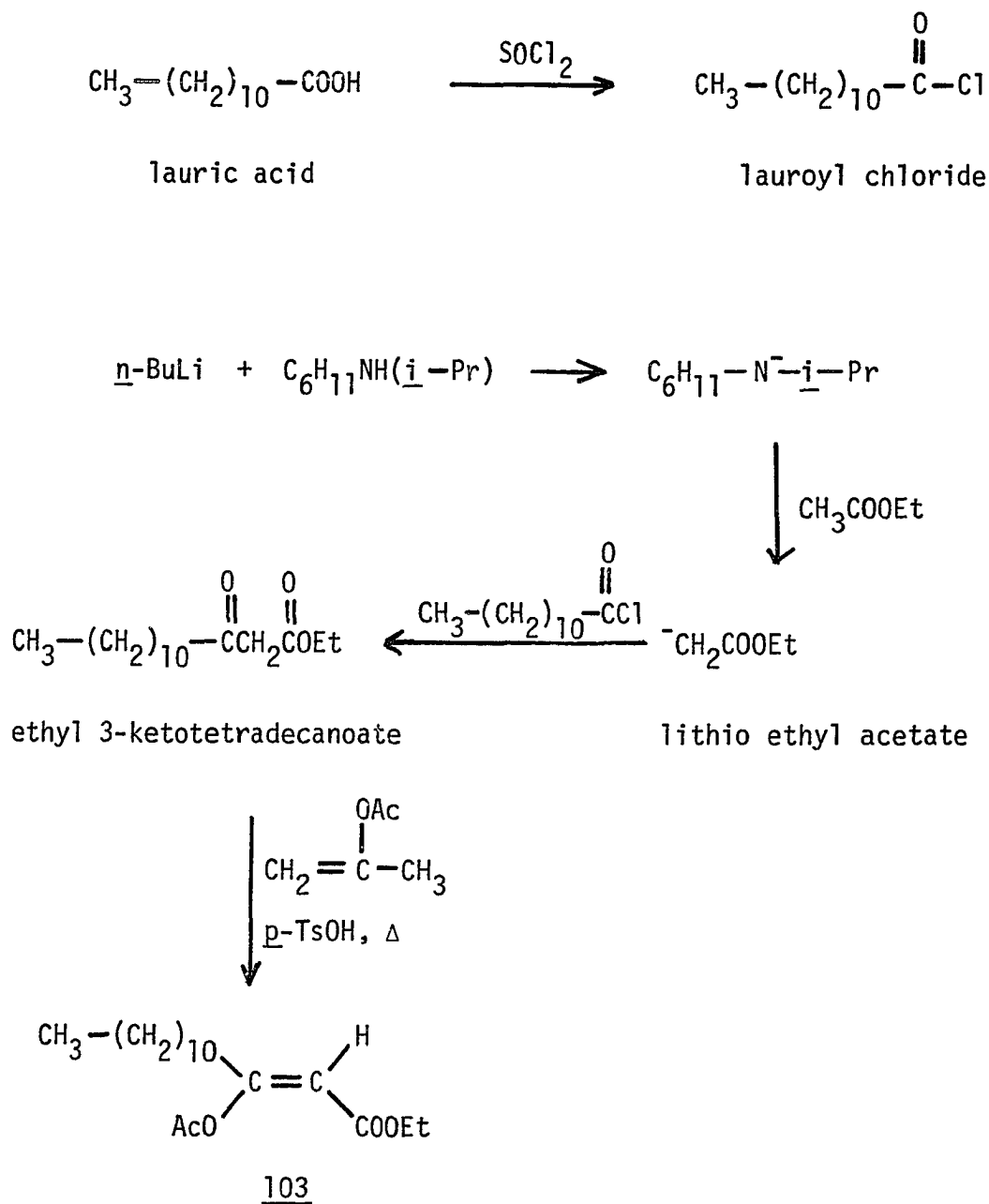
Figure 29. The synthesis of (Z)-ethyl 3-acetoxytetradec-2-enoate from lauric acid.

At this stage, numerous problems were encountered in the synthesis. Very low yields of the β-keto esters were obtained due to decomposition of the products upon distillation. Due to such difficulties, impure samples were converted to the enol acetates, (103) and (104). Very low yields were obtained and this method was not viable for the preparation of long chain aliphatic β-keto esters. One can speculate that, had it been possible to obtain the β-keto esters in a purer form, the preparation of the enol acetates would have proceeded smoothly and in good yield.

The results of a series of reductions of (Z)-(100) with Wilkinson-type catalysts containing a large number of ligands are reported in Table 10. Reaction mixtures were analyzed directly by glpc to obtain percent reduction, percent conversion, and percent hydrogenolysis. The percent reduction was based on the total amount of hydrogenated product present in the reaction mixture. The percent conversion was determined from the weight ratio of starting material to all products. The percent hydro-genolysis (cleavage of OAc) was based on the amount of ethyl butyrate in the total reaction mixture. In a few hydrogenations, some ethyl crotonate was observed as a product. Apparently, ethyl crotonate is formed during hydrogenation and then is rapidly reduced to ethyl butyrate. After the glpc analysis was completed on the hydrogenation solution the samples were worked-up for specific rotation measurements. The specific rotation values were very low (0.00-0.69°). There is no literature value for the maximum rotation of ethyl-3-acetoxybutanoate. Attempts to determine this value by use of the chiral shift reagent Eu(dcm)$_3$[73] were unsuccessful since variations in peak areas as small as one nmr chart paper division caused major variations in the rotation calculations. It was only possible to

Table 10. Reduction of (Z)-ethyl-3-acetoxybut-2-enoate with a variety of
neutral and cationic catalysts.[5]

Ligand	% Reduction $\frac{}{gc^2}$	% Conversion $\frac{}{gc^2}$	% Hydrogenolysis $\frac{}{(gc)^2}$	$[\alpha]_D^{T}$ [3,4]
2	35	100	65	0.53
12	60	100	40	0.69
20	85	100	15	0.14
18	27	29	7	0.12
94	41	45	8	0.10
80	85	100	15	0.34
84	60	66	17	0.03
21	42	53	20	0.14
45	30	55	13	0.48
41	78	100	22	0.27
37	66	78	16	0.00

1) Ligands were used as the cationic form of the catalyst.
2) 10% SE 30 on Varaport 30, 80-100 mesh, 10' x 1/4", 147, 30 ml/min He, 150 mA.
3) Density assumed to be 1.0.
4) Values of incompletely converted samples corrected to 100% reduction.
5) All hydrogenations were run in a stirred reactor at 400 psi H_2, 50°C, in absolute ethanol for 24 hours, with the exception of hydrogenations with DIPAMP which were complete in 6 hours.

estimate that the maximum specific rotation lies between 1.5-$3.5°$; no more precise value could be established using the shift reagent technique.

As Table 10 shows, widely different hydrogenation yields and chiral efficiencies (as indicated by the magnitude of $[\alpha]$) were observed. Rh/DIPAMP (12) gave the highest rotation ($[\alpha]_D 0.69$) but this positive aspect was counterbalanced by the fact that there was 40% hydrogenolysis. On the other hand, catalysts prepared from NMDPP (18) and CMDPP (94) gave only 7-8% hydrogenolysis but unfortunately, specific rotations of only 0.10-$0.12°$. A result between these two "extreme cases" just cited was obtained with Rh/BUPHOS (80) which gave only 15% hydrogenolysis and a specific rotation of $[\alpha]_D 0.34°$ was observed. If both chemical and optical yield are important then BUPHOS has to be considered the most successful ligand. If optical purity is of the utmost concern then DIPAMP is the most effective ligand. Table 10 also shows that ligands (20), (37), (41), and (45) which have all been rather successful with other substrates (e.g.,(72)) are very inefficient in this system.

It was noted repeatedly that in hydrogenations characterized by incomplete conversion, the small amount of E-isomer present in the substrate appeared to hydrogenate less rapidly than the Z-isomer. Indeed reduction of a sample containing (E)-(100) with Rh/BUPHOS gave only 30% conversion in the same amount of time required for 100% conversion of the Z-isomer.

A maximum rotation of $[\alpha]_D^{21} 0.54°$ (neat) has been reported for methyl-3-acetoxybutanoate.[74,75] It seems likely that the maximum rotation of the ethyl ester should be similar, although the chiral shift reagent work does not support this conclusion nor does the fact that a specific

rotation of 0.69° was obtained for the ethyl ester in the hydrogenation of (100) with Rh/DIPAMP. Attempts were made to reduce the methyl enol acetate (Z)-(101) with the Wilkinson-type catalyst containing DIPAMP, ACMP or BUPHOS but it was never possible to achieve any reduction of the substrate. This strange result has defied rationalization, and should be re-investigated.

Results for hydrogenations of the longer chain enol acetates, (102), (103), and (104) are shown in Table 11. (Z)-Ethyl-3-acetoxyhex-2-enoate (102) was hydrogenated with Rh/DIPAMP (12) and Rh/BUPHOS (80) to give products having $[\alpha]_D 2.17°$ (neat) and $[\alpha]_D -0.51°$ (neat), respectively. The maximum rotation is not known and attempted analysis with the chiral shift reagent $Eu(dcm)_3$ was unsuccessful (no clearly discernable doubling due to overlapping peaks). Once again, as observed with (Z)-(100), DIPAMP caused more extensive hydrogenolysis (74%) than BUPHOS (28%).

Attempted reductions of (Z)-(103) and (Z)-(104) with Rh/BUPHOS gave either heterogeneous reaction mixtures or no hydrogenation. Further investigation is required with these long chain aliphatic substrates. As mentioned previously, these substrates were impure and must be purified.

Aryl Enol Acetates. The only reported example of the asymmetric homogeneous hydrogenation of enol acetates involves the hydrogenation of (Z)-ethyl-2-acetoxy-3-phenylprop-2-enoate (73) and (E)- and (Z)-ethyl-3-acetoxy-3-phenylprop-2-enoate (74) with Rh/DIPAMP (12).[46] Originally, greater than 90% ee was presumed with both (Z)-(73) and (Z)-(74)[76]

Table 11. Reduction of long chain aliphatic enol acetates with a Rh/BUPHOS catalyst and a Rh/DIPAMP catalyst.[a]

Substrate	Catalyst Ligand	% Hydrogenation	% Conversion	% Hydrogenolysis	$[\alpha]_D^T$
102	12[b]	26	100	74	2.17°
102	94	70	97	28	-0.51°
103	"	-	-	-	-
104	"	-	-	-	-

a) Hydrogenations were run at 400 psig of H_2, and 50° for 24 hr.
b) This ligand was used in a cationic catalyst form, $[Rh(COD)(DIPAMP)]^+BF_4^-$.

based on literature maximum rotation values.

$$Ph-C=C-H$$
$$AcO \quad COOEt$$
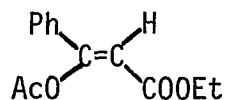
(Z)-(74)

Reduction of (Z)-(74) in our laboratory with Rh/ACMP (2) gave ethyl-3-acetoxy-3-phenylpropanoate, $[\alpha]_D$-32.4° (neat).[77] Based on the accepted literature value for the maximum rotation, ($[\alpha]_D^{17}$5.28° (neat)[78] or $[\alpha]_D^{17}$5.24° (neat)[79]) the apparent % ee for the Rh/ACMP reduction was thus greater than 600%! It was concluded that the literature value must be incorrect. The hydrogenation of (Z)-(74) was repeated using Rh/DIPAMP. Ethyl-3-acetoxy-3-phenylpropanoate with a specific rotation of $[\alpha]_D$-4.15° (neat) was obtained. This corresponds to Knowles' result with the same catalyst. Based on the literature rotation (presumably incorrect) this value corresponded to about 80% ee. Products from the Rh/DIPAMP and the Rh/ACMP hydrogenations were analyzed with the chiral shift reagent $Eu(dcm)_3$.

The product from the Rh/DIPAMP reduction was found to contain 3-5% ee of the (-)-enantiomer rather than 80% ee, and the sample from the reduction involving ACMP was found to contain 38% ee of the same enantiomer.

As a result of the above findings it seemed appropriate to investigate the preparation of chiral ethyl-3-acetoxy-3-phenylpropanoate in order to ascertain the source of the erroneous maximum rotation.

A sample of ethyl-3-hydroxy-3-phenylpropanoate (107) was prepared by the Reformatsky reaction of benzaldehyde, ethyl bromoacetate and zinc in the presence of trimethylborate. The ester was saponified with KOH/ methanol to give 3-hydroxy-3-phenylpropanoic acid (108) (Figure 30).[80] Resolution of (108) has been reported by various workers; with morphine, lit.[81] $[\alpha]_D^{18}$19.2° (c5, ethanol); with brucine, lit.[79] $[\alpha]_D^{17}$18.9° (c5.00, ethanol). The resolution was repeated in this laboratory with brucine and a specific rotation of $[\alpha]_D$17.9° (c5.01, ethanol), corresponding to 95% ee based on the literature value, was obtained.*[80] It would appear that the maximum rotation of (108) is indeed about 19° based on the experience of several workers who have resolved the compound.

The methyl ester of (108) was prepared by esterification with diazomethane. The literature value for the specific rotation of methyl-3-hydroxy-3-phenylpropanoate is $[\alpha]_D^{24}$19.3° (c4.78, ethanol).[81] The methyl ester prepared in this laboratory had $[\alpha]_D$17.6° (c5.44, ethanol) which corresponded to 96% ee based on the literature rotation.[80] The methyl ester was analyzed with the chiral shift reagent $Eu(Dcm)_3$. Nmr analysis of the racemic methyl ester in the presence of $Eu(dcm)_3$ showed a symmetrical doublet (two enantiomers present in equal amounts) for the methyl protons. The shifted spectrum for the methyl ester from 95% ee acid showed a singlet indicating essentially optically pure material. As expected, there was no racemization during esterification with diazomethane.

_____

*Kenyon's directions for resolution with brucine indicated the formation of a 1:1 acid:brucine salt. Using this stoichiometry we were unable to repeat this work and subsequently found a later report by Noyce that described formation of a 2:1 acid:brucine salt.[82] The 2:1 salt was found to be the actual species involved in the resolution.

PHCHO + BrCH$_2$COOEt

$\downarrow$ B(OMe)$_3$, Zn

$\downarrow$ NH$_4$OH
glycerol

($\pm$) ─ PhCHCH$_2$COOEt
|
OH

<u>107</u>

$\downarrow$ KOH, methanol

PhCHCH$_2$COOH
|
OH

<u>108</u>
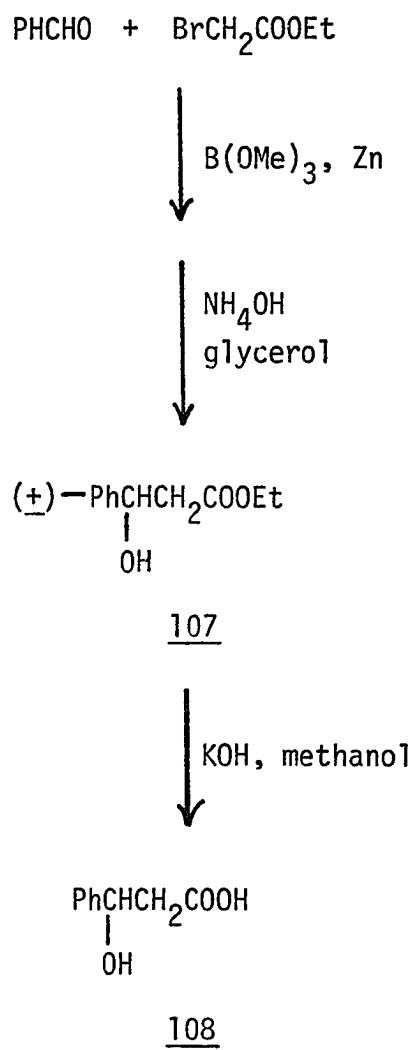
Figure 30.   The synthesis of racemic 3-hydroxy-3-phenylpropanoic acid.

The methyl ester was acetylated with acetic anhydride and the resulting methyl 3-acetoxy-3-phenylpropanoate was analyzed using $Eu(dcm)_3$. Two symmetrical doublets of equal intensity were observed in the lanthanide induced shift (LIS) nmr spectrum for racemic methyl 3-acetoxy-3-phenyl-propanoate; one doublet for the protons in the methyl ester and another for the acetoxy methyl protons. The LIS nmr spectrum of the optically active material, on the other hand, showed singlets for the methyl ester and acetoxy methyl protons, indicating at least 95% ee; $[\alpha]_D 65.3^{\circ}$ (neat).

From this series of experiments it was obvious that the literature value for the maximum rotation of the precursor β-hydroxy acid (108) was correct and also that no racemization occurred during acetylation of the β-hydroxy methyl ester. This left esterification of the β-hydroxy acid to the ethyl ester as the one questionable step in the synthesis of ethyl 3-acetoxy-3-phenylpropanoate. In the preparation of ethyl 3-acetoxy-3-phenylpropanoate originally described by Kenyon and coworkers[79] and repeated by Koga and coworkers,[78] the esterification was accomplished by dissolving the β-hydroxy acid in absolute ethanol and bubbling HCl gas through the heated solution for 10 hr. Neither of these groups reported any complication with this procedure. However, in our hands, when optically active β-hydroxy acid (108) was treated in this way, a mixture of products was obtained and a low or negligible optical rotation was observed (Figure 31). The reaction was run twice. The first time, some ester (109) was formed (glpc, nmr); but the second time, none was observed and the optical rotation was zero. Analysis by nmr indicated the presence of the β-ethoxy ester (110) and a mixture of cis and trans alkenes (111)

PhCHCH$_2$COOH $\xrightarrow[\text{HCl(g)}, \Delta]{\text{EtOH}}$ PhCHCH$_2$COOEt

| |
OH   OH

<u>109</u>

+

PhCH=CHCOOEt   +   PhCHCH$_2$COOEt

| |
OEt

<u>111</u>   <u>110</u>
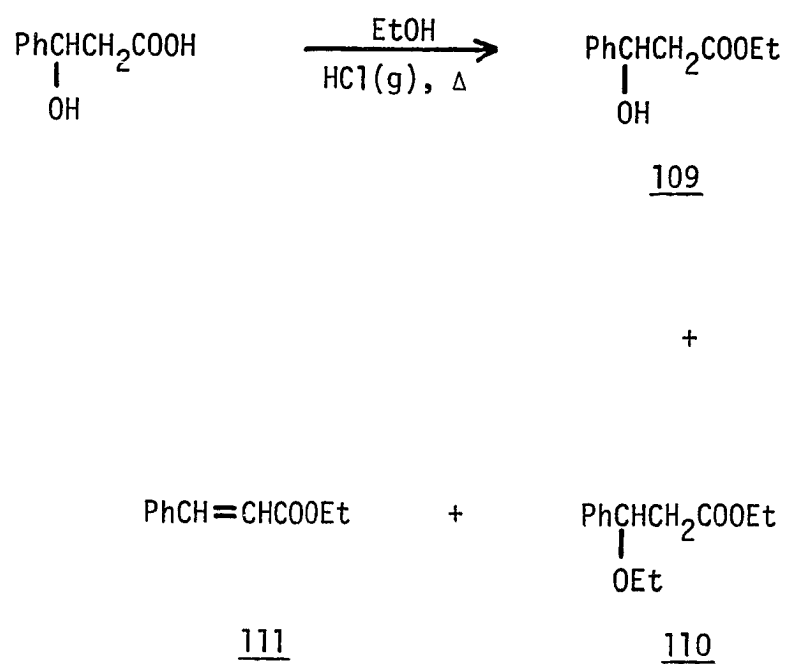
Figure 31. Esterification of 3-hydroxy-3-phenylpropanoic acid with
ethanol and HCl gas.

(four singlets in the vinyl proton region). To verify the existence of

(110) the authentic compound was prepared by reaction of (108) with

ethyl iodide in the presence of silver(I) oxide.[83] Analysis of the

reaction mixture from the esterification and the authentic β-ethoxy

ester (110) by glpc and nmr confirmed that a by-product from the ester-

ification was indeed (110).

$$PhCHCH_2COOEt \quad \xrightarrow[\Delta]{EtI, \ Ag_2O} \quad PhCHCH_2COOEt$$
$$\underset{OH}{|} \qquad\qquad\qquad\qquad\qquad\qquad \underset{OEt}{|}$$

110
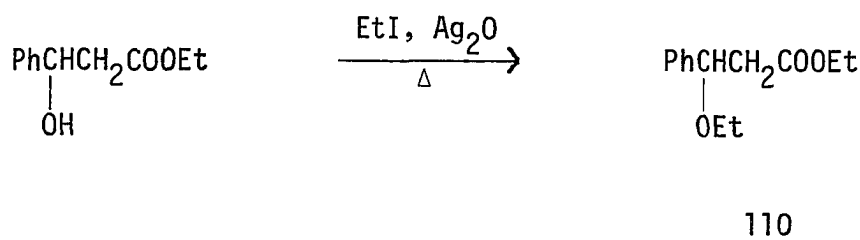
Figure 32. Synthesis of ethyl 3-ethoxy-3-phenylpropanoate.

From this evidence it appeared that the esterification procedure

(ethanol and HCl gas) was the source of the literature error. It remained

to synthesize the β-acetoxy ester by a non-racemizing technique.

A mild method for esterification involving the reaction of (108)

with dimethylformamide diethylacetal was attempted (Figure 33).[84] However,

the esterification did not proceed even under reflux conditions. A

standard procedure involving esterification with ethyl iodide and triethyl-

amine was successful for the preparation of (109).[85] The specific rotation

of the ester, prepared from a sample of (108) having $[\alpha]_D 12.74°$ (c5, ethanol)

(67% ee) was found to be $[\alpha]_D^{26} 16.85°$ (neat). This sample of ester (109)

was then acetylated with acetic anhydride to give ethyl 3-acetoxy-3-phenyl-

propanoate (112) (Figure 34). Analysis of the acetoxy ester (112) with

$Eu(dcm)_3$ indicated a 67% ee, the same as that of the hydroxy ester precursor.

When the optical purity of the starting ester (67% ee) was taken into account,

PhCHCH$_2$COOH $\xrightarrow[]{\underset{\displaystyle Me_2NC(OEt)_2}{H}}$ PhCHCH$_2$COOEt
| |
OH   OH

PhCHCH$_2$COOH $\xrightarrow{Et_3N, EtI}$ PhCHCH$_2$COOEt
| |
OH   OH
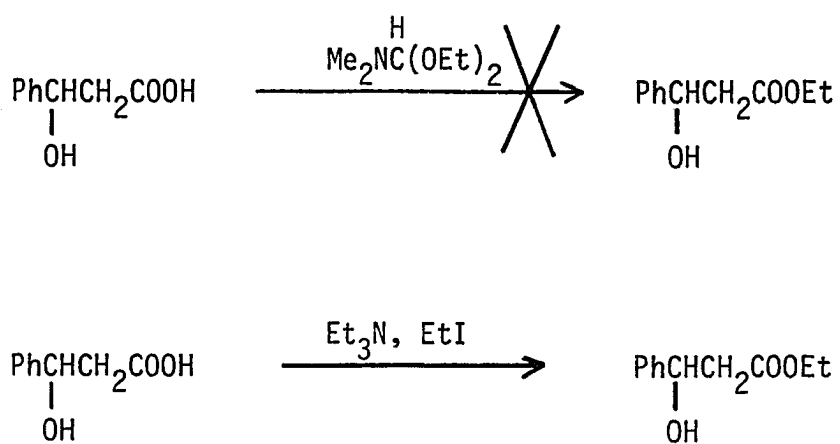
__109__

Figure 33. Synthesis and attempted synthesis of ethyl 3-hydroxy-3-phenylpropanoate.

the maximum rotation of the acetoxy ester (112) was calculated to be
$[\alpha]_D 60.6°$ (neat) (d=1.088).

$$PhCHCH_2COOEt \quad \xrightarrow[\Delta]{Ac_2O} \quad PhCHCH_2COOEt$$
$$\overset{|}{OH} \qquad\qquad\qquad \overset{|}{OAc}$$

<div align="center">112</div>
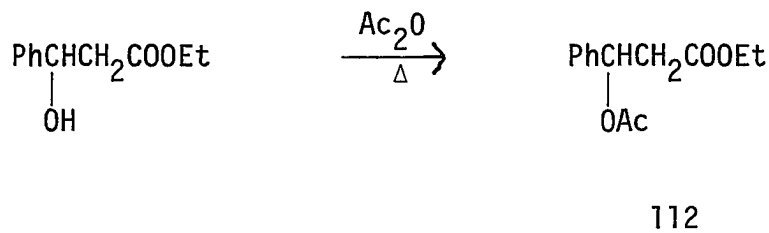
Figure 34. Acylation of ethyl-3-hydroxy-3-phenylpropanoate.

This maximum rotation value is more than ten times that previously reported for (112). Thus the reduction of (E)- and (Z)-ethyl-3-acetoxy-cinnamate with Rh/DIPAMP reported by Knowles[46] and coworkers actually gave only about a 5% ee rather than the 90% that would be calculable based on the literature rotation for (112).

A general comment intended to assist future workers who will continue this study involves hydrogenation technique. The key to obtaining undisputable and repeatable hydrogenation results is to always maintain scrupulously clean equipment (glassware and hydro-genators); to keep the hydrogenators in good working order; to be consistent in reaction conditions; and to always work under a nitrogen atmosphere with well-degassed solvents. Failure to observe these warnings will result in a large number of heterogeneous, non-asymmetric hydrogenations.

EXPERIMENTAL

General

Gas-liquid Partition Chromatographic Analyses: (glpc) were performed on a Varian Aerograph Model 90-P gas chromatograph coupled to a Sargent Welch Model SRG recorder. Helium was used as the carrier gas. Table A lists the analytical columns and retention times for the compounds used in this study.

Infrared Spectra: (ir) were recorded on a Perkin-Elmer 337 grating spectrophotometer and calibrated using the 1601.4 cm^{-1} band of polystyrene. The spectra of liquids were obtained neat while those of solids were taken as mulls.

Nuclear Magnetic Resonance Spectra: (nmr) were obtained on a Jeolco Model JNM-MH 100, 100 MHz nmr. All 100 MHz spectra are numbered less than 7100. A Varian Model A-60 Spectrometer was used to record 60 MHz spectra. All 60 MHz spectra are numbered over 16,500. Chemical shifts are reported relative to internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are given in Hertz.

Elemental Analyses: Elemental analyses were performed on an F and M Model 185 Carbon, Hydrogen, Nitrogen Analyzer by Ms. D. Cardin and Ms. J. Daigle.

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Melting Points: Melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected.

Optical Rotations: Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005°, equipped with a deuterium light source and filtered to give readings at 578 and 546 nm. Rotations are reported at the sodium-D line (589 nm) and were calculated from the Drude equation.

$$
\alpha_D = \left(\frac{\dfrac{\alpha_{578}}{\alpha_{546} - \alpha_{578}}}{\dfrac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} + 1.3727} \right) \alpha_{546}
$$

High Performance Liquid Chromatography: (hplc) was performed on a Waters ALC/GPC-202 chromatograph equipped with a model 6000 delivery system, U6K injector and refractive index and ultraviolet detection systems. Preparative hplc was performed on a Waters PrepLC/500 with a refractive index detector.

Unless otherwise noted, compounds were purchased from commercial sources and were used as received.

Dry Solvents: Dry solvents such as Diethyl ether and tetra-hydrofuran (THF) were distilled from lithium aluminum hydride and used immediately or stored over sodium wire or molecular sieves, respectively.

Pyridine was dried by storing over potassium hydroxide pellets.

Hydrogenations: Hydrogenations were run in a stirred low pressure hydrogenator described by Masler et al., a Parr Model 3911 low pressure

hydrogenator or a Parr Model 4501 Medium Pressure Hydrogenator.

Gases: Nitrogen was bubbled through concentrated sulfuric acid and passed through a calcium chloride drying tube. Hydrogen (prepurified, 99.95%) was used with no further treatment.

Table A. Gas chromatographic retention times for compounds used in this study.[a]

Compound	Column	Temp. °C	Retention Time, Min
Pulegone	A	205	2.6
2-(2-Phenylpropyl)-5-methylcyclohexanone	A	205	4.9
2-(2-Phenylpropyl)-5-methylcyclohexanol	A	205	5.8
2-t-Butyl-5-methyl-cyclohexanone	B	100	4.4
Pulegone	B	100	2.7
(+)-NMDPP	B	230	2.6
(+)-NMDPP oxide	B	230	4.6
Benzene	B	230	0.2
(Z)-Ethyl-3-acetoxy-3-phenyl-2-propenoate	C	250	3.7
Ethyl-3-acetoxy-3-phenyl-propanoate	C	250	3.0
Ethyl cinnamate	C	250	2.3
Ethyl-3-phenylpropanoate	C	250	2.0
Ethyl-3-acetoxy-3-phenyl-propanoate	A	185	8.5

Table A. (continued)

Compound	Column	Temp. °C	Retention Time, Min
Ethyl-3-hydroxy-3-phenyl-propanoate	A	185	9.3
Ethyl-3-ethoxy-3-phenyl-propanoate	A	185	4.2
Ethyl-3-acetoxybut-2-enoate	C	175	3.2
Ethyl-3-acetoxybutanoate	C	175	3.1
Ethyl caproate	C	175	1.4
(Z)-Ethyl-3-acetoxybut-2-enoate[b]	C	147	3.2
(E)-Ethyl-3-acetoxybut-2-enoate	C	147	3.6
Ethyl-3-acetoxybutanoate[b]	C	147	3.0
Ethyl butyrate	C	147	1.3

Column A: 10' × 1/4" 5% Carbowax 20 M on Chromasorb W, 80-100 mesh.

Column B: 5' × 1/4" 3% SE 30 on Chromasorb W, 60-80 mesh.

Column C: 10' × 1/4" 10% SE 30 on Varaport 30, 80-100 mesh.

[a]A constant flow rate of 50 mL/min of helium gas was maintained on all columns.

[b]The response ratios were determined for (Z)-ethyl-3-acetoxybut-2-enoate and ethyl-3-acetoxybutanoate on column C at 147° and found to be 1:1.68, respectively.

General Procedure for Use of Chiral Shift Reagent, Eu(dcm)$_3$:

Reagents	Quantity
Eu(dcm)$_3$	0.080 g
Carbon disulfide	0.35 mL
Compound	0.025 mL
TMS	0.05 mL

The reagents were mixed in a clean test tube in the order listed, as rapidly as possible. The yellow solution was transferred to an nmr tube by pipet and the spectrum was run within 30 min. If excess shift reagent was needed to induce a greater shift, then 0.040 g portions were added directly to the nmr tube containing the already prepared mixture and the spectrum read immediately. Ratios of stereoisomers were determined by measuring peak height and by integration.

Dimethylethylphosphonoacetate: Trimethylphosphite (100 g, 0.806 mol) was added dropwise to a solution of ethyl bromoacetate (100 g, 0.6 mol) which had been warmed to about 100°, under nitrogen. Heating was continued throughout the reaction and the methyl bromide was removed with a nitrogen stream. The product was isolated by distillation of the residue and two fractions were collected; bp 70-80° (14 mm), 40 g; bp 140-143° (14 mm), 92 g (83.6%). Analysis by nmr (16699, CDCl$_3$) indicated that the higher boiling fraction was the desired product.

Ethyl-β-methylcinnamate: Dimethylethylphosphonoacetate (112 g, 0.57 mol) was added dropwise to a cooled suspension of sodium hydride

(50% dispersion in Nujol, 24 g, 0.5 mol) in dry dimethoxyethane (400 mL) so that the temperature did not rise about 30°. The reaction mixture was allowed to stir for 1 hr at room temperature and then acetophenone (60 g, 0.5 mol) was added dropwise so that the temperature remained below 30°. The reaction mixture was stirred for 2 hr at room temperature and then at 50° for 2 hr. After cooling, the reaction mixture was treated with water (75 mL) and saturated sodium chloride (75 mL) to decrease the solubility of the dimethoxyethane. The reaction mixture was extracted into ether and was concentrated to give a light brown oil. The oil was distilled, bp 58-112° (2.5 mm), yield, 80.6 g (83.6%). Analysis of the distillate by nmr showed the presence of both the (Z)- and (E)-isomers in about a 1:9 ratio, respectively. nmr (16700, $CDCl_3$) (E)-isomer: δ 5.90 (s, 1, C=C$\underline{H}$); (Z)-isomer: δ 5.70 (s, 1, C=C$\underline{H}$).

(E)-β-Methylcinnamic Acid: Ethyl-β-methylcinnamate (80.6 g, 0.41 mol) was heated with a solution of potassium hydroxide (44 g, 0.79 mol) in water (300 mL) and the reaction mixture was allowed to reflux for 2 hr. The reaction mixture was cooled and was washed with ether. The aqueous solution was acidified with hydrochloric acid and the clear oil which separated was extracted with ether (2 × 150 mL). The ether solution was dried (Na_2SO_4) and concentrated to give a white crystalline product which was recrystallized from 3:1 heptane: ethyl acetate (350 mL) to yield 21.1 g (32%) of white prisms, mp 95-97°; mp lit.[86] 98.5°; nmr (16709, $CDCl_3$) (E)-isomer: δ 6.0 (s, 1, C=C$\underline{H}$). A second crop of crystals was collected, mp 76-101°, yield 21.2 g (32%), nmr (16710, $CDCl_3$) δ 5.70 (s, 1, C=C$\underline{H}$) Z-isomer δ 6.0 (s, 1, C=C$\underline{H}$, E-isomer). The nmr analysis indicated that the first crop was pure (E)-acid whereas the second crop was a 5:3 mixture of (E):(Z), respectively.

<u>(E)-α-Methylcinnamic Acid</u>:[87]   In a 500 mL round-bottomed flask,
benzaldehyde (106 g, 1.0 mol), propionic anhydride (160 g, 1.23 mol),
and sodium acetate (82 g, 1.0 mol) were heated and allowed to reflux for
24 hr. The reaction mixture was poured onto ice and water (1.2 L) and
was then acidified with concentrated hydrochloric acid. The crude acid
was extracted into ethyl ether (400 mL) and the ether solution was then
washed repeatedly with water. The ether solution was extracted with a
solution of sodium hydroxide (80 g, 2.0 mol) in water (1 L) and the basic
aqueous extract was separated and washed with ether. The aqueous layer
was acidified with concentrated hydrochloric acid and the product sepa-
rated as an oil which was extracted into ether. The ether extract was
washed with water, dried ($MgSO_4$) and concentrated <u>in</u> <u>vacuo</u> to give crude
(E)-α-methylcinnamic acid which crystallized on standing. The crude
product was recrystallized once from 60-110° pet ether to give 93 g (58%)
of (E)-acid, mp 70-76°; lit.[87] mp 81-82°; nmr (16659, $CDCl_3$) δ 7.60
(s, 1, C<u>H</u>=C).

<u>(Z)-α-Methylcinnamic Acid</u>:   (E)-α-methylcinnamic acid (37 g) in
400 mL of 95% ethanol was placed in a quartz flask and subjected to
radiation for eight days in a photochemical reactor (128 watt, 2537 Å).
The reaction mixture was then concentrated to dryness. The resultant
solid was weighed, dissolved in 30-60° pet ether (10 mL/g) and the solu-
tion was filtered. The filtrate was seeded with authentic (Z)-acid
(obtained from Dr. W. F. Masler) and allowed to stand at room temperature
for 24 hr. Very large, parallelogram-shaped, yellow crystals formed,
yield 10.5 g (28.4%). These were recrystallized from cyclohexanol (100 mL)

to yield 8.3 g of off-white crystals, mp 92-95°; lit.[88] mp 91-92°.

<u>(Z)-β-Methylcinnamic Acid</u>: A solution containing (E)-β-methyl-cinnamic acid (10 g, 0.06 mol) in 100 mL of 95% ethanol was irradiated as described previously for α-methylcinnamic acid. The reaction mixture was concentrated to dryness, weighed, dissolved in carbon disulfide (6 mL/g), and seeded with authentic (Z)-acid. After 24 hr, the light-yellow crystals were collected and recrystallized from 3:2 cyclohexane: ethyl acetate (4 mL/g), yield, 8 g, mp 130-133°; lit.[20] mp 131.5°.

<u>(Z)-α-Acetamidocinnamic Acid</u>:[89] A mixture of acetylglycine (58.5 g, 0.5 mol), sodium acetate (30 g, 0.37 mol), benzaldehyde (79 g, 0.74 mol), and acetic anhydride (134 g, 1.25 mol) was heated until solution occurred and then heating was continued on a steam bath for 1 hr. The mixture was allowed to stand overnight at 5°. The solid mass of brown and yellow crystals was mixed with 125 mL of cold water and broken up. The crystals were filtered, washed with cold water and then dried <u>in vacuo</u> to yield 64 g (68.6%) of the stable yellow azlactone intermediate. The azlactone was dissolved in 600 mL of acetone and 250 mL of water and refluxed for 4 hr. At the end of this time the acetone was distilled off, 800 mL of water was added and the mixture was boiled for 5 min to ensure complete hydrolysis.

The mixture was filtered hot (a small amount of solid remained on the filter). The filter was washed with a small quantity of hot water then the filtrate was decolorized with Norite. Upon standing, large yellow prisms formed in the decolorized filtrate. The prisms were re-crystallized from 1100 mL of water to yield 56 g (60%) of large off-white prisms, mp 190-192°; lit. mp[89] 191-192°. Analysis by nmr gave a Z:E ratio of 9:1; nmr (77588, TFA) (Z)-isomer δ 7.32 (s, 1, C<u>H</u>=C); (E)-isomer

δ 7.45 (s, 1, C$\underline{H}$=C).

Lauroyl Chloride: Lauric acid (20 g, 0.1 mol) and purified

thionyl chloride[90] (23.7 g, 0.2 mol) were combined and refluxed for

six hours. The gold colored solution was cooled and then distilled

to give a quantitative yield of lauroyl chloride, bp 92-94° (0.9 mm),

lit.[91] bp 134-137° (11 mm).

Ethyl-3-ketotetradecanoate:[72] A solution of $\underline{n}$-butyl lithium

in hexane (15 mL, 1.6 M) was added, under nitrogen, to a flame dried

250 mL round-bottomed flask containing a magnetic stirrer. Freshly

dried (distilled from barium oxide) cyclohexylisopropylamine (7.05 g,

50 mmol) was then added dropwise. After ten min the hexane was removed

in vacuo to give a clear glass. The glass was dissolved in 25 mL of

dry THF and the resulting solution was cooled in a dry ice/acetone bath.

Purified ethyl acetate (pre-dried over potassium carbonate then distilled

from phosphorus pentoxide) (2.2 g, 25 mmol) was added dropwise followed

ten min later by dropwise addition of lauroyl chloride (5.45 g, 25 mmol).

Lithium chloride formed. After stirring for ten min, 15 mL of 20% hydro-

chloric acid was added to quench the reaction. The reaction was allowed

to come to room temperature then enough water was added to dissolve the

lithium chloride. The THF and water were separated and the water layer

was washed with ethyl ether. The ether extracts and the THF layer were

combined, dried (MgSO$_4$) and concentrated to yield a light yellow oil.

The oil was distilled bp 70-135° (1.0 mm) to yield 5.1 g (38%)

of a cloudy colorless oil which upon analysis by ir and nmr proved to

contain some of the desired β-keto ester; ir (23034, heat) 1710 cm^{-1}

(C=O, ester), 1730 cm^{-1} (C=O, ketone); nmr (6053, CDCl$_3$) δ 3.4

(s, 2, CO-C$\underline{H}_2$-CO). Attempted analysis by glpc gave decomposition;

decomposition was also observed upon attempted distillation.

Attempts to separate the β-keto ester as a copper chelate using copper acetate were unsuccessful.

(Z)-Ethyl-3-acetoxytetradec-2-enoate:[69]   In a 250 mL round-bottomed flask were placed unpurified ethyl-3-ketotetradecanoate (5 g, 18.5 mmol), p-toluenesulfonic acid (0.75 g), and freshly distilled isopropenyl acetate (100 mL). The solution was distilled very slowly for ten hr with continuous addition of fresh isopropenyl acetate to maintain the original volume. At the end of this time the mixture was cooled and 5 g of sodium bicarbonate was added. The remaining isopropenyl acetate was removed in vacuo below 30°. The residue was extracted with ether, washed with ice water and saturated sodium chloride, dried (Na_2SO_4) and concentrated below 30° to yield a brown oil.

The oil was distilled to give two fractions; bp 105-125° (0.7 mm), bp 140-152° (0.8 mm). Analysis by ir (23062, 23063, neat) 1690-1770 cm^{-1} (C=C-O-C=O, and ester C=O); nmr (6081, $CDCl_3$) δ 5.2 (s, 1, C=C$\underline{H}$) indicated product in both fractions, approximately 2.5 g total weight. Attempted analysis by glpc on column C at 250° and 310° gave decomposition of product; numerous decomposition products were observed.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 68.4; H, 10.7.

Undecanoyl Chloride: Undecanoic acid (37.2 g, 0.2 mol) was allowed to react in the same manner as lauric acid to yield 36.4 g (94%) of undecanoyl chloride, bp 84° (0.8 mm).

Ethyl-3-ketotridecanoate: Undecanoyl chloride (36.4 g, 0.19 mol) was allowed to react in the same manner as lauroyl chloride to yield

approximately 10 g of impure β-keto ester, bp 140-169° (1.2 mm); glpc on Column C indicated at least 60% product plus starting material and many other impurities.

(Z)-Ethyl-3-acetoxytridec-2-enoate: Ethyl-3-ketotridecanoate (10 g of impure material) was reacted in the same manner as ethyl-3-ketotetradecanoate to yield approximately 3 g of the enol acetate.

Anal. Calcd for $C_{17}H_{30}O_4$: C, 67.96; H, 10.74. Found: C, 70.18; H, 11.44. The sample smelled of acetic acid after standing.

(Z)-Ethyl-3-acetoxybut-2-enoate: In a 500 mL round-bottomed flask were placed ethyl acetoacetate (43.3 g, 0.33 mol), freshly distilled isopropenyl acetate (200 mL), and p-toluenefulfonic acid (6.5 g). The solution was distilled very slowly for 10 hr with continual addition of isopropenyl acetate to maintain the original volume. At the end of this time, the mixture was cooled and sodium acetate (25 g) was added. The remaining isopropenyl acetate was removed in vacuo below 30°. The mixture was extracted with ether, and washed successively with ice water and saturated sodium chloride. The extract was dried (Na_2SO_4) and concentrated, below 30°, to yield an orange oil. The oil was distilled to yield 48 g (83%) of product, bp 75° (1.1 mm). Analysis by glpc on Column C showed the presence of Z and E isomers in a 95:5 ratio; nmr (6954, $CDCl_3$) δ 1.24 (t, 3, -CH₂-C̲H̲₃); δ 1.96 (s, 3, C̲H̲₃-C); δ 2.18 (s, 3, C̲H̲₃-COO); δ 4.08 (q, 2, -C̲H̲₂-CH₃); δ 5.56 (s, 1, C=C̲H̲).

(Z)-Methyl-3-acetoxybut-2-enoate: Methyl acetoacetate (11.6 g, 0.1 mol) was treated in an identical manner as ethyl acetoacetate to form the methyl ester of the enol acetate; yield, 13.1 g (83%); bp 52° (0.4 mm),

glpc on Column C indicated only traces of impurities (probably less than 1%).

Attempted Preparation of (E)-Ethyl-3-acetoxycinnamate: Acetyl chloride (10.6 g, 0.12 mol) was added dropwise over 0.5 hr, to a cool (ice-salt), mechanically-stirred solution of ethyl benzoylacetate (18.2 g, 0.095 mol) and triethylamine (12 g, 0.12 mol) in HMPA (20 mL). A thick suspension formed; it was stirred at room temperature for 2.5 hr. At the end of this time 50 mL of water and 50 mL of ether were added. Two clear layers formed. The aqueous layer was extracted with ether and the ether extracts were combined with the ether layer, dried ($MgSO_4$), and concentrated to yield a brown oil. The oil was distilled to yield two fractions; bp 120-148° (0.4 mm), bp 148-156° (0.4 mm); the nmr spectrum (7043, 7044, $CDCl_3$) indicated the presence of several compounds. It was concluded that the (E)-enol acetate cannot be formed efficiently in this manner due to an equilibrium between the β-keto ester and enolized ester function.

Ethyl-β-hydroxyhydrocinnamic Acid by Esterification with Ethanol and Hydrogen Chloride Gas:[79] A sample of β-hydroxyhydrocinnamic acid (12.5 g, 0.075 mol), $[\alpha]_D^{24}$-6.16° (c5.03, ethanol) (33%ee based on $[\alpha]_D^{17}$ 18.9 (c5, ethanol)), was dissolved in absolute ethanol (125 mL) and heated on a steam bath under a slow flow of hydrogen chloride gas for 10 hr. At the end of this time the hydrogen chloride flow was stopped, the heat was removed and the reaction was allowed to stand overnight. The ethanol was removed in vacuo to yield a yellow oil.

The oil was distilled, bp 92-122° (0.8 mm) to yield a clear colorless liquid. Analysis of the liquid by nmr (5847, $CDCl_3$) indicated the presence of the desired product δ 1.05 (t, 3, $-CH_2-CH_3$), δ 2.60

(m, 2, -C$\underline{H}_2$-C=O), δ 4.05 (q, 2, -C$\underline{H}_2$-CH$_3$), δ 4.3 (s, 1, -OH), δ 5.10

(m, 1, C$\underline{H}$-OH), δ 7.40 (m, 5, C$_6\underline{H}_5$); but an unsaturated product

(possibly a dehydration product, both cis and trans isomers) was also

indicated by the presence of 4 singlets between δ 6.1 and δ 7.6. A

third product, presumed to be the β-ethoxy ester(110)due to the presence

of overlapping peaks present near δ 1.05 and δ 4.05: $[\alpha]_D^{22}$-3.83° (neat)

was also present. The specific rotation of the product mixture corre-

sponded to less than 2! ee based on the literature value of $[\alpha]_D^{17}$19.17°

(neat)[79] for the pure β-hydroxy ethyl ester.

The product was distilled a second and third time; bp 90-110°

(0.8 mm) each time, and the rotation was taken after each distillation.

The specific rotation for the doubly distilled material was $[\alpha]_D^{22}$-1.49°

(neat) and for the triply distilled product it was $[\alpha]_D^{22}$-0.96° (neat).

Analysis of the triply distilled product by nmr (5849, CDCl$_3$) indicated

the same composition as the once distilled material.

The reaction was repeated with 95% ee hydroxy acid ($[\alpha]_D$17.86°(neat)).

A sample of β-hydroxyhydrocinnamic acid (108)(5 g, 30 mmol) was dissolved in

absolute ethanol (50 mL) and heated on a steam bath under a slow flow of

hydrogen chloride gas for 9 hours. At the end of this time the hydrogen

chloride flow was stopped, the heat was removed and the reaction was

allowed to stand overnight. The ethanol was removed in vacuo and the

residue was taken up in ether and washed with 5% sodium bicarbonate. The

ether layer was dried (MgSO$_4$) and concentrated to yield a light yellow oil.

The oil was distilled, bp 88-103° (0.7 mm) to yield a clear liquid. Analysis

by nmr (77747, CDCl$_3$) indicated that the hydroxyl proton, δ 4.05 was missing;

ir (22940, neat) no OH present.

Attempted Esterification of β-Hydroxyhydrocinnamic Acid with
Dimethylformamide Diethylacetal: A sample of β-hydroxyhydrocinnamic
acid (108)(1.66 g, 0.01 mol) was suspended in absolute ethanol (10 mL)
and dimethylformamide diethylacetal (5.62 g, 0.038 mol) was added all at
once. The suspension turned yellow and the acid went slowly into solu-
tion. Constant gas evolution was observed. The gas smelled like
dimethylamine.

After refluxing for 24 hr no product ester was observed (glpc on
Column A).

Ethyl-β-hydroxyhydrocinnamate by Esterification with Triethylamine
and Ethyl Iodide:[85] A sample of β-hydroxhydrocinnamic acid (108)(3.32 g,
0.02 mol) ($[\alpha]_D$12.74° (c5, ethanol)67%ee) was suspended in 25 mL of dry
toluene then triethylamine (2.02 g, 0.02 mol) was added. A clear solution
formed. Ethyl iodide (3.12 g, 0.02 mol) was added and the clear solution
was refluxed for 6 hr.

At the end of the reflux period the mixture (2 layers) was washed
successively with water and 2% sodium hydroxide. The organic layer was
dried (Na_2SO_4) and concentrated to yield a yellow oil, 1.9 g (49%); nmr
(6013, $CDCl_3$) δ 1.05 (t, 3, CH_2-CH_3), δ 2.60 (m, 2, CH_2-C=O), δ 4.05
(q, 2, CH_2-CH_3), δ 4.3 (s, 1, OH), δ 5.10 (m, 1, CH-OH), δ 7.40
(m, 5, C_6H_5); glpc on Column A showed only one peak: $[\alpha]_D^{26}$17.02° (neat).

The product was distilled, bp 100-110° (0.7 mm) to yield 1.4 g
(36.1%); $[\alpha]_D^{28}$16.85° (neat).

Ethyl-3-ethoxyhydrocinnamate:[83] A sample of ethyl-β-hydroxy-
hydrocinnamate (109)(9.7 g, 0.05 mol) was dissolved in ethyl iodide
(20.1 g, 0.18 mol) and placed in an ice bath. Silver (I) oxide (20.9 g,
0.09 mol) was added slowly through Gooch tubing to the mechanically

stirred solution. A thick brown suspension formed. The ice bath was removed and the flask was placed on a steam bath to reflux for 12 hr then ethyl iodide (10 g, 0.09 mol) was added and the reflux was continued for 12 hr longer. The reaction was allowed to stand overnight and then was distilled to yield 5 g (45%) of a clear oil, bp 95-100° (0.9 mm); nmr (77762, $CDCl_3$) δ 1.1 (t, 3, CH_2-$C\underline{H}_3$ ether), δ 1.25 (t, 3, CH_2-$C\underline{H}_3$ ester), δ 2.55 (d, 2, $C\underline{H}_2$-C=O), δ 3.42 (q, 2, $C\underline{H}_2$-CH_3 ether), δ 4.02 (1, 2, $C\underline{H}_2$-CH_3 ester), δ 4.65 (t, 1, $C\underline{H}$-O), δ 7.15 (s, 5, $C_6\underline{H}_5$); glpc on Column A showed only one peak.

Ethyl-β-acetoxyhydrocinnamate:[79]   A sample of β-hydroxyester (1.0 g, 5.2 mmol), $[\alpha]_D^{28}$16.85° (neat), (67% ee) was combined with freshly distilled acetic anhydride (2.0 g, 19.6 mmol) and refluxed for 10 hr. The excess acetic anhydride was removed in vacuo and the product was distilled, bp 114-115° (0.7 mm), yield 0.9 g (75%); nmr (6020, $CDCl_3$) δ 1.95 (s, 3, C-$C\underline{H}_3$); $[\alpha]_D^{24}$44.18° (neat), d = 1.088, glpc on Column A showed only one peak. Assuming no racemization the maximum rotation was calculated, $[\alpha]_D^{max}$60.61° (neat).

Analysis with the chiral shift reagent Eu(dcm)$_3$ (nmr 6026, 6027) indicated approximately 67% ee therefore no racemization occurred.

Menthyl Tosylate: To a stirred, cooled ice-methanol solution of (-)-menthol (7.8 g, 0.05 mol) in 100 mL of dry pyridine was added p-toluenesulfonyl chloride (9.5 g, 0.05 mol) in one portion. A drying tube was attached and the mixture was allowed to stir for one hr at -10°; it was then stored at 5° for 12 hr.

At the end of this time water (100 mL) was added and two layers formed. The organic layer crystallized as menthyl tosylate, was

filtered and then was recrystallized from 95% ethanol to form white crystals, yield 9.9 g (63.5%), mp 90-92°.

Neomenthyldiphenylphosphine: To a solution of diphenylphosphine (6.7 g, 0.036 mol) in THF (100 mL) was added potassium metal (1.4 g, 0.036 mol). The mixture was stirred at room temperature for 6 hr and then menthyl tosylate (9.9 g, 0.032 mol) was added. The bright red mixture was refluxed for 19 hr, and then was stirred until it cooled to room temperature. At this point the mixture was light yellow. Degassed water (50 mL) was added and two clear layers formed. The organic layer was separated and was evaporated on a rotary evaporator until a white solid was left. The solid was crystallized from ethanol to yield 1.5 g (10%) of NMDPP. The nmr spectrum (77319, $CDCl_3$) matched that of an authentic sample; glpc on Column B at 230° indicated about 85% NMDPP (18) and 15% NMDPP oxide.

Phenylmagnesium Bromide: A total base titration of the reagent, prepared from bromobenzene (52.3 g, 0.33 mol) and triply sublimed magnesium metal (8.0 g, 0.33 mol) in the usual way, indicated 0.234 mol (130 mL of 1.8 N) Grignard reagent, 70.3% yield.

2-(2-Phenylpropyl)-5-methylcyclohexanone:[63,64] To an ether solution of phenylmagnesium bromide (115 mL, 0.207 mol) under nitrogen at room temperature was added copper (I) chloride (0.17 g, 1 mol %) in dry ether (50 mL). A solution of (+)-pulegone (25.4 g, 0.167 mol) in ether (150 mL) was then added over a one hour period. The resulting mixture was refluxed for two hr and then was allowed to stand overnight. The resultant black mixture was poured onto ice and acidified with hydrochloric acid. The ether layer was separated, washed with water, dried ($MgSO_4$), and concentrated to yield a yellow oil. The oil was distilled, bp 120-130° (0.7 mm),

to yield 25 g of material; nmr (77284, $CDCl_3$) δ 7.85 (m, 5, C_6H_5); glpc on Column B at 205° indicated about 80% of the desired product and about 20% pulegone.

Equilibration of 2-(2-Phenylpropyl)-5-methylcyclohexanone to Give Predominantly the trans-Ketone:[65]

A sample of 2-(2-phenylpropyl)-5-methylcyclohexanone (96) was refluxed in 100 mL of 5% ethanolic potassium hydroxide for 2 hr. The reaction mixture was distilled, bp 125-145° (1.5 mm) to yield 19.0 g (88.8%) of ketone; presumed to be trans:cis 85:15; the nmr (77299, $CDCl_3$) was indistinguishable from that of the unequilibrated product.

Preparation of 2-(2-Phenylpropyl)-5-methylcyclohexanol:[66]

Sodium chips (5.3 g, 0.23 mol) in dry toluene (62.3 mL) were melted at 110° with stirring under nitrogen. A solution of 2-(2-phenylpropyl)-5-methylcyclo-hexanone (18.5 g, 0.804 mol) and 2-propanol (14.5 g, 0.257 mol) was added and the resulting suspension was allowed to stir under reflux for 1.5 hr. Ice water (300 mL) was added carefully to the cooled reaction mixture. Extraction with ether, drying ($MgSO_4$) and concentration gave a crude oil which upon distillation, bp 130-140° (0.7 mm), yielded 11.2 g (53.7%) of a clear oil. The nmr spectrum (77304, $CDCl_3$) δ 3.4 (m, 1, CH-OH) indicated formation of the desired alcohol.

Purification of 2-(2-Phenylpropyl)-5-methylcyclohexanol by hplc:

Thin layer chromatography of the alcohol (97) in 90:10 hexane:ethyl acetate and development with iodine, indicated the presence of at least four components; the spots were well separated and assumed to represent the four possible diastereomers. The sample was examined on the analytical hplc in the same solvent system and at least seven uv active peaks were observed.

A 1.5 g sample of the alcohol was injected into the prep hplc in a solvent system of 90:10 hexane:ethyl acetate at a flow rate of 300 mL/min. Six fractions were collected and analyzed by nmr and ir. Fraction five (1 g) was determined to be the desired (all equatorial) product; nmr (77441, CDCl$_3$) δ 0.88 (t, 1, CH-C$\underline{H}_3$), δ 1.27, δ 1.40 (2s, 6, C-(C$\underline{H}_3)_2$), δ 0.60-1.95 (m, 8, ring $\underline{H}$'s), δ 3.3 (m, 1, C$\underline{H}$-OH), δ 7.08 (m, 5, C$_6\underline{H}_5$); ir (22288, neat) 3300-3600 cm^{-1} (OH). Fractions four, five and six had identical nmr and ir spectra. Fractions one, two, and three were present in only trace amounts. In a subsequent separation 20.7 g of (97) were purified in this manner from 33 g of alcohol mixture.

All Equatorial 2-(2-Phenylpropyl)-5-methylcyclohexyltosylate: A sample of purified 2-(2-phenylpropyl)-5-methylcyclohexanol (97) (20 g, 86 mmol) was tosylated according to the procedure described for the preparation of menthyl tosylate. After recrystallizing from ethanol and drying in vacuo, 25 g (78%) of tosylate (98) were obtained, mp 68-71°; nmr (77374, CDCl$_3$) δ 2.3 (s, 3, C$_6$H$_4$-C$\underline{H}_3$), δ 6.8-7.7 (characteristic tosylate peaks plus phenyl) indicates the tosylate had formed.

Attempted Preparation of 2-(2-Phenylpropyl)-5-methylcyclohexyldi-phenylphosphine: To a solution of diphenylphosphine (6.7 g, 0.036 mol) in dry THF was added potassium metal (1.4 g, 0.036 mol) and the deep-red solution stirred for 6 hr under nitrogen. A solution of 2-(2-phenylpropyl)-5-methylcyclohexyltosylate (12.4 g, 0.032 mol) in 30 mL of THF was added dropwise and the resulting yellow suspension refluxed for 18 hr. The mixture was cooled to room temperature and 50 mL of degassed water was added. Two clear layers were formed and the organic layer was taken up in ether, dried (MgSO$_4$) and concentrated to yield an

oil. The oil was dissolved in ethanol in an attempt to crystallize it. Crystallization did not occur and the ethanol was removed in vacuo. The oil crystallized upon standing at room temperature for about one week. Analysis by nmr (5069, CDCl$_3$) suggested that elimination had occurred (δ5.55) and also that there was contamination of the alkene with diphenyl- phosphine oxide (δ7.5).

(+)-2-Phenylsuccinic Acid: Racemic 2-phenylsuccinic acid (100 g, 0.57 mol) was dissolved in 2000 mL of ethyl ether and (-)-α-methyl- benzylamine (145 g, 1.25 mol) was added. A heavy white precipitate formed immediately. The salt was allowed to stand overnight then was filtered and dried. The salt was recrystallized four times from 95% ethanol (12 mL/g). The salt (28 g) was hydrolyzed with 3.7% hydrochloric acid. The free acid was washed with water then was extracted into 10% sodium hydroxide and washed with ether to remove any traces of amine. The free acid was then liberated with dilute hydrochloric acid, taken up in ether, dried (MgSO$_4$) and concentrated in vacuo to yield crude resolved acid (81) . The acid was recrystallized from water to yield 20 g (10%) of fine white crystals; $[\alpha]_D^{23}$137.63° (c4, methanol), 98.3% ee. Hydrolysis of a small sample of the salt after only two crystallizations gave material of 73% ee and after three crystallizations of 86% ee.

(+)-2-Phenylbutyric Acid: The cinchonidine salt of (+)-2-phenyl- butyric acid (77) (170 g), prepared by R. W. Ridgway was hydrolyzed with dilute hydrochloric acid and the free acid was extracted with ether. The ether extract was washed with water, extracted with 10% sodium hydroxide, washed with ether, neutralized with dilute hydrochloric acid, taken up in ether, dried (MgSO$_4$) and concentrated in vacuo to yield 54 g of light

yellow oil. The oil was distilled, bp 118-120° (0.1 mm) to yield 52 g of clear oil; $[\alpha]_D^{23}$96.8° (neat), lit.[1] $[\alpha]_D^{23}$95.8° (neat).

2-Phenyl-1,4-butanediol: To a stirred solution, under nitrogen, of lithium aluminum hydride in ether (300 mL of what was at one time a 1.1 M solution which had partially evaporated and deposited a precipitate on standing over one year) was added resolved (+)-2-phenylsuccinic acid (20 g, 0.103 mol) (98.3%ee) in 1200 mL of dry ether. The mixture was refluxed for 9.5 hr. At the end of this time, 10 mL of ethyl acetate, 10 mL of 15% sodium hydroxide, and 22 mL of water were added to hydrolyze any remaining LiAlH$_4$. The mixture was stirred overnight, was then acidified with concentrated hydrochloric acid and extracted with ether for 24 hr (liquid-liquid extractor). The ether from the extractor was dried and concentrated to yield a gray wet oil. An attempt was made to remove the water by distillation with benzene (benzene-water azeotrope, bp 69°) but this was not entirely successful. The oil was distilled to yield 5 fractions. Four fractions of clear oils distilled from 60-142° (0.1 mm) and these appeared to be a mixture of esters, unreduced acid, and diol. The pot residue (10 g) of light brown grease appeared to be mainly unreduced acid. Analysis of the distillate and pot residue by nmr (77584, 77585, CDCl$_3$) δ 12.9 (s, 2, COO$\underline{H}$) showed non-reduction. All of the fractions were combined (16 g) and reduced again with non-precipitated liquid LiAlH$_4$ as before followed with only a base work-up (the reaction mixture was not acidified). The ether from the base work-up was dried (K$_2$CO$_3$) and concentrated to yield 5 fractions. F-1 (pot residue, 8 g) of viscous oil would not distill but the ir spectrum (22785, neat) indicated that it was the desired alcohol (OH, 3400 cm^{-1}). The ir spectra of fractions 2-5, which distilled between 67-112° (0.1 mm) indicated no OH

stretching peaks but showed a C=C stretching band at 3020 cm^{-1}. The pot residue (possibly an aluminum chelate of the desired diol) was used for tosylation. Separate reduction of racemic and 73% ee 2-phenylsuccinic acid gave 2-phenyl-1,4-butanediol without complication when a different source of liquid $LiAlH_4$ was used.

2-Phenylbutanol: Optically pure (+)-2-phenylbutyric acid (16.4 g, 0.1 mol) in 75 mL of dry ether was added dropwise to a stirred solution of liquid $LiAlH_4$ (60 mL, 1.8 M) under nitrogen. The mixture was refluxed for 22 hr then cooled in an ice bath before successive addition of 10 mL of ethyl acetate and 100 mL of 10% hydrochloric acid. The two clear layers which formed were separated, and the aqueous layer was extracted with ether. The ether extracts were combined, dried ($MgSO_4$) and concentrated to yield 15.6 g of light yellow oil. The oil was distilled, bp 110-111° (10 mm) to yield 10.3 g (67%) of clear oil. The nmr spectrum (77592, $CDCl_3$) identified it as the alcohol (78) δ 3.3 (s, 1, OH). The pot residue (5 g of heavy yellow oil) was identified by nmr (77591, $CDCl_3$) as unreduced acid.

2-Phenyl-1,4-ditosylbutanediol: Crude, undistilled 2-phenyl-1,4-butanediol (6 g, 0.036 mol) was tosylated according to the procedure described for the preparation of menthyl tosylate; yield 5.2 g (25%) mp 64-68°; the nmr spectrum (77589, $CDCl_3$) shows appearance of the tosyl group at δ 6.7-7.5 and disappearance of OH at δ4.0.

Similar results were obtained with racemic and 73% ee material.

2-Phenyl-1-tosylbutanol: Optically pure 2-phenylbutanol (10.1 g, 0.067 mol) was tosylated according to the procedure described for the formation of menthyl tosylate; yield 14.0 g (70%) of white crystals; mp 42-43.5°; the nmr spectrum (77600, $CDCl_3$) shows appearance of a tosyl

group at δ 6.7-7.5 and loss of OH at δ 2.8.

2-Phenylbis(1,4-diphenylphosphino)butane, (SUPHOS): A sample of 2-phenyl-1,4-ditosylbutanediol (4.2 g, 8.9 mmol) was treated according to the procedure for the preparation of NMDPP. A white solid formed after treatment with water. The solid was crystallized from ethanol in the freezer to yield 2.5 g (53%) of fluffy white crystals $[\alpha]_D^{20}$66.6° (c5.04, benzene) (84); nmr (5687, CDCl$_3$) δ 1.60-2.05 (m, 4, CH$_2$-CH$_2$-PPh$_2$), δ 2.22 (d, 2, CH$_2$-PPh$_2$), δ 2.60 (m, 1, Ph-CH), δ 7.08 (m, 25, C$_6$H$_5$).

Anal. Calcd for C$_{34}$H$_{32}$P$_2$: C, 81.26; H, 6.42. Found: C, 80.30; H, 6.11.

Racemic and 73% ee phosphine were prepared in the same manner.

2-Phenyl-1-diphenylphosphinobutane, (BUPHOS): A sample of 2-phenyl-1-tosylbutanol (13.7 g, 0.046 mol) was treated according to the procedure for the preparation of NMDPP. A yellow oil formed and was distilled, bp 190-191° (0.05 mm) to yield 6.4 g (44%) of BUPHOS (80); $[\alpha]_D^{29}$10.65° (c19.4, benzene); nmr (5686, CDCl$_3$) δ 0.75 (t, 3, CH$_2$-CH$_3$), δ 1.30-2.05 (m, 2, CH$_2$-CH$_3$), δ 2.3-2.7 (m, 3, Ph-CH-CH$_2$-PPh$_2$).

Anal. Calcd for C$_{22}$H$_{23}$P: C, 82.99; H, 7.28. Found: C, 82.65; H, 7.07.

Dihydrocarveol:[59] A sample of 1-carvone (50 g, 0.33 mol) $[\alpha]_D^{20}$-58° ± 2°, was dissolved in 500 mL of absolute ethanol and sodium metal (60 g, 2.7 mol) was added at a rate sufficient to maintain reflux. The mixture was refluxed for 2 hr after the addition and then was stirred until cool and allowed to stand overnight. The product was steam distilled over a 6 hr period. A light yellow oil was extracted with ether from the aqueous distillate, dried (MgSO$_4$) and distilled, bp 96.5-102° (9 mm) to

yield 37 g (73%) of clear oil; the nmr spectrum (5403, $CDCl_3$) shows loss of a vinyl proton at δ 6.6 and appearance of an OH proton signal at δ 3.7 and a carbinol H at δ 3.1.

Attempted Preparation of Carvomenthol:[60]   Palladium chloride (0.1 g) was mixed with warm (60-70°) water (10 mL) and then 2 drops of 2 N hydrochloric acid were added. Gum arabic (0.2 g) was added to 50 mL of hot water and then added to the palladium chloride—hydrochloric acid—water mixture along with dihydrocarveol (7.7 g, 0.05 mol). The black, heterogeneous mixture was placed under a hydrogen atmosphere (40 psi) for 2 hr. There was continual hydrogen pressure drop (apparently due to a slow leak). The reaction mixture was filtered and extracted with ether. The ether extract was concentrated and dried ($MgSO_4$) to yield 6 g of clear oil; the nmr spectrum (5408, $CDCl_3$) indicated recovery of unreduced starting material.

Carvomenthol:[61]   A sample of dihydrocarveol (37 g, 0.24 mol) and 5% Pd/C (3.5 g) were mixed with 700 mL of 95% ethanol and hydrogenated at 1 atm of hydrogen for 2 hr at room temperature. Initially a rapid hydrogen uptake was observed, but this ceased in less than 2 hr. The catalyst was filtered off and the ethanol solution was concentrated and distilled, bp 94-95° (9 mm) to yield 31 g (84%) of clear oil; the nmr spectrum (5925, $CDCl_3$) showed the disappearance of vinyl hydrogens at δ 4.7, indicating the saturated product.

Purification of Carvomenthol by hplc: Distilled carvomenthol (33 g), bp 94-95° (9 mm) (1-2 spots in 4 different tlc systems, pure sample by nmr) was analyzed by analytical hplc. Separation on a Porasil column in 20% ethyl acetate/hexane gave 4 peaks. Samples of 5 and 10 mL

size were then injected onto 2 silica gel columns in the prep hplc. The solvent was 20% ethyl acetate/hexane at a flow rate of 200 mL/min. Four fractions were collected and the solvent removed in vacuo. Fraction 1 (3.1 g) was identified as 1,2,5,6-menthadiene; nmr (5944, CDCl$_3$) vinyl hydrogens at δ 6.5-7.0, loss of OH at δ 3.8. Fraction 2 (1.5 g) was identified as either neocarvomenthol (89) or neoisocarvomenthol (90) ; nmr (5945, CDCl$_3$). Fraction 3 (18.7 g) was identified as carvomenthol (88) ; nmr (5946, CDCl$_3$) δ 3.04 (m, 1, CH-OH), δ 3.37 (s, 1, CH-OH). Fraction 4 (5.25 g) was identified as either neocarvomenthol (89) or neoisocarvomenthol (90) plus some carvomenthol (difficulty in clearly cutting the fractions); nmr (5947).

Carvomenthyl Tosylate: A sample of purified carvomenthol (15.6 g, 0.1 mol) was tosylated as described for the preparation of menthyl tosylate; yield, 20 g (66%) of white crystals after recrystallization from ethanol.

Carvomenthyldiphenylphosphine, (CMDPP): A sample of carvomenthyl tosylate (93) (20 g, 0.065 mol) was allowed to react according to the procedure described for the preparation of NMDPP. The resultant oil crystallized upon storage in the freezer, yield 3.1 g (14%) of white crystals (94) mp 63-65° after recrystallization from degassed ethanol [α]$_D^{20}$98.9° (c6.01, benzene); nmr (5688, CDCl$_3$) δ 0.25-1.0 (m, 9, CH-(CH$_3$)$_2$, CH-CH$_3$) δ 1.0-2.0 (m, 9, aliphatic H's), δ 2.8 (s, 1, CH-PPh$_2$), δ 6.9-7.65 (m, 10, Ph).

Anal. Calcd for C$_{22}$H$_{29}$P: C, 81.44; H, 9.01. Found: C, 80.91; H, 9.24.

[Rh(COD)Cl]$_2$:[93] A mixture of rhodium trichloride trihydrate (5 g, 19 mmol) and 1,5-cyclooctadiene (10 mL) in absolute ethanol (225 mL) was heated and allowed to reflux for 3 hr. The yellow-orange crystalline product was filtered and washed with ethanol; yield 2.75 g (59%) after recrystallization from acetic acid (90 mL/g).

[Rh(COD)(DIOP)]$^+$BF$_4^-$: A sample of (-)-DIOP (33 mg, 66 umol) and [Rh(COD)Cl]$_2$ (14.8 mg, 30 umol) were dissolved in 1.5 mL of degassed methanol under nitrogen and a deep red solution formed. A solution of sodium tetrafluoroborate (650 mg, 6 mmol) in 3.2 mL of water was added and a sticky yellow solid immediately precipitated. The solid was filtered, was washed with water and was dried _in vacuo_ to yield a yellow powder, mp 140-142° dec.

Anal. Calcd for C$_{39}$H$_{44}$O$_2$P$_2$BF$_4$Rh: C, 58.82; H, 5.57. Found: C, 58.33; H, 5.67.

[Rh(COD)(CMDPP)$_2$]$^+$BF$_4^-$: A sample of CMDPP was allowed to react in the manner described above for DIOP to form a red glass which was ground into a crystalline powder, mp 116-125°.

Anal. Calcd for C$_{52}$H$_{70}$P$_2$BF$_4$Rh: C, 65.97; H, 7.45. Found C, 66.62; H, 7.55.

[Rh(COD)(NMDPP)$_2$]$^+$BF$_4^-$: A sample of NMDPP was allowed to react in the same manner as DIOP and a yellow crystalline product was obtained, mp 120-132°.

Anal. Calcd for C$_{52}$H$_{70}$P$_2$BF$_4$Rh: C, 65.97; H, 7.45. Found: C, 65.44; H, 7.35.

Attempted Preparation of [Rh(COD)(SUPHOS)]$^+$BF$_4^-$: A sample of SUPHOS was allowed to react in the same manner as DIOP and a yellow

crystalline solid was obtained which did not give a proper carbon and hydrogen analysis.

Anal. Calcd for $C_{42}H_{44}P_2BF_4Rh$: C, 65.11; H, 5.23. Found: C, 57.71; H, 5.20.

Attempted Preparation of $[Rh(COD)(BUPHOS)_2]^+BF^-$: A sample of BUPHOS was allowed to react in the manner described above for DIOP. An intractable red gum formed.

General Catalytic Hydrogenation Procedures: A) Reduction of substituted cinnamic acids with neutral catalysts: A catalyst solution was prepared from $[Rh(COD)Cl]_2$ (16.6 mg, 0.0337 mmol) and a monophosphine (0.5 mmol) or a diphosphine (0.25 mmol) by stirring the above compounds in degassed 1:1 benzene:ethanol (100 mL) under 3.5 atmosphere of hydrogen for 0.5 hr.

The catalyst solution was added to a solution of the substituted cinnamic acid (4.05 g, 25 mmol) and triethylamine (0.4 g, 4 mmol) in 1:1 benzene:ethanol (100 mL). The mixture was then hydrogenated at 300 psi and 60° for 24 hr.

At the end of this time, the reaction mixture was concentrated to dryness and the concentrate was taken up in methylene chloride (50 mL). The acid was extracted into 50 mL of 10% sodium hydroxide. The sodium hydroxide layer was removed, was washed with ether and was acidified with concentrated hydrochloric acid. The liberated acid was taken up in ether (100 mL), and was dried and concentrated to give an oil. The crude product was analyzed by nmr and the percent reduction determined by comparing the integrations of the signals for phenyl hydrogens in the starting material

and reduced product. The product was then distilled and the specific rotation was measured.

B) Reduction of substituted cinnamic acids with cationic catalysts: To a solution of the substituted cinnamic acid (4.05 g, 25 mmol) and triethylamine (0.4 g, 4 mmol) in 200 mL of freshly degassed 1:1 benzene:ethanol was added the cationic catalyst, $[Rh(COD)(Phosphine)_n]^+BF_4^-$ (0.0337 mmol) (n=1 for diphosphines and n=2 for monophosphines). The solution was hydrogenated at 300 psi and 60° for 24 hr.

Further treatment was identical to that in Procedure A.

C) Reduction of (Z)-α-acetamidocinnamic acid with neutral catalysts: A chiral phosphine ligand (125 umol of monophosphines or 62.5 umol of diphosphines) and $[Rh(COD)Cl]_2$ (4.1 mg, 8.4 umol) were dissolved in 25 mL of nitrogen degassed methanol and prereduced at 3 atm of hydrogen and 50° for 0.5 hr. At the end of this time, (Z)-α-acetamido-cinnamic acid (1 g, 5.1 mmol) was added as a solid and the reaction was allowed to continue at 50° and 3 atm of hydrogen for varying lengths of time. The solution was then allowed to cool to room temperature and its rotation was taken, without further treatment. The rotation of a solution containing the same amount of catalytic species in methanol was measured at the same time; no rotation was ever observed for the blank.

The methanol was removed _in vacuo_ to yield an off-white solid. The solid was dissolved in trifluoroacetic acid and an nmr spectrum was obtained to determine the percent reduction (comparison of the integrals of the signals for phenyl hydrogens in the starting material and reduced product).

D) Reduction of (Z)-α-acetamidocinnamic acid with cationic catalysts: A solution of (Z)-α-acetamidocinnamic acid (1 g, 5.1 mmol) and $[Rh(COD)(Phosphine)_2]^+BF_4^-$ (5.2 umol) in 25 mL of degassed methanol was hydrogenated at 3 atm of hydrogen and 50° for varying lengths of time.

Further treatment was identical to that in Procedure C. The blank used for the specific rotation measurement in this procedure contained the cationic catalyst species.

E) Reduction of enol acetates with neutral catalysts: A catalyst solution was prepared from $[Rh(COD)Cl]_2$ (8.3 mg, 18.9 umol) and a monophosphine ligand (37.8 umol) or a diphosphine ligand (18.9 umol) by stirring the above compounds in degassed absolute ethanol (30 mL) at room temperature under 3.5 atm of hydrogen for 0.5 hr. At the end of this time, the enol acetate (25 mmol) was added to the prereduced catalyst solution with a syringe. The solution was then hydrogenated at 400 psi and 50° for 24 hr.

An aliquot was removed and analyzed by glpc (Columns A and C) to determine the ratios of hydrogenolysis product, reduced product, and starting material. The ethanol was then removed in vacuo and the product distilled from the catalyst. Hydrogenolysis by-products were easily removed from the product or starting material by distillation. A sample of the distillate was taken for measurement of the specific rotation. Products of unknown maximum rotation were also analyzed by nmr using the chiral shift reagent $Eu(dcm)_3$.

F) Reduction of enol acetates with cationic catalysts: To a solution of $[Rh(COD)(Phosphine)_2]^+BF_4^-$ (49 umol) in 30 mL of degassed

absolute ethanol was added the enol acetate (11.3 mmol) via syringe. The solution was hydrogenated at 400 psi and 50° for 6 hr.

Further treatment was identical to that in Procedure E.

Individual hydrogenation data specific for substrate and ligand including general procedure used, pertinent conditions, and physical data obtained

Reduction of (E)-α-Methylcinnamic Acid with a Neutral (+)-NMDPP

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (16584, $CDCl_3$) indicated complete reduction. The product was distilled, bp 95-100° (0.1 mm); yield 1.91 g (47%). The specific rotation $[\alpha]^{19}$-17.0° ($\underline{c}$11.22, benzene) corresponded to 63% ee based on $[\alpha]_D^{max}$27.02°.[93]

Reduction of (E)-α-Methylcinnamic Acid with a Neutral (-)-DIOP

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (16675, $CDCl_3$) indicated 75% reduction. The product was distilled, bp 94-96° (0.3 mm); yield 3.3 g (81%). The specific rotation $[\alpha]_D^{20}$6.65° ($\underline{c}$10.82, benzene) corresponded to 24.6% ee based on $[\alpha]_D^{max}$27.02°.[93]

Reduction of (E)-β-Methylcinnamic Acid with a Neutral (-)-DIOP

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general procedure A to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr indicated complete reduction. The product was distilled, bp 93-96° (0.3 mm); yield 3.4 g (83%). The specific rotation $[\alpha]_D^{20}$-2.85° (c11.85, benzene) corresponded to 5% ee based on $[\alpha]_D^{max}$-56.5°.[94]

Reduction of (Z)-α-Methylcinnamic Acid with a Neutral (-)-DIOP

Catalyst: (Z)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-propanoic acid.

Analysis by nmr (16507, CDCl$_3$) indicated complete reduction. The product was distilled, bp 95.5-97° (0.35 mm); yield 3.05 g (74%). The specific rotation $[\alpha]_D^{22.5}$-8.89° (c11.92, benzene) corresponded to 33% ee based on $[\alpha]_D^{max}$27.02°.[93]

Reduction of (Z)-β-Methylcinnamic Acid with a Neutral (-)-DIOP

Catalyst: (Z)-β-Methylcinnamic acid was hydrogenated according to general procedure A to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (16606, CDCl$_3$) indicated complete reduction. The product was distilled, bp 94.5-96° (0.3 mm); yield 3.3 g (81%). The specific rotation $[\alpha]_D^{21}$15.8° (c11.62) corresponded to 28% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (Z)-β-Methylcinnamic Acid with a Cationic ACMP

Catalyst: (Z)-β-Methylcinnamic acid was hydrogenated according to general procedure B to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (16708, CDCl$_3$) indicated complete reduction. The product was distilled, bp 98-99.5° (0.35 mm); yield 3.5 g (85%). The specific rotation $[\alpha]_D^{22}$20.95° corresponded to 37% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-β-Methylcinnamic Acid with a Cationic ACMP

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general

procedure B to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (16718, $CDCl_3$) indicated complete reduction. The product was distilled, bp 98-100° (0.45 mm); yield 3.3 g (81%). The specific rotation $[\alpha]_D^{24}$-7.45° (c10.38, benzene) corresponded to 13% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-α-Methylcinnamic Acid with a Neutral BUPHOS

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77667, $CDCl_3$) indicated complete reduction. The product was distilled, bp 114-116° (0.5 mm); yield 3.4 g (83%). The specific rotation was zero.

Reduction of (E)-β-Methylcinnamic Acid with a Neutral BUPHOS

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general procedure A to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (77675, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.5 mm); yield 3.4 g (83%). The specific rotation $[\alpha]_D^{23}$1.58° (c5.85, benzene) corresponded to 2.8% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-α-Methylcinnamic Acid with a Neutral SUPHOS

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77680, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.5 mm); yield 3.6 g (88%). The specific rotation $[\alpha]_D^{24}$-2.09° (c5.91, benzene) corresponded to 7.7% ee based on $[\alpha]_D^{max}$27.02°.[93]

nalysis of the crude product by nmr indicated complete reduction.

ct was distilled, bp 93-96° (0.3 mm); yield 3.4 g (83%). The

rotation $[\alpha]_D^{20}$-2.85° (c11.85, benzene) corresponded to 5% ee

$[\alpha]_D^{max}$-56.5°.[94]

eduction of (Z)-α-Methylcinnamic Acid with a Neutral (-)-DIOP

(Z)-α-Methylcinnamic acid was hydrogenated according to general

A to give 2-methyl-3-propanoic acid.

nalysis by nmr (1650[7], CDCl$_3$) indicated complete reduction. The

as distilled, bp 95.5-97° (0.35 mm); yield 3.05 g (74%). The

rotation $[\alpha]_D^{22.5}$-8.89° (c11.92, benzene) corresponded to 33% ee

$[\alpha]_D^{max}$27.02°.[93]

eduction of (Z)-β-Methylcinnamic Acid with a Neutral (-)-DIOP

(Z)-β-Methylcinnamic acid was hydrogenated according to general

A to give 3-phenylbutanoic acid.

nalysis of the crude product by nmr (16606, CDCl$_3$) indicated

reduction. The product was distilled, bp 94.5-96° (0.3 mm);

g (81%). The specific rotation $[\alpha]_D^{21}$15.8° (c11.62) corresponded

based on $[\alpha]_D^{max}$56.5°.[94]

eduction of (Z)-β-Methylcinnamic Acid with a Cationic ACMP

(Z)-β-Methylcinnamic acid was hydrogenated according to general

B to give 3-phenylbutanoic acid.

nalysis of the crude product by nmr (16708, CDCl$_3$) indicated

reduction. The product was distilled, bp 98-99.5° (0.35 mm);

g (85%). The specific rotation $[\alpha]_D^{22}$20.95° corresponded to

sed on $[\alpha]_D^{max}$56.5°.[94]

eduction of (E)-β-Methylcinnamic Acid with a Cationic ACMP

(E)-β-Methylcinnamic acid was hydrogenated according to general

procedure B to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (16718, $CDCl_3$) indicated complete reduction. The product was distilled, bp 98-100° (0.45 mm); yield 3.3 g (81%). The specific rotation $[\alpha]_D^{24}$-7.45° ($\underline{c}$10.38, benzene) corresponded to 13% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-α-Methylcinnamic Acid with a Neutral BUPHOS

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77667, $CDCl_3$) indicated complete reduction. The produc̶ ̶14-116° (0.5 mm); yield 3.4 g (83%). The spe̶

Reduction of (E)-ß ̶tral BUPHOS

Catalyst: (E)-ß-Methylci ̶ ̶ording to general procedure A to give 3-pher ̶

Analysis of the cru̶ ̶ DCl_3) indicated complete reduction. The produc̶ 115-116° (0.5 mm); yield 3.4 g (83%). The specific rotation $[\alpha]_D^{23}$1.58° ($\underline{c}$5.85, benzene) corresponded to 2.8% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-α-Methylcinnamic Acid with a Neutral SUPHOS

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77680, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.5 mm); yield 3.6 g (88%). The specific rotation $[\alpha]_D^{24}$-2.09° ($\underline{c}$5.91, benzene) corresponded to 7.7% ee based on $[\alpha]_D^{max}$27.02°.[93]

Reduction of (E)-β-Methylcinnamic Acid with a Neutral SUPHOS

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general procedure A to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (77681, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.5 mm); yield 3.4 g (83%). The specific rotation $[\alpha]_D^{24}$1.65° (c5.70, benzene) corresponded to 2.9% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-α-Methylcinnamic Acid with a Neutral CMDPP

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure A to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77683, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.5 mm); yield 3.6 g (88%). The specific rotation $[\alpha]_D^{24}$-7.57° (c5.56, benzene) corresponded to 28% ee based on $[\alpha]_D^{max}$27.02°.[93]

Reduction of (E)-β-Methylcinnamic Acid with a Neutral CMDPP

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general procedure A to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (77686, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.5 mm); yield 3.4 g (83%). The specific rotation $[\alpha]_D^{23}$22.04° (c5.72, benzene) corresponded to 39% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-α-Methylcinnamic Acid with a Cationic DIPAMP

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure B to give 2-methyl-3-phenylpropanoic acid.

Analysis by nmr (77692, $CDCl_3$) indicated only 30% reduction. No additional data were collected.

Reduction of (E)-β-Methylcinnamic Acid with a Cationic DIPAMP

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general procedure B to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (77693, $CDCl_3$) indicated only 33% reduction. No additional data were collected.

Reduction of (E)-α-Methylcinnamic Acid with a Cationic NMDPP

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure B to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77731, $CDCl_3$) indicated only 56% reduction. No additional data were collected.

Reduction of (E)-α-Methylcinnamic Acid with a Cationic CMDPP

Catalyst: (E)-α-Methylcinnamic acid was hydrogenated according to general procedure B to give 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77730, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.7 mm); yield 3.7 g (90%). The specific rotation $[\alpha]_D^{24}$5.20° (c10.98, benzene) corresponded to 19.3% ee based on $[\alpha]_D^{max}$27.02°.[93]

Reduction of (E)-β-Methylcinnamic Acid with a Cationic CMDPP

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to general procedure B to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (77732, $CDCl_3$) indicated complete reduction. The product was distilled, bp 115-116° (0.7 mm); yield 3.8 g (92%). The specific rotation $[\alpha]_D^{24}$10.6° (c11.29, benzene) corresponded to 18.7% ee based on $[\alpha]_D^{max}$56.5°.[94]

Reduction of (E)-β-Methylcinnamic Acid with a Cationic NMDPP

Catalyst: (E)-β-Methylcinnamic acid was hydrogenated according to

general procedure B to give 3-phenylbutanoic acid.

Analysis of the crude product by nmr (77733, $CDCl_3$) indicated only 50% reduction. No additional data were collected.

Reduction of (E)-α-Methylcinnamic Acid with a Cationic CMDPP

Catalyst at Low Pressure: (E)-α-Methylcinnamic acid (0.9 g, 5.5 mmol) was hydrogenated according to general procedure B except at 45 psi of hydrogen and one-quarter scale to yield 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77741, $CDCl_3$) indicated 90% reduction. The product was distilled, bp 115-116° (0.7 mm); yield 0.85 g (84%). The specific rotation, uncorrected for incomplete (90%) hydrogenation, $[\alpha]_D^{24}$-6.11° ($\underline{c}$10.94, benzene) corresponded to 23% ee based on $[\alpha]_D^{max}27.02°$.[93]

Reduction of (E)-α-Methylcinnamic Acid with a Cationic DIPAMP

Catalyst at Low Pressure: (E)-α-Methylcinnamic acid (0.9 g, 5.5 mmol) was hydrogenated according to general procedure B except at 45 psi of hydrogen and one-quarter scale to yield 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77755, $CDCl_3$) indicated only 17% reduction. No additional data were collected.

Reduction of (E)-α-Methylcinnamic Acid with a Cationic DIOP

Catalyst at Low Pressure: (E)-α-Methylcinnamic acid (0.9 g, 5.5 mmol) was hydrogenated according to general procedure B except at 45 psi of hydrogen and one-quarter scale to yield 2-methyl-3-phenylpropanoic acid.

Analysis of the crude product by nmr (77754, $CDCl_3$) indicated only 5% reduction. No additional data were collected.

Reduction of (Z)-α-Acetamidocinnamic Acid with a Cationic NMDPP

Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to

general procedure D for 4.5 hr to give N-acetylphenylalanine.

The specific rotation of the hydrogenation solution was zero. Analysis of the crude product by nmr (77605, TFA) indicated 10-15% reduction.

Reduction of (Z)-α-Acetamidocinnamic Acid with a Cationic DIPAMP Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to general procedure D for 4.5 hr to give N-acetylphenylalanine.

The specific rotation $[\alpha]_D^{24}$37.2° (c4, methanol) corresponded to 92.8% ee based on $[\alpha]_D^{20}$40.1° (c1, methanol).[46]

Reduction of (Z)-α-Acetamidocinnamic Acid with a Neutral CMDPP Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to general procedure C for 24 hr to give N-acetylphenylalanine.

The specific rotation $[\alpha]_D^{23}$-1.92° (c4, methanol) corresponded to 4.8% ee based on $[\alpha]_D^{max}$40.1° (c1, methanol).[46] Analysis of the crude product by nmr (77628, TFA) indicated complete reduction.

Reduction of (Z)-α-Acetamidocinnamic Acid with a Neutral BUPHOS Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to general procedure C for 48 hr to give N-acetylphenylalanine.

The specific rotation $[\alpha]_D^{23}$-3.24° (c4, methanol) corresponded to 8.1% ee based on $[\alpha]_D^{max}$40.1° (c1, methanol).[46] Analysis of the crude product by nmr (77629, TFA) indicated complete reduction.

Reduction of (Z)-α-Acetamidocinnamic Acid with a Neutral NMDPP Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to general procedure C for 64 hr to give N-acetylphenylalanine.

The specific rotation was zero. Analysis of the crude product by nmr (77634, TFA) indicated 25% reduction.

Reduction of (Z)-α-Acetamidocinnamic Acid with a Neutral DIOP

Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to general procedure C for 24 hr to give N-acetylphenylalanine.

The specific rotation $[\alpha]_D^{24}$-30.6° (c4, methanol) corresponded to 76.3% ee based on $[\alpha]_D^{max}$40.1° (c1, methanol).[46] Analysis of the crude product by nmr (77645, TFA) indicated complete reduction.

Reduction of (Z)-α-Acetamidocinnamic Acid with a Neutral SUPHOS

Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated according to general procedure C for 60 hr to give N-acetylphenylalanine.

The specific rotation $[\alpha]_D^{22}$-4.79° (c4, methanol) corresponded to 12% ee based on $[\alpha]_D^{max}$40.1° (c1, methanol).[46] Analysis of the crude product by nmr (77648, TFA) indicated 75% reduction.

Reduction of (Z)-α-Acetamidocinnamic Acid with a 73% EE Neutral

SUPHOS Catalyst: (Z)-α-Acetamidocinnamic acid was hydrogenated with 73% ee SUPHOS ligand according to general procedure C for 96 hr to give N-acetylphenylalanine.

The specific rotation $[\alpha]_D^{24}$-2.38° (c4, methanol) corresponded to 5.9% ee based on $[\alpha]_D^{max}$40.1° (c1, methanol).[46] Analysis of the crude product by nmr (77660, TFA) indicated 75% reduction. The rotation is uncorrected for either the optical purity of the ligand or the % reduction. Nine percent ee would be expected compared to the value obtained with optically pure SUPHOS in the preceeding experiment but the 6% ee value is within experimental error.

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Cationic ACMP

Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to

general procedure F to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 35% reduction, 100% conversion, and 65% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 0.5 g (25%). The hydrogenolysis product, ethyl butyrate was removed with the solvent on the rotary evaporator prior to distillation. The maximum rotation of the product is not known but the specific rotation was measured; $[\alpha]_D^{26}$ 0.53° (neat). Data obtained upon analysis of the product with the chiral shift reagent $Eu(dcm)_3$ could not be used to compute an accurate maximum rotation. It would appear to be between 1-3°, but small discrepancies in integration of the nmr signals caused major variations in maximum rotation calculations.

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Cationic DIPAMP Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure F to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 60% reduction, 100% conversion and 40% hydrogenolysis. The product was distilled, bp 52° (0.2 mm); yield 0.35 g (12%); $[\alpha]_D^{26}$ 0.47° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral DIOP Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 85% reduction, 100% conversion, and 15% hydrogenolysis. The product was distilled, bp 48° (0.2 mm); yield 0.5 g (25%); $[\alpha]_D^{20}$ 0.14° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral NMDPP Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 27% reduction, 29% conversion, and 7% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.3 g (65%); $[\alpha]_D^{21}$ 0.12° (neat). The rotation is uncorrected for incomplete conversion and it is assumed that there is no effect on the rotation of the product due to the presence of unreduced starting material.

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral CMDPP Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 41% reduction, 45% conversion, and 8% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.3 g (65%); $[\alpha]_D^{21}$ 0.10° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral BUPHOS Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 85% reduction, 100% conversion, and 15% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.1 g (55%); $[\alpha]_D^{21}$ -0.34° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral SUPHOS Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 60% reduction, 66% conversion, and 17% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.4 g (70%); $[\alpha]_D^{21}$ -0.02° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral CAMPHOS Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated

according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 42% reduction, 53% conversion, and 20% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.4 g (70%); $[\alpha]_D^{21}$ 0.058° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral CHIRAPHOS Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-acetoxybutanoate.

Analysis by glpc (Column C) indicated 30% reduction, 44% conversion, and 13% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 0.8 g (40%); $[\alpha]_D^{21}$ -0.144° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral BPPM Catalyst: (Z)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 78% reduction, 100% conversion, and 22% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.0 g (50%); $[\alpha]_D^{21}$ 0.274° (neat).

Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral trans-1,2-Bis(diphenylphosphinomethyl)cyclobutane Catalyst: (Z)-Ethyl-acetoxybut-2-enoate was hydrogenated according to general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 66% reduction, 78% conversion, and 16% hydrogenolysis. The product was distilled, bp 50° (0.2 mm); yield 1.3 g (67%); $[\alpha]_D^{21}$ 0.000° (neat).

Reduction of (E)-Ethyl-3-acetoxybut-2-enoate with a Neutral BUPHOS Catalyst: (E)-Ethyl-3-acetoxybut-2-enoate was hydrogenated according to

general procedure E to give ethyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 23% hydrogenation, 30% conversion, and 30% hydrogenolysis. No additional data were collected.

Reduction of (Z)-Methyl-3-acetoxybut-2-enoate with a Neutral BUPHOS Catalyst:

(Z)-Methyl-3-acetoxybut-2-enoate (1.93 g, 25 mmol) was hydrogenated according to general procedure E to give methyl-3-acetoxybutanoate.

Analysis by glpc (Column C) indicated 49% hydrogenation, 54% conversion, and 9% hydrogenolysis. The product was distilled, bp 48° (0.2 mm); yield 1.3 g (68%); $[\alpha]_D^{22}$0.000° (neat).

Attempts to hydrogenate the methyl ester with cationic DIPAMP and ACMP catalysts gave less than 20% hydrogenation and 60-80% hydrogenolysis.

Reduction of (Z)-Ethyl-3-acetoxyhex-2-enoate with a Cationic DIPAMP Catalyst:

(Z)-Ethyl-3-acetoxyhex-2-enoate (2.3 g, 11.3 mmol) was hydrogenated according to general procedure F to yield ethyl-3-acetoxyhexanoate.

Analysis by glpc (Column C) at 175° indicated 26% hydrogenation, 100% conversion, and 74% hydrogenolysis. The product was distilled, bp 95-96° (10 mm); yield 0.2 g (9%); $[\alpha]_D^{21}$2.17° (neat), assume d=1.

Reduction of (Z)-Ethyl-3-acetoxyhex-2-enoate with a Neutral BUPHOS Catalyst:

(Z)-Ethyl-3-acetoxyhex-2-enoate (2.3 g, 11.3 mmol) was hydrogenated according to general procedure E to give ethyl-3-acetoxyhexanoate.

Analysis by glpc (Column C) at 175° indicated 70% hydrogenation, 97% conversion, and 28% hydrogenolysis. The product was distilled, bp 95-96° (10 mm); yield 0.6 g (26%); $[\alpha]_D^{21}$-0.51° (neat), assume d=1.

<u>Attempted Reduction of (Z)-Ethyl-3-acetoxytetradec-2-enoate with</u>
<u>a Neutral BUPHOS Catalyst</u>: (Z)-Ethyl-3-acetoxytetradec-2-enoate (3.12 g,
10 mmol) was hydrogenated according to general procedure E to give ethyl-
3-acetoxytetradecanoate.

The reaction was heterogeneous at the end of the reduction and no
additional data were collected.

<u>Attempted Reduction of (Z)-Ethyl-3-acetoxytridec-2-enoate with a</u>
<u>Neutral BUPHOS Catalyst</u>: (Z)-Ethyl-3-acetoxytridec-2-enoate (3.0 g,
10 mmol) was hydrogenated according to general procedure E to give ethyl-
3-acetoxytridecanoate.

Analysis by glpc (Column C) showed unreacted starting material
only. No additional data were collected.

<u>Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral</u>
<u>Triphenylphosphine Catalyst</u>: (Z)-Ethyl-3-acetoxybut-2-enoate (2.13 g,
11.3 mmol) was hydrogenated with $RhCl(PPh_3)_3$ (0.349 g, 0.378 mmol) in
60 mL of degassed 1:1 benzene:ethanol according to general procedure E.

Analysis by glpc (Column C) indicated 100% reduction, 100%
conversion, and no hydrogenolysis. No additional data were collected.

<u>Reduction of (Z)-Ethyl-3-acetoxybut-2-enoate with a Neutral</u>
<u>Neopentyldiphenylphosphine Catalyst</u>: (Z)-Ethyl-3-acetoxybut-2-enoate
was hydrogenated according to general procedure E to give ethyl-3-
acetoxybutanoate.

Analysis by glpc (Column C) indicated 10% hydrogenation, 9%
conversion, and 3% hydrogenolysis. No additional data were collected.

BIBLIOGRAPHY

1. S. H. Wilen, "Tables of Resolving Agents and Optical Resolutions," University of Notre Dame Press, Notre Dame, 1972.

2. S. H. Wilen, A. Collet, and J. Jacques, Tetrahedron, 33, 2725 (1977).

3. J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1971.

4. E. L. Eliel, Tetrahedron, 30, 1503 (1974).

5. J. W. Scott and D. Valentine, Jr., Science, 184, 943 (1974).

6. W. S. Knowles and M. J. Sabacky, Chem. Commun., 1445 (1968).

7. J. S. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, J. Chem. Soc., A, 1711 (1966); idem., Chem. Ind. (London), 560(1965).

8. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, Chem. Commun., 10 (1972).

9. L. Horner, H. Siegel, and H. Buthe, Angew. Chem. Int. Ed. Engl., 7, 942 (1968).

10. R. R. Schrock and J. A. Osborn, J. Amer. Chem. Soc., 98, 2134 (1976).

11. G. Dolcetti and N. W. Hoffman, Inorg. Chim. Acta, 9, 269 (1974).

12. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, Ann. N. Y. Acad. Sci., 214, 119 (1973).

13. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, "Homogeneous Catalysis - II." Advances in Chemistry Series, No. 132, American Chemical Society, Washington, D. C., 1974, pp. 274-282.

14. P. Bonvicini, A. Levi, G. Modena, and G. Scorrano, Chem. Commun., 1188 (1972).

15. R. E. Burnett, Ph.D. Thesis, University of New Hampshire, Durham, N. H., 1971.

16. W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, J. Amer. Chem. Soc., 97, 2567 (1975).

17. J. Solodar, Chem. Technol., 421 (1975).

18. C. Fisher and H. S. Mosher, Tetrahedron Lett., 2487 (1977).

19. T. P. Dang and H. B. Kagan, Chem. Commun., 481 (1971).

20. W. F. Masler, Ph.D. Thesis, University of New Hampshire, Durham, N. H., 1974.

21. T. P. Dang, J. C. Poulin, and H. B. Kagan, J. Organometal. Chem., 91, 105 (1975).

22. H. B. Kagan, Pure Appl. Chem., 43, 401 (1975).

23. W. Dumont, J. C. Poulin, T. P. Dang, and H. B. Kagan, J. Amer. Chem Soc., 95, 8295 (1973).

24. N. Takaishi, H. Imai, C. A. Bertelo, and J. K. Stille, J. Amer. Chem. Soc., 100, 264 (1978).

25. T. Masuda and J. K. Stille, J. Amer. Chem. Soc., 100, 268 (1978).

26. K. Hamada, Northwestern University, Personal Communication, 1975.

27. P. Aviron-Violet, U. S. Patent 3,978,101 (1976).

28. R. Glaser, M. Twaik, S. Geresh, and J. Blumenfeld, Tetrahedron Lett., 4635 (1977).

29. K. Achiwa, J. Amer. Chem. Soc., 98, 8265 (1976).

30. K. Achiwa, T. Kogure, and I. Ojima, Tetrahedron Lett., 4431 (1977).

31. M. D. Fryzuk and B. Bosnich, J. Amer. Chem. Soc., 99, 6262 (1977).

32. M. Tanaka, Y. Ikeda, and I. Ogata, Chem. Lett., 1115 (1975).

33. K. Tamao, H. Yamamoto, H. Matsumoto, N. Miyaki, T. Hayashi, and M. Kumada, Tetrahedron Lett., 1389 (1977).

34. T. Hayashi, T. Mise, S. Mitachi, K. Yamamoto, and M. Kumada, Tetrahedron Lett., 1133 (1976).

35. K. Achiwa, Tetrahedron Lett., 3735 (1977).

36. T. Iwami, T. Yoshida, and M. Sato, Nippon Kagaku Kaishi, 10, 1652 (1976).

37. M. Tanaka and I. Ogata, Chem. Commun., 735 (1975).

38. T. Hayashi, M. Tanaka, and I. Ogata, Tetrahedron Lett., 295 (1977).

39. R. H. Grubbs and R. A. DeVries, Tetrahedron Lett., 1879 (1977).

40. Y. Kawabata, M. Tanaka, and I. Ogata, Chem. Lett., 1213 (1976).

41. G. Pracejus and H. Pracejus, Tetrahedron Lett., 3497 (1977).

42. M. E. Wilson and G. M. Whitesides, J. Amer. Chem. Soc., 100, 306 (1978).

43. O. Korpium and K. Mislow, J. Amer. Chem. Soc., 89, 4784 (1967).

44. O. Korpium, R. A. Lewis, J. Chickos, and K. Mislow, J. Amer. Chem. Soc., 90, 4842 (1968).

45. W. B. Farnham, R. K. Murray, Jr., and K. Mislow, J. Amer. Chem. Soc., 92, 5810 (1970).

46. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, J. Amer. Chem. Soc., 99, 5946 (1977).

47. H. B. Kagan and T. P. Dang, J. Amer. Chem. Soc., 94, 6429 (1972).

48. J. D. Morrison, W. F. Masler, and S. Hathaway in "Catalysis in Organic Syntheses 1976," P. N. Rylander and H. Greenfield, Eds., New York, N. Y., Academic Press, Inc., pp. 203-233.

49. J. D. Morrison, W. F. Masler, and M. K. Neuberg, Adv. in Catal., 25, 81 (1976).

50. M. Tanaka, Y. Watanabe, T. Mitsudo, Y. Yasunori, and Y. Takegami, Chem. Lett., 137 (1974).

51. H. B. Kagan, N. Langlois, and T. P. Dang, J. Organometal. Chem., 90, 353 (1975).

52. D. Sinou and H. B. Kagan, J. Organometal. Chem., 114, 325 (1976).

53. N. Takaishi, H. Imai, C. A. Bertelo, J. K. Stille, J. Amer. Chem. Soc., 98, 5400 (1976).

54. R. Glaser and S. Geresh, Tetrahedron Lett., 2527 (1977).

55. G. Gelbard and H. B. Kagan, Tetrahedron, 32, 233 (1976).

56. R. Glaser, S. Geresh, J. Blumenfeld, B. Vainas, and M. Twaik, Israel J. Chem., 115, 17 (1976/77).

57. R. Glaser and B. Vainas, J. Organometal. Chem., 121, 249 (1976).

58. R. Glaser, Tetrahedron Lett., 2127 (1975).

59. R. G. Johnston and J. Read, J. Chem. Soc., 233 (1934).

60. R. G. Johnston and J. Read, J. Chem. Soc., 1138 (1935).

61. R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, p. 57.

62. S. H. Schroeter and E. L. Eliel, J. Org. Chem., 30, 1 (1965).

63. E. J. Corey and H. E. Ensley, J. Amer. Chem. Soc., 97, 6908 (1975).

64. H. E. Ensley, Ph.D. Thesis, Harvard University, Cambridge, Massachusetts, 1976.

65. T. Suga, K. Imamura, and T. Shishiboni, Chem. Commun., 126 (1971).

66. Sukh Dev, J. Indian Chem. Soc., 33, 769 (1956).

67. R. Glaser, S. Geresh, and J. Blumenfeld, J. Organometal. Chem., 112, 355 (1976).

68. R. Filler and S. M. Nagui, Tetrahedron, 19, 879 (1963).

69. C. P. Casey and D. F. Marten, Tetrahedron Lett., 925 (1974).

70. S. Singer and P. Zuman, J. Org. Chem., 39, 836 (1974).

71. M. W. Rathke and J. Deitch, Tetrahedron Lett., 2953 (1971).

72. M. W. Rathke and A. Lindert, J. Amer. Chem. Soc., 93, 2318 (1971).

73. M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, J. Amer. Chem. Soc., 96, 1038 (1974).

74. K. Serck-Hanssen, S. Stallberg-Stenhagen, and E. Stenhagen, Ark. Kemi, 5, 203 (1952).

75. K. Serck-Hanssen, Ark. Kemi, 8, 401 (1955).

76. W. S. Knowles, private communication.

77. H. J. Wolfhagen, unpublished results.

78. K. Koga, C. C. Wu, and S. Yamada, Chem. Pharm. Bull. (Japan), 20, 1271 (1972).

79. J. Kenyon, H. Phillips, and G. R. Shutt, J. Chem. Soc., 1663 (1935).

80. G. D. Hanson, B. S. Thesis, University of New Hampshire, Durham, N. H., 1977.

81. C. Schöpf and W. Wust, Justus Liebigs Ann. Chem., 626, 150 (1959).

82. D. S. Noyce and C. A. Lane, J. Amer. Chem. Soc., 84, 1635 (1962).

83. P. G. Stevens, J. Amer. Chem. Soc., 54, 3732 (1932).

84. G. Büchi, K. Steen, and A. Eschenmoser, Angew. Chem. Internat. Edit., 3, 62 (1964).

85. R. L. Merker and M. J. Scott, J. Org. Chem., 26, 5180 (1961).

86. R. Stoermer, F. Grimm, and E. Laage, Chem. Ber., 50, 959 (1917).

87. L. Edeleano, Chem. Ber., 20, 616 (1887).

88. C. Sandris, Tetrahedron, 24, 3569 (1968).

89. R. M. Herbst and D. Shemin, Org. Syn., Coll. Vol. II, 1 (1943).

90. A. I. Vogel, "A Text-Book for Practical Organic Chemistry," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 189.

91. J. R. Husman, Ph.D. Thesis, University of New Hampshire, Durham, N. H., 1976.

92. J. Chatt and L. M. Venanzi, J. Chem. Soc., 4743 (1957).

93. R. H. Pickard and J. Yates, J. Chem. Soc., 95, 1011 (1909).

94. D. J. Cram, J. Amer. Chem. Soc., 74, 2137 (1952).

95. After this thesis was prepared, the following review appeared. A. J. Birch and D. H. Williamson in "Organic Reactions," vol. 24, Dauben, W. G., Ed., John Wiley & Sons, Inc., New York, N. Y., 1976, Chapter 1.