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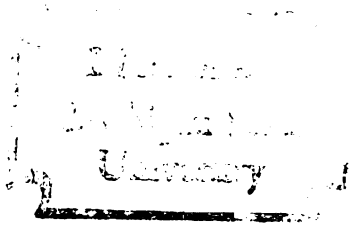

This is to certify that the

thesis entitled

ASYMMETRIC HYDROGENATION OF ALKENES USING CHIRAL RHODIUM CATALYSTS

presented by

Robert A. DeVries

has been accepted towards fulfillment of the requirements for

Ph.D. degree in Chemistry

Major professor

Robert H. Grubbs
(Major Professor)

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ASYMMETRIC HYDROGENATION OF ALKENES USING CHIRAL RHODIUM CATALYSTS

By

Robert Allen DeVries

A DISSERTATION

Submitted to

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ABSTRACT

ASYMMETRIC HYDROGENATION OF ALKENES USING
CHIRAL RHODIUM CATALYSTS

By

Robert A. DeVries

The use of asymmetric hydrogenation catalysts has been under intensive investigation in recent years. Previous experiments have mainly used optically active phosphine ligands with either chiral carbon or phosphorus centers. The bulk of this work was aimed at maximizing the asymmetric induction of amino acid precursors. However, these studies did not usually employ ligands other than phosphines or ligands which contained a great deal of conformational mobility.

This study investigated the synthesis and development of two new catalyst systems for the asymmetric hydrogenation of prochiral alkenes. Both systems gave relatively high optical yields.

A bidentate phosphinite ligand was made from resolved 1,1'-Bi-2-naphthol whose chirality is the result of only an axial element of symmetry (i.e. atropisomerism), rather

than the presence of an asymmetric carbon or phosphorus. Although hydrogenation occurred only at high pressures, the optical yields for selected substrates were higher than other bidentate phosphine catalyst systems.

A second ligand, a chiral bidentate phosphine, which had a high degree of conformational mobility was also prepared. This system was also active at high pressures. The optical yields were moderately high in some cases and a large base effect seen.

To

Claire

ACKNOWLEDGMENTS

I would like to thank Dr. Robert H. Grubbs for his guidance, support, and patience during the course of this study.

I would also like to thank my research committee, my fellow graduate students, and my parents and in-laws for their support.

A special thanks goes to my wife, Claire, who helped me through these years.

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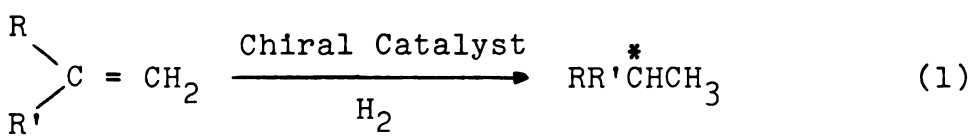
THE S (-)1,1'-Bi-2-NAPHTHYLBIS(DIPHENYLPHOSPHINITE) OR S-(-)-NAPHIN CATALYST SYSTEM

INTRODUCTION

The use of organometallic complexes in catalysis has spurred a rapid growth in asymmetric synthesis. Using a complex with a chiral ligand to catalyze a reaction asymmetrically is advantageous in that a difficult resolution of the normally racemic product may not be necessary. For example, in asymmetric hydrogenation, using a transition metal catalyst, the addition of hydrogen is almost always cis and to the alkene face coordinated to the metal.



$$\begin{matrix} R \\ \diagdown \\ C = CH_2 \\ \diagup \\ R' \end{matrix} \xrightarrow[H_2]{\text{Chiral Catalyst}} RR'\overset{*}{C}HCH_3 \qquad (1)$$

When one olefinic face is preferentially coordinated, then the cis-endo-addition produces a chiral center(s).

The terms optical yield and ee (enantiomeric excess) are used synonymously and express the excess of one enantiomer over the other. For example: 50% ee means a 75%-25% mixture of R and S forms.

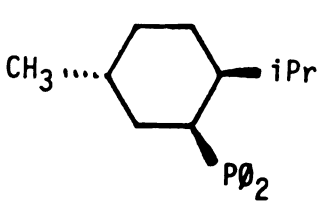
In 1968 two groups reported the use of chiral phosphines, rather than triphenylphosphine, in preparing

Wilkinson's catalyst $RhCl(P\phi_3)_3$. Horner's group[1] used a catalyst formed *in situ* from the precursor $[Rh(diene)Cl]_2$

$$MeP\overset{*}{\phi}R \qquad R = n\text{-}Pr, \quad i\text{-}Pr, \quad n\text{-}Bu, \quad t\text{-}Bu$$

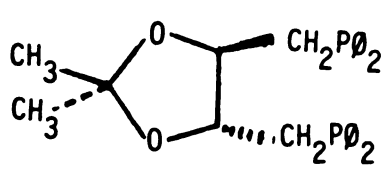
and $MeP\overset{*}{\phi}R$ phosphines to hydrogenate α-substituted styrenes, getting up to 19% optical yield. About the same time Knowles *et al.*[2] (the Monsanto group) reported the use of the same catalyst on α,β-unsaturated acids giving up to 28% ee. The hydrogenation rates and optical yields were increased by using salts of the olefinic acids. This was rationalized by more effective coordination through the carboxylate. The main drawbacks of these P-chiral ligands were their difficult synthesis and resolution.

In 1971 two new chiral ligands were reported based on commercially available, inexpensive, chiral precursors. In both cases the ligands had asymmetric carbon centers. Morrison's group[3] synthesized neomenthyldiphenylphosphine [(+)-NMDPP] 1 from (-) menthol. Kagan's group[4] synthesized



(+)-NMDPP

1

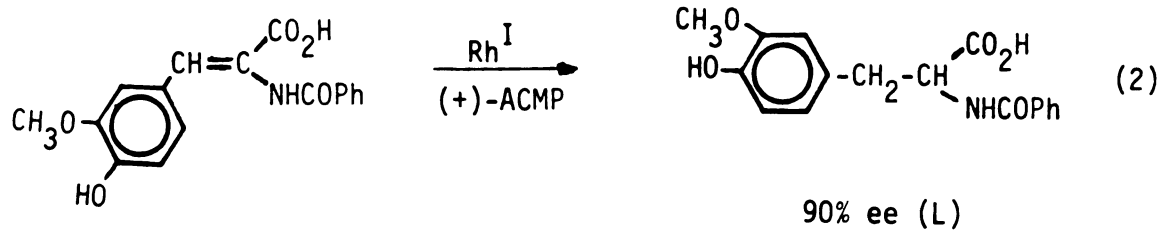


(-)-DIOP

2

2,3-o-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(-)-DIOP] 2 from tartic acid. In situ catalysts (P:Rh = 2) were prepared in alcohol-benzene from $[Rh(alkene)_2Cl]_2$ precursors. Optical yields of 60-80% were realized for some α,β-unsaturated acids, such as α-acylamidoacrylic acids.

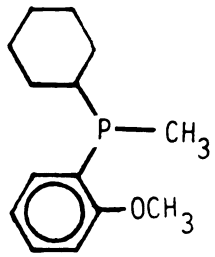
Hydrolysis of the -NHCOR' group provides an excellent route to optically active amino acids. An example is the important drug L-DOPA (3,4-dihydroxyphenylalanine), which is used in treating Parkinson's disease. Monsanto[5,33] has developed a process to yield L-DOPA derivatives with



(2)

90% ee (L)

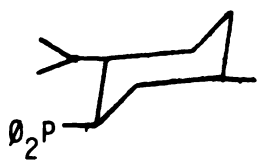
up to 90% optical purity. An in situ catalyst is made from (+) R o-anisylcyclohexylmethylphosphine (ACMP) 3 in methanol at 50°C and 3 atmospheres of hydrogen pressure. Approximately 1 pound of catalyst is used to make 1 ton of L-DOPA



(+)-ACMP

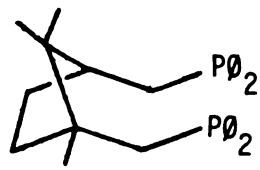
3

Other diphenyl phosphine derivatives similar to DIOP and NMDPP can be prepared from chiral carbon skeletons in naturally occurring compounds. These include (-)-menthyldiphenylphosphine (MDPP 4)[6,7], (+)-1,2,2-trimethyl-1,3-bis(diphenylphosphinomethyl)-cyclopentane (CAMPHOS 5),[8] and cis-myrtanyldiphenylphosphine (MYRTPHOS 6).[9] The CAMPHOS and MDPP systems in general were less active and gave lower induction than the NMDPP catalyst.



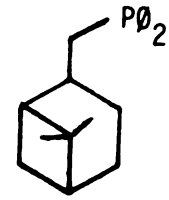
(-) MDPP

4



(+) CAMPHOS

5



MYRTPHOS

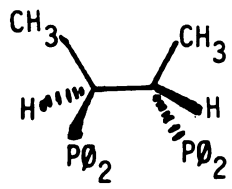
6

Morrison and coworkers[6] examined a wide variety of chiral catalyst systems for the hydrogenation of both cis and trans isomers of α,β-unsaturated acids. Catalyst

systems using NMDPP 1, DIOP 2, ACMP 3, MDPP 4, and CAMPHOS 5 as ligands were compared under identical reaction conditions. Their conclusion was that matching of ligands with substrates for the best optical yield is unpredictable. No stereocorrelation model was apparent.

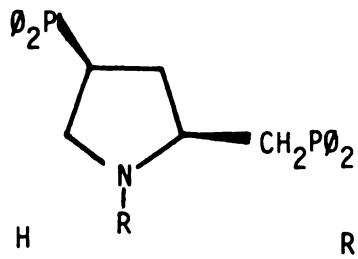
Several other useful ligands have been reported in the last few years. Fryzuk and Bosnich[10] found 2S,3S-bis(diphenylphosphino)butane or S,S-Chiraphos 7 to give good optical yields with the Z-isomers of prochiral α-N-acylaminoacrylic acid substrates. The leucine and phenylalanine derivatives were obtained in complete optical purity. Catalytic deuteration led to pure chiral α and β centers in the leucine and phenylalanine systems.

Achiwa has developed a series of chiral ligands from naturally occurring L-hydroxyproline. These include 2S,4S-4-diphenylphosphine-2-diphenylphosphinomethylpyrrolidene (PPM 8),[11] and the N-butoxycarbonyl derivative (BPPM 9).[11] Again, optical yields in excess of 90% were realized for a number of substrates.



S,S-CHIRAPHOS

7



R = H

PPM

8

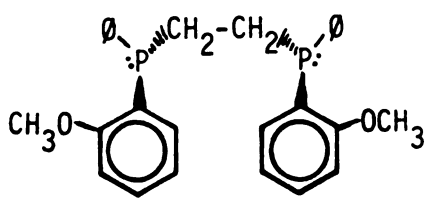
R = CO_2tBu

BPPM

9

Since some substrates were very polar, alcohol-benzene solvent mixtures were needed for complete dissolution. The *in situ* rhodium catalysts under these conditions should be considered $[Rh(diene)(P^*)_2] + Cl^-$, where P* and $(P^*)_2$ represent monodentate and bidentate chiral phosphines, respectively. In nonpolar mediums the active catalyst is believed to be $Rh(P^*)_2Cl$ (solvent). To extend this idea, cationic forms of the catalyst systems were made by adding anions such as $B\phi_4^-$, PF_6^-, or BF_4^- to the *in situ* mixture in a minimum of alcohol. The $[Rh(diene)(P^*)_2]^+ BF_4^-$ complexes could be isolated and characterized in this manner.

The Monsanto group[12,36] has developed a number of new chiral bidentate phosphines. One of the best is R,R-bis-[(anisole)(phenylphosphine)] ethane (BAPPE *10*)



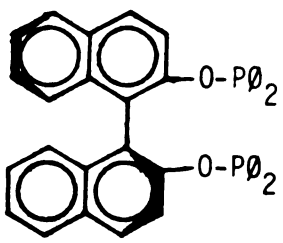
R,R-BAPPE

10

These cationic catalyst systems reduce α-acylaminoacrylic acids in basic alcohol solutions to products of 95-96% optical purity. The optical yields were not found to

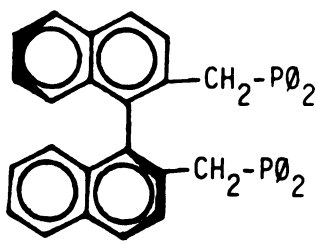
be dependent upon temperature or pressure.

All of the ligands and catalyst systems mentioned have contained chiral carbon or phosphorus centers. In 1977 Grubbs and DeVries[13] reported an optically active ligand whose chirality is the result of only an axial element of symmetry or atropisomerism. Furthermore, this ligand (-)1,1'-Bi-2-naphthylbis(diphenylphosphinite) (NAPHIN) 11 was the second example of a phosphinite used



NAPHIN

11

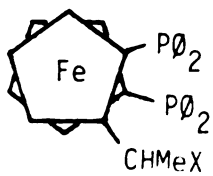


NAPHOS

12

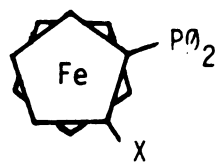
for asymmetric hydrogenation. Simultaneously, Kumada[14] reported the analogous phosphine 2,2-bis(diphenylphosphinomethyl)-1,1'binaphthyl NAPHOS 12.

Kumada[15] also introduced a fourth class of chiral ligands using a variety of ferrocenylphosphines. These contain only a planar element of symmetry. Optical yields of 94% were achieved for L-alanine derivatives using (S,R)-BPPFA in methanol.



X = OH, H, NMe_2 (S,R-BPFFA)

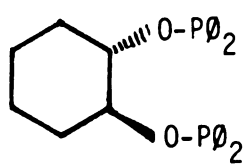
13



X = Et, CH_2NMe_2, $C^*HMeNMe_2$

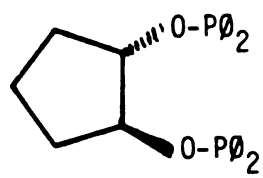
14

The first report of a phosphinite ligand in asymmetric hydrogenation was by Tanaka[16] late in 1975, and described the use of trans-1,2-bis(diphenylphosphinoxy)cyclohexane (BDPCH 15). In 1977 Grubbs and DeVries synthesized



BDPCH

15

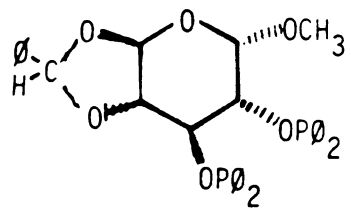


BDPCP

16

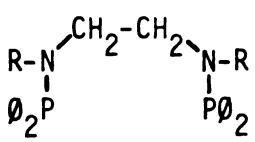
NAPHIN 11, and Tanaka published[17] studies on another bidentate phosphinite trans-1,2-bis(diphenylphosphinoxy)cyclopentane (BDPCP 16).

A bidentate phosphinite 17 based on D-Glucose was active at ambient conditions for α-acetamidoacrylic acid and ester substrates giving up to 80% ee.[18]

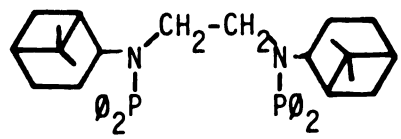


17

In addition to chiral phosphines and phosphinites, a third class of ligands, aminophosphines,[8] have been used for asymmetric hydrogenation. The optical yields can be quite high and often the rates are enhanced. Use of 18 gave results similar to DIOP 2 for amino acid precursors.



18



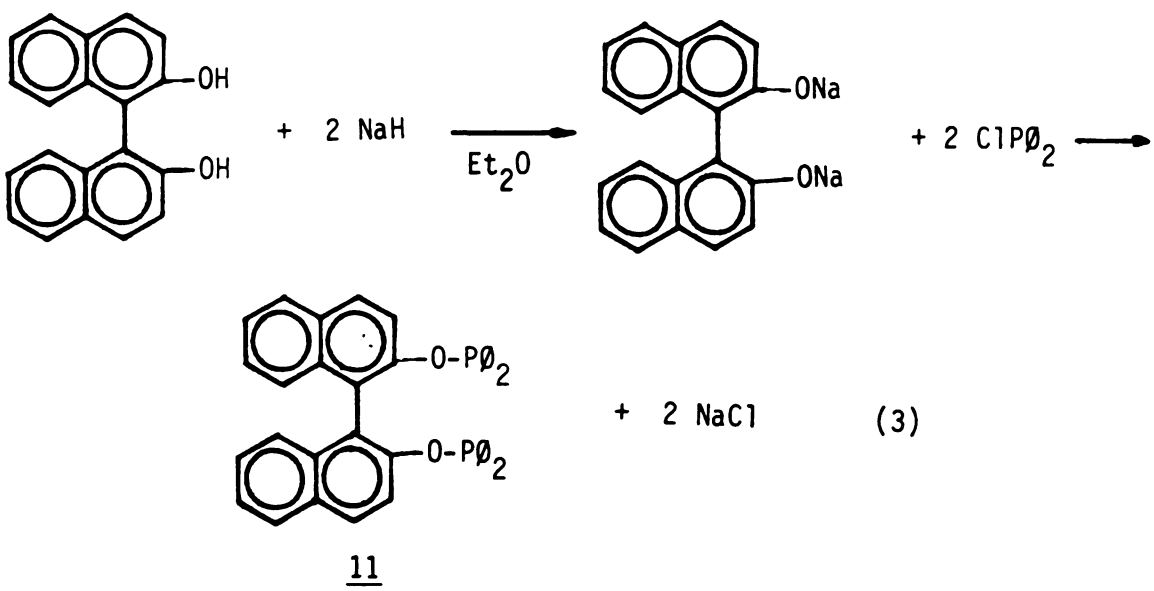
19

A number of aminophosphines such as 19 have recently[8] been derived from terpenes.

RESULTS AND DISCUSSION

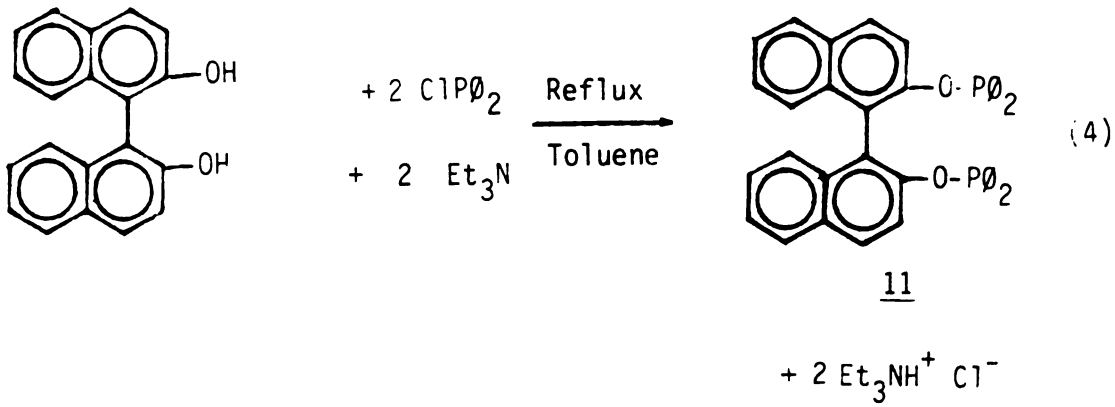
Preparation of Racemic Naphin

Several attempts were made to prepare racemic NAPHIN from 1,1-bi-2-naphthol. Simple addition of 2 equivalents of triethylamine and chlorodiphenylphosphine to 1,1-bi-2-naphthol in toluene did not result in any appreciable product after 24 hours of reflux. The di-sodium salt of



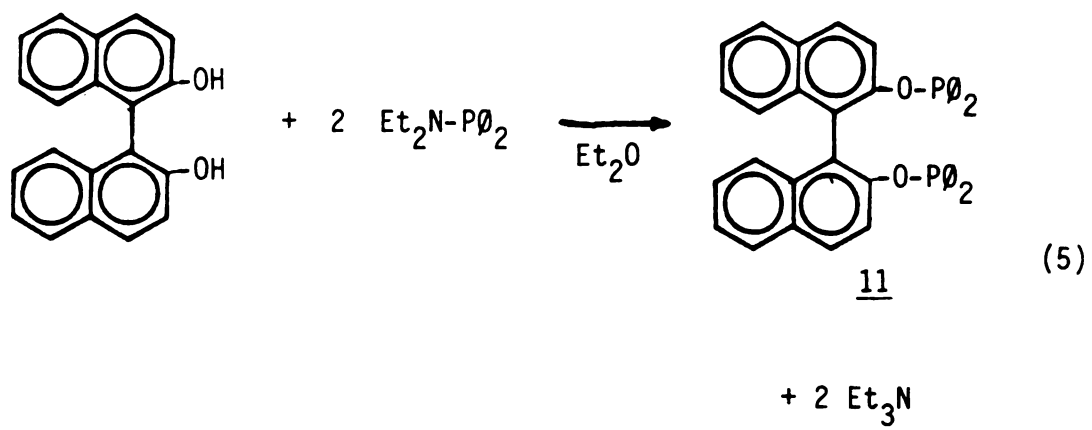
11

1,1-bi-2-naphthol was made with sodium hydride and then reacted with chlorodiphenylphosphine. Although some product did form, it proved difficult to isolate. A third attempt was made using diethylamino-diphenylphosphine. This reagent is reported to react with alcohols



(4)

and thus was expected to react with phenols. The main advantage was that the by-product could easily be removed by vacuum.



(5)

Screening of Racemic NAPHIN for Catalytic Activity

The crude ligand together with dicyclooctenechlororhodium dimer and excess cyclooctene in toluene absorbed hydrogen at room temperature. The fastest rate occurred at 1 atmosphere of hydrogen and a rhodium-to-ligand ratio of 2:1.

$$\text{NAPHIN} + \tfrac{1}{2}[Rh(COE)_2Cl]_2 \rightarrow \text{Active Catalyst}$$

Based on this catalytic activity, the resolution and preparation of the chiral NAPHIN was then undertaken.

Resolution of 1,1'-Bi-2-naphthol 20

The starting material for the NAPHIN synthesis, 1,1'Bi-2-naphthol was resolved by the procedure of Sousa and Cram, (See Figure 1). The chemical yields for each step were somewhat lower, but the optical impurities were comparable.

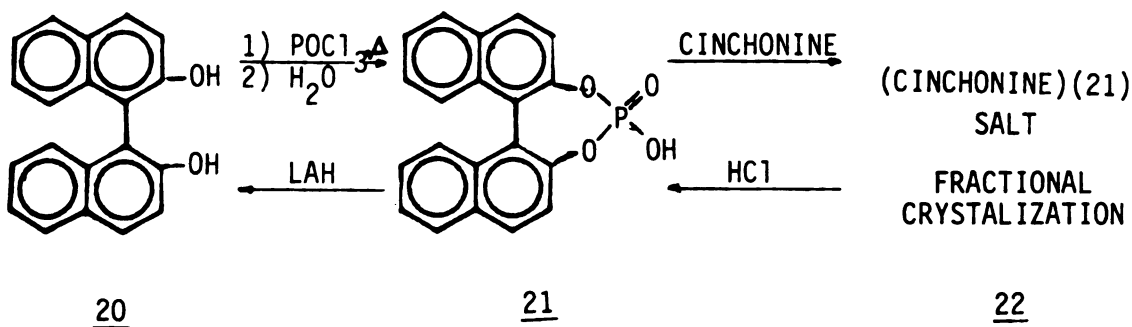
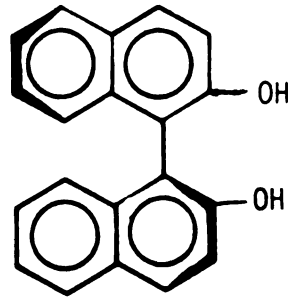


Figure 1.. Resolution Scheme of 1,1'-Bi-2-naphthol.

The absolute rotation and configuration of 1,1'-Bi-2-naphthol have been well-studied. Sousa estimated the absolute rotation to be 34 ±0.5°, with literature reports of -34.3 and +34.1 (c=1.0, THF). In this case the S(-)

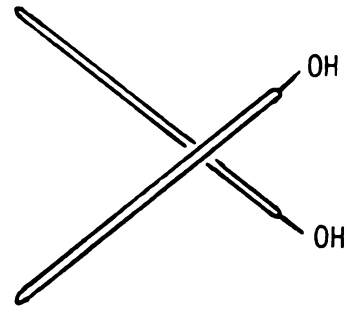
enantiomer was obtained in 34% yield and gave a rotation of -31.68 (c=1.01, THF). The R(+) enantiomer was isolated in 21% yield, but with a higher rotation; +35.32° (c=1, THF). Using an absolute rotation value of 35.2°, the S(-) enantiomer used to make S(-) NAPHIN was calculated to be 90% optically pure.

The absolute configuration shown in Figure 2 was assigned[19] by an x-ray diffraction study.



S (-)

20



END ON VIEW

Figure 2. Configuration of S (-) 1,1'-Bi-2-naphthol.

Racemization studies were conducted by D. J. Cram[20]

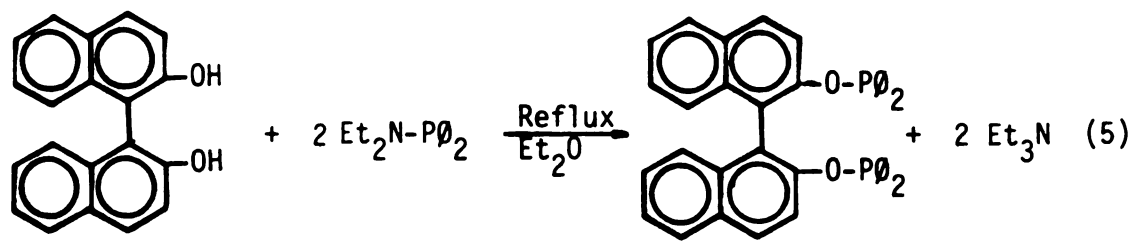
Optically Stable	100°-24 hrs (in Dioxane-water)
72% Racemization	1.2N HCl (Room Temp) ", (24 hrs)
69% Racemization	.667N NaOH " " "

1,1'-Bi-2-naphthol should not racemize by refluxing in diethylether; however, it might be racemized by the diethylamine or aminophosphine reagent used to make NAPHIN by the reaction shown in Equation (5).

NAPHIN was prepared by reaction of 1,1'-bi-2-naphthol with diphenyl diethylaminophosphine which was prepared from chlorodiphenylphosphine and diethylamine.

Preparation of S(-) NAPHIN 11

This reagent slowly decomposes, so it was freshly made from chlorodiphenylphosphine. In this reaction the basic amine probably helps to deprotonate the phenol, while phosphorus attacks the oxygen.



20 11

The reaction was run in refluxing ether to minimize the possibility of racemization. As a rough check the NAPHIN ligand was reduced with Lithium aluminum hydride in THF to give fairly pure 1,1-Bi-2-naphthol. The crude product showed a rotation of -27°, or 77% of the original value.

Considering this was a crude product and that LAH reduction may also cause some racemization, gross racemization does not seem to occur during the production of NAPHIN.

The volatile by-product, diethylamine, was easily removed under vacuum, leaving the crude product. This could be recrystallized to give fine transparent needles of NAPHIN which appeared to be air stable when dry.

Characterization of NAPHIN II

Unlike many chiral ligands used for asymmetric hydrogenation catalysis, NAPHIN forms nice needles, mp 172-172.5°C, which are not air sensitive when kept dry. When dissolved or wet with solvent the ligand is susceptible to oxidation of the phosphine(s). The easiest way to observe this is by checking the mass spectrum for oxide peaks at M + 16, and M + 32. These oxides are in fact the main impurity in the crude product and are almost completely removed by recrystallization from ethanol.

The proton and carbon NMR's give little useful information, but the phosphorus NMR will distinguish the phosphinite from its oxide.

Elemental analysis of the recrystallized ligand was very good, including the oxygen content that might be expected to be high if slow air oxidation occurred.

That S-(-)1,1-Bi-2-naphthol produces S-(-)NAPHIN was confirmed by reduction of S(-)NAPHIN back to S-(-)

1,1'-Bi-2-naphthol. The highest observed rotation for NAPHIN in benzene was $[a]_D^{RT}$ -38.7° (c=1.098, Benzene). The ligand did not racemize at room temperature either as a solid or when dissolved in benzene and checked 6 months later.

Rhodium Complexes Used in Making the Active Catalyst

Several different rhodium complexes were used to generate the asymmetric hydrogenation catalyst. In the initial runs $[Rh(cyclooctene)_2Cl]_2$ was used, while later runs used $[Rh(ethylene)_2Cl]_2$. It was found that $[Rh(ethylene)_2Cl]_2$ darkened over long periods of time at room temperature and thus may in time decompose to some elemental rhodium. The use of $[Rh(cyclooctene)_2Cl]_2$ was resumed at this time. Another complex in common use is $[Rh(cyclooctadiene)Cl]_2$. In each case the *in situ* asymmetric hydrogenation catalyst formed easily and readily reduced ethylene, cyclooctene, or cyclooctadiene.

Preparation of Prochiral Substrates

Although many prochiral substrates are now commercially available, most were synthesized according to literature procedures.[21] The unreported methyl, ethyl, and isopropyl esters of β-methylcinnamic acid and the methyl ester of α-methylcinnamic acid were prepared in good yield.

All of the acid forms of the substrates later became commercially available, with the exception of β-methylcinnamic acid.

Although the racemic catalysts could hydrogenate cyclooctene at ambient temperatures and pressures, these conditions did not reduce bulkier substrates such as β-methylcinnamic acid. The required pressures, temperatures, and ligand to rhodium ratios were determined using the chiral ligand.

Maximization of Pressure, Ligand to Rhodium Ratio, and Temperature

Although no hydrogenation was observed with β-methylcinnamic acid at 1 atmosphere, attempts were made at 30, 60, 800, and 1600 psi. The latter two attempts required a high pressure autoclave. A reasonable conversion occurred only at 1600 psi for over 20 hours giving an 18.7% optical yield. Reaction conditions held constant while pressure was varied were: temperature (25°C), ligand to rhodium ratio (1:1), substrate to rhodium ratio (100:1), solvent (toluene), and catalyst preparation (*in situ*).

The use of ligand to rhodium ratios greater than 1:1 resulted in no hydrogenation using the above conditions (Table 1). When the ligand to rhodium ratio was lower than 1:1, no optical induction was observed, but complete hydrogenation occurred, presumably by way of elemental rhodium.

Table 1. Effect of Ligand to Rhodium Ratio with the NAPHIN Catalyst System Using Z-Acetamidoacrylic Acid.

Ratio Ligand:Rhodium	Conversion	Optical Yield
.5 : 1	100%	0
1.0 : 1	41%	18.7%
1.5 : 1	0	---
2.0 : 1	0	---

The effects of temperature on the conversion and optical yield were examined using alpha and beta methyl cinnamic acids. Hydrogenations were carried out at room temperature and at zero degrees. The results were not reproducible due to an irregular stirring rate in the autoclave. In general lower conversion was found at the lower temperature. The optical yield data were also not reproducible. Since the rate was quite slow, it would be better to keep the temperature at the higher value.

The NAPHIN system required a fairly high hydrogen pressure to be an active catalyst for hydrogenation of β-methylcinnamic acid. A study of the effect of small pressure changes on the conversion and optical yields was conducted. All of the runs in Table 2 were 24 hours long with identical concentrations of catalyst and substrate.

Table 2. Effect of Hydrogen Pressure with the NAPHIN Catalyst System Using Z-acetamidoacrylic Acid.

Pressure (psi)	Conversion (%)	Optical Yield (%)
1300	90	12
1350	62	12
1400	44	22
1450	50	21
1500	41	19

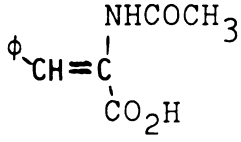
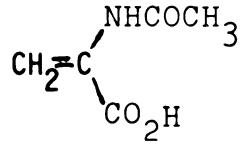
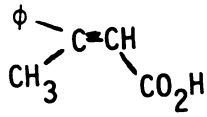
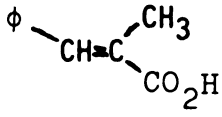
At the two lowest pressures the stirring rate was extremely fast, as seen in the high conversions. When the stirring rate was held constant, as in the three higher pressures, then the conversion and optical yields remained constant. The narrow pressure range in this study was imposed by two factors. No hydrogenation occurred below 1200 psi of hydrogen, and commercial hydrogen cylinders are loaded to about 1600 psi which sets the top pressure for pure hydrogen.

Effect of Added Base on Optical Yield and Rate

In most asymmetric hydrogenation systems the addition of base to an acidic substrate will speed the reaction and increase the overall optical yield of the reduction. In the four cases studied here, it slowed the reaction rate

3 out of 4 times and decreased the optical yield in 3 out of 4 cases. Another unusual result is that the preferred enantiomer actually changes upon adding base. No trend

Table 3. Effect of Added Et_3N on the NAPHIN System.

Substrate	With No Base	With Et_3N
	S[1] 9.0[2] (100)[3]	R 33.8 (1)
	R 6.8 (90)	S 1.5 (100)
	S 29.3 (44.3)	R 1.3 (25)
	S 25.0 (50.7)	0.0 (0)

[1]Predominant enantiomer.
[2]% Optical Yield.
[3]% Conversion.

of this kind appeared in the literature until relatively recently. Addition of base, usually Et_3N or NaOH, was thought to convert acidic substrates to the carboxylate anion. The

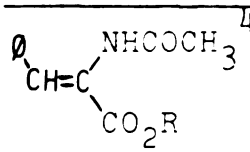
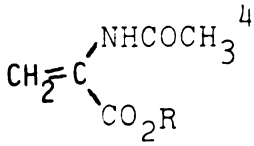
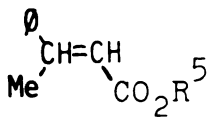
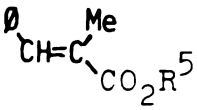
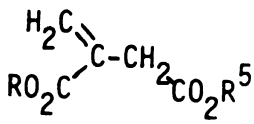
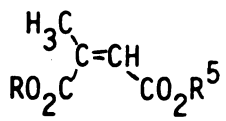
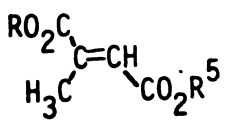
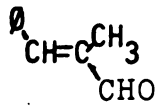
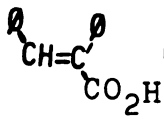
resulting prochiral salts with their own steric requirements, would behave as a unique substrate. Recently,[24] catalytic amounts of base have been reported to have a large effect. In this case the base may change the reaction mechanism by altering the catalyst or enhancing olefin coordination.

Comparison of Acid and Ester Substrates

Some of the highest optical induction was found with esters of the prochiral substrates. The methyl ester of N-acetylphenylalanine for example was made in 95% enantiomeric excess. A value of 76% ee was reported earlier, but is based on an incorrect optical rotation for N-acetyphenylalanine. At the time, this value would have been the highest optical yield reported in asymmetric hydrogenation; however, it is not unusual today to achieve over 90% ee with any amino acid precursor. The methyl ester of N-acetylalanine was also high at 53% ee. Both of these asymmetric induction values are much higher than those for the corresponding acid (See Table 4).

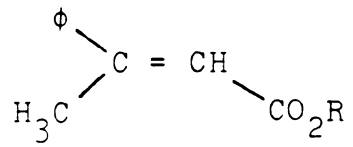
Unexpectedly, the optical yields obtained with the methyl esters of α and β methylcinnamic acid were lower than the values obtained with the acids. A series of esters were prepared from β-methylcinnamic acid. Changing from a methyl to an ethyl ester had a profound effect on the induction, which increased from 3.5% ee to 47.7% ee.

Table 4. Asymmetric Hydrogenations Using S(-) NAPHIN and $[Rh(alkene)_2Cl]_2$.

Substrate	R = H, Et_3N	R = H, No Base	$R = CH_3$	R = Et	R = iPr
	R[1] 33.8[2] (1)[3]	S 9.0 (100)	R 95.3 (41)	------	-----
	S 1.5 (100)	R 6.8 (90)	R 53.1 (100)	------	-----
	R 1.3 (25)	S 29.3 (44.3)	S 3.5 (69.5)	S 47.7 (82)	0.05 (0)
	0.0 (0)	S 25.0 (50.7)	S 15.3 (82)	------	-----
	S 1.6 (51)	------	------	------	-----
	R 30.5 (26)	------	------	------	-----
	S 1 (21.5)	------	------	------	-----
	0	------	------	------	-----
	S 6.0 (54)	------	------	------	------

[1]Predominant enantiomer. [2]Percent optical yield. [3]Percent conversion. [4]Run in toluene:acetone. [5]Run in toluene.

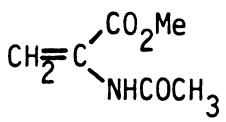
The isopropyl ester could not be reduced at 1600 psi for 24 hours.

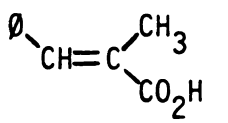


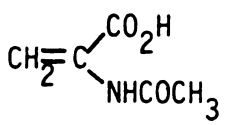
R=H	$R=CH_3$	R=Et	R=iPr
29.3	3.5	47.7	---
S	S	S	

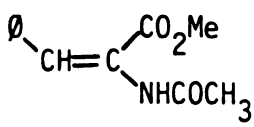
Relative Rates of Substrates

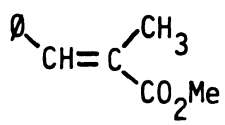
Although the data are quite rough due to irregular stirring rates, the relative rates between substrates should average out.

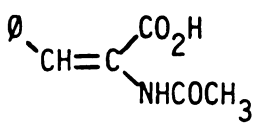

7+


1.0


7


.8


1.4


.6

Disubstituted alkenes are reduced much faster than trisubstituted alkenes. Esters hydrogenate faster than the corresponding acids. Overall the catalyst is very slow

compared to other asymmetric hydrogenation catalysts with rates about 500 times slower than the (-)DIOP[22] catalyst.

Cationic NAPHIN Catalyst System

Since many substrates used in asymmetric hydrogenation are soluble in polar solvents like alcohols, it would be desirable to prepare a chiral cationic catalyst. This would have the advantage of eliminating weighing errors

$$\text{NAPHIN} + \tfrac{1}{2}[\text{Rh(COE)}_2\text{Cl}]_2 + \text{NaBF}_4 \xrightarrow[\text{MeOH}]{} [\text{Rh(NAPHIN)}]^+\text{BF}_4^-$$

in preparing the catalyst mixture.

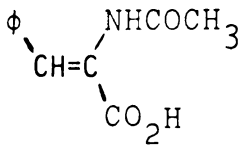
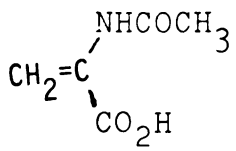
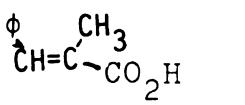
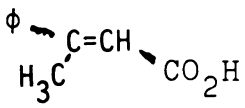
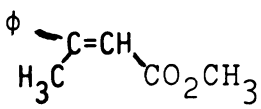
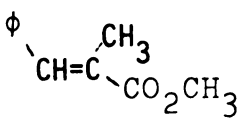
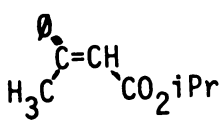
Many groups have reported faster hydrogenation rates and higher or similar amounts of optical induction by changing to a cationic catalyst. Looking at Table 5 it is easy to see that NAPHIN does not follow this pattern.

Indeed, slower rates and lower optical yields were usually found.

Comparison with Other Catalyst Systems

Many research groups have reported only those results which depict their catalyst system as the best. It is common to see only the highest optical yield values for a specific substrate or group of substrates. One unique study by Morrison[6] examined a number of catalyst systems

Table 5. In Situ vs Cationic NAPHIN System.

Substrate	Et_3N Added			
	In Situ	Cationic	In Situ	Cationic
	R 33.8* (1)	±0.0 (100)	S 9.0 (100)	R 2.3 (13.3)
	S 1.5 (100)	S .5 (100)	R 6.8 (90)	S 31.6 (100)
	0.0 (0)	0.0 (0)	S 25.0 (50.7)	0.0 (0)
	R 1.3 (25)	0.0 (0)	S 29.3 (44.3)	0.0 (0)
	-----	-----	S 3.5 (69.5)	± 0.0 (15.2)
	----	----	S 15.3 (82)	± 0.0 (60.5)
	----	----	± 0.0 (8.1)	0.0 (0)

*For example: R enantiomer predominant, 33.8% optical yield, 1% conversion

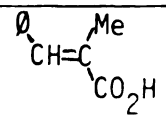
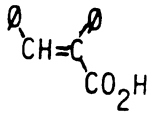
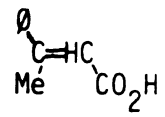
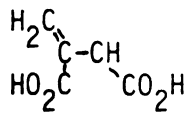
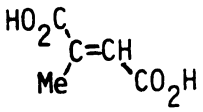
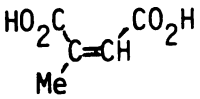
under identical reaction conditions with groups of substrates not known for unusually high optical induction. In Table 6 these results are listed with those of the NAPHIN system, although the reaction conditions were somewhat different. There is no clear trend one can distinguish except that each catalyst system has substrates with which higher inductions are possible.

The source of optical induction must be related to steric interactions between catalyst and substrate. The active catalyst, the degree of chemical interaction, and the degree of steric interaction should vary with each catalyst-substrate combination and the reaction conditions. Therefore, it comes as no surprise that no single model for predicting which enantiomer will be favored, and the degree of optical induction has been found. If a detailed examination of the mechanism of a particular catalyst system under a given set of conditions and for a particular substrate is made, then one has a model[23] for only that system and only with substrates similar to the test example.

Comparison of Phosphine to Phosphinite Ligands

One of the best comparisons between a bidentate phosphine and bidentate phosphinite is that made between the NAPHOS and NAPHIN systems.[13] Unfortunately, one

Table 6. Comparison of the NAPHIN System to Other Asymmetric Hydrogenation Systems. Values Indicate % Optical Yield and Configuration.

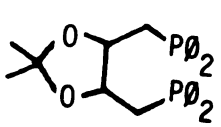
Substrate	ACMP	DIOP	NMDPP	MDPP	CAMPHOS	NAPHIN[2]
	12(R)[3]	25(S)	60(R)	17(S)	15(R)	25(S)
	24(S)	15(R)	34(S)	27(R)	12(S)	6(S)
	37(S)	14(R)	62(S)	1(S)	9.7(S)	29.3(S)
	----	----	8.1(R)	18(R)	11(R)	1.6(S)
	----	----	5.9(R)	7.2(S)	1.8(R)	1(S)
	----	----	----	----	----	30.5(R)

[1]All runs made at 300 psi, r.t., with 3 equivalents Et_3N per substrate, except NAPHIN which was run at 1500 psi.

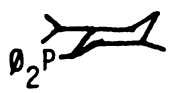
[2]No base was used in this case.

[3]% ee (enantiomer).

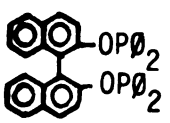
(+) ACMP 3 P(Me)(Ⓢ)(orthoØ-OMe)

(-) DIOP 2 

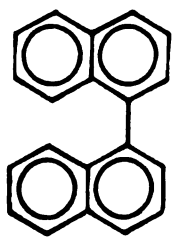
(+) NMDPP 1 

(-) MDPP 4 

(+) CAMPHOS 5 

(-) NAPHIN 11 

substrate has been reported by Kumada[14] since 1977. The reaction solvent and percent conversion were not reported for NAPHOS. The hydrogen pressure was high for both systems and the S enantiomer of each ligand favored the S aminoacid precursor but in different optical yields.

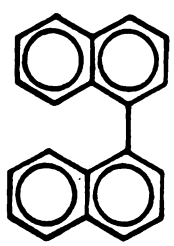


$CH_2\text{-}P\emptyset_2$
$CH_2\text{-}P\emptyset_2$

$\emptyset CH{=}C(NHCOCH_3)CO_2H \xrightarrow[15hr,\ r.t.]{50\ Atm\ H_2} \emptyset CH_2\text{-}CH(NHCOCH_3)CO_2H$ (6)

54% ee S

S (-) NAPHOS 12



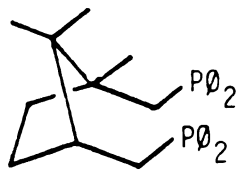
$O\text{-}P\emptyset_2$
$O\text{-}P\emptyset_2$

$\emptyset CH{=}C(NHCOCH_3)CO_2H \xrightarrow[24hr,\ r.t.]{100\ Atm\ H_2} \emptyset CH_2\text{-}CH(NHCOCH_3)CO_2H$ (7)

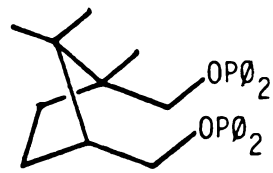
34% ee R (With added base)
9% ee S (No added base)

S (-) NAPHIN 11

Johnson et al.[25] found that higher optical yields from esters were obtained with a phosphinite ligand than with the corresponding phosphine ligand. However, the comparison between these two ligands may hold little significance, since CAMPHOS would form a smaller chelate with a metal than CAMPHINITE and thus give a clear steric difference as well.



(+) CAMPHOS 5



CAMPHINITE 23

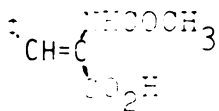
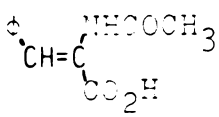
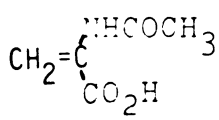
A good comparison of phosphine to phosphinite ligands in catalytic asymmetric hydrogenation was made by Tanaka. In this study the chelate size remained the same (See Table 7). Small structural changes within these phosphinites had a great effect on the induction.

Since the beginning of this work many new chiral phosphine,[27] phosphinite,[16] and aminophosphine[29] ligands have been used in asymmetric hydrogenation. In general, aminophosphine ligands give the most active catalysts. Phosphine ligand systems result in slower reaction, and phosphinite based systems are slower yet. The required hydrogen pressure usually is quite high for the phosphinite systems.

Conclusions

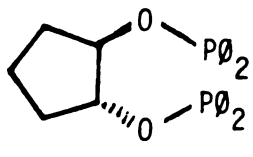
Every type of chiral ligand has the potential to give high optical induction in catalytic hydrogenation.

Table 7. Comparison of Phosphine and Phosphinite Systems.*[26] Values Indicate % Optical Yield and Configuration.

Substrate	Temp.	16 d-trans BDPCP	15 d-trans-BDPCH	2 (-)-DIOP
	0	12(s)	68.5(s)	63(R)
	50	43(s)	----	55(R)
	-20	±0	78.9(s)	73(R)

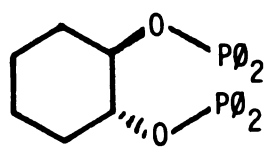
*Run at 1 atm; others run at 50 atm.

d-trans BDPCP



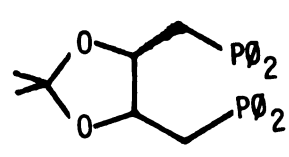
16

d-trans BDPCP



15

(-)-DIOP



2

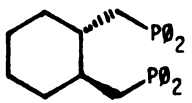
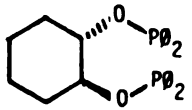
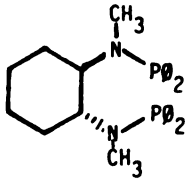
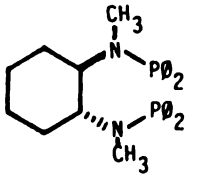
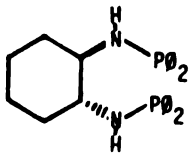
In Table 8 the structurally related phosphine, phosphinite, and aminophosphines are compared. One could also compare ligands with different sources of chirality and find similar results. Each class of chiral catalysts can achieve high induction under the proper conditions and with the right substrate.

EXPERIMENTAL

Instrumentation

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained using a Varian T-60 spectrometer. Carbon and phosphorus NMR spectra were recorded using a Varian CFT-20 and modified Varian DA-60 spectrometer, respectively. All optical rotations were obtained with a Perkin-Elmer 141 polarimeter. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. High pressure hydrogenations were done using a 200 ml Autoclave Engineer's Magnedrive Packless Autoclave with a glass liner. Elemental analysis was determined by Schwarzkopf Microanalytical Laboratory. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer.

Table 8. Comparison of Phosphine, Phosphinite, and Aminophosphine Ligands in Asymmetric Hydrogenation.

Substrate / Ligand	ϕCH=C(NHCOCH$_3$)CO$_2$H	ϕCH=C(NHCOϕ)CO$_2$H	CH$_2$=C(NHCOCH$_3$)CO$_2$H	Conditions	Ref.
	S 35%*	58%	------	1 atm, RT, 24 hrs EtOH/ = 2.3 In Situ	27
	S 68.5%	---	S 78.5%	50 atm, 0°, 24 hrs	16
	S 73%	S 85%	----	1 atm, RT, 2-4 hrs EtOH In Situ	28
	S 92.1%	----	S 90.9%	1 atm, 25°, 10-40 min EtOH; Cationic	29
	R 47%	----	R 24%	1 atm, 25°, 10-40 min EtOH; Cationic	29

*For example: S enantiomer predominant, 35% optical yield.

Reagents and Solvents

The following code is used for the various sources of reagents and solvents.

1. Mallinckrodt, Inc.
2. Aldrich Chemical Company, Inc.
3. Engelhard Industries Incorporated
4. Fluka AG (sold through Tridom Chemical Inc.)
5. Eastman Organic Chemicals
6. Alfa Products
7. Stohler Isotope Chemicals
8. Fisher Scientific Company
9. Drake Brothers
10. Chem Samples
11. AIRCO
12. Baker Chemical Company

Material

	Source[a]	Treatment[b]
1,1'-Bi-2-naphthol	2	(E)
Phosphorusoxychloride	2	(E)
Cinchonine	5	(E)
Lithium aluminum hydride	6	(E)
Chlorodiphenylphosphine	2	(A)
Triethylamine	1	(E)

Diethylamine	1	(A)
Deuterated solvents	7	(E)
Ethyl acetate	8	(E)
Benzene	12	(E)
THF	9	(B)
Diethyl ether	1	(B)
Toluene	1	(B)
Acetone	8	(C)
Chloroform	1	(C)
Methanol	1	(C)
Petroleum ether	1	(E)
Sodium tetrafloroborate	6	(E)
Rhodium trichloride ($RhCl_3 \cdot 3H_2O$)	3	(E)
Ethylene	11	(E)
Hydrogen	11	(E)
Argon	11	(D)
Nitrogen	11	(D)
Isopropanol	8	(E)
α-Methylcinnamic acid	2	(E)
β-Methylcinnamic acid	5	(E)
α-Phenylcinnamic acid	2	(E)
α-Methylcinnamaldehyde	2	(E)
Itaconic acid	2	(E)
Citraconic acid	2	(E)
Mesaconic acid	2	(E)
α-Acetamidocinnamic acid	4	(E)

α-Acetamidoacrylic acid	2	(E)

[a]See list on page 34.

[b]The following code is used for the various treatments of reagents and solvents prior to use:

(A) Vacuum distilled and stored under an inert atmosphere.

(B) Distilled under an inert atmosphere from sodium or potassium benzophenoneketyl. Stored under inert atmosphere.

(C) Dried over 4 Å molecular sieves. Degassed and stored under an inert atmosphere.

(D) Passed through BASF-BTS catalyst heated at 140°C followed by 4 Å molecular sieves.

(E) Used without further purification.

Substrates

Preparation of Methyl α-Methylcinnamate

α-Methylcinnamic acid (5.0871 g) was dissolved in 25 ml of dry methanol in a 50 ml round bottom flask equipped with a stir bar, heating mantel, and condenser. After adding one-half ml of concentrated hydrochloric acid to the stirred solution, the contents were brought to reflux for 23 hours.

The solution was cooled and 25 ml of benzene was added. The solution was extracted twice with aqueous sodium bicarbonate followed by drying of the benzene layer with magnesium sulfate. The benzene was removed by vacuum and

the product vacuum distilled at 65-72°C and .005 mm. The product will solidify in a cooled condenser. The white solid (4.7765 g) was isolated in 86% yield. mp 36-37°. Proton NMR and mass spectrum showed only the ester.

Preparation of Methyl β-Methylcinnamate

β-Methylcinnamic acid (13.7152 g) was dissolved in 100 ml of dry methanol in a 200 ml round bottom flask equipped with stir bar, steam bath, and condenser. After adding one-half ml of concentrated hydrochloric acid to the stirred solution, the contents were brought to reflux for 48 hours.

The cooled solution was extracted with methylene chloride, and extracted twice with aqueous sodium bicarbonate. The methylene chloride was rotovaped off leaving a fairly pure product. The crude product was vacuum distilled at 70°C/.25 mm. The NMR of the distilled ester showed no acid impurity. Total 9.6243 g of clear liquid or 65% yield of the ester was isolated.

Preparation of Ethyl β-Methylcinnamate

Three different procedures were used to make this ester. The original method involved a zinc coupling reaction of acetophenone and ethyl bromoacetate. The overall yield in this case was 66%. A second method was a modified

Wittig synthesis using triethyl phosphonoacetate and acetophenone. The yield was also 66% by this method. The third method was from β-Methyl cinnamic acid which is no longer commercially available.

β-Methylcinnamic acid (5 g) was dissolved in 63 ml of dry ethanol in a 100 ml round bottom flask equipped with a stir bar, heating mantel, and condenser. After adding one-half ml of concentrated hydrochloric acid to the stirred solution, the contents were brought to reflux for 86 hours.

The ethanol was distilled off and the remaining oil vacuum distilled around 72°C/.10 mm. The ester was isolated in 89% yield (5.2019 g). The proton NMR showed only the ester.

Preparation of isoPropyl β-Methylcinnamate

β-Methylcinnamic acid (22.5 g) was dissolved in 350 ml of dry isopropanol in a 500 ml round bottom flask equipped with a stir bar, steam bath, and a condenser. After adding one-half ml of concentrated hydrochloric acid to the stirred solution, the contents were brought to reflux for 70 hours.

The cooled solution was extracted with methylene chloride, and extracted twice with sodium bicarbonate. The methylene chloride was evaporated leaving a thick oil. This was vacuum distilled at 77-80°C/.025 mm yielding an 80% yield (24.4505 g) of clear liquid. Proton NMR and a

mass spectrum confirmed this was pure ester.

The sodium bicarbonate rinses were acidified and extracted with methylene chloride. Evaporation of methylene chloride yielded 4.5 grams of recovered β-methyl cinnamic acid.

Preparation of Methyl α-Acetamidocinnamate

α-Acetamidocinnamic acid (2.2228 g) was dissolved in 50 ml of water along with sodium hydroxide (.4680 g). To this was added an aqueous solution of silver nitrate (2.597 g in 50 ml water) whereupon a thick white precipitate immediately formed. This was stirred an additional 15 minutes and then filtered by suction with a sinstered glass funnel. The precipitate was rinsed with water and dried in a desiccator under vacuum for 10 hours. The precipitate was protected from light during this time.

The crude silver salt of α-acetamidocinnamic acid (1.8071 g) was dissolved in 50 ml of ether and methyl iodide (11.4 g) slowly was added over 15 minutes. The solution was stirred an additional hour and then the solution was evaporated off. The crude ester was extracted into ether and the ether distilled off. The crude ester was recrystallized from ethyl acetate-pet ether. Total yield was .6529 grams or 27.5% yield. White powder mp 120-121°C. The proton NMR confirmed the powder as pure ester.

Preparation of Methyl α-Acetamidoacrylate

Methyl α-acetamidoacrylate was made from α-acetamidoacrylic acid by an analogous procedure to that above. Overall 30% yield. White crystals mp 48-52°C. Structure confirmed by proton NMR and mass spectrum.

Preparation of Methyl α-Benzamidocinnamate

The Z-azelactone of α-Benzamidocinnamic acid (4.8236 g) obtained from Mr. Han-Min Chang was dissolved in 50 ml of dry toluene along with sodium methoxide (2.0922 g). The solution became a shade lighter after several hours. Dilute hydrochloric acid was carefully added to the solution. After 100 ml of acid had been added the toluene layer became cloudy and precipitated white fluffy crystals. The precipitate was filtered, washed with water several times, and then redissolved in methylene chloride. The methylene chloride was washed with sodium bicarbonate twice and then evaporated off. The fine white solid (1.3239 grams) was isolated in 24% yield. Mp 141-142°C. The proton NMR showed only the ester.

Resolution of 1,1'-Bi-2-Naphthol 20 (See Figure 1)

Preparation of Cyclic Binaphtholphosphoric Acid 21

1,1'-Bi-2-naphthol (168 mmole) 20 was placed in a 200 ml round bottom flask with bulb trap and large condenser. Phosphorus oxychloride (219 mmole) was added by syringe after flushing the system with nitrogen. The flask was heated to 210-230°C by a sand bath for 3 days at which time HCL evolution had ceased.

The reaction pot was allowed to cool to room temperature while under nitrogen and then was broken by means of a hammer into a plastic bucket. Most of the pot's contents was a brittle black glass. The pieces of glass and black glassy solid were put into a liter erlenmeyer flask and 160 ml of a 2% sodium carbonate solution was added slowly with the volution of carbon dioxide. Another 400 ml of 2% sodium carbonate solution was added and the mixture brought to reflux on a hot plate to dissolve the black glassy solid. The jet black solution was filtered on a preformed mat of celite on a large sinstered glass funnel. The filtrate was placed in a 2 liter erlenmeyer and allowed to stand for 2 days.

The black solution deposited white crystals on cooling. These crystals were collected on a large Büchner funnel. The wet solid was slurried in a 2 liter erlenmeyer flask with 715 ml of water for 1 hr before the addition of 286 ml

of water with 25 ml of concentrated hydrochloric acid. This mixture was slurried 24 hrs followed by suction filtration on a Büchner funnel. The crude solid was dried in a vacuum oven at approximately 110°C for two and one-half days. The crude product was cooled to room temperature to yield 45.7192 grams of cyclic binaphtholphosphoric acid.

Cinchonine salt of Cyclic Binaphtholphosphoric Acid 22

The entire cyclic binaphtholphosphoric acid sample was dissolved with an equal molar quantity of cinchonine in 556 ml of hot methanol in a liter erlenmeyer flask. Water (243 ml) was added and the brown solution was allowed to stand 1 hour. The warm solution was suction filtered through a celite mat to remove a brown floculent precipitate impurity. The solution was left at room temperature to crystalize out the S(+) salt 2 days later. A second crop from the rinsing of the mat also formed the S(+) salt. The crystals from both crops were collected on a Büchner funnel and rinsed with a 70/30 mixture of methanol water. Total 24.5542 grams or 60% yield. Rotation S(+) 1st crop $[\alpha]_D$ + 350.25° (c=1.007 DMF). Sousa's best value was +374°.

S(+) Cyclic Binaphtholphosphoric Acid 21

The first crop of the cinchonine salt (22.5651 g) was dissolved in 81 ml of absolute ethanol and heated to

a boil on a steam bath. Hydrochloric acid (81 ml of 6N) was also heated on the steam bath and then slowly added to the ethanol solution. Adding the acid too fast or too slow will result in an oil rather than crystals upon cooling. After the acid had been added, the solution was cooled to room temperature and allowed to stand 2 days. The crude S(+) cyclic binaphtholphosphoric acid crystallize out and was collected on a Büchner funnel.

Digestion of the crude product in hydrochloric acid slowly increases the optical purity. The crude acid was digested in 43 ml of hot 6N hydrochloric acid and then collected on a sinstered glass funnel. This was repeated three more times with digestions of 15, 11, and 11 hours. The fine white crystals were filtered and dried in the vacuum oven to give 9.5064 grams or 76% yield. $[\alpha]_D$ + 605.26° (c=1.007, MeOH). Sousa's value was +622 ± 10°.

S(-) 1,1'-Bi-2-naphthol 20

S(+) cyclic binaphthylphosphoric acid (9.5064 g) was slurried in 475 ml of ice cooled dry THF under nitrogen. Lithium aluminum hydride (7.13 g) was added quickly to this slurry under high nitrogen flow. The slurry was allowed to warm to room temperature. After 20 hours the grey slurry was ice cooled again and 95 ml of cold 6N hydrochloric acid added extremely slowly. Much foaming occurred

initially. After all the hydrochloric acid had been added, the solution was stirred an additional hour while warming to room temperature. The pot contents were poured into a liter separatory funnel and the aqueous and THF layers separated. The water phase was extracted twice with 285 ml of diethylether. The combined organic phases were washed with saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent left a slightly yellow solid. This was redissolved in diethylether, stirred with norit, and filtered through a glass frit with a celite mat. A total of 8.0120 grams of S(-) 1,1'-Bi-2-naphthol 20 was isolated. $[\alpha]_D$ -31.68° (c=1.01, THF). Sousa reported the absolute value at 34 ± .5° in THF.

R(-) Cyclic Binaphthylphosphoric Acid 21

The R(-) cyclic binaphthylphosphoric acid was isolated out of the ethanol rinses of the S(+) acid. Adding 200 ml of 6N hydrochloric acid to the ethanol solution eventually will cause it to crystalize out. This also can be digested in 6N hydrochloric acid to improve optical yield. Total 14.524 grams.

R(+) 1,1'-Bi-2-naphthol 20

Just as with the S enantiomer, a reduction with lithium aluminum hydride in THF of R(-) cyclic binaphthylphosphoric acid (10.7565 g) gave a 21% yield of R(+) 1,1-Bi-2-naphthol.

Very large crystals were formed with maximum rotation of $[\alpha]_D$ + 35.2° (c=1.370, THF). This is higher than Sousa's value and will be taken as the absolute rotation. The S(-) 1,1'-Bi-2-naphthol should therefore be 90% optically pure.

Preparation of S(-) NAPHIN

Preparation of Diethylaminodiphenylphosphine

Chlorodiphenylphosphine and diethylamine were freshly distilled and stored under nitrogen. Chlorodiphenylphosphine (39 ml) was transferred by syringe to an argon purged 3-necked round bottom flask equipped with addition funnel, stir bar, and nitrogen line adapter. Dry oxygen free diethyl ether (200 ml) was added by syringe and the solution stirred. Diethylamine was transferred by syringe to the addition funnel and slowly added to the stirred contents. The heat of the reaction caused the ether to boil. The contents were stirred 2 hours after the addition was complete.

The ether was removed by vacuum and the product was vacuum distilled under nitrogen at 140°C/.1 mm. A total of 42.9 grams of diethylaminodiphenylphosphine were collected or a 76% yield. The product was used immediately.

Preparation of S(-) 1,1'-Bi-2-naphthyl Diphenylphosphinite 11

A three-necked 500 ml round bottom flask fitted with a condenser, stir bar, addition funnel, and heating mantel was purged with three vacuum-nitrogen cycles. S(-) 1,1'-Bi-2-naphthol 20 (7.811 g) was quickly loaded into the flask and the contents purged again with vacuum and nitrogen.

Preparation of S(-) NAPHIN

Preparation of Diethylaminodiphenylphosphine

Chlorodiphenylphosphine and diethylamine were freshly distilled and stored under nitrogen. Chlorodiphenylphosphine (39 ml) was transferred by syringe to an argon purged 3-necked round bottom flask equipped with addition funnel, stir bar, and nitrogen line adapter. Dry oxygen free diethyl ether (200 ml) was added by syringe and the solution stirred. Diethylamine was transferred by syringe to the addition funnel and slowly added to the stirred contents. The heat of the reaction caused the ether to boil. The contents were stirred 2 hours after the addition was complete.

The ether was removed by vacuum and the product was vacuum distilled under nitrogen at 140°C/.1 mm.

A total of 42.9 grams of diethylaminodiphenylphosphine were collected or a 76% yield. The product was used immediately.

Preparation of S(-) 1,1'-Bi-2-naphthyl Diphenylphosphinite 11

A three-necked 500 ml round bottom flask fitted with a condenser, stir bar, addition funnel, and heating mantel was purged with three vacuum-nitrogen cycles. S(-) 1,1'-Bi-2-naphthol 20 (7.811 g) was quickly loaded into the flask and the contents purged again with vacuum and nitrogen.

Catalytic Precursors

Preparation of Biscyclooctenerhodium(I) Chloride dimer $[Rh(COE)_2Cl]_2$

Several different methods have been used to prepare the title compound. The procedure listed is by far the easiest and most economical for this expensive reagent. A slight modification of the procedure reported in Inorganic Synthesis[30] results in a much higher yield of the product.

$$2\ RhCl_3 \cdot 3H_2O + 4\ C_8H_{14} + 2\ CH_3CH(OH)CH_3 \rightarrow [Rh(COE)_2Cl]_2 + 2\ CH_3COCH_3 + 4\ HCl \quad (8)$$

In a 100 ml three-necked round bottom flask, rhodium trichloride trihydrate (41% rhodium Englehard, 2.03 g) was dissolved in an argon degassed mixture of 40 ml of 2-propanol and 10 ml of water. To this mixture freshly distilled cyclooctene (6 ml) was added by syringe. The mixture was degassed again with a gas diffusion tube and argon and then left undisturbed under argon.

After 8 days, 1.5557 grams of product was isolated by filtration under argon washing with 5 ml of dry oxygen free ethanol, and drying under a full vacuum. A second crop was isolated 2 days later (.5150 grams) and a third crop was isolated 10 days later (.5152 grams). Total yield of the orange microcrystals was 2.5859 grams or 93% yield.

Preparation of u-Dichlorotetraethylenedirhodium I, $[Rh(C_2H_4)_2Cl]_2$

u-Dichlorotetraethylenedirhodium I was prepared by the method of R. Cramer.[31]

$$2RhCl_3 \cdot 3H_2O + 6C_2H_4 \xrightarrow{MeOH} [Rh(C_2H_4)_2Cl]_2 + 4HCl + 4H_2O + 2CH_3CHO \quad (9)$$

A solution of rhodium trichloride trihydrate (3.3850 in 5 ml water) was added to 85 ml of methanol in a 250 ml round bottom flask with a side arm, stir bar, and rubber

septum. A slow stream of ethylene gas was slowly bubbled into the stirred solution using a syringe needle through the rubber septum placed just under the surface of the liquid. An oil bubbler was attached to the side arm to monitortthe gas flow.

After 4 hours the red solution had precipitated an orange-red powder (the red tint comes from the solution). The precipitate was collected under nitrogen by suction filtration, washed with 10 ml of methanol, washed with 5 ml of diethylether, and vacuum dried. Total 1.1852 grams or 90% yield of fine orange-brown crystals. The complex will darken over several months under argon at room temperature. Long term storage should be at 0°C.

Preparation of u-Dichlorobiscyclooctadienedirhodium $[Rh(COD)Cl]_2$

The title compound was made by the procedure of Chatt.[32] The straw colored crystals were not recrystallized.

Preparation of In Situ Catalyst

S(-) NAPHIN (.05 mmol) and $[Rh(alkene)_2Cl]_2$ were added dry along with substrate (5 mmol) when the substrate was a solid to the autoclave glass liner. After degassing with high nitrogen pressure, the solvent (50 ml) was added along with any liquid substrates while under nitrogen and the

mixture stirred for about 1 minute. Longer stirring times did not seem to effect conversion or optical yield.

Preparation of $[Rh(NAPHIN)]^+BF_4^-$

The cationic catalyst was prepared similar to preparations made by W. S. Knowles.[33] NAPHIN (.2 mmol) and $[Rh(COE)_2Cl]_2$ (.1 mmol) were slurried in 2 ml of methanol degassed with argon. A solution of sodium tetrafluoroborate (.2 mmol in 1 ml of water) was added slowly. A thick yellow precipitate resulted which was filtered, washed with a little methanol and dried in vacuo. A yield of 74% was isolated. Elemental analysis Calculated: C 65.3, H 5.6, P 5.2; Found: C67.7, H 5.6 and P 5.2.

Hydrogenation Procedure

The in situ catalyst was prepared as previously described. The cationic catalyst was added as a powder to the liner before adding solvent. In a typical hydrogenation the substrate was added as a powder or dissolved in the solvent if a liquid. After stirring for about 1 minute, the autoclave contents were brought to the required pressure. The stirred contents after 24 hours were removed after releasing the hydrogen pressure slowly. The substrate and/or products were isolated. (See Table 3.)

Product Isolation

The work-up and isolation of the hydrogenation products follows Kagan's procedures[21] with minor variations for the differences between the catalysts. Each substrate and product were carefully characterized by melting point, mass spectrum, and proton NMR initially. Routine characterization was by proton NMR and optical rotation. Rotation values were corrected for incomplete conversions. Table 9 lists each substrate and how it's hydrogenated product was isolated and characterized. The code to the isolation and characterization follows the table.

The isolation procedures were checked to insure racemization did not occur by reckecking the rotation after a second isolation. 2-Methyl-3-phenyl propanoic acid and 3-phenylbutanoic acid methyl ester appear to undergo some racemization if distilled at temperatures over 100°C.

In the isolation of N-acetylphenylalanine the product is isolated by extraction with ether. The product is easily extracted while the substrate is less soluble so using less than ten 50 ml quantities of ether will give false conversions to product.

Both α and β-methylcinnamic acids can be distilled directly after the solvent has been evaporated off rather than isolating out their sodium salts. Either method gives the same result.

Table 9. Product Isolation and Characterization.

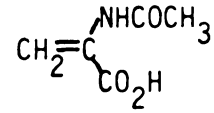
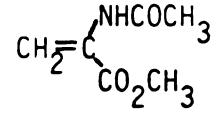
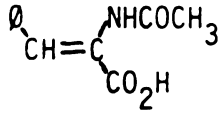
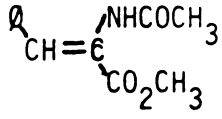
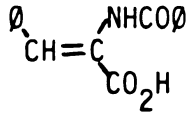
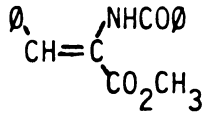
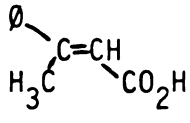
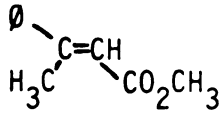
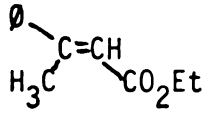
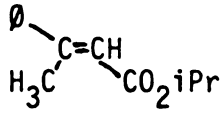
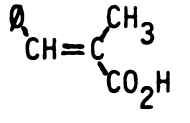
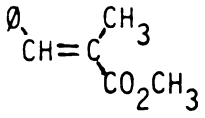
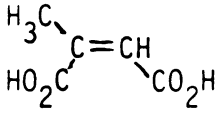
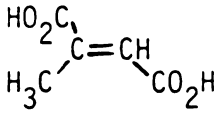
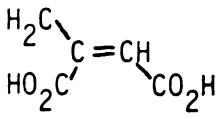
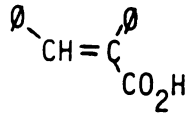
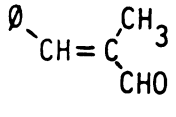
Substrate	Isolation	Characterization	
	1,2,3,4,9,7	1B,C	2B
	1,6,7	1B,C	2B
	1,2,3,4,9,7	1C	2C
	1,6,7	1C	2D
	1,2,3,4,9,7	1C	2D
	1,6,7	1C	2D
	1,2,3,5 or 1,5	1D	2E
	1,5	1D	2E
	1,5	1D	2E
	1,5	1D	2G
	1,2,3,5, or 1,5	1D	2C

Table 9. Continued.

Substrate	Isolation	Characterization	
	1,5	1D	2C
	1,2,3,4,9,7	1B	2C
	1,2,3,4,9,7	1B	2C
	1,2,3,4,9,7	1B	2C
	1,2,10,9	1C	2C
	1,5	1D	2C

Isolation

1. Evaporated off solvent.
2. Dissolved in aqueous NaOH (5 fold excess), filtered, acidified with HCl until acidic.
3. Evaporated off water.
4. Extracted into diethyl ether (10 x 50 ml).
5. Vacuum distilled.
6. Isolated by column chromatography using silica gel and ethyl acetate. Evaporated off ethyl acetate.
7. Vacuum dried.

Table 9. Continued.

8. Filtered.
9. Evaporated off ether.
10. Extracted into 100 ml diethyl ether.

Characterization

1. NMR in
   A. $CDCl_3$
   B. D_2O
   C. DMSO-d_6
   D. Neat
2. Rotation in
   A. Neat
   B. Water
   C. Ethanol
   D. Methanol
   E. Benzene
   F. Acetone
   G. Chloroform

Absolute Rotations

The best value of the absolute rotation for each substrate is always subject to change. The values currently acceptable and the ones used are listed in Table 10.

Table 10. Absolute Rotations of Products.

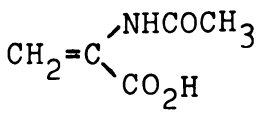
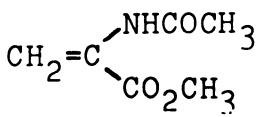
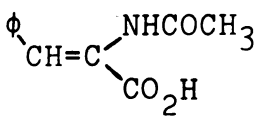
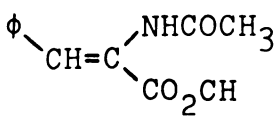
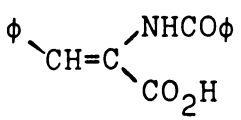
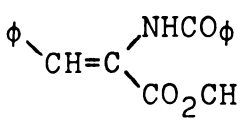
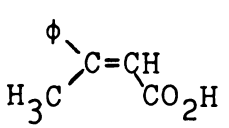
Substrate	Specific Rotation			Product
	+66.5	R	(c=2,H_2O)[34]	N-Acetylalanine
	-91.7	S	(c=2%, H_2O)[35]	N-Acetylalanine, Methyl ester
	+47.4	S	(c=1,EtOH)[36]	N-Acetylphenylalanine
	+15.9	S	(c=2,MeOH)[37]	N-Acetylphenylalanine, Methyl ester.
	-40.3	S	(c=1,MeOH)[38]	N-Benzoylphenylalanine
	-45.3	S	(c=1.3,MeOH)[38]	N-Benzoylphenylalanine, Methyl ester
	+52.3	S	(benzene)[40]	3-Phenylbutanoic acid

Table 10. Continued.

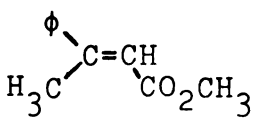
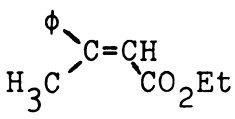
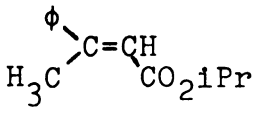
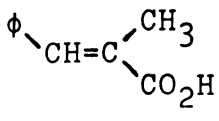
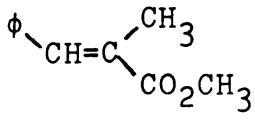
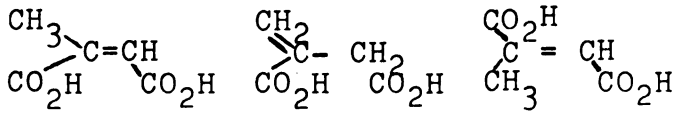
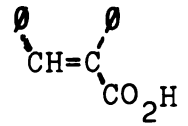
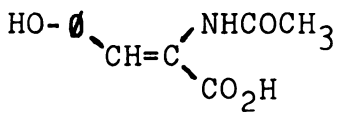
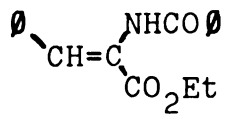
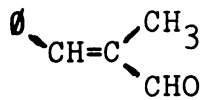
Substrate	Specific Rotation			Product
	-38	R	Neat[41]	3-Phenylbutanoic acid, Methyl ester
	+45	S	(benzene)[42]	3-Phenylbutanoic acid, Ethyl ester
	+27.74	S	Neat,corrected[43]	3-Phenylbutanoic acid, isoPropal ester
	+17.87	S	(c=5.034,EtOH)[44]	2-Methyl-3-phenyl propanoic acid
	+26.75	S	Neat[45]	2-Methyl-3-phenyl propanoic acid, methyl ester
	+17.09	R	(c=4.41,EtOH)[46]	α-Methylsuccinic acid
	+133.7 +127	S S	(c=.537 Acetone)[47] (c=1, EtOH)	2,3-Diphenylpropanoic acid

Table 10. Continued.

Substrate	Specific Rotation	Product
	+51.5 S (c=1,MeOH)[38]	N-Acetyltyrosine
	-42.7 S (c=1,MeOH)[38]	N-Benzoylphenylalanine ethyl ester
		2-Methyl-3-phenyl propanal

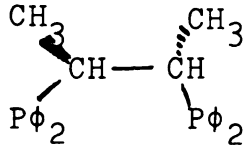
CHAPTER II

The (2S,8S)-2,8-Bisdiphenylphosphinomethyl-1,7-dioxaspiro[5.5]undecane or S,S-SPIPHOS CATALYST SYSTEM

INTRODUCTION

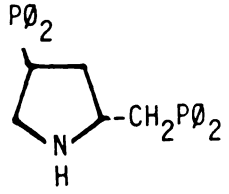
Research in asymmetric hydrogenation has expanded at an exponential rate. The mechanism of such reactions has been investigated by deuteration studies, by complicated phosphorus NMR techniques, and by crystal structure determinations of possible intermediates. There is evidence for at least three general reaction mechanisms, many variations of the form of reaction intermediates, and considerable debate over the step controlling optical induction. The fine details of asymmetric hydrogenation will take some time to investigate due to the wide selection of catalysts, substrates, and especially, reaction conditions.

A second generation of asymmetric hydrogenation catalysts has started. Bosnich has used S,S-CHIRAPHOS[10] to

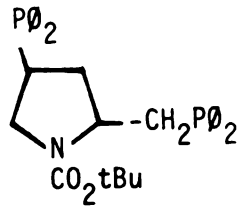
S,S-CHIRAPHOS  7

hydrogenate 10 different amino acid precursors, all in over 80% enantiomeric excess. N-Acetylleucine and N-acetylphenylalanine were isolated in complete optical

purity. Achiwa's PPM and BPPM catalyst systems[11] can achieve extremely high inductions not only with the amino acid precursors, but also many other prochiral substrates.



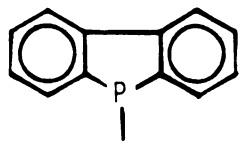
PPM
8

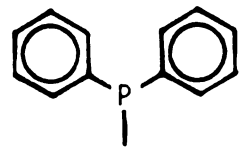


BPPM
9

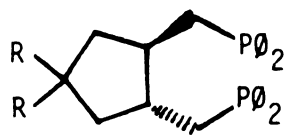
It would be desirable to custom-build a chiral ligand and catalyst to reduce a particular substrate or group of substrates at a reasonable rate and in very high optical yield. An understanding of the mechanism(s), which is under active examination by many groups, is an important part in meeting this goal. Another approach to this problem is to examine the structural and conformational differences between ligands and to determine how these affect the optical induction.

Many structural variations of DIOP have been made, since it is an effective ligand, well-studied, and commercially available. Substitution with methyl groups at the meta position on each aromatic ring increased the optical yield to 90% from 80% for a DOPA precursor.[48] Substitution of methyl groups at one or two ortho positions on each aromatic ring decreased the optical yield.





Using a phosphole derivative rather than a diphenylphosphine group also proved less effective.[48,49] Changing the remote gem-methyl groups in DIOP gave essentially the

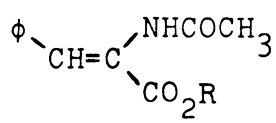


R = H,Ph

R = $(CH_2)_5$

same results as DIOP itself.[48]

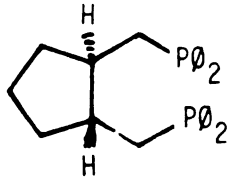
Glaser et al. used DIOP to hydrogenate a series of Z-α-acetamidocinnamate esters with optical yields of 69-77%. Increasing the size of the ester increased the optical yield with the exception of the 1-adamantyl ester which underwent Z to E isomerization.[37,50]

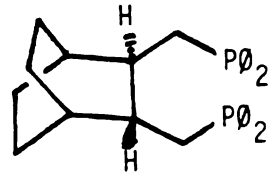


R = CH_3,Et,i-Pr,t-Bu,1-Adamantyl

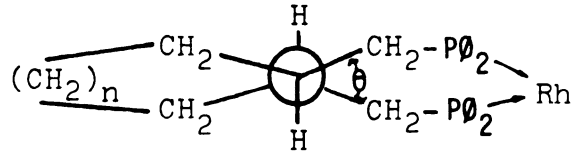
The acetonide ring in DIOP has been replaced by carbon ring systems. These ligands formed catalysts which gave 63-80% enantiomeric excesses with N-α-acylamidoacrylic

acid substrates.[48]



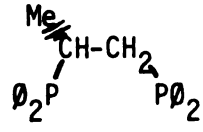


The cyclobutane and cyclohexane analogs of DIOP have also been made. N-Acetylphenylalanine has been made with increasing optical yields as the torsional angle increased within the seven membered chelate ring incorporating the rhodium.[9]

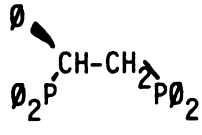


n = 0,1,2

Bosnich et al.[51] reported R-PROPHOS,[25] which yielded catalysts that reduced many amino acid precursors in the 90% optical yield range or better. R. B. King et al. reported[52] a ligand similar to R-PROPHOS with a phenyl group at the chiral center 26. Optical yields using this ligand were in the low 80% enantiomeric excess range.



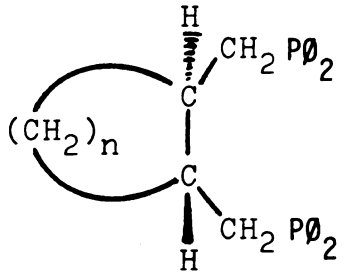
R-Prophos 25



26

It is generally accepted that the high stereoselectivities found in DIOP and similar systems are due to the conformational rigidity caused by the transfused ring in these systems. High induction in systems such as S, S-CHIRAPHOS and R-PROPHOS are attributed to a rigid chelate. In these two systems the smaller chelate size serves to increase the induction.

In a very recent study[53] different prochiral substrates were hydrogenated with eight catalyst systems derived from DIOP, in which the acetonide ring of DIOP was replaced with a hydrocarbon chain. The concept of the rigid chelate

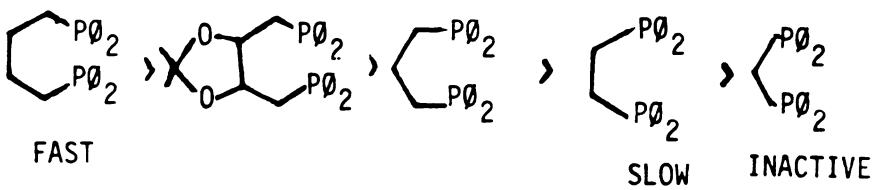


n = 1,2,3,4

inducing the high optical yields was pushed to the limits by including a three membered hydrocarbon chain and using a variety of substrates. Recent results by P. Aviron-Violet reported in a private communication[9] to B. R. James were confirmed; higher optical yields were realized by decreasing the hydrocarbon ring size from n = 4 to n = 2 for Z-α-acetamidocinnamic acid. However, n = 2 or 4 generates the R enantiomer, while n = 3 forms the S isomer. Going

to the even more rigid n = 1 hydrocarbon ring severly decreases the optical yield obtained. In general, the best overall system for obtaining high enantiomeric excesses is when n = 2, except for Z-α-acetamidoacrylic acid which is reduced in high optical yields when n = 3.

The effects of changes in the chelate ring size of bidentate phosphines in the hydrogenation of α-acetamidocinnamic acid has also been studied[54] to compare reaction rates with that of DIOP. As the chelate ring size decreased from seven to four, the rates also decreased; and

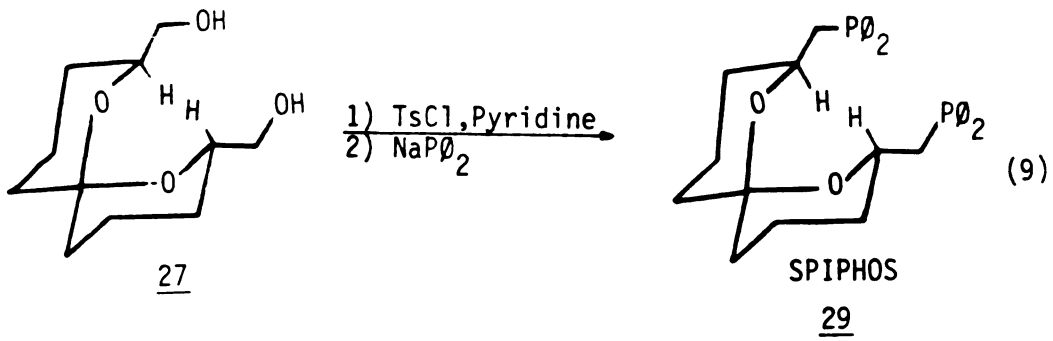


when the chelate ring size increased to nine the rate again dropped. Some of the best-known catalysts today form a five-membered chelate ring.

Achiwa's ligands PPM and BPPM should exhibit a great deal of mobility and form a seven membered chelate ring. A recent analysis[55] of this active catalyst system by ^{31}P NMR revealed two conformations present in solution. The prochiral substrate appears to coordinate with only one of these conformations.

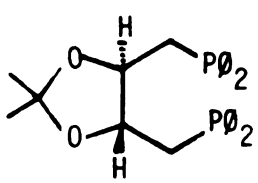
A new chiral ligand was recently synthesized from

(2S,8S)-2,8-bishydroxymethyl-1,7-dioxaspiro[5.5]undenane 27 and used in asymmetric hydrogenation catalysis. The

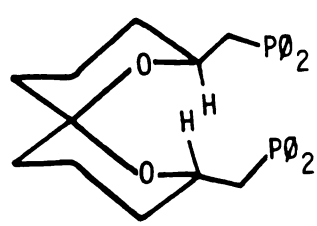


27 SPIPHOS 29 (9)

starting spiro compound was generously donated by D. A. Evans.[33] The spiro phosphine, nicknamed SPIPHOS 29, should have a great deal of conformational flexibility when used as a catalyst. This ligand is electronically very similar to DIOP and has the same effective phosphorus to phosphorus distance.



DIOP 2



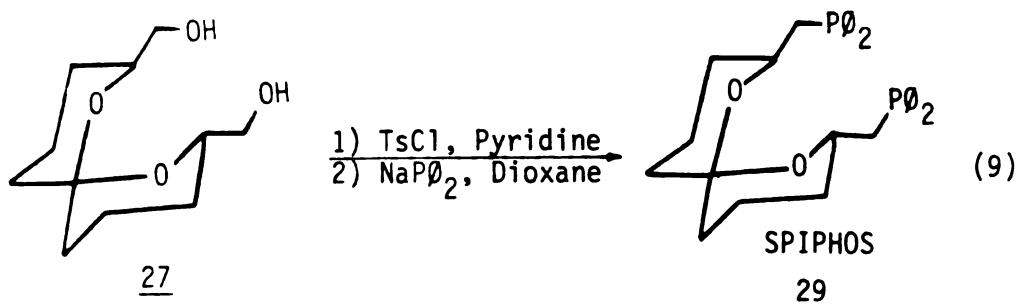
SPIPHOS 29

In this study, the main difference between DIOP 2 and SPIPHOS 29 is the degree of conformational mobility. Other comparisons made to study this effect either changed the electronic nature of the phosphine or changed the effective phosphorus to phosphorus distance by torsional strain in carbocyclic rings.

RESULTS AND DISCUSSION

Preparation of Chiral SPIPHOS 29

Two attempts were made to prepare SPIPHOS from (2S,8S)-2,8-bishydroxymethyl-1,7-dioxaspiro[5.5]undecane 27.



27 29 (9)

The preparation of the bidentate phosphine from the dialcohol is a fairly routine[8] synthesis. The dialcohol 27 is converted into the ditosylate 28 which is isolated and purified. The ditosylate was then reacted with a slight excess of sodium diphenylphosphide, freshly prepared from chlorodiphenylphosphine and sodium metal. This technique was tested first by preparing DIOP by the literature method. The generation of sodium diphenylphosphide can be difficult and could be a problem in the isolation of the desired product. DIOP is relatively easy to isolate.

The first attempt to make SPIPHOS by this method failed. Only two grams of starting alcohol was available,

the tosylate formed was an oil, and the final product was air oxidized on workup. The crude product is a sticky oil.

After obtaining a larger sample of the starting dialcohol 27 from D. A. Evans, a second attempt was made. The ditosylate 28 was isolated in 90.5% yield and dried well under vacuum. The sodium diphenylphosphide was made and the ditosylate was added. Stirring reaction time was lengthened. Great care was taken to isolate the product under purified argon. The crude product was recrystallized twice with dry oxygen free ethanol to form white needles melting at 99-100°C. The mass spectrum was taken and no parent peak observed. A second mass spectrum was taken run at much higher amplitude and this revealed the parent peak. Proton, carbon 13, and phosphorus 31 NMR confirmed the unoxidized structure. The ligand is oxidized in solution, but stable to the air when dry.

Optical Purity of SPIPHOS 29

The specific rotation for the starting dialcohol supplied by D. A. Evans is reported at +69°. This was determined by proton NMR analysis of diastereomeric ester derivatives. The rotation value sent along with the sample by D. A. Evans was 60.5°; however, our measurement showed the rotation to be 67.84° (approximately 98% optically pure). D. A. Evans also reports a melting point of an

earlier sample of the dialcohol at 92-96°C, whereas the sample received melted at 54-56°C after the oil crystallized.

In the preparation of SPIPHOS at no time was heat supplied to the chiral materials. Assuming no racemization occurred, the ligand should be about 98% optically pure.

Preparation of an Active Catalyst

The catalyst was made *in situ* by adding one equivalent of SPIPHOS to one-half equivalent of $[Rh(cyclooctene)_2Cl]_2$ or $[Rh(cyclooctadiene)Cl]_2$ in a three-to-one mixture of dry, oxygen-free ethanol and toluene. A deep yellow color resulted. The prochiral substrate, Z-acetamidocinnamic acid, along with 3 equivalents of triethylamine per equivalent of substrate were added and the system put under hydrogen. No hydrogen uptake occurred at 1 atmosphere of hydrogen. Hydrogenation was tried at 40 psi of hydrogen in a Parr apparatus but no product was detected. Using a high-pressure autoclave, hydrogenation was found to occur at 1000 and 1332 psi of hydrogen. The optical yields in both cases were similar (See Table 11).

Table 11. Required Pressure for In Situ SPIPHOS Catalyst. Hydrogenation of Z-Acetamidoacrylic Acid.

Hydrogen Pressure	Hydrogenation	Optical Yield
1 atmosphere	0	0
40 psi	0	0
1000 psi	9%	17%
1332 psi	60%	20%

Maximization of Chemical and Optical Yields as a Function of Temperature, Pressure, and Time

The effects of changing temperature, hydrogen pressure, or time can be very large in asymmetric hydrogenation. These three variables were changed while keeping the solvent, added triethylamine, hydrogen purity, substrate to catalyst ratio, ligand to rhodium ratio, and catalyst concentration constant. It would be rather impractical to maximize each substrate to all of these conditions so a typical amino acid precursor, Z-α-acetamidocinnamic acid, was studied (See Table 12). Three temperatures, three pressures, and two reaction times were chosen based on earlier screening experiments for catalytic activity.

The complete isolation of the products including the amount of conversion was done late in the study so it

Table 12. Effect of Temperature, Pressure, and Time on the SPIPHOS Catalyst System. Hydrogenation of Z-acetamidoacrylic Acid.

Optical Yield	Conversion %	Temperature (°C) 60°	25°	0°	Pressure (psi) 1600	1400	300	Time (Hrs) 30	15
47.6%	100%	x			x			x	
46.7	100	x			x				x
48.8	100	x				x		x	
46.0	100	x				x			x
47.0	100	x					x		x
48.0	100		x		x			x	
51.7	100		x		x			x	
54.1	100		x		x				x
47.1	100		x		x			2 Hours	
47.4	100		x			x		x	
47.0	100		x			x			x
51.4	100		x			x			x
48.3	100		x				x		x
41.3	100			x	x			10 Days	
34.4	86.7[1]			x	x			x	
42.1	84.2[1]			x	x				x
46.7	100			x		x		x	
40.0	79.4[1]			x		x			x
42.2	100			x			x		x
00.0	0		x		1 Atm.			8 Days	

Table 12. Continued.

Hydrogenation of Z-α-acetamidocinnamic acid and 3 equivalents of Et_3N. Solvent 3:1 ethanol:toluene. Substrate:catalyst 100:1 Ligand:rhodium 1:1.

[1]Stirring was not efficient due to bulky ice bath on autoclave.

[2]No hydrogen uptake was observed with or without base.

was not realized complete conversion was occurring in 15 hours. The reaction is completely done in two hours. In three cases, all at zero degrees, the position of the ice bath made the stir rate very slow resulting in low conversion. Since the reaction appears to be over in 15 hours, the 30 hour reaction times should give the same results as the 15 hour reaction times and can be averaged together. (See Table 13).

The effect of hydrogen pressure on optical yield is very small if at all. The optical yield was only 3% higher at 1600 psi of hydrogen over the optical yield at 300 psi. No hydrogenation was found at 1 atmosphere of hydrogen either when the catalyst was first being screened or when it was retested. No hydrogenation occurred at 40 psi during the catalyst screening.

The temperature effect on optical yield is small but larger than any pressure effect. The optical yield increased 17% from zero to room temperature and then decreased by 5% increasing the temperature to 60°C. One would expect more stereoselectivity at lower temperatures rather than lower optical induction. A conformational isomer of the active catalyst may be competing at lower temperatures to give a lower optical yield or a competitive mechanism may be operating.

Table 13. Averaged Temperature and Pressure Effects on the SPIPHOS Catalyst System. Hydrogenation of Z-acetamidoacrylic acid.

Average Optical Yield	Temperature (°C) 60	25	0	Pressure (psi) 1600	1400	300	Reaction Number(s)
47.15	x			x			133,134
47.4	x				x		135,136
47.0	x					x	138
51.3		x		x			129,131,132
48.6		x			x		128,130,137
48.3		x				x	144
41.7			x	x			139,140
43.35			x		x		142,146
42.2			x			x	143

Average Values

Temperature	60°	47.22% ee
	25°	49.71% ee
	0°	42.46% ee
Pressure	1600 psi	47.37% ee
	1400 psi	46.76% ee
	300 psi	45.83% ee

General Catalysis Conditions

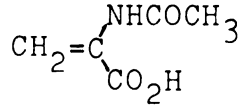
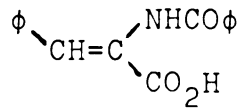
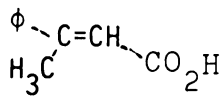
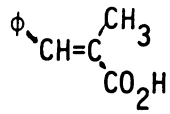
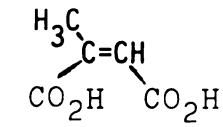
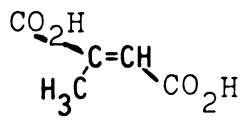
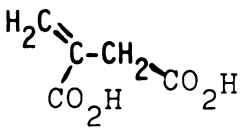
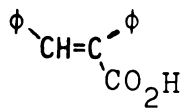
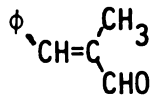
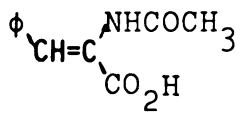
The optimum conditions for Z-α-acetamidocinnamic acid were used with all other substrates. The reaction times were cut back to 2 hours in some cases, but no longer than 10 hours. After doing the ester hydrogenations in toluene where some black residue was observed in the glass liner, the reactions were rerun in the three to one ethanol to toluene mixture. All substrates were soluble in this mixture (See Table 21).

Effect of Added Et_3N

The effect of adding three equivalents of triethylamine to the acid substrates was large. Not only the optical, but also the chemical yields were effected. In each case the use of base increased the rate. Usually, adding base tends to increase the optical yield. In this case it increased in 5 substrates and decreased in 4 substrates. The most remarkable effect the base had was to change the preferred enantiomer in four out of nine substrates. There is no obvious trend which would predict which substrate would be expected to give a different enantiomer with added base (See Table 14).

This base effect also was found when the cationic form of the catalyst was used. The cationic catalyst system will be discussed later.

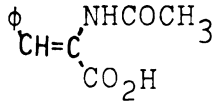
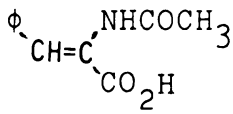
Table 14. Effect of Added Et_3N on the SPIPHOS System.

Substrate	Et_3N	No Base
	R 3.8% [1] (100%)	R 13.3% (100%)
	S 23.5% (100%)	R 9.9% (100%)
	R 31.7% (100%)	S 41.8% (100%)
	S 4.0% (100%)	S 5.4% (100%)
	S 7.5% (100%)	- 0.0% (83%)
	R 23.7% (100%)	R 22.0% (100%)
	S 13.7 (100%)	S 15.2% (100%)
	R 26.6% (100%)	S --- (low)
	-.4° (40%)	---
	S 54.1% (100%)	R 39.3% (100%)

Using catalyst generated *in situ*.

[1]For example: configuration R, 3.8% ee, (100%) conversion

Table 14. Continued.

Substrate	Et_3N	No Base
	S 50.4% (100%)	R 34.8% (31.4%)
	S 53.4% (100%)	R 42.2% (100%)

Using a cationic form of the catalyst.

Amino Acid Precursors

The amino acid precursors, including the methyl esters, were hydrogenated in fairly low optical yields compared to the extremely high values obtained today. The N-acetylphenylalanine was reduced in 54% optical yield when base was used but this substrate also was the one used to optimize the reaction conditions (See Table 15.).

Table 15. Asymmetric Hydrogenation of Amino Acid Precursors Using the In Situ SPIPHOS System.

Substrate	R = H		R = CH_3
	Et_3N	No Base	
$CH_2=C(NHCOCH_3)(CO_2R)$	R 3.8%[1] (100%)	R 13.3% (100%)	R 29% (100%)
$\phi CH=C(NHCO\phi)(CO_2R)$	S 23.5% (100%)	R 9.9% (100%)	R 7.6% (100%)
$\phi CH=C(NHCOCH_3)(CO_2R)$	S 54.1% (100%)	R 39.3% (100%)	R 33.8% (100%)

[1]For example: R configuration, 3.8% ee, 100% conversion.

Acid vs Ester Substrates

The esters of five prochiral substrates were tested along with a series of esters of β-methylcinnamic acid. In each case the preferred enantiomer of the acid without any base was also the preferred enantiomer of the ester. The optical yields of the esters ranged from much better for the methyl ester of α-methylcinnamic acid to much worse for the methyl ester of β-methylcinnamic acid.

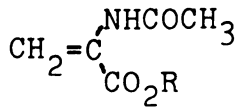
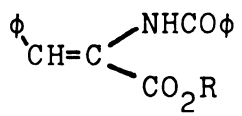
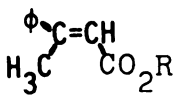
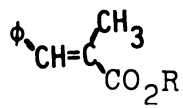
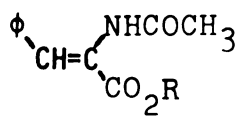
The methyl, ethyl, and isopropyl esters of β-methylcinnamic acid were reduced. The ethyl ester gave a fairly large optical yield of 52% considering that extra functionality to coordinate to rhodium is lacking with this substrate (See Table 16).

Formation of Cationic Catalyst

The cationic SPIPHOS system was made by mixing the ligand and rhodium complex in methanol with an excess of sodium tetrafluoroborate. The catalyst salt falls out of solution and was dried under a vacuum.

The cationic catalyst was tested with the N-α-acetylcinnamic acid substrate under conditions favorable for the *in situ* catalyst. It was active and gave approximately the same optical yields as the in situ catalyst regardless if base was present or not. The in situ catalyst was not active at 1 atmosphere of hydrogen pressure. The cationic

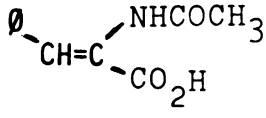
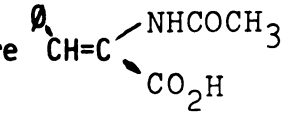
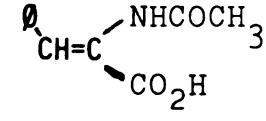
Table 16. Asymmetric Reduction of Prochiral Acids vs. Esters.

Substrate	R = H		R = CH_3	R = Et	R = iPr
	Et_3N	No Base			
	R 3.8%[1] (100%)	R 13.3% (100%)	R 29% (100%)	---	---
	S 23.5% (100%)	R 9.9% (100%)	R 7.6% (100%)	---	---
	R 31.7% (100%)	S 41.8% (100%)	S 9.3% (45%)	S 52% (100%)	S 30.4% (32%)
	S 4.0% (100%)	S 5.4% (100%)	S 61.7% (68.3%)	---	---
	S 54.1% (100%)	R 39.3% (100%)	R 33.8% (100%)	---	---

[1]For example: R configuration, 3.8% ee, 100% conversion.

catalyst did hydrogenate at one atmosphere of hydrogen, but very slowly. The optical yield at the low pressure was just a little lower than that at high hydrogen pressure. Since the optical yields were similar between the in situ and the cationic catalyst with the test substrate and the cationic system was very slow at low hydrogen pressures, then there was no real advantage in further testing of this system (See Table 17).

Table 17. The In Situ vs Cationic SPIPHOS Systems.

	Substrate	Et_3N	No Base
In Situ		S 54.1%[1] (100%)	R 39.3% (100%)
Cationic Low Pressure		S 50.4% (100%)	R 34.8% (31.4%)
Cationic High Pressure		S 53.4% (100%)	R 42.2% (100%)

[1]For example: S configuration, 54.1% ee, 100% conversion.

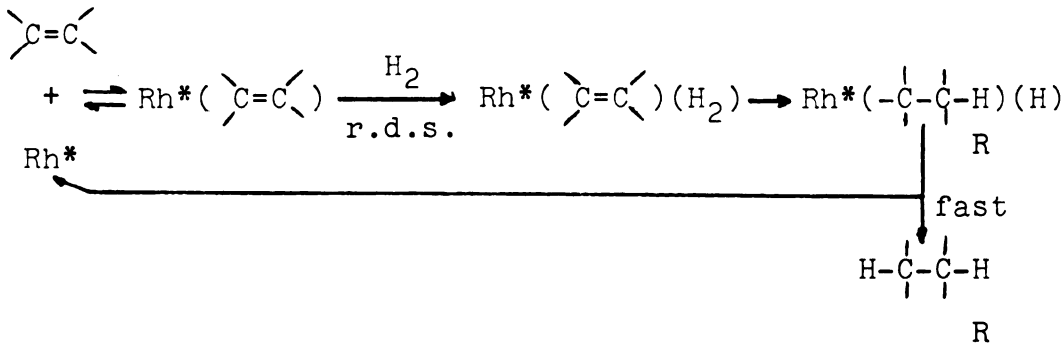
The cationic form of the catalyst was not soluble in toluene, but only in the ethanol-toluene mixture. In toluene it did not appear to dissolve and would deposit a black residue assumed to be elemental rhodium at high hydrogen pressure.

Pressure Effects on the Catalyst Systems

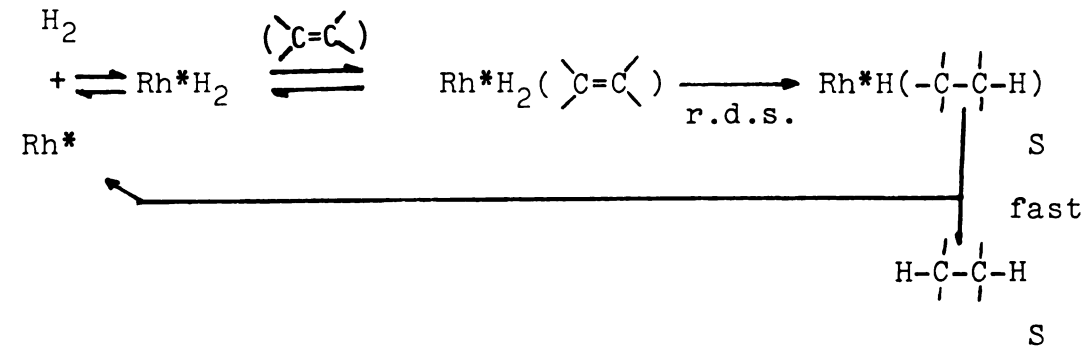
I. Ojima *et al.* have restudied[24] the BPPM, DIOP, and DIPAMP systems with and without triethyl amine and both the *in situ* as well as the cationic catalysts. They found a remarkable pressure effect on optical yields. This pressure effect was inhibited by using triethylamine. Competitive mechanisms were proposed (See Figure 3). Mechanism A which has been supported by Halpern[56] would be favored under low hydrogen pressure. Mechanism B would be favored under high hydrogen pressure. The unusual effect of triethylamine may be explained by the generation of the carboxylate anion of the substrate which reacts with the rhodium catalyst to give the alkene complex much faster than the non-ionized form. Both the *in situ* and cationic system behaved similarly.

Examining the pressure effects with the SPIPHOS system it appears there is no large change in optical yield (See Table 18). The base effect is very large in some cases, changing from one enantiomer to another. This may represent a complete change in mechanism or merely be a steric

Mechanism A



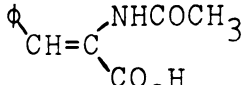
Mechanism B



(r.d.s. = rate determining step)

Figure 3. Possible Mechanisms for Asymmetric Hydrogenation Using Chiral Rhodium Catalysts.

Table 18. Pressure Effects on the In Situ vs Cationic SPIPHOS Catalyst System.

Substrate 		Et_3N	No Base
In Situ	1 atm	------ (0%)	------ (0%)
In Situ	100 atm	S 54.1% [1] (100%)	R 39.3% (100%)
Cationic	1 atm	S 50.4% (100%)	R 34.8% (31.4%)
Cationic	100 atm	S 53.4% (100%)	R 42.2% (100%)

[1]For example: S configuration, 54.1% ee, 100% conversion.

consequence of the carboxylate. One way to accommodate the dual mechanisms is to assume some substrates go by only one mechanism, some by the other. Those which are hydrogenated by Mechanism B can be altered to Mechanism A by adding base. Those that are hydrogenated by Mechanism A continue to follow this mechanism with added base.

The large pressure effects would be expected only by those substrates usually occurring by Mechanism A, but able to be reduced also by Mechanism B at high hydrogen pressure. This may explain why Ojima found this pressure dependence only with selected substrates.

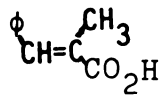
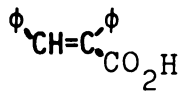
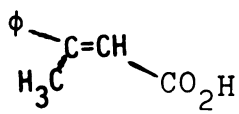
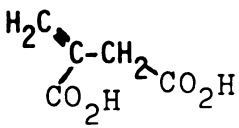
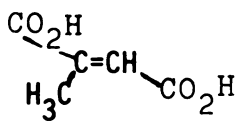
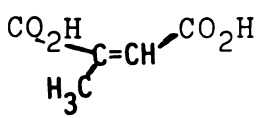
Comparison with Other Catalyst Systems

The hydrogenation results of six substrates using SPIPHOS and five other catalyst systems are listed in Table 18. Even the well known DIOP does not give high induction with these substrates. The NMDPP, MDPP, and CAMPHOS systems give very low optical yields with amino acid precursors. SPIPHOS in general gives reasonable optical yields in comparison with other ligand systems. The highest optical induction of mesaconic acid to date is with the SPIPHOS system at 23.7% ee.

Bosnich *et al.* have not reported the use of either R-Prophos[51] or S,S-Chiraphos[10] with anything other than amino acid precursors. The hydrogenation of the esters of the amino acid precursors also have not been cited in the literature. It would be very interesting to see what these catalysts would do with the substrates in Table 19.

The chiral synthesis of amino acids is important commercially. Several amino acid precursors and their esters are listed in Table 20. Both of Bosnich's catalyst systems, Knowles' ACMP catalyst, and Kagan's DIOP system are listed along with the SPIPHOS system's results. It is clear that the SPIPHOS system gives lower optical yields in each case. The best value was obtained with N-acetylphenylalanine which happened to be the hydrogenation which was optimized.

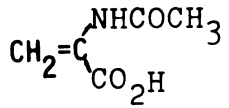
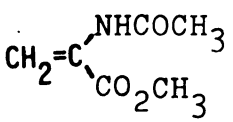
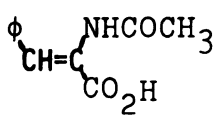
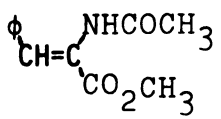
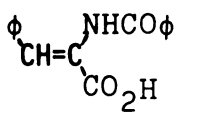
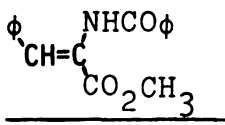
Table 19. Comparison of SPIPHOS System with Other[5] Asymmetric Hydrogenation Catalysts. Values indicate % ee and Configuration.

Substrate	ACMP	DIOP	NMDPP	MDPP	CAMPHOS	SPIPHOS[4]	
	12(R)	25(S)	60(R)	17(S)	15(R)	4(S)[2]	5.4(S)[3]
	24(S)	15(R)	34(S)	27OR)	12(S)	26.6(R)	low(s)
	37(S)	14(R)	62(S)	1(S)	9.7(S)	31.7(R)	41.8(S)
	-----	-----	8.1(R)	18(R)	11(R)	13.7(S)	15.2(S)
	-----	-----	5.9(R)	7.2(S)	1.8(R)	23.7(R)	22(R)
	-----	-----	-----	-----	-----	7.5(S)	±

[1]All reactions made at 300 psi of hydrogen pressure, room temperature, with three equivalents of Et_3N per substrate. Includes base.

[2]Three equivalents of Et_3N used. [3]No base was used. [4]SPIPHOS hydrogenations were done at about 1500 psi, room temperature, from 3 to 24 hours. [5]Date taken from Ref. 6.

Table 20. Comparison of SPIPHOS and Other Systems with[6] Amino Acid Precursors. Values Indicate % ee and Configuration.

Substrate	ACMP[1]	DIOP[1]	SPIPHOS[2]		PROPHOS[3,5]	CHIRAPHOS[3,5]
	60(?)	73(R)	3.8(R)[3]	13.3(R)[4]	90(S)	91(R)
	-----	-----	29(R)	-----	-----	-----
	85(?)	63(R)	54.1(S)	39.3(R)	90(S)	89(R)
	-----	55(R)	33.8(R)	-----	-----	-----
	85(?)	64(S)	23.5(S)	9.9(R)	91(S)	95(R)
	-----	-----	7.60R)	-----	-----	-----

[1]300 psi hydrogen pressure, r.t., with Et_3N. [2]Approx. 1500 psi hydrogen pressure, r.t
[3]No base. [4]Three equivalents of Et_3N per substrate. [5]Table taken from References 4, 5, 6, 10, 33, 51.

Almost every catalyst system listed in Tables 18 and 19 were used under different reaction conditions so any comparison may be meaningless. However, if this is disregarded, DIOP and SPIPHOS systems could be compared. Looking at Table 18 it appears that a rigid chelate may not always be necessary since the SPIPHOS system gave higher optical yields in 2 of 3 cases. Looking only at the amino acid precursors in Table 20, the opposite conclusions could be drawn.

Conclusions

The lock and key concept in optical induction certainly should apply in asymmetric hydrogenation. It would be foolish to assume one lock would fit all keys, or one key fit all locks. Each catalyst system must be stereoselective to a particular prochiral substrate.

Some degree of steric interaction must be present to have an optical induction between catalyst and substrate. The bulk steric interaction does not cause optical induction; it is the difference between the steric interaction of the chiral catalyst and the two faces of the prochiral olefin. Therefore, altering the rigidity of the ligand, the torsional strain or size of the chelate ring, or the total bulk of the ligand may not change stereoselectivity at all. The structural change of the catalyst must alter the preference for the faces of the alkene to

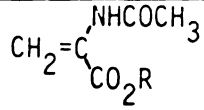
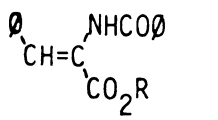
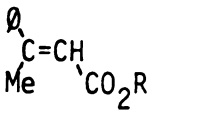
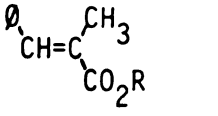
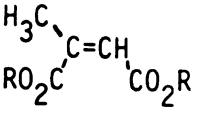
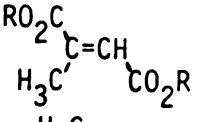
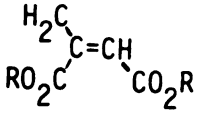
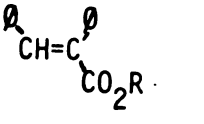
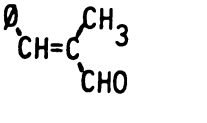
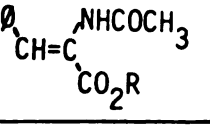
alter the optical yield.

Changing the steric bulk of the ligand can and often does change the chemical properties of the catalyst. For example: changing the chelate size can grossly change the reactivity of the catalyst for hydrogenation.

The optical induction is caused by the difference between the interactions of the catalyst and the two prochiral faces of the substrate. Steric interactions are always involved in this induction, but other interactions such as hydrogen bonding, multiple coordination, and chemical addition also may occur.

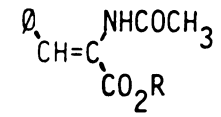
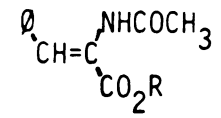
A new catalyst system based on the bidentate phosphine ligand SPIPHOS was synthesized and developed to hydrogenate prochiral alkenes to optically active products. The catalyst was active at high hydrogen pressures with a reasonable reaction turnover rate. The optical induction was slightly sensitive to temperature and greatly altered by addition of base to the system. The optical yields using amino acid precursors were not very high, ranging from 4 to 54% enantiomeric excess. Fairly good induction was found in other classes of prochiral substrates where high optical yields are not common.

Table 21. Asymmetric Hydrogenation Using the SPIPHOS Catalyst System. Values Indicate Configuration, % ee, and % Conversion.

Substrate	R = H Et_3N	R = H No Base	R = CH_3	R = Et	R = iPr
	R 3.8%[1] (100%)	R 13.3% (100%)	R 29% (100%)	------	------
	S 23.5% (100%)	R 9.9% (100%)	R 7.6% (100%)	------	------
	R 31.7% (100%)	S 41.8% (100%)	S 9.3% (45%)	S 52% (100%)	S 30.4% (32%)
	S 4.0% (100%)	S 5.4% (100%)	S 61.7% (68.3%)	------	------
	S 7.5% (100%)	- 0.0% (83%)	------	------	------
	R 23.7% (100%)	R 22.0% (100%)	------	------	------
	S 13.7 (100%)	S 15.2% (100%)	------	------	------
	R 26.6% (100%)	S --- (low)	------	------	------
	-.4° (40%)	------	------	------	------
	S 54.1% (100%)	R 39.3% (100%)	R 33.8% (100%)	------	------

Catalyst generated in situ. Hydrogenation at 100 Atm.

Table 21. Continued.

Substrate	R = H		R = CH_3	R = Et	R = iPr
	Et_3N	No Base			
	S 50.4% (100%)	R 34.8% (31.4%)	------	------	1 Atm H_2
			Cationic Complex		
	S 53.4% (100%)	R 42.2% (100%)	------	------	100 Atm H_2

[1] R enantiomer predominate, 3.8% optical yield, 100% conversion.

EXPERIMENTAL

Instrumentation

The same instrumentation listed in the experimental section of Chapter 1 was used. The low pressure hydrogenations were carried out using gas burets attached to the department's hydrogenation apparatus.

Reagents and Solvents

The following code (a) is used for the various sources of reagents and solvents which are not already listed in the Experimental portion of Chapter 1:

(a)

1. Mallinckrodt, Inc.
2. Aldrich Chemical Company, Inc.
3. Generously donated by Dr. D. A. Evans of the Laboratories of Chemistry, California Institute of Technology, Pasadena, CA

The following code (b) is used for the various treatments of reagents and solvents prior to use:

(b)

(A) Vacuum distilled and stored under an inert atmosphere.

(B) Distilled under an inert atmosphere from sodium or potassium benzophenoneketyl. Stored under an inert gas.

(C) Dried over 4 Å molecular sieves. Degassed and stored under an inert atmosphere.

(D) Dried under vacuum one day.

(E) Used without further purification.

(F) Rinsed in pentane to remove excess oil.

Material	Source[a]	Treatment[b]
(2S,8S)-2,8-bishydroxymethyl-1,7-dioxaspiro[5.5]undecane	3	D
p-Toluenesulfonyl chloride	2	E
Pyridine	1	A
Sodium metal	2	F
Dioxane	2	B

All other reagents and solvents are listed in Chapter 1.

Preparation of Substrates

The following cinnamic esters were prepared according to the procedures listed in Chapter 1: methyl α-methylcinnamate, methyl β-methylcinnamate, ethyl β-methylcinnamate, and isoPropyl β-methylcinnamate.

The methyl esters of α-acetamidocinnamic acid, α-acetamidoacrylic acid, and α-benzamidocinnamic acid were prepared by the procedures reported in Chapter 1.

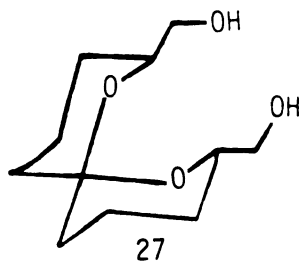
All other prochiral substrates were used without further purification as received from the commercial sources.

Preparation of SPIPHOS

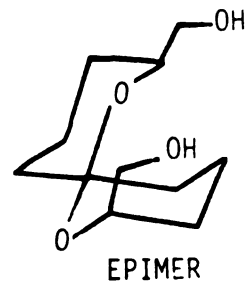
Characterization of (2S,8S)-2,8-bishydroxymethyl-1,7-Dioxaspiro[5.5]undecane 27

The crude dialcohol 27 was prepared by R. A. Whitney and reported in November of 1977 to D. A. Evans. The crude yellow oil was purified on neutral alumina (activity III). The dialcohol is a rigid structure with only a C_2 axis of symmetry. It is not in equilibrium with its epimer at room temperature.

The crude dialcohol was vacuum dried one day. The mass spectrum gave the following data: m/e (relative intensity) 216(5), 185(69), 131(69), 113(100), 85(260),



27



EPIMER

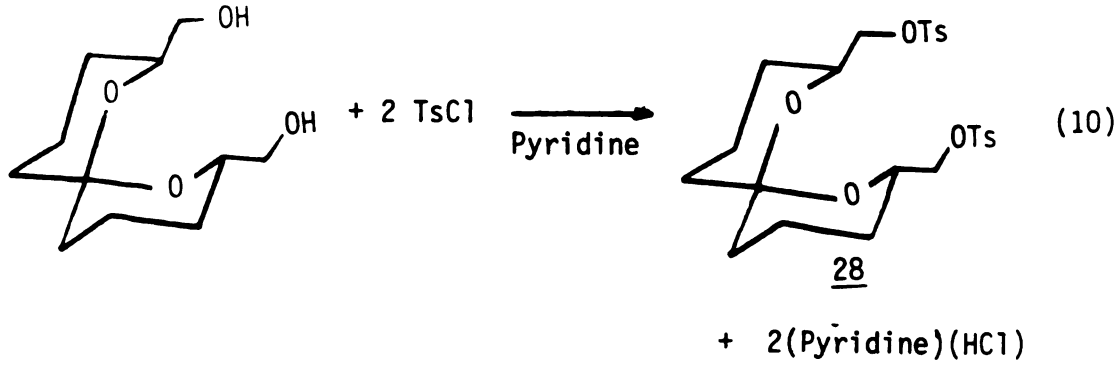
83(400). The infrared spectrum agreed with that reported by Whitney: ($CHCl_3$) cm^{-1} 3590, 3200-3600, 3000, 2940, 2870, 1450, 1430, 1380, 1370, 1280, 1200-1230, 1155, 1080, 1040, 1010, 980. The 60 MHz proton NMR in $CDCl_3$ gave the following signals: ppm (area), 1.2-1.8 p(broad multiplet, 12H), 2.5-2.6 (singlet,2H), 3.3-3.8 (multiplet,6H). The 20 MHz carbon 13 NMR in $CDCl_3$ gave the following signals: ppm (area) 18.3(2), 26.45(2), 35.29(2), 66.23(2), 69.84(2), 96.09(1). The dialcohol had a rotation of $[a]_D^{rt}$ = +67.84° (c=1.092,$CHCl_3$). This corresponds to an optical purity of 98%. Whitney had reported a rotation of +60.5° for this same sample.

The small amount of oily dialcohol which was not used to make SPIPHOS crystallized on standing one month. The white solid still remained sticky.

Preparation of (2S,8S)-2,8-bistosylmethylene-1,7-dioxaspiro[5.5]undecane 28

To a 250 ml round bottom flask containing 7.055 grams

of (2S,8S)-2,8-bishydroxymethyl-1,7-dioxaspiro[5.5]undecane 27 was added a stir bar and 150 ml of dry freshly distilled pyridine. The mixture was stirred until the oily dialcohol had been dissolved. After cooling the pyridine solution in an ice bath for ten minutes, 13.5 g of p-toluenesulfonyl chloride was added in 4 portions. Stirring was continued one hour before warming to room temperature where it was stirred an additional 24 hours.



After 24 hours a white precipitate started forming in the yellow-brown solution. Stirring for an additional 12 hours resulted in more fine white precipitate.

The entire solution was poured into an ice water mixture in a one liter erlenmeyer. Dilute (10%) hydrochloric acid was slowly added until the solution became acidic to pH paper. The acidic solution was extracted with diethyl ether (4 x 100 ml) and the ether layers combined. The ether layer was washed with water (200 ml) and saturated sodium chloride solution (2 x 200 ml) before drying over

sodium sulfate for 30 minutes. The ether solution was filtered, distilled off, and the crude product dried under vacuum. A total of 15.488 g was isolated or 90.5% yield.

Characterization of (2S,8S)-2,8-bistosylmethylene-1,7-dioxaspiro[5.5]undecane 28

The crude tosylate was a thick sticky oil which started to form crystals. The crystals were too sticky to get a melting point. The mass spectrum gave the following: m/e (relative intensity) 524(1.7), 439(10.2), 352(18), 339(19.3), 285(72), 155(100). The infrared spectrum gave the following signals: 3600, 2950, 2880, 2200, 1610(s), 1500, 1470, 1450, 1370(s), 1200, 1180, 1105(s), 1005, 965, 915 cm^{-1}. The 60 MHz proton NMR in $CDCl_3$ gave the following data: shift ppm (area) 1.2-1.8 mul (12H), 2.5 sing (6H), 3.8-4.0 mul (6H), 7.2-7.8 quar (8H). The 20 MHz carbon 13 NMR in $CDCl_3$ gave the following signals: ppm (rel area), 17.87(37), 21.56(36), 26.31(38), 34.53(38), 67.08(46), 72.71(42), 96.26(23), 127.83(95), 129.82(100), 133.18(30), 144.70(32). Elemental analysis for $C_{25}H_{32}O_8S_2$ requires: C 57.3, H 6.1, O 24.4, S 12.2 found: C 54.88, H 6.24, O 27.64 (difference), S 11.54. The product had the following rotation: $[a]_D^{RT}$ = +10.46° (c=2.14,$CHCl_3$).

Preparation of Sodium Diphenylphosphide 30

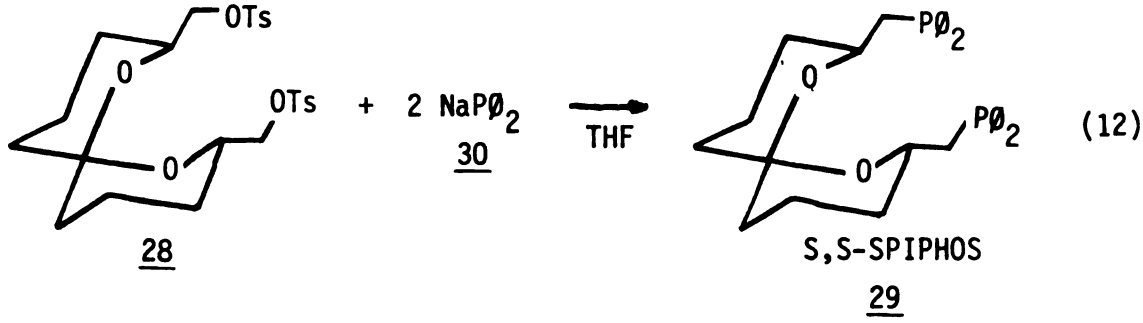
A one-liter three-necked flask was evacuated and filled with argon three times. Ten ml of chlorodiphenylphosphine and 100 ml of dry oxygen free dioxane were loaded into the flask while under argon. The system was degassed again before 7.5 g of small pieces of sodium metal were added under an argon flow. The sodium was rinsed in pentane before addition.

$$2Na^{\circ} + ClP\phi_2 \xrightarrow[\text{Dioxane}]{\Delta} NaP\phi_2 + NaCl \qquad (11)$$

The mixture was brought to a strong reflux which was maintained for 6 hours at which time a bright yellow solution existed with fine beads of molten sodium floating on top.

The dioxane solution was cooled to room temperature over one hour leaving the sodium diphenylphosphide 30 in solution as the bright yellow color indicated.

Preparation of SPIPHOS 29



28 (12) S,S-SPIPHOS 29

To the cooled solution of sodium diphenylphosphide 30 already described, 70 ml of dry oxygen free THF was added. This changed the color from a bright yellow to a yellow-orange. The ditosylate 28 (.02915 mol) was dissolved in 50 ml of dry oxygen free THF under an argon flow and then was added to the sodium diphenylphosphide 30 solution through an addition funnel over 2 hours. The color change was to a more reddish tint. The reaction mixture was stirred at room temperature under argon for 12 hours.

The THF and dioxane were removed by vacuum keeping the entire system under argon at all times. After 7 hours under vacuum (the dioxane clogs in the trap) most of the solvent had been removed. To the remaining yellow-orange slurry, 50 ml of dry oxygen free toluene was added. After stirring a few minutes, the mixture was filtered under argon. Clogging was a problem. Argon pressure and full vacuum on the sinstered glass filter tube did not help the filtration. A second filter tube was set up which was larger and a large celite mat was prepared with toluene and full vacuum. The orange solution was transferred into the large filter tube under an argon flow with a funnel. This tube also clogged, but slowly. Using a full vacuum to pull the solution through and stirring the celite mat every few minutes, the solution was filtered. The filtered solution was kept under argon and was a light yellow.

Both filter tubes were carefully cleaned with ethanol.

The red to orange sodium diphenylphosphide is quickly destroyed with the generation of heat. The excess sodium was in very small beads and was active. The entire apparatus smelled badly, probably due to diphenylphosphine, so all glassware was soaked in a peroxide solution before removing from the hood.

The crude product (17.9 g) was isolated by removing the toluene under vacuum and kept under argon. Recrystallizing this in dry oxygen free ethanol gave the first crop of white powder (7.927 g). A second crop of crystals was attempted, but only a thick smelly oil resulted. A column was attempted on neutral alumina using diethyl ether as the solvent on this oil. Twelve fractions were taken, but all were oils ranging from orange to clear. These fractions were combined. Another attempt to recrystallize was somewhat successful and a second crop was isolated. This may be fairly oxidized.

The product after one recrystallization had a melting point of 87-92° and was a fine white powder. The mass spectrum did not give the parent peak, but resembled the spectrum obtained in the first attempt to make SPIPHOS which was considered a failure. When the sensitivity of the spectrum was increased, the parent appeared at m/e 552. The main fragment is the loss of one diphenylphosphine group leaving m/e 367. The oxide at m/e 384 also appeared. The proton NMR and carbon 13 NMR seemed

reasonalbe as did the infrared spectrum. The elemental analysis for $C_{35}H_{38}O_2P_2$ requires: C 76, H 6.8, O 5.8, P 11.2; Found: C 73.52, H 6.8, O 8.92 (by difference), P 10.76. The oxide is probably present to some extent in this sample.

Since the material still melts over a five degree range, and the possibility of oxides is present, a second recrystallization was done.

A second recrystallization of SPIPHOS gave a first crop of white needles (5.0382 g) with a melting point of 99-100°, a second crop of off-white needles (1.2023 g) with a melting point of 86-100° - still a little wet, and a yellow oil (.9392 g) which formed crystals on standing one week. The first two crops would give a total overall yield of 39% of the very pure ligand.

Characterization of Recrystallized SPIPHOS 29

The recrystallized SPIPHOS ligand existed as white needles melting at 99-100°. The melting point remained constant after storing in the air for one month. The mass spectrum gave the following data: m/e (relative intensity), 552(1.1), 476(.3), 384(1.8), 367 (off scale), 351(4.0), 276(3.8), 271(1.8), 262(5), 253(3.2), 219(4.8). Lower sensitivity 367(5.4), 201(.2), 185(6.3), 165(.9), 45(7.7), 31(14.5). The infrared spectrum was taken in

KBr: 4000-2600 broad, 3050, 2870(s), 1920, 1875, 1800, 1570(s), 1460, 1415(s), 1370, 1175(s), 1010(s), 950(s) cm^{-1}. The 60 MHz proton NMR was taken in acetone-d_6 and gave the following: ppm (area), 1.2-1.6 broad (12H), 2.1 mul (2H), 3.8-4.0 broad (2H), 7-7.2 mult (21). The 20 MHz carbon 13 NMR also in acetone-d_6 was complicated and not well resolved in the aromatic region: ppm (area) 18.65(11), 35.21(12), 68.5(4), 67.62(5), 96.5(8), 128.34 and 128.57(43), 132.11 and 132.69 and 133.27 and 133,68 (43), 140.22 and 140.37(9), 140.94 and 141.09(10). An additional signal was probably buried under the deuterated solvent by comparing with the dialcohol and ditosylate. The 60 MHz phosphorus 31 NMR in acetone-d_6 was run by Mr. Fred Smetena at 30° for 10 minutes with phosphoric acid as an external standard. Only one signal was observed at 21.7 ppm upfield from the external standard which was about three times as broad as the standard signal. No oxide peak was observed.

The ligand was not very soluble in ethanol, so the rotation was taken in acetone. The following rotations were observed at c=.517, acetone: $[\alpha]^{rt}$ (wavelength), -33.46° (589), -35.20° (578), -40.61° (546), -74.07° (436), -132.66° (365). Elemental analysis for $C_{35}H_{38}O_2P_2$ requires: C 76, H 6.9, P 11.2; Found: C75.6, H 6.83, P 10.91.

Partially oxidized samples gave lower melting points, whereas the sample sent in melted over one degree. Another

mass spectrum was taken on the new mass spectrometer. The main fragments were m/e: 553 (fragment ionized), 475, 367, 185, 183, 108.

Preparation of Catalytic Precursors

The entire procedures[30] for preparing $[Rh(cyclooctene)_2Cl]_2$ and $[Rh(cyclooctadiene)Cl]_2$ have been discussed in Chapter 1 of this thesis. These were both made several times from rhodium trichloride.

$$2\ RhCl_3 \cdot 3H_2O + 4\ C_8H_{14} + 2\ CH_3CH(OH)CH_3 \rightarrow$$

$$[Rh(cyclooctene)_2Cl]_2 + 2\ CH_3COCH_3 + 4\ HCl \qquad (13)$$

Preparation of the SPIPHOS In Situ Catalyst

(S,S)-SPIPHOS (.05 mmol) and $[Rh(alkene)_nCl]_2$ (.025) were mixed as solids along with substrate (5 mmol) when the substrate was a solid in the autoclave glass liner. The system was degassed under high pressure with nitrogen and the solvent (50 ml, 3:1 ethanol:toluene) was added along with any liquid substrate. The solution was stirred approximately one minute before pressurizing with hydrogen.

Preparation of the SPIPHOS Cationic Catalyst

The cationic catalyst was prepared according to similar preparations made by W. S. Knowles.[33] SPIPHOS (.6 mmol) and u-dichlorobiscyclooctadienedirhodium (.3 mmol) was slurried in 25 ml of dry oxygen free methanol in a 50 ml round bottom flask under argon. This formed a deep orange solution.

$$2\ \text{SPIPHOS} + [\text{Rh(COD)Cl}]_2 + 2\ \text{NaBF}_4 \xrightarrow[\text{MeOH}]{}$$

$$2\ [\text{Rh(SPIPHOS)COD}]^+\text{BF}_4^- + 2\ \text{NaCl} \qquad (14)$$

A solution of sodium tetrafluoroborate (6 g in 29 ml of water) was degassed with argon and then quickly added to the methanol solution. A thick yellow precipitate immediately formed.

The folution was filtered under argon in a filter tube and washed with argon saturated water (2 x 25 ml). The light yellow powder was dried by vacuum for two hours. A total of .4447 g or 88% was isolated. The catalyst is a deep yellow in alcohol solvents and this does not darken with oxygen or addition of N-α-acetamidocinnamic acid. The catalyst may be fairly air stable when in solution.

General Hydrogenation Procedure

The *in situ* catalyst was prepared as previously described. The cationic catalyst was added as a powder to the glass autoclave liner. A stir bar was added to the glass liner and the liner was positioned into the autoclave and the stir rate set. In the hydrogenations run at 60° a heating mantel equipped with multiple thermocouples was attached and preheated to the required temperature. In the hydrogenations run at 0°C, an ice bath was positioned under the autoclave and allowed to cool the catalyst and glass liner for at least 15 minutes before solvent was added. In the hydrogenations run at room temperature the liner was put into place, the stir rate set, and the top of the autoclave bolted down. The autoclave was loaded to at least 1000 psi of nitrogen pressure to help degas the system and also check for pressure leaks. Almost all of the nitrogen pressure was released. The solvent, including any liquid substrate premixed in, was loaded into the autoclave through a sampling valve after the remaining nitrogen pressure had purged this valve. The solvent was loaded while at the same time another valve attached to an oil bubbler was open to relieve back pressure. The entire system was closed and pressurized to the required hydrogen pressure. The pressure will drop about 25 psi as it is fully absorbed into the solvent and then remain constant. When the autoclave leaked, it was

monitored and repressured as needed. After the required time, usually 24 hours initially, the hydrogen pressure was released slowly to prevent frothing. The autoclave was unbolted, the head removed, the glass liner removed, and the solution noted for color and the presence of any residue.

Product Isolation

A summary table was given in Chapter 1 which lists the isolation procedure and characterization used for each substrate. The same substrates were used with the SPIPHOS system.

One of the key parts of the isolation was the initial evaporation of the solvent after each hydrogenation. This could be done by evacuating the sample, but it takes quite long and often is complicated by traps clogging. A more efficient technique was to evaporate off the solvent, including water, by placing the solution in a recrystallization dish and putting this under the sash door of an exhaust hood. One hood with an oven underneath was particularly effective as the bottom of the slate was always 30°C. Since all of the substrates and products are not very volatile, they were easily isolated, while at the same time the catalyst was air oxidized and precipitated out. In the case of added base, the excess is also removed making less salt later in the acidification step.

β-Methyl cinnamic acid as well as its methyl, ethyl, and iso-propyl esters could be vacuum distilled after this evaporation. α-Methyl cinnamic acid and its methyl ester were also distilled in this manner. When these acids had base added, it was necessary to first make the sodium salt of the acids, filter off the residue, and reacidify with hydrochloric acid. The crude acids were then extracted into diethyl ether, the ether removed, and the product vacuum distilled.

With the three amino acid precursors N-a-acetamidocinnamic acid, N-a-acetamidoacrylic acid, and N-a-benzamidocinnamic acid isolation of the products was by evaporation of the solvent, making the sodium salt of the acids, filtering off any residue, acidification of the solution, evaporation of the water to leave salt and the product, extraction of the product into diethylether (10 x 50 ml), evaporation of the ether, and vacuum drying of the powder products. The methyl esters of these acids had to be isolated by column chromatography on silica gel with ethyl acetate after evaporation of the solvent. The products and starting substrates were taken together and came off before a dark brown band. The ethyl acetate was removed by vacuum to leave the products and substrates.

Three substrates form α-methylsuccinic acid upon hydrogenation and share a common work up. After the solvent is evaporated off, the residue is dissolved in aqueous

sodium hydroxide and stirred. After about 30 minutes the sample is filtered through a course sinstered glass funnel, and the solution acidified until acidic to pH paper. The product and substrate are extracted into diethyl ether (10 x 50 ml) and the ether is evaporated off. The remaining solid is transferred into a small round bottom flask and vacuum dried. The product is difficult to dry and will pick up moisture from the air.

2,3-Diphenylpropanoic acid is also isolated by evaporation of the solvent, preparing the sodium salt, filtering, and preparing the acid with hydrochloric acid. Both the product and the substrate can be extracted in only 100 ml of diethyl ether which is then evaporated off or by filtering the fluffy material directly from the acidic water solution.

2-Methyl-3-phenylpropanal can be isolated by direct distillation after the solvent is removed by evaporation. This yellow product has a very bad odor and should be kept in the hood.

The physical properties of the substrates and hydrogenation products have been described in the literature. The proton NMR's of each substrate and product are listed in the literature. The residual solvent signals can be used to compare the chemical shifts.

Rotation Values

The absolute rotation values are reported in Chapter 1. The samples were checked for purity by NMR and then measured into 10 ml graduated flasks. The rotations were taken, often at all five wavelengths. When the sample was too cloudy to give a proper rotation, then the sample was filtered through a medium sinstered glass funnel and the rotation repeated. The rotation was corrected for the purity of the sample, but not for the purity of the ligand and catalyst.

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